The current state of understanding of oncology expanded access programs in Malaysia

Fung Lin Yong, PhD, Wuan Chin Tan, Bachelor of Science

Medical Affairs, Pfizer, Malaysia

ABSTRACT

Introduction: An expanded access program (EAP) is a regulatory mechanism that provides access to an investigational drug, which is not approved for use, in treating life-threatening conditions when all the standard-of-care treatments are exhausted.

Materials and Methods: An online, anonymous, voluntary survey was conducted to assess the level of knowledge and understanding about EAPs among Malaysian oncologists using SurveyMonkey® between April 2020 and June 2020. Oncologists who had enquired about EAP in the past, were invited at random to participate in the survey. Participants who did not provide consent or failed to complete the survey were excluded.

Results: A total of 15 oncologists participated in the survey, from both public (46.6%) and private (46.6%) practices. Most respondents (80%) had filed between 1 to 10 EAP applications in the past 12 months. For 73.3% respondents, resources or training were not provided for EAPs from institutions. Around 53% of the respondents reported that their knowledge of EAPs and application processes including country regulations is 'good'. The majority of respondents (73.3%) reported that the educational modules on an overview of EAPs, country regulations and the EAP application process will be beneficial. Most participants received information about the existing EAPs either by reaching out to a pharmaceutical sponsor or through another health care provider and some received information about the existing EAPs through their institutions or patients/caregivers. Most of the respondents recommended that pharmaceutical companies should have readily available information related to the availability and application of EAPs for all pipeline products on their websites.

Discussion: EAPs are crucial treatment access pathways to provide investigational drugs to patients who have exhausted their treatment options and are not eligible for participation in clinical trials. Malaysian oncologists have a fair understanding about the EAPs and the application processes.

Conclusion: Additional training and awareness are needed for Malaysian oncologists to upscale the utilisation of EAPs.

KEYWORDS:
Expanded access program, oncology, investigational drug, life-threatening conditions

INTRODUCTION

Expanded access program (EAP) is one of the treatment access pathways that provides the use of investigational medicinal products (IMP), which is otherwise not approved for use, at a defined conditions to patients.[1] Depending on the country or region of the world, these programs are known by different terms such as 'Expanded access', 'Compassionate use', 'Compassionate drug use', 'Preapproval access', 'Special access', 'access' and 'Treatment use'.[2] These programs are made available to patients who are not eligible for a clinical trial and have exhausted all standard of care treatments for a life-threatening or serious diseases.[1] Compared to clinical trials, the eligibility criteria for EAPs are usually less rigorous and are more in line with the indication of the drug for which the approval is sought.[3-7]

In Malaysia, EAPs are available for the treatment of patients with life-threatening diseases with high unmet medical needs.[3] There is a guideline in place for importing/manufacturing products which are not registered with the Ministry of Health (MOH) Malaysia Drug Control Authority (DCA) for treating life-threatening diseases. Unregistered products may be brought to Malaysia via approved import license issued by DCA. Any serious or unexpected adverse drug reactions of the treatment is required to be reported to the Centre for Investigational New Products.[3]

In this study, we report result of a survey that primarily focuses on assessing the level of understanding of Malaysian oncologists for EAPs based on the different parameters including educational needs, perceptions and perspectives.

MATERIALS AND METHODS

An online survey that was anonymous, voluntary, structured and self-administered was conducted using SurveyMonkey® online questionnaire tool between 29 April 2020 and 17 June 2020. Randomly invited oncologists took part in the survey and were required to answer all the survey questions. The oncologists who had contacted Pfizer previously for oncology related EAPs were eligible to be a part of the survey. The exclusion criteria of the survey involved participants who could not furnish informed consent (e. g., language barriers and unavailability of an interpreter)8 or failed to complete the survey (exclusion was confirmed at the discretion of the principal investigator). The participants were excluded from the study, if they were not comfortable with the language of the interview that was taken.

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Corresponding Author: Wuan Chin Tan
Email: wuanchin.tan@pfizer.com

The survey questionnaire consisted of 13 questions and qualitative data was extracted based on the questionnaire. The questionnaire comprised of three subscales: i) 'demographics and experience in practice with EAPs applications' (four items), (ii) 'educational needs' (three items) and (iii) 'perception and perspectives' (six items).

