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ORIGINAL RESEARCH

Comparison of efficacy and toxicity between nedaplatin and cisplatin in treating malignant pleural effusion

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Objective: To evaluate the efficacy and safety of nedaplatin versus cisplatin in treating malignant pleural effusion (MPE) caused by cancers.

Methods: The clinical data of 219 MPE patients treated from January 2013 to December 2016 were retrospectively reviewed. Intrapleural infusion with nedaplatin 80 mg/m^2 (n=110) or with cisplatin 40 mg/m^2 (n=109) were used as the treatment.

Results: There was no significant difference in the overall response rate between the nedaplatin group (62.73%) and the cisplatin group (54.13%) (P=0.154). The nedaplatin group had significantly lower rates of gastrointestinal side effects and significantly less incidence of increased serum creatinine levels in comparison with the cisplatin group. The overall rate of toxicity in the nedaplatin group (40.00%) was significantly lower than in the cisplatin group (78.90%) ($P<0.001$).

Conclusion: The efficacy of pleural perfusion with nedaplatin is noninferior to cisplatin in treating malignancy-induced MPE. Nedaplatin is associated with less toxicity in comparison with cisplatin.

Keywords: malignant pleural effusion, pleural perfusion, platinum-based drug, toxicity

Introduction

Malignant pleural effusion (MPE) is a common complication in patients with advanced malignancies. This condition can severely compromise heart and lung functions, and significantly decrease the quality of life in patients. Due to its poor response to systemic treatment, MPE is usually managed with intrapleural perfusion chemotherapy. Cisplatin and carboplatin are the mostly used drugs in treating MPE, and their efficacy is well-established. However, these 2 drugs are associated with gastrointestinal side effects and myelosuppression, which has limited their clinical use.[1–4]

Nedaplatin is a second-generation platinum-based drug. The present study aimed to investigate the efficacy and toxicity of nedaplatin versus cisplatin in treating MPE caused by malignant tumors.

Materials and methods

Patients

The clinical data of 219 consecutive patients with MPE caused by malignant tumors were retrospectively reviewed. These patients were treated from January 2013 to December 2016 at our hospital. There were 114 males and 105 females with a mean age of 52 years (age range, 28–77 years). Our study was approved by the ethics committee of China–Japan Union Hospital of Jilin University. Patient consent to review

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their medical records was not required by the institutional review board because the review of the patient data was anonymous.

Intrapleural perfusion

The location of pleural effusion was identified using ultrasonography. A central venous catheter was inserted under ultrasound guidance. The pleural fluid was drained for 3–5 days at a rate of 800–2,000 mL/d. Albumin was infused in the meantime. One hundred and ten patients received intrapleural infusion with nedaplatin 80 mg/m^2 in 50 mL normal saline, and 109 patients received intrapleural infusion with cisplatin 40 mg/m^2 in 50 mL normal saline. Granisetron 5 mg was used 30 min prior to the intrapleural infusion for antiemetic purpose. The patient was instructed to change body position every 10 min after the intrapleural infusion for 1 hr to disperse the drug in the pleural cavity. Drainage was resumed after 72 h and was performed weekly for at least 2 consecutive weeks.

Evaluation of efficacy

Complete remission was a complete disappearance of the pleural effusion for 4 consecutive weeks. Partial remission was a reduction in the pleural effusion ≥50% accompanied by symptom improvement ≥4 weeks. Progressive disease was an increase in the pleural effusion >25%. Stable disease was a reduction in the pleural effusion <50% or an increase <25%. Overall response rate was the sum of complete remission rate and partial remission rate. Treatment-associated toxicity was evaluated using the World Health Organization anticancer drug toxicity criteria.

Statistical analysis

The continuous data are presented as mean ± standard deviation. The normally distributed data were compared using the paired sample *t*-test, and the nonnormally distributed data were compared using the Wilcoxon 2-sample test. The categorical data were presented as frequencies or percentages and compared using the Fisher's exact test. Efficacy and adverse events were compared using the Cochran–Mantel–Haenszel test. All statistical analyses were performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). A *P*-value <0.05 was considered statistically significant.

Results

Patients' general information

All patients had an ECOG score ≤3 and a medium or large volume of intrapleural fluid evaluated as assessed using ultrasound. The underlying malignancy included 115 cases of lung cancer, 52 cases of breast cancer, and 52 cases of gastrointestinal cancer. Systemic chemotherapy was administered 6 months earlier in 162 patients, within 1 month in 39 patients, and concomitantly with the intrapleural perfusion treatment in 18 patients.

