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Pharmacoeconomic Evaluations of Oral Anticancer Drugs: a Systematic Review

Nazish Matti [1], Gul Majid [*1], Muhammad Faisal Nadeem [2], Tahir Mehmood KHAN [2], Muhammad Nabeel Shahid [2]

1. *Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan*
   **** Corresponding Author:** Gul Majid KHAN* Email: gmkhan@qau.edu.pk
2. University of Veterinary and Animal Sciences, Lahore, Pakistan

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ABSTRACT

Background: Oral anticancer drugs (OACDs) have been used since the 1950s and are expected to be linked with enhanced life quality which helps patients receive treatment at home. Although more convenient in use than intravenous or other infused drugs, the high costs of these OACDs have been proven controversial.

Methods: The literature was searched systematically from PubMed, Cochrane, Embase, and Scopus according to the PRISMA guidelines. The inclusion criteria included studies in the English language, evaluating Pharmacoeconomics, and evaluating cost-utility and cost-effectiveness related to OACDs. The information on the included studies was synthesized in the form of summary tables.

Results: Thirteen studies were included for quantitative analysis, which evaluated the costs or cost-effectiveness of different OACDs used for various types of cancer. It was found that the average cost for the OACDs was $80979/year in attaining (quality-adjusted life per year) QALY across different countries. The costs of different OACDs were highly varied alone in the US. The included studies' results were highly varied, limiting the findings' interpretations.

Conclusion: Various studies about cost-effectiveness persist insufficiently represented in the literature regarding OACDs, suggesting the requirement of more cost-effectiveness analysis shortly. The increased costs of these OACDs require careful evaluation of the cost-effectiveness studies.

Introduction

Oral anticancer drugs (OACDs) have been used since 1950the s after their approval by the Food and Drug Administration (FDA), which developed rapidly during the early 2000s, surpassing the development of intravenous chemotherapy (Hirschfeld, Ho, Smith, & Pazdur, 2003) (Al Kadour, Al Marridi, & Al-Badriyeh, 2018). It has been assessed that more than one-fourth of the 400 anticancer drugs are developed as oral agents (Kavookjian & Wittayanukorn, 2015). These OACDs are expected to be linked with enhanced life quality. The administration of these drugs orally helps patients in receiving treatment at home. The enhanced occurrences of cancer, scarcity of hospital resources, and accessibility of more therapeutic options have headed toward developing and using OACDs (Schott et al., 2011). Imatinib was first approved for OACD by FDA in 2001 and has been considered the first accessible targeted OACD in the U.S. Since then, these drugs have maintained to expand rapidly. These oral drugs represented an estimated 25–30 % of the field of oncology during 2008, and nearly all of them were targeted (Geynisman & Wickersham, 2013).

Most of these OACDs are tyrosine kinase inhibitors (TKIs), some of which down-regulate the proliferation of cells such as nilotinib, vemurafenib, imatinib, lapatinib, etc. a large class of these TKIs helps to block angiogenesis associated with tumors such as pazopanib and regorafenib. The third class involves the Hedgehog pathway and myelofibrosis inhibitors involving drugs such as isomeric and ruxolitinib. The fourth class involves drugs used to inhibit histone deacetylase with broad anticancer activity, such as orinasal and lenalidomide, etc. (Richon, 2010; Zhu, Kortuem, & Stewart, 2013). Another class of OACDs involves antihormonal agents like inhibitors of aromatase receptors and antagonists of estrogen receptors such as abiraterone and enzalutamide (Mitsiades, 2013). Cancer is a resource-demanding illness requiring a significant amount of healthcare expenditure globally, and it is the second leading cause of death (Sohi et al., 2020). There have downsides to OACDs compared to intravenous therapy regarding nonadherence and cost. As they are given to the patient at home, and the patients are not monitored closely by the oncologists, hence causing the chances of nonadherence (Geynisman & Wickersham, 2013). Most of the OACDs cost thousands of dollars monthly, and hence the long-lasting treatment with single or multiple drugs causes an economic burden on the healthcare system (Shen, Chien, Geynisman, Smieliauskas, & Shih, 2014). The problem of high costs linked with drugs for targeted treatment endures and might have been increased for targeted OACDs since most patients are needed to continue these treatments until the signs of cancer progression have not remained (Shen et al., 2014). The risen costs of targeted OACDs have prompted an intense dispute in various cases. For instance, the decision to compensate imatinib drug for patients with chronic myelogenous leukaemia in the U.K. has been condemned as a funding choice "without a clear and public justification" (O'SBrien, 2001).