The study met the tenets of the 18th World Medical Assembly, Helsinki, 1964, and its subsequent revisions. Potential participants were notified about the study objective and the scope of the participants involvement. The survey participants did not receive any financial incentives and no approval was required from the ethics committee (EC).

A literature search was carried out using PubMed and Google Scholar databases to identify articles published on EAPs in Malaysia. Studies published between 1st January 2011 and 31st December 2021 were screened for information related to EAPs in Malaysia, the current regulation, the procedure, the Health Care Providers (HCPs) experiences, and other associated challenges.

RESULTS

A total of 15 oncologists from Malaysia answered the survey questions. Most of the respondents either practiced in a public or government hospital/clinic (7 (46.6%)) or a private hospital/clinic (7 (46.6%)). One of the respondents worked in both public and private hospital/clinic (Figure 1a). Among the participants, eight respondents (53.3%) reported having an oncology practice experience between 10 to 20 years (Figure1b). A total of 12 (80%) respondents reported having filed between 1 to 10 applications for EAPs in the past 12 months when the survey was undertaken (Figure 1c).

According to 11 (73.3%) of the respondents, their institutions did not provide the resources/training for EAPs applications whereas only four (26.6%) of the respondents reported having the resources/training for EAPs at their institution (Figure 2a). The total number of respondents that reported having 'good' knowledge of EAPs and application processes including country regulations was eight (53.3%) (Figure 2b). In addition, among other respondents, one (6.6%) participant rated their adequacy of knowledge as 'very good', one (6.6%) rated it as 'excellent', two (13.3%) rated their knowledge to be 'poor' and three (20%) rated it as 'Fair' (Figure 2b). Majority of the respondents (10 (66.6%)) reported being 'mostly clear' about the application process set in place by pharmaceutical sponsors for applying for EAPs while the rest of participants reported that they were either 'very clear' (2 (13.3%)) or 'somewhat unclear' (2 (13.3%)) regarding the application process set in for applying for EAPs (Figure 3b). Additionally, most respondents 10 (66.6%) stated being 'mostly clear' about their country's regulations and processes set in place by the regulatory authorities for applying for EAPs, other respondents were 'somewhat unclear' or 'totally unclear' (4 (26.6%) and (1 (6.6%)) (Figure 2d). Furthermore, most of the participants got to know about an existing EAPs either by reaching out to a pharmaceutical sponsor or through another health care provider (Figure 2c). Few other respondents stated that they were informed about an existing EAPs either through their institutions or through patients or caregivers. In addition, most respondents (12 (80%)) reported that global pharmaceutical sponsors provide more options for EAPs related to their practice (Figure 2e).

According to majority of the respondents (10 (66.6%)), it was not very challenging to educate the eligible patients about EAPs (Figure 3a). Most of the respondents (11 (73.3%)) stated that the educational model on 'Overview of compassionate use programs', 'Country EAPs regulations and overview', and 'EAPs application process' would be a beneficial educational initiative (Figure 3c). Two of the respondents stated that there is no major difference between the global and domestic sponsors, whereas one respondent reported that domestic sponsors provide more options for EAPs related to their practice. Many respondents recommended that pharmaceutical companies should have information related to the availability and application of EAPs for all pipeline products that are readily available on their websites (Figure 3d).

Among the 29 articles screened, no articles were found related to EAPs in Malaysia. A similar search was conducted on Google Scholar with the same search strings which resulted in 16,11,900 hits. Out of the total hits only two articles were relevant and had some information related to EAPs in Malaysia.

