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Patient access to anti-cancer medicines under public health insurance schemes in Thailand: A mixed methods study

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ABSTRACT

Background: Patient access to anti-cancer medicines is challenging in Thailand and worldwide. **Objective:** This study aimed to explain and quantify access to anti-cancer medicines in Thailand. **Methods:** Mixed methods of literature review and in-depth interview were conducted. Access to anticancer medicines was compared to the World Health Organization-Model List of Essential Medicines (WHO-EML), and recommendations of the National Comprehensive Cancer Network (NCCN). **Results:** Access to National List of Essential Medicines (NLEM) is indifferent among the three public schemes. Universal coverage scheme (UCS) and Social security scheme (SSS) limit access to non-NLEM anticancer medicines by reimbursement caps. Civil Servant Medical Benefit Scheme (CSMBS) provides broader access through Oncology Prior Authorization program. Non-NLEM, non-negative listed medicines are reimbursable if physicians deem necessary. Patient access programs were offered by pharmaceutical companies to assist access to non-reimbursable medicines for self-paying patients. UCS-SSS and CSMBS had 89.7% and 100% of medicines in WHO-EML. However, UCS-SSS had 19.2–100% of NCCN medicines for early-stage and 5.9–52.6% for advanced-stage cancers, while CSMBS had more access (57.7–100% and 41.2–84.2%, respectively). **Conclusion:** Access inequity to anti-cancer medicine was confirmed. However, Thais have adequate access to first- and second-line medicines for both early- and advanced-stage cancers. All stakeholders should consider formulating innovative financial models for high-cost anticancer medicines.

Keywords: Anti-cancer medicines, patient access, reimbursement, Thailand

INTRODUCTION

Thailand, an upper middle-income country, has achieved universal health coverage since 2002. The total health-care expenditures were 19.81 billion United States Dollar (USD) in 2017, which accounted for 4.02% of gross domestic product.[1]

Three main public health insurance schemes covered 99.94% of the population in 2018; the Civil Servant Medical Benefit Scheme (CSMBS) for government workers, pensioners, and their dependents (7.6%), the Social Security Scheme (SSS) for private-sector employees (18.5%), and the Universal Coverage Scheme (UCS) for those who are not enrolled to the two previous schemes (72.2%).[1] Payers of the three health insurance schemes utilize different payment mechanisms. For UCS, outpatient services are paid prospectively as capitation, and inpatient services are paid on the diagnosis-related groups (DRGs) with global budget basis. The contracted hospitals of SSS are paid on a capitation basis to cover for both outpatient and inpatient services. For CSMBS, outpatient services are paid on a fee-for-service basis, and inpatients are paid on the DRGs basis.[2,3] All payers provide medicines listed under the National List of Essential Medicines (NLEM) with full coverage to their beneficiaries. As of 2019, there are six categories of medicines in the NLEM.[4] The revision of NLEM is published annually by the sub-committee on the development of the NLEM under Thai Food and Drug Administration (Thai FDA). However, the NLEM opens for submission every 3 years.

- List A: Standard medicines for preventing and treating common health problems
- List B: Alternative medicines to List A medicines
- List C: Medicines prescribed in specialty diseases
- List D: Medicines with many indications that are likely to be misused

- List E1: Medicines for special programs proposed and responsible by government organizations
- List E2: Very high-cost medicines for specific groups of patients.

Statistics from the World Health Organization (WHO) as of 2014 revealed that 76,861 new cancer cases were diagnosed, and 82,800 deaths were reported in Thailand.[5] Costs of cancer care place a substantial financial burden on Thailand's health-care system. The National Health Security Office (NHSO), the payer of UCS, reimbursed 297 million USD for cancer care in 2018.[6] Health-care expenditures are expected to increase along with the increasing cost of innovative medicines, especially targeted cancer therapies.

Variations in access to high-cost anti-cancer medicines across the three health benefit schemes in Thailand were also disclosed in many studies. CSMBS patients (67%) were more likely to receive new medicines for lung cancers compared with UCS (19%) and SSS patients (10%).[3] The 6-year progression-free survival among patients with diffuse large B-cell lymphoma was superior in CSMBS than UCS patients (34.2 vs. 23.2%). Lack of access to rituximab (non-NLEM) was blamed for the inferior survival among UCS patients at that time.[7] Significantly higher proportion of CSMBS patients with colorectal cancer started with a capecitabine-based regimen compared with those in UCS. The UCS patients had to pay out-of-pocket because capecitabine was reimbursable only for breast cancer indication.[8]

The preceding evidence regarding access to anti-cancer medicine in Thailand was scattered, and a few types of cancers and related anticancer medicines were covered. None of the studies evaluated overall patient access to anti-cancer medicines across the three public insurance schemes. Therefore, the overall objectives of this study were to describe the current situation of patient access to anti-cancer medicines in Thailand focusing on high-cost anti-cancer medicines and to explore the variations in patient access across the major public health insurance schemes.

MATERIALS AND METHODS

This mixed-methods study comprised literature review and in-depth interview to describe the current situation regarding patient access to high-cost anti-cancer medicines in Thailand. Anticancer medicines included chemotherapy, hormonal therapy, and targeted therapy according to the antineoplastic and immunomodulating agents defined by the Anatomical Therapeutic Chemical.[9] PubMed and Google Scholar were searched for any articles explaining the coverage of anti-cancer medicines provided by the three health insurance schemes in Thailand using the keywords of access, anticancer medicines, and Thailand. Government and official payer websites were further searched for relevant documents. Content analysis was conducted. The results were then confirmed by in-depth interviews with selected key informants; including government officers, medical oncologists, oncology nurses, pharmacists from tertiary hospitals, and heads of market access from multinational pharmaceutical companies. This study was approved by the Ethics Review Committee for Research involving Human Research Subjects, Health Science Group, Chulalongkorn University (No. 173/2561).

