

Print ISSN: 2434-9186 Online ISSN: 2434-9194



GHM

Global Health & Medicine

Volume 3, Number 1
February, 2021



Downtown San Diego COVID-19 vaccination supersite

"What will be the future of SARS-CoV-2 and of 'normal' life returning after widespread vaccination?"

(Page 3, Editorial by Dr. Douglas D. Richman)

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English



Global Health & Medicine

Global Health & Medicine

Global Health & Medicine (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal, published by the National Center for Global Health and Medicine (NCGM), which is a national research and development agency in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration.

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English



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(As of February 2021)

EDITORIAL

- 1-5 **COVID-19 vaccines: implementation, limitations and opportunities.**
Douglas D. Richman

POLICY FORUM

- 6-10 **Business models for sustainable development: Projects of global extension of medical technologies of Japan.**
Ikuma Nozaki, Yasuo Sugiura, Noriko Fujita, Hiroyasu Iso, Tamami Umeda
- 11-14 **For further collaboration on strengthening Universal Health Coverage (UHC): Partnership project between Japan and Thailand.**
Munehito Machida, Yumiko Miyashita

REVIEW

- 15-23 **Secondary dyslipidemia: its treatments and association with atherosclerosis.**
Hidekatsu Yanai, Hiroshi Yoshida
- 24-30 **Current state and prospect of the perioperative strategy for nonsmall cell lung cancer.**
Hiroshi Takumida, Yuichiro Takeda, Go Naka
- 31-36 **Current status of doublet combinations of platinum and fluoropyrimidines using oxaliplatin for advanced gastric cancer.**
Shusuke Yagi, Kazuhiko Yamada, Masayoshi Terayama, Hitomi Wake, Naoki Enomoto, Kyoko Nohara, Nobuyuki Takemura, Tomomichi Kiyomatsu, Norihiro Kokudo

ORIGINAL ARTICLE

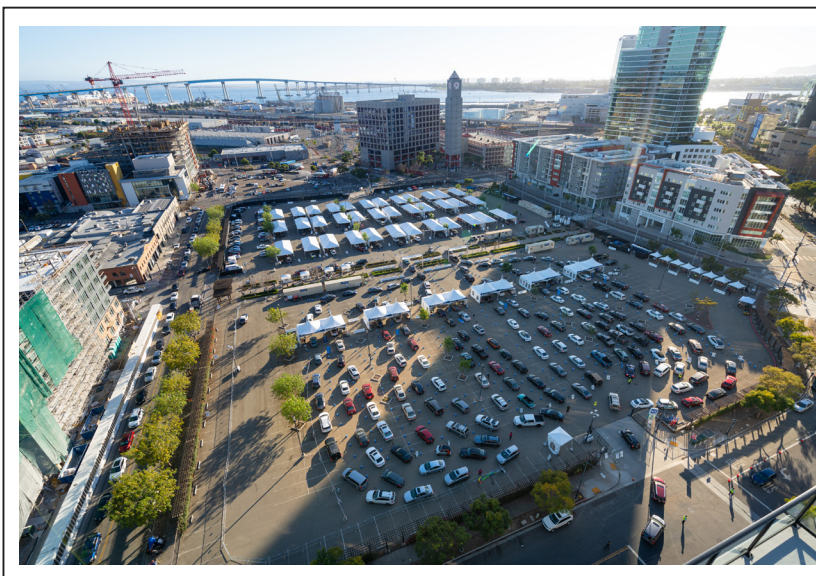
- 37-43 **Investigation of users' experiences for online access to their electronic health records in Japan.**
Lalla Soundous Elkhaili El Alami, Asuka Nemoto, Yoshinori Nakata

COMMUNICATION

- 44-47 **What is the current status of Japan's efforts to meet global goals and targets to eliminate cervical cancer?**
Rei Haruyama, Hiromi Obara, Noriko Fujita
- 48-51 **Enhancing the blood safety program in Myanmar: Report on projects of global extension of medical technologies of Japan.**
Ikuma Nozaki, Thida Aung, Nwe Nwe Oo, Haruka Kodoi, Yui Ito, Takashi Inaba, Katsuyuki Shiratori

- 52-55 **Enhancing the use of computed tomography and cardiac catheterization angiography in Zambia: A project report on a global extension of medical technology in Japan.**
Yuzuru Kono, Eiichi Shimizu, Futoshi Matsunaga, Yuriko Egami, Kohei Yoneda, Kayo Sakamoto, Muwindwa Mubita, Veronica Sunkutu Sichizya, Kazuyuki Wakamatsu, Misato Terashima, Noriko Fujita

COVER PHOTO OF THIS ISSUE



Downtown San Diego COVID-19 vaccination supersite. The photo shows the Petco Park (stadium for the San Diego baseball team) parking lot where one of the county COVID-19 vaccination sites is located. The site is run by the county health department and University of California, San Diego. (Submitted by Douglas D. Richman. The photo by Kyle Dykes, UC San Diego Health Sciences.)

COVID-19 vaccines: implementation, limitations and opportunities

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Abstract: The speed of development and the magnitude of efficacy of recently developed vaccines directed against SARS-CoV-2 has been truly remarkable. This editorial will not summarize the highly publicized and reviewed information about the design and clinical trial results of these vaccines. Rather, I will speculate about several issues regarding *i*) considerations of the rollout and implementation of the multiple vaccines, *ii*) the use of the vaccines in ways different from those used in the registrational phase 3 studies, *iii*) the future both of SARS-CoV-2 in the human population and of "normal" human life returning after widespread vaccination, and *iv*) the implications of the success of these SARS-CoV-2 vaccines for vaccine development against other pathogens.

Keywords: COVID-19, SARS-CoV-2, vaccine

The speed of development and the degree of efficacy of vaccines directed against SARS-CoV-2 has exceeded expectations of the most optimistic of us. To proceed within a single calendar year from the availability of the viral sequence to the initiation of immunization of tens of millions of people in several countries is the scientific breakthrough of the decade (if not longer) (1). The Moderna and Pfizer/BioNTech mRNA-based vaccines are safe and 94-95% effective. The efficacy of various vaccines based on adenovirus vectors or viral protein preparations are rapidly becoming available. Up to 200 additional investigational vaccines are in pre-clinical or early clinical studies. Numerous reviews of the design, development and evaluation of all these products have been published and will not be recapitulated here (2). What I will address are speculations on several specific issues about the future that result from these remarkable accomplishments.

What is the utility and role of several different, potentially competing vaccines?

To date, all the available data indicate no safety concerns to preclude general use for any vaccines in phase 3 development. The efficacy of the two mRNA-based vaccines has exceeded any expectations (3,4). The chimpanzee adenovirus-vectored Oxford/AstraZeneca vaccine (ChAdOx1) achieved 62% efficacy in initial trials, thus not attaining the 94-95% level of protection of the mRNA vaccines (5); however, the Russian Sputnik V heterologous adenovirus 26 prime with adenovirus 5 boost resulted in 92% efficacy in the preliminary report

of the phase 3 results (6). More results are anticipated. The preliminary phase 3 reports of the adenovirus 26-based J&J/Janssen vaccine indicated a 72% efficacy against symptomatic disease in the United States and a 66% efficacy in all participating countries with an 85% efficacy against severe disease or death (7). It should be acknowledged that the various vaccine studies were performed at different times in different locations and thus cannot be directly compared. For example, a significant proportion of the study subjects in South Africa were infected with the new B.351 variant, which has been shown to be less susceptible to antibodies elicited with the original Wuhan strain of antigen, which is in the composition of all the vaccines currently being evaluated (see below). The results of the study in the United States of the Janssen vaccine evaluating the benefits of a booster injection are eagerly awaited. The Novavax nanoparticle, protein-based vaccine appears as least as immunogenic as the mRNA-based vaccines (8). Preliminary phase 3 results from the United Kingdom indicated 89% efficacy with over 50% of cases attributable to the more transmissible B.1.1.7 variant, and a phase 2b trial in South Africa showed 60% efficacy, in which approximately 90% of the endpoints occurred in subjects infected with the B.351 variant (9).

Consequently, multiple vaccines should be at our disposal to draw upon to quench the global pandemic. Even with the widespread application of the highly effective Pfizer and Moderna vaccines in the United States and several other countries, these vaccines will not be sufficient to immunize the majority of the 7 billion people on the planet. Even should other vaccines

fall short of the 94-95% efficacy of these first two vaccines, multiple vaccines will be essential, and some may prove more appropriate for application among different populations living in different circumstances, especially low- and middle-income countries (LMIC). First, cost per dose of an adenovirus-vectored vaccine is approximately 2 US\$, while mRNA vaccines are approximately ten times more expensive. Second, the ultra-cold chain requirements for the mRNA-based vaccines are not feasible in most parts of less resource-rich countries, as well as in more rural and remote areas of the rest of the world. Third, billions of doses of vaccine are needed, and no vaccine manufacturer can produce sufficient vaccine alone. Fourth, the Janssen adenovirus 26-based vaccine has been originally tested with a single administration. For immunizing very large numbers of individuals, especially in LMIC, this would have very substantial benefits with regard to cost, health care resources and widespread rollout to benefit public health. This single-dose regimen would thus have numerous benefits, although a boosting injection does enhance immune responses and thus potential efficacy (10). Consequently, the implementation of global immunization will require multiple vaccines from different companies, and equally important, a rational strategy for selecting the most practical vaccine for each country, coordinated with allocation, distribution and administration processes to immunize as much of the world as expeditiously as possible. In the interests of public health, greater protection will result from immunizing many fold more members of the population with a vaccine conferring 70% efficacy than restricting use to a vaccine with 95% efficacy. These processes need to be conducted in parallel with information and educational efforts to overcome vaccine hesitancy and disinformation campaigns. Emerging data about safety, efficacy, production, cost, ease of administration, *etc.* will modulate decisions over time.

What alternative regimens should be considered for the administration of these vaccines?

With only millions of vaccine doses available in 2021 and billions of people in need of vaccination, alternative regimens for the use of the available vaccines have been proposed to stretch the supply to meet the demand and save lives. One is to administer half doses, for example of the Pfizer vaccine. This approach of halving the dose to double the available doses has proven very useful for addressing the recent yellow fever outbreaks (11); however, data to support the efficacy and durability of lower dose vaccine for COVID-19 have resulted in concern in the majority in the scientific community. Similarly, suggestions that different vaccines could be mixed for the prime and boost administrations have been proposed; however, once again there are simply no data regarding immunogenicity, safety or efficacy. It

is conceivable there may be a benefit to such a strategy, especially since vector-based vaccines do elicit anti-vector immunity which dampens responses (12). This is in fact the rationale behind the Russian Sputnik V vaccine, which uses an adenovirus 26 prime and an adenovirus 5 boost, using the same SARS-CoV-2 spike construct (13). Nevertheless, without clinical trial data it is hard to justify employing this approach with different products; however, in cases of severe interruptions in vaccine supply, an argument can be made that individuals in need of a second dose should receive whatever vaccine is available.

Controversial with knowledgeable proponents on both sides is the proposal that, with inadequate supplies of vaccines early in the rollout, all available vaccine should be used to immunize as many people as possible with the first injection, while assuming that supplies for the second injection may be delayed by a month or two. Although the protocols for the registrational studies specified a 3-week interval between the two doses for the Pfizer vaccine and 4 weeks for the Moderna vaccine, from a public health point of view many more individuals would be protected early by not withholding half of the vaccine supply to insure availability of the second injection at the specified interval. The argument for withholding relies on the evidence from the 30,000-44,000 person phase 3 trials that demonstrated efficacy according to protocols with just a few days of leeway with regard to the timing of the boosting dose and with no clinical trial data to show that a longer interval would be at least as effective or durable. The argument for immunizing as many as possible quickly with the possibility of a delayed second injection is based on several points: 1) The data show almost equivalent protection approximately 12 days after injection 1 for both Moderna and Pfizer, as for the period after dose 2. This means that with a disease incubation time of 5-7 days, protection is close to full after injection 1 for both vaccines within a week of exposure, consistent with the 5-7 day interval to detect neutralizing antibodies for most new antigens; 2) We do not know the durability of only 1 injection, but it is not showing any diminution at one month. Protecting twice as many people as fast as possible is better for public health than protecting half as many, even if there were a slight diminution of efficacy at least for several months (which I do not think is likely). The diminution will not be 50%; 3) Delaying a boost beyond a month theoretically and in mice permits the peak and potentially interfering neutralizing antibody titer to decay while permitting T cell and perhaps B cell memory to mature (14). Boosts are less effective at < 3-4 weeks following prime, but are as good as or better over the interval after one month for at least 6 months (and for measles for 4 years) (14). Recent data from the AstraZeneca ChAdOx1 trials suggest both better immune responses and increased protection the longer the interval between

3 weeks and 3 months or more (15). Consequently, this writer supports the "first doses first" strategy, *i.e.*, immunizing as many people as quickly as possible while awaiting additional supplies and information, acknowledging that this rationale is based on some extrapolations, rather than the data generated by clinical trials with a pre-specified injection interval.

What will be the future of SARS-CoV-2 and of "normal" life returning after widespread vaccination?

It is highly unlikely that SARS-CoV-2 will be extinguished like SARS-CoV-1. SARS-CoV-2 is clearly more transmissible than SARS-CoV-1, and is thus not amenable to the same transmission control measures. It can spread to the billions of remaining uninfected individuals on the planet, as well as the many millions who enter the population as a new birth cohort annually. The polio and measles eradication programs have struggled to eradicate these pathogens for decades because of the difficulties in reaching all corners of the globe, as well as the continual replenishment of new susceptibles by the annual birth cohort. Further complicating eradication are two factors, one shared with the polio and measles eradication challenges and one unique to SARS-CoV-2. As with all vaccination programs, vaccine hesitancy and misguided disinformation campaigns will diminish the penetration of protective vaccines in populations to sustain a large proportion of susceptibles. Unless overcome, this obstacle will confound the prospects of effective herd immunity. Unique to SARS-CoV-2 is the likelihood of the establishment of new animal reservoirs. The multiple introductions of SARS-CoV-2 into mink colonies with resulting transmission back into humans appears to threaten the industry of mink farming (16). Introductions into feline and canine species have been well documented, as well as the ability of the virus to infect numerous other species (17). Moreover, a chance transfer back into a bat population is not inconceivable. Consequently, it is almost certain that SARS-CoV-2 will not be extinguished and will likely remain a human pathogen, albeit controllable with effective vaccines.

One specter on the horizon, which may add to the threat of persistence of SARS-CoV-2, is the prospect of antigenic variants that escape immunity conferred by infection or vaccine. Several variants of concern have emerged since the Wuhan outbreak that appear to have occurred during human infection, rather than in a different species, like mink. The D614G and B.1.1.7 variants appear to be more fit by having been selected for increased transmissibility, but with no antigenic escape and possibly not significant virulence (18-20). Additionally concerning, are early data that indicate that the B.351 South African variant represents a neutralization escape variant to convalescent sera (21-23).

Speculation about the future applies to the lives of

people as well as the virus. Will we be able to resume life as we knew it before COVID-19? To some extent, the pandemic has been sustained because many people never modulated their behavior during the threat of COVID-19. For many of us, who have been secluded at home and gone to work or shopping while exercising careful masking and other precautions, the opportunity to resume greater and more open contact with friends and family, to travel, and go to restaurants, theater and sporting events is greatly anticipated. Prolonging life and fully enjoying life should not be mutually exclusive. Following more widespread vaccination, many of us may gradually be able to resume most of these activities that we have avoided; however, there will likely be some permanent changes as the pandemic becomes controlled. As is the practice in many Asian societies, many individuals will increase their use of masks in public, not only for prevention of infection with SARS-CoV-2, but to reduce the risk of influenza and other respiratory virus infections, which appear to have diminished in incidence during the pandemic. Working remotely has had both benefits and frustrations. The benefits of reduced travel with cost savings for transportation and for meeting and office space will result in a greater proportion of work performed remotely than pre-pandemic. There may very well be substantial impacts on schooling, especially at higher levels and on business and scientific meetings. The loss of personal interactions at meetings (scientific, business, government and otherwise) has been a substantial loss, but remote meetings provide advantages of wider global participation, reduced costs, and diminished pollution and carbon footprint. More explicit predictions are well beyond the expertise of this writer.

What scientific opportunities will be provided by the progress of COVID-19 vaccine accomplishments?

The remarkable speed of COVID-19 vaccine development, clinical trials, emergency use authorization and rollout occurring in less than a year after the release of the virus sequence is remarkable and unprecedented. These accomplishments are a direct consequence of at least a decade of research in investigating new delivery platforms for HIV and other viruses. Of the first four vaccines developed in the United States and Western Europe, two were based on mRNA delivery and two on adenovirus vectors. What has been learned in the process of these successful vaccines, which extends over design, evaluation, production and delivery will certainly expand and accelerate vaccine development against the panoply of pathogens for which effective, or more effective, prevention is needed. A short list of pathogens that comprise this category includes HIV, influenza, respiratory syncytial virus (RSV), human

metapneumovirus (hMPV), and other paramyxoviruses, dengue and other flaviviruses, rotavirus, Lassa virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, hepatitis C virus, tuberculosis, syphilis, gonococcus, cholera, borreliosis, pertussis, rabies, and malaria. Some of these targets may not be amenable to the delivery of one or a few protein antigens and the appropriate antigen for many of these pathogens has not been defined. Nevertheless, the flexibility offered by these platforms, especially the mRNA-based platforms, and their implementation have now matured from unknowns to well-characterized, thus opening a generational opportunity for further applications to vaccines, the most effective and economical contribution of medical science to public health (24).

Funding: None.

Conflict of Interest: The author has no conflict of interest to disclose.

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post-COVID-19 era. Proc Natl Acad Sci U S A. 2021; 118:e2020368118.

Received January 31, 2021; Accepted February 4, 2021.

Released online in J-STAGE as advance publication February 11, 2021.

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Business models for sustainable development: Projects of global extension of medical technologies of Japan

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Abstract: Japan has been implementing projects of global extension of medical technologies under an official development assistance policy to improve public health and medicine by promoting Japanese medical technologies worldwide. The current work examines the impact and goals of implementing this new scheme. The scheme has involved dozens of projects that sent Japanese experts to partner countries and that invited their counterparts to Japan to showcase Japanese medical technologies. Approximately 50 projects have been implemented in 24 countries over 5 years, and 19,638 individuals have been trained. As a result, the introduced technology was adopted in national guidelines in 4 projects and the introduced equipment was procured in the partner country in 17 projects. In total, 912,334 individuals have benefitted from the introduction of these medical technologies. The concept of "creating shared value" (CSV) could help promote project success by both creating economic value and encouraging social progress. However, the sustainability of that business model remains in question in terms of the internationalization of CSV. Several successful projects improved medical care and led to new business opportunities.

Keywords: sustainable business, creating shared value, official development assistance

Introduction

The advent of the era of sustainable development goals (SDGs) has transformed the development paradigm. The role of the private sector in development is widely recognized (1), and the private sector has welcomed this trend. The SDGs define a common framework of action that helps the private sector identify future business opportunities, enhance the value of corporate sustainability, enhance stakeholder relations and keep pace with policy developments, stabilize societies and markets, and use a common language and shared purpose (2). Companies that do not promptly change their business model to align with the SDGs may not survive in this era. In Japan, the Ministry of Economy, Trade, and Industry published the "Guide for SDG Business Management" to lead discussions on how to do business in the era of SDGs (3).

To activate the stagnant Japanese economy, the Government of Japan implemented the "Japan Revitalization Strategy" in 2013 (4). Under this strategy, health and medical care were prioritized to improve the health and longevity of the citizenry. The strategy also included the worldwide promotion of Japan's medical care and technology because of the nation's comparative advantage in health and medical care (5). In light of these initiatives, various programs and projects were

formulated by related ministries (Table 1; (6)).

The Ministry of Health, Labour, and Welfare has been implementing its "projects of global extension of medical technologies" to improve public health and medicine in developing countries by sharing Japanese experiences in public agencies and medical facilities under the health insurance scheme and to promote excellent medical technologies, drugs, and devices. The National Center for Global Health and Medicine, one of the leading organizations in global health in Japan, has been implementing this project since 2015 (7). Therefore, the current work discusses the significance of implementing this new scheme of developmental assistance in collaboration with the private sector.

Projects of global extension of medical technologies

A major component of the projects is exchange programs where experts from Japan travel abroad and foreign experts travel to Japan to learn about health topics, health systems, and medical devices. Each year, proposals are submitted by various bodies such as universities, the private sector, and the National Center for Global Health and Medicine, and projects are selected. From 2015 to 2020, approximately 50 projects have been implemented in 24 countries. Table 2 presents a list of the projects of global extension of medical technologies in 2019.

