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Outcomes comparison of patients with nasopharyngeal carcinoma who treated with combination of carboplatin and paclitaxel with other regimens: A systematic review

Raditya Maulana Akbar [1,*] and Rosa Falerina [2]

[1] *Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is among the top five cancers, with the highest number in Indonesia. One of the treatments for NPC is chemotherapy. The most common regimen used at Airlangga University Hospital, Surabaya, is a combination of carboplatin and paclitaxel. This study aims to assess the difference in outcomes of NPC patients who are given a combination therapy of carboplatin and paclitaxel with the outcomes of patients who are given regimen therapy other than the combination of the two drugs.

Methods: This study is a systematic review using PRISMA guidelines. Articles used were taken from e-databases, PubMed and Cochrane. The inclusion criteria used were articles that showed the outcomes of NPC patients who received carboplatin and paclitaxel combination therapy compared with other regimens.

Results: This study included one research journal that met the criteria. The combination of carboplatin and paclitaxel could reduce serious adverse events by 84% compared to the 3-drug combination. Based on progression-free survival (PFS), the 3-drugs combination showed better results (median: 7.5 months) compared to the combination of carboplatin and paclitaxel (median: 6.5 months).

Conclusion: Results showed that the overall outcome of patients treated with carboplatin and paclitaxel combination was not better than those treated with a 3-drug combination of carboplatin, paclitaxel, and bevacizumab. However, the combination of carboplatin and paclitaxel had minimal side effects compared to those given the combination of the three drugs.

Keywords: Paclitaxel; Carboplatin; NPC; Treatment

1. Introduction

Cancer is something that is a concern in the community because cancer is one of the leading causes of death, especially in developing countries [1]. One of the cancers in Indonesia is Nasopharyngeal Carcinoma (NPC). Nasopharyngeal carcinoma attacks the part of the throat that connects the back of the nose with the back of the mouth (pharynx) [2]. NPC is in the top five cancers with the highest number in Indonesia, along with uterine cervical cancer, breast cancer, cancer of the lymph nodes, and skin cancer [3]. The incidence of NPC in Indonesia is around 19,943 new cases (5%) and 13,399 deaths (5.7%) [4]. One of the treatments for NPC is chemotherapy. Chemotherapy is one of the most commonly used cancer treatments to treat cancer. Chemotherapy is a treatment that uses strong chemicals to kill cells that

* Corresponding author: Raditya Maulana Akbar

proliferate in the body [5]. Judging from the more significant improvements, chemotherapy causes more significant improvements than radiotherapy [6].

The incidence of NPC globally is increasing in certain regions, such as South China and Southeast Asia [7]. The area with the highest number of NPC cases worldwide is Guangdong Province in South China, with 20 to 40 cases per 100,000 population. Meanwhile, NPC cases in Southeast Asia are at a medium level; for example, Singapore has 15 cases per 100,000 population, Malaysia has almost 10 cases per 100,000 population, Vietnam has nearly 8 cases per 100,000 population, and the Philippines has practically 7 cases per 100,000 population. Different from the situation in South China and Southeast Asia, NPC is rarely found in Europe, Japan, Korea, and America because NPC is influenced by racial distribution and geography [8]. Around 400 thousand new cases of cancer in Indonesia in 2020 [9]. Based on the research results conducted by Faizah in 2016 [10] at the Regional General Hospital Dr. Soetomo Surabaya, the most chemotherapy regimens received by NPC patients in the study were Paclitaxel and Cisplatin. In addition, based on data obtained from Airlangga University Hospital, Surabaya, the most widely used chemotherapy regimen for NPC patients is a combination of paclitaxel and carboplatin. Meanwhile, according to the NCCN guideline, the gold standard chemotherapy regimen used is cisplatin and gemcitabine. So, from some of these differences, the author is interested in conducting a systematic review that discusses the outcome of a combination of paclitaxel and carboplatin regimens in NPC patients.

