



Impact of a New Cost-Effectiveness Threshold Implementation on Cancer Formulary Decisions in Jordan

Imad Treish¹ · Abeer Al Rabayah¹ · Saad Jaddoua¹ · Haitham Tuffaha²

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Abstract

Rising prices of novel cancer medications are increasing the economic burden from cancer in Jordan, risking the ability of cancer patients to access lifesaving and life-extending treatments. Furthermore, in the absence of a national health technology assessment (HTA) framework, medication prices in Jordan are set based on manufacturers' pricing considerations and not a value proposition. In response to these challenges, King Hussein Cancer Center (KHCC), the de facto national cancer institute, developed a first-in-country, cancer-specific, cost-effectiveness threshold (CET) to aid institutional decision makers in approving only cost-effective medications. Over the past 10 years, cost-effectiveness analyses based on this CET have led to the introduction of > 70% of requested novel cancer medications after manufacturers agreed to lower prices, beyond registration prices, to meet the CET. Future work is warranted to empirically derive a CET for Jordan to better guide reimbursement decisions.

Key Points for Decision Makers

We describe the development and application of a cost-effectiveness threshold (CET) at a comprehensive cancer center in Jordan.

The application of the CET threshold in the health technology assessment of new cancer drugs resulted in significant reductions in acquisition costs.

Future work is needed to empirically derive a country-specific CET.

1 Introduction

The economic burden of cancer has been increasing in Jordan similar to other countries in the world [1]. In Jordan, this increase is fueled by an increase in the prices of novel cancer medications [2, 3] and an increase in cancer incidence (5556 new cancer cases in 2015 vs 3670 in 2005) [4]. The main driver for cancer incidence increase is the near-doubling of the population (9.53 million in 2015 vs 5.48 million in 2005) [5]. Additionally, the incidence rate of cancer has also increased (age-standardized incidence rate [ASIR] 113/100,000 in 2005 vs 118/100,000 in 2015), which is attributed to aging (life expectancy at birth was 72.9 in 2007 vs 74.3 in 2017), environmental exposure and lifestyle changes [4–6].

The World Bank classifies Jordan as an upper-middle-income economy country [7]. The gross domestic production national income (GDP) per capita grew from US\$3398 in 2008 to US\$40,163 in 2017 [8]. Total health care expenditure (THE) in Jordan has doubled in the last decade, reaching US\$3.62 billion in 2017 [8]. Moreover, the per-capita THE has increased from 177.50 Jordanian dinar (JD) to JD255.00 in the same period. Jordan's THE is higher than similar-income countries in the region (9% vs 5% of GDP), leading to improved access to health care services such as cancer care. A 1999 royal decree ensured that all Jordanians diagnosed with cancer receive cancer

✉ Abeer Al Rabayah
ARabaiah@KHCC.JO

Imad Treish
itreish@khcc.jo

Haitham Tuffaha
h.tuffaha@uq.edu.au

¹ Department of Pharmacy, Center for Drug Policy and Technology Assessment (CDPTA), King Hussein Cancer Center, Amman, Jordan

² Centre for the Business and Economics of Health, The University of Queensland, Brisbane, QLD 4067, Australia

treatment at no cost in the public-sector hospitals and the King Hussein Cancer Center (KHCC) [9].

KHCC was established in 2002 to provide much-needed comprehensive care for cancer patients in Jordan and the region [10]. Care is delivered using a multidisciplinary approach based on institutional clinical practice guidelines (CPGs) adapted from various international guidelines [9]. Furthermore, KHCC implemented a robust formulary management system to provide safe and cost-effective medications for cancer patients under the auspices of the Pharmacy & Therapeutics Committee (P&T). Pharmacy expenditure, mostly on cancer medications, grew by 63% from 2005 to 2008. In 2006, the P&T became concerned that the increasing rate of novel cancer medicines' introduction to the market would lead to detrimental financial consequences for KHCC and the national health budget if local pharmacoeconomic metrics were not considered in the evaluation of new medication additions. Conversely, excluding such medications from the formulary would limit patients' access to life-saving and life-prolonging medications. Unfortunately, Jordan did not have a health technology assessment (HTA) framework to guide decision makers in approving new health interventions [11].