Table 1. List of supporting organizations, projects of global extension of medical technologies, and services of Japan

Supporting Organizations	Projects [Year]	Services
Cabinet Office	<ul style="list-style-type: none"> ● Task Force for Global Reach of Japanese-style Medical Technology and Services [2013] 	Based on the Healthcare and Medical Strategy, the task force was established to coordinate multi-ministerial efforts to promote the global deployment of Japanese medical care.
Ministry of Economy, Trade, and Industry	<ul style="list-style-type: none"> ● Medical Excellence JAPAN [2009] 	A general association was established to serve as the central organizational hub to facilitate overseas expansion of the health care and medical care sector based on one of Japan's growth strategies.
	<ul style="list-style-type: none"> ● Project to Establish a Strategic Base for the Promotion of Medical Technology [2015] 	A program that supports the establishment of a Japanese strategic base overseas to promote the global deployment of Japanese medical technologies and services.
Ministry of Health, Labour, and Welfare	<ul style="list-style-type: none"> ● Support Project to Establish an Accreditation System for Medical Institutions Accepting International Patients [2011] 	The Japan Medical Education Foundation evaluates an institution's capacity to accept international patients in order to create a system so that international patients can safely and reliably receive world-class Japanese medical care.
	<ul style="list-style-type: none"> ● Japan Medical Service Accreditation for International Patients [2012] 	The accreditation system facilitates the acceptance of international patients to easily and safely receive medical care.
	<ul style="list-style-type: none"> ● Projects of Global Extension of Medical Technologies [2015] 	The projects aim to cooperate with ministries of health in various developing countries in order to facilitate the global spread of medical technologies. The projects also aim to improve public health and medicine in developing countries by sharing the experiences of medical facilities, such as public health insurance, and to promote excellent medical technologies, drugs, and devices.
	<ul style="list-style-type: none"> ● Project to Assist the Medical Industry to Acquire pre-qualification from the World Health Organization [2017] 	To assist the Japanese medical industry in acquiring pre-qualification from the World Health Organization in order for developing countries to procure pharmaceuticals and medical devices, the project aims to promote the global spread of quality Japanese pharmaceuticals and medical devices.
Ministry of Foreign Affairs	<ul style="list-style-type: none"> ● JICA- Public-Private Partnership Projects [2008] 	The projects support companies by considering the use of social enterprises for development, and they use information obtained and networks built overseas through official development assistance projects.
	<ul style="list-style-type: none"> ● Ministry of Health, Labour, and Welfare/Ministry of Foreign Affairs, GHIT Fund [2012] 	The Japan-based GHIT Fund is an international public-private partnership fund for global health R&D that mobilizes Japanese industry, academia, and research institutes to create new drugs, vaccines, and diagnostics for malaria, tuberculosis, and neglected tropical diseases, in collaboration with global partners.

In total, 19,638 individuals have been trained to use Japanese medical technologies from 2015 to 2019: 1,013 were trained in Japan, and 18,625 were trained abroad (Figure 1).

As a major outcome of the project, four Japanese medical technologies have been adopted in other countries' national plans or guidelines to improve health there. For instance, technical guidelines were developed and adopted in collaboration with Japanese experts and their counterparts in respective countries: guidelines for preventing medical accidents at hospital and guidelines for incident reports were developed in Vietnam, national guidelines for blood transfusions were adopted in Myanmar, and standard operational procedures for preparing reagents for ABO blood typing were adopted by the National Blood Center in Mongolia.

In addition to those outcomes, medical devices or consumables introduced by this project were procured in 17 instances. For instance, a project in Vietnam

introduced dysphagia diets and a thickener for the care of patients after cerebral infarction, and dysphagia diets are now included as part of medical care in Vietnam. Another example is a project in Myanmar where the health risks to blood donors such as the vasovagal reflex were not fully recognized. During a tour of Japan, the Japanese Red Cross Society expressed their strong commitment to interventions to protect the health of blood donors. As a result, blood collection beds that can elevate the legs of donors, made by Terumo, were procured by Myanmar's Ministry of Health to improve donor safety. Terumo also supported the advancement of medical care in Myanmar, by offering stem cell transplantation technology for hematology treatments and leukocyte removal filters to hospitals in order to reduce the risk of adverse events related to blood transfusion.

As an indicator of its impact, 912,334 individuals are expected to benefit from the medical technologies introduced by this project according to calculations.

Table 2. The projects of global extension of medical technologies in 2019

No.	Country	Project	No. of trainees	
			in country	in Japan
1	Cambodia	Pathological Capacity and System Improvement for Cervical Cancer in Cambodia	6	406
2	Cambodia	Strengthening the Emergency Medical System in Provincial Cities of Cambodia	0	330
3	Cambodia	The Project for Quality Improvement of Clinical Testing for Microbiology, Hematology, and Clinical Chemistry in Kingdom of Cambodia	11	299
4	Cambodia	Cooperation for Development of Cambodian Rehabilitation Specialists in NCDs	4	123
5	Cambodia	Technical Training Program for School Health Check in Cambodia	0	62
6	China	Construction of International Linkage for Improvement of Liver Surgery in China	8	246
7	Ethiopia & Nigeria	The Project for Developing Basis of Expanding Japanese Medical Devices in Africa under the Projects for Global Growth of Medical Technologies, Systems and Services by Ministry of Health, Labour and Welfare	4	4
8	Indonesia	Development of Human Resources for "Infection Prevention and Control (IPC)" and "Antimicrobial Stewardship Program (ASP)" Based on Indonesian Situation to Tackle Antimicrobial Resistance (AMR)	6	128
9	Indonesia	The Medical Program for International Promotion of Japan's Healthcare Technologies and Services for Rheumatic Disease in Indonesia	5	350
10	Indonesia	Building a Management System for Dialysis Equipment in Indonesia	6	123
11	Laos	Technical Support for Department of Radiology and Clinical Laboratory in Laos	4	267
12	Mongolia	Project to Strengthen Capacity of Emergency Medical Care Using POCUS in Mongolia	6	172
13	Mongolia	International Collaboration on Human Resource Development in Pediatric Acute Medicine in Mongolia	7	165
14	Mongolia	Training of Blood Morphology Testing for Clinicians and Laboratory Technologists in Mongolia	10	20
15	Mongolia	Development of Human Resources in Clinical Sleep Medicine in Mongolia	3	198
16	Myanmar	The Project for Safer Blood Transfusion and Stem Cell Transplantation in Myanmar	7	267
17	Myanmar	Effective Management of Hyperbilirubinemia in Myanmar	0	36
18	Myanmar	A Human Resources Development Project for Filling the Gaps of Medical Standards in Myanmar	15	138
19	Myanmar	Project to Develop Surgical Oncologists for Gastrointestinal Cancer in Myanmar	3	55
20	Myanmar	Project for Enhancement of Diagnostic Skills for Prenatal Ultrasound among Myanmar Obstetricians	2	29
21	Myanmar	Project for Development of Human Resource of Emergency and Disaster Medicine/DHED	4	70
22	Myanmar	Training of Orthopedics Specialists in Myanmar	4	11
23	Philippines	Project to Reinforce Medical Treatment, Care, and the Promotion of Mental Health among Children and Adolescents	5	40
24	Philippines	Philippines National Dissemination Project of Dialysis Fluid Purification & Control	2	83
25	Philippines	Capacity Building on the Quality of Medical Imaging and Its Diagnosis in Philippines	8	28
26	Thailand	Implementation of Endoscopic Surgical Skill Qualification System into Thailand	13	12
27	Thailand	Establishment of Thai Biomedical Engineer's Job System through Collaboration with Japanese Clinical Engineers-To Assist Japanese Product Installation to a Newly Planned Medical-hub Hospital in Bangkok	14	181
28	Viet Nam	Project for a Surgical Team Approach to Health and Medicine Based on Bac Mai Hospital	17	745
29	Viet Nam	Strengthening Management Capabilities of Medical Staff for Quality and Safe Healthcare to Accelerate Hospital-wide Cooperation in Vietnamese Hospitals	7	286
30	Viet Nam	Development of Bronchoscopy Techniques and Spreading related Devices in Viet Nam	20	455
31	Viet Nam	Perioperative Management, Including Technical Cooperation in Surgery for 4 Major Hospitals in Vietnamese Big Cities, with a View to Hospital Cooperation	6	215
32	Viet Nam	Introduction of Perioperative Care by Using Noninvasive Techniques in Viet Nam	6	1336
33	Viet Nam	Development of Medical Human Resources for Gynecology, Echography, Pathology, Radiology, Endoscopy, and General Diagnostic Practice in Viet Nam	11	47
34	Viet Nam	Project for Promoting Health Screening Program in Northern Viet Nam	6	141
35	Viet Nam	A Spread of Fitting technology for Hearing Aids & Promotion of Diagnosis Equipment in Viet Nam	13	150
36	Viet Nam	Promotion of Proper Use of Medicines with Medication Guiding Tools through Clinical Pharmacists Intervention in Viet Nam	2	79
37	Viet Nam & Indonesia	Support for Strengthening Medical Treatment Ability of Childhood Cancer in Developing Countries	6	208
38	Zambia	Project for Strengthening Operations of Image Diagnostic Using Computed Tomography Device and Intervention Using Angiography Device at University of Teaching Hospital in the Republic of Zambia	3	4
Total			254	7,509

Discussion

The projects of global extension of medical technologies

have two objectives: promotion of Japanese medical technology and improvement of public health and medicine abroad. Thus, appropriately balancing,

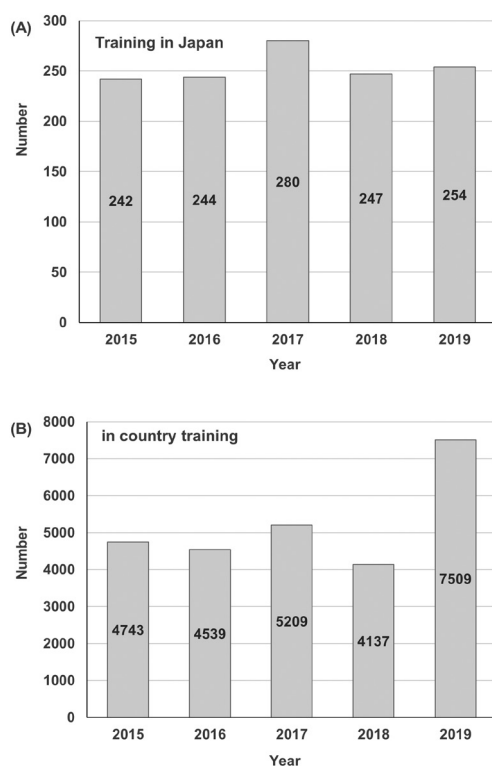


Figure 1. The Number of participants in training in Japan (A) and in-country training (B).

coordinating, and combining these two objectives is a challenge, and an effective solution is essential to the project's success.

The concept of "creating shared value" (CSV) (8) was proposed by Porter *et al.* and could help identify a solution to this challenge. Business practices that prioritize profits over humanity have been a major cause of social, environmental, and economic problems. Thus, today, the public widely regards companies as prospering at the expense of communities, their confidence in corporations is continuing to decrease, and government officials are responding to the public outcry with policies that protect the environment and human health but that decrease competitiveness and economic growth – at least in the short-term. Instead of focusing on optimizing short-term financial performance, businesses should focus on the biggest unmet needs in the market and opportunities that promote their long-term success. Porter *et al.* described CSV as a means to reconnect company success with social progress by redefining a company's purpose as creating "shared value" – generating economic value in a manner that also produces value for society by addressing its challenges.

Corporate social responsibility is a concept that is similar to and often compared to CSV. The biggest difference between corporate social responsibility and CSV is the consideration of social contribution in risk management or a business opportunity. In CSV, solving social problems is not an obligation but a business opportunity where the private sector proposes

solutions to social problems that the government cannot implement. The private sector emphasizes the corporate and economic aspects of CSV to promote its wide acceptance as part of mainstream management.

Hwy-Chang Moon *et al.* proposed the internationalization of CSV to strategically extend Porter's concept (9). They categorized corporations into four types: stupid, selfish, good, and smart. One of the strategies they proposed to change a corporation from a good one to a smart one was internationalization of CSV, and Porter argued that internationalization has more costs than benefits. They supposed that additional business opportunities and benefits for both the domestic and foreign markets could be provided by the internationalization of CSV and that the effects of CSV would be enhanced by collaborating with other organizations domestically and internationally. Therefore, an analysis of the current authors' experiences with the projects of global extension of medical technologies could provide additional insights into the internationalization of CSV.

In this era of SDGs, the expectation is that the health sector will lead the development of business models. Notably, health was preferentially addressed in the era of Millennium Development Goals (MDGs), but the paradigms for these models have changed substantially (10). Health is often considered a public good (11) and holds a critical position in building a business model in the era of SDGs. Japan's health care system is unique in terms of its medical care provided by the private sector but funded by the public sector. Thus, some of the projects have included the transfer of systems (*e.g.*, medical insurance) and may contribute to the establishment of new sustainable business models in health.

Another possibility is that the project could spur sustainable business among the health business sector. The foundations for corporate social responsibility and CSV in Japan began in ancient times, as represented by the phrase "Sanpo-yoshi (triple win)," which means "satisfaction of sellers and buyers and social contributions are crucial to good business" (12). Those were the words of the Omi shonin, merchants from Omi Province (present-day Shiga Prefecture) who were active in business in the Kamakura and Edo eras. The Terumo case is a good example and suggests that participation in projects could be a catalyst for companies to return to this principle of "good business." In addition, an analysis of the motivation of a participating company might provide insights into how to motivate the company to promote sustainable business in health care, a topic that will be discussed elsewhere.

In the spirit of the adage "no one left behind," ensuring inclusivity in business models is essential to sustainable development (13). Looking back at the business approaches thus far, the interests of individuals have not been compromised merely by including private

businesses in the development of the health sector. In order to ensure inclusiveness while conducting sustainable business in health care, the projects cited here should serve as inspiring examples, such as Vietnam's inclusion of dysphagia diets in its medical insurance.

Several studies have investigated how official development assistance (ODA) can trigger sustainable business practices (14,15). "Value" has become a keyword in an era when individuals involved in the development and the private sector are required to change their mindset (16). Several successes, such as dysphagia diets in Vietnam and blood transfusion in Myanmar, have been achieved among the projects implemented over the past 5 years. Further research should conduct a detailed analysis of successes to determine how they were implemented to answer the following questions: what are the "shared values" in sustainable business in the health sector, and what are the strengths of Japanese ODA and companies in this field.

Conclusion

Projects for the global spread of medical technologies have been implemented since 2015 based on Japan's ODA policy. Several successes at improving medical care abroad have resulted in business opportunities for Japanese medical manufacturers. CSV is a key concept of sustainable business practices, and companies are attempting to integrate this concept while receiving government support to achieve that goal. Therefore, the health sector should lead the discussion on CSV in the context of the legacy of the era of MDGs. Further study of these projects should be considered to find a Japanese way to contribute to sustainable business.

Acknowledgements

The authors wish thank colleagues from the secretariat of the projects of global extension of medical technologies in the Bureau of International Health Cooperation, the National Center for Global Health and Medicine who provided insight and expertise that greatly assisted this research.

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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Received August 13, 2020; Revised September 25, 2020; Accepted October 6, 2020.

Released online in J-STAGE as advance publication November 7, 2020.

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For further collaboration on strengthening Universal Health Coverage (UHC): Partnership project between Japan and Thailand

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Abstract: Thailand achieved Universal Health Coverage (UHC) in 2002 ahead of other low-middle income countries. Through its experiences, Thailand has actively assisted other developing countries in working towards UHC. However, Thailand is now facing new challenges such as increasing healthcare costs, differing service coverage and purchasing mechanisms among its three health care schemes, and the impact of a rapidly aging population on its health systems. Thailand requested technical support from the Japanese government. Japan achieved UHC in 1961 and its extensive experience of introducing and implementing UHC is a fitting example for Thailand and other countries struggling toward a stable health care system. Thus, the partnership project for Global Health and Universal Health Coverage was launched in July 2016 as a four-year flagship project for "North-South-South Cooperation". Japan and Thailand will further focus to support other countries to achieve UHC, which will be conducive to promoting leading roles of the two countries in the global health arena.

Keywords: Universal Coverage Scheme, North-South-South Cooperation, JICA

Introduction

Thailand, an upper middle-income country with a population of 69.6 million people, has been known worldwide for achieving and sustaining Universal Health Coverage (UHC) ahead of other low-middle income countries. Thailand government started to provide free healthcare services for the poor in 1975, and gradually increased the population coverage (1). In 2002, when the country's GDP per capita was still relatively low at \$1,900 (2), Thailand launched the new health insurance system, "Universal Coverage Scheme (UCS)", targeting the population that had not been insured by other health insurance schemes (the Civil Servant Medical Benefit Scheme (CSMBS) for government officials and dependents and the Social Security Scheme (SSS) for corporate employees). This significant health reform enabled the entire population of Thailand to be covered by one of these three health schemes for comprehensive essential healthcare including preventive, curative, palliative and long-term care (1,3). UCS empirically reduced the level of Out-Of-Pocket payment (OOPs), the incidence of catastrophic health spending, and contributed to reductions in the regional gaps in child mortality (4).

Through its rich experiences in designing and implementing UHC, Thailand has actively assisted other

developing countries in recent years in working towards UHC. A notable example is that Thailand played a key role as chairperson and secretariat for ASEAN Plus Three UHC network, established in 2014 to promote UHC in the region. More recently, Thailand serves as an advisory and technical partner to Kenya under a memorandum of understanding (MoU) signed in 2019. Promoting Thailand's leading role in global health areas, including UHC, is now a national strategy. The Ministry of Public Health and Ministry of Foreign Affairs issued a directive for the national Global Health Strategic Framework (2016-2020) to ensure health security for Thai people as well as providing technical assistance for health development in other countries (5).

Conversely, the Thailand UHC system has been facing new challenges such as increasing healthcare costs, differing service coverage and purchasing mechanisms among the three health schemes, and the impact of the rapidly aging population on the health systems. Financial sustainability and quality services are of critical importance for the three health insurance schemes (3,4,6). Thailand needed learning from the experience of other countries.

As is well known, Japan achieved UHC in 1961, almost 40 years after social health insurance was first legislated in 1922 (7). This process of introducing UHC is an apt example for Thailand and other countries

struggling to establish a stable health care system. The Japanese government, as part of its strategy for global health diplomacy, declared its willingness to contribute to resolving the challenge that countries have in common for introducing UHC (8).

Under these circumstances, Thailand requested technical support from the Japanese government, thereby facilitating groups of Thai officials and personnel to participate in trainings organized by the Japan International Cooperation Agency (JICA) in Japan in 2013 and 2014. They gained insight into Japan's experiences in managing social health insurance and health systems through the medical fee schedule and the roles of both central and local governments in the financial management of health insurance. Consequently, the Government of Thailand concluded that it was imperative to *i*) improve its UHC operation, *ii*) cooperate with Japan in helping other developing countries to promote achievement of UHC, *iii*) promote the strong implementation of UHC at the international level. Thus, Thailand and the Government of Japan jointly agreed to work together for a technical cooperation project based on the concept of "Partnership".

Activities and achievements

In July 2016, the partnership project for Global Health and Universal Health Coverage (GLO+UHC) was launched as a four-year flagship project for "North-

South-South Cooperation", meaning in this context that the Japan-Thai collaboration team support third countries (Figure 1). The facilitating organizations in Thailand were the Ministry of Public Health (MOPH) and the National Health Security Office (NHSO), the responsible agency for managing UCS. The project identified main focus areas including health care finance (fee schedule), health information systems (data platform and data utilization), health workforce, and UHC for children. Through the project period, various wide range activities were planned and carried out based on continuous discussions between Thailand and Japan through the Joint Project Management Team, which monitored and evaluated the activities of the project in detail. The following activities were implemented.