The status of patient access in Thailand was further determined in terms of access to essential anti-cancer medicines and guideline-recommended anti-cancer medicines. Anti-cancer medicines for the 10 most prevalent cancers reported by the National Cancer Institute of Thailand in 2017 were used as a proxy.[10] Breast, liver and intrahepatic bile duct, colorectal, lung, cervical, lip and oral cavity, corpus uteri, prostate, ovarian, and esophageal cancer were solid tumors. Diffuse large B-cell lymphoma was further included as the representative of hematologic malignancy. The WHO-Model List of Essential Medicines (WHO-EML) 2017 edition and anti-cancer medicines advised by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines version 2019 were used as a benchmark. The WHO-EML is the minimum list of medicines which should be publicly accessible for everyone while the NCCN clinical practice guidelines represent the current standard of cancer cares or the maximum list.[11,12] Patient access to anti-cancer medicines was scoped as availability and accessibility. Availability was expressed as the percentage of Thai FDA approved anti-cancer medicines[13] compared to both WHO-EML and NCCN recommendations. Accessibility was determined by comparing the list of reimbursable anticancer medicines under UCS, SSS, and CSMBS to both the WHO-EML and NCCN recommendations. The results were categorized by disease stages as early or advanced. A sub-group analysis of patient access to high-cost anticancer medicines was also presented. As of now, there was no explicit definition of how much cost of an anticancer medicine to be considered as expensive. For this study, high-cost anticancer medicines were defined as medicines which were described as high-cost or expensive in the literature or government documents.

RESULTS

Results were divided into two parts; first an overview of access to anticancer medicines across the three public health insurance schemes, and second the performances of patient access to anticancer medicines benchmarking with the WHO-EML and NCCN clinical practice guidelines.

Overview of Access to Anti-cancer Medicines Across Three Public Insurance Schemes

Patient access to high-cost anti-cancer medicines under each of the three health insurance schemes was summarized below. Differences in pharmaceutical benefits package across schemes are shown in Table 1. The findings from the literature and document review were consistent with the result from eight key informants' interviews conducted from July 2018 to November 2018. One government officer, four health-care professionals, and three heads of market access from multinational pharmaceutical companies were interviewed.

Universal coverage scheme

UCS beneficiaries can access to the medicines listed on the NLEM with full coverage. To improve access to high-cost medicines, the NLEM List E2 or E2 access program was introduced in 2008.[14] The 2019 NLEM list E2 includes seven anti-cancer medicines for 11 indications which are dasatinib, docetaxel, imatinib, letrozole, nilotinib, rituximab, and trastuzumab.[4]

Table 1: Pharmaceutical benefits for anti-cancer medicines by different health insurance schemes

Medicine category	UCS		SSS		CSMBS	
	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient
NLEM list A-E1	FFS for 20 Protocol CA cancers		FFS for 10 SSO listed cancers		FFS	
NLEM list E2	Reimburse as medicinal products for 20 Protocol CA cancers		Reimburse as medicinal products for 10 SSO listed cancers		FFS (with prior authorization for OCPA medicines)	
NLEM and Non-NLEM not comply with the protocols	FFS (Max 2,300 THB/visit)	Bundle payments under DRGs	FFS (Max 50,000 THB/year)		N/A	
NLEM and Non-NLEM for non-protocol cancers	FFS (Max 4,000 THB/visit)	Bundle payments under DRGs	FFS (Max 50,000 THB/year)		N/A	
Non-NLEM	N/A		N/A		FFS: Prior authorization for OCPA medicines, Non-NLEM prescribing criteria for non-OCPA, non-negative listed medicines	

CSMBS: Civil servant medical benefit scheme, FFS: Fee-for-service payments, N/A: Not applicable, NLEM: National List of Essential Medicines, OCPA: Oncology prior authorization, SSO: Social security office, SSS: Social security scheme, THB: Thai Baht, UCS: Universal coverage scheme

The NHSO established the Protocol CA in 2008 as reimbursement criteria for their eligibilities.[15] The objective of the Protocol CA is to ensure the quality of cancer treatments by unbundling the costs of anticancer medicines out of the capitation for outpatients and the DRGs with global budget for inpatients. The Protocol CA describes the providers' qualifications and specifies 20 treatment protocols which were developed by the Thai Society of Clinical Oncology and the Thai Society of Hematology. The coverage of the Protocol CA includes only medicines in the NLEM. For 20 cancers in the Protocol CA, if physicians comply with the protocol, anti-cancer medicines in the A-E1 list will be retrospectively reimbursed on a fee-for-service basis at the reimbursement price listed in the Protocol CA or the standard drug prices to the hospitals for both outpatients and inpatients. For E2 medicines, NHSO will reimburse as medicinal products instead of money.

If physicians treat the 20 cancers listed in the Protocol CA as outpatient, but do not conformingly prescribe medicines according to the protocol CA recommendations, the NHSO will reimburse hospitals based on fee-for-service payment, but not exceeding 71.19 USD (2300 Thai Baht) per visit. For other cancers not yet included in the Protocol CA, the NHSO will reimburse the medicines based on fee-for-service payment, but not exceeding 125.08 USD (4000 Thai Baht) per visit. These reimbursements include both NLEM and non-NLEM medicines. For inpatients, the costs of anticancer medicines which do not follow the Protocol CA or treating other cancers not listed on the Protocol CA will not be reimbursed as add-on payments but will be bundled under the DRGs payments.[16]

The providers are prohibited from charging patients the excess price. However, data from the interview revealed that mostly when the providers suggested the NLEM and non-NLEM medicines not strictly followed the protocol CA. They would ask the patients to pay out-of-pocket instead of let the hospital bare the cost.

The NHSO together with the Government Pharmaceutical Organization (GPO) arranges procurement process for E2 medicines for NHSO's and Social Security Office's (SSO) beneficiaries. NHSO countrywide pools E2 anticancer medicines' demand and negotiates for lower prices. Once the procurement price was set, both NHSO and SSO asked the GPO to support procurement and distribution process through the Vendor Inventory Management (VMI) system.[14] It was noted from the interview that brand switching as a result of GPO procurement was a frequently found phenomena.