Similarly, matters have been stated concerning the attention decision to use vemurafenib for melanoma treatment in Australia (Kefford, 2012) and the same concern for sorafenib to treat renal cell carcinoma in Canada (Laupacis, 2009). The considerations regarding the high-cost label of several targeted OACDs are understandable because their various linked clinical advantages have encouraged the scientist's discovery of the cost-effectiveness of these OACDs. Suggestions from the analysis of cost-effectiveness could provide valuable knowledge for decision creators when choosing the use of these high-cost treatments, which is mainly based on the cost-effectiveness threshold (Santos, Guerra-Junior, Godman, Morton, & Ruas, 2018) which relies on economic and non-economic reasons, and considerably varies from country to country (Cleemput, Neyt, Thiry, De Laet, & Leys, 2011). In the U.S., several economic estimations of OACDs to cure breast cancer have been performed employing several cost-effectiveness thresholds. Many review articles summarize the cost-effectiveness of targeted OACD drugs, such as erlotinib (Yeung & Carlson, 2012). Producers' preferred pricing could influence the costs of OACDs through dose modifications. Flat pricing strategy involves applying a single fixed price for every single tablet irrespective of the dose intensity, and linear pricing strategy involves a rise in price with the increase in dosage. It was shown in a study that flat pricing had more costs of doses than linear pricing, which is opposite to anticipation that the price of doses must reduce with a decrease in dose. So, the consequently enhanced expenditure on medicines purchase cause economic wastage (Truong et al., 2019).

Several systematic reviews are available for analysis of cost-effectiveness, but they only concentrate on particular chemotherapy regimens or specific cancer types (Takeda, Jones, Loveman, Tan, & Clegg, 2007; Ward et al., 2007) or hormonal treatment (Annemans, 2008; Frederix, Severens, Hövels, Raaijmakers, & Schellens, 2012; John-Baptiste, Wu, Rochon,

Anderson, & Bell, 2013). Hence, no comprehensive systematic review and meta-analysis have been carried out of studies across all types of OACDs. This meta-analysis aimed to comprehensively estimate the cost-effectiveness of OACDs of all types to comprehend their financial influence on the healthcare system and the patients.

Materials and Methods

A systematic review and meta-analysis were performed to comprehensively estimate the costs of OACDs in different countries for all types of cancers. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines checklist for this study (Moher, Altman, Liberati, & Tetzlaff, 2011).
Literature search: The literature was searched systematically from PubMed, Cochrane, Embase, and Scopus. Moreover, Google Scholar, Google, and published abstracts were explored, and the relevant articles were selected for references to distinguish any disordered or non-authentic published literature. The key terms of the search strategy were oral anticancer drugs, Pharmacoeconomics cost-effectiveness, cost-utility, economic estimations, drug treatments, and cost analysis. The 'AND' Boolean operator was used to link major search areas, and the exact domain keywords were linked by applying the 'OR' Boolean operator. This search strategy was used for every database with specific filters, for example, English language, original and complete text, excluding some studies not involving oral anticancer drugs.
Eligibility criteria: Those studies included which were available in full text, in the English language, evaluated Pharmacoeconomics, cost-utility, and cost-effectiveness related to OACDs. Those studies that did not involve oral drugs and did not report the costs of OACD used were excluded. As this was a comprehensive review, studies with all types of cancers and OACDs were included. Figure 1 shows the selection process of studies according to PRISMA guidelines.
Data extraction: The data from these studies were extracted by two independent persons with the help of a guided data-gathering form. A total of 609,909 studies were identified through databases. Information about several variables was collected from studies relating to the characteristics of studies, such as the country where the study was carried out, type of cancer for which OACD is given, type of OACD used, methodology of costing, and elements of direct cost. Mainly, comprehensive economic information regarding the use of the methodology for estimation of costs and prices, such as unit cost, currency, rate of discount, etc., were evaluated. The International currencies were first transformed to USD rates for the subsequent year, then expanded to the financial year 2022. Risks of bias: All the incorporated studies were evaluated critically with the help of the Drummond Checklist, which is a questionnaire having 10 points score, and all the studies were scored against ten questions out of the 10 points that the National Institutes of Health proposed to evaluate the risk-of-bias in economic assessments (Drummond & Jefferson, 1996). All the studies were independently evaluated. The studies with ≤ 6.5 scores were thought to be of low quality, those with 6.51 to 7.5 scores were regarded as mild quality, and those with ≥ 8 scores were believed to be of superior quality as suggested by standards of Healthcare Research and Quality (Saxton et al., 2016).

Data Analysis

The quantitative data analysis was achieved with the help of Microsoft Excel (2016), and summary measures were determined, such as median, range, quartiles, outliers, and interquartile range. The Heterogeneity was predicted, and sensitivity evaluations were proposed and deduced consequently. It was assumed that the low-quality studies would miscalculate the utility costs due to failure to report the related causes of expenses. On the other hand, high-quality studies were expected to report costs and resources rigorously and thus generate detailed and coherent evaluations of utility costs.

