Nedaplatin- versus cisplatin-based chemotherapy in the survival time of patients with non-small cell lung cancer

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Abstract. Nedaplatin (NDP) has been extensively used to treat patients with non-small cell lung cancer (NSCLC) in the last decade. The present study compared the survival benefits of NDP and cisplatin (DDP) in the treatment of NSCLC. Patients (n=392) with NSCLC were treated with at least two cycles of platinum-based chemotherapy. Among these patients, 202 received DDP-based chemotherapy, and 190 received NDP-based chemotherapy. The overall survival time of the two groups and the toxicity of drugs were analyzed. The results showed that only the chemotherapy cycle duration was found to be statistically different between DDP and NDP groups in all the characteristics. The mean chemotherapy duration was 3.3 cycles in the DDP group, and 4.1 cycles in the NDP group (χ^2=20.206, P<0.001). Additionally, the chemotherapy cycle number was also an independent predictive factor for the overall survival time in the multivariate analysis (HR=0.539, P<0.001). The median survival time (MST) was 15 months in the DDP group, and 20 months in the NDP group (χ^2=5.189, P=0.023). The 1-, 2- and 3-year overall survival rates were 62.4, 25.7 and 15.8%, and 78.9, 38.9, and 16.8% in the DPP and NDP groups, respectively. The incidence of grade 3-4 nausea/vomiting, anorexia and weight loss was higher in the DDP compared to the NDP group (36.1 vs. 8.4%, 17.3 vs. 5.8%, and 9.9 vs. 1%, respectively). In conclusion, NDP-based chemotherapy had a survival benefit compared to DDP-based chemotherapy for NSCLC patients, due to the lower toxicity of NDP, which renders this drug more tolerable, thus allowing patients to undergo more cycles of chemotherapy.

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide and is expected to remain a major health problem (1). The morbidity and mortality rates of lung cancer in China are the highest among all the malignant tumors. The majority of patients are diagnosed at an advanced stage, at which the cancer is inoperable. Thus, chemotherapy has become the primary treatment. However, the adverse effects of certain agents, which lead to failure to complete the scheduled regimen, extension of chemotherapy intervals or reduction of the recommended dosage, have limited their clinical application. Therefore, it is extremely important to investigate and identify effective chemotherapy agents with low toxicity.

Nedaplatin [NDP; *cis*-diamine (glycolate) platinum II] is a second-generation platinum analog, synthesized by Shionogi & Co. Ltd. (Osaka, Japan). NDP has a higher aqueous solubility than cisplatin (DDP), and was found to be highly effective against solid tumors, in preclinical studies (2-4). Koshiyama *et al* (5) reported that the mean tumor inhibition rate for NDP was equal to or higher than that for DDP in 15 cervical (70.7 vs. 63.9%), 65 ovarian (61.7 vs. 54.8%) and 57 endometrial (52.1 vs. 47.7%) carcinoma patients. Compared to DDP, NDP-induced emesis and nephrotoxicity are substantially reduced, bypassing the requirement for hydration therapy for renal protection (6). The dose-limiting toxicity of NDP is characterized by thrombocytopenia.

Numerous cancers, including nasopharyngeal cancer, NSCLC, esophageal cancer, urothelial carcinoma and cervical cancer, have been reported to be effective to NDP-based chemotherapy in clinical studies (7-13). However, the majority of recent studies have focused on the therapeutic effect of NDP on esophageal cancer, although this type of cancer does not respond well to platinum-based chemotherapy. Limited studies have addressed the effect of NDP on the treatment of lung cancer. Sasaki *et al* (14) reported that NDP shows equivalent antitumor activity to DDP against lung cancer cell lines *in vitro*. Furuse *et al* (15) reported that a combination of NDP and vindesin (VDS) was a safe and effective regimen for the treatment of NSCLC, generating antitumor effects equivalent to that of the DDP/VDS regimen. Thus far, no study has compared the survival benefit between NDP and DDP in the treatment of NSCLC.