Social security scheme

SSS patients also can access to the medicines listed on the NLEM with full coverage. Although the Protocol CA was initiated and implemented by the NHSO in 2008, it was later on adopted and implemented by the SSO in 2013. However, the SSO listed only 10 cancers [Table 2].[17] For the list A-E1 anticancer medicines treating 10 cancers, the providers will be retrospectively reimbursed on a fee-for-service basis at the reimbursement prices set by the SSO. The E2 medicines will be reimbursed as medicinal products distributed through the VMI system. The costs of anticancer medicines which do not follow the SSO's protocol or treating other cancers not listed by the SSO will be reimbursed on a fee-for-service basis, but not exceeding 1580.13 USD (50,000 THB)/year.[17,18]

Civil servant medical benefits scheme

The Comptroller General's Department (CGD) is responsible for CSMBS beneficiaries. The pharmaceutical benefits package of CSMBS can be divided into different categories; NLEM, Oncology Prior Authorization (OCPA), negative list, and others. CGD will reimburse medicines in the NLEM and OCPA. Other than that, CGD will consider reimbursement based on a case-by-case basis.

CSMBS beneficiaries can access to anticancer medicines in the NLEM A-E2 list with full coverage on a fee-for-service basis for outpatient's service. The eligibilities pay nothing at the point of service as the CGD implement electronic direct payment system. Cancer cares for inpatient are paid under the closed-end payment using DRGs with add-on payments on a fee-for-service for the costs of anticancer medicines.

Unlike UCS and SSS, E2 medicines treating CSMBS patients are reimbursed on a fee-for-service basis. Monitoring the use of E2 medicines can deviate from medicine use guidelines recommended by the NLEM when medical

Table 2: Lists of cancers covered by different payers

National health security office	Social security office
Breast cancer	Breast cancer
Cervical cancer	Cervical cancer
Ovarian cancer	Ovarian cancer
Nasopharyngeal cancer	Nasopharyngeal cancer
Lung cancer	Lung cancer
Esophageal cancer	Esophageal cancer
Colorectal cancer	Colorectal cancer
Liver and cholangiocarcinoma	Liver and cholangiocarcinoma
Bladder cancer	Bladder cancer
Prostate cancer	Prostate cancer
Uterine cancer	
Stomach cancer	
Acute lymphoblastic leukemia	
Lymphoma	
Acute myeloid leukemia	
Acute promyelocytic leukemia	
Chronic myeloid leukemia	
Myeloma	
Osteosarcoma	
Pediatric cancer	

necessities are endorsed, and appropriate reasons are indicated in the medical records.[19]

Health benefits package has long been considered as a fringe benefit for the CSMBS eligibilities. When CSMBS complies to use NLEM as a reimbursement list, many eligibilities raised tremendous concern as their access to care were diminished. In 2005, CGD established a program called OCPA. OCPA was initiated to ensure rational drug use which would result in cost containment. Six medicines for seven cancer indications were included in OCPA by experts from the Thai Society of Clinical Oncology and the Thai Society of Hematology and the representatives from the CGD.[20] As of 2019, there are 17 anti-cancer medicines with 29 indications included in the OCPA [Tables 3 and 4]. Physicians who would like to prescribe medicines in OCPA must register with the CGD. Cancer patients who need OCPA medicines have to be registered to the online program for medicine cost reimbursement. Medicines can be prescribed only after they were approved from CGD. Approval time is guaranteed within 7 working days. The approval has to be renewed from time to time as indicated in the medicine use guidelines. Furthermore, the physicians have to report to the CGD when treatments are terminated. If medicines in OCPA were prescribed with diverted indication, reimbursement will not be approved.[21]

The managed entry agreements (MEAs) were officially introduced in Thailand through OCPA channel. The example of medicine utilized MEAs was osimertinib for metastatic lung cancer with EGFR mutation. In this case, the pharmaceutical company offered to support free medicines to the eligible patients after they underwent 10 months of osimertinib.[21]

Table 3: High-cost anti-cancer medicines in different programs

Medicine category
E2 access program (*n*=7)
Dasatinib, docetaxel, imatinib, letrozole, nilotinib, rituximab, trastuzumab
Oncology Prior Authorization (*n*=17)
Abiraterone, bevacizumab, bortezomib, ceritinib, dasatinib, enzalutamide, gefitinib, imatinib, lenalidomide, nilotinib, osimertinib, panitumumab, pazopanib, rituximab, sorafenib, sunitinib, trastuzumab
CGD negative list of high-cost oncology and hematology medicines (*n*=36)
Oncology medicines (*n*=20): Ado-trastuzumab emtansine, afatinib, aflibercept, albumin-bound paclitaxel, atezolizumab, cabazitaxel, degarelix, denosumab, erlotinib, ipilimumab, nintedanib, nivolumab, PEG-filgastim, pembrolizumab, radium-233, ramucirumab, regorafenib, temsirolimus, vinorelbine oral
Hematology medicines (*n*=16): Alemtuzumab, basiliximab, brentuximab vedotin, carfilzomib, clofarabine, daratumumab, decitabine, nivolumab, obinutuzumab, PEG-filgastim, plerixafor, pomalidomide, ponatinib, pralatrexate, romiplostim, ruxolitinib

E2 access program is for all health insurance schemes. CGD: Comptroller General's Department, PEG: Polyethylene glycol

Table 4: Indications of anti-cancer medicines listed on both E2 access program and Oncology Prior Authorization

Medicines	Indications in E2 access program	Indications in Oncology Prior Authorization
Dasatinib	Chronic myeloid leukemia	Chronic myeloid leukemia, acute lymphoblastic leukemia
Imatinib	Chronic myeloid leukemia, gastrointestinal stromal tumors	Chronic myeloid leukemia, gastrointestinal stromal tumor, acute lymphoblastic leukemia
Nilotinib	Chronic myeloid leukemia	Chronic myeloid leukemia
Rituximab	Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia
Trastuzumab	Early breast cancer	Early breast cancer, advanced breast cancer

Another design of MEAs was found in the interviews when the pharmaceutical companies offered to cover the costs of genetic testing required for prescribing targeted cancer therapies.