Results

The systematic review included 13 studies for the quantitative analysis, which were selected as shown in Figure 1. Table 1 shows the characteristics of the selected studies which were: (Bussabawalai, Thiboonboon, & Teerawattananon, 2019; Carr, Carroll, Muszbek, & Gondek, 2010; Chen, Wang, Xu, & Feng, 2009; Contreras-Hernandez et al., 2008; Delea et al., 2012; Ebara, Ohno, & Nakano, 2013; Ghatnekar, Hjalte, & Taylor, 2010; Hoyle, Rogers, Moxham, Liu, & Stein, 2011; Le & Hay, 2009; Liao et al., 2021; Majer, Gelderblom, van den Hout, Gray, & Verheggen, 2013; Reed, Anstrom, Li, & Schulman, 2008; Shih, Xu, Liu, & Smieliauskas, 2017). It was found that 9 out of 13 included studies were about cost-effectiveness analysis, 1 study was about cost-

utility analysis, 1 study was about the rising prices of OACDs, and two studies were about pharmacoeconomic analysis and economic evaluations of the OACDs. Most of the included studies involved complete economic assessments in which the administration costs were only a part of the economic standard. The most frequently described types of cancer were gastrointestinal stromal tumors (4 studies) and Chronic Myeloid Leukaemia (4 studies).

Of these studies, significant studies were highly expected to generate complete cost estimations because the assortment of data frequently observed the style of micro-costing strategy, which could produce better internal authenticity, although it could decrease generalizability. It was analyzed that 5 out of 13 studies were from the US, two from the UK, and the other six were from different countries like China, Japan, Mexico, Thailand, Netherlands, and Sweden. It was found that the average cost for the OACDs was $80979/year for all the cancer types. Figure 2 shows the graph for the costs/ year of the included studies from different countries. It has been shown that a study by (Ghatnekar et al., 2010) represents the maximum cost for the OACD used from Sweden, which was $387325/year. The lowest cost for OACD was $32969 /year shown by (Majer et al., 2013) from the Netherlands. The average cost for OACDs across all the studies from countries was $80979/year. The median value among all the included studies was $132285, and the interquartile range was (Q3-Q1) 220393-50122= $170270. This significant difference in costs explains the importance of the country where the economic analysis was performed to determine the costs of OACDs.

Cost-effectiveness comparisons: A range of different OACDs were used in the included studies, but the mainly used OACDs were Imatinib, Dasatinib, and Lapatinib. 5 out of 13 studies used Imatinib as OACD in patients in patients with Chronic Myeloid Leukaemia and gastrointestinal tumors (Bussabawalai et al., 2019; Chen et al., 2009; Contreras-Hernandez et al., 2008; Majer et al., 2013; Reed et al., 2008). The treatment of cancer using Imatinib is somewhat bitter for the patients because of the cost, which has been increased from $US30,000/year to $US92,000, according to a study in 2013 (Leukemia, 2013). Two studies (Chen et al., 2009) and (Reed et al., 2008) found the costs of Imatinib in comparison with conventional therapy using interferon. Both studies testified that Imatinib was cost-effective. Both studies found incremental cost-effectiveness ratios, which proved to be cost-effective Imatinib for its cost per quality-adjusted life-year (QALY). Two studies (Contreras-Hernandez et al., 2008) and (Bussabawalai et al., 2019) found the cost of Imatinib in comparison with Sunitinib. Bussabawalai et al. found that treating patients with gastrointestinal tumors using Imatinib enhanced the health benefits. However, it was not satisfactory to meet the cost-effectiveness criteria compared to no adjuvant therapy. Contreras-Hernandez et al. found that Sunitinib was more cost-effective than Imatinib and palliative care because Sunitinib showed more survival benefits and progression-free months than Imatinib. A study by (Majer et al., 2013) compared the cost-effectiveness of Imatinib for three years vs. one-year therapy. It was found that treatment for three years was more cost-effective than one year because QALY was higher in the three years group and showed an incremental cost-effectiveness ratio per QALY achieved. Dasatinib was another OACD mainly used in the included studies. (Hoyle et al., 2011) assessed the cost-effectiveness of nilotinib and dasatinib compared with the high dose of Imatinib for treating chronic myeloid leukemia. It was found that both nilotinib and dasatinib were improbable to be cost-effective compared to Imatinib and interferon. (Ghatnekar et al., 2010) Compare the cost-effectiveness of dasatinib with high doses of Imatinib for treating myeloid leukemia. It was found from the results that dasatinib was cost-effective because its incremental cost-effectiveness ratio (ICER) was $US9,562/QALY. In brief, Imatinib was shown to be cost-effective as a primary treatment in contrast to interferon, which acts as a conventional immunotherapy. The most significant proof observes that dasatinib appeared to be cost-effective in patients resistant to Imatinib. Also, nilotinib was proven to be cost-effective in some studies. It has been shown that the cost-effectiveness of Imatinib was probably improved when it turned off the patent in 2015 (Smieliauskas, Chien, Shen, Geynisman, & Shih, 2014). A study by (Shih et al., 2017) estimated the rising prices of targeted OACDs and the financial burden related to them on Medicare Beneficiaries. It was found that the price index of OACDs was raised to 12% per year from 2007 to 2012. (Liao et al., 2021) performed the cost-effectiveness analysis for Ripretinib vs. placebo in patients with gastrointestinal stromal tumors. The ripretinib was not cost-effective because it produced an ICER of $244,010/QALY achieved for ripretinib compared to the placebo. A study by (Carr et al., 2010) performed the economic estimation for sorafenib in patients with hepatocellular carcinoma. It was a double-blind, randomized phase III trial in which outcomes for sorafenib were compared with placebo vs. hospital

