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Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: A cost-effectiveness analysis

Weiting Liao[a,b,#], Jiaxing Huang[a,b,#], Qiuji Wu[a,b], Guiqi Zhu[c], Xinyuan Wang[a,b], Feng Wen[a,b], Pengfei Zhang[a,b], Nan Zhang[a,b], Qiu Li[a,b,*]

[a] Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China
[b] West China Biomedical Big Data Center, Sichuan University, Chengdu 610041, China
[c] Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai 200032, China

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ABSTRACT

Background: Nedaplatin-based concurrent chemoradiotherapy became an alternative doublet treatment strategy to cisplatin-based concurrent chemoradiotherapy in patients with locoregional, advanced nasopharyngeal carcinoma.

Materials and methods: Using a Markov model, we simulated patients with nasopharyngeal carcinoma from disease-free to death. Input data for the model were collected from published literature and the standard fee database of West China Hospital. The outcome was expressed in quality-adjusted-years (QALYs), net monetary benefit at the threshold of $25,841, three times the Gross Domestic Product of China in 2017. The costs and benefits were discounted at 3% annually and a half-cycle correction was considered. The input parameters were varied in one-way sensitivity analysis to confirm the robustness of the model. All of the primary analyses used second-order probabilistic sensitivity analysis to capture the impact of parameter uncertainty based on 10,000 Monte-Carlo simulations.

Results: The mean QALYs of treatment in stage II-IVB nasopharyngeal carcinoma were comparable: 2.90 QALYs for nedaplatin and 3.12 QALYs for cisplatin. Nedaplatin cost $34,505 compared with $27,167 for cisplatin, generating an incremental net monetary benefit of nedaplatin versus cisplatin of $-13,357 at the ceiling ratio of $25,841. The results of nedaplatin remained cost-ineffective over the majority of the sensitivity analyses. The cost-effectiveness curve showed that the probability of strategies being cost-effective were 0% for nedaplatin and 100% for cisplatin in stage II-IVB nasopharyngeal carcinoma at any willingness-to-pay threshold.

Conclusions: Nedaplatin is a dominated, cost-ineffective alternative to concurrent chemoradiotherapy in stage II-IVB nasopharyngeal carcinoma compared with cisplatin from the perspective of Chinese society.

Introduction

Nasopharyngeal carcinoma has a distinct, unbalanced pattern of geographical distribution. Worldwide, high-prevalence regions include east and southeast parts of Asia, along with south-central Asia, and the north and east parts of Africa [1]. More than 70% of newly diagnosed cases of nasopharyngeal carcinoma are classified as locoregionally advanced disease in stage II-IVB [2]. For this subgroup, combination chemotherapy with radiotherapy remains the pivotal standard treatment, in which cisplatin was the most common chemotherapeutic agent of choice [3,4]. Although cisplatin provides patients with a substantial survival benefit, limitations are poor treatment compliance and side effects, including nausea, vomiting, nephrotoxicity, ototoxicity, and neurotoxicity [5,6]. Furthermore, cisplatin-based concurrent chemoradiotherapy requires both prior- and post-hydration treatment for renal protection during administration [7–9], which can prolong the length of hospital visits and increase the treatment cost. A new platinum derivative, nedaplatin, which has similar effectiveness, was designed to reduce the adverse events (AEs) induced by cisplatin, including nephrotoxicity and gastrointestinal toxicity [10,11]. A phase III randomized trial was conducted to directly compare the efficacy and safety of concurrent chemotherapies in combination with intensity-modulated

* Corresponding author at: Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, No. 37, GuoXue Xiang, Chengdu 610041, China.
E-mail address: fbqiu9@163.com (Q. Li).
# These authors have contributed equally to this work.