In the last decade, NDP-based chemotherapy has been extensively used in Chinese NSCLC patients (16). The present study reports a retrospective study comparing the efficacy of NDP and DDP in the treatment of NSCLC. In the study, a retrospective analysis based on 392 patients diagnosed with NSCLC revealed that NDP-based chemotherapy increased the median survival time (MST) of NSCLC patient compared to DDP. The observed survival benefit is due to the reduced toxicity of NDP, which allows patients to tolerate more cycles of chemotherapy.

Patients and methods

Eligibility criteria. A total of 966 patients diagnosed with NSCLC at the Cancer Center of Daping Hospital at the Third Medical University (Chongqing, China), in the period between January 2003 and December 2007 were retrospectively reviewed. Every patient was evaluated for age, gender, smoking status, stage, histology type, chemotherapy regimen, overall chemotherapy cycles and other treatments. Eligibility criteria for the study were as follows: Histological or cytological confirmation of NSCLC, previously untreated with chemotherapy, at least two cycles of platinum-based therapy (DDP- or NDP-based chemotherapy), no surgical treatment of the primary site and no changing to a different platinum agent or to a non-platinum regimen in a subsequent treatment. Based on the above criteria, a total of 392 NSCLC patients were selected. Among them, 202 patients received DDP-based chemotherapy and 190 patients received NDP-based chemotherapy. Table I shows that the two patient groups were not significantly different in terms of demographics, disease severity and treatment regimen.

Clinical data from these patients were acquired and stored according to protocols approved by the local ethics committee.

Treatment schedule. The patients received one of the following combination chemotherapies by intravenous injection: Gemcitabine + platinum (GP), paclitaxel + platinum (TP), navelbine + platinum (NP), docetaxel + platinum (DP) and cyclophosphamide + doxorubicin + platinum (CAP). In each regimen, the platinum-based compound was either DDP or NDP. The dose of gemcitabine was 1000 mg/m^2 on days 1 and 8; docetaxel was 75 mg/m^2 on day 1; paclitaxel was 135-175 mg/m^2 on day 1; navelbine was 25 mg/m^2 on days 1 and 8; cyclophosphamide was 600 mg/m^2 on day 1; doxorubicin was 50 mg/m^2 on day 1; and DDP and NDP were 80 mg/m^2 on day 1.

All the patients received dexamethasone and the 5-hydroxytryptamine receptor antagonist on days 1, 2 and 3, or days 8 and 9, to prevent chemotherapy-induced nausea and vomiting. Dexamethasone was also used prior to the administration of paclitaxel, to prevent allergic reaction. Hydration with 3 to 6 l of intravenous fluids and mannitol was conducted before and at the day of the administration of DDP. All the chemotherapy regimens were repeated every 21-28 days. Chemotherapy was continued until unacceptable toxicity was observed, or until the patient refused further treatment.

Evaluation. The overall survival time and toxicities observed were analyzed in each patient group. Overall survival time was calculated from the first day of chemotherapy until the last follow-up or until the patient succumbed. For patients with longer survival times, follow-up was discontinued at 5 years. The severity of all the toxicities associated with chemotherapy was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) grading system (17). Anemia, neutropenia, thrombocytopenia, nausea/vomiting, anorexia, renal toxicity, neurotoxicity and weight loss were the symptoms of toxicities that were evaluated.

Statistical analysis. Statistical analysis was performed using a statistical software package (SPSS for Windows, version 13.0; SPSS, Chicago, IL, USA). Survival curves were estimated using the Kaplan-Meier method, with censoring to correct for loss to follow-up. Survival difference was analyzed by

Table I. Patient characteristics.