supportive care. The results were found as incremental cost per life-years achieved, indicating that sorafenib was cost-effective compared to supportive care at hospitals. Lapatinib was also reported by two studies (Le & Hay, 2009) and (Delea et al., 2012) for patients with HER-2–positive breast cancer and capecitabine. It has been demonstrated from these existing studies about targeted OACDs for the medication of breast cancer that lapatinib and capecitabine together might not be cost-effective compared to capecitabine only for the customarily assumed thresholds, which are from $50,000 to $100,000/QALY. A study by (Ebara et al., 2013) determined the cost-effectiveness analysis of several targeted anticancer drugs. The findings suggested that some drugs were not cost-effective, with direct costs ranging from $9,060 to $18,833 per month, and some drugs were proved cost-effective because they were involved in increasing the overall survival among patients.

Generally, this literature review indicated that the most cost-effective drugs were Imatinib and Sunitinib for gastrointestinal tumors and dasatinib for Chronic Myeloid Leukemia. The striking differences in costs of OACDs across different countries, giving distinct outcomes, have impersonated challenges regarding cancer treatments.

Comparison among countries:
Considerable price differences were observed across different countries from these included studies, which suggests enormous discrepancies in the prices of OACDs around the world. The highest prices were observed in Sweden, and the lowest prices were observed in US and Mexico. While observing the prices alone in the US, different studies reported different prices of OACDs for different types of cancer. This study suggests that price variance might be a suitable strategy to guarantee international access and affordability for OACDs.

Risk of bias:
The risk of bias was assessed using the Drummond checklist, as shown in the figure, which shows the yes numbers from the checklist. The numbers of yes from 1 to 10 for each study decide the quality of the study. To assess the results of any published economic assessment, a checklist was developed by (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015) to recognize components they thought to determine an excellent economic estimation. Remarkably it is improbable that each analysis would fulfill every point from the checklist. Though this checklist gives a guide for the forms of questions a person ought to ask while examining these cost evaluations so that the strengths and limitations can be evaluated for any study and could build their particular judgment about the effectiveness and significance of the results for their analysis. The checklist questions are presented in (Charles & Edwards, 2016).

Discussion

The increased prices of innovative medications for cancer, involving targeted OACDs have caused immense challenges to the world in attaining access to high-quality and affordable medication and care for different types of cancer (Levit, Balogh, Nass, & Ganz, 2013; Shih et al., 2013). The increased prices for cancer medThe increased prices of innovative medications for cancer involving targeted OACDs have caused immense challenges to the world in attaining access to high-quality and affordable medication and care for different types of cancer (Levit, Balogh, Nass, & Ganz, 2013; Shih et al., 2013). The increased prices for cancer medications are a global concern. In this study, we analyzed the yearly costs of different OACDs used for different types of cancers in studies from different countries. A review of 13 studies determined the average administration cost of $80979/year globally and $156003/year in the US. Robust economic analyses are required to establish better healthcare for cancer because of recent cost restraints and increasing healthcare costs. In countries such as Australia and UK, the community payers do not offer considerations for targeted medications in various conditions for which officials have approved them.