Public (selling) prices of medications in Jordan are set by the Jordan Food and Drug Administration (JFDA) under the External Reference Pricing (ERP) Policy [12]. The set price should be the lowest of the reference prices (benchmarks): the country-of-origin price, the reference basket median price, the manufacturer export price, and Saudi Arabia's public price. Pharmacoeconomic evidence has a limited impact on pricing decisions [13]. The public price is applied in community pharmacies and private hospitals for self-paying patients. Private insurance companies typically apply a contractual discount to the public price. Reimbursement rates in the public-sector hospitals are based on acquisition costs of the Joint Procurement Department (JPD), which initiates public tenders to purchase medications that are on the Rational Drug List (RDL) on behalf of the public-sector hospitals. The RDL represents Jordan's national formulary and it is an output of the work of both technical and national committees that represent all related health sectors. However, cost-effectiveness analysis (CEA) does not impact the listing decision of new medications to the RDL [11, 13].

Although the government has not set a specific budget for cancer care, KHCC sought to implement an HTA framework to ensure that only cost-effective medications are added to its formulary, therefore attempting to strike a balance between ensuring access to new medications and the increasing expenditure on medications. Furthermore, the framework would empower KHCC to directly negotiate

medication costs with pharmaceutical companies in a more objective and transparent way. Lastly, an HTA framework would serve not only KHCC but also other providers in the country due to KHCC's professional influence over other institutions.

The objective of this paper is to describe the development of a cancer-specific cost-effectiveness threshold (CET) for the first time in Jordan and the impact of this CET on formulary decisions related to novel cancer medications at KHCC.

2 Cost-Effectiveness Threshold (CET) Development and Application

2.1 Overview

KHCC considered several options for setting the CET. One option was to adopt the World Health Organization (WHO) recommendation of considering interventions with an incremental cost-effectiveness ratio (ICER) of $< 3 \times \text{GDP per capita/disability-adjusted life-year (DALY)}$ to be cost effective [14]. However, this approach produced a CET of US\$7539 (based on 2006 data), which would not have allowed the introduction of most cancer therapies, thereby limiting access to life-saving or life-extending medications. Alternatively, the adoption of a CET from a developed economy would have overestimated the CET. This led KHCC to develop a CET based on local considerations. Given pharmacoeconomics expertise limitations and the absence of international guidelines/methods at that time to estimate thresholds based on the opportunity cost to our health budget, a decision was made to follow a precedent-based approach [15], whereby a CET is determined in relation to the cost effectiveness of an oncology medication that met the following criteria:

1. Novelty medication for cancer treatment to make our CET applicable to the new class of cancer-targeted therapies;
2. Considered by clinical experts as the standard of care based on its significant clinical benefit and established safety profile.

Imatinib (Glivec™) met the agreed-upon criteria. It was first approved in Jordan in 2003 for chronic myelogenous leukemia (CML). Despite the cost difference, imatinib immediately replaced interferon-based treatment for CML due to the dramatic improvement in outcome and the low side-effect profile [16]. At that time, only bone marrow transplantation was more expensive than imatinib, yet there was a clear consensus that imatinib should be the standard of care for CML.

2.2 Cost-Effectiveness Analysis of Imatinib

A CEA was conducted from the perspective of a Jordanian health care system as a paying source. Details of the model were previously presented [17] and additional details are included in Appendix 1 (see electronic supplementary material). Briefly, a state transition (Markov) model was developed to estimate the expected costs and outcomes (life-years) of imatinib. The model included three health states: chronic phase CML, accelerated/blast phase CML, and death. Newly diagnosed patients with CML were expected to enter the model at the chronic phase. The mean starting age of CML patients was 50 years. Transition probabilities between health states were estimated based on the IRIS trial [16]. Mortality from non-cancer-related causes was estimated from the 2005 WHO life tables for Jordan. CML-related death was estimated from the IRIS trial [16].