Besides the NLEM and OCPA, the CGD classified medicines into negative list and medicines not included in the three previously defined lists. Negative list refers to the medicines not intended to be covered for CSMBS beneficiaries. The CGD first published negative list in 2018, and as of 2019, there are 36 medicines announced in the negative list [Table 3]. Anti-cancer medicines granted marketing authorization in Thailand after January 1, 2018, are automatically included in the negative list. If physicians need to use medicines in negative list which are considered alternative for OCPA medicines (for example, erlotinib

and gefitinib for advanced lung cancer), authorization can be applied through the OCPA process. If the authorization is not granted, CSMBS eligibilities have to pay out of their own pockets.[22] The anti-cancer medicines in the negative list and those not listed in NLEM and OCPA are gradually considered enlisting into the OCPA. However, no clear and formal enlisting criteria have been announced.

For medicines not included in the NLEM, OCPA, and negative list, access to these medicines are varied. CSMBS beneficiaries can access to some of these medicines free-of-charge through the non-NLEM prescribing criteria.[23] The non-NLEM medicines are reimbursable when prescribing with indications approved in Thailand, and the physicians have to indicate the reasons for not prescribing NLEM medicines in the medical records. There are six reasons within the criteria; five of them are medical necessities which are eligible for reimbursement through the electronic direct payment system.

- A: Adverse drug reactions or hypersensitivity from using NLEM medicines
- B: Treatment failure after using NLEM medicines
- C: Lack of NLEM medicines for particular indications
- D: Contraindications or drug interactions with NLEM medicines
- E: NLEM medicines are more expensive
- F: Patients are willing to purchase medicines out-of-pocket (Not reimbursable).

Patient access program (PAP): Alternatives for non-reimbursable anti-cancer medicines

Apart from all the previously mentioned pharmaceutical benefits packages for beneficiaries, PAPs are established by the pharmaceutical companies to support self-paying cancer patients. These PAPs support self-paying patients who need non-NLEM medicines. As of the end of 2018, at least 46 PAPs were available in Thailand for biologics and targeted therapies.[24] However, the exact number of PAPs for anti-cancer medicines in Thailand was not publicly available.

The interview revealed that PAPs varied in design and could be broadly categorized into two groups. First, PAP utilize fixed scheme which provides the fixed promotional pattern of "Buy X get Y boxes free" for every patient under the same indication such as trastuzumab (Buy 3 and get 1 free). The PAPs' feature of "Buy X get Y free" is frequently utilized because the pharmaceutical companies consider this as supporting the patients without direct discount to the hospitals. Second, PAPs utilize patient financial eligibility tool to assess patient's socioeconomic status and provide differential pricing according to patient's income such as Nilotinib. A patient whose annual income was <3180 USD (100,000 THB) received free nilotinib.[14] One medicine may have many PAPs separately for each indication. For example, PAPs for bevacizumab which was approved for many cancers were found to be different by indications. At least 15 PAPs were found from interviews to be currently implemented in Thailand (Ado-trastuzumab emtansine, alectinib, atezolizumab, bevacizumab, eribulin, imatinib, lenalidomide, nivolumab, palbociclib, pembrolizumab, pertuzumab, pomalidomide, ponatinib, ribociclib, and trastuzumab). The availability of PAPs was found to vary by hospitals.

Benchmarking Performances of Patient Access to Anti-cancer Medicines

Patient access to anti-cancer medicines in Thailand compared to WHO-EML

There were 40 anti-cancer medicines in the WHO-EML [Table 5]. Availability of essential anticancer medicines was very high as 39 anti-cancer medicines have been approved in Thailand (97.5%). Accessibility of essential anticancer medicines was high for all schemes, from 35 anti-cancer medicines in the 2019 NLEM for UCS and SSS (89.7%), to 39 anti-cancer medicines in the CSMBS Medicine List (100%). The NLEM included 12 anti-cancer medicines not listed on the WHO-EML (arsenic trioxide, busulfan, carmustine, flutamide, idarubicin, letrozole, megestrol acetate, melphalan, mitomycin, mitotane, mitoxantrone, and Tegafur/Uracil).

Among 40 WHO-EML anti-cancer medicines, six of them (Bendamustine, dasatinib, imatinib, nilotinib, rituximab, and trastuzumab) were considered high-cost. Most of these medicines were reimbursable under NLEM for all health insurance schemes, except bendamustine which was reimbursable only by CSMBS.

Patient access to anti-cancer medicines in Thailand benchmarking with NCCN

Patient access to anti-cancer medicines treating 11 cancers as advised by the NCCN is shown in Table 6 with results of subgroup analysis of patient access to high-cost anti-cancer medicines in Table 7. Overall availability of guideline-recommended anti-cancer medicines was ranging from 72.7% to 100% in early-stage cancers and 75% to 100% in advanced-stage cancers. In terms of accessibility, the percentages of anti-cancer medicines which were reimbursable for the UCS and SSS for treating early-stage cancers and advanced-stage cancers were 19.2–100% and 5.9–52.6%, respectively. For the CSMBS, the percentages of reimbursable anti-cancer medicines for treating early-stage cancers and advanced-stage cancers were 57.7–100% and 41.2–84.2%, respectively.