In contrast, isolated treatment strategies use administered ways of care, for example, authorization or approval prior to treatment to bound approach to high-cost medicines (Cheema et al., 2012). The cost-effectiveness analysis provides knowledge about the cost of targeted OACDs required by sponsors to produce improved medication analysis and decisions (Smieliauskas et al., 2014). In this review, it was found that analysis of cost-effectiveness was presented by 9 of 13 OACDs. The drugs included in these studies were imatinib, sorafenib, sunitinib, lapatinib, Dasatinib, Nilotinib, and Ripretinib. These drugs were used for several types of cancer: Chronic Myeloid Leukaemia, gastrointestinal stromal tumors, metastatic breast cancer, and hepatocellular carcinoma. In most studies,

considered OACD treatment was compared with non-targeted OACD treatment.

In this review, it was confirmed that there were considerable differences in the costs of patented OACDs and their economic forms worldwide. The highest prices of OACDs were in Europe, though these OACDs are found to be more reasonable in some other high-income countries such as the UK, Mexico, and the US as compared to middle-income countries such as China and Netherlands. Even though previous analyses have exhibited cost variations across the globe (Goldstein et al., 2017; Kantarjian, Mathisen, & Lipton, 2015; Vogler & Vitry, 2016), this study was unique because it included cost variations across different countries comprehensively with substantial inconsistency in the capital. A transparent variance could be observed in the costs of OACDs which depends on that the prices were transformed from regional currency to USD. This difference could be due to different exchange rates. The difference in prices might also depend on the income of countries.

As economic estimations regarding health are comparatively limited to a particular care system of health, interpretation of the outcomes of any economic analysis for various care systems could be challenging (Ebara et al., 2013). This study found dasatinib to be more cost-effective than imatinib, but these results were opposite to the study (Pavey et al., 2012). There was nono uniformity regarding the costs, prices, and cost-effectiveness among the included studies. This review has comprehensively identified the gaps in the literature regarding the costs and prices of OACDs and recommends future research on OACDs, irrespective of the drug used or the underlying type of cancer. Unlike earlier studies, it is imperative to see that this study was not meant to produce proof or recommend a drug depending on its cost or cost-effectiveness for a specific cancer type; instead, its objective was to compare the prices of different OACDs worldwide, providing QALY. A study by Shen et al. reviewed the economic estimations of targeted oral chemotherapies only aiming at cost impact evaluations (Shen et al., 2014).

Similarly, two studies involved analysis of economic estimation approaches; however, they concentrated on only a single type of cancer which was advanced colorectal cancer, and only incorporated the “cost-effectiveness” assessments (Krol, Koopman, Uyl-de Groot, & Punt, 2007; Leung, Chan, Leung, & Lu, 2013). According to a study, the prices for cancer drugs are not limited to symptoms which are only influenced by pricing strategies. There have also been increases in prices for several non-patented drugs for cancer, ensuing company alterations; however, they are now alleviating. The substantial price decrease in some countries indicates that health organizations must promote everyday cancer drug use.

In chronic diseases like cancer, QALY is most important in evaluating the outcomes in pharmacoeconomics analysis. Most of the included studies assessed the outcomes using QALY (Bussabawalai et al., 2019; Chen et al., 2009; Ghatnekar et al., 2010; Hoyle et al., 2011; Le & Hay, 2009; Liao et al., 2021; Majer et al., 2013; Reed et al., 2008). However, the estimations of QALY are established upon the preferences or benefits, so none of the included studies reported data about the quality of life. Because of all the differences in the methodology of included studies, the whole conclusion of the studies involving cost-effectiveness was not consistent.

Some studies used dasatinib or nilotinib in patients with imatinib intolerance. It was analyzed that nilotinib and dasatinib, compared to interferon-α, had high ICERs. The reason for this was that although significant, the predicted QALY, even though considerable, was inadequate to compensate for highly high anticipated prices of OACDs. It was also seen that dasatinib was much more costly per person per day than interferon-α, and they are expected to take far longer. According to a study by (Pavey et al., 2012), nilotinib and dasatinib had substantial benefits compared to imatinib; however, dasatinib was not cost-effective. From this review, the included study by (Ghatnekar et al., 2010) had more advantages versus imatinib and had more cost-effectiveness. It was hard to evaluate the amount to which these OACDs generate better responses because of the inadequate data that could influence the long-term results.