2. Method

The method used in this systematic review begins with determining the clinical question. The clinical question was, “Does the combination of paclitaxel and carboplatin have better outcomes than other regimens for the treatment of nasopharyngeal carcinoma?”. After that, the PICO (population, intervention, comparison, and outcome) approach was determined based on the clinical question that had been chosen. The population was adult patients with nasopharyngeal carcinoma. The intervention was a combination of carboplatin and paclitaxel. The comparison used was other chemotherapy regimens besides the combination of carboplatin and paclitaxel. The outcome was the quality of patients using the combination of paclitaxel and carboplatin, assessed by hospital admission, management outcomes, death, or mortality.

Once the PICO was determined, the next step was to develop inclusion and exclusion criteria for the articles that would later be used. The inclusion criteria used in this systematic review were articles containing the keywords “Nasopharyngeal Carcinoma” AND (“Paclitaxel” AND “Carboplatin” AND “Combination”) AND “Treatment Outcome” available in e-databases: PubMed and Cochrane, articles can be read in full-text, using Indonesian or English, and the study design used are RCT, clinical trial, or cohort. Exclusion criteria were studies conducted other than in humans, articles that were not available in full-text and did not compare the effects of the combination of carboplatin and paclitaxel with other regimens.

In this systematic review, Rayyan AI was used to detect duplicates. PRISMA diagrams were also used to outline the article's journey to get the final articles that fit the inclusion and exclusion criteria. The tools used to assess research journals based on study type were taken from the University of Oxford.

Research journals that met the inclusion and exclusion criteria were collected and extracted, starting from the title, study location, population, intervention, comparison, outcomes, and results. After that, each research journal obtained was also reviewed using predetermined tools. Conclusions were then determined from all articles used.

3. Results

Based on the keywords applied in the e-databases, 7 suitable articles were obtained, 3 from PubMed and 4 from Cochrane. After that, 3 articles were excluded because they were duplicates. After that, the articles were excluded based on the title and abstract and 2 articles were excluded because they did not meet the predetermined inclusion criteria. After that, articles were screened based on full-text availability and 0 articles were excluded. Then, the article was screened again, and 1 article was excluded because there was no comparison. So, 1 article was obtained, which would be reviewed because it met the predetermined inclusion and exclusion criteria (Figure 1).