From the results of literature and government document review, high-cost anti-cancer medicines which were described as expensive or high-cost included those listed on the E2 access program, OCPA, the CGD negative list of high-cost oncology and hematology medicines, and anti-cancer medicines granted marketing authorization in Thailand after January 1, 2018. The subgroup analysis of patient access to high-cost anticancer medicines found that the NCCN guidelines did not recommend any medicines for four out of 11 early-stage cancers. Overall availability was ranging from 50% to 100% in early-stage cancers and 66.7% to 100% in advanced-stage cancers. For all schemes, the percentage of reimbursable high-cost anticancer medicines was 60% for early breast cancer, while there was no reimbursable high-cost medicine for treating other six early-stages cancers at all (0%). On the other hand, the CSMBS had greater patient access to reimbursable high-cost medicines treating advanced-stage cancers (0–50%) compared with the UCS and SSS (0–20%).

DISCUSSION

This study was the first peer-reviewed research to demonstrate patient access to high-cost anti-cancer drugs in Thailand by

Table 5: Patient access to essential anti-cancer medicines in Thailand

Anticancer medicines listed on the 20th WHO-EML (2017)	Anti-cancer medicines approved in Thailand	Number of approved anti-cancer medicines	
		Listed on the NLEM category (2019)	Listed on the CSMBS medicine list (2019)
L01A alkylating agents			
Bendamustine*	/	No	/
Cyclophosphamide	/	C	/
Chlorambucil	/	C	/
Dacarbazine	/	D	/
Ifosfamide	/	D	/
L01B antimetabolites			
Capecitabine	/	D	/
Cytarabine	/	C	/
Fluorouracil	/	C	/
Fludarabine	/	D	/
Gemcitabine	/	D	/
Mercaptopurine	/	C	/
Methotrexate	/	C	/
Tioguanine	/	D	/
L01C plant alkaloids and other natural products			
Docetaxel	/	E2	/
Etoposide	/	C	/
Paclitaxel	/	D	/
Vinblastine	/	C	/
Vincristine	/	C	/
Vinorelbine	/	D	/
L01D cytotoxic antibiotics and related substances			
Bleomycin	/	C	/
Dactinomycin	/	C	/
Daunorubicin	Discontinued		
Doxorubicin	/	C	/
L01X other antineoplastic agents			
All-trans retinoid acid	/	D	/
Asparaginase	/	C	/
Cisplatin	/	C	/
Carboplatin	/	C	/
Dasatinib*	/	E2	/
Hydroxyurea	/	C	/
Imatinib*	/	E2	/
Irinotecan	/	No	/
Nilotinib*	/	E2	/
Oxaliplatin	/	D	/
Procarbazine	/	D	/
Rituximab*	/	E2	OCPA
Trastuzumab*	/	E2	OCPA
L02A hormones and related agents			
Leuprorelin	/	D	/

(*Contd...*)

Table 5: (*Continued*)

Anticancer medicines listed on the 20th WHO-EML (2017)	Anti-cancer medicines approved in Thailand	Number of approved anti-cancer medicines	
		Listed on the NLEM category (2019)	Listed on the CSMBS medicine list (2019)
L02B hormone antagonists and related agents			
Anastrozole	/	No	/
Bicalutamide	/	No	/
Tamoxifen	/	C	/
Total (n = 40), n (%)	39 (97.5)	35 (89.7)	39 (100)

*: High-cost anti-cancer medicines, /: Yes, CSMBS medicine list: Civil Servant Medical Benefit Scheme medicine list, NLEM: National List of Essential Medicines, OCPA: Oncology Prior Authorization, WHO-EML: World Health Organization Model List of Essential Medicines

comprehensively reviewing the literature and government documents. The results of implementing policies were shown as patient access to essential and guideline-recommended anti-cancer medicines in 11 most prevalent cancers.

Access to anti-cancer medicines in Thailand as of 2019 in comparison with the WHO-EML was considered higher (89.7%) than the previous study in 2012 (72.92%).[25] The current NLEM covers almost all of the targeted cancer therapies recommended in the 2017 WHO-EML. The NLEM further includes 12 anti-cancer medicines not listed on the WHO-EML. The previous study by Saerekul *et al*. found that market access to anti-cancer medicines was 49% (88 out of 180 active ingredients in the WHO granted approval in Thailand) and patient access to these medicines was 43% (38 out of 88 medicines listed on the 2016 NLEM),[26] which were relatively low compared to this study. This study determined patient access to anti-cancer medicines recommended by the WHO-EML and NCCN. Therefore, the results could better reflect the adequacy of patient access to anticancer medicines in Thailand.

Variations in patient access to high-cost anticancer medicines under the three health insurance schemes in Thailand were shown in this study. Anti-cancer medicines and indications listed on the NLEM are provided with full coverage for beneficiaries from all three health insurance schemes with differences in reimbursement criteria. The reimbursement protocol must be followed to get anti-cancer medicines reimbursed for UCS and SSS. Normally, all services provided are reimbursed under the prospective closed-end payments. However, the reimbursement of anti-cancer medicines is different from other diseases because of the retrospective add-on payments. Therefore, the financial pressures on the providers are relieved, and the quality of cancer services is better assured. On the contrary, NLEM medicines treating CSMBS patients can be reimbursed without any restricting criteria. Furthermore, the reimbursement of E2 medicines for the UCS and SSS as returned medicinal products resulted in frequent brand switching. It raises concern regarding medication error, adverse drug reaction and medical compliance for both patients and health-care professionals. This concern is especially true among biologic medicines as switching might affect efficacy and safety.

The variations are much more prominent for patient access to anti-cancer medicines and indications not listed on the NLEM. Prescribing non-NLEM medicines for UCS and SSS patients are paid with prespecified maximum reimbursement, but this would not be enough to cover the costs of innovative anticancer medicines. Patients mostly need to pay out-of-pocket with limited cases which the providers decide to absorb the financial burdens. Even though patients can receive any treatment without restrictions under the National Health Security Act, B.E.2545,[27] the prospective closed-end payments along with the insufficient retrospective add-on payments push the providers to charge non-NLEM medicines from the patients.