Although this study reviewed the costs of OACDs comprehensively, significant gaps in knowledge about cost-effectiveness remain, which are needed to be addressed in the future. Some of the approved OACDs had no valid cost-effectiveness analysis. Some OACDs are approved for many types of cancer, like imatinib approved for chronic eosinophilic leukemia, Myeloid Leukaemia, lymphoblastic leukemia, and systemic mastocytosis (Piccaluga et al., 2007). So, a cost-effectiveness analysis for drugs like imatinib used for such conditions must be performed. The greatest challenge for a study evaluating pharmacoeconomics is to produce assumptions because of a massive difference in costs or medical procedures among countries

using OACDs. Usually, the average price of patented medicines in industrialized countries is 19 to 45% lower than in the US (Danzon & Furukawa, 2008). However, from this study, the results were inconsistent regarding prices and cost-effectiveness of the OACDs across different countries.

ications are a global concern. In this study we analyzed yearly costs of different OACDs used for different types of cancers in studies from diffarnt countries. Review of 13 studies determined the average administration cost of 80979$/year globally, and 156003$/year in the US. Strong economic analyses are required for the establishment of better healthcare for cancer because of recent costing restraints and increasing costsof healthcare. In countries such as Australia and UK, the community payers do not offer considerations for targeted medications in various of the conditions for which officials have approved them whereas isolated treatment strategies use administered ways of care for example authorization or approval prior to treatment to bound approach to high-cost medicines (Cheema et al., 2012). The analysis of cost-effectiveness gives knowledge about the cost of targeted OACDs required by sponsors to produce improved analysis and decisions for medications (Smieliauskas et al., 2014). In this review, it was found that analysis of cost-effectiveness was presented by 9 of 13 OACDs. The drugs included in these studies were imatinib, sorafenib, sunitinib, lapatinib, Dasatinib, Nilotinib and Ripretinib. These drugs were used for several types of cancer: Chronic Myeloid Leukaemia, gastrointestinal stromal tumours, metastatic breast cancer and hepatocellular carcinoma. In most of the studies, considered OACDs treatment were compared with non-targeted OACD treatment.

In this review it had been confirmed that there were considerable differences in costs of patented OACDs and their economic forms and all around the world. The highest prices of OACDs were in the Europe, though these OACDs are found to be more reasonable in some other high-income countries sucha as UK, Mexico and US as compared to middle-income countries such as China and Netherlands. Even though previous analyses have exhibited cost variations across the globe (Goldstein et al., 2017; Kantarjian, Mathisen, & Lipton, 2015; Vogler & Vitry, 2016), this study was unique because it included cost variations across different countries comprehensively with substantial inconsistency in capital. A clear variance could be observed in costs of OACDs which depends on that the prices were transformed from regional currency to USD. This difference could be due to different exchange rates. The difference in prices might also depend on income of countries.

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Although, this study reviewed costs of OACDs comprehensively, significant gaps in knowledge about cost-effectiveness still remains which are needed to be addressed in future. Some of the approved OACDs had no valid cost-effectiveness analysis. As some of the OACDs are approved by many types of cancer like imatinib approved for chronic eosinophilic leukemia, Myeloid Leukaemia, lymphoblastic leukemia and systemic mastocytosis (Piccaluga et al., 2007). So, analysis of cost-effectiveness for the drugs like imatinib used for such conditions are needed to be performed. The greatest challenge for a study evaluating pharmacoeconomics is to produce assumption because of a huge difference in costs or medical procedures among countries using OACDs. Normally the average prices of patented medicines in industrialized countries is 19 to 45% lower than prices in US (Danzon & Furukawa, 2008) but from this study, the results were inconsistent regarding prices and cost-effectiveness of the OACDs across different countries.

Conclusion

The OACDs are novel therapeutic interventions used in oncology. But the increased costs of these OACDs require careful evaluation of the cost-effectiveness of these OACDs. The analysis of data from included studies showed that the average administration costs of OACDs across different countries used for several types of cancer were approximately $80979/year, which was highly varied across different countries. Substantial gaps in the literature were present, including a lack of analysis of cost-effectiveness in various studies. The elevated prices of approved OACDs and their quick dispersion and constant fast development of more targeted OACDs suggest that more cost-effectiveness analyses are required shortly for more OACDs used for different types of cancer.

Ethical Considerations

All ethical considerations were taken into account.

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Conflict of interest

The authors report no conflict of interest relevant to the subject of this article.

Tables

Table 1. Drummond Checklist for Methodological Quality Assessment1

	Questions												
	Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Points**	**Quality**
1	(Shih et al., 2017)	Y	N	N	N	Y	Y	Y	N	N	UN	4.5	low
2	(Reed et al., 2008)	Y	Y	Y	N	N	Y	Y	Y	Y	N	7	Mild
3	(Chen et al., 2009)	Y	Y	Y	Y	Y	Y	Y	N	Y	UN	8.5	High
4	(Hoyle et al., 2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UN	9.5	High
5	(Ghatnekar et al., 2010)	Y	Y	Y	Y	N	N	Y	Y	N	N	6	low
6	(Bussabawalai et al., 2019)	Y	Y	N	N	Y	Y	N	Y	N	UN	5.5	Low
7	(Liao et al., 2021)	Y	N	Y	Y	Y	N	Y	N	Y	UN	6.5	Mild
8	(Majer et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	8	High
9	(Contreras-Hernandez et al., 2008)	Y	Y	N	Y	Y	Y	Y	N	Y	UN	7.5	Mild
10	(Carr et al., 2010)	Y	Y	Y	Y	N	Y	N	Y	Y	N	7	Mild
11	(Le & Hay, 2009)	Y	Y	Y	Y	Y	N	Y	Y	Y	UN	8.5	High
12	(Ebara et al., 2013)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9	High
13	(Delea et al., 2012)	Y	Y	Y	N	Y	Y	N	Y	Y	N	7	Mild