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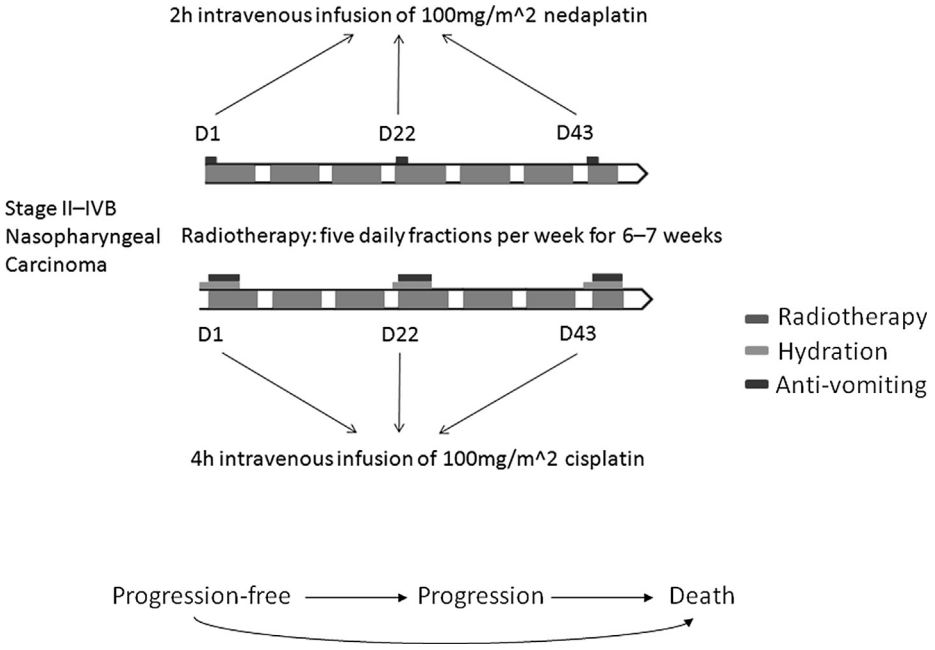

Fig. 1. Concurrent chemoradiotherapy pipeline and model structure. The enrolled patients received 2 h intravenous infusion of 100 mg/m^2 nedaplatin or 4 h intravenous infusion of 100 mg/m^2 cisplatin on days 1, 22, and 43 for three cycles with concurrently intensity-modulated radiotherapy using simultaneously integrated boosts at the recommended radiotherapy dose of 2.00–2.33 Gy per fraction with five daily fractions per week for 6–7 weeks. In the cisplatin group, patients were administered hydration on days 0–3 and diuretics on the day of cisplatin administration of each cycle. Antiemetic drugs were applied to ameliorate chemotherapy-induced nausea and vomiting in both the nedaplatin (on days 1, 22, and 43) and cisplatin (on days 1–3, 22–24, and 43–45) groups. After completion of treatment, patients underwent physical examinations annually or when clinical response suggests tumor relapse.

Table 1
Input data values, ranges and distributions.

Variable	Nedaplatin	Cisplatin	Distribution	Reference
Costs for PFS (one and a half month) -$				
Anticancer drug	622.15 (435.50–808.80)	57.92 (40.54–75.30)	Gamma	[12]
Radiotherapy	6876.97 (4813.88–8940.06)	6876.97 (4813.88–8940.06)	Gamma	[12]
Hospitalization	210.53 (147.37–273.69)	392.80 (274.96–510.64)	Gamma	[12]
Test	230.13 (161.09–299.17)	230.13 (161.09–299.17)	Gamma	[12]
AE	75.77 (53.04–98.50)	88.57 (62.00–115.14)	Gamma	[12]
Total	8016	7646		
Costs for PD (one and a half month) -$				
Supportive treatment	74.20(51.94–96.46)	80.68 (56.47–104.88)	Gamma	[12]
Transition probability				
pPD-PD	0.986 (0.690–1)	0.995 (0.697–1)	Beta	[12]
pPD-Death	0.014 (0.010–0.018)	0.005 (0.003–0.007)	Beta	[12]
pPFS-PD	0.004 (0.003–0.005)	0.003 (0.002–0.004)	Beta	[12]
pPFS-PFS	0.995 (0.697–1)	0.996 (0.697–1)	Beta	[12]
pPFS-Death	0.001 (0–0.002)	0.001 (0–0.002)	Beta	[12]
Utility				
PFS	0.76 (0.532–0.988)	0.76 (0.532–0.988)	Beta	[23]
PD	0.57 (0.399–0.741)	0.57 (0.399–0.741)	Beta	[23]
Death	0	0		

AE, adverse event; PFS, progression-free survival; PD, progression disease; pPD-PD, transition probability for progression disease state to progression disease; pPD-Death, transition probability for progression disease state to death; pPFS-PD, transition probability for progression-free state to progression disease; pPFS-PFS, transition probability for progression-free state to progression-free state; pPFS-Death, transition probability for progression-free state to death.

radiotherapy for stage II-IVB nasopharyngeal carcinoma, and the result demostrated the non-inferiority of nedaplatin compared with cisplatin, suggesting that nedaplatin represents a potential alternative chemotherapeutic agent in a doublet treatment strategy [12].

