Compassionate Use Program สำหรับยารักษาโรคมะเร็ง ในประเทศไทย: การวิเคราะห์ความพร้อมในปัจจุบันและทบทวนช่องว่างที่สำคัญของโครงการ
Oncology Compassionate Use Program in Thailand: Analysis of Current Readiness Status and Review of Critical Gaps

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินความตระหนักรู้และความพร้อมของแพทย์อายุรศาสตร์มะเร็งในประเทศไทยเกี่ยวกับ compassionate use ในแง่ของความต้องการข้อมูล ความเข้าใจ และมุมมองที่มีต่อ compassionate use programs (CUPs) ต่อยามะเร็งรายการที่ยังไม่ได้ถูกอนุมัติให้ใช้โดยทั่วไป **วิธีการศึกษา:** ใช้แบบสำรวจที่มีโครงสร้างที่เข้าถึงได้แบบออนไลน์โดยสมัครใจและไม่เปิดเผยตัวส่งให้กับแพทย์อายุรศาสตร์มะเร็งที่เข้าร่วมโครงการ CUP ของบริษัทไฟเซอร์ ระหว่างวันที่ 29 เมษายน ถึง 17 มิถุนายน 2563 **ผลการศึกษา:** มีแพทย์อายุรศาสตร์มะเร็งจำนวน 6 ท่านเข้าร่วมการสำรวจนี้แบบไม่เปิดเผยชื่อ จากผลการศึกษาไม่มีผู้ร่วมทำแบบสอบถามท่านใดทำการรักษาในสถานพยาบาลเอกชนเพียงอย่างเดียว (private practice) ผู้ร่วมทำแบบสอบถามส่วนใหญ่ (ร้อยละ 66.7) รายงานว่าสถาบันที่ตนสังกัดอยู่ไม่ได้ให้ความรู้หรือมีแหล่งข้อมูลเกี่ยวกับหลักการปฏิบัติของ CUP โดยครึ่งหนึ่งของผู้ร่วมทำแบบสอบถามมีความรู้เกี่ยวกับ CUP และหลักปฏิบัติรวมถึงความรู้เรื่องระเบียบการขึ้นทะเบียนภายในประเทศในระดับปานกลาง และครึ่งหนึ่งของผู้ร่วมทำแบบสอบถามเชื่อว่าการให้ความรู้ในหัวข้อ ‘ภาพรวมและระเบียบการขึ้นทะเบียน CUP ภายในประเทศ’ จะเป็นประโยชน์กับพวกเขา **สรุป:** แพทย์อายุรศาสตร์มะเร็งมีความต้องการการเผยแพร่การตระหนักรู้และความรู้ความเข้าใจในเรื่อง CUPs นอกจากนี้ ยังต้องการให้เกิดความชัดเจนที่มากขึ้นแง่ของกฎหมายและขบวนการสำหรับการนำเข้ายา compassionate use มาภายในประเทศ

คำสำคัญ: compassionate use, ประเทศไทย, ต้นแบบการศึกษา, แพทย์อายุรศาสตร์มะเร็ง, การสำรวจและแบบสอบถาม, ยารักษามะเร็ง

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Original Article

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Abstract

Background: To evaluate the current knowledge and awareness of oncologists from Thailand on compassionate use of oncology products that are not approved for use in terms of educational needs, perceptions, and perspectives on compassionate use programs (CUPs). **Methods:** An anonymous, voluntary, structured, self-administered online survey was shared with the participating oncologists between 29 April 2020 and 17 June 2020. **Results:** A total of 6 oncologists participated in the survey. None of the respondents belonged to private practice. Majority of the respondents (66.7%) reported that their institutions do not provide the resources/training for CUP applications. Half of the respondents reported that their knowledge of CUP and application process including knowledge on country regulations is ‘Fair.. Half of the respondents believed that an educational model on ‘Country CUP regulations and overview’ would be helpful to them. **Conclusion:** There is a need for spreading awareness and educating the oncologists about CUP. There is also a need for providing clarity on regulations for importing drugs under compassionate use. The authors suggest that a clear roadmap with definitive timelines and easy to access procedure should be developed which will help the physicians to extend the support to more patients.