DISCUSSION

This study summarises the results of a survey that was conducted with a focus to understand the current standing of EAPs and its associated challenges pertaining to the regulations, resources/training available, and overall knowledge of its application process among Malaysian oncologists. In this survey, an equal number of oncologists took part from both public and private practices. Most of the participants involved had experience of about 10 to 20 years of oncology practice. Furthermore, most of the oncologists reported that no resources/training was provided by their institutions related to the EAPs applications. Overall, more than half of the respondents reported having a good knowledge of EAPs and application processes including country's regulations. Most respondents stated that they were very clear about the application process and the local regulations that have been set in place by the pharmaceutical sponsors and the regulatory authorities for applying for EAPs. However, most respondents think an educational model on different topics such as overview of EAPs, country EAPs regulations and overview, and EAPs application process can be a beneficial educational initiative. Information related to EAPs is mostly obtained from pharmaceutical sponsors or through other health care providers. Moreover, the global pharmaceutical sponsors are considered to provide more options for EAPs related to their practice. In terms of patient education, most respondents did not feel it to be very challenging to educate the eligible patients about EAPs. Even though more than half (53.3%) of the oncologists participated represented having a good understanding of EAPs, there is still a need to have clearer regulations and processes in place.[6] This can help address issues and create further awareness among physicians regarding EAPs application process which can lead to better

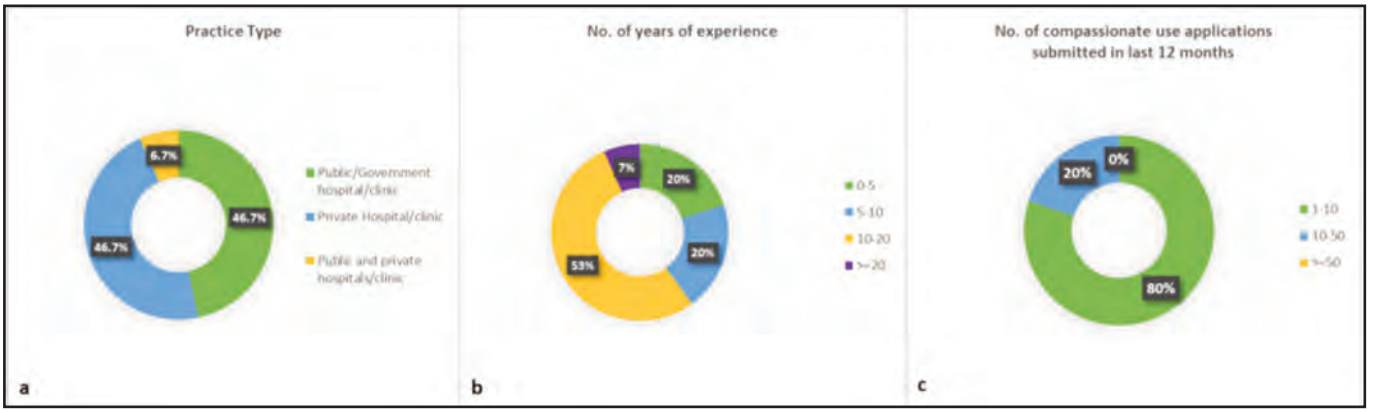

Fig. 1: Demographics of the survey participants.