Output1: Capacity on improving implementation of UHC is strengthened in Thailand

Through a wide range of activities including 21 study visits to Japan and 19 workshops in Thailand focused on fee schedule system, integrated community care, patient safety, health information system, data utilization, maternal and child health (MCH), etc., the capacity of Thailand's relevant parties for improving the implementation of UHC was strengthened. Study visits created great opportunities of knowledge and experience sharing between both sides. Upgrading UHC practice in Thailand resulted in the establishment and strengthening

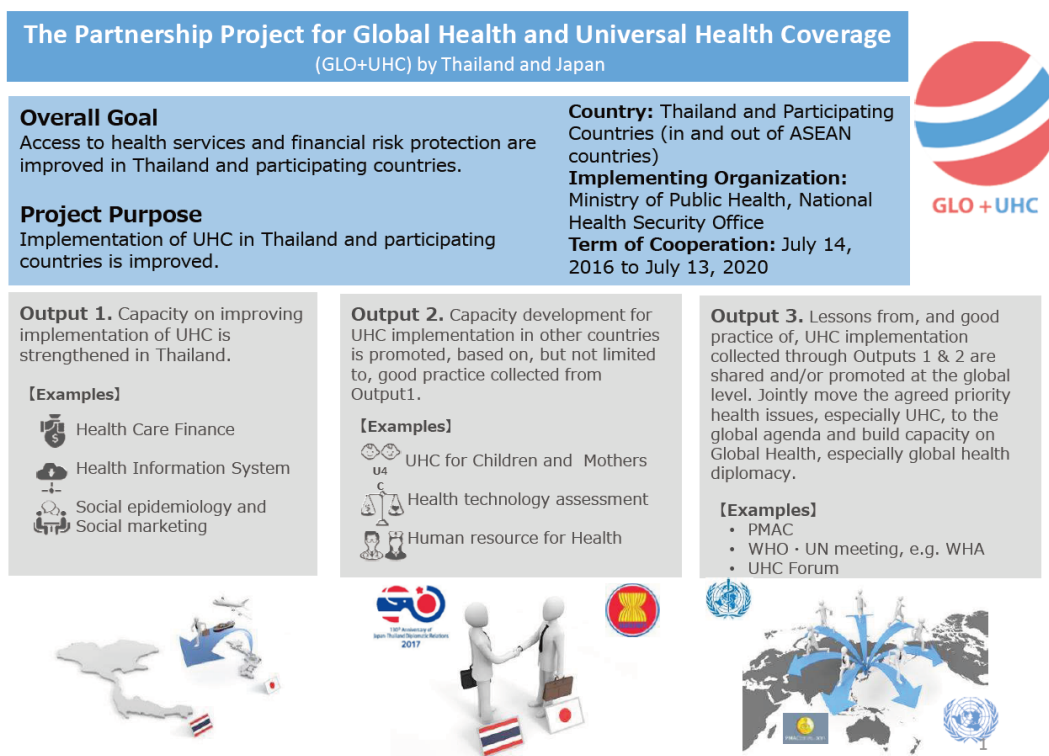


Figure 1. Outline of the GLO+UHC project. This partnership project is aimed to implement 3 Outputs for achieving Overall Goal. Universal health coverage (UHC) means that all people and communities can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship. (https://www.who.int/health_financing/universal_coverage_definition/en/)

of some mechanisms or infrastructure during this four-year project period. Some examples are a fee schedule committee in Bangkok modelled on Japan's Central Social Insurance Medical Council, called "Chuikyo", hardware and software for Big Data architecture, *etc.*. Collaborating work was also conducted between researchers of both countries in the community health and data science fields. One example of accomplishment is the acceptance of a manuscript on UHC and primary care by a world-level journal (6).

Output 2: Capacity development for UHC implementation in participating countries is promoted

Through more than 20 educational activities, mostly requested by Asian and African countries (participating countries), The experience of Thailand and Japan on putting UHC into the policy agenda and its successful implementation were shared with other low- and middle-income countries now striving for UHC. By utilizing the existing network of JICA office, the project prioritized Output 2 activities in the latter half. GLO+UHC contributed to MCH workshop in Myanmar and the "Thai UHC in action" inviting countries which aimed to introduce universal insurance system by learning from the Thailand and Japanese experience. Due to COVID-19 travel restrictions, other planned activities and workshops in health finance and MCH were postponed. Thai experts contributed to the Inter-professional Education (IPE) workshop held in Japan to share their educational and practical-type experience as Thailand is the leading country to disseminate the concept of IPE in Southeast Asia.

Output 3: Lessons from, and good practice of, UHC implementation collected through Outputs 1 & 2 are shared and/or promoted at the International level

Experience on UHC implementation was shared through various international platforms. Panel discussions at the Prince Mahidol Award Conference, PMAC, in Thailand were successful for sharing UHC experience in Thailand and Japan with partner countries. This conference attracts health concerned parties all around the world and hosts more than 1,000 participants in January every year.

By not only direct contribution by the Project activities, but indirect or spill-over effects (*e.g.* Thailand-Japan collaboration at a high-level meeting on UHC and on drafting a political declaration and south-south technical collaboration in essential areas of UHC), the presence of Thailand and Japan in the global health arena was enhanced.

Lessons learned

The GLO+UHC Project has tried to cover wide areas of implementing UHC in Thailand, Japan and participating

countries, especially in health care finance, health workforce, health information, UHC for children, and knowledge sharing/transfer/management. Among the three project outputs, Output 1 (Capacity development for improving the implementation of UHC in Thailand) and Output 3 (Sharing lessons learned and good practice of UHC implementation at the global level) are performing well with tangible outcomes based on the cooperation of Japan and Thailand. Some of the outcomes were successfully linked with policy implementation and better management of UHC in Thailand. The project provided many occasions to highlight the importance of UHC on a global stage. Regarding Output 2 (Capacity development of UHC implementation in other countries), the project had attempted to build a network with other participating countries through each activity. This network will serve as a basis for further collaboration. For further implementing Output 2, it would be desirable for Japan to take the initiative of the discussion on prospective collaboration among Japan, Thailand and participating countries through use of the existing technical cooperation and collaboration network that Japan has been constructing for more than half a century. Proactive support for third countries jointly by Japan and a partner country, like Thailand, will lead to the enhancement of skills of international technical support by the partner country itself. This effect will add to the value of Japan's international cooperation.

Way forward

It is expected that the next project phase of GLO+UHC, to be launched in later 2020, will focus on supporting the participating countries, related to Output 2, in accelerating UHC by sharing the experiences of Japan and Thailand. This partnership project is expected to have the synergistic effect of strengthening, on a global level, UHC not only in Japan and Thailand but also in other countries striving toward UHC. Through promoting joint support for participating countries by Japan and a partner country, bilateral exchanges of UHC will be beneficial for Japan's maintenance of its social security system by learning from the pioneering efforts of the partner country.

Acknowledgements

Munehito Machida submitted this article as a former chief advisor for GLO+UHC project. We thank Tatsuya Ashida, Yukari Maeda, Asumi Endo at JICA headquarter and Chieko Kajisawa at JICA Thailand office for supporting daily project activities in detail.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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- Received October 23, 2020; Revised December 21, 2020; Accepted January 6, 2021.
- Released online in J-STAGE as advance publication January 17, 2021.
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Secondary dyslipidemia: its treatments and association with atherosclerosis

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Abstract: Dyslipidemia is classified into primary and secondary types. Primary dyslipidemia is basically inherited and caused by single or multiple gene mutations that result in either overproduction or defective clearance of triglycerides and cholesterol. Secondary dyslipidemia is caused by unhealthy lifestyle factors and acquired medical conditions, including underlying diseases and applied drugs. Secondary dyslipidemia accounts for approximately 30-40% of all dyslipidemia. Secondary dyslipidemia should be treated by finding and addressing its causative diseases or drugs. For example, treatment of secondary dyslipidemia, such as hyperlipidemia due to hypothyroidism, by using statin without controlling hypothyroidism, may lead to myopathy and serious adverse events such as rhabdomyolysis. Differential diagnosis of secondary dyslipidemia is very important for safe and effective treatment. Here, we describe an overview about diseases and drugs that interfere with lipid metabolism leading to secondary dyslipidemia. Further, we show the association of each secondary dyslipidemia with atherosclerosis and the treatments for such dyslipidemia.

Keywords: hypothyroidism, low-density lipoprotein, nephrotic syndrome, triglyceride

Introduction

Dyslipidemia is classified into primary and secondary dyslipidemia. Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of triglycerides (TG) and low-density lipoprotein (LDL), or in underproduction or excessive clearance of high-density lipoprotein (HDL). Secondary dyslipidemia is induced by other underlying diseases and drugs. Almost 30-40% of dyslipidemia is categorized into secondary dyslipidemia (1). Secondary dyslipidemia should be treated by finding and addressing its causative diseases or drugs. For example, treatment of secondary dyslipidemia due to hypothyroidism by using statin, without controlling hypothyroidism, may lead to myopathy and serious adverse events such as rhabdomyolysis. This indicates the importance of differential diagnosis of secondary dyslipidemia.

Causes of secondary dyslipidemia are shown in Table 1. Among secondary dyslipidemia, there are types which show elevation of cholesterol such as hypothyroidism, types which show elevation of TG such as alcohol intake, and types which show elevation of both cholesterol and TG such as nephrotic syndrome.

Hypothyroidism

When addressing dyslipidemia due to hypothyroidism,

we should separately consider overt hypothyroidism, in which thyroid hormone levels are low, and subclinical hypothyroidism in which thyroid stimulating hormone (TSH) levels are high despite normal thyroid hormone levels. In overt hypothyroidism, elevations of total cholesterol (TC), LDL-cholesterol (LDL-C), apolipoprotein (Apo) B and lipoprotein (a) [Lp(a)] are observed (2). LDL-C is remarkably elevated by about 30% (2). Thyroid hormone stimulates LDL-C degradation and the conversion of cholesterol to bile acids by inducing LDL-receptor and 7 alpha-hydroxylase expression, respectively (3); which explains elevated LDL-C levels in hypothyroidism.

Subclinical hypothyroidism is observed in 4-10% of patients with dyslipidemia. In the meta-analysis which studied the effect of dyslipidemia due to subclinical hypothyroidism on carotid artery intima-media thickness (cIMT), subclinical hypothyroidism with TSH ≥ 10 μ U/mL was associated with elevations of TC, LDL-C, TG and cIMT (4). In the meta-analysis which studied thyroid hormone replacement therapy on dyslipidemia, those with a duration of over 6 months were associated with reductions of TC and LDL-C regardless of TSH values (5). Furthermore, the thyroid hormone replacement therapy reduced IMT in patients with subclinical hypothyroidism (6,7). However, there is presently no evidence which shows thyroid hormone replacement therapy reduces cardiovascular events (8).

Table 1. Causes of secondary dyslipidemia

Items	Cholesterol	Triglyceride
1. Hypothyroidism	↑	
2. Nephrotic syndrome	↑	↑
3. Chronic kidney disease (CKD)		↑
4. Primary biliary cholangitis (PBC)	↑	
5. Obstructive jaundice	↑	
6. Diabetes	↑	↑
7. Obesity		↑
8. Cushing's syndrome	↑	↑
9. Pheochromocytoma	↑	↑
10. Drugs	Drug dependent	
11. Alcohol intake		↑
12. Smoking		↑

Hypothyroidism is a risk factor for statin-induced myopathy (9). A reported case of a patient developing acute renal failure due to rhabdomyolysis after statin use (10) shows the importance of differential diagnosis of secondary dyslipidemia due to hypothyroidism.

Hypothyroidism can be the cause of secondary dyslipidemia, and thyroid hormone replacement therapy may improve dyslipidemia and prevent progression of atherosclerosis.

Nephrotic syndrome

An excess urinary protein loss-induced hepatic overproduction of lipoproteins, including LDL and very low-density lipoprotein (VLDL), a reduced clearance of TG-rich lipoproteins due to decreased activities of hepatic lipase (HL) and lipoprotein lipase (LPL), and an impaired maturation of HDL were associated with the development of dyslipidemia in patients with nephrotic syndrome (11,12). Recently, the association of proprotein convertase subtilisin/kexin type 9 (PCSK9) which determines LDL-receptor turnover with dyslipidemia due to nephrotic syndrome was proposed (13). Plasma PCSK9 levels were significantly higher in patients with nephrotic syndrome as compared with healthy individuals, and plasma PCSK9 levels were significantly and positively correlated with TC and LDL-C levels (13).

Regarding the relationship between nephrotic syndrome and arteriosclerosis, cIMT values in children with nephrotic syndrome were higher than controls (14). cIMT values were not correlated with dyslipidemia, but, were significantly and positively correlated with age, relapse frequency, and disease duration of nephrotic syndrome. Augmentation index (AI) which reflects systemic arteriosclerosis was significantly higher in patients with nephrotic syndrome than healthy individuals, and univariate linear correlation analysis showed that AI was significantly and positively correlated with TG, TC, LDL-C, non-HDL-C (15).

In the cohort study, the unmatched analysis adjusted by hypertension and smoking at diagnosis of nephrotic

syndrome showed that relative risks of myocardial infarction and coronary death were 5.5 [95% confidence interval (95% CI): 1.6-18.3] and 2.8 (95% CI: 0.7-11.3), respectively (16). The development of thromboembolism was observed in 2.8% of children and 26.7% of adults with nephrotic syndrome (17). Thromboembolism is induced by loss of anti-thrombotic factors into urine, and hepatic overproduction of prothrombotic factors (17,18). Various observational studies showed that patients with nephrotic syndrome frequently develop arterial and venous thromboembolism, however, neither of them showed the association of dyslipidemia with development of thromboembolism (19-22).

In the dietary intervention for nephrotic syndrome, a soy diet (low fat; protein, 0.71g/kg/day; cholesterol-free; mono- and poly-unsaturated fatty acids (PUFA)-rich; the ratio of PUFA to saturated fatty acids, 2.5; dietary fiber, 40g/day) was tried (23,24) (Table 2). The soy diet significantly reduced TC, LDL-C, HDL-C, Apo A, Apo B and urinary protein in patients with nephrotic syndrome. An intake of omega-3 fatty acids significantly reduced TG, VLDL-C, small dense LDL, remnant-like lipoprotein particles (RLP)-C and RLP-TG in patients with nephrotic syndrome (25). Various studies, including randomized controlled trials (RCTs), showed that statin reduced TC, LDL-C and TG safely and effectively (26-32). However, evidence showing beneficial effects of statin for renal outcomes was very limited, and one study showed that statin significantly improved urinary protein, serum albumin, creatinine, renal interstitial fibrosis and renal fat deposits (27). In the interventional studies using fibrates, gemfibrozil significantly reduced TG, TC, LDL-C and Apo B and significantly increased HDL-C (33,34). However, beneficial effects of fibrates for renal outcomes was not reported. In patients with treatment-resistant focal segmental glomerulosclerosis or nephrotic syndrome, the combination therapy of LDL-apheresis with steroid significantly reduced LDL-C and induced remission in 47.7-71.0% of such patients (35-38). In the meta-analysis which studied lipid-lowering agents on cardiovascular events in patients with nephrotic syndrome, the beneficial effects of these agents on mortality, cardiovascular death and non-fatal myocardial infarction were not obtained (39). For patients with minimal change nephrotic syndrome, which is steroid-responsive, the lipid-lowering therapy may not be needed. However, for patients with treatment-resistant nephrotic syndrome such as membranous nephropathy, the lipid-lowering therapy may be needed because such patients are middle-aged, prone to develop thromboembolism, and have prolonged steroid treatment.

Although they were no studies with patients who met the diagnostic criteria for nephrotic syndrome, several studies have shown beneficial effects of hypolipidemic agents on suppression of progression of proteinuria, and cardiovascular events, in patients with renal diseases.

Table 2. Effects of hypolipidemic interventions on serum lipids and renal outcomes in patients with nephrotic syndrome

Interventions	Effects on serum lipids	Effects on renal outcomes
Soy diet (<i>n</i> = 2)	<ul style="list-style-type: none"> • Reduction of TC, LDL-C, HDL-C • Reduction of apolipoprotein A, B • No change of TG 	<ul style="list-style-type: none"> • Reduction of urinary protein
Omega-3 fatty acids (<i>n</i> = 1)	<ul style="list-style-type: none"> • Reduction of TG, VLDL-C, small dense LDL • Reduction of RLP-C and RLP-TG • No change of HDL-C 	<ul style="list-style-type: none"> • No available data
Statin (<i>n</i> = 7)	<ul style="list-style-type: none"> • Reduction of TC, LDL-C, TG (<i>n</i> = 5) • Reduction of TG (<i>n</i> = 4) • Reduction in apolipoprotein B (<i>n</i> = 3) • Increase of apolipoprotein A (<i>n</i> = 1) 	<ul style="list-style-type: none"> • Reduction of proteinuria (<i>n</i> = 1) • Increase of serum albumin (<i>n</i> = 2) • Reduction of renal fat deposits (<i>n</i> = 1) • No change of proteinuria or serum albumin (<i>n</i> = 2)
Fibrates (<i>n</i> = 2)	<ul style="list-style-type: none"> • Reduction in TC, LDL-C, TG, apolipoprotein B (<i>n</i> = 2) • Increase of HDL-C (<i>n</i> = 1) • No change of HDL-C (<i>n</i> = 1) 	<ul style="list-style-type: none"> • No change of renal outcomes (<i>n</i> = 1) • No available data (<i>n</i> = 1)
LDL-apheresis (<i>n</i> = 4)	<ul style="list-style-type: none"> • Reduction in TC, LDL-C (<i>n</i> = 4) • No change of TG and HDL-C (<i>n</i> = 2) • Decrease of TG (<i>n</i> = 1) 	<ul style="list-style-type: none"> • Complete or partial remission rate, 47.7-71.0%

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density-cholesterol; RLP, remnant-like particles; TC, total cholesterol; TG, triglyceride.

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, type 2 diabetic patients (*n* = 9,795) aged 50 to 75 years were randomly assigned to fenofibrate (*n* = 4,895) or placebo (*n* = 4,900) for 5 years (40). Fenofibrate reduced urine albumin concentrations by 14% ($p < 0.001$), with 14% less progression and 18% more albuminuria regression ($p < 0.001$) than placebo. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial randomized 5,518 participants to either fenofibrate and simvastatin, or placebo and simvastatin (41). A post hoc analysis in the ACCORD Lipid Trial showed that fenofibrate was associated with lower rates of incident albuminuria and a slower estimated glomerular filtration rate (eGFR) decline as compared with placebo (42). In both FIELD study and ACCORD Lipid Trial, fenofibrate did not show a significant suppression of atherosclerotic cardiovascular disease (ASCVD) in the overall analysis, however, it did show a significant suppression of ASCVD in the sub-analysis using patients with high TG and low HDL-C (43). However, the fibrate use should be cautioned for patients with impaired renal function.

Chronic kidney disease (CKD)

Recently, an innovative established analysis method for lipoprotein profiles using high-performance anion-exchange liquid chromatography (AEX-HPLC) is accelerating the understanding of secondary dyslipidemia such as CKD and diabetes (44). In patients with CKD and proteinuria, a loss of Apo C-II, an activator of LPL, into urine impairs catabolism of VLDL (45). In patients with CKD and reduced GFR, hepatic VLDL production is not elevated, and the catabolism of VLDL is impaired. Further, serum Apo C-III, an inhibitor of

LPL, is increased and HL activity is reduced (46,47). Therefore, serum intermediate-density lipoprotein (IDL) levels increase in patients with CKD. We examined the lipoprotein profiles measured by AEX-HPLC in patients undergoing hemodialysis (HD), and found decreased HDL-C levels and increased levels of IDL-C and VLDL-C in HD patients as compared with healthy individuals (48).

CVD is the most common cause of mortality in patients with CKD. Dyslipidemia may be highly associated with the development of CVD in patients with CKD.

Primary biliary cholangitis (PBC)

PBC is an autoimmune liver disease characterized by positive anti-mitochondrial antibody. In PBC, the impaired secretion of cholesterol and bile acid into bile juice increases serum cholesterol. LDL-C is elevated regardless of disease stage of PBC, and HDL-C is relatively high even at the end stage of disease (49). In the systematic review which studied the association between PBC and coronary artery disease (CAD), PBC was not associated with the development of CAD (49). An observational study showed that 12% of PBC patients died of CVD (50), suggesting the existence of a population which needs the management of serum lipids.

Obstructive jaundice

Obstructive jaundice is induced by cholestasis due to obstruction of the extra-hepatic bile duct by gallstone or tumor. Intestinal cholesterol production is increased due to the impaired secretion of bile juice into the intestine

resulting in a disturbed absorption of fat. Hepatic and intestinal HDL productions are decreased by liver dysfunction and insufficient fat supply to the intestine. Therefore, LDL-C is elevated and HDL-C is reduced. Phospholipids-rich and free cholesterol-rich lipoprotein, lipoprotein X, increases in the blood of patients with obstructive jaundice (51).

Diabetes

When patients with type 1 (insulin-dependent) diabetes develop diabetic ketoacidosis, a remarkable elevation of chylomicron (CM) with TG > 1,000 mg/dL and a resulting acute pancreatitis are sometimes observed. However, such hyperchylomicronemia or hypertriglyceridemia is transient and is not associated with the development of atherosclerosis. In type 2 diabetes and obesity, insulin resistance induces dyslipidemia (52). Insulin resistance activates hormone-sensitive lipase (HSL) which hydrolyzes TG to free fatty acids (FFAs), and then serum FFAs increase. Increased FFAs enter the liver and increase hepatic VLDL production. Insulin resistance decreases LPL activity, which impairs VLDL metabolism and results in increased VLDL and decreased HDL. Our previous study using the AEX-HPLC showed lower values of HDL-C and higher values of IDL-C and VLDL-C in the order of type 2 diabetic patients with obesity, type 2 diabetic patients without obesity, low Framingham risk score subjects, young lean men (53).