Compared to nedaplatin, cisplatin has a lower drug price, although it also has more symptomatic AEs, and additional processes are needed, such as hydration [13] and anti-vomiting pretreatment [14,15]. In contrast, the benefits of nedaplatin include reduced toxicity and increased patients' compliance [16,17], but these benefits accompany a higher drug price. What remains ambiguous is the cost-effectiveness of the two concurrent chemoradiotherapeutic approaches, an economic model based on the disease pattern of stage II-IVB nasopharyngeal carcinoma will help to study whether nedaplatin is a valid alternative to cisplatin [18]. Thus, we constructed this analysis to determine the most cost-effective strategy in patients with locoregional, advanced nasopharyngeal carcinoma from the perspective of the Chinese society.

Materials and methods

Model construction

A Markov model was developed to simulate patients with stage II-IVB nasopharyngeal carcinoma to compare nedaplatin-based and cisplatin-based concurrent chemoradiotherapy, consisting of three mutually exclusive health states: progression-free (PF), progressive disease (PD), and death. The cycle length was one and a half months. During each cycle, patients either stayed in the initial health status or progressed to another health status, as shown in Fig. 1. Transition probabilities of health states per cycle were calibrated from Kaplan-Meier survival data in the trial (Table 1), and the fit curves are shown in

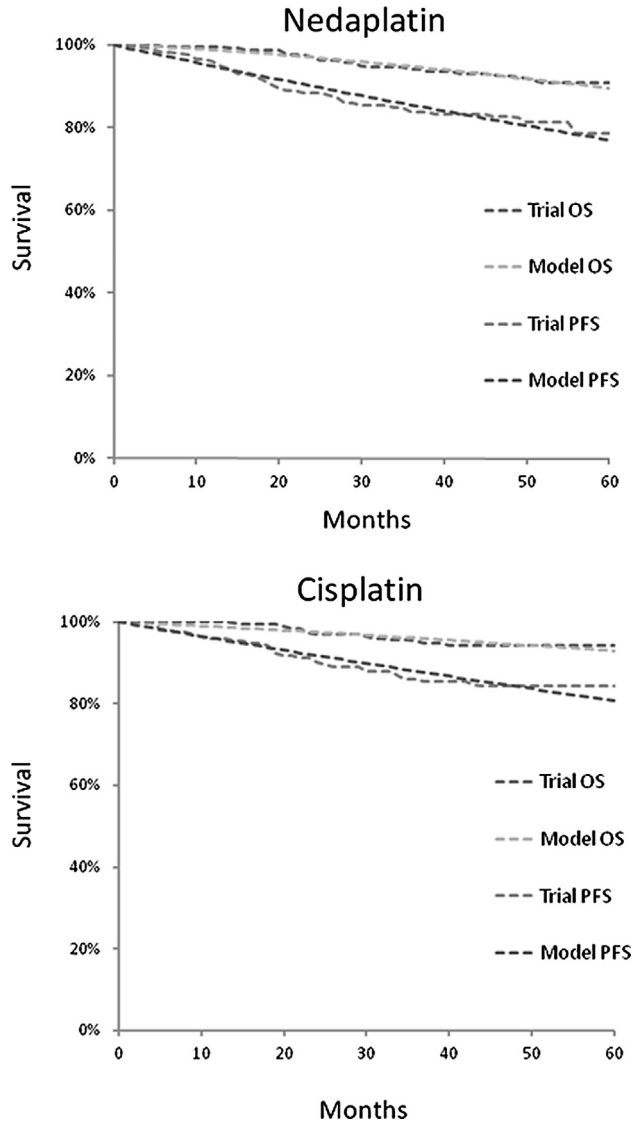

Fig. 2. Survival Kaplan-Meier plot for patients for the nedaplatin and cisplatin arms and fit curves for the nedaplatin and cisplatin arms generated from the cost-effectiveness model. Fit curves of our model panel were in agreement with the target data across overall survival (OS), progression-free survival (PFS) in Tang's randomized trial.