The mean estimated survival with first-line treatment with imatinib for CML in the chronic phase was 11.59 life-years. Undiscounted lifetime costs were approximately US\$500,690 with imatinib. Imatinib, therefore, provided a threshold of approximately US\$43,164/life-year gained (LYG). In this model, and due to the relatively mild toxicity profile of imatinib compared with interferon, it was assumed that LYG from imatinib was considered an approximation for quality-adjusted life-year (QALY), as demonstrated by Reed and colleagues [18]. Henceforth, KHCC adopted a CET of US\$43,000/QALY.

In 2016, the KHCC Board of Trustees approved a modification to the 2006 threshold to account for inflation in the past 10 years. The newly approved CET would range between US\$42,000 and US\$56,000 per QALY. The upper end of this new range allowed for more flexibility when considering the approval of novel medications, whereas the lower end was used to negotiate the prices of new medications with similar entities that are already on the formulary.

2.3 Health Technology Assessment (HTA) Pathway at KHCC and the Application of CET

Effective 2006, all new formulary requests for novel cancer medications would be subjected to cost-effectiveness (CE) assessment. KHCC established the Center for Drug Policy and Evaluation (CDPTA) to conduct pharmacoeconomic analyses and conduct and appraise CE studies [19]. In 2012, a formulary submission pathway targeting pharmaceutical manufacturers was introduced under the formulary system policy. A CEA model would be either submitted by the pharmaceutical company as part of the HTA submission or developed internally. The CDPTA presents its CE assessment report to the P&T. The report is based on a standardized template that addresses clinical pharmacology, clinical efficacy/effectiveness, safety, and economic evaluation along with expected resource utilization. The results of the

adapted CE model, along with assessments of uncertainty and resource implications, are included in the economic evaluation section [19]. The P&T may authorize the pharmacy department to initiate negotiations with the manufacturers to reduce acquisition costs in line with the CET.

2.4 Impact of CET Application on Formulary Listing Decisions

After obtaining institutional review board (IRB) approval, we conducted a review of P&T records over the past 10 years to determine the impact of the new HTA framework on medication approvals.

CEAs of 30 anti-neoplastic medications were assessed from 2008 to 2018, including seven that were developed by the CDPTA staff. Of these, 22 (73%) medications were added to the formulary, and eight were rejected. Ninety-three percent of listed medications were subject to financial risk sharing agreements with manufacturers to reach the KHCC threshold, whereas 7% were listed based on the JFDA public price. Details are provided in Table 1.

3 Discussion

In the absence of national guidelines in Jordan, KHCC developed an HTA framework to ensure that only cost-effective medications are added to its formulary. Based on unanimous consensus among KHCC and national medical experts supporting the use of first-line imatinib to treat CML in Jordan, we developed a CE model for imatinib in CML. The results of the model were used to set a CET that was adopted by KHCC's HTA framework.

Our approach to developing a CET is pragmatic in the sense that we have adopted a cancer-specific figure based on the cost effectiveness of imatinib mesylate in CML. To our knowledge, this is the first published work describing the development of a cancer-specific CET that has been successfully used for more than 10 years to assess the cost effectiveness of newly approved targeted and non-targeted treatments for cancer. Our approach of setting a CET based on the results of the decision modelling of imatinib in CML is analogous to using CEA of dialysis in end-stage renal disease as the basis for the CET figure most commonly cited in the US [20]. The principles that should be followed in choosing a reference drug include innovation (e.g., being a new class of drugs), significant clinical benefits (e.g., survival benefit relative to the standard of care), and safety [21]. Therefore, we believed that imatinib could be considered a reference drug against which the value for money of other cancer treatments could be compared [22, 23].