In addition, large VLDL (VLDL1) and small dense LDL are increased, and apolipoproteins are glycosylated in the serum of patients with diabetes (54). Obesity and overweightness induce an abnormal fat accumulation which induces metabolic disorders such as type 2 diabetes. Adiponectin is released by adipose tissue, and plasma adiponectin levels are inversely correlated with body mass index (BMI) (55). High levels of circulating adiponectin can protect against atherosclerosis by the improving lipid and glucose metabolism (56). We estimated correlations between lipoprotein profiles and serum adiponectin levels in patients with type 2 diabetes and found an inverse correlation between adiponectin levels and VLDL-C levels (57).

Elevations of RLP which include CM remnant and VLDL remnant are associated with the progression of atherosclerosis and CAD (58). A high RLP-C (> 0.12 mmol/L) is a significant risk factor for CAD in Japanese patients with type 2 diabetes (59). We found that RLP-C is significantly correlated with IDL-C and VLDL-C measured by AEX-HPLC (60), suggesting that IDL-C and VLDL-C are also crucial risk factors for CAD in Japanese patients with type 2 diabetes.

Obesity

Obesity is associated with a number of deleterious

changes in lipoprotein metabolism, including high serum levels of TC, LDL-C, VLDL-C, and TG, and a reduction in serum HDL-C concentration of about 5 percent (61). Loss of body fat can reverse hypercholesterolemia and hypertriglyceridemia. However, improvements in serum levels of TC, HDL-C, and Apo A-I were primarily limited to patients with LDL subclass A (LDL peak particle size \geq 26 nm), and one-third of patients with LDL subclass B (LDL peak particle size \leq 25.5 nm), albeit a small-sized study of obese subjects with a mean age of 60 years (62).

Cushing's syndrome

Cushing's syndrome is caused by over-secretion of cortisol, which induces central obesity, impaired glucose tolerance, and dyslipidemia. Cortisol increases hepatic VLDL production, and patients with Cushing's syndrome show elevations of serum cholesterol and TG (63). The meta-analysis showed that Cushing's syndrome was associated with IMT thickening, carotid arterial plaque development, and endothelial dysfunction (64).

Cushing's syndrome can be a cause for secondary dyslipidemia and is associated with progression of atherosclerosis.

Pheochromocytoma

Pheochromocytoma is a rare neuroendocrine tumor arising from chromaffin cells of the adrenal medulla. The varied signs and symptoms of pheochromocytoma mainly reflect the hemodynamic and metabolic actions of catecholamines produced and secreted by the tumor. Increased catecholamines may activate HSL which increase serum FFAs, and enhance hepatic VLDL production. However, phenotypes of dyslipidemia due to pheochromocytoma and effect of its treatment on dyslipidemia varies by case reports (65-67).

Drugs

Among the most common causes of secondary dyslipidemia are drugs used for other indications. Causative drugs which induce dyslipidemia are shown in Table 3.

Table 3. Causative drugs which induce dyslipidemia

Causative drugs	LDL-C	TG	HDL-C
Diuretics (thiazide)	→	↑	→
β -blockers	→	↑	↓
Steroid	↑	↑	↑
Estrogen	↓	↑	↑
Progesterone	↑	↓	↓
Immunosuppressants	↑	↓	No available data
Anti-HIV drugs	↑	↑	↓
Atypical antipsychotics	→	↑	↓
Retinoids	↑	↑	↓

Diuretics

The meta-analysis of clinical trials, which investigated the effects of antihypertensive agents on lipids, showed that the use of diuretics, especially thiazides, in the treatment of hypertension has been associated with increased TC, LDL-C and TG levels (68). Among thiazide diuretics, chlorthalidone led to a greater increase in LDL-C, whereas indapamide did not alter TG levels at all. The effects of diuretics on TG were diminished over time, but the effects on cholesterol levels were not associated with study duration (68).

β -blockers

The conventional β -blockers exert adverse effects on weight, heart rate, and lipid and glucose metabolism, which may impair glucose tolerance, leading to elevations of TG and VLDL and a reduction in HDL (69). They may have a negative impact on total energy expenditure, which leads to weight gain (70). However, β -blockers with cardioselectivity and intrinsic sympathomimetic activity (ISA) decreased TC and LDL-C levels and increased HDL-C (68,71,72). Pindolol, a cardioselective β -1 blocker with ISA, lowered TG and increased HDL-C. However, atenolol, a cardioselective β -1 blocker without ISA, reduced HDL-C levels and did not affect TC and LDL-C levels (72).

Steroid

Steroids increase hepatic VLDL production and HDL production, which induce elevations of serum levels of TG, LDL-C and HDL-C. The effects of steroid treatment on serum lipids may vary depending on the daily dose and duration of steroid treatment (73). Corticosteroid-treated transplant recipients showed increased frequency of hypercholesterolemia and hypertriglyceridemia, with elevations of both LDL-C and HDL-C levels (74-77). Short-term prospective studies of the effects of prednisone in healthy men and patients with various disorders requiring corticosteroid therapy have shown an increase in TC by 8-17% and an increase in HDL-C by 36-68%, with insignificant changes in LDL-C levels (78,79).

Estrogen, Progesterone

Estrogen increases hepatic VLDL production, suppresses HL activity, and increases expression of LDL receptors (80-82). These effects of estrogen eventually decrease LDL-C and increase HDL-C and TG (83). Progesterone acts as an antagonist for estrogen, increases LDL-C, and decreases TG and HDL-C (83). Therefore, the effects of female hormones on serum lipids vary depending on the ratio of estrogen to progesterone included in drugs. When estrogen and progesterone are used as hormone

replacement therapy for menopausal disorders or as treatment for prostate cancer, it is known to affect lipid metabolism in a dose-dependent manner. However, dyslipidemia is rarely a problem with low-dose pills intended for contraception.

Immunosuppressants

A longitudinal cohort review of 102 outpatient pediatric liver recipients surviving greater than 6 months and immunosuppressed with cyclosporine and prednisone was undertaken (84). Half of the children had a mean cholesterol greater than 75th percentile (170 mg/dl); 20% were above the 95th percentile; 56% had a mean TG level greater than 140 mg/dl. Switching from cyclosporine to tacrolimus was significantly associated with decrease of TG, Apo A1, Apo B, LDL-C, HDL-C, and TC levels (85). Switching from cyclosporine to tacrolimus was associated with a more favorable cardiovascular risk profile by improving dyslipidemia. Since the patients undergoing transplant surgery are young, it is necessary to observe the effects of immunosuppressants on future cardiovascular events.

Anti-human Immunodeficiency Virus (HIV) drugs

Anti-HIV drugs improve endothelial function due to an improvement of chronic inflammation by HIV reduction. However, recently, anti-HIV drugs have been reported to increase the development of myocardial infarction. The prospective observational study of 23,437 patients infected with HIV showed that the incidence of myocardial infarction increased from 1.53 per 1,000 person-years in those not exposed to protease inhibitors to 6.01 per 1,000 person-years in those exposed to protease inhibitors for more than 6 years (86). The increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia (86). Elevations of TG, TC, and LDL-C and HDL-C reduction are commonly observed as dyslipidemia due to protease inhibitors (87,88). In a variety of anti-HIV drugs, protease inhibitors may cause dyslipidemia, while integrase inhibitors, a new-generation anti-HIV drug, have a minimal impact on serum lipid profile (89).

Atypical antipsychotics

Atypical antipsychotics such as olanzapine induce obesity and insulin resistance (90), which induce TG elevation and HDL-C reduction (91).

Retinoids

Hypertriglyceridemia is a metabolic complication of systemic retinoid therapy, which may occur in up to 17% of individuals treated with such therapy (92). Apo

C-III appears to be a target gene for retinoids acting via retinoid X receptor. The increased Apo C-III expression may contribute to hypertriglyceridemia due to retinoid therapy (92,93). LDL-C elevation and HDL-C reduction are also induced by systemic retinoid therapy (92).

Alcohol intake

Moderate alcohol intake induces elevations of HDL-C and Apo A-I, which might be anti-atherogenic (94). However, over-consumption of alcohol increases inflammatory cytokines, deteriorates insulin resistance (95), and results in an increase of VLDL. Patients with over-consumption of alcohol usually show type IV dyslipidemia. Alcoholism was associated with 7-day myocardial infarction fatality in the crude analysis (96), and is a risk factor for ischemic stroke (97).

Smoking

Cigarette smoking is associated with an increase in TG, a decrease in HDL-C and the deterioration of insulin resistance (98). The effect of smoking was more prominent if adjusted for concomitant alcohol intake; in such patients, smoking was associated with a 5 to 9 mg/dL decline in serum HDL-C (99). These effects are reversible within one to two months after smoking cessation (100,101). Smoking also causes the production of dysfunctional HDL3 particles that are characterized by an increased sensitivity to glycation and a reduced antioxidative capacity; it also impairs HDL function including cellular cholesterol efflux (102,103). Smoking is one of crucial risk factors for atherosclerosis (104,105).

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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- Received September 1, 2020; Revised December 1, 2020; Accepted December 7, 2020.
- Released online in J-STAGE as advance publication December 14, 2020.
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Current state and prospect of the perioperative strategy for non-small cell lung cancer

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Abstract: This paper provides an overview of perioperative treatment for non-small cell lung cancer (NSCLC), including the current widespread use of cytotoxic anticancer agents, promising molecular targeted agents, and immuno-checkpoint inhibitors. Multiple clinical trials have confirmed that postoperative chemotherapy with cytotoxic anticancer agents should be given for stage IIB to III (according to the 8th edition of the TNM classification for NSCLC) if possible, and preoperative treatment also is recommended for patients with N2 or higher stage. However, advances in concurrent chemoradiotherapy are expected to change the significance of neoadjuvant therapy. Perioperative treatment with molecular targeted agents appears to extend disease-free survival, but there is currently no evidence that it can extend overall survival. Perioperative treatment with immune checkpoint inhibitors requires further evidence but is likely to be effective. Although perioperative treatment of NSCLC could be costly it continues to evolve in hopes of a cure.

Keywords: postoperative, preoperative, chemotherapy, molecular targeted therapy, EGFR-TKI, immune-checkpoint inhibitor

Introduction

Perioperative chemotherapy has been used to improve the cure rate for non-small cell lung cancer (NSCLC) for some time, with many options emerging in recent years from the development of anticancer drugs.

This paper provides an overview of current widely used perioperative chemotherapy treatment (centered on cytotoxic anticancer agents) for NSCLC and the promising development of molecular-targeted drugs and immunotherapies.

Perioperative treatment with cytotoxic anticancer agents

The current common perioperative treatment strategy is chemotherapy with cytotoxic anticancer agents. Surgery is performed for early-stage and surgically resectable NSCLC because recurrent or inoperable NSCLC is quite difficult to cure. Unfortunately, although the 5-year survival rate is 80 to 90% for stage IA1 to IA3 disease in the 8th edition of the TNM staging system, stage IB or higher has a poorer outcome; with 70% for stage IB disease, 50 to 60% for stage II disease, and less than 50% for stage III disease (1). These survival rates, as a result of multidisciplinary treatment with cytotoxic anticancer agents, continues to improve. The rationale for these treatments had been tested in clinical

trials, which use strategies to increase the possibility for the cure of entirely resectable NSCLC by adding systemic treatment before and after surgery. A typical clinical trial is shown in Table 1. The pooled meta-analysis found chemotherapy to be useful preoperatively and postoperatively (2,3); therefore, these are now established as standards of care.

First, we describe the postoperative treatment of chemotherapy with cytotoxic anticancer agents. A meta-analysis in 1995 suggested the use of cisplatin (CDDP) based regimens (4), and subsequent clinical trials showed an improvement in disease-free survival (DFS) (5-7). Then, a meta-analysis, Lung Adjuvant Cisplatin Evaluation (LACE), based on individual data from 4,584 patients showed that postoperative adjuvant chemotherapy prolonged 5-year survival (hazard ratio (HR) 0.89, 95% confidence interval (CI): 0.82-0.96) and subgroup analyses showed that the therapy was highly efficacious for stage II and stage III (TNM 7th edition, IIB to III in 8th edition) (8). Therefore, if possible, postoperative chemotherapy should be performed for stage IIB and stage III. For disease stages lower than IIB, there are still controversial studies showing the efficacy of postoperative chemotherapy. A Japanese clinical trial showed that tegafur/uracil was effective for lower stage disease (9), and it is often done as a standard of care in Japan. However, there is no international consensus for lower stage disease.

Table 1. Clinical trials of perioperative therapy using chemotherapy

Authors (Ref.)	Abbreviation of trials	Year	Stage*	Adjuvant/NeoAdjuvant	HR (of what)	Regimen
Wada <i>et al.</i> (9)	(Not applicable)	1996	I to III	Adjuvant	0.55 (OS)	Tegafur/Uracil
Arriagada <i>et al.</i> (5)	IALT	2004	I to III	Adjuvant	0.86 (OS) 0.83 (DFS)	CDDP base
Winton <i>et al.</i> (6)	JBR-10	2005	IB to II	Adjuvant	0.69 (OS) 0.60 (DFS)	CDDP + VNR
Douillard <i>et al.</i> (7)	ANITA	2006	IB to IIIA	Adjuvant	0.80 (OS)	CDDP + VNR
Strauss <i>et al.</i> (12)	CALGB 9633	2008	IB	Adjuvant	0.83 (OS) [§]	CBDCA + PTX
Felip <i>et al.</i> (16)	(Not applicable)	2010	IA to IIB or T3N1	Neoadjuvant	0.92 (DFS) [‡] 0.96 (OS)	CBDCA + PTX
Scagliotti <i>et al.</i> (15)	ChEST	2012	IB to IIIA	Neoadjuvant	0.70 (PFS) 0.63 (OS)	CDDP + GEM

CBDCA, carboplatin; CDDP, cisplatin; DFS, disease-free survival; GEM, gemcitabine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; VNR, vinorelbine. *Classification according to TNM 7th edition. [§]HR was not significantly different. However, there were significant differences in the subgroup analysis for tumors 4 cm or larger. [‡]HR was not significantly different in both DFS and OS.

Table 2. Clinical trials of perioperative therapy using EGFR-TKI

Authors (Ref.)	Phase	Abbreviation of trials	Year	Stage*	HR (of what)	Regimen
Goss <i>et al.</i> (18)	III	CTSUBR19	2013	IB to IIIA	1.24 (OS) [§] 1.22 (DFS)	gefitinib
Kelly <i>et al.</i> (19)	III	RADIANT	2015	IB to IIIA	0.61 (DFS) [‡]	erlotinib
Zhong <i>et al.</i> (21)	III	CTONG1104	2018	II to IIIA (N1-N2)	0.60 (DFS) 0.96 (OS)	gefitinib
Yue <i>et al.</i> (23)	II	EVAN	2018	IIIA	0.54 (DFS)	erlotinib
Wu <i>et al.</i> (24)	III	ADAURA	2020	IB to IIIA	0.20 (DFS)	osimertinib

DFS, disease-free survival; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival. *Classification according to TNM 7th edition. [§]Only 15 patients (3.0%) with EGFR mutations were included. [‡]A subset analysis of 161 patients (16.5%) with EGFR-positive mutations was provided.

In terms of the regimen of chemotherapy for the postoperative treatment, a subgroup analysis of LACE showed that CDDP + vinorelbine (VNR) was highly effective for 5-year survival benefits (HR 0.80, 95% CI: 0.70-0.91) (10). However, various other regimens have been studied, for example, CDDP + docetaxel (DTX) (11) and carboplatin (CBDCA) + paclitaxel (PTX) (12). Although the CBDCA-based regimen may be appropriate for patients who cannot tolerate CDDP, the risks and benefits of chemotherapy for those patients should be considered. In elderly patients, for example, the effect of postoperative chemotherapy is reduced after five years (13).

A meta-analysis of preoperative treatment showed that this prolonged overall survival (OS) compared with surgery alone (2). Besides, preoperative chemotherapy and postoperative chemotherapy are equally effective (14). However, the early establishment of postoperative chemotherapy led to early discontinuation of many preoperative clinical trials thereby limiting evidence. Moreover, due to the evolution of chemoradiation therapy, preoperative chemotherapy is used less frequently in clinical practice. Also, two study results suggested that the effect of preoperative chemotherapy is poorly efficacious for the N0 and N1 stage. Those two results were the subgroup analysis of stage IB to IIA (TNM 7th edition, IB to IIB in 8th edition), in other words, stage N0 and N1 in the phase III study using CDDP + gemcitabine (GEM);

the ChEST study (HR for OS 1.02, 95% CI: 0.58-1.19) (15) and the results of the phase III study which excluded N2 and used CBDCA + PTX (HR for disease-free survival (DFS) 0.92, 95% CI: 0.81-1.04) (16).

On the other hand, in N2 or higher stage patients, the subgroup analysis of stage IIB to IIIA (TNM 7th edition, IIB to IIIB in 8th edition) in the ChEST trial (15) showed improved overall survival compared with surgery alone (HR for OS 0.42, 95% CI: 0.25-0.71). However, as we mentioned before, according to the development of chemoradiation therapy such as intensity-modulated radiation therapy, as well as the effectiveness of consolidation therapy following chemoradiation therapy in patients with unresectable stage III lung cancer treated with durvalumab (the PACIFIC study) (17), the usefulness of preoperative chemotherapy in patients with N2 or higher stage should be reviewed in future.

Perioperative treatment with molecular targeted agents

The best-tested molecular targeted agent for perioperative use is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI). Since EGFR-TKI was first developed as a molecular targeting agent for advanced NSCLC, the efficacy of perioperative treatment with EGFR-TKI has been studied as well as cytotoxic anticancer agents (Table 2). The CTSUBR19

study, which compared gefitinib with placebo as a postoperative treatment, failed to show an improvement in OS (HR for OS 1.24, 95% CI: 0.94-1.64), and the trial was stopped early (18). Similarly, the RADIANT study, in which patients were treated with erlotinib, failed to show prolongation of DFS (19). However, because the discovery of EGFR-sensitive mutations (20) occurred after design and conduct of these studies, they were not performed using appropriate patients. Specifically, the CTSUBR19 study included only 15 patients with EGFR-sensitive mutations, and the RADIANT study included only 16.5% (161 patients) of the total, so it cannot be interpreted literally. For reference, a subgroup analysis of positive patients with EGFR-sensitive mutations in the RADIANT study showed prolonged DFS (HR for DFS 0.61, 95% CI: 0.38-0.98).

Subsequently, several trials compared EGFR-TKI with cytotoxic anticancer agents as a postoperative treatment in patients with EGFR-sensitive mutations. The CTONG1104 trial comparing gefitinib with chemotherapy also showed an increase in DFS (HR for DFS 0.60, 95% CI: 0.42-0.87) (21) but no improvement in OS (22). A similar trend was seen in the EVAN trial, a phase II trial comparing erlotinib with chemotherapy (23). In June 2020, the phase III double-blinded randomized trial of osimertinib, the ADAURA trial, showed a more significant effect on DFS (HR for DFS 0.20, 95% CI: 0.14 to 0.30) compared with placebo (24). This trial was unblinded early because the results were more positive than anticipated, with expectations of a similar effect for OS. However, at present, EGFR-TKI only prolongs DFS in perioperative chemotherapy, with no evidence that it prolongs OS. Current knowledge suggests that it is necessary to consider the pros and cons of extending only the DFS in regard of medical-economic issues.

As of September 2020, the only ongoing perioperative treatment trials, involve the use of other molecular targeted agents. We look forward to these future reports. The ALCHEMIST trial (NCT02201992) and the ALINA trial (25) for patients with ALK mutations, and a phase II trial to confirm the safety of a perioperative treatment, including patients with ROS1, NTRK, and BRAF mutations, are ongoing (NCT04302025).

Perioperative treatment with an immune checkpoint inhibitor

Perioperative therapies using immune checkpoint inhibitors (ICI) are likely to better develop in the future, but unfortunately, they are only investigational at present. ICI have been used in many different ways in advanced NSCLC, including single-agent therapy, combined use with another ICI, and combined chemotherapy use. Therefore, even in perioperative therapies, ICI have been extensively studied in many strategies as in the advanced NSCLC setting. Only representative trials are listed in Table 3. The rationale for perioperative treatment

with ICI is characterized by preoperative treatment, which is essentially tumor-rich, to obtain lymphocyte aggressiveness for cancer.