Table 2
Base-case results.

Strategy-based chemoradiotherapy	Nedaplatin	Cisplatin
Cost -$	34,505	27,167
Incremental Cost -$	7338	
Effective -QALYs	2.90	3.12
Incremental Effective -QALYs	−0.22	
Incremental Cost-effective Ratio -$/QALY	−31,937	
Net Monetary Benefit -$	41,346	54,703
Differential Net Monetary Benefit -$	−13,357	
Marginal effect	Dominated	

QALYs, quality adjusted life-years.

Fig. 2. A time horizon of 18 years was applied to track the treatment modality coupled with the following adjustments: 3% annual discount rate and half-cycle correction [19].

Patients and interventions

The intervention pipeline is illustrated in Fig. 1 according to Tang's randomized trial [12].

Costs

All of the costs were sourced from the standard fee database of West China Hospital, 2017. Direct medical costs were from anticancer drugs, radiotherapy, hospitalization, tests, and prevention and management of AEs. The cost for radiotherapy preparation was $630.97, and the costs for the radiotherapy fractions were, in total, $6246, based on a 33-treatment course costing $189.27 for each treatment. The cost for nedaplatin (per 50 mg) was $51.845, and the cost for cisplatin (per 30 mg) was $3.22. Based on the mean Asian body surface area of 172 cm^2 [20], nedaplatin and cisplatin cost $622.15 and $57.92, respectively, for a course. Detailed costs for tests (fiber optic nasopharyngoscopy, radiography, bone scan and blood examinations), hospitalization (services and pretreatments) and frequency-weighted grade 3–4 AEs management are described in Supplementary Table.

Health outcome

The Euro-Qol five-dimensional questionnaire (EQ-5D), which encompasses a descriptive system of health-related quality of life expressed as utility indexes, was employed in this economic evaluation, ranging from perfect health (1) to death (0) [21,22]. According to a previous cost-effectiveness model of nasopharyngeal carcinoma, the utility for disease-free status was 0.76, and for progression after treatment was 0.57 [23].

Sensitivity analysis

A series of one-way sensitivity analyses were conducted on all variables listed in Table 1 to test the variables within 30% ranges [20]. To explore the impact of parameter uncertainty, a second-order probabilistic sensitivity analysis was performed based on 10,000 Monte-Carlo simulations. Cost-effectiveness acceptability curves were developed to reflect the probability that a treatment to be cost-effective by varying ceiling ratios [24].

Statistical analysis

Costs, quality adjusted life years (QALYs) and net monetary benefit (NMB) were estimated for the different treatments. Costs were converted to US dollars at the exchange rate of $1 = ¥6.34 (April 2018). QALYs were essentially calculated as duration in a health state multiplied by the utility weight of the corresponding health status [25–27]. NMB was calculated by multiplying the QALYs by the willingness-to-pay (WTP) and subtracting the total costs [28]. A WTP threshold of $25,841 was applied to the analysis according to WHO guidelines, three times the GDP in China in 2017 [29]. Incremental net monetary benefits (INMB) can be computed as the differential effects multiplied by the WTP minus the differential costs. Accordingly, when the INMB ≥ 0, the intervention of interest is defined as cost-effective relative to the alternative, or vice versa [30].

Results

Base-case results

The total costs of the nedaplatin strategy were $34,505, and the total costs of the cisplatin strategy were $27,167 (Table 2). The nedaplatin strategy provided 2.90 QALYs compared with 3.12 QALYs for the cisplatin strategy. The mean NMB according to the EuroQoL questionnaire was slightly lower in the nedaplatin group ($41,346) than in