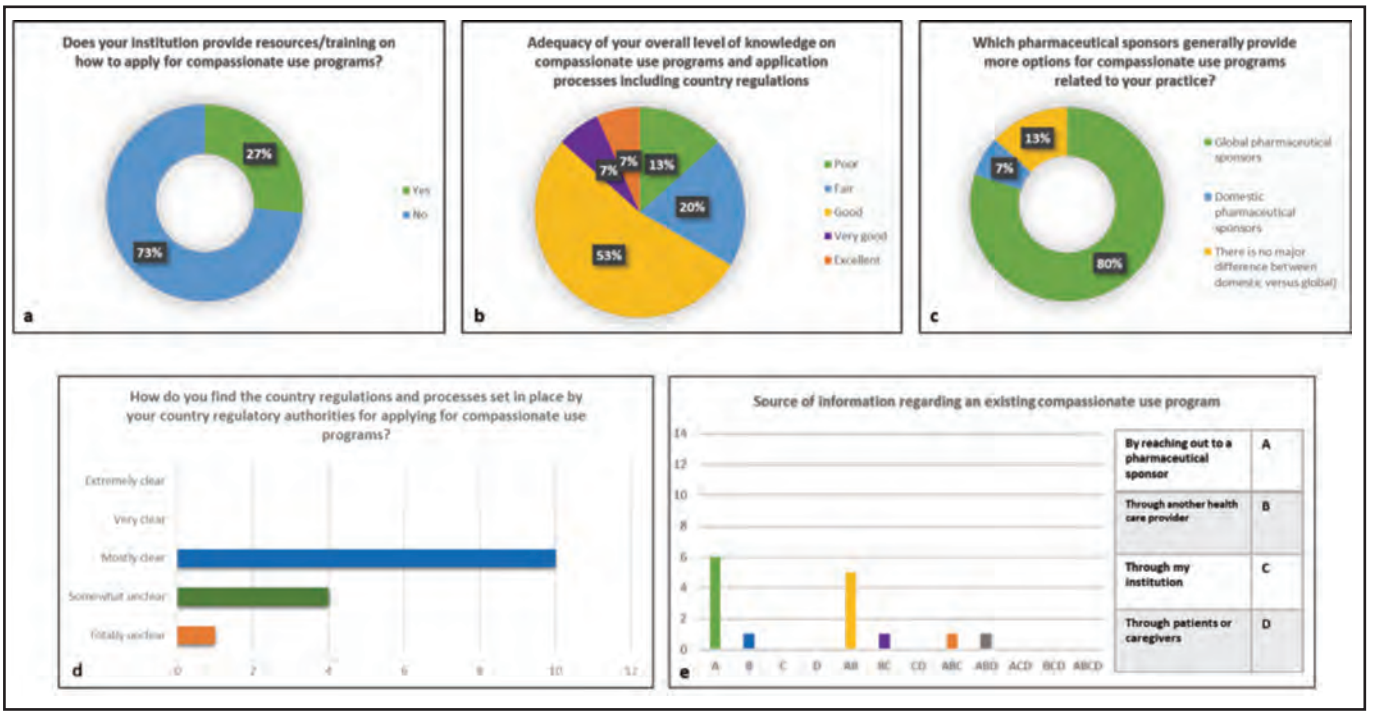

Fig. 2: Survey participants knowledge on compassionate use program in Malaysia.

outreach of the programs, patient access and ultimately patient outcomes.[6]

Our study results were found to be in line with the results of the overall study conducted by Singh et al., 2021, which included oncologists from various parts of Asia and has shown that majority of the respondents were clear about the EAPs application processes including the country regulations (88.23%). It was also shown that physicians had clarity regarding the EAPs application process through a pharmaceutical sponsor (71.56%), and EAPs regulations and processes set by country's regulatory authorities (53.92%).[6] Most respondents stated that their institutions did not provide any resources/training for EAPs application and felt that educational model on 'Country EAPs regulations and overview' would be beneficial for such application processes. In Malaysia, according to the Regulation 15(6) of the Regulations Drug and Cosmetic Control 1984, medical experts from private hospital or institutes or from organisation that are not under the Ministry of Health Malaysia are required to apply for import/manufacture of products that are not registered with the MOH Drug Control Authority.[3] Such application for unregistered drugs through EAPs are only indicated for patients with life-threatening disease.(3) The ongoing scenario with respect EAPs in Malaysia indicates that apart from government institutes, private physicians can also apply for EAPs and get access to life saving drugs. The results witnessed in this study could be due to lack of clarity related to countries regulation and paucity of information related to EAPs in Malaysia.

One of the other challenges of expanded access (EA) use is the time and effort needed to be invested by the treating physicians to this process. The physicians must be willing to