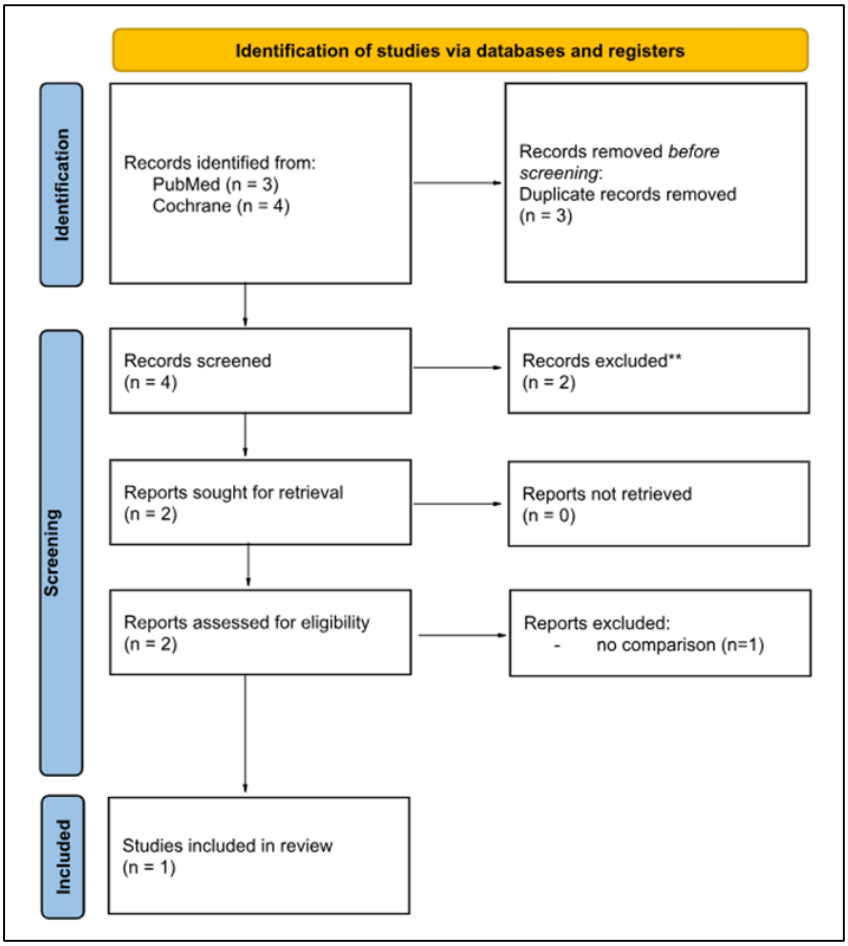

Figure 1 PRISMA Flow Chart 2020

Articles were then reviewed using tools sourced from the University of Oxford. The criteria reviewed included randomization, population homogeneity, intervention homogeneity, intention to treat, blinding, and the effect of the treatment (Table 1).

Table 1 Article Validity

Title	**Authors**	**Type of Study**	**Was the assignment of patients to treatments randomized?**	**Were the groups similar at the start of the trial?**	**Aside from the allocated treatment, were groups treated equally?**	**Were all patients who entered the trial accounted for? And were they analyzed in the groups to which they were randomized?**	**Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?**
Bevacizumab versus placebo in combination	Zhou T., et al.	RCT	☑ Yes Reason:	☑ Yes Reason:	☑ Unclear Reason:	☑ Yes Reason:	☑ No Reason:

with paclitaxel and carboplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase II trial			It is mentioned in the methods section that eligible patients are randomly grouped.	It is mentioned in the methods section that patients have the same criteria that have been adjusted based on the inclusion and exclusion criteria.	The article does not mention whether the patient was given any other additional treatment or not.	The article states that patients are followed up every 3 months until consent is withdrawn, lost to follow-up, or death.	The article states that the study was open label.
- Carboplatin + Paclitaxel combination: 1/42 (2.3%) patients experienced serious adverse events (SAE) - Carboplatin + Paclitaxel + Bevacizumab combination: 6/42 (14.28%) patients experienced SAE **Relative Risk (RR):** 0.023/0.1428 = 0.16 Interpretation: The combination of Carboplatin + Paclitaxel has a SAE risk of 0.16 times compared to the combination of Carboplatin + Paclitaxel + Bevacizumab.	**Absolute Risk Ratio (ARR):** 0.1428 - 0.023 = 0.1198 (11.98%) Interpretation: Carboplatin + Paclitaxel combination decreased SAE by 11.98%.			**Relative Risk Reduction (RRR):** 1 - RR = 1 - 0.16 = 0.84 = 84% Interpretation: Carboplatin + Paclitaxel combination decreased SAE by 84% compared to Carboplatin + Paclitaxel + Bevacizumab combination.		**Number Needed to Treat (NNT):** 1/ARR = 1/0.1198 = 8.3 = 8-9 orang Interpretation: It takes 8-9 patients treated with Carboplatin + Paclitaxel Combination to get 1 patient with a reduced risk of SAE.	

The articles used were also extracted based on their characteristics: title, study location, population, intervention, comparator, outcomes, and results (Table 2).

Table 2 Article Characteristic

Article	Country, Setting	Population	Intervention	Comparator	Outcome	Design	Results
Bevacizumab versus placebo in combination with paclitaxel and carboplatin as first-line treatment for recurrent or metastatic nasopharyngeal	China	Patients with histologically confirmed NPC, aged ≥ 18 years, life expectancy ≥ 12 weeks, and lesions based on RECIST 1.1	Carboplatin (area under the curve 6) + paclitaxel (175 mg/m2) IV on day 1 and once every 3 weeks for 6 cycles	Carboplatin (area under the curve 6) + paclitaxel (175 mg/m2) IV on day 1 and every 3 weeks for 6 cycles + bevacizumab (7.5 mg/kg) on	- Adverse Events - Drug related events - Disease progression	RCT	Overall survival showed no significant difference between the 2 treatment groups. Progression-free survival showed better