Table 1 General characteristics of the patients

	Cisplatin group (n=109)	Nedaplatin group (n=110)	*P*-value
Male, n (%)	60 (55.05)	54 (49.09)	0.378
Age (year)	52.05±11.53	51.95±11.48	0.953
Body mass index (kg/m^2)	21.1±2.16	20.86±2.05	0.594
Diabetes, n (%)	7 (6.42)	11 (10.00)	0.335
Cardiovascular disease, n (%)	17 (15.60)	17 (15.45)	0.977
Pulmonary heart disease, n (%)	6 (0.06)	5 (0.045)	0.745

Note: Data presented as mean ± SD.

The cisplatin group and the nedaplatin group were not significantly different with regard to gender, age, body mass index, diabetes, and cardiovascular disease (Table 1). The 2 groups also did not differ significantly in Karnofsky score, underlying malignancy, tumor pathology, mediastinal metastasis, and pleural effusion volume (Table 2).

Efficacy and toxicity

The overall response rate of the MPE treatment was 62.73% in the nedaplatin group versus 54.13% in the cisplatin group,

Table 2 Comparison of the underlying diseases between the 2 groups

Baseline data	Cisplatin group (n=109)	Nedaplatin group (n=110)	*P*-value
Karnofsky score	77.52±8.84	77.73±10.01	0.646
Underlying malignancy, n (%)			0.895
Lung cancer	57 (52.29)	58 (52.73)	
Colon cancer	9 (8.26)	7 (6.36)	
Breast cancer	24 (22.02)	28 (25.45)	
Gastric cancer	8 (7.34)	9 (8.18)	
Rectal cancer	11 (10.09)	8 (7.27)	
Tumor pathology, n (%)			0.708
Infiltrative cancer	17 (15.60)	18 (16.36)	
Squamous cell cancer	33 (30.28)	25 (22.73)	
Adenocarcinoma	37 (33.94)	39 (35.45)	
Small-cell lung cancer	11 (10.09)	16 (14.55)	
Other	11 (10.09)	12 (10.91)	
Mediastinal metastasis, n (%)	40 (36.70)	50 (45.45)	0.188
Pleural effusion volume, n (%)			0.656
Large	47 (43.12)	52 (47.27)	
Medium	24 (22.02)	19 (17.27)	
Small	38 (34.86)	39 (35.45)	
Cachexia, n (%)	6 (5.50)	7 (6.36)	0.788
Targeted therapy, n (%)	6 (5.50)	7 (6.36)	0.788
Concomitant chemotherapy with the intrapleural treatment, n (%)	8 (7.34)	10 (9.09)	0.637

Note: Data presented as mean ± SD.

Table 3 Comparison of efficacy between nedaplatin and cisplatin in treating MPE

	Cisplatin group (n=109)	Nedaplatin group (n=110)	*P*-value
Lung cancer, n (%)			0.072
CR	17 (29.82)	24 (41.38)	
PR	9 (15.79)	10 (17.24)	
SD	12 (21.05)	14 (24.14)	
PD	19 (33.33)	10 (17.24)	
Breast cancer, n (%)			0.767
CR	9 (37.50)	10 (35.71)	
PR	7 (29.17)	11 (39.29)	
SD	5 (20.83)	4 (14.29)	
PD	3 (12.50)	3 (10.71)	
Gastrointestinal cancer, n (%)			0.686
CR	8 (28.57)	9 (37.50)	
PR	8 (28.57)	5 (20.83)	
SD	8 (28.57)	7 (29.17)	
PD	4 (14.29)	3 (12.50)	
All cancers, n (%)			0.081
CR	34 (31.19)	43 (39.09)	
PR	24 (22.02)	26 (23.64)	
SD	25 (22.94)	25 (22.73)	
PD	26 (23.85)	16 (14.55)	
Overall response, n (%)	58 (53.21)	69 (62.73)	0.154

Abbreviations: CR, complete remission; MPE, malignant pleura effusion; PD, progressive disease; PR, partial remission; SD, stable disease.

which was not significantly different (*P*=0.154). The 2 drugs also did not differ significantly in MPE treatment efficacy in patients with lung cancer, other cancers, or any cancer (Table 3).