The first reported article was a retrospective analysis of the TOP1201 study by Yang and colleagues. In this paper, they retrospectively analyzed a phase II trial of the anti-CTLA-4 antibody, ipilimumab, plus chemotherapy before or after surgery, and reported that the addition of immunotherapy did not significantly alter safety (26). Forde and colleagues reported preoperative immunotherapy with nivolumab, an anti-PD-1 antibody, in a pilot study. There were no significant safety issues, and 45% achieved a major pathological response (MPR) (27). In the same year, previous results from the NEOSTAR study (28), a preoperative phase II study of nivolumab plus ipilimumab, and results from the MK3475-223 study (29), a phase I study of pembrolizumab, were reported, both of which had similar safety and MPR values of 20-30%. Other Phase II and Ib studies of various drugs (atezolizumab and durvalumab, an anti-PD-L1 antibody, and sintilimab, a recently emerging anti-PD-1 antibody) in combination with chemotherapy have been reported, all of which have shown similar results (30-32).

The final contribution to survival by immunotherapy in perioperative treatment awaits the results of ongoing phase III trials, which may affect long-term prognosis considering the efficacy of immunotherapy in advanced NSCLC. On the other hand, anticancer therapy after relapse for NSCLC has progressed steadily, so it is expected that it will need a very long period to evaluate preoperative treatment by use of OS. Therefore, event-free survival (EFS) and DFS are primary endpoints in many developing clinical trials. However, a certain degree of caution should be exercised in interpreting the results because it may prolong DFS only as described in the EGFR-TKI chapter. Besides, unlike molecular targeted agents, because ICI and chemotherapy are relatively non-selective drugs, many people are likely to benefit from them. However, ICIs are costly so medical and economic issues need to be considered more carefully.

Conclusion

We described the current evidence and prospects for perioperative therapy in treating NSCLC. First, standard postoperative chemotherapy with cytotoxic anticancer agents should be given for stage IIB to III if possible, and preoperative treatment is recommended for patients with N2 or higher disease. However, advances in chemoradiotherapy can be predicted to change the significance of preoperative therapy. Although perioperative therapy with molecular targeted agents, including osimertinib, appears efficacious for DFS, effective for OS remains unknown. Perioperative treatment with ICI requires further investigation of

Table 3. Clinical trials of perioperative therapy using ICI

Authors (Ref)	Abbreviation of trials	Phase	Trial number	Status*	Stage	Result†	Regimen
Bott <i>et al.</i> (34)	NA_00092076	I	NCT02259621	Recruiting	I to IIIA [§]	MPR 45%	Nivo
Forde <i>et al.</i> (27)	NA_00092076	II	NCT02259621	Recruiting	I to IIIA [§]	MPR 45%	Nivo
Cascone <i>et al.</i> (28)	NEOSTAR	II	NCT03158129	Recruiting	I to IIIA [§]	MPR 24%	Nivo or Nivo + Ipi
Yang <i>et al.</i> (26)	TOP1201	II	NCT01820754	Completed	IB to IIIA [§]	Equivalent in safety	Ipi + CDDP or CBDCA + PTX
Zimmer <i>et al.</i> (35)	(NA)	II	NCT03366766	Active, not recruiting	IB to IIIA [§]	MPR 46%	Nivo + CDDP + PEM or Nivo + CDDP + GEM
Chaff (36)	ANVIL	III	NCT02595944	Active, not recruiting	IB to IIIA [§]	DFS, OS	Nivo
Forde <i>et al.</i> (37)	Checkmate 816	III	NCT02998528	Active, not recruiting	IB to IIIA [§]	MPR	Nivo
Bristol-Myers Squibb (38)	(NA)	III	NCT04025879	Recruiting	IIA to IIIB	EFS	Nivo + platinum-based doublet chemotherapy
Ben Nun <i>et al.</i> (29)	MK3475-223	I	NCT02938624	Recruiting	I to II [§]	MPR 33%	Pembro
Paz-Ares <i>et al.</i> (39)	PEARLS	III	NCT02504372	Active, not recruiting	IB to IIIA [§]	DFS	Pembro
Fernando <i>et al.</i> (40)	KEYNOTE-671	III	NCT03425643	Recruiting	IIB to IIIA	EFS, OS	Pembro + CDDP + PEM or Pembro + CDDP + GEM
Sands <i>et al.</i> (41)	ALCHEMIST	III	NCT02194738	Recruiting	IB to IIIA [§]	DFS	Pembro ± platinum-based doublet chemotherapy
Kwiatkowski <i>et al.</i> (30)	LCMC3	II	NCT02927301	Active, not recruiting	IB to IIIA [§]	MPR 18%	Atezo
Hoffmann-La Roche (42)	IMpower010	III	NCT02486718	Active, not recruiting	IB to IIIA [§]	DFS	Atezo
Hoffmann-La Roche (43)	IMpower030	III	NCT03456063	Recruiting	IIA to IIIB	MPR, EFS	Atezo+ platinum-based doublet chemotherapy
Rothschild <i>et al.</i> (31)	SAKK 16/14	II	NCT02572843	Active, not recruiting	IIIA [§]	1-yr EFS 73.3%	Durva
Heymach (44)	AEGEAN	III	NCT03800134	Recruiting	IIA to IIIB	MPR, EFS	Durva+ platinum-based doublet chemotherapy
Peters (45)	MERMAID-1	III	NCT04385368	Recruiting	II to III	DFS	Durva+ platinum-based doublet chemotherapy
Gao <i>et al.</i> (32)	(NA)	IB	ChiCTR-OIC-17013726	Not yet recruiting	IA to IIIB	MPR 40.5%	Sintilimab

Atezo, atezolizumab; CBDCA, carboplatin; CDDP, cisplatin; Durva, disease-free survival; DFS, disease-free survival; Durva, durvalumab; EFS, event free survival; GEM, gemcitabine; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; MPR, major pathological response; NA, not applicable; Nivo, nivolumab; OS, overall survival; PEM, pemetrexed; Pembro, pembrolizumab; PTX, paclitaxel. *As of November, 2020. †Classification according to TNM 7th edition, the others according to 8th edition. ‡Important results were described for those reported, and primary end points were described for those not reported.

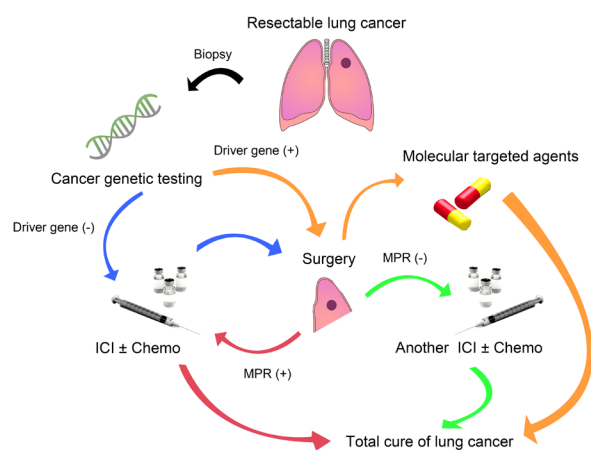


Figure 1. Possible future treatment of resectable lung cancer. This figure is a schematic view of our consideration for future resectable lung cancer treatment. Genetic testing of the biopsy specimen determines the presence of a driver gene. If not, ICI ± Chemotherapy is used as preoperative therapy. Subsequent surgery confirms the pathologic response, followed by postoperative chemotherapy with the same regimen as preoperative if there is a response, or a change in the regimen if there is no response. No preoperative treatment is given if the driver gene is present, and molecular targeting is introduced into the postoperative treatment. These strategies will be used to achieve a total cure for lung cancer. ICI, immune checkpoint inhibitor; Chemo, chemotherapy; MPR, major pathological response.

the evidence, but is likely to be effective and may be a promising method. Based on these findings, we show a schematic diagram of future operable lung cancer treatment in Figure 1. Preoperative biopsy should be performed to confirm the presence or absence of mutations in the driver gene, and if present, treatment with molecular targeted agents should be performed after surgery. If not, ICI ± chemotherapy should be performed before surgery, and if a pathological response is not confirmed, a switch should be made to another postoperative treatment. Such a strategy may reduce postoperative recurrence and increase the chances of cure. Although there are various difficulties, perioperative treatment continues to evolve toward a cure for NSCLC.

Funding: None.

Conflict of Interest: YT has received grants from Boehringer Ingelheim, Chugai Pharmaceutical, outside of this study. The remaining authors declared no competing interests for this work.

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- Received October 7, 2020; Revised January 19, 2021; Accepted January 22, 2021.
- Released online in J-STAGE as advance publication January 29, 2021.
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Current status of doublet combinations of platinum and fluoropyrimidines using oxaliplatin for advanced gastric cancer

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Abstract: The most common treatment for advanced gastric cancer (AGC) is systemic chemotherapy. The standard treatment for advanced gastric cancer differs worldwide. In Japan, two phase III clinical trials demonstrated the non-inferiority of S-1 compared with 5-fluorouracil (5-FU) and superiority of cisplatin plus S-1 (CS), compared with S-1, with respect to overall survival (SPIRITS trial). Oxaliplatin (L-OHP) has a favorable toxicity profile compared with cisplatin; hence, a phase III clinical trial (G-SOX trial) demonstrated the progression-free survival (PFS) and overall survival in CS was 5.4 and 13.1 months and those in SOX was 5.5 and 14.1 months, respectively. Serious adverse events were more frequently seen in CS than in SOX. So, SOX is as effective as CS for advanced gastric cancer with favorable safety profile. After the publication of this G-SOX trial, the combination of oral or intravenous 5-FU and various doses of L-OHP have been reported. And FOLFOX6 regimen (FOLFOX: a combination of 1-LV and FU with L-OHP) was approved for the treatment of AGC in Japan in 2017. FOLFOX was promising for patients with severe peritoneal metastasis from AGC, because the FOLFOX regimen does not require hydration and does not include oral agents. This review summarizes the efficacy and safety of doublet combinations of platinum and fluoropyrimidines using L-OHP for advanced gastric cancer.

Keywords: advanced gastric cancer, oxaliplatin, S-1, FOLFOX

Introduction

Gastric cancer is the fifth most common type of malignancy in the world and the third common cause of cancer mortality worldwide (1). The prevalence of gastric cancer is highest in East Asia. The treatment options for gastric cancer, such as surgery, chemotherapy, and radiotherapy, dependently vary on the tumor status. The mainstay of the treatment for advanced gastric cancer (AGC) is systemic chemotherapy. In the 1990s, prospective clinical trials and meta-analyses were conducted, which indicated the better prognosis of systemic chemotherapy, compared with the best supportive care (2-5).

S-1 is an oral anti-cancer preparation that combines tegafur, a pro-drug of 5-fluorouracil (5-FU), with two modulators, namely, gimeracil and oteracil (6). In Japan, two phase III clinical trials conducted by the Japan Clinical Oncology Group (JCOG) demonstrated the non-inferiority of S-1 compared with 5-FU and the superiority of cisplatin plus S-1 (CS) compared with S-1, with respect to overall survival (OS) (SPIRITS trial) (7,8). After these trials, CS was regarded as the standard first-line AGC treatment in Japan (9).

Oxaliplatin (L-OHP) is a third-generation platinum-based compound that has tolerability and ease of administration, compared with cisplatin. Several phase II studies have addressed the usefulness of the S-1 plus L-OHP (SOX) regimen as a first-line therapy at various doses and schedules (10-14). A phase III clinical trial (G-SOX trial) conducted by the JCOG demonstrated the efficacy and safety of SOX as a CS alternative in first-line chemotherapy for AGC (15). L-OHP was approved for AGC on the basis of the G-SOX trial in 2014 (9). SOX has several advantages in terms of toxicity and administration, compared with CS; hence, SOX has been widely used in clinical practice. This review summarizes the efficacy and safety of doublet combinations of platinum and fluoropyrimidines using L-OHP for AGC treatment.

Dose of L-OHP and efficacy

In a REAL-2 study, a randomized two-by-two phase III study of triplet therapy consisting of epirubicin, 5-FU or capecitabine, and cisplatin or L-OHP showed the non-inferiority of L-OHP (130 mg/m² every 3 weeks) to cisplatin (60 mg/m² every 3 weeks), with respect to

survival (16). In Japan, L-OHP (130 mg/m² every 3 weeks) was approved for AGC in 2014, on the basis of the results of the REAL-2 study. However, a phase II trial to evaluate the safety of SOX and a G-SOX trial were conducted using S-1 plus L-OHP (100 mg/m²) (SOX₁₀₀). Table 1 shows major clinical trials of first-line chemotherapy, including L-OHP, for AGC. The progression-free survival (PFS) in these two trials using SOX₁₀₀ was 6.5 and 5.5 months, and OS was 16.5 and 14.1 months, respectively (13,15). The PFS and OS of CS in a SPIRITS trial were 6.0 and 13.0 months, respectively (8). Although the G-SOX trial statistically failed to show the non-inferiority of SOX compared with CS, it was thought that the OS was comparable between the two regimens. A phase II trial to evaluate the feasibility of S-1 plus L-OHP (130 mg/m²) (SOX₁₃₀) was conducted because of the lack of data on SOX₁₃₀ for AGC in Japan (17). In the trial, the PFS and OS were 5.7 and 13.1 months, respectively. In an SOPP study, a phase III clinical trial to assess the non-inferiority/superiority of SOX₁₃₀ compared with CS in terms of PFS in Korean AGC patients showed that the PFS and CS in SOX₁₃₀ were 5.6 and 5.7 months, and the OS and CS in SOX₁₃₀ were 12.9 and 11.4 months, respectively (18). The SOPP study concluded that SOX₁₃₀ was non-inferior to CS, but not superior to CS. Considering the SOPP and the G-SOX trials, the SOX regimen can be one of the standard options for first-line AGC treatment in East Asian countries.

Feasibility and safety of SOX

In the G-SOX trial, L-OHP (100 mg/m²) was used because of possible bleeding from the primary lesion site and to maintain the S-1 dose intensity. Table 2 summarizes adverse events (AEs) in major clinical trials of first-line chemotherapy, including SOX for AGC. The

most common \geq grade 3 AEs over 10% were neutropenia (19.5%), anorexia (15.4%), anemia (15.1%), and thrombocytopenia (10.1%) (15). Among hematologic AEs, leukopenia, neutropenia, and anemia were less observed in SOX₁₀₀ than in CS (4.1% versus 19.4%, 19.5% versus 41.8%, and 15.1% versus 32.5%). The rate of \geq grade 3 febrile neutropenia was significantly lower in SOX₁₀₀ than in CS (0.9% versus 6.9%). Among the non-hematologic AEs, hyponatremia was seen less in SOX₁₀₀ than in CS (4.4% versus 13.4%). Grade 3 or worse sensory neuropathy was more frequently observed in SOX₁₀₀ than in CS (4.7% versus 0.0%). The difference in AE profiles between SOX₁₃₀ and CS in the SOPP trial was similar to that in the G-SOX trial (18). However, there were several differences in AEs between SOX₁₀₀ and SOX₁₃₀. In the SOPP trial, thrombocytopenia of all grades, and nausea and vomiting of all grades were more common with SOX₁₃₀ than with CS (70.5% versus 57.9%, 56.6% versus 43.3%, and 32.4% versus 20.1%). In the G-SOX trial, nausea of all grades was more frequent with CS than with SOX₁₀₀ (69.0% versus 61.5%). The phase II trials using SOX₁₃₀ for Japanese AGC patients showed that the frequency of \geq grade 3 thrombocytopenia and nausea of all grades was similar to that of the G-SOX trial (16.0% versus 10.1% and 56.0% versus 61.5%) (17). In the HIGHSOX trial, which was a multicenter phase II trial to investigate the efficacy and safety of the combination chemotherapy of trastuzumab plus SOX₁₃₀ for patients with Japanese HER2-positive AGC, the lower rate of \geq grade 3 thrombocytopenia (all grades, 78.7%; \geq grade 3, 1.3%) and higher rate of nausea (all grades, 65.3%; \geq grade 3, 4.0%) were seen, relative to those in G-SOX (19). These results indicated that SOX₁₃₀ has a higher frequency of gastrointestinal toxicities, compared with SOX₁₀₀. In the aforementioned two phase II trials to evaluate the feasibility of SOX₁₃₀, the dose of L-OHP was reduced if the platelet count was

Table 1. Clinical trials of first-line chemotherapy, including oxaliplatin, for advanced gastric cancer: a summary of major trials

Trial/authors	Phase	Regimens	No. of patients	OS (months)	HR (95% CI)	PFS (months)	HR (95% CI)
REAL-II (16)	III	Epirubicin (50 mg/m ²) + cisplatin (60 mg/m ²) + fluorouracil (200 mg/m ² /day)	249	9.9	1 (Reference)	6.2	1 (Reference)
		Epirubicin (50 mg/m ²) + cisplatin (60 mg/m ²) + capecitabine (2,000 mg/m ² /day)	241	9.9	0.92 (0.76-1.11)	6.7	0.98 (0.82-1.17)
		Epirubicin (50 mg/m ²) + oxaliplatin (130 mg/m ²) + fluorouracil (200 mg/m ² /day)	235	9.3	0.96 (0.79-1.15)	6.5	0.97 (0.81-1.17)
		Epirubicin (50 mg/m ²) + oxaliplatin (130 mg/m ²) + capecitabine (2,000 mg/m ² /day)	239	11.2	0.80 (0.66-0.97)	7.0	0.85 (0.70-1.02)
G-SOX (15)	III	Cisplatin (60 mg/m ²) + S-1 (80-120 mg/day)	324	13.1	0.958 (0.803-1.142)	5.4	1.004 (0.840-1.199)
		Oxaliplatin (100 mg/m ²) + S-1 (80-120 mg/day)	318	14.1		5.5	
SOPP (18)	III	Cisplatin (60 mg/m ²) + S-1 (80-120 mg/day)	164	11.4	0.86 (0.66-1.11)	5.7	0.85 (0.67-1.07)
		Oxaliplatin (130 mg/m ²) + S-1 (80-120 mg/day)	173	12.9		5.6	
Kito <i>et al.</i> (17)	II	Oxaliplatin (130 mg/m ²) + S-1 (80-120 mg/day)	25	13.1	-	5.7	-

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval.

Table 2. Adverse events in major clinical trials of first-line chemotherapy, including SOX, for advanced gastric cancer

Variables	G-SOX (15)		SOPP (18)		Kito <i>et al.</i> (17)	HIGHSOX (19)
	SOX ₁₀₀ (n = 338)	CS (n = 335)	SOX ₁₃₀ (n = 173)	CS (n = 164)	SOX ₁₃₀ (n = 25)	SOX ₁₃₀ + T-mab (n = 75)
Neutropenia						
Any (%)	68.9	79.4	57.2	71.3	68.0	78.7
≥ Grade 3 (%)	19.5	41.8	16.2	39.6	12.0	10.7
Anemia						
Any (%)	55.3	73.7	22.0	29.9	96.0	96.0
≥ Grade 3 (%)	15.1	32.5	5.2	11.0	20.0	6.7
Thrombocytopenia						
Any (%)	78.4	69.3	70.5	57.9	92.0	78.7
≥ Grade 3 (%)	10.1	10.4	7.5	4.9	16.0	1.3
Febrile neutropenia						
Any (%)	0.9	6.9	0.6	4.9	0.0	0.0
≥ Grade 3 (%)	0.9	6.9	0.6	4.9	0.0	0.0
Nausea						
Any (%)	61.5	69.0	56.6	43.3	56.0	65.3
≥ Grade 3 (%)	3.8	3.9	3.5	2.4	4.0	4.0
Vomiting						
Any (%)	34.9	35.5	32.4	20.1	24.0	20.0
≥ Grade 3 (%)	0.6	1.5	1.2	1.8	0.0	4.0
Diarrhea						
Any (%)	48.2	58.5	28.9	22.0	24.0	52.0
≥ Grade 3 (%)	5.6	7.5	4.0	3.7	0.0	6.7
Anorexia						
Any (%)	74.6	80.9	50.9	56.1	92.0	77.3
≥ Grade 3 (%)	15.4	18.5	8.7	6.7	24.0	5.3
Peripheral sensory neuropathy						
Any (%)	85.5	23.6	59.0	34.8	76.0	84.0
≥ Grade 3 (%)	4.7	0.0	8.7	3.7	0.0	16.0

CS, a combination of S-1 and cisplatin; SOX, a combination of S-1 and oxaliplatin; T-mab, trastuzumab.