carcinoma: a multicentre, randomised, open-label, phase II trial				day 1 and every day 1 of each cycle			improvement in the 3-drug combination group (median: 7.5 months) compared to the 2-drug combination group (median: 6.5 months). Patients treated with the 3-drug combination had a better tumor reduction rate compared to the paclitaxel and carboplatin combination. Serious adverse events (hematological toxic, diarrhea, and epistaxis) occurred in 6 out of 42 patients (14.3%) who used 3 drug combinations. Meanwhile, serious adverse events (epistaxis) occurred in 1 out of 40 patients (2.5%) who used the combination of carboplatin and paclitaxel.

4. Discussion

Chemotherapy is the most commonly used treatment to treat cancer [5]. In stage IVb NPC, complete dose chemotherapy (neoadjuvant) for 3 cycles and followed by chemoradiation [11]. Drugs that can be used in combination therapy are cisplatin or carboplatin combined with docetaxel or paclitaxel, cisplatin or 5-FU, carboplatin, cisplatin or gemcitabine, and taxanes combined with platinum and 5-FU. Drugs that can be used in single therapy are cisplatin, 5-FU, carboplatin, methotrexate, paclitaxel, docetaxel, and gemcitabine [12]. Another regimen that can be used is bevacizumab. The maximum tolerated dose of bevacizumab is 20 mg/kg, of which 25% of patients will experience grade ≥3 toxicity (scale 1-5, according to General Toxicity Criteria), including headache, nausea, and vomiting [13].

In addition to having benefits, chemotherapy also has side effects; the drugs used in chemotherapy can also affect normal cells that are not the target [14]. The affected cells include mucous membrane cells in the mouth and throat area, mucous membranes in the digestive system, hair cells, and cells that produce blood. The effect is that people who receive chemotherapy can feel symptoms such as diarrhea, mouth infection, nausea, vomiting, hair loss, and anemia [15].

A study conducted by Zhou T et al. [16] compared the outcomes of NPC patients who received a combination management of 3 drugs, namely carboplatin, paclitaxel, and bevacizumab (CPB), with NPC patients who received a combination management of 2 drugs, namely carboplatin and paclitaxel (CP). When viewed from overall survival (OS), there was no significant difference between the CPB and CP groups. When viewed from progression-free survival (PFS), the CPB group had better results (median: 7.5 months) compared to the CP group (median: 6.5 months). However, the confidence intervals were vast (6.53-8.45 months and 5.53-7.42 months). The article also showed that patients in the CPB group had a better tumor reduction rate than those in the CP group. However, when viewed from the adverse events, it was mentioned in the article that serious adverse events (hematological toxicity, diarrhea, and epistaxis) occurred in 6 out of 42 patients (14.3%) in the CPB group. Meanwhile, serious adverse events (epistaxis) occurred in 1 of 40 patients (2.5%) in the CP group. Thus, the CP combination can reduce serious adverse events by 84% compared to CPB. However, the confidence interval (CI) was not presented.

The limitation of this systematic review is the small number of articles that were screened and met the inclusion and exclusion criteria. To overcome this, the authors have tried to find articles with other keywords that still answer the clinical questions decided at the beginning. Other limitations may occur due to other research limitations, such as language.

5. Conclusion

Overall, the outcomes of patients treated with the combination of carboplatin and paclitaxel were not better than those treated with the 3-drug combination of carboplatin, paclitaxel, and bevacizumab. However, when viewed from the adverse events, the combination of carboplatin and paclitaxel has minimal adverse events compared to those who were given the 3 drugs combination. Further research is needed regarding the outcomes resulting from the combination of carboplatin and paclitaxel compared to other regimens to find the optimal management in terms of efficacy and side effects.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest is present in this study

Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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