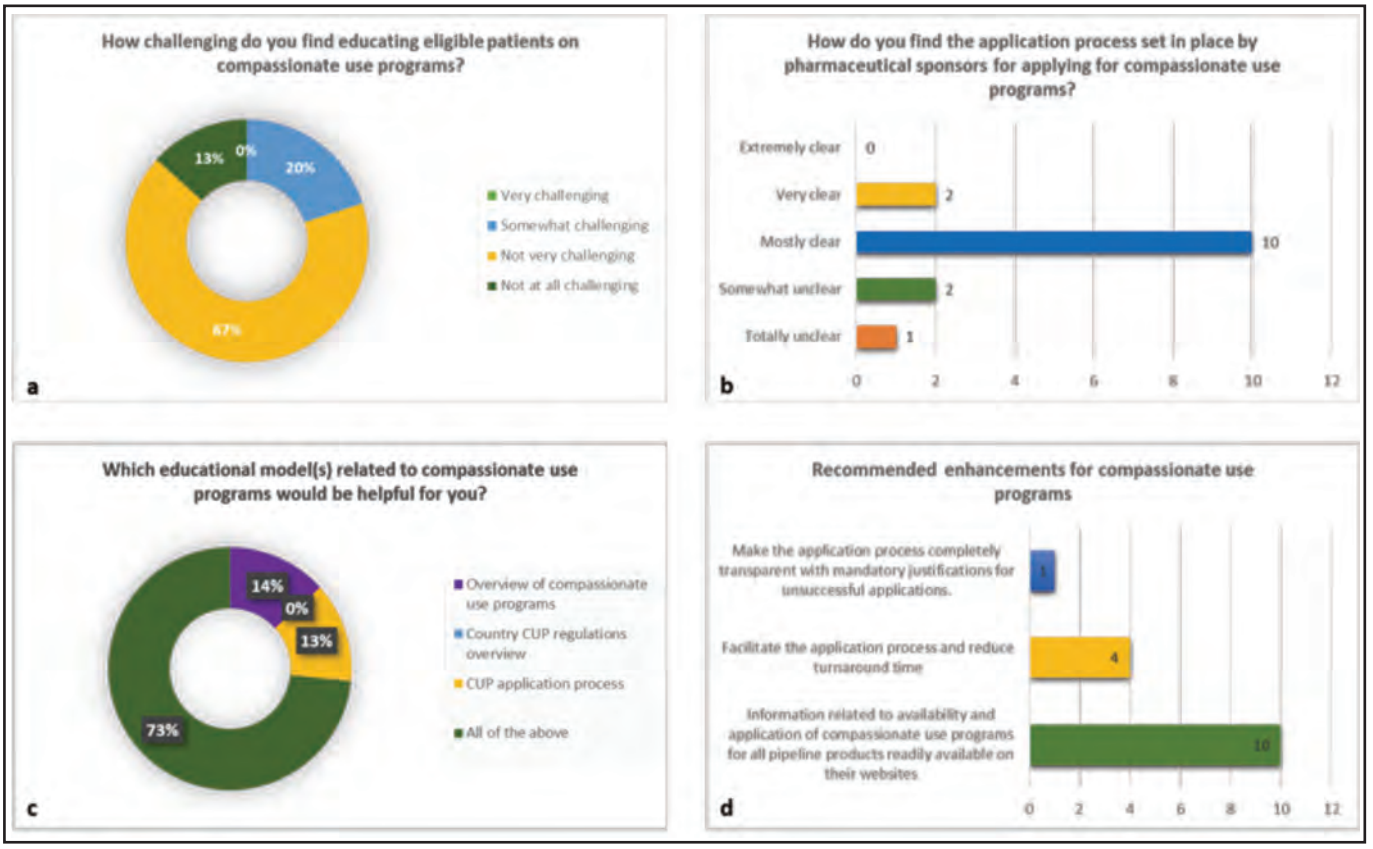

Fig. 3: Survey participant's educational needs.

be actively involved in the EA process and must be familiar with the investigational drug.[9] In general, the request of EA use of a treatment by a physician is infrequent due to complexity of the process. Physicians often face the pressure of helping the patients to decide whether to receive an investigational treatment, frequently without having adequate data. Such processes are usually a time-consuming affair, and the physician is usually uncompensated for their work.[9] There are also concerns of legal issues, as there are no defined boundaries regarding whether the physician will be held responsible in the case of a fatal adverse event and whether the patient's informed consent will be considered adequate.[9]