75,000-100,000/ μ L on the day of its administration, in accordance with the SOFT trial criteria, which evaluated the non-inferiority between SOX₁₃₀ plus bevacizumab and modified FOLFOX6 plus bevacizumab in terms of the PFS of Japanese patients with advanced colorectal cancer (20). These results suggested that the L-OHP dose reduction protocol recommended by the SOFT trial may have contributed to the safer profile, especially thrombocytopenia, compared with that by the G-SOX trial. The safety profile of SOX₁₃₀ was considerably acceptable, although several different patterns of AEs were seen between SOX₁₀₀ and SOX₁₃₀.

Peripheral sensory neuropathy (PSN) is a common dose-limiting toxicity observed with L-OHP (21,22). It is crucial to discontinue L-OHP before developing severe PSN, because there is no effective method for PSN prevention. A retrospective observational study using data from the AGAMENON registry, wherein 31 Spanish centers and 1 Chilean center participated, reported that platinum discontinuation, followed by fluoropyrimidine maintenance, was an effective strategy for first-line chemotherapy for AGC to maintain treatment efficacy, with a low rate of serious AEs (23). The "stop-and-go" strategy was also reported as an appropriate approach to reduce the incidence of severe neurotoxicity while maintaining treatment efficacy

(24). These results suggested that the maintenance strategy, such as discontinuation of L-OHP, followed by fluoropyrimidine maintenance until progression or chemotherapy-free interval, followed by doublet combinations of L-OHP and fluoropyrimidine re-introduction at the progression stage, was a valuable method to reduce AEs while maintaining therapeutic efficacy.

Application of L-OHP for AGC with ascites or inadequate oral intake

Peritoneal metastasis is the most common recurrent or metastatic site for AGC (25-28). Peritoneal metastasis from AGC frequently causes complicated ascites, intestinal stenosis/obstruction, paralytic ileus, and ureteral obstruction (hydronephrosis); hence, patients with peritoneal metastasis have poor prognosis, because it is difficult to give the standard treatment for these patients (29,30). S-1 or capecitabine, in combination with cisplatin or L-OHP, is the first-line standard treatment regimen for AGC in Japan (9). However, oral fluoropyrimidine plus cisplatin cannot be administered to these patients because of inadequate oral intake or renal dysfunction. JCOG0106 demonstrated that methotrexate and 5-FU therapy was not superior to

continuous infusion of 5-FU (OS: 10.6 months versus 9.4 months; hazard ratio: 0.94; 95% confidence interval, 0.72-1.22; one-sided $p = 0.31$) (31). On the basis of JCOG0106, 5-FU/l-leucovorin (l-LV) is the drug that is most often administered to this population. However, the efficacy of 5-FU/l-LV is not sufficient, compared with combination chemotherapy of fluoropyrimidine and platinum. After 5-FU/l-LV/L-OHP (FOLFOX) had been approved for AGC in Japan, FOLFOX was promising for patients with severe peritoneal metastasis, because the FOLFOX regimen does not require hydration and does not include oral agents. Table 3 shows prospective or retrospective studies about the safety and efficacy of chemotherapy for AGC with ascites or inadequate oral intake. In JCOG0106, the median OS in the 5-FU group was 9.4 months, and the rate of grade ≥ 3 neutropenia, grade ≥ 3 anorexia, and treatment-related mortality in the 5-FU group were 0.9%, 27.4%, and 1.7%, respectively. An improved oral intake was observed in 41.2% of patients in the 5-FU group. Osumi *et al.* and Masuishi *et al.* conducted retrospective studies to evaluate the modified FOLFOX6 (mFOLFOX6) regimen in patients with AGC with severe peritoneal

metastasis, massive ascites, or inadequate oral intake (32,33). In those studies, the median PFS and OS were 4.2 and 7.5 months and 8.8 and 13.2 months, respectively. Interestingly, the proportion of patients exhibiting improvement in oral intake were 83.0% and 57.0%, respectively, which were higher than other treatment regimens for the same previously reported population. These findings suggest that mFOLFOX6 is a favorable regimen for patients with AGC with severe peritoneal metastasis, massive ascites, or inadequate oral intake. Neutropenia was the most common AE, and dose modification was required in about half of the patients because of the AEs in each study, because most patients have poor performance status. Furthermore, 5-FU/l-LV plus paclitaxel (FLTAX) is another promising regimen for AGC with severe peritoneal metastasis. However, a randomized phase II/III trial conducted by the JCOG and West Japan Oncology Group showed that FLTAX was not significantly superior to 5-FU/l-LV in terms of OS (34). Recently, a multicenter phase II trial evaluating the feasibility and efficacy of mFOLFOX6 for the same population (WJOG10517G: jRCTs041180007) is ongoing in Japan (35).

Table 3. Safety and efficacy of chemotherapy for AGC with massive ascites or inadequate oral intake

Variables	JCOG0106 (31)	Oh <i>et al.</i> (36)	Masuishi <i>et al.</i> (33)	Osumi <i>et al.</i> (32)	JCOG1108/WJOG7312G (34)
	Total (n = 119) Number of patients (%)	Total (n = 48) Number of patients (%)	Total (n = 10) Number of patients (%)	Total (n = 17) Number of patients (%)	Total (n = 50) Number of patients (%)
Regimen	5-FU	mFOLFOX4	mFOLFOX6	mFOLFOX6	FLTAX
Age (year)					
Median	61	60	64.5	67	65
Range	(31-75)	(60-70)	(40-94)	(29-74)	(29-75)
Sex					
Male	66 (55.5)	32 (66.7)	2 (20.0)	6 (35.3)	30 (60.0)
ECOG PS					
≥ 2	4 (3.4)	22 (45.8)	5 (50.0)	4 (23.5)	14 (28.0)
No. of metastatic sites					
≥ 2	40 (33.6)	18 (37.5)	5 (50.0)	12 (70.6)	NE
Prior chemotherapy					
≥ 1	0 (0.0)	27 (56.2)	0 (0.0)	0 (0.0)	0 (0.0)
Measurable lesion					
Yes	NE	30 (62.5)	3 (30.0)	10 (58.8)	NE
Ascites					
Yes	84 (70.6)	48 (100.0)	9 (90.0)	12 (70.6)	32 (64.0)
Inadequate oral intake					
Yes	17 (14.3)	NE	7 (70.0)	13 (76.4)	27 (54.0)
Improvement in oral intake					
Yes	7 (41.2)	NE	4 (57.0)	11 (83.0)	10 (37.0)
Relative dose intensity (%)					
L-OHP or paclitaxel	NE	95.5	64	90	82.5
5-FU		97.7 (total)	62 (bolus) 77 (ci)	63.4 (bolus) 99.7 (ci)	83 (total)
Response					
RR	NE	12 (33.3)	3 (100.0)	5 (50.0)	NE
DCR		25 (69.4)	3 (100.0)	6 (60.0)	
PFS (months)	NE	3.5	7.5	4.2	5.4
OS (months)	9.4	8.4	13.2	8.8	7.3

DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLTAX, a combination of l-leucovorin and fluorouracil with paclitaxel; FOLFOX, a combination of l-leucovorin and fluorouracil with oxaliplatin; L-OHP, oxaliplatin; NE, not evaluated; OS, overall survival; PFS, progression-free survival; RR, response rate.

Conclusion

In conclusion, L-OHP has been widely used for Japanese AGC patients in clinical practice because of several advantages in terms of toxicity and ease of administration, compared with cisplatin. Depending on the patient's status, combined oral or intravenous 5-FU and adjustment of the L-OHP dose were considered to contribute to a favorable improvement in the prognosis of AGC patients.

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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- Received August 18, 2020; Revised December 12, 2020; Accepted December 15, 2020.
- Released online in J-STAGE as advance publication December 20, 2020.
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Investigation of users' experiences for online access to their electronic health records in Japan

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Abstract: The solution of sharing electronic health records (EHR) with patients has the potential to improve patients' understanding and remembering of their health information. We call this solution the patient open-EHR. In Japan, this solution is not yet widespread, and experiences of actual users are not known. Our aim is to explore the needs and satisfaction of patients who are actually using one patient open-EHR system in Japan that allows registered patients online access to part of their EHR. A cross-sectional study was done using an online questionnaire. Patients registered with our patient open-EHR system were invited to participate by posting an invitation message on the system login page and sending them invitation emails. We investigated their needs regarding the system and their views regarding the system's ability to improve their understanding, remembering, and other perspectives. Answers from 95 patients, collected between August 10 and October 20, 2019 were analyzed. The need to further understand and remember the information received from the doctor was among the top four reasons behind using the system. However, only 48% of patients agreed that the system improved their remembering and 68% agreed that it improved their understanding. Thirty-seven percent of respondents expressed dissatisfaction with access to only blood test results and prescriptions. Despite this dissatisfaction, respondents were positive about the future of the system. Hospitals need to recognize the needs of patients and to consider them when providing patient open-EHR service. The EHR has potential not only for hospitals but also for patients.

Keywords: electronic health record, patient needs, user experience, understanding, remembering

Introduction

Healthcare information technology (HIT) is changing how the healthcare industry operates globally and has already begun to reduce waste and help improve health outcomes (1). Electronic health records (EHR) are major components of HIT and they were originally developed to allow sharing of medical information between health care providers. The impact of sharing electronic medical and health records with patients on different aspects of quality and safety of care was largely studied in Europe and the USA (2-6). We call this solution of sharing EHR with patients the patient open-EHR. We believe that the patient open-EHR solution, if adequately provided, could contribute to enhanced patient understanding and remembering of health condition and care plan. Patient understanding and remembering are key intermediate variables towards an effective patient-doctor communication, enhanced patient satisfaction and improved health outcomes (7,8). The OpenNotes initiative in the USA had shown positive results concerning the impact of sharing physicians' notes, which are part of the EHR, on patients' understanding and remembering and other

aspects (9-11). After reviewing their visit notes, 76% to 85% of patients reported better understanding and remembering (11).

In Japan, regional EHR networks started nearly 20 years ago in order to help and promote sharing of EHR data between hospitals or medical institutions in the same region (12). Some of them allow sharing of EHR data with patients online. However, the number of registered patients nationwide is still very low. Based on a survey done by the Japan Medical Association Research Institute (JMARI) on these regional networks in March 2016, approximately 250 regional EHR networks existed nationwide and the number of registered patients at 154 of these networks was less than 1.2 million (13,14). Out of these registered 1.2 million, approximately 700,000 patients only got access to their EHR data. To the best of the authors' knowledge, there is limited research regarding sharing of electronic medical and health records with patients in Japan (15-17). None was done on experiences of actual users of patient open-EHR systems.

The objective of the present study is to explore the needs and experiences of patients registered with one patient open-EHR system, and to investigate its benefits

by focusing on patients' understanding, remembering perspectives, and weak points in order to improve it in the future.

Materials and Methods

Overall design

A cross-sectional study was done using an online questionnaire by SurveyMonkey. The questionnaire was based on the survey done by the OpenNotes initiative original study conducted after having doctors' notes open to patients (11). This original study targeted patients after having one year intervention of doctors' notes open to patients (11). Doctors' notes, which are part of the EHR, contain a summary of the most important information discussed between the patient and doctor during the visit (9). After translation, the questionnaire items were examined and adapted through discussions with coresearchers including clinicians, public health researchers and researchers working with the Millennial Medical Record (MMR) system. Ease, usability, and comprehensibility were tested in ten users by the research team of the MMR system before launching the survey. Respondents could skip individual questions or exit at any point. Responses up to the point of exit were used in the data analysis. The questionnaire was designed to take less than 20 minutes. No incentives were given to the respondents. The institutional review board of Teikyo University approved the research protocol (Approval ID: TUIC-COI 18-0851).

The patient open-EHR system: Millennial Medical Record

We recruited patients who were registered with the MMR system. The MMR project started in 2015 as a national EHR, which was financially supported by the Japan Agency for Medical Research and Development (AMED) (12). As of January 2020, 112 medical institutions participated in the project (18). The MMR system allows the sharing of EHR data not only between participating institutions involved in patient care but also with the registered patients. The EHR data to be shared online is classified into 18 documents that include test results, prescriptions, medical history and other medical records. Currently, access rights for patients and participating facilities are set by the medical institution according to department, physician and the document (12). Regarding patient accessibility, the patient doesn't have a choice regarding what documents he or she can access online but he or she can select the medical institutions from the history of examining medical institutions to which he or she does not want the medical information to be shared (12). The official number of registered patients who access their EHR online is unknown, but the number of active users is assumed to be still very low. The operating

agency of the MMR project is the NPO Japan Medical Network Association (JMNA).

Participants

Participants were patients registered with the MMR system. They were recruited through an invitation message in the login page and an icon to jump to our survey link in the top page of the MMR system after login (only people registered with the MMR system could see and access) and also through sending an invitation email to all registered patients who had registered their email addresses in the MMR system. The email invitation was sent by the chairman of the NPO JMNA that is operating the MMR system. While the icon on the homepage was activated in the beginning of August 2019, the email was successfully sent to 353 valid registered email addresses. The first email was sent on August 10, 2019 and a reminder was sent on September 16, 2019. Answers collected up to October 2019 were used in the analysis.

Measurements

We investigated the reasons behind using the MMR system, using multiple-choice style questions, and participants' views on experiencing some benefits (better understanding, remembering, and others) and risks (confusing and others). Our key questions regarding experiencing potential benefits and risks asked about participants' views on the statements listed in Table 1. Participants could respond to each item on a five-point Likert scale, where the response choices ranged from "strongly disagree" to "strongly agree". Short expressions in Table 1 would be used when summarizing results in the later part below for space purpose. The following socio-demographic data were collected: age, gender, educational level, and overall health status. Other patients' characteristics were also evaluated using already validated scales' questions as follows: Patient preference for decision making (DM), measured using decision making preference scale (19); health literacy (HL), measured using communicative and critical HL score (20); patient trust in physicians, measured using trust in physician score (21); and patient ability to ask/understand/remember, using ask understand remember assessment (AURA) score (22). Participants needs/expectations from the MMR system were further investigated using free comments/requests' section and also by additional question asking views on some new features that were thought to be useful for better patient understanding and remembering (a patient-input feature that allows patient users to input their own comments to their EHR and another feature to allow other family members or friends to access their own EHR). Participants' care feeling about the MMR system was investigated by asking participants on their views

Table 1. Key statements used in the questionnaire

		Statement	Short expression
Potential benefits	1	In general, making EHR accessible to patients on a secure Internet website or application is a good idea.	Good idea
	2	After starting using the MMR system, I better understand my health and medical conditions.	Understand
	3	After starting using the MMR system, I better remember the plan for my care.	Remember
	4	After starting using the MMR system, I take better care of myself.	Self-care
	5	After starting using the MMR system, I am more likely to take my medications as prescribed.	Take medication
	6	After starting using the MMR system, I feel more in control of my health care.	In control
	7	After starting using the MMR system, I am better prepared for visits.	Prepared
Potential risks	8	After starting using the MMR system, I worry* more.	Worry
	9	After starting using the MMR system, I am concerned about my privacy.	Privacy
	10	After starting using the MMR system, the EHR is more confusing** than helpful.	Confusing

*Worry about health condition. **The contents make me feel confused about my understanding of health condition.

Table 2. Characteristics of respondents to the study questionnaire (n = 95)

Characteristic	Value
Age, n (%)	
18-29	1 (1)
30-39	9 (10)
40-49	18 (19)
50-59	28 (29)
60-69	20 (21)
≥ 70	19 (20)
Female, n (%)	40 (42)
Education, n (%)	
Elementary or junior high school	4 (4)
High school	18 (19)
Some college or 2-year degree	14 (15)
4-year university graduate	45 (47)
Graduate school	14 (15)
Overall health, n (%)	
Good	8 (9)
Fairly good	25 (26)
Fair	24 (25)
Fairly poor	33 (35)
Poor	5 (5)
Smartphone users, n (%)	74 (78)
Decision making preference score	
Mean (SD)	11.9 (3.9)
Median	12.0
Communicative and critical HL score	
Mean (SD)	19.1 (3.4)
Median	19
Trust in physician score	
Mean (SD)	16.6 (2.9)
Median	17
AURA score	
Mean (SD)	13.5 (2.6)
Median	14

AURA, ask understand remember assessment; HL, health literacy; SD, standard deviation.

if the MMR system was turned off and if its existence would influence their decisions in selecting a doctor in the future.

Statistical analysis

The software used for statistical analysis was SAS 9.4. The responses, regarding the views on experiencing the potential benefits and risks, were dichotomized into two

Table 3. Answers to the question "Why do you use the MMR system? (check all that apply)" (n = 95)

Answer	n	(%)
I want to know about my health condition	65	(68)
I want to remember what happened in the visit	52	(55)
I have a right to see what's in my medical record	45	(47)
I want to be sure I understood what the doctor said	42	(44)
I want to check the records to see if they were right	24	(25)
I want to know what my doctor thinks of my condition	17	(18)
Other (please specify)	14	(15)

categories: the "agree" category that combined the "agree" and "strongly agree" responses, and another category that combined other responses. We examined the relationship between patients' responses, on the potential benefits and risks of the system, and patients' characteristics, such as sex, age, education, health status, preference for decision making, health literacy and patient trust in physicians, with a chi-square test. A p-value < 0.05 was considered statistically significant for a two-sided test.

Results

Respondents' characteristics

As of October 20, 2019, 122 users participated in our survey from which 95 completed responses to our analysis questions. Table 2 shows respondents' characteristics. Overall, respondents were more likely to be male (58%) and 89% were 40 years old and older. Respondents were well educated; 77% with a 2-year college degree and more. Only 35% of the respondents reported that their overall health was good or fairly good.

Reasons behind using the MMR system

When asked about the reasons behind using the MMR system, three out of the top four answers were related to understanding and remembering (Table 3). Sixty-eight percent of the participants wanted to know about their health condition, 55% wanted to remember what happened in the visit and 44% wanted to be sure of their own understanding regarding what the doctor said.

Respondents' views on experiencing potential benefits/risks while using the MMR system

Table 4 shows participants' views on experiencing the potential benefits and risks. Respondents were positive about the patient open-EHR concept; 99% of participants agreed that sharing the EHR with patients through a secured site was a good idea. Only 48% agreed that the MMR system helped them remember their health plan and 68% agreed that the MMR system helped them understand their health condition. On the other hand, for concerns on potential risks of the system, the respondents

were not very concerned about risks; about 2% agreed with the concern regarding being confused, about 7% agreed with the concern about worry and 15% agreed with the concern regarding privacy.

Table 4. Proportion of respondents who agreed or somewhat agreed with statements about the potential benefits/risks (n = 95)

Statement (short expression)		n	(%)
Potential benefits	Good Idea	94	(99)
	Understand	65	(68)
	Remember	46	(48)
	Self-care	53	(56)
	Take medication	29	(31)
	In control	44	(46)
	Prepared	38	(40)
Potential risks	Worry	7	(7)
	Privacy	14	(15)
	Confusing	2	(2)

Relationship between participants' views on Understand/Remember and respondents' characteristics

Tables 5-6 show results on the relationship between the agree proportion on experiencing some of the potential benefits of the system. A statistically significant relationship between overall health and the agree proportion on Remember statement was demonstrated. A smaller proportion of participants with fair and poor health status (25% of those with fair health condition and 47% of those with poor or fairly poor health condition) agreed that the system could help them remember their health care plan.

Expectations from the future of the MMR system

Regarding the need for new features in the future, we found that the patient-input feature idea was welcome but giving access to others involved in their care was not. When asked about wishing to be able to add their comments to the EHR in the future, 54% agreed or somewhat agreed on the idea (Table 7). When asked about wishing to be able to let others have access to their

Table 5. Relationship between the agree proportion on Understand and respondents' characteristics (n = 95)

Characteristic	Total n	Agree		p-value
		n	(%)	
Sex				0.778
Male	55	37	(67)	
Female	40	28	(70)	
Age				0.094
18-29	28	24	(86)	
30-39	28	18	(64)	
40-49	20	13	(65)	
≥ 50	19	10	(53)	
Education				0.730
Up to 2 years college degree	36	26	(72)	
4-year university graduate	45	29	(64)	
Graduate school	14	10	(71)	
Overall health				0.079
Good/Fairly good	33	25	(76)	
Fair	24	12	(50)	
Poor/Fairly poor	38	28	(74)	
Decision making preference score				0.431
Low (< 10)	32	23	(72)	
Moderate (≥ 10 and ≤ 16)	52	33	(64)	
High (> 16)	11	9	(82)	
Communicative and critical HL score				0.405
Low (< 15)	10	8	(80)	
High (≥ 15)	85	57	(67)	
Trust in physician score				0.467
Low (< 15)	21	13	(62)	
High (≥ 15)	74	52	(70)	

HL, health literacy.