Variables	DDP, n (%) (n=202)	NDP, n (%) (n=190)	χ^2	P-value
Gender				
Female	61 (30.2)	50 (26.3)	0.727	0.394
Male	141 (69.8)	140 (73.7)		
Age, years				
<60	110 (54.5)	103 (54.2)	0.002	0.961
≥60	92 (45.5)	87 (45.8)		
Smoking status				
Non-smoker	105 (52.0)	89 (46.8)	1.034	0.309
Current smoker	97 (48.0)	101 (53.2)		
Histology type				
Sq	74 (37.6)	58 (30.5)	2.192	0.139
Non-Sq	128 (62.4)	132 (69.5)		
Stage				
I-II	18 (8.9)	22 (11.6)	4.371	0.112
III	118 (58.4)	91 (47.9)		
IV	66 (32.7)	77 (40.5)		
Regimen				
GP	24 (11.9)	30 (15.8)	39.706	<0.001
TP	114 (56.4)	90 (47.4)		
DP	24 (11.9)	61 (32.1)		
CAP	22 (10.9)	3 (1.6)		
NP	18 (8.9)	6 (3.2)		
Cycles				
2-3	114 (56.4)	70 (36.8)	20.206	<0.001
4-5	70 (34.7)	78 (41.1)		
≥6	18 (8.9)	42 (22.1)		
Other treatments				
Radiotherapy	162 (80.2)	137 (72.1)	1.796	0.180
Target therapy	11 (5.4)	16 (8.4)		

Sq, squamous cancer; GP, gemcitabine + platinum; TP, paclitaxel + platinum; DP, docetaxel + platinum; CAP, cyclophosphamide + doxorubicin+platinum; NP, navelbine + platinum.

the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model. To calculate statistical significance between categorical variables, χ^2 or the Fisher exact test were used. Pearson correlation analysis was used to assess the association between the two groups. Two-tailed P-values were assessed and P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The retrospective study analyzed a total number of 392 patients diagnosed with NSCLC between January 2003 and December 2007. Among them, 202 had received DDP-based chemotherapy and 190 had received NDP-based chemotherapy. The patient characteristics are shown in Table I. No statistical difference was observed between the two groups with regard to gender, age, smoking status, histology type and stage, as analyzed by the Pearson χ^2 test (P<0.05).

All the enrolled patients had received at least two cycles of chemotherapy. The mean chemotherapy duration was 3.3 cycles in the DDP and 4.1 cycles in the NDP group. The number of patients receiving >4 chemotherapy cycles was 88/202 (43.6%) for the DDP group and 120/190 (63.2%) for the NDP group (χ^2=20.206, P<0.001, Table I).

Enrolled patients had undergone multiple regimens as the first-line regimen, including GP, TP, DP, NP and CAP. Although there were significant differences between the DDP and NDP groups (χ^2=39.706, P<0.001), ~50% of patients had received the TP regimen in each group (Table I).

Certain patients received radiotherapy or targeted therapy in the subsequent treatment, but there was no statistical difference between the percentages of patients receiving this therapy in the two groups (Table I).

Survival. Overall survival (OS) was considered from the start of treatment to the date of data analysis or the date of loss from follow-up for the remaining patients. The median follow-up time was 28 months (range, 4-60 months). As a result, the MST was 15 months [95% confidence interval (CI), 13.4-16.6] for the DDP group and 20 months (95% CI, 17.0-23.0) for the NDP group. Statistical analysis indicated that the NSCLC patients treated with NDP survived significantly longer than those with DDP (χ^2=5.189, P=0.023) (Table II and Fig. 1). Multivariate analyses showed that the type of platinum agent used was an independent predictive factor for the overall survival time of NSCLC patients [hazard ratio (HR), 0.764; 95% CI, 0.606-0.963; P=0.022] (Table II). The 1-, 2- and 3-year overall survival rates were 62.4, 25.7 and 15.8% for the DDP group, and 78.9, 38.9 and 16.8% for the NDP group, respectively. A statistical difference was observed between the two groups in the 1- and 2-year overall survival rates (χ^2=13.904, P<0.001; χ^2=7.827, P=0.005, respectively).

