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Comparative analysis of the treatment costs of cisplatin-paclitaxel and cisplatin-gemcitabine in patients with advanced nsclc: a narrative review

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ABSTRACT

Platinum-based chemotherapy is the first-line treatment for patients with advanced NSCLC. Cancer treatment is known to be time-consuming and expensive, resulting in numerous studies evaluating the costs of commonly used chemotherapy regimens. This narrative review aims to analyze and compare two of the most widely used regimens, cisplatin-paclitaxel and cisplatin-gemcitabine, in terms of costs and clinical outcomes. Articles were searched through various databases, including PubMed, Science Direct, the Cochrane Library, Scopus, and Google Scholar, used a combination of keywords ("cisplatin-paclitaxel" OR "cisplatin-gemcitabine") AND "advanced NSCLC" AND "cost", with a publication timeframe from 2000 to the most recent year of the search. Articles were reviewed based on topic relevance and content suitability. Articles were selected based on topic relevance and compliance with the inclusion criteria, then data related to treatment costs were extracted and compared descriptively. Six of the seven selected articles showed that the cisplatin-gemcitabine regimen resulted in lower total therapy costs than cisplatin-paclitaxel. Although the clinical outcomes produced by both regimens were generally comparable, cisplatin-gemcitabine tended to have slightly higher efficacy, but not significantly different. These findings suggest that cisplatin-gemcitabine may be a more cost-effective alternative in the treatment of patients with advanced NSCLC. The results of this review can be used as supporting data for consideration in selecting chemotherapy regimens for patients with advanced NSCLC.

ABSTRAK

Kemoterapi berbasis platinum menjadi pengobatan lini pertama bagi pasien NSCLC stadium lanjut. Pengobatan kanker diketahui memakan waktu dan biaya, sehingga banyak penelitian dilakukan dengan topik evaluasi biaya dari regimen kemoterapi yang banyak digunakan. Tinjauan naratif ini bertujuan untuk menganalisis dan membandingkan dua regimen yang paling banyak digunakan, yakni cisplatin-paclitaxel dan cisplatin-gemcitabine dari segi biaya yang dikeluarkan dan luaran klinis. Proses penelusuran artikel dilakukan melalui berbagai pangkalan data, yaitu PubMed, Science Direct, Cochrane Library, Scopus, dan Google Scholar dengan menggunakan kombinasi kata kunci ("cisplatin-paclitaxel" OR "cisplatin-gemcitabine") AND "advanced NSCLC" AND "cost", dengan rentang waktu publikasi dari tahun 2000 hingga tahun terakhir pencarian. Artikel diseleksi berdasarkan relevansi topik dan kesesuaian dengan kriteria inklusi, kemudian data terkait biaya pengobatan diekstraksi dan dibandingkan secara deskriptif. Enam dari tujuh artikel terpilih menunjukkan bahwa regimen cisplatin-gemcitabine menghasilkan total biaya terapi yang lebih rendah dibandingkan cisplatin-paclitaxel. Meskipun luaran klinis yang dihasilkan oleh kedua regimen umumnya sebanding, cisplatin-gemcitabine cenderung memiliki efektivitas yang sedikit lebih tinggi, tetapi tidak berbeda secara signifikan. Temuan ini menunjukkan bahwa cisplatin-gemcitabine dapat menjadi alternatif yang lebih *cost-effective* dalam pengobatan pasien NSCLC stadium lanjut. Hasil *review* ini dapat menjadi data penunjang sebagai pertimbangan dalam pemilihan regimen kemoterapi pada pasien NSCLC stadium lanjut.

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INTRODUCTION

In 2022, the WHO's Global Cancer Observatory (GLOBOCAN) reported that the number of new cancer cases in Indonesia reached 408,661, with 242,988 deaths. Lung cancer ranks second in incidence and is one of the main causes of cancer death in the world, and also in Indonesia. Lung cancer contributes significantly to the cancer death rate in Indonesia, reaching 34,339 (14.1%) cases.[1] Lung cancer consists of two main types, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell lung cancer (NSCLC) occurs in 80% of lung cancer cases, and most patients experience advanced stages and metastasis.[2] The recommended first-line chemotherapy regimen for NSCLC therapy is platinum-based chemotherapy, such as cisplatin or carboplatin, combined with paclitaxel, gemcitabine, docetaxel, pemetrexed (for adenocarcinoma only), and vinorelbine.[3]