Table 6. Relationship between the agree proportion on Remember and respondents' characteristics (n = 95)

Characteristic	Total n	Agree		p-value
		n	(%)	
Sex				0.325
Male	55	29	(53)	
Female	40	17	(43)	
Age				0.714
18-29	28	15	(54)	
30-39	28	14	(50)	
40-49	20	10	(50)	
≥ 50	19	7	(37)	
Education				0.429
Up to 2years college degree	36	16	(44)	
4-year university graduate	45	21	(47)	
Graduate school	14	9	(64)	
Overall health				0.008
Good/Fairly good	33	22	(67)	
Fair	24	6	(25)	
Poor/Fairly poor	38	18	(47)	
Decision making preference score				0.906
Low (<10)	32	15	(47)	
Moderate (≥ 10 and ≤ 16)	52	25	(48)	
High (>16)	11	6	(55)	
Communicative and critical HL score				0.218
Low (<15)	10	3	(30)	
High (≥ 15)	85	43	(51)	
Trust in physician score				0.283
Low (< 15)	21	8	(38)	
High (≥ 15)	74	38	(51)	

HL, health literacy.

Table 7. Opinions on statements regarding the future of the MMR system

Answer	Statement 1*		Statement 2**	
	n	(%)	n	(%)
Agree	26	(28)	9	(10)
Somewhat agree	25	(26)	21	(22)
No opinion	23	(24)	26	(27)
Somewhat disagree	18	(19)	25	(26)
Disagree	3	(3)	14	(15)

*"In the future, I should be able to add my own comments to the EHR" (n = 95). **"In the future, I would like the option of letting family members or friends who help me with my health care have their own access to my EHR" (n = 95).

EHR in the future, only 32% agreed or somewhat agreed on the idea. Forty-one percent disagree or somewhat disagree (Table 7).

When asked about the feeling if the MMR system was turned off, 92% answered they would be very or somewhat disappointed (Table 8). When asked about the importance of the availability of the patient open-EHR in selecting a doctor in the future, about 97% answered that it is very or somewhat important.

Free comments regarding the MMR system

Seventy-eight percent (n = 74) of respondents provided a comment/request in the free comments section. Forty-seven percent (47%, n = 35) of these comments showed dissatisfaction from the limited contents disclosed; currently only blood test results and prescriptions are accessible online. All these respondents requested the disclosure of more records. Some given examples were X-ray images, computerized tomography (CT) scan results, magnetic resonance imaging (MRI) scan results, bone density test results, pulmonary function test results, cardiovascular testing results, consultation notes, summary reports, and radiologists' findings.

Discussion

We found that respondents' demand for the MMR system was driven by their need to further understand and remember information exchanged during consultation with the doctor (Table 3). However, the proportions of respondents, who agreed on the ability of the MMR system in improving understanding of their health condition and remembering their care plan were low (Table 4). These proportions were much lower than the results of the OpenNotes initiative, where 77% to 85% of patients agreed that open notes could help improve understanding of their health condition and 76% to 84% agreed open notes could help improve remembering their care plan (11). The main cause for these low proportions is, as understood from the free comments, due to the limited contents disclosed in the current system; mainly

Table 8. Answers to the question "How would you feel personally if the MMR system was turned off?" (n = 95)

Answer	n	(%)
Very disappointed- I do not want my online access to my EHR turned off	65	(69)
Somewhat disappointed	22	(23)
Would not care	8	(8)
Somewhat pleased	0	(0)
Very pleased- I would like to stop being able to read my EHR online	0	(0)

only blood test results and prescriptions are available online and doctors' summary notes are not available online. For hospitals and physicians, the EHR is a tool for sharing data with other healthcare providers. Therefore, when sharing these data with patients, we assume that doctors mainly intend to provide convenience to patients who need to show their health records to other medical providers who do not have direct access to the MMR system. This is because for patients, as demonstrated from our survey, they want to have access to their health records online to further understand their health condition and remember the visit. There seems to be a gap between users' needs from the MMR system and provider's objectives.

On the other hand, regarding respondents' experiencing potential risks while using the MMR system, we found that a minor proportion of respondents were worried or confused by the contents or concerned about their privacy after starting to use the MMR system (Table 4). This could be also due to the limited contents currently accessible online. There might be a tradeoff between the amount of information disclosed and the potential benefits and risks that patients perceive for the patient open-EHR system.

No significant relationship was detected between the studied patients' characteristics and the agree proportion on Understand statement (Table 5). This could be also due to the limited contents currently accessible online. Due to this limitation, understanding of the medical condition for different categories of patients was not impacted. On the other hand, a statistically significant relationship between overall health and agree proportion on Remember statement was seen (Table 6). A small proportion of participants with fair and poor health status agreed that the MMR system could help them remember their health care plan. This maybe because the currently accessible contents online might not be enough to help these patients remember their care plan. Patients with fair and poor health status might feel they need more information accessible online to remember their care plan. Additional attention and information should be given to patients from this category to help them better remember their care plan. On the other hand, participants with good/fairly good health responded in more agreement than those in the other categories. This could be because patients from this category might not

be receiving a large amount of medical information from their care provider regarding their health condition and plan, and that they need to remember, unlike patients with more severe health condition.

Through our investigation regarding users' needs and expectations from the MMR system, we understood from the free comments of respondents that patients are wishing for a wide range of EHR contents to be disclosed. Some examples of these contents were: X-ray images, CT scan results, MRI scan results, bone density test results, pulmonary function test results, cardiovascular testing results, consultation notes, summary reports, and radiologists' findings. Some respondents even wished for full disclosure of all EHR data. However, there could be several reasons for not disclosing a wide range of contents: burden on the server caused by image data that needs huge capacities; limited understanding caused by the lack of patients' medical knowledge; healthcare providers' anxiety about giving unnecessary confusion to patients; and healthcare providers' feelings of fear from the increased workload that would be caused by patients' further inquiries. We also found that 54% of the respondents wished they would be able to add their comments to their EHR (Table 7), which suggests that such tool could make patients more engaged in their care. It could also be used for "e-communication" between patient and doctor. This result was similar to the OpenNotes initiative study where 59% to 62% of respondents agreed on the idea of adding their own comments (11). On the other hand, regarding the idea of letting family members have access to their own EHR, in our study 32% agreed or somewhat agreed with the idea (Table 7), which was low as compared to the OpenNotes study where 49% to 56% of patients agreed or somewhat agreed (11). This result was not consistent with the result of a previous study comparing attitudes toward ethical decision making and autonomy issues among patients in Japan and the USA, where it was suggested that family opinions were accorded a larger role in clinical decision making by the Japanese patients than by those in the USA (23). However, in our survey the proportion of participants with "No opinion" was 27% (Table 7). We suspect that respondents who were not satisfied with the current system might be hesitant on giving their opinion regarding the future of the system. We believe that as the level of satisfaction with the system increases, the proportion of patients who agree on giving access to their family would increase as well.

Despite the respondents' dissatisfaction, which was basically due to the MMR system's limited contents, respondents were positive about the patient open-EHR concept (Table 4). Ninety-two percent of respondents claimed they would be very or somewhat disappointed if the system is turned off, meaning they want it to continue (Table 8). Moreover, 97% think that availability of patient open-EHR would matter when selecting doctors and health plans in the future. These results were similar

to the OpenNotes study where nearly 99% of patients wanted continued access to their visit notes and 86% to 89% agreed that open notes would matter when selecting doctors and health plans in the future (11).

Regarding future studies, doctors' attitudes toward patient open-EHR should also be addressed. Previous studies, such as in the OpenNotes original study, had suggested that physicians are more skeptical of the potential benefits of patient open-EHR and more sensitive to potential risks (10,11). This is mainly because for hospitals and physicians, the EHR is a tool for sharing data with other hospitals/physicians. For physicians to be supportive of programs to increase patients' access to their EHR, the potential benefits of these programs will need to be demonstrated more definitively. Before-and-after studies will better reveal how to enhance patients' experience using the patient open-EHR and how to mitigate any serious problem that may arise as the EHR becomes not only a sharing tool between medical professionals but also a tool for patients as well.

Our study has some limitations. The number of valid responses used in our analysis was relatively small and may not represent all users of the MMR system; users who had not registered their email addresses did not receive the notification email, and they might have not accessed the MMR system recently to notice the survey icon; and those who were invited to participate in the survey through email might have just ignored or forgotten the request in the email. However, we expect that active users were fairly approached through our recruiting methods. Also, our results may not be generalized for all patient open-EHR users since the MMR system used is just one example of such a system. However, it is considered to be the widest coverage for all national regions in Japan.

In conclusion, patients' needs regarding the patient open-EHR solution were indicated through our study targeting actual patient-users in Japan. This solution could bring benefits toward improving patient understanding and remembering of information received from the doctor and therefore improve doctor-patient communication efficiency and patient satisfaction. Providers of this kind of solution need to recognize their patients' needs and try to address them when deploying the system.

Acknowledgements

Our sincere thanks go to Prof. Hiroyuki Yoshihara (Professor Emeritus at Kyoto University and Representative Director of LDI), Prof. Kenji Araki (Professor at Miyazaki University and the chairman of Japan Medical Network Association NPO), Mrs. Janice Walker, co-founder of the OpenNotes initiative and assistant professor at Beth Israel Deaconess Medical Center, John Santa, Director, Dissemination at the

OpenNotes initiative, Prof. Kazue Yamaoka and Prof. Hirono Ishikawa, at the Teikyo University School of Public Health.

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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Received August 17, 2020; Revised October 28, 2020; Accepted November 24, 2020.

Released online in J-STAGE as advance publication December 8, 2020.

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What is the current status of Japan's efforts to meet global goals and targets to eliminate cervical cancer?

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Abstract: Following the global call to action by the World Health Organization (WHO), the world is currently moving to eliminate cervical cancer as a public health problem. To eliminate the cancer within this century, which is defined as an age-adjusted cervical cancer incidence rate (ASIR) below 4 per 100,000 women, WHO recommends all countries to achieve "90-70-90" targets for human papilloma virus (HPV) vaccination, cervical cancer screening, and treatment of precancer and cancer by 2030. In Japan, ASIR has been rising since the late 1990s to 11.1 per 100,000 women, and this rise is particularly prominent in women of reproductive age. HPV vaccination coverage is as low as 0.3%, largely due to the Government's ongoing suspension of proactive recommendations for the vaccine. Given the absence of centralized, population-based cervical cancer screening program and a nationwide surveillance system for systematic monitoring, the exact screening participation rate and treatment rate are difficult to estimate. A national survey suggested that only around 40% of women between the ages of 20 and 69 years underwent cervical cancer screening within the last two years. National policies and systems for HPV vaccination and screening should be updated in a more efficient way as new evidence and innovations become available. In the wake of powerful global momentum, actions must be taken now to further enhance cervical cancer control and ensure that Japanese girls and women are no longer left behind.

Keywords: cervical cancer control, monitoring, WHO Global Strategy

Introduction

Cervical cancer is one of the few cancers that is preventable with established interventions at both the population and individual levels. In May 2018, the Director-General of the World Health Organization (WHO) announced a global call to action to eliminate cervical cancer and called for all stakeholders to unite behind this common goal (1). Just recently in August 2020, the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem was adopted by the WHO Member States, which defines the goal of elimination as an age-standardized incidence rate (ASIR) below 4 per 100,000 women-years (1). To achieve this goal within the 21st century, the Strategy recommends concomitant attainment of "90-70-90" targets by 2030: *i*) 90% of girls fully vaccinated with human papilloma virus (HPV) vaccine by 15 years of age, *ii*) 70% of women screened using a high-performance test by 35 and again by 45 years of age, and *iii*) 90% of women identified with cervical precancer or cancer are treated. These "90-70-90" are global targets that all countries should aim for, including Japan. What is the current status of Japan's efforts to meet global goals and targets to eliminate cervical cancer?

Age-standardized cervical cancer incidence rate (goal: below 4 per 100,000 women)

According to the most recent national cancer registry data of Japan, there were 11,012 new cases of cervical cancer in 2017 (2). This corresponds to an ASIR of 11.1 per 100,000 women, which is higher than the estimate for high-income countries (8.3 per 100,000 women) (3). Data further show that the ASIR decreased from the 1980s until the late 1990s, but it has increased since then (2). The rise is particularly prominent in women in their 20-30s (Figure 1) (2).

HPV vaccination coverage by 15 years of age (target by 2030: 90%)

Bivalent and quadrivalent HPV vaccines have been included in Japan's national immunization program for girls ages 12-16 years. However, following media reports of girls having various symptoms such as chronic pain and motor impairment after vaccination, the Ministry of Health, Labour, and Welfare (MHLW) suspended proactive recommendations for the vaccine in June 2013 (4). HPV vaccine is still being provided for free to girls and parents seeking vaccination, but individuals are not approached with informational

materials. Over the last seven years, large-scale epidemiological studies in Japan indicated the effectiveness and safety of the vaccine (5-7). Medical consultations and facilities for patients concerned about symptoms after vaccination have been instituted in every prefecture (8). Nevertheless, due to the MHLW's ongoing suspension of recommendations, confusion over vaccination remains among the general population and the estimated vaccination coverage has stagnated

at a low level (< 1%), in contrast to Mexico, the Cook Islands, Portugal, and the Seychelles, which have already attained the 90% target (Figure 2) (9).

Participation rate in cervical cancer screening using a high-performance test by 35 and by 45 years of age (target by 2030: 70%)

Cervical cancer screening using cytology started relatively



Figure 1. Cervical cancer incidence by age group in 1975, 1990, 2005, and 2017. Data source: National estimates from regional population-based cancer registries 1975-2015, National cancer registry 2016-2017 (2).

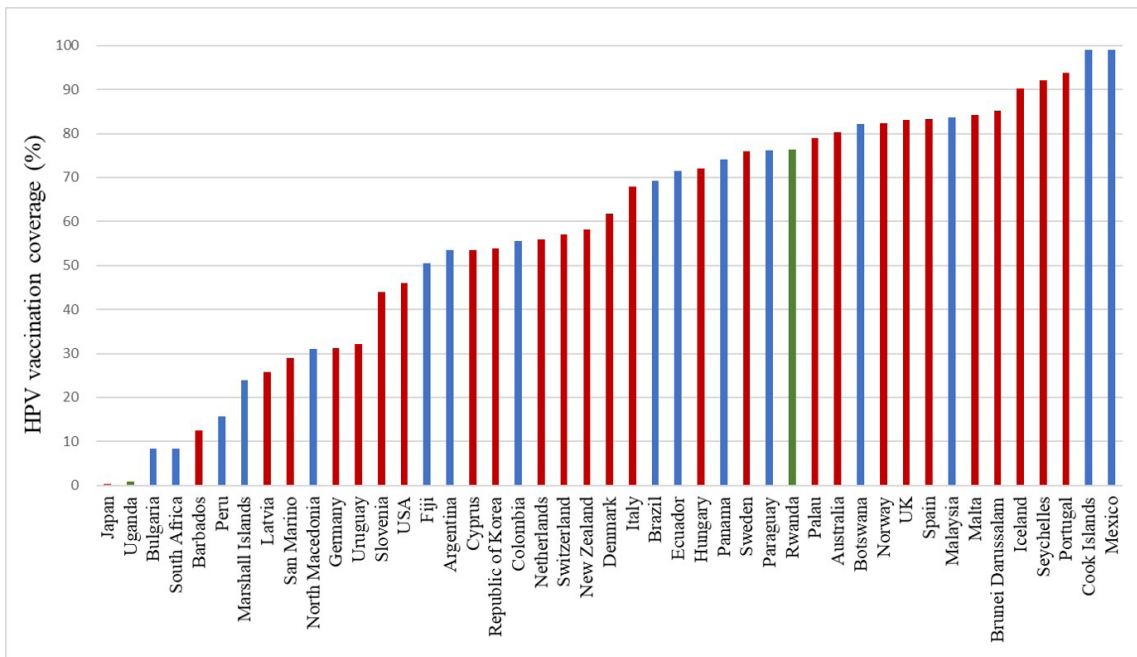


Figure 2. Estimated coverage of girls fully vaccinated with HPV vaccine by 15 years of age. Based on the World Bank's classification of income levels in 2019, red indicates high-income countries, blue indicates middle-income countries, and green indicates low-income countries. Data source: WHO estimates of human papillomavirus immunization coverage 2010-2018 (9).

early on, in around the 1960s, in Miyagi Prefecture (10). The screening program was subsequently expanded nationwide in 1983 for women ages 40 years and over under the Health and Medical Service Act for the Elderly. However, 15 years later in 1998, the MHLW transferred the responsibility for screening to the prefectural and municipal levels for economic reasons (11). Since then, Japan has not had a centralized, population-based cervical cancer screening program, although women have several opportunities to undergo screened for cervical cancer, including at organized screening programs run by municipalities and opportunistic screening offered by employers, by insurers, or in clinical settings. The cervical screening program run by municipalities uses conventional or liquid-based cytology and varies widely in program management (e.g. call-and-recall system), quality, and cost (11). In addition, the exact participation rate is unknown due to the absence of a nationwide surveillance system to systematically monitor screening. A national questionnaire-based survey conducted in 2019 suggests that only 43% of women between the ages 20 to 69 years underwent cervical cancer screening within the last two years, and this rate has remained at that level over the last six years (12). The most common reasons why some women do not undergo screening are that they do not have time, they are confident that they are healthy and do not feel the need to be screened, and they feel that they can always seek medical attention if necessary (13).

Treatment rates of cervical precancer and cancer (target by 2030: 90%)

Treatment rates are also very difficult to estimate in the absence of a systematic monitoring system. A report on 4.3 million cytology samples collected in 2017 during cervical cancer screening done in municipalities found that 85,426 samples required further testing, but 25% were lost to follow-up (14). With a universal health insurance system and easy access to gynecologists, women requiring follow-up may have undergone further testing and treatment without notifying municipalities (11). However, there is no system to obtain this information. The treatment rate for women diagnosed with cancer is also unknown, although the survival rate for invasive cervical carcinoma that was managed appropriately is relatively high. The most recent report has indicated that the 5-year survival rates for the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I, II, III and IV carcinomas are 93.1%, 75.9%, 59.1% and 31.2%, respectively (15).

The way forward in Japan

As shown here, Japan faces multiple challenges in monitoring and achieving the goal and "90-70-90"

targets for elimination of cervical cancer. Recently, however, signs of progress have become apparent. One is the regulatory approval of the nonavalent HPV vaccine in July 2020. Expectations are that this vaccine will be widely used, as it would cover 84% of the types of HPV that cause cervical cancer in Japan (16). Resumption of proactive recommendation of vaccination by the MHLW and increased public confidence in the vaccine will nevertheless be required to increase coverage. A modeling study predicted that gradual, if not immediate, restoration of HPV vaccination coverage to 70% in 12-year-olds over the period 2020-2025 could prevent 32,000-36,900 new cases of cervical cancer over the next 50 years in Japan (17). Colombia and Denmark have once faced a similar HPV vaccination crisis, and their experiences indicate that coverage can be restored with a strong political will (18). Another is the publication of updated evidence-based cervical cancer screening guidelines (19). The guidelines now recommend physician-sampled HPV DNA testing as the primary method for screening, in addition to cytology. This will allow the screening interval to be extended to five years for HPV-negative women; if started at age 30 and ended at age 60, women would only need to undergo screening seven times at a minimum. The optimal follow-up for HPV-positive women and the applicability of self-sampled HPV DNA testing in Japan are currently being studied further (19). In any event, additional efforts should be made at the national and local levels to increase the participation rate as well as to implement a surveillance system to systematically monitor participation, follow-up, and treatment rates.

Conclusion

At the global level, some countries are moving at a fast pace to attain the "90-70-90" targets by 2030 in collaboration with various actors and stakeholders such as professional societies, patient advocacy groups, the private sector, United Nations organizations, and non-government organizations. Japan is a leader of the call for universal health coverage and the creation of a world where "no one is left behind" (20). Ironically, it is currently Japanese girls and women who are left behind. It is time for actions to be taken to further enhance cervical cancer control.

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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- Received August 12, 2020; Revised September 17, 2020; Accepted September 23, 2020.
- Released online in J-STAGE as advance publication September 30, 2020.
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Enhancing the blood safety program in Myanmar: Report on projects of global extension of medical technologies of Japan

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Abstract: The National Center for Global Health and Medicine has long collaborated with the blood program in Myanmar, and the Center started a new project in 2015 to enhance blood transfusion safety as part of a new set of projects of global extension of medical technologies that aims to improve public health and medicine in developing countries under public-private partnerships. The project resulted in remarkable achievements, including maintaining a high proportion of voluntary blood donations despite a rapidly growing demand for blood, ensuring blood safety from the donor to the recipient, and creating public-private partnerships. The project supported the introduction of blood grouping using the tube method at hospital blood banks, safety measures during blood transfusions, and effective use of blood products including component blood. The project identified the need for medical devices such as leukocyte filters, serofuges, and refrigerators to store blood products. The success of the project may depend on mutual understanding and trust based on the duration of collaboration, improvement of the requirement for medical safety (including blood safety) in the country, and shifting the mindset of partner companies in public-private partnerships to create new demand by encouraging improvement of the quality of care and requiring the safety of medical care. In this era of sustainable development goals, the hopes are that these experiences will help other countries seeking to improve their public health through public-private partnerships.