Keywords: compassionate use; Thailand; educational model; oncologists; surveys and questionnaires; cancer drugs

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Introduction

Compassionate use refers to the therapeutic use of drugs which have not been approved for use in a given country or region. This provides an additional pathway for patients to get access to life-saving drugs to mitigate a life-threatening condition or a serious disease.[1] When all approved drugs fail to produce the required response and the patient runs out of treatment options, they can seek treatment using unauthorized drugs through these programs.[2] Compassionate use is also known as expanded access and is a complex process which requires engagement of various stakeholders. These stakeholders include patients, patient advocacy groups, physicians, pharmaceutical drug manufacturers, regulatory agencies, and institutional review boards (IRBs).[2,3] The procedure for getting a single Investigational New Drug (IND) application approved for compassionate use is similar to conducting a clinical trial, but only for one person. A clinical trial protocol needs to be developed with inclusion/exclusion

criteria and needs approval from the IRB. Furthermore, the application might face hurdles from local regulatory agency.[3,4]

In Thailand, there are no specific regulations developed for compassionate use. Import of drugs which have not been approved for use or are under investigation is allowed to ministries, sub-ministries and departments which deal with prevention or treatment of diseases. Additionally, the Thai Red Cross Society and the Government Pharmaceutical Organization can import drugs not approved in Thailand. The person exempted for importing unapproved drugs is expected to comply with the conditions, rules, and procedures established as mandated by Ministerial Regulation.[5]

The approval process involves a complex set of formalities, clubbed with pharmaceutical manufacturer-wise varying criteria for evaluation of requests, and IRB approvals which usually take extra time and efforts.[3,4] Another major concern regarding compassionate use program is a lack of publicly available information.[4] Participating in a clinical trial is not always an option for patients owing to the strict eligibility criteria.[6] Unequitable access to the medication is also important since some patients or physicians cannot make an outreach to the program because of logistic difficulties and a lack of awareness about such program.[7] Against this background, it may be challenging to seek access to investigational drugs. It is hence vital that physicians are educated on the procedures and requirements for providing compassionate use access to their patients. Hence, the planning for compassionate use programs (CUPs) should be early as a part of the drug development process rather than need-based responses.[8] In Asia, we found that education and supports from the pharmaceutical companies were crucial to the success of programs.[8]

The physicians are required to know the appropriate procedures and requirements to apply for importing a drug for compassionate use. Hence, the survey was conducted to evaluate the educational needs, perceptions, and perspectives of oncologists from Thailand about compassionate use. A literature search was also conducted to understand and highlight the critical gaps based on the insights previously reported.

Methods

An anonymous, voluntary, structured, self-administered online survey was shared with the participating oncologists between 29 April 2020 and 17 June 2020. The survey consisted of closed ended questions and was hosted on SurveyMonkey website.

The oncologists who had contacted Pfizer for oncology-related compassionate use programs were selected at random for survey participation and were invited to fill out the self-administered questionnaire. The participants were excluded if they either did not provide informed consent (e.g., language barriers and unavailability of an interpreter) or did not finish the survey (exclusion was confirmed upon the discretion of the principal investigator).

The study followed the principles and recommendations of the 18th World Medical Assembly, Helsinki, 1964, and its subsequent revisions. The potential participants were informed about the objectives of the survey and the scope of their involvement. Financial incentives in any form were not given to any of the participants. Approval from the ethics committee (EC) was not required.

Qualitative data were collected using the questionnaire which consisted of 13 items. The survey had three subscales specifically demographic characteristics and experiences in practice and with CUP applications (4 items), educational needs (3 items), and perception and perspectives (6 items). The collected responses were subject to descriptive analysis.

For the document study, a literature search was conducted for articles published on compassionate use program in Thailand. Articles published between 1st January 2011 and 31st December 2021 were screened for information on compassionate use program in Thailand. Insights on regulations regarding CUP, the procedure, experience of physicians, and challenges were investigated. The literature search was conducted using PubMed and Google Scholar. Following search strings, “(Thailand) AND (Compassionate Use Program),” “(Thailand) AND (Expanded Access), and “(Thailand) AND (Name Patient Program)” were used to conduct the literature search.

Results

The survey was answered by 6 oncologists from Thailand. Among the respondents, 4 (66.7%) practiced in a public or government hospital/clinic and 2 (33.3%) practiced at public as well as private hospital/clinic. None of the respondents had private practice alone. Half of the respondents reported that they have been in oncology practice between 5 to 10 years.

All the respondents had filed between 1 to 10 applications for CUP in the last 12 months when the survey was conducted (Table 1).

Table 1 Demographic charatceristics of the participants (N = 6).

Characteristics	N (%)
Type of practice	
Public/government hospital/clinic	4 (66.7%)
Public/government and private hospital/clinic	2 (33.3%)
Number of years in oncology practice	
0 – 5	1 (16.7%)
5 – 10	3 (50.0%)
10 – 20	0
≥ 20	2 (33.3%)

The majority of the respondents (66.7%) reported that their institutions did not provide the resources/training for CUP applications. Additionally, 50% of the respondents felt their knowledge of CUP and application process including knowledge on country regulations is 'Fair.' Half of the respondents reported that an educational model on 'Country CUP regulations and overview' would be helpful to them (Table 2).