From Table II, the chemotherapy cycle number was an independent predictive factor for the overall survival time of NSCLC patients (HR, 0.539; 95% CI, 0.451-0.643; P<0.001). Table III showed that the MST of the patients with 2-3, 4-5 and ≥6 chemotherapy cycles in the DDP group and in the NDP group was 10, 18 and 24 months vs. 12, 20 and 26 months, respectively. However, no statistical difference was identified between the DDP and NDP groups (χ^2=0.040, P=0.980). Table III also showed that NDP-based chemotherapy was beneficial regardless of smoking status. No statistical differences were observed between the two groups for female patients, patients aged >60 years and patients with non-squamous cancer. However, younger patients (<60 years), male patients, patients with squamous cancer and stage III in the NDP group had a longer survival time compared to patients with the same characteristics in the DDP group (21 vs. 16 months, P<0.001; 20 vs. 14 months, P<0.001; 24 vs. 16 months, P=0.021; and 20 vs. 15 months, P<0.001, respectively). For further study in these subgroups, the distribution of the chemotherapy cycles was significantly different in the different platinum agent groups (Fig. 2). Thus, the chemotherapy cycles were the main reason that caused the different survival time.

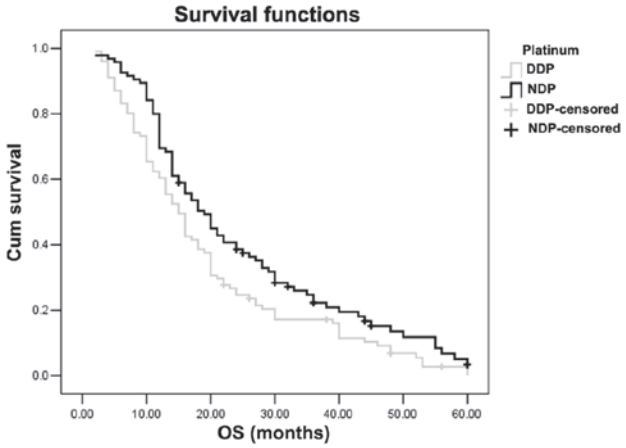

Figure 1. Kaplan-Meier analysis of overall survival (OS) times in patients receiving different platinum-based treatments. MST was 15 months (95% CI, 3.4-16.6) in the DDP group and 20 months (95% CI: 17-23) in the NDP group (Log-rank test: χ^2=5.189, P=0.023). MST, median survival time; CI, confidence interval; DDP, cisplatin; NDP, nedaplatin.

Table II also showed that stage was an independent predictive factor for the overall survival time of NSCLC patients (HR=2.099; 95% CI, 1.756-2.510; P<0.001). As the characteristic baseline regarding stage between DDP and NDP groups was balanced, further analysis was not performed.

Toxicity. The hematological and non-hematological toxicities are summarized in Table IV. No grade 3 or 4 renal toxicity or neurotoxicity was observed in either of the two groups. A significant difference was observed in thrombocytopenia, nausea/vomiting, anorexia and weight loss between the two groups. The rates of thrombocytopenia were higher in the NDP compared to the DDP group (12.1 vs. 5.4%, P=0.019). However, the rates of nausea/vomiting, anorexia and weight loss were higher in the DDP compared to the NDP group (36.1 vs. 8.4%, P<0.001; 17.3 vs. 5.8%, P<0.001; and 9.9 vs. 1.0%, P<0.001, respectively).

Discussion

Chemotherapy is the major method for treatment of lung cancer, owing to its high mortality and morbidity rates; recently, the use of platinum-based chemotherapeutic agents have allowed for significant advances in the survival of patients

Table II. Association between patient characteristics and overall survival time.