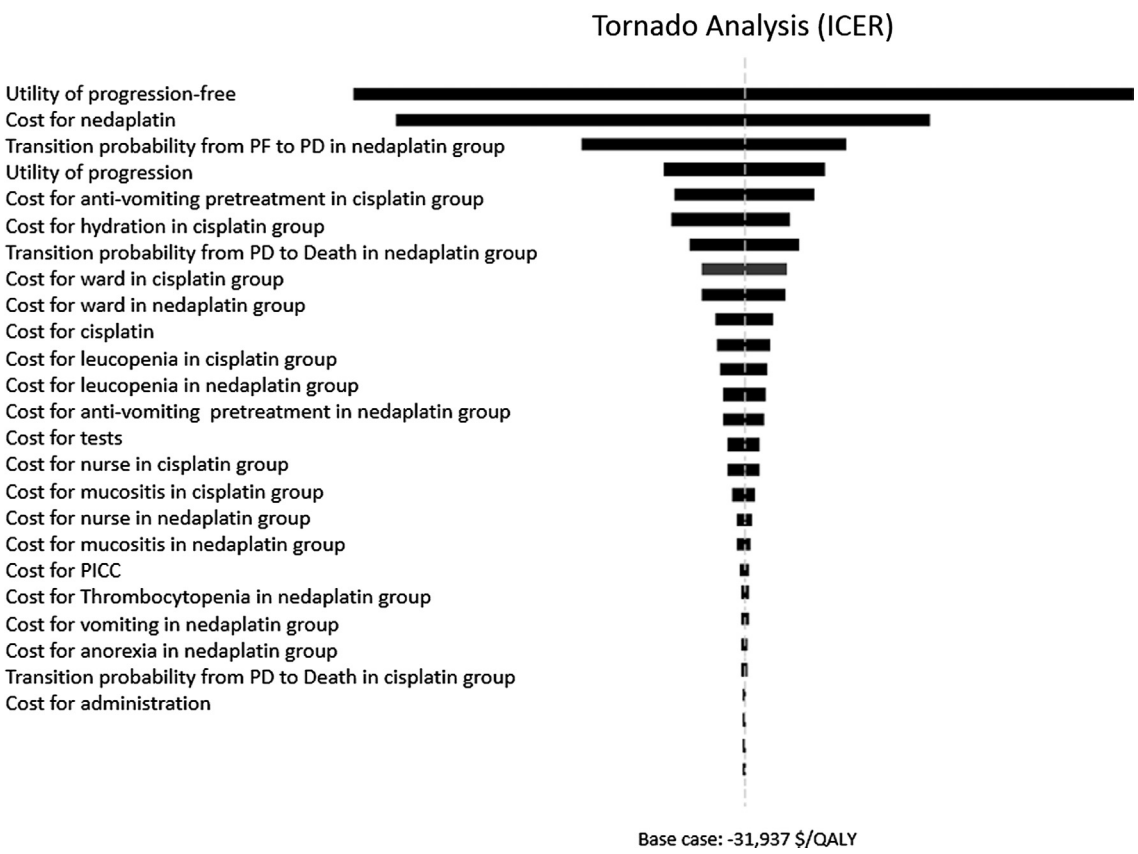

Fig. 3. Tornado diagram. The tornado diagram shows the one-way sensitivity analyses within the appropriate range for each variable.

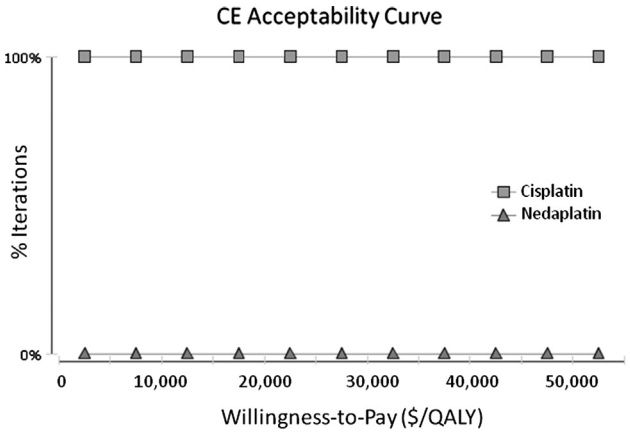

Fig. 4. Probabilistic sensitivity analysis. The cost-effectiveness acceptability curve indicates the probability (y-axis) of nedaplatin being cost effective compared with cisplatin given the threshold value (x-axis).

the cisplatin group ($54,703) across the entire time course, yielding an incremental NMB of −$13,357. The bootstrapped cost and effectiveness pair for cisplatin versus nedaplatin illustrates the superiority of cisplatin over nedaplatin, and the value is located in the southeast quadrant of the cost-effectiveness plane (Supplementary Fig. 1).