Table 2 Educational needs for compassionate use program in Thailand (N = 6).

Needs	N (%)
1. Does your institution provide resources/training on how to apply for compassionate use programs?	
Yes	2 (33.3%)
No	4 (66.7%)
2. Adequacy of your overall level of knowledge on compassionate use programs and application processes including country regulations.	
Poor	0
Fair	3 (50.0%)
Good	2 (33.3%)
Very good	1 (16.7%)
Excellent	0
3. Educational model(s) related to compassionate use programs which would be helpful.	
Overview of CUP	2 (33.3%)
Country CUP regulations overview	3 (50.0%)
CUP application process	0
All of the above	1 (16.7)

One-third of the respondents were unsure about the country regulations on CUP and application process for CUP set in place by the pharmaceutical companies. Many of the respondents (66.7%) found it challenging to educate the eligible patients on CUP. The responses to the questions related to perception and perspectives about compassionate use program in Thailand are summarized in Table 3.

Table 3 Perception and perspectives about compassionate use program in Thailand.

Questions	Response, % (n/N)	
Clarity of application process set in place by pharmaceutical sponsors for applying for compassionate use programs	Totally unclear	0% (0/6)
	Somewhat unclear	33.3% (2/6)
	Mostly clear	33.3% (2/6)
	Very clear	33.3% (2/6)
	Extremely clear	0% (0/6)
Clarity about country regulations and processes set in place by your country regulatory authorities for applying for compassionate use programs	Totally unclear	33.3% (2/6)
	Somewhat unclear	0% (0/6)
	Mostly clear	33.3% (2/6)
	Very clear	33.3% (2/6)
	Extremely clear	0% (0/6)
How challenging do you find educating eligible patients on compassionate use programs	Very challenging	0% (0/6)
	Somewhat challenging	66.7% (4/6)
	Not very challenging	33.3% (2/6)
	Not at all challenging	0% (0/6)
Source of knowledge about an existing compassionate use program	By reaching out to a pharmaceutical sponsor through institution	50.0% (3/6)
	By reaching out to a pharmaceutical sponsor	16.7% (1/6)
	By reaching out to a pharmaceutical sponsor **AND** through another health care provider	16.7% (1/6)
	By reaching out to a pharmaceutical sponsor **AND** through another health care provider **AND t**hrough my institution	16.7% (1/6)
Type of pharmaceutical sponsors which generally provide more options for compassionate use programs related to your practice	Global pharmaceutical sponsors provide more options	33.3% (2/6)
	Domestic pharmaceutical sponsors provide more options	50.0% (3/6)
	There is no major difference.	16.7% (1/6)
Enhancements for compassionate use programs recommended to the pharmaceutical companies as "top Information priority"	Information related to availability and application of compassionate use programs for all pipeline products readily available on their websites	16.7% (1/6)
	Facilitate the application process and reduce turnaround time	83.3% (5/6)
	Make the application process completely transparent with mandatory justifications for unsuccessful applications	0% (0/6)

According to the respondents, the oncologists acquired the knowledge about an existing compassionate use program by reaching out to a pharmaceutical sponsor, through their institution or through another healthcare provider. Majority of the respondents (50%) believed that domestic pharmaceutical sponsors provide more CUP options as compared to global sponsors. Most of the respondents recommended that pharmaceutical companies should facilitate the application process and improve CUPs procedure in the country by reducing turnaround time.

The literature search conducted yielded a total of 34 hits on PubMed. Among the 34 articles, 4 articles were related to evaluating efficacy or safety of drugs made available to the patients under expanded access program. There were no articles on either compassionate use or expanded access which provided information on compassionate use program in Thailand, the regulation, the procedure, experience of physicians, and challenges. The literature search on Google Scholar with the same search strings gave 95,670 hits. Only one article was found to contain relevant information and was the publication of overall survey results published by Singh et al (2021).

Discussions and Conclusion

The results of the survey conducted with oncologists from Thailand highlighted the challenges pertaining to clarity of CUP regulations and inadequacy of resources/training for CUP. The overall knowledge level of half of the respondents (50.0%) about CUP and its application process was found to be “Fair.” Only one-third of respondents found the application process set by pharmaceutical sponsors to be “Very clear.” Similarly, only one-third of respondents found the country regulation and application process set by country regulatory authorities to be “Very clear.” Thus, it is evident that there is a need for education on the CUP process and awareness among Thai oncologists to ensure more patients benefit from the program.