Table 1 Results of health technology assessments

Intervention	Comparator	HTA and cost-effectiveness modelling development status	ICER: Cost (US\$) per QALY	Risk sharing agreement	Final recommendation ^a
Bevacizumab in combination with chemotherapy for first-line treatment of metastatic colorectal cancer	FOLFOX	Developed by KHCC CDPTA	460,020	Financial risk-sharing agreement was not reached	Not recommended
Lenalidomide for the treatment of multiple myeloma in patients who received at least one prior therapy	Dexamethasone	Submitted by manufacturer/adapted by CDPTA	59,138	Financial risk-sharing agreement was reached	Recommended
Sunitinib for first-line treatment of metastatic renal cell carcinoma	Interferon alpha	Developed by KHCC CDPTA	87,214	Financial risk-sharing agreement was reached	Recommended
Gefitinib for first-line treatment in metastatic, chemo-naïve, EGFR+ NSCLC	Docetaxel + cisplatin	Developed by KHCC CDPTA	58,085	Financial risk-sharing agreement was reached	Recommended
Erlotinib for first-line treatment of metastatic, chemo-naïve EGFR+ NSCLC	Docetaxel + cisplatin	Developed by KHCC CDPTA	94,153	Financial risk-sharing agreement was not reached	Not recommended
Pemetrexed + cisplatin for first-line treatment of metastatic, non-squamous EGFR+ NSCLC	Docetaxel + cisplatin	Developed by KHCC CDPTA	66,004	Financial risk-sharing agreement was reached	Recommended
Lapatinib with capecitabine for first-line treatment in HER2+ metastatic breast cancer	Trastuzumab + capecitabine	Submitted by manufacturer/adapted by KHCC CDPTA	- 18,905	Financial risk-sharing agreement was reached	Recommended
Nilotinib for first-line treatment for high-risk newly diagnosed Philadelphia chromosome-positive CML patients in the chronic phase	Imatinib	Submitted by manufacturer/adapted by KHCC CDPTA	174,211	Financial risk-sharing agreement was reached	Recommended
Cabazitaxel for second-line treatment of metastatic castration-resistant prostate cancer	Mitoxantrone	Submitted by manufacturer/adapted by KHCC CDPTA	137,199	Financial risk-sharing agreement was not reached	Not recommended
Bendamustin for the treatment of elderly chronic lymphocytic leukemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate	Chlorambucil	Submitted by manufacturer/adapted by KHCC CDPTA	31,177	Financial risk-sharing agreement was reached	Recommended
Bendamustin for first-line treatment of non-Hodgkin lymphomas (mantle cell and indolent lymphomas: follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and splenic marginal zone lymphoma)	Rituximab-CHOP	Submitted by manufacturer/adapted by KHCC CDPTA	3,404	Listed without financial risk sharing agreement	Recommended

Table 1 (continued)

Intervention	Comparator	HTA and cost-effectiveness modelling development status	ICER: Cost (US\$) per QALY	Risk sharing agreement	Final recommendation ^a
Fulvestrant for third-line treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following tamoxifen and aromatase inhibitors therapy	Anastrozole Letrozole	Submitted by manufacturer/adapted by CDPTA	55,926	Financial risk-sharing agreement was reached	Recommended
Ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera (post-PV) myelofibrosis, and post (post-ET) essential thrombocythemia myelofibrosis	Hydroxyurea	Submitted by manufacturer/adapted by CDPTA	124,413	Financial risk-sharing agreement was reached	Recommended
Everolimus in combination with exemestane for the treatment of advanced postmenopausal hormone receptor-positive, HER2-negative breast cancer patients after failure of treatment with letrozole or anastrozole	Exemestane	Submitted by manufacturer/adapted by CDPTA	96,610	Financial risk-sharing agreement was reached	Recommended with restriction to studied indication
Bevacizumab for first-line treatment of high-risk ovarian cancer patients	Carboplatin + paclitaxel	Submitted by manufacturer/adapted by CDPTA	97,740	Financial risk-sharing agreement was reached	Not recommended
Cetuximab for first-line treatment of KRAS wild-type (without mutation), EGFR-expressing metastatic colorectal cancer as determined by an approved test in combination with chemotherapy	Chemotherapy	Submitted by manufacturer/adapted by CDPTA	70,556	Financial risk-sharing agreement was reached	Recommended
Cetuximab for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck in patients with contraindication to cisplatin or at high risk for renal failure/impairment with cisplatin	Radiotherapy	Submitted by manufacturer/adapted by CDPTA	10,224	Listed without financial risk sharing agreement	Recommended
Pertuzumab for the treatment of neoadjuvant treatment of operable locally advanced, inflammatory or early-stage HER2+ breast cancer in combination with trastuzumab and docetaxel	Trastuzumab+ docetaxel	Submitted by manufacturer/adapted by CDPTA	118,412	Financial risk-sharing agreement was reached	Recommended