On the other hand, CSMBS beneficiaries have more choices of anti-cancer medicines without patients paying out-of-pocket. Even though the NLEM serves as the reimbursement list for all three schemes, five out of seven E2 anti-cancer medicines are also listed on the OCPA list. When comparing the reimbursement indications of these five medicines, there are six indications indicated in the NLEM whereas OCPA provides reimbursement for 13 indications. One explanation for the broader indications was that cost-effectiveness study was not required for the OCPA and it should be noted that the NLEM and OCPA selection process is done separately. Prescribing these five medicines for CSMBS eligibilities must be followed what is stated in the OCPA rather than E2. Since the management process of E2 medicines and OCPA is different, this might lead to confusion for the health-care providers.

PAPs were the main programs providing financial support to self-paying patients who need high-cost medicines, especially cancer patients. Without PAPs, the patients have to pay at full prices. However, the complexity of PAPs has caused administrative burdens to the providers. One university hospital in Thailand is trying to solve this problem by combining all PAPs within the hospital into one place. PAPs have to become simple, such as one PAP for one medicine is allowed. All patients under PAPs have to be registered and monitored. The collected data will be further summarized to evaluate treatment effectiveness.

Even though variations in the coverage of anticancer medicines exist across the three health insurance schemes, overall patient access to these medicines is considered sufficient. Patient access to essential anti-cancer medicines is high because 35 out of 40 WHO recommended medicines are listed on the NLEM. Since the objective of the NLEM was the optimum list of medicines for Thai population, it was not surprising that the coverage of the NLEM was high compared to the WHO EML which served as the minimum list.[11] Furthermore, the NLEM includes sufficient number of the

Table 6: Patient access to guideline-recommended anticancer medicines in Thailand

Cancer site (Number of unique anti-cancer medicines)	Number of anti-cancer medicines		Number of approved anti-cancer medicines	
	Recommended by NCCN	Approved in Thailand	Listed on the NLEM (2019)	Listed on the CSMBS Medicine List (2019)
Breast cancer (*n*=33)				
Early, *n* (%)	16	16 (100)	9 (56.3)	13 (81.3)
Advanced, *n* (%)	33	30 (90.9)	12 (40)	20 (66.7)
Liver and intrahepatic bile duct cancer (*n* = 11)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	11	11 (91.7)	2 (18.2)	6 (54.5)
Colorectal cancer (*n*=20)				
Early, *n* (%)	3	3 (100)	2 (66.7)	3 (100)
Advanced, *n* (%)	20	17 (85)	1 (5.9)	7 (41.2)
Lung cancer (*n*=36)				
Early, *n* (%)	11	10 (90.9)	5 (50)	9 (90)
Advanced, *n* (%)	34	30 (88.2)	9 (30)	17 (56.7)
Cervical cancer (*n*=15)				
Early, *n* (%)	3	3 (100)	3 (100)	3 (100)
Advanced, *n* (%)	15	15 (100)	3 (20)	11 (73.3)
Lip and oral cavity cancer (*n*=12)				
Early, *n* (%)	7	7 (100)	4 (57.1)	5 (71.4)
Advanced, *n* (%)	11	11 (100)	4 (36.4)	6 (54.5)
Corpus uteri cancer (*n*=27)				
Early, *n* (%)	27	26 (96.3)	5 (19.2)	15 (57.7)
Advanced, *n* (%)	27	26 (96.3)	5 (19.2)	17 (65.4)
Prostate cancer (*n*=16)				
Early, *n* (%)	11	8 (72.7)	2 (25)	5 (62.5)
Advanced, *n* (%)	16	12 (75)	3 (25)	9 (75)
Ovarian cancer (*n*=36)				
Early, *n* (%)	13	13 (100)	3 (23.1)	8 (61.5)
Advanced, *n* (%)	33	31 (93.9)	10 (32.3)	23 (74.2)
Esophageal cancer (*n*=13)				
Early, *n* (%)	12	12 (100)	4 (33.3)	8 (66.7)
Advanced, *n* (%)	13	13 (100)	4 (30.8)	8 (61.5)
Diffuse large B-cell lymphoma (*n*=19)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	19	19 (100)	10 (52.6)	16 (84.2)

CSMBS Medicine List: Civil Servant Medical Benefit Scheme medicine list, NCCN: National Comprehensive Cancer Network (NCCN) clinical practice guidelines version 2019, NLEM: National List of Essential Medicines, N/A: Not applicable

guideline-recommended anti-cancer medicines for patients from any health insurance schemes to be able to access to at least one anti-cancer medicine for treating 11 cancers in both early-stage and advanced stage. However, access to high-cost anticancer medicines was still limited in all health insurance schemes, especially targeted cancer therapies. Most reimbursable anti-cancer medicines are cytotoxic agents and hormones. There were only five targeted cancer therapies listed on the NLEM and 15 medicines in the OCPA compared to 50 medicines recommended by the NCCN. OCPA may seem to markedly increase access to high-cost anticancer medicines and widen the gap across the health insurance schemes. However, OCPA was established as a cost-containment measure because without OCPA; physicians could possibly prescribe any anti-cancer medicines under the non-NLEM prescribing criteria A-E. Moreover, with the negative list set by the CGD, CSMBS patients could not receive high-cost anti-cancer medicines without control. Therefore, the variations of access across the three health insurances schemes actually decreased.