Platinum-based chemotherapy is recommended as first-line treatment and is known to increase response rates by approximately 20–40% and prolong overall survival by 7–12 months.[4] There is no significant difference in response rates and survival between the four platinum-based chemotherapy regimens for advanced NSCLC, but carboplatin-paclitaxel has lower toxicity, while cisplatin-gemcitabine prolongs disease progression time but with higher renal toxicity.[5]

Indonesian Health Insurance Agency (BPJS Kesehatan) expenditures for cancer treatment continue to increase annually and currently represent the second largest cost burden after heart disease.[6] Although numerous studies have evaluated the effectiveness and costs of chemotherapy regimens in patients with advanced NSCLC, most of these studies were conducted in isolation or within the context of specific healthcare systems, making their results inconclusive and not directly applicable to other populations. Furthermore, few reviews have comprehensively compared the costs and clinical outcomes of cisplatin-paclitaxel and cisplatin-gemcitabine regimens. Differences in healthcare financing systems, including within the context of the National Health Insurance (JKN) in Indonesia, make this cost-comparative analysis crucial for efficient therapeutic decision-making. Therefore, this study was conducted to analyze and compare these two regimens in terms of costs and clinical outcomes.

MATERIALS AND METHODS

This article used a narrative review study design, where the analysis was conducted narratively by comparing study results related to treatment costs. The article selection process was conducted by two independent reviewers who separately screened the titles, abstracts, and full texts of articles based on established inclusion and exclusion criteria. Differences of opinion are resolved through discussion until agreement is reached, or by involving a third reviewer. Each reviewer was responsible for identifying, selecting, and evaluating the suitability of articles for inclusion in the analysis.

Article searches were conducted

through PubMed, Science Direct, Cochrane Library, Scopus, and Google Scholar databases, with publication dates ranging from 2000 to the last year of the search. The search strategy used a combination of keywords ("cisplatin-paclitaxel" OR "cisplatin-gemcitabine") AND "advanced NSCLC" AND "cost" in each database.

Inclusion criteria for the article search included: 1). Health economic studies comparing costs between cisplatin-paclitaxel and cisplatin-gemcitabine regimens. 2). Cost analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-minimization analysis (CMA) studies. 3). Clinical studies (RCTs and observational studies) that explicitly included cost data or analysis. 3). Adult patients (≥18 years) diagnosed with advanced NSCLC (stage IIIB or IV).

Articles not available in English and focusing solely on clinical effectiveness or side effects were excluded. Submitted articles were then screened based on title duplication, relevance of title to keywords, inclusion criteria, and concordance of content.

RESULTS

Article selection

The initial results of the article search obtained 729 articles, consisting of 404 articles from Science Direct, 322 articles from Google Scholar, 1 article from PubMed, 1 article from the Cochrane Library, and 1 article from Scopus. The distribution of articles obtained from each database showed a limited number, particularly in PubMed and Scopus. This was likely due to the use of quite specific inclusion criteria and the study's focus on comparing two specific regimens, resulting in a limited number of articles meeting the criteria. After a selection process based on title duplication, 688 articles were obtained. Next, a selection was carried out based on the relevance of keywords in the article titles, resulting in 34 articles. After re-selection based on the inclusion criteria and reading the entire contents of the articles, 7 relevant articles were obtained. These seven articles were used to discuss the cost comparison of cisplatin-paclitaxel and cisplatin-gemcitabine therapy in patients with advanced stage Non-Small Cell Lung Cancer (NSCLC) (IIIB and IV) which can then be the basis for selecting the most effective and efficient therapy. The stages of the search, selection, and results of the article search are presented in a flowchart (FIGURE 1).

Characteristics of articles

This narrative review included seven articles comparing the treatment costs of cisplatin-paclitaxel and cisplatin-gemcitabine regimens in patients with advanced NSCLC. These articles included one randomized clinical trial (RCT), one observational study, four cost-minimization analyses, and one cost-effectiveness analysis. Each article reported several chemotherapy regimens administered to patients with advanced NSCLC, including cisplatin-paclitaxel and cisplatin-gemcitabine. The cost components analyzed are not limited to chemotherapy costs, but also include various other treatment costs (TABLE 1).