Table 1 (continued)

Intervention	Comparator	HTA and cost-effectiveness modelling development status	ICER: Cost (US\$) per QALY	Risk sharing agreement	Final recommendation ^a
Abiraterone for the treatment of asymptomatic or minimally symptomatic castration-resistant prostate cancer patients before chemotherapy with EGFR	Prednisolone	Submitted by manufacturer/adapted by CDPTA	201,598	Financial risk-sharing agreement was reached	Recommended
Afatimib for treating NSCLC patients with EGFR	Gefitinib	Submitted by manufacturer/adapted by CDPTA	69,178	Financial risk-sharing agreement was reached	Recommended
Pembrolizumab for treating unresectable melanoma	Dacarbazine	Submitted by manufacturer/adapted by CDPTA	96,643	Financial risk-sharing agreement was reached	Recommended
Pembrolizumab for first-line treatment of NSCLC with PDL expression $\geq 50\%$	Cisplatin+ pemetrexed	Submitted by manufacturer/adapted by CDPTA	104,228	Financial risk-sharing agreement was reached	Recommended
Pembrolizumab for second-line treatment for patients with PDL expression of $\geq 1\%$	Docetaxel	Submitted by manufacturer/adapted by CDPTA	115,967	Financial risk-sharing agreement was reached	Recommended
Nivolumab for second-line treatment of renal cell carcinoma	Best supportive care	Submitted by manufacturer/adapted by CDPTA	90,821	Financial risk-sharing agreement was reached	Recommended
Trastuzumab for first-line treatment of metastatic gastric cancer	Capecitabine/cisplatin	Submitted by manufacturer/adapted by CDPTA	208,099	Financial risk-sharing agreement was not reached	Not recommended
Enzalutamide for the treatment of metastatic castration-resistant cancer before chemotherapy	Watchful waiting	Submitted by manufacturer/adapted by CDPTA	125,045	Financial risk-sharing agreement was not reached	Not recommended
Enzalutamide for the treatment of metastatic castration-resistant cancer after chemotherapy	Best supportive care	Submitted by manufacturer/adapted by CDPTA	123,839	Financial risk-sharing agreement was not reached	Not recommended
Pertuzumab for first-line treatment of metastatic HER2-positive breast cancer in combination with trastuzumab and docetaxel	Trastuzumab+ docetaxel	Submitted by manufacturer/adapted by CDPTA	215,516	Financial risk-sharing agreement was reached	Recommended
Ribociclib for first-line treatment of hormonal positive post-menopausal breast cancer	Letrozole	Submitted by manufacturer/adapted by CDPTA	138,984	Financial risk-sharing agreement was reached	Recommended
Palbociclib for first-line treatment of hormonal positive post-menopausal breast cancer	Letrozole	Submitted by manufacturer/adapted by CDPTA	283,772	Financial risk-sharing agreement was not reached	Not recommended

CDPTA Center for Drug Policy and Technology Assessment, CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, CML chronic myelogenous leukemia, EGFR epidermal growth factor receptor, FOLFOLX infusional fluorouracil/folinic acid and oxaliplatin, HER2 human epidermal growth factor receptor-2, HTA health technology assessment, ICER incremental cost-effectiveness ratio, KHCC King Hussein Cancer Center, KRAS KRAS oncogene, NSCLC non-small cell lung cancer, PDL programmed death-ligand receptor, QALY quality-adjusted life-year

^a Approval recommendation includes formulary restriction to the studied and approved indication