Table 7: Patient access to high-cost guideline-recommended anticancer medicines in Thailand

Cancer site (Number of unique anti-cancer medicines)	Number of anti-cancer medicines		Number of approved anticancer medicines	
	Recommended by NCCN	Approved in Thailand	Listed on the NLEM (2019)	Listed on the CSMBS Medicine List (2019)
Breast cancer (*n*=15)				
Early, *n* (%)	5	5 (100)	3 (60)	3 (60)
Advanced, *n* (%)	15	13 (86.7)	2 (15.4)	3 (23.1)
Liver and intrahepatic bile duct cancer (*n*=7)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	7	6 (85.7)	0 (0)	1 (16.7)
Colorectal cancer (*n*=15)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	15	12 (80)	0 (0)	2 (16.7)
Lung cancer (*n*=22)				
Early, *n* (%)	2	1 (50)	0 (0)	0 (0)
Advanced, *n* (%)	21	17 (81)	1 (5.9)	4 (23.5)
Cervical cancer (*n*=4)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	4	4 (100)	0 (0)	0 (0)
Lip and oral cavity cancer (*n*=5)				
Early, *n* (%)	2	2 (100)	0 (0)	0 (0)
Advanced, *n* (%)	5	5 (100)	0 (0)	0 (0)
Corpus uteri cancer (*n*=9)				
Early, *n* (%)	9	9 (100)	0 (0)	0 (0)
Advanced, *n* (%)	9	9 (100)	0 (0)	0 (0)
Prostate cancer (*n*=9)				
Early, *n* (%)	5	3 (60)	0 (0)	0 (0)
Advanced, *n* (%)	9	6 (66.7)	1 (16.7)	3 (50)
Ovarian cancer (*n*=11)				
Early, *n* (%)	5	5 (100)	0 (0)	0 (0)
Advanced, *n* (%)	9	8 (88.9)	0 (0)	1 (12.5)
Esophageal cancer (*n*=5)				
Early, *n* (%)	4	4 (100)	0 (0)	0 (0)
Advanced, *n* (%)	5	5 (100)	0 (0)	0 (0)
Diffuse large B-cell lymphoma (*n*=5)				
Early, *n* (%)	N/A	N/A	N/A	N/A
Advanced, *n* (%)	5	5 (100)	1 (20)	2 (40)

CSMBS Medicine List: Civil Servant Medical Benefit Scheme medicine list, NCCN: National Comprehensive Cancer Network (NCCN) clinical practice guidelines version 2019, NLEM: National List of Essential Medicines, N/A: Not applicable

Patients can indifferently access to high-cost anti-cancer drugs in the NLEM, but still the reimbursement decision process is lengthy. The NLEM opens for submission every 3 years. Therefore, access to innovative high-cost anticancer drugs will be delayed for years or decades. For example, it took 20 years for rituximab to be listed on the NLEM. Rituximab was granted marketing authorization in 1998, and listed on the NLEM in 2018.[13,28] There might be some high-cost anticancer medicines which the pharmaceutical companies consider their medicinal products to be cost ineffective and decide not to submit them to the NLEM in the first place. On the contrary, the OCPA selection process was much faster. After being inactive for 10 years, the medicines on the OCPA increased from six medicines for seven indications to 17 medicines for 29 indications. However, the selection process and criteria are not publicly available.

The targeted cancer therapies which are extremely expensive would unlikely be cost-effective under Thailand's cost-effectiveness threshold of 4738 USD (160,000 Thai Baht).[29] These medicines have changed the treatment paradigm from a well-defined number of cycles of chemotherapy to lifelong which results in increased budgetary constraint.[30] Innovative

funding models are needed to make these medicines accessible to patients. The MEAs could be a reasonable alternative reimbursement for cost-ineffective anti-cancer medicines, especially financial-based MEAs. The MEAs were previously utilized for the reimbursement of imatinib where Max Foundation provided free imatinib to UCS patients.[14] With these agreements, the risks were shared among payers and the companies. One of the most appropriate financial-based MEAs for Thailand could be the utilization capping, where pharmaceutical companies offered free medicines to patients who respond to the medicines. With this design, the costs of lifelong treatment of high-cost anti-cancer medicines will be mitigated for the payers. The pharmaceutical companies also benefit from utilizing MEAs as they can conceal the net price of the medicines, preventing the other countries from using Thai prices for reference pricing system.

The E2 access program utilizes retrospective authorization system. The OCPA also utilizes prior authorization system. Therefore, the collected data for authorization process should be shared among the payers to establish real-world effectiveness of medicines in Thai population. Moreover, the collected data from the OCPA medicines should provide the real-world evidence of treatment effectiveness that could be beneficial when submitting the OCPA medicines for listing on the NLEM. The NLEM could reimburse high-cost anticancer medicines under the condition that further evidences of real-world effectiveness are collected and will later be reevaluated after several years, also known as coverage with evidence development. However, coverage with evidence development is unlikely to be successful in Thailand because of two main reasons. First, the quality of the collected data needs to be improved. Second, if the future evidences show that the medicine is not effective, it is not easy to delist the medicine. Beneficiaries would feel threatened as their treatment choices are decreasing.

This study had several limitations. Patient access to anticancer medicines was quantified using only 11 cancers as a proxy. Moreover, the sources of information used in this study were mostly derived from government documents because there were a lack and fragmented researches in this area in the country. Patient access to anti-cancer medicines under the three health insurance schemes was not fully captured. There might be variations in access to high-cost anticancer medicines, especially across hospitals since some university hospitals have developed internal authorization system for the high-cost medicines. Therefore, more researches on patient access to medicines in Thailand should be encouraged.

CONCLUSION

There are variations in patient access to high-cost anti-cancer medicines across the three health insurance schemes. However, patient access to these medicines is considered sufficient. Thai patients under the three health benefit schemes can indifferently access with full coverage to high-cost anti-cancer medicines listed on the NLEM. Apart from that, UCS and SSS patients are likely have to pay out-of-pocket because of insufficient payments from the coverage schemes. In contrast, CSMBS patients still have alternative pathways to obtain these medicines, such as the OCPA. PAPs also play a major role in supporting self-paying patients, but they have to be simpler to reduce burdens to health-care professionals. MEAs were found to be implemented in Thailand. New funding strategies are required to ensure timely access to innovative high-cost anti-cancer medicines.