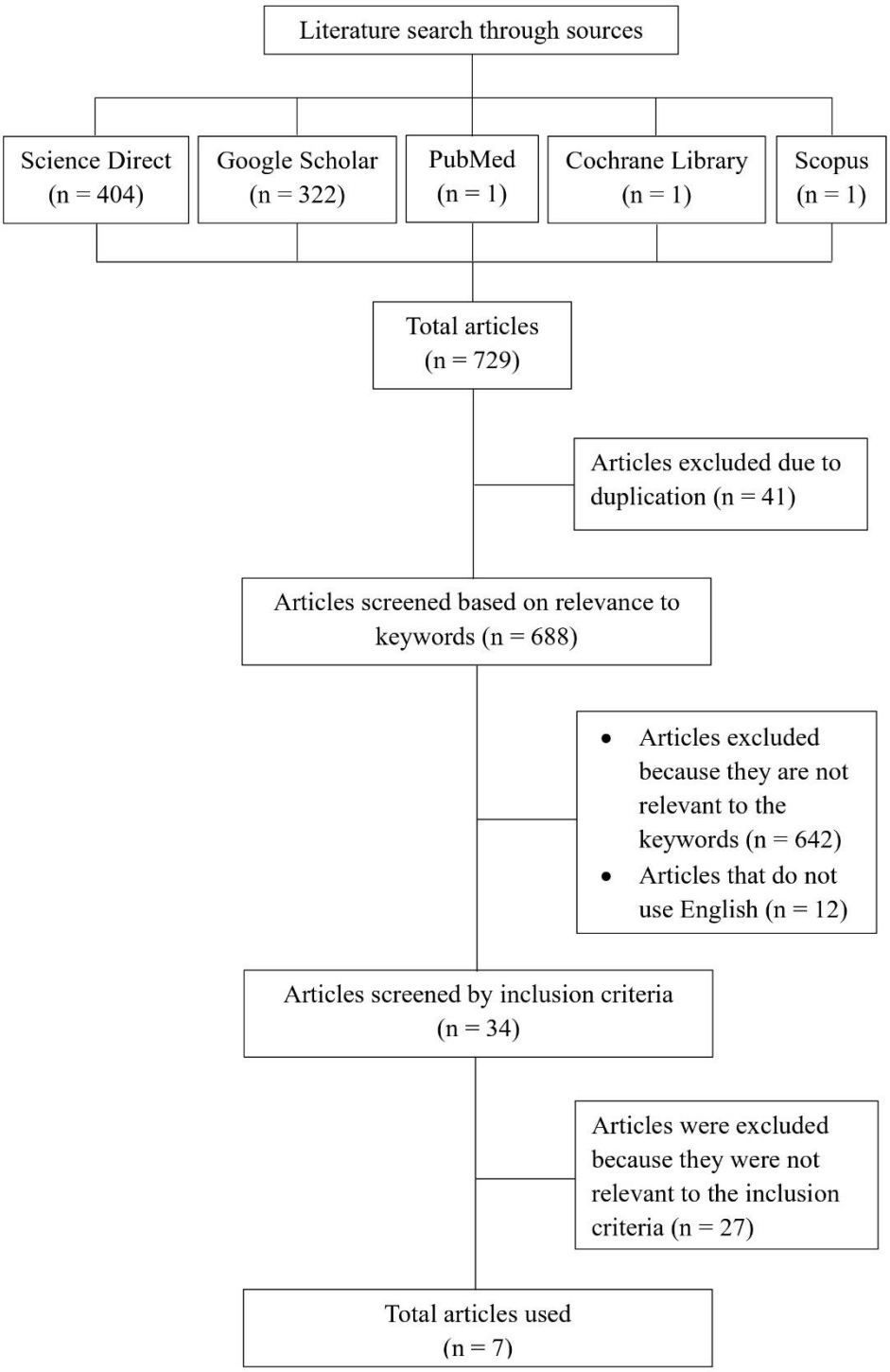

FIGURE 1. Article Selection Process

TABLE 1. Study Characteristics

Author	Types of Study	Research Location	Regimen	Cost Breakdown
Yildirim *et al.*,[7]	Retrospective observational	Türkiye	Cisplatin-gemcitabine Cisplatin-paclitaxel Cisplatin-docetaxel	Chemotherapy costs
Launois *et al.*,[8]	Cost minimization analysis with Markov model	France	Gemcitabine-cisplatin Vinorelbine-cisplatin Docetaxel-cisplatin Paclitaxel-cisplatin Paclitaxel-carboplatin	Chemotherapy costs Administration costs Transportation costs Costs for severe side effects Initial diagnosis costs Palliative care costs.
Pimentel *et al.*,[9]	Cost minimization analysis using the approach of two randomized phase III trials	Portugal	Gemcitabine-Cisplatin Vinorelbine-Cisplatin Paclitaxel-Cisplatin Gemcitabine-Cisplatin Docetaxel-Cisplatin Paclitaxel-Carboplatin	Chemotherapy costs Administration costs Hospitalization costs due to side effects Other medical costs (outpatient care, radiotherapy, transfusions, other medications).
Neymark *et al.*,[10]	Cost-effectiveness analysis based on clinical trial data	Netherlands	Cisplatin-paclitaxel Cisplatin-gemcitabine Paclitaxel-gemcitabine	Inpatient costs Outpatient costs Consultation costs Blood transfusion costs Supportive medication costs (premedication) Therapy costs (chemotherapy, radiotherapy, surgery)
Schiller *et al.*,[11]	Cost minimization analysis using the approach of two randomized phase III trials	France, Germany, Italy, Spain, dan England	Gemcitabine-vincristine Vincristine-cisplatin Vincristine-gemcitabine-cisplatin Paclitaxel-carboplatin Gemcitabine-cisplatin Paclitaxel-cisplatin Docetaxel-cisplatin	Chemotherapy costs Administration costs Hospitalization costs due to side effects Other costs
Smit *et al.*,[12]	Randomized controlled trial	Netherlands	Paclitaxel-cisplatin Gemcitabine-cisplatin Paclitaxel-gemcitabine	Inpatient costs Outpatient costs Administrative costs Chemotherapy costs Consultation costs Cytotoxic drug costs Transfusion costs Second-line therapy costs.