Table 2. characteristics of included studies

No.	Study	Country	Cancer type	OACDs type	Cost	Control vs test	Study details	Targeted population
1	(Shih et al., 2017)	US	Lungs, kidney, and myeloma	Targeted OACDs	$7,719 per patient monthly	$4,427 vs $7,719	Increased costs (2007 vs 2012)	Males and females
2	(Reed et al., 2008)	US	Chronic Myeloid Leukaemia	imatinib vs interferon	609,587 quality-adjusted life-year	$609,587 vs. $220,419	Imatinib vs interferon	
3	(Chen et al., 2009)	China	Chronic Myeloid Leukemia	imatinib vs interferon	$132,285 quality-adjusted life-year	$20,945 vs $20,600	Incremental cost	
4	(Hoyle et al., 2011)	UK	Chronic Myeloid Leukemia	Dasatinib vs Nilotinib	$143,294/ quality-adjusted life-year	$137143.39 vs $108195.26	Dasatinib vs interferon	
5	(Ghatnekar et al., 2010)	Sweden	Chronic Myeloid Leukemia	Dasatinib vs imatinib	$9,016.23/ QALY	$387325.77 vs $382411.36	Dasatinib vs imatinib	
6	(Bussabawalai et al., 2019)	Thailand	gastrointestinal stromal tumour	Imatinib vs sunitinib	$77970.35/ QALY	$49288.56 and $77970.35	Imatinib and followed by sunitinib	

No.	Study	Country	Cancer type	OACDs type	Cost	Control vs test	Study details	Targeted population
7	(Liao et al., 2021)	US	Gastrointestinal Stromal Tumors.	Ripretinib vs placebo	$244,010/ QALY		Incremental cost-effectiveness	
8	(Majer et al., 2013)	Netherlands	gastrointestinal stromal tumour	Imatinib 3year vs 1 year	$32969.28/ QALY	$82369.12 vs $30482.68	incremental cost-effectiveness/ QALY	
9	(Contreras-Hernandez et al., 2008)	Mexico	advanced gastrointestinal stromal tumours	imatinib or sunitinib vs palliative care		$35 225.61 or $17 805.87 vs $2071.86	cost-effective sunitinib regarding life-years gained	
10	(Carr et al., 2010)	US	hepatocellular carcinoma	Sorafenib VS supportive care	$US62473/ life-year gained	$40639 vs $7804	cost-effective sorafenib regarding life-years gained	
11	(Le & Hay, 2009)	US	HER-2–positive breast cancer	lapatinib	$166,113/ QALY		Lapatinib + capecitabine vs capecitabine alone	females
12	(Ebara et al., 2013)	Japan	Various cancer types	molecular-targeting cancer drugs	Direct costs: $9,060	$4,708 and $3,922-$18,833	Bevacizumab and sorafenib	
13	(Delea et al., 2012)	UK	HER2+ metastatic breast cancer	lapatinib plus capecitabine	$37772.39 for lapatinib + capecitabine	$18331.72 for capecitabine and $37913.96 for capecitabine and trustuzumab	lapatinib plus capecitabine is dominant over capecitabine plus trastuzumab	