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REFERENCES

1. National Health Security Office. Report on the Creation of the National Health Security for Fiscal Year BE 2561 (AD 2018). Bangkok, Thailand: National Health Security Office; 2019.
2. Jongudomsuk P, Srithamrongsawat S, Patcharanarumol W, Limwattananon S, Pannarunothai S, Vapatanavong P. The Kingdom of Thailand Health System Review 2015. Manila, Philippines: World Health Organisation, Regional Office for the Western Pacific; 2016.
3. Hirunrassamee S, Ratanawijitrasin S. Does your health care depend on how your insurer pays providers? Variation in utilization and outcomes in Thailand. Int J Health Care Finance Econ 2009;9:153-68.
4. Thai Food and Drug Administration. National List of Essential Medicines BE 2562 (AD 2019) Thailand: Bureau of Drug Control, Ministry of Public Health; 2019 Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2562/E/095/T_0008.PDF. [Last accessed on 29 Apr 19].
5. World Health Organization. Cancer Country Profiles. Thailand Geneva, Switzerland: World Health Organization; 2014. Available from: https://www.who.int/cancer/country-profiles/tha_en.pdf?ua=1. [Last accessed on 29 Apr 19].
6. National Health Security Office, Thailand. Universal Coverage Scheme Treats 234,000 Cancer Patients in 2018 2018 Available from: https://www.nhso.go.th/FrontEnd/NewsInformationDetail.aspx?newsid=MjQ4Nw==. [Last accessed on 29 Apr 19].
7. Intragumtornchai T, Bunworasate U, Siritanaratkul N, Khuhapinant A, Nawarawong W, Norasetthada L, *et al.* Inferior progression-free survival for Thai patients with diffuse large B-cell lymphoma treated under universal coverage scheme: The impact of rituximab inaccessability. Leuk Lymphoma 2013;54:83-9.
8. Sermsri N, Boonpipattanapong T, Prechawittayakul P, Sangkhathat S. Influence of payer source on treatment and outcomes in colorectal cancer patients in a university hospital in Thailand. Asian Pac J Cancer Prev 2014;15:9015-9.
9. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2019. Available from: https ://www.whocc.no/atc_ddd_index/?code=L&showdescription=yes. [Last accessed on 01 May 19].
10. National Cancer Institute. Thailand. Hospital-based Cancer Registry Annual Report 2017. Bangkok, Thailand: National Cancer Institute; 2018.
11. World Health Organization. WHO Model List of Essential Medicines. 20th List March 2017, Amended August 2017. Geneva: World Health Organization; 2017.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; 2019 Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. [Last accessed on 01 May 19].
13. Thai Food and Drug Administration. FDA Search Center Thailand; 2019. Available from: https ://www.porta.fda.moph.go.th/FDA_SEARCH_ALL/MAIN/SEARCH_CENTER_MAIN.aspx. [Last accessed on 01 May 19].
14. Sruamsiri R, Ross-Degnan D, Lu CY, Chaiyakunapruk N,

Wagner AK. Policies and programs to facilitate access to targeted cancer therapies in Thailand. PLoS One 2015;10:e0119945.
15. National Health Security Office, Thailand. The 2018 Protocol CA for the Reimbursement of Healthcare Services under the National Health Security System; 2018. Available from: https://www.nhso.go.th. [Last accessed on 2019 May 17].
16. National Health Security Office. The Practice Guidelines for the Reimbursement of Healthcare Services for Fiscal Year BE 2561 (AD 2018). Thailand: National Health Security Office; 2018.
17. Social Security Office. The Reimbursement Criteria for Non-occupational Injury and Illness. Thailand: Social Security Office; 2013.
18. Social Security Office. The Reimbursement Criteria for Non-occupational Injury and Illness. Thailand: Social Security Office; 2018.
19. Comptroller General's Department. The Reimbursement of the Costs of Medicines Listed on the National List of Essential Medicines, List E2. Thailand: Comptroller General's Department; 2017.
20. Comptroller General's Department. The Reimbursement of the Medical Services under the Oncology Prior Authorization (OCPA) Program. Thailand: Comptroller General's Department; 2005.
21. Comptroller General's Department. The Reimbursement of Medical Services for Patients Requiring High-cost Oncology and Hematology Medicines. Thailand: Comptroller General's Department; 2019.
22. Comptroller General's Department. The Reimbursement of Medical Services for Patients Requiring High-cost Oncology and Hematology Medicines. Thailand: Comptroller General's Department; 2018.
23. Comptroller General's Department. The Prescribing Criteria for Medicines not Listed on the National List of Essential Medicines. Thailand: Comptroller General's Department; 2012.
24. Kittirotruji K, Lommuang K, Chumchaiyo C, Taychakhoonavudh S. Use of patient assistance programs (Paps) to increase access to innovative drugs in Thailand. Current situations and prospects. Value Health 2018;21:S20.
25. Cuomo RE, Mackey TK. The availability of essential cancer medication: An analysis of national formularies. J Cancer Policy 2017;12:49-54.
26. Saerekul P, Limsakun T, Anantachoti P, Sakulbumrungsil R. Access to medicines for breast, colorectal, and lung cancer in Thailand. Thai J Pharm Sci 2018;42:221-9.
27. National Health Security Office. National Health Security Act BE 2545 (AD 2002). Thailand: National Health Security Office; 2002.
28. Thailand National List of Essential Medicines; 2018. Available from: http://www.drug.fda.moph.go.th:81/nlem.in.th/node/10630. [Last accessed on 2018 Jan 24].
29. Tanvejsilp P, Taychakhoonavudh S, Chaikledkaew U, Chaiyakunapruk N, Ngorsuraches S. Revisiting roles of health technology assessment on drug policy in universal health coverage in Thailand: Where are we? And what is next? Value Health Reg Issues 2019;18:78-82.
30. McCabe C, Bergmann L, Bosanquet N, Ellis M, Enzmann H, von Euler M, *et al.* Market and patient access to new oncology products in Europe: A current, multidisciplinary perspective. Ann Oncol 2009;20:403-12.