The nedaplatin group had significantly lower rates of gastrointestinal side effects and significantly less incidence of increased serum creatinine levels in comparison with the cisplatin group (Table 4). The overall rate of toxicity in the nedaplatin group (40.00%) was significantly lower than that in the cisplatin group (78.90%). These results suggested that nedaplatin is superior to cisplatin in toxicity in the treatment of MPE.

Table 4 Comparison of toxicity between nedaplatin and cisplatin in treating MPE

Toxicity	Cisplatin group (n=109)	Nedaplatin group (n=110)	*P*-value
Gastrointestinal side effects, n (%)			<0.001
Grade III	14 (12.84)	6 (5.45)	
Grade II	45 (41.28)	2 (1.82)	
None	50 (45.87)	102 (92.73)	
Increased serum creatinine levels, n (%)	20 (18.35)	2 (1.82)	<0.001
Chest pain, n (%)	33 (30.28)	32 (29.09)	0.848
Myelosuppression, n (%)			0.714
Grade IV	4 (3.67)	5 (4.55)	
Grade III	12 (11.01)	13 (11.82)	
None	93 (85.32)	92 (83.64)	
Fever	6 (5.50)	8 (7.27)	0.593
Total	86 (78.90)	44 (40.00)	<0.001

Abbreviation: MPE, malignant pleural effusion.

Discussion

MPE is commonly seen in patients with end-stage tumors when the pleural cavity is involved. Normally, 3–15 mL fluid is present in the pleural cavity and functions as lubricant. About 500–1,000 mL pleural fluid is secreted and absorbed daily, to maintain a dynamic balance. Malignant diseases may disrupt this balance and cause MPE. Excessive pleural fluid can severely affect patient breathing, and even result in apnea. Effective control of MPE is essential for improving the quality of life of patients with end-stage disease. Surgical pleurodesis is available for the management of MPE but is not popular in practice due to its traumatic nature.[5,6] Conservative treatment is usually preferred to treat MPE, which consists of pleural effusion drainage as the first step and intrapleural perfusion with drugs as the second step. The drugs for intrapleural perfusion include chemotherapeutic agents or immunosuppressants, or the both in combination.[4,7,8] Intrapleural perfusion with chemotherapeutic agents causes pleural adhesion, reduces pleural permeability, and decreases pleural effusion. In addition, cytotoxicity of the chemotherapeutic agents also helps control the intrapleural metastasis.[9]

Nedaplatin has been approved in Japan for the treatment of various solid tumors of the esophagus, ovary, cervix, bladder, lung, and head and neck.[10] Nedaplatin has the same therapeutic mechanisms as cisplatin but is 10 times more water-soluble than cisplatin. Due to its lower gastrointestinal side effects and renal toxicity in comparison with cisplatin, nedaplatin is being used increasingly in chemotherapy.

Nedaplatin was used in the present study as an intrapleural perfusion drug for the treatment of MPE. Because nedaplatin is not metabolized by the liver, it can maintain a high concentration in the pleural fluid, and constantly kills the tumor cells in the pleural membrane and fluid.

The present study found that the overall response rate of the nedaplatin group was 62.73%, which was not significantly different from the 54.13% overall response rate in the cisplatin group. The 2 drugs also did not differ significantly in MPE treatment efficacy in patients with lung cancer, breast cancer, or gastrointestinal cancer. However, nedaplatin was associated with significantly lower rates of gastrointestinal side effects and significantly less incidence of increased serum creatinine levels in comparison with cisplatin, suggesting that nedaplatin is superior to cisplatin in toxicity in the treatment of MPE. These results were consistent with

previous findings that nedaplatin is superior to cisplatin in toxicity.[11–15] Less toxicity means better tolerability and better patient compliance, which can help to achieve better treatment efficacy.

The present study has some limitations. First, this was a retrospective study and the patient selection and treatment assignment might be affected by confounding factors. Second, the sample size was relatively small. Third, the patient survival results were not available for the analysis.

Conclusion

In conclusion, the efficacy of pleural perfusion with nedaplatin was found to be noninferior to cisplatin in treating malignancy-induced MPE. Nedaplatin is associated with less toxicity in comparison with cisplatin. These results need further confirmation with well-designed prospective studies.

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Li-Zhe Zhong and Hong-Yan Xu are co-first authors for this study.

Disclosure

The authors report no conflicts of interest in this work.

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