Figures

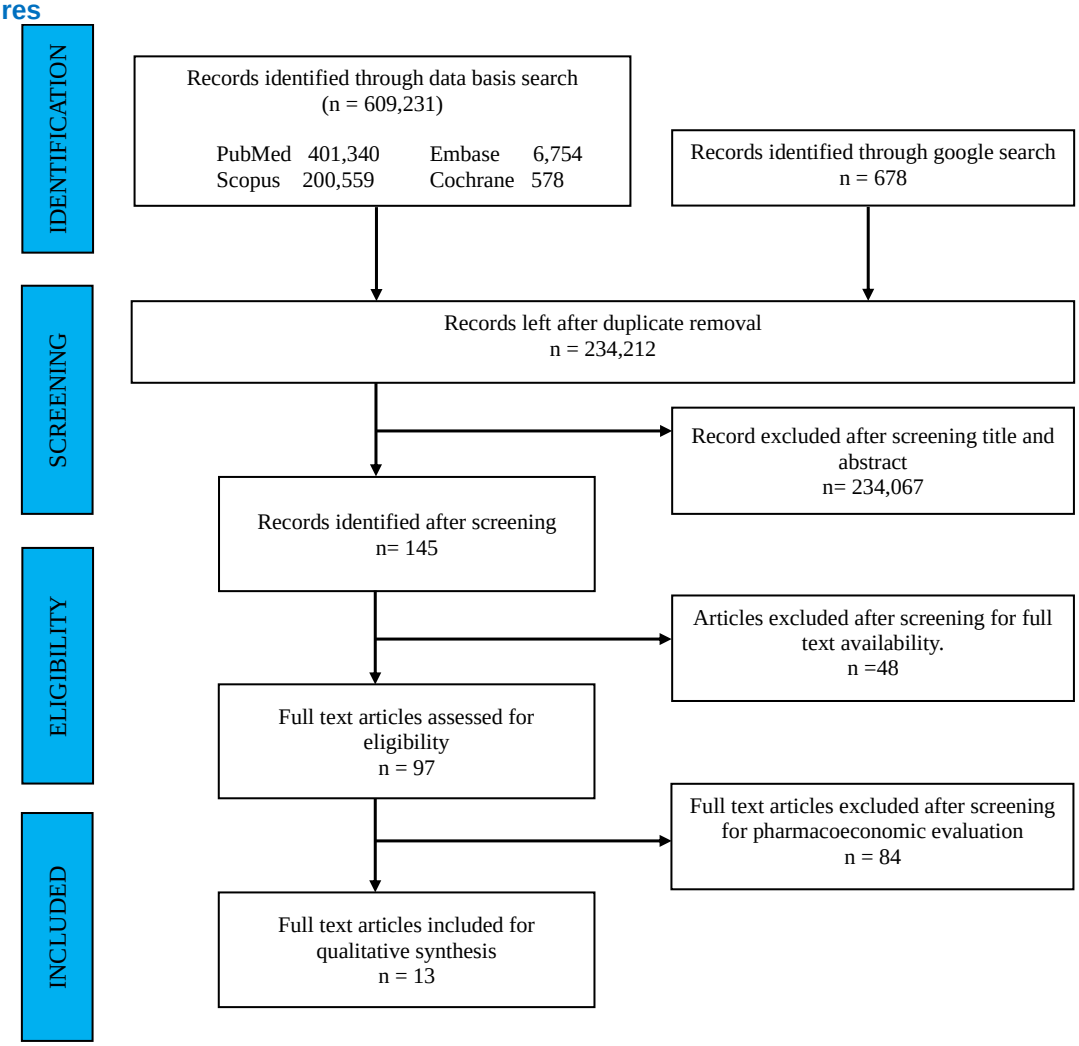

Figure 1. Selection process of studies

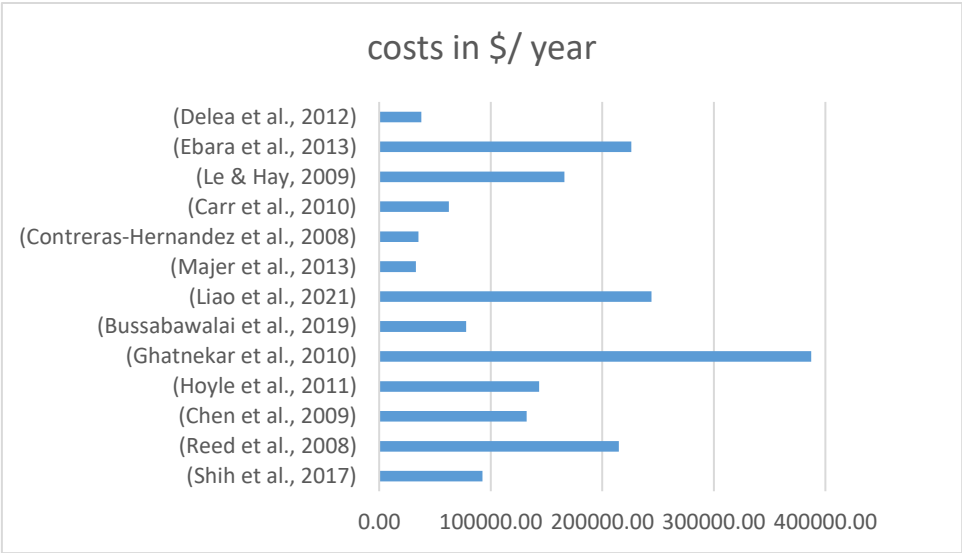

Figure 2. Graph showing costs of OACD in different studies

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