The establishment of the CET and the HTA framework provided us with a powerful and transparent tool to explain to our stakeholders (physicians, patients, and the pharmaceutical industry) how formulary decisions are made at KHCC. Furthermore, this approach effectively secured substantial discounts to bring the prices of medications in line with our CET or even better. Nonetheless, due to limited technical capacity and lack of expertise within KHCC at that time, limitations to our approach should be noted. The CET developed represents the average cost-effectiveness ratio (not the ICER), which is the ratio of the cost to benefit of an intervention without reference to a comparator. Moreover, we did not discount long-term costs and outcomes, and assumed a LYG equivalent to QALY gained. The latter assumptions were based on the work by Reed et al [18], which informed our analyses. Moreover, changing the threshold into a range was based on a Board decision due to increased societal pressures to increase access to new cancer treatments. In terms of the HTA framework overall impact, we did not develop clear indicators to comprehensively assess the outcomes of our decisions including overall savings to the Jordan healthcare system, impact on patient-reported outcomes, and impact on other institutions.

In a recent review of CETs worldwide, Santos and colleagues highlighted the lack of an empiric approach to determining the CET for most countries [15]. Existing CETs in many jurisdictions are based on either historic (e.g., NICE) or heuristic approaches (e.g., WHO threshold) that are not accurate as they can over- or underestimate the actual CET. Importantly, these CETs do not consider the opportunity cost from additional spending on the limited health budget and may lead to decisions that reduce rather than improve health gains. Similarly, CETs estimated based on studies of willingness to pay/accept (e.g., contingent valuation) tend to overestimate CET, and they also fail to account for the opportunity cost falling on the constrained health budgets. Despite its popularity, so much doubt has been cast on the genesis of NICE's CET figure [24]. In 2013, Claxton and colleagues developed a model for calculating CET based on opportunity cost using UK NHS data [25]. The estimated CET for the NHS was calculated to be US\$18,609 (£12,936)/QALY, which is much lower than the NICE threshold range. NICE has expressed its unwillingness to adopt this new CET as it would not allow for the entry of most new medications [26]. Interestingly, when this model was applied to estimate the CETs in several low- to middle-income countries (LMICs) based on their relative per-capita GDP and statistical life values, the CET for Jordan was between US\$1971 and US\$7757 per QALY [27]. Like NICE, Jordan would not adopt such a range as it would virtually eliminate most new cancer treatments. Thus, setting the CET too high may lead to inefficient budget allocation, whereas a CET that is too low would preclude the listing of novel health technologies.

Thus, a valid, reliable, and relevant CET remains elusive as policy makers around the world aim to strike a balance between improving access to new cancer treatments and maintaining budgetary controls; and between a CET that expresses the society's monetary valuation of health gains versus opportunity cost resulting from required disinvestment when adopting new technology. Future efforts, therefore, should be directed toward deriving a country-specific CET for Jordan based on the opportunity cost by considering marginal health spending and health gains. It is also essential to develop a national HTA framework that is responsive to stakeholders' needs in an equitable way [28, 29]. Such a framework should be supported by practical but rigorous evaluation methods and transparent reporting and governance to enhance the uptake of HTA recommendations and their implementation in practice. Of note, economic evaluation, as part of any framework, is intended to inform rather than prescribe reimbursement decisions. In making decisions, it is vital to consider other essential and relevant value elements that may not be captured in the typical cost-utility analyses, such as equity considerations and other societal benefits. This can be achieved through an augmented CEA approach, multiple-criteria decision analysis (MCDA), or a deliberative approach to decision making [30].

4 Conclusion

King Hussein Cancer Center has successfully developed a CET based on the CEA of imatinib in the treatment of CML. The application of the CET in the HTA for cancer medications has allowed for significant reductions in acquisition costs and therefore inclusion of most of the new cancer treatments on the formulary, which would not have been otherwise approved based on their registration prices. A valid, reliable, and relevant CET remains elusive as we strive to strike a balance between opportunity-cost-derived CET and societal and political pressure on the health care system.

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