In the overall study conducted by Singh et al (2021), 53.92% of the respondents belonged to the private practice.[8] None of the respondents from Thailand belonged to private practice alone. In Thailand, only physicians from government hospitals can apply for importing non-registered drug products through compassionate use route.[9] Under the section 13(5) of Drugs Act, ministries, public bodies, departments responsible for disease prevention and treatment, Thai Red Cross Society, and the Government Pharmaceutical Organization are allowed to import pharmaceutical products without applying for an import license or drug product license for compassionate use program.[5,9] There are no separate/dedicated regulations governing the compassionate use of drugs in Thailand. Occasionally, a drug which is not approved for use in Thailand but is available in some other country can be imported as a donation (see provided reference in Thai).[10]

In the Singh et al (2021) study, majority of respondents had clarity on CUP application processes including country regulations (88.23%), CUP application process through a pharmaceutical process (71.56%), and CUP regulations and processes set by country’s regulatory authorities (53.92%).[8] Among the Thai respondents, only one-third respondents had proper clarity about the CUP application processes set by regulators and pharmaceutical companies. However, in-line with findings of Singh et al (2021), majority of respondents reported that their institutions did not provide the resources/training for CUP application and felt that educational model on ‘Country CUP regulations and overview’ would be helpful to them. This could be due to limited literature on CUP in Thailand and unclear regulations mentioned in the section 13(5) of the Drugs Act. The need for support from sponsor reported by the respondents and the lack of literature, highlights the need for developing educational materials and programs to spread awareness about CUP in Thailand.

The US Food and Drug Administration (FDA) had developed a pathway for expanded access of unapproved drugs in 1987. The revised regulations which were published in 2009 have outlined guidelines for allowing use of investigational new drugs which are not approved for use. As per the regulations, getting access via expanded access requires involvement from IRB, pharmaceutical companies, healthcare providers apart from FDA’s review and authorization. FDA has also published 3 guidances on expanded access. These guidances have detailed processes, forms, conditions under which expanded access is approved, how to apply, and other required information pertaining to expanded access.[11] Similarly the European Union (EU) has developed a legal framework for compassionate use under Article 83 (1) of Regulation (EC) No 726/2004 of the European Parliament and of the Council.[12,13] The article states the two requirements under which compassionate use is granted i.e. for a chronic or serious debilitating or life-threatening disease for which the approved medicinal products cannot provide satisfactory treatment and the medicinal product must be under review for centralized marketing authorization or undergoing clinical trials.[2]

In India, the Central Drugs Standard Control Organization (CDSCO) which is the regulatory body governing approval of medicinal drugs and devices has not developed separate guidance for CUP. However, there are provisions in place to import small quantities of drug for the treatment of patients suffering from life-threatening diseases or diseases causing serious permanent disability, or disease requiring therapies for unmet medical needs. These provisions are found under Rule 33A and 34A of the Drugs and Cosmetic Act, 1940 and Rules, 1945. Such applications for import are to be submitted to the Drug Controller General of India (DCGI) by a hospital (government or autonomous), patient, or a pharmaceutical company.[14] In Japan, there is “Advanced Medical Care B”, via which patients can access unapproved drugs or medical devices.[1] Compassionate use of unapproved drugs is permitted via special access routes (SARs) in Singapore if the required conditions are fulfilled. The Health Products (Therapeutic Products) Regulations 2016 provide the

guidance for SAR and requires approval from Health Sciences Authority (HSA).[15]

The main limitation of this survey was the small sample size. The overall survey provides a comprehensive picture about CUPs across various countries within Asia. However, due to low participation rate from Thailand, the current results represent a small fraction of oncologists. Future studies with a larger sample size should be planned to get a better understanding about the education level and needs of the physicians about CUP. The study included only oncologists and hence provides a picture about only the oncology field. Other specialties utilizing CUPs have not been represented.

The survey has highlighted the need for spreading awareness about CUP in the country and the need for clarity of the regulations among physicians and patients. Compassionate use is an indispensable tool which can help a lot of patients in need of life-saving medicines. A clear roadmap with definitive timelines and easy to access procedure will help the physicians to extend the support to more patients. Educational material for patients can be developed to disseminate information among patients and caregivers. Future studies can be planned with a larger sample size inclusive of other specialties to draw a comprehensive picture of compassionate use of drugs in Thailand. The future surveys can include comparison between various specialties about their knowledge on CUPs. Awareness campaigns at hospital level will facilitate spread of information to the patients as well as physicians to increase the uptake of CUP. The health authorities and hospitals can work together for organizing such awareness campaigns to ensure maximum number of patients benefit from CUPs.

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