Keywords: medical technologies, blood transfusion, sustainable business, medical safety

Introduction

Blood transfusions are widely used to manage various medical conditions such as acute and chronic blood loss and are an essential and lifesaving form of medical care even in resource-limited countries. The demand for blood products has been increasing due to improvement in the levels of medical care and the introduction of advanced medical treatment, all of which are attributable to economic growth, aging of society, and a population increase. However, adverse events, including transfusion-transmissible infections and acute hemolytic transfusion reactions, are possible and can cause life-threatening complications requiring immediate supportive care. Transfusion-related risks can be reduced by taking necessary actions, however, they cannot be entirely avoided. Therefore, the World Health Organization and all its member states have agreed on the importance of enhancing blood establishments and ensuring the quality, safety, and efficacy of blood products (1).

The National Center for Global Health and Medicine (NCGM) supported blood transfusion services in

Myanmar through JICA's Major Infectious Disease Control Project from 2005 to 2015 (2). Thus, blood transfusion services in Myanmar have improved remarkably, particularly in terms of blood product safety (3,4).

Several advanced therapies including transplantation, which requires quality blood transfusion as supportive therapy, have concurrently been introduced. The demand for blood has also increased after a free blood policy was introduced by the government. Therefore, the clinical use of blood products needs to be promptly improved. Given the increasing need for technical assistance, the NCGM decided to institute a new project in 2015 to enhance blood transfusion safety under a new program of the Japanese Ministry of Health, Labour, and Welfare, *i.e.*, projects of global extension of medical technologies, which aims to improve public health and medicine in developing countries under public-private partnerships.

Approach

Since 2015, the National Blood Center (NBC) has

collaborated with the project to enhance blood safety in Myanmar to tackle remaining challenges and further improve safety; approximately 30 policymakers and high-ranking officials, including members of Parliament, the President of the Myanmar Medical Association, the President of the Myanmar Medical Academy, the Director General of the Department of Medical Services of the Ministry Health and Sports, and directors of medical care in the public and private sectors, were invited on a 7-day tour to observe the institution of a nationwide blood program in Japan, including hemovigilance, supply management, blood collection and blood product manufacturing, and blood transfusion management in hospitals, to further improve safety. During this 7-day trip, the person in charge of the blood program and decision-makers talked extensively and reached a consensus on the future direction of improved blood safety.

Moreover, Japanese experts were sent to Myanmar to hold annual meetings with blood banks in Myanmar and the Educational Symposium on Blood Safety, in collaboration with the International Society of Blood Transfusion. The heads of the blood banks were invited to the annual meetings, and hospital administrators and clinicians were invited to the symposium to discuss further improvements in blood safety. In addition, hands-on training in blood grouping for laboratory technicians in hospital blood banks was also conducted by experts from Japan. In addition, training on bedside safety measures and infection control during blood

transfusions was provided to nurses and nursing students. Figure 1 shows the number of the participants in the tour of Japan and the educational symposium and training in Myanmar each year.

Several Japanese medical device manufactures supported the project, namely Daido Industry providing refrigerators and blood storage; Kubota Corporation providing laboratory centrifuges; and Terumo Corporation providing blood bags, leukocyte filters, blood donation beds, and other consumables.

Outcomes

As advanced medical care has been introduced in the country, the requirement for blood safety as supportive therapy has also increased both quantitatively and qualitatively. Therefore, when the project started, maintaining a high proportion of voluntary blood donation was critical due to the growing demand for blood. The NBC has maintained the high proportion of voluntary donations and also increased the number of hospitals with access to a direct supply of quality blood from the NBC, even though hospital-based blood banking is common in Myanmar. Policymakers and high-ranking officials, including the President of the Myanmar Medical Association, were invited to Japan and were major supporters of capacity development in the NBC. They helped the NBC to establish the National Blood Transfusion Committee as members of the advisory group for the Ministry of Health. That committee endorsed the revision of the National Guidelines on Blood Transfusion.

Demand for safe and quality blood has spawned a need for medical devices that were not required previously. For instance, leukocytes remaining in blood products might cause adverse effects such as infection (5,6). A leukoreduction filter (Terumo) should be utilized in specific wards requiring special care, such as Hematology. To improve donor safety and comfort, blood collection beds (Terumo and others) were also procured by blood centers. Since the advantages of component therapy (7) are widely acknowledged, the usage of component blood products has gradually increased. Assessment of the quality of component blood products has indicated that a higher platelet concentration is achieved when using Kubota's blood product centrifuge. Because storage conditions differ for each blood component (8,9), the demand for storage devices increases when component transfusions become common. Hence, a platelet agitator and cooling table (Daido) were introduced to maintain products.

Earlier, blood was grouped only *via* cell typing using the conventional tile method. The tube method has been introduced for both cell and serum typing to improve the accuracy of testing and to avoid a group transfusion. Introduction of the tube method requires necessary equipment such as a serofuge

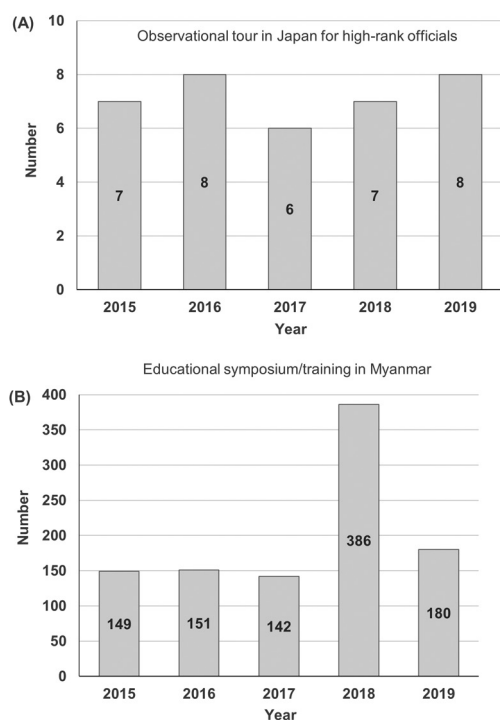


Figure 1. The number of participants of the observational tours in Japan (A) and the educational symposium and training in Myanmar (B).

Table 1. Medical technologies/systems and medical devices introduced during this project

Items	Contents
Medical technology/system	<ul style="list-style-type: none"> ● Blood grouping using the tube method at hospital blood banks ● Safety measures for blood transfusion including monitoring of adverse reactions (Draft standard operational procedure) ● Safe, proper, and effective use of blood products, including component blood
Japanese medical devices that were newly procured by the Ministry of Health and Sports	<ul style="list-style-type: none"> ● Leukocyte filter (Terumo) ● Serofuge for blood grouping using the tube method (Kubota) ● Centrifuge for component blood preparation (Kubota) ● Refrigerator for blood packs (Daido) ● Platelet agitator (Daido) ● Blood collecting bed for donors (Terumo)

and consumables. Some hospitals that started blood grouping using the tube method procured a serofuge from Japan (Kubota) because of its ease of use. Based on National Guidelines, standard operating procedures for a safe blood transfusion have been drafted by medical professionals who perform transfusions at hospitals.

Table 1 presents a summary of the medical technologies/systems and medical devices introduced during this project.

Discussion

Mutual understanding and trust based on long-standing collaboration between the Myanmar Ministry of Health and Sports and the NCGM has played a key role in the successful implementation of this project. Since 2000, experts have been dispatched to JICA technical cooperation projects for blood safety (2). The current project has taken over from the JICA project since 2015. Over the past 5 years, remarkable outcomes have been achieved. The National Blood Transfusion Committee was created in 2018, and it has played an important role in blood safety. The centralized blood supply system has been improved by increasing the number of hospitals receiving blood from the NBC. Blood grouping has gradually shifted from the conventional tile method to the more accurate tube method.

Public-private partnerships in health care have gained considerable attention over the last two decades, and especially after setting of the Sustainable Development Goals in 2015 (10,11). However, public-private partnerships are also associated with several risks, including conflicting visions and scopes of activity for corporations and public health agencies (12). The mindset of both the private and public sectors should be changed so that public-private partnerships are successful. A member of a company that cooperated with the project remarked, “Japanese medical device manufacturers have trouble beating prices in developing countries. We need to shift to selling value-added products, and the market should be aware of this value. Therefore, we have decided to invest in future markets

by helping to improve levels of medical standards in those countries.” Collaboration with companies that have such a mindset seems effective. In fact, they improved medical standards by introducing medical devices such as leukoreduction filters and serofuges in this project.

Commitment by policymakers is always the key to successful implementation of a public health program. Fortunately, the Ministry of Health and Sports has prioritized medical safety, including blood safety. This has had a positive impact on improving blood safety, *i.e.*, an increased national budget for the program and staff assignment. However, a challenge was that policymakers were not fully aware of the risks of transfusion. They were satisfied since blood donors did not need to be recruited as the NBC increased voluntary blood donations, and they were unaware of remaining risks regarding the clinical use of the blood, the quality of blood grouping and other testing, and hemovigilance (13,14). This project could help those policymakers to better understand the Japanese blood program and the supporting healthcare system, which is considered one of the world's safest.

In conclusion, the project helped to improve blood safety and create a public-private partnership as a sustainable business. As the lessons from this project, we believed that the success of the project may depend on: *i*) Mutual understanding and trust based on the duration of collaboration, *ii*) Improvement of the requirement for medical safety (including blood safety) in the country, and *iii*) Shifting the mindset of partner companies in public-private partnerships to create new demand by encouraging improvement of the quality of care and requiring the safety of medical care. The hope is that this experience will help other countries seeking to improve public health through public-private partnerships.

Acknowledgements

The authors wish to thank the Japan Red Cross Society for its technical support with regard to project implementation as the solo blood establishment in

Japan. The authors would also like to thank Professor Hiroyasu Iso of the Institute for Global Health Policy Research for his comments that greatly improved this manuscript.

Funding: The projects of global extension of medical technologies were funded by the Japanese Ministry of Health, Labour, and Welfare.

Conflict of Interest: The authors have no conflict of interest to disclose.

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Received August 13, 2020; Revised September 26, 2020; Accepted October 6, 2020.

Released online in J-STAGE as advance publication November 7, 2020.

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Enhancing the use of computed tomography and cardiac catheterization angiography in Zambia: A project report on a global extension of medical technology in Japan

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Abstract: Cardiovascular disease (CVD) is one of the leading causes of death in adults in Zambia among the non-communicable diseases. The Government of the Republic of Zambia through the Ministry of Health procured Japanese radiological systems, computed tomography, and angiography for the University Teaching Hospitals (UTHs) – Adult in 2015. However, the operation of these diagnostic systems has not been optimal due to lack of a proper maintenance service plan, lack of competent health professionals, and erratic supply of medical consumables. In this study, we report our experiences of providing intensive training to multidisciplinary healthcare teams of the radiology department at UTHs – Adult from 2017 to 2019 to strengthen the quality management system of the radiological equipment so as to provide effective healthcare services. However, the COVID-19 pandemic has had enormous negative impact on essential healthcare. Long-term support through continuous hands-on training must be provided to establish sustainable healthcare services.

Keywords: diagnostic radiology, quality management, multidisciplinary team, coronary computed tomography angiography, percutaneous coronary intervention

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in adults in Zambia among the non-communicable diseases (1). Zambia is experiencing a significant increase in non-communicable diseases and their risk factors, along with decreasing incidence of communicable diseases (such as HIV, malaria, and tuberculosis). In 2012, CVD comprised 8% of the total deaths in Zambia (2). Its cultural beliefs and economic factors, such as unhealthy diet, physical inactivity, smoking, and alcohol abuse, increase the risk of CVD (3). Computed tomography (CT) and angiography systems are useful for accurate diagnosis and proper treatment of CVD. With these systems, coronary CT and coronary angiography (CAG) are performed for accurate diagnosis of coronary stenosis, the most common cause of heart attack. Percutaneous coronary angiography (PCI) is performed to treat coronary stenosis whenever required. However, as of 2018, only 13 CT and one angiography systems exist in Zambia (4).

To strengthen the diagnosis and treatment of CVD in

the top referral and teaching hospital, the Government of Zambia, through the Ministry of Health, procured Japanese-made CT and angiography systems for the University Teaching Hospitals (UTHs) – Adult in 2015. However, the operation of these diagnostic systems has not been consistent due to lack of proper maintenance service plan, lack of competent health professionals, and erratic supply of medical consumables. In addition, Japanese companies, due to their poor strategy, have been unsuccessful at marketing high-priced medical consumables in low- and middle-income countries.

Therefore, a number of patients with serious CVD visit neighboring countries (e.g., South Africa and Egypt) for definitive diagnosis and specialist treatment. The government has experienced a large increase in spending on CVD treatment abroad where the Government of Zambia and private Zambians spend not less than \$10,000 USD per treatment (5). The Government of Zambia offers full financial support for patients identified and referred by the Ministry of Health to a medical institution abroad.

To cut down government spending on treatment

abroad and upon the request from UTHs – Adult, the National Center for Global Health and Medicine (NCGM) provided intensive training to multidisciplinary healthcare teams from 2017 to 2019. This study aims to report our experience in order to strengthen the quality management system of the radiological equipment, eventually provide quality health services, and draw lessons to help other low- and middle-income countries facing similar problems.

Approach

This project adopted three pragmatic approaches:

i) Capacity building focusing on a multidisciplinary healthcare team. Instead of traditional training targeted on the physician only, this project provided training in a multidisciplinary team, comprising two medical doctors, three cardiac catheterization laboratory nurses, and six radiologic technologists who went to Japan to acquire proficiency.

ii) Training programs unique to the project. The training program consisted of lectures, observations at the NCGM hospital, factory visits, and hands-on practice with a simulator. The lecture series ran the gamut of diagnostic radiology with the aim of developing the quality management system in the radiology department at UTHs – Adult, such as the standard procedures for coronary and radiation dose control (6), quality assurance (QA), standard procedures for CAG and PCI, and their radiation dose optimization (7,8), medical safety, and infection control (9). Zambian trainees were exposed to advanced diagnostic radiology through factory visits to two medical device manufacturers.

They observed an assembly line for cutting-edge products (e.g., 320 lines of area detector CT and magnetic resonance imaging enabling a 90% reduction of sound during examinations). They also visited a simulation laboratory to practice catheterization techniques on human anatomical models. Additionally, they participated in the use of consumables made in Japan for coronary intervention (e.g., stents, intravascular ultrasound, and diagnostic catheters).

iii) Follow-up training using Japan-made medical devices and consumables. An annual follow-up training was conducted several months after the initial training in

Japan. A multidisciplinary team including a cardiology specialist from Japan visited UTHs – Adult to provide mentorship. Mentoring programs comprised of on-the-job training, question-and-answer sessions, and consultation operations and QA manuals.

Outcomes

The outcomes of this project are summarized below:

i) Zambians performed their first Coronary CT, CAG, and PCI. The UTHs – Adult team successfully performed the first coronary CT in February 2018, and CAG and PCI in November 2019 (second country in Southern Africa after the Republic of South Africa) (10). Table 1 displays a summary of diagnostic CT imaging and cardiac catheterization procedures at UTHs – Adult during and after the project. Remarkably, the number of CT exams increased by 129.6% between 2017 and 2019, reflecting local demands for CT exams at a tertiary-level hospital in Zambia. In the detailed breakdown, no coronary CT studies were conducted in 2019 and 2020, whereas 33 have been conducted in 2018 (from a personal communication of the UTHs annual activity report in 2018-2020). This may be due to unexpected breakdowns of the CT scanner, power failure, and/or an absence of a dedicated 3D workstation to perform coronary CT as in normal clinical setting. To sustain their activities and help confirm diagnosis that allows better visualization, UTHs – Adult is in the process of procuring a high-end workstation.

ii) UTHs – Adult created a quality management system. The UTHs – Adult team has incorporated daily QA data collection tasks into a routine practice to prevent unnecessary breakdowns. The collected daily QA data was analyzed in case of problems.

iii) UTHs – Adult is in the process of concluding a maintenance contract. The UTHs – Adult team has recognized their responsibility in providing medical services to patients without any breakdowns. The team realized the advantage of a sustainable quality control circle and maintenance services. As a consequence, the UTHs – Adult is in the process of concluding a maintenance contract of the CT system.

iv) UTHs – Adult opened new marketing channels. Based on observations in Japan, and handling their

Table 1. The number of computed tomography and cardiac catheterization procedures at the University Teaching Hospitals – Adult in Lusaka

Items	2017	2018	2019	2020 (Jan. to Sep.)
Total Computed Tomography	3,057	5,289	7,018	4,389
Cardiac Catheterization Procedure				
Coronary Angiography	0	0	57	27
Percutaneous Coronary Intervention	0	0	30	10
Pacemaker Insertion	0	0	20	13
Total Cardiac Catheterization Procedure	0	0	107	50

own in the local context, UTHs – Adult healthcare professionals recognized the value of high-quality catheters and consumables high-quality catheters and consumables, enabling the success of coronary interventions. They also realized that the quality is worth the price. Eventually, a distribution channel for Japanese consumables was opened for UTHs – Adult.

Discussion

This project demonstrates the following four main successes: (1) Performance of coronary CT, CAG, and PCI by Zambian trainees; (2) Creation of a quality management system; (3) Conclusion of a maintenance contract; and (4) Opening of new marketing channels for Japan-made products. Points of arguments concerning the achievement are described below:

i) Multidisciplinary team training to promote advanced quality healthcare. The advanced healthcare team requires sustained team effort and its members with various specialty roles identified in a team. The trainees should develop a patient-centered safety culture. These learning strategies substantially contributed to Zambia's first achievements in performing coronary CT, CAG, and PCI in such a short time period (11).

ii) Quality management observation resulting in maintenance agreement. Quality management observation at the NCGM hospital and manufacturing factories aided in implementation of a QA program. A maintenance contract is being concluded, and new channels of marketing were opened. Factory visits by the trainees raised the spirits and confidence of Japanese manufacturers. The Zambian team concluded that a maintenance contract is cost saving in the long-term and extends the life expectancy of the equipment. Through this project, the Japanese manufacturer has come to learn the importance of value-for-money-oriented marketing strategies.

iii) Future perspective for sustainable development. Continuous professional and system development including improved radiation safety is critical for quality health service delivery. In this project, the UTHs – Adult has acquired best clinical practices from the NCGM despite race and ethnic differences. The PCI procedure is specifically associated with high radiation exposure. The possibility of radiation injuries should be explained to the patient (12). Thus, radiation safety measures should be put into practice to limit exposure to as low as reasonably achievable (8). For this purpose, we introduced recently published Japanese guidelines (13) emphasizing three points: a) explanation of possible radiation-induced skin injuries should be provided to the patient while obtaining informed consent before CAG or PCI; b) each institution should develop a protocol based on reference doses used in the institution and monitor radiation dose with dosimetry; and c) if skin exposure dose is estimated to be ≥ 3 Gy, the patient's medical history and subsequent

health should be followed up. These practices are expected to be firmly established at the UTHs – Adult and should extend to the rest of the country.

iv) COVID-19 pandemic has significant negative influence on sustainability. The COVID-19 pandemic has significant negative effects on their activities. Table 1 illustrates the significantly reduced number of CT exams and cardiac catheterization procedures performed in 2020. This is one of the immediate and serious effects of COVID-19. With factories closed and rail transport suspended, this pandemic resulted in a serious shortage of imported medical supplies (*e.g.*, contrast materials and syringes) and their price inflation. Supply chain disruptions and lockdowns in the Republic of South Africa have caused delivery delays and higher freight rates. Additionally, newly opened marketing channels are not yet established. Honoring maintenance contracts requires frequent communication and occasional site visits.

In conclusion, intensive training (focusing on QA) for multidisciplinary healthcare teams of the UTHs – Adult contributes to a better quality management system of the radiological equipment, resulting in greatly improved healthcare services. However, the COVID-19 pandemic has had enormous negative impact on essential healthcare needs. Long-term support through continuous hands-on training must be provided to establish sustainable healthcare services.

Funding: The project was funded by the projects of global extension of medical technologies, Japanese Ministry of Health, Labor and Welfare.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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- Received November 25, 2020; Revised January 28, 2021; Accepted February 8, 2021.
- Released online in J-STAGE as advance publication February 18, 2021.
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1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan
URL: www.globalhealthmedicine.com
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Print ISSN: 2434-9186 Online ISSN: 2434-9194



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Global Health & Medicine

Volume 1, Number 1
October, 2019



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