Sensitivity analysis

One-way sensitivity analyses are illustrated in the tornado diagram in Fig 3. The utility of PF, cost for nedaplatin, and transition probability from PF to PD in the nedaplatin group were the most sensitive variables in the model. Following that, utility of PD, costs for anti-vomiting pretreatment or hydration in the cisplatin group produced certain influence, and costs for cisplatin, hospitalization, AEs and tests had marginal impacts on the outcomes.

The cost-effectiveness acceptability curve (Fig 4) showed that the probability of the strategies being cost-effective was 0% for nedaplatin and 100% for cisplatin in stage II-IVB nasopharyngeal carcinoma at any WTP threshold. The value for INMB versus WTP in the comparison of nedaplatin with cisplatin was less than −$5,000, demonstrating that the cisplatin strategy is superior to the nedaplatin strategy.

Discussion

Our study is the first economic evaluation to quantify the cost-effectiveness of nedaplatin versus cisplatin with concurrent radiotherapy in locoregionally advanced nasopharyngeal carcinoma. The total costs were lower ($27,167 vs $34,505) and the QALY outcomes (3.12 QALYs vs 2.90 QALYs) were better in the cisplatin group than in the nedaplatin group. While the social WTP varied, the incremental NMB of nedaplatin versus cisplatin remained negative, suggesting that nedaplatin is unlikely to be cost-effective compared with cisplatin in concurrent chemoradiotherapy for stage II-IVB nasopharyngeal carcinoma.

Nedaplatin is known to exhibit antitumor activity similar to that of cisplatin. The most substantial advantage of nedaplatin over cisplatin is that it has fewer side effects [31]. Confounding was questioned for toxicity differences between these two groups in contrast to patient compliance; nedaplatin has lower toxicity, but the reason for the higher discontinuation rate is unclear. In addition, the current conclusion is that it is premature to deem nedaplatin as a valid alternative to cisplatin for concurrent chemotherapy in nasopharyngeal carcinoma [32].

Cisplatin-based regimen increased the acute and late toxicities of intensity-modulated radiotherapy [33,34]. Nedaplatin remarkably reduced acute toxicities, including grade 3–4 vomiting, nausea, anorexia, weight loss, hypokalemia, and hyponatremia, while it led to a higher incidence of grade 3–4 thrombocytopenia (6%) than that in the

cisplatin group (2%). Auditory loss was the only late toxicity less frequent in the nedaplatin group compared with the cisplatin group [12]. A recent clinical trial published in the NEJM in June 2018, found that the delayed addition of sodium thiosulfate to cisplatin administered 6 h after cisplatin chemotherapy resulted in a 48% lower risk of hearing loss with no risk to the survival benefits [35], which strengthens the potential superiority of the cisplatin-based strategy by guaranteeing the recovery of auditory function.

The most influential factor driving our model was the utility of PF status, which was equal in the two groups of the model due to a lack of reference. However, in the trial, nedaplatin with less toxicity might create greater utility. Considering this property, we conducted one-way sensitivity analysis by varying the utility of PF in the nedaplatin group from 0.75 to 1, for which the comparable cut-off value in regard to NMB was 0.904 (Supplementary Fig. 2). Based on our result, nedaplatin needs to be more tolerable compared with cisplatin to achieve the best competitive edge.

Limitations in this cost-effectiveness study arise primarily from the quality of inputs used to inform our cost-effectiveness model. Although the utility of disease pattern used previously published nasopharyngeal carcinoma economic models, they may not accurately reflect the hypothetical patients with stage II-IVB nasopharyngeal carcinoma. An updated health quality survey for a population with platin-based concurrent chemoradiotherapy might improve accuracy and robustness. Second, the costs for supportive treatment are estimated according to AEs for the difficulty of capturing real-world cost data in the analysis. However, the varying costs of supportive treatment have little impact on the outcome of the model. Last but not least, future prospective cost-effectiveness study of nedaplatin in nasopharyngeal carcinoma is expected to further verify our results.

In conclusion, our study indicates that the use of nedaplatin for patients with stage II-IVB nasopharyngeal carcinoma fails to reduce costs and is a dominated alternative compared to cisplatin. The current cost-effectiveness analysis should give suggestions for the decision-making process to make recommendations regarding the therapy for patients with stage II-IVB nasopharyngeal carcinoma.

Disclosure statement

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Conflict of interest

All the authors declare no conflict of interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Informed consent: Informed consent was not necessary because none of individual participants were included in the study.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.04.003.

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