Lees *et al.*,[13]	Cost minimization and effectiveness analysis based on clinical trial data	England and Wales	Gemcitabine (monotherapy) Supportive therapy Cisplatin-gemcitabine Cisplatin-etoposide Platinum-taxanes	Chemotherapy costs Chemotherapy administration costs Hospitalization costs Palliative care costs Additional therapy costs (radiotherapy, surgery, transfusion) Healthcare provider visits costs Other medication costs

TABLE 2. Cost Comparison of Cisplatin-Paclitaxel and Cisplatin-Gemcitabine

Author	Service Perspective	Cisplatin-Paclitaxel Cost	Cisplatin-Gemcitabine Cost	Unit Cost	Type of Cost
Yildirim *et al.*[7]	Not mentioned	2.905,92 TL	3.246,66 TL	TRY/cycle	Chemotherapy costs
Launois *et al.*[8]	French health care system in 2004	€9.043	€8.103	EUR/cycle	Total costs of full hospitalization
Pimentel *et al.*,[9]	Portugal's health care system in 2003	€8.800	€7.083	EUR/cycle	Total costs
Neymark *et al.*,[10]	Dutch health insurance system in 2002	€5.214	€4.449	EUR/cycle	Total costs
Schiller *et al.*,[11]	National health services of each of the five European countries	€9.166,60	€7.099,40	EUR/cycle	Average therapy costs from five countries
Smit *et al.*,[12]	Dutch health insurance system in 2002	€16.067	€14.009	EUR/cycle	Average total costs per patient
Lees *et al.*,[13]	UK health service in 2000	£9.043	£5.537	GBP/cycle	Total therapy costs

DISCUSSION

Cost comparison of cisplatin-paclitaxel and cisplatin-gemcitabine regimens

The seven articles analyzed in this review largely demonstrated that the cisplatin-gemcitabine regimen resulted in lower treatment costs compared to cisplatin-paclitaxel (TABLE 2). A study by Launois *et al.*,[8] conducted in France confirmed that the cisplatin-gemcitabine regimen with a three-week dosing schedule was the most cost-effective compared to other combinations. This is because the regimen can be administered flexibly outside the hospital, thereby reducing outpatient and transportation costs. Other regimens, such as cisplatin-vinorelbine, are also quite cost-effective when administered partially at home, but remain more expensive than cisplatin-gemcitabine. Meanwhile, taxane-based combinations are more expensive because they can only be administered in the hospital and tend to cause severe side effects that require additional treatment. The cisplatin-paclitaxel regimen cost €9,043, higher than the €8,103 cost of cisplatin-gemcitabine.[7]