In the USA, the fundamental public policy goal associated with the regulatory approval of drugs is to ensure only safe and effective drugs reaches the market. Such drugs are extensively tested in both animals and humans.[10,11] Yet, individuals who are critically ill are often in a state, where they are unable to wait for such new drugs that are yet to be approved.[10,11] In such context, for maximizing the chances of cure or remediation, patients seek investigational drugs regardless of the lack of information about their efficacy or safety through EAPs.[10,11] The U.S. Food and Drug Administration's (FDA) initiated EAPs, for critically ill patients, where an investigational product can be used as a last resort of cure or remedy when no other comparable or effective treatments are available,[7,11,12] to patients who are either ineligible or have already participated in a clinical trial.[13] Access to investigational drugs is completely supported by the FDA for patients that are in most need. Though, the most preferred option is to enrol patients in clinical trials, whenever possible, for those patients who wish to gain access to investigational drugs.[14]

In the case of individual patients, expanded access usually depends on the cooperation and expertise of many parties, that includes the physician (who applies on behalf of the patient), the drug company, the institutional review board (IRB), and the FDA. Each of these involved individuals have an important role and must work together for the expanded access process to succeed.[14]

According to the Code of Federal Regulation (CFR) of the Food and Drug Administration (FDA) EAPs, sometimes also known as Compassionate Use Programmes (CUPs).[13] The definition of EAP varies across the world. According to the European Medicines Agency (EMA) recommendation, which is meant for EU countries, suggests including EAP patients who were previously treated in a clinical trial and wished to continue the treatment further. Nevertheless, around the world, it is recognised that patients treated in a clinical trial could have the option of continuing treatment for an extended period in an Open-label Extension study to generate long-term data on the intervention efficacy, safety, tolerability, and administration of the drug. Furthermore, in contrast with the FDA, the meaning of CUPs and EAPs are different in Europe.[13] In Europe, the EMA permits companies that manufacture promising medicines to run CUPs to allow early access to their medicine and to extend its use to patients who can

benefit from it. In addition, the EMA also allows patients that have been treated with the medicine during a clinical trial and who wish to continue using it may be able to do so via an EAP.[13]

There are numerous healthcare decisions that are faced by patients diagnosed with life threatening cancerous diseases, which have various implications on their life expectancy and quality of life.[11] In scenarios when patients do not respond to the standard anti-cancer treatments, opting for medication by participating in clinical trial remains to be the last choice, especially when the preliminary result of the research is promising.[11,15] But, in such instances there might be some set of patients who might not be eligible to be a part of such trials and through EAPs access to such drugs can be obtained.[11,15] A study conducted by Moerdler et al. 2018 involved paediatric patients under 18 years of age where enrolling of such patients in critical clinical trials is often difficult.[15] In this study the primary focus was to evaluate the experiences of paediatric oncologists in terms of applying and obtaining access to EAPs.[15] During this study it was reported that about 37% of respondents considered themselves as either competent or very competent in seeking approval from pharmaceutical companies for the use of an investigational drug.[15] The study also reported that participation in EAPs is influenced by physician's experience in clinical practice, size of institution, and availability of educational resources and administrative support.[15] Besides, the most common challenges in terms of utilisation of the EAPs were reported to be the inability to identify a drug which has a potential efficacy and lack of understanding and knowledge about the application process.[15]

EAPs involves various strategies being assessed to simplify the processes and reduce the approval time. Many expanded access requests are being initiated based on the evidence that demonstrate treatment matched to a patient's tumour molecular/biologic aberrations that maybe associated with superior clinical outcomes compared to treatment not matched to patients' alterations.[9] Generating and using real-world evidence from expanded-access patients provides an opportunity to offer critical data on patient outcomes that can serve regulatory approval in conjunction with other observational datasets or clinical trials, and in limited circumstances may be the best data available for regulatory review.[16] In addition, it may also support and encourage patient-centred care and a personalised medicine approach towards drug development.[16]

In this survey some of the country-based limitations have been highlighted related to EAPs. Devising proper channels and strategies to increase awareness among physicians and patients is crucial. Availability of adequate information, resources and trainings can make the program to be more accessible to a larger population who are in dire need of some life-saving medicines. A well-defined landscape of EAPs can be a game changer for providing effective treatment to oncology patients that doesn't have any other medical alternatives in Malaysia.

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