Research by Pimentel *et al.*,[9] showed comparable results, namely cisplatin-gemcitabine provided an average cost savings per patient of €326 compared to cisplatin-docetaxel, €1,201 compared to cisplatin-vincristine, €1,717 compared to cisplatin-paclitaxel, and €2,925 compared to carboplatin-paclitaxel. This study suspected that varying toxicity profiles could cause differences in hospitalization costs for each regimen. Cisplatin-gemcitabine is known to have a higher number of hospitalizations due to toxicity, but it is still chosen as a cost-effective treatment.[9]

Neymark *et al.*,[10] conducted a cost-effectiveness analysis of three regimens and found that cisplatin-gemcitabine was potentially more cost-effective than cisplatin-paclitaxel, with a cost difference of €765. Meanwhile, other regimens such as paclitaxel-gemcitabine were much more expensive and less effective than cisplatin-paclitaxel.[9] A study by Schiller *et al.*,[11] also showed similar results, where cisplatin-gemcitabine was the most cost-

effective regimen compared to other paclitaxel-containing regimens in most countries, especially when administered as an outpatient. These lower costs were primarily due to the lower drug price and lower frequency of administration.[11]

A study conducted by Lees *et al.*[13] compared gemcitabine both as monotherapy and in combination with cisplatin. Although the costs of gemcitabine monotherapy were higher than best supportive care (BSC), the cisplatin-gemcitabine regimen remained more cost-effective than taxane-based regimens. In a randomized controlled trial, cost was also a consideration in therapy selection. The treatment costs and total hospitalization costs incurred using the cisplatin-gemcitabine regimen (£5,537) were significantly lower compared to other regimens, particularly cisplatin-paclitaxel (£9,043).[11]

Research by Yildirim *et al.*,[7] in Turkiye showed results that were inversely proportional to previous studies. The treatment cost for 3 cycles of therapy with gemcitabine-cisplatin on an average body surface area was 3,246.66 TL. The cost of the paclitaxel-cisplatin combination was 2,905.92 TL, while the cost of the docetaxel-cisplatin combination was 3,885.12 TL. Therefore, in terms of cost, the taxane combination was the cheapest compared to cisplatin-gemcitabine. This is likely because this study only analyzed the cost of chemotherapy without considering the costs of other treatments, resulting in the higher cost of the cisplatin-gemcitabine regimen.[12]

The cost differences between cisplatin-gemcitabine and cisplatin-paclitaxel regimens found in most studies may be influenced by various factors. Cisplatin-gemcitabine generally has different dosing patterns and potential side effects that may influence the need for additional treatment, thus impacting the total cost of therapy. Furthermore, variations in results between studies may also be influenced by differences in cost analysis methods, calculated cost components, and the context of the healthcare system in each country. Contextual factors such as drug pricing policies, health insurance systems, and local clinical practices also play a significant role in determining the total cost of therapy, so interpretation of the results cannot be separated from the context of each country.

The currency variations used in the analyzed studies were not standardized to a single currency. This is because the focus of this review was to compare the relative costs of two regimens in each study context, rather than to conduct cross-country cost comparisons. Therefore, interpretation of the results was based on differences in healthcare financing systems and cost structures across studies.

Clinical effectiveness in the context of cost analysis

The clinical efficacy of cisplatin-paclitaxel and cisplatin-gemcitabine regimens in the treatment of advanced NSCLC was a consideration in selecting a pharmacoeconomic study design, specifically a cost-minimization analysis, in several studies reviewed in this article. Most articles assessed that both regimens had comparable clinical outcomes, so the comparison focused on cost-efficiency.

In a study conducted by Schiller *et al.*,[11] the disease progression time resulting from the use of cisplatin-gemcitabine was longer, namely 4.2 months compared to cisplatin-paclitaxel which was only 3.4 months. Meanwhile, a study by Smit *et al.*,[12] reported that the overall survival (OS) values of the two regimens were not significantly different, namely 8.9 months in the cisplatin-gemcitabine regimen and 8.1 months in the cisplatin-paclitaxel regimen. Although the resulting difference was not very significant, this still places cisplatin-gemcitabine as a more effective therapeutic option.

The results of the study by Yildirim *et al.*,[7] differed slightly from the two

previous studies, namely the median OS values of the two regimens were quite different. The taxane-based group, namely cisplatin-docetaxel and cisplatin-paclitaxel, had a higher median OS value of 14 months, while the cisplatin-gemcitabine regimen only reached 8.1 months. However, the incidence of side effects caused by the taxane group was higher than that of cisplatin-gemcitabine, making this regimen superior in terms of safety. Other clinical outcomes such as median survival and response to therapy were also examined in several studies reviewed in this article. Neymark *et al.*[10] reported that cisplatin-gemcitabine provided a slightly higher survival (0.98 years) compared to cisplatin-paclitaxel (0.94 years). Meanwhile, the response to therapy given cisplatin-gemcitabine (21%) was equivalent to cisplatin-paclitaxel (21.3%).[10]

Although there were small differences in clinical outcomes between the two regimens, cisplatin-gemcitabine produced slightly better clinical outcomes than cisplatin-paclitaxel. Therefore, both regimens are considered to be comparable in effectiveness, requiring consideration of other aspects such as cost, safety, and individual patient characteristics when selecting therapy.

Implications for the health system in indonesia

Seven articles in this review showed that the combination of cisplatin-paclitaxel and cisplatin-gemcitabine produced comparable clinical outcomes, while the costs were inversely related. Not all studies yielded consistent results, likely due to variability in patient characteristics and healthcare systems in each country. Therefore, these results may not be relevant to the Indonesian patient population.

Response to chemotherapy is influenced by genetic factors, so each individual can respond differently to the same treatment. Because genetic variation is strongly influenced by ethnic background, the response of Indonesian patients to chemotherapy may differ from that of patients from other countries. Several studies have shown that genetic variations that influence the effectiveness of chemotherapy abroad do not have the same effect on Indonesian patients. This is likely due to the genetic diversity of the Indonesian population, so it is important to conduct research in local populations to determine differences in effectiveness.[14]

The accuracy of therapy selection affects the treatment costs borne by both patients and the government through the National Health Insurance (JKN). If therapy is inappropriate, treatment costs can increase, and public trust in health services can decrease.[15] In the JKN system, therapies that can provide equivalent or better clinical outcomes but at a lower cost can be an option to provide more patients with access to treatment. Furthermore, therapy decisions are also influenced by the national e-catalog and hospital formulary, which can sometimes limit choices if the drug is not regularly available. Based on the results of a review of several articles, cisplatin-gemcitabine is more flexible in its administration because it can be given as an outpatient or even with home care services, depending on local systems and policies.

The findings of this review suggest that cisplatin-gemcitabine may be a more economically viable therapeutic option than cisplatin-paclitaxel. These results can be used in clinical decision-making, particularly in healthcare financing systems like the National Health Insurance (JKN) in Indonesia. However, the choice of therapy must still consider other factors such as drug availability, the patient's clinical condition, potential side effects, and local healthcare system policies.

STRENGTH AND LIMITATION

The main strength of this study

lies in its comprehensive approach to evaluating two chemotherapy regimens through the integration of pharmacoeconomic aspects and clinical outcomes from various study types. The use of multiple databases increased the scope of the analyzed literature, while the focus on regimens commonly used in clinical practice provided high relevance for the application of the study results. Furthermore, the findings of this review have the potential to contribute to supporting cost-effectiveness-based decision-making in healthcare systems.

This narrative review has several limitations. It is not a systematic review, so the article selection process did not follow the PRISMA-based selection process, and potential selection bias is unavoidable. The cost data reported in each article originates from various countries with different healthcare systems and financing, so direct generalization of the results to the Indonesian system will be limited and require adjustment. The articles included in this review are limited to older publication years because more recent studies have focused on targeted therapy and immunotherapy. Differences in currency, publication year, and calculated cost components may also affect the comparability of the results. The clinical outcomes studied in each article are not completely identical, and not all articles present complete clinical outcome data. Therefore, the interpretation of effectiveness in this review is carried out descriptively.

CONCLUSION

Based on a review of various studies, the cisplatin-gemcitabine regimen tends to be more cost-effective than cisplatin-paclitaxel in patients with advanced NSCLC. Most studies show that both regimens have comparable clinical outcomes, with a trend toward slightly higher effectiveness for cisplatin-gemcitabine. These findings suggest that cisplatin-gemcitabine may be a more cost-effective alternative in various healthcare settings.

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