Variables	n	MST, months (95% CI)	P-value (Univariate analysis)	HR (95% CI)	P-value (Multivariate analysis)
Gender					
Female	111	16 (13.1-18.9)	0.380	0.952 (0.694-1.307)	0.761
Male	281	17 (13.1-18.9)			
Age, years					
<60	212	18 (16.2-19.8)	0.066	0.994 (0.791-1.249)	0.958
≥60	180	15 (12.7-17.3)			
Smoking status					
Non-smoker	194	18 (15.6-20.4)	0.241	0.829 (0.616-1.115)	0.214
Current smoker	198	16 (13.9-18.1)			
Histology type					
Sq	132	18 (15.7-20.3)	0.102	0.898 (0.682-1.164)	0.416
Non-Sq	260	16 (14.0-18.0)			
Stage					
I-II	40	36 (29.5-50.5)	<0.001	2.099 (1.756-2.510)	<0.001
III	209	17 (14.8-19.2)			
IV	143	13 (11.8-14.2)			
Regimen					
GP	54	18 (16.8.0-23.2)	0.060	0.952 (0.866-1.046)	0.304
TP	204	15 (12.6-17.4)			
DP	85	17 (15.4-18.6)			
CAP	25	14 (9.4-18.6)			
NP	24	18 (12.8-23.2)		0.539 (0.451-0.643)	<0.001
Cycles					
2-3	184	12 (10.6-13.4)	<0.001		
4-5	148	19 (17.7-24.3)			
≥6	60	23 (19.8-32.2)			
Platinum					
DDP	202	15 (13.4-16.6)	0.023	0.764 (0.607-0.962)	0.022
NDP	190	20 (17.0-2.30)			

Sq, squamous cancer; GP, gemcitabine + platinum; TP, paclitaxel + platinum; DP, docetaxe + platinum; CAP, cyclophosphamide + doxorubicin + platinum; NP, navelbine + platinum; DDP, cisplatin; NDP, nedaplatin; MST, median survival time; HR, hazard ratio.

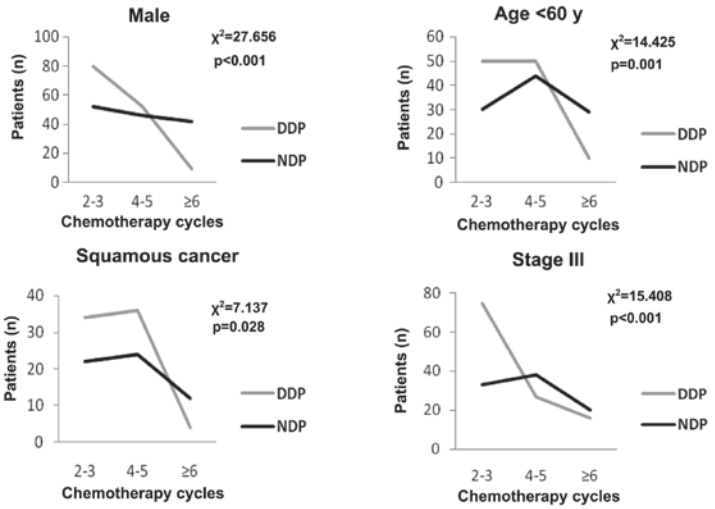

Figure 2. χ^2 analysis of the distribution of chemotherapy cycles with different platinum agent groups in the subgroups. DDP, cisplatin; NDP, nedaplatin.

Table III. Log-rank test for comparing overall survival time in the subgroups.

Variables	n	Median survival time (95% CI) DDP (n=202)	NDP (n=190)	χ^2	P-value
Gender					
Female	111	16 (15.1-16.9)	16 (9.9-22.1)	0.582	0.445
Male	281	14 (11.7-16.3)	20 (16.8-23.2)	14.225	<0.001
Age, years					
<60	212	16 (14.5-17.5)	21 (12.4-29.6)	21.121	<0.001
≥60	180	14 (11.6-17.3)	16 (13.2-17.8)	0.068	0.795
Smoking status					
Non-smoker	194	16 (14.4-17.6)	20 (14.6-25.4)	7.029	0.008
Current smoker	198	15 (10.2-19.8)	19 (16.2-21.2)	6.217	0.013
Histology type					
Sq	132	16 (10.4-19.6)	24 (20.4-31.6)	10.305	<0.001
Non-Sq	260	15 (14.4-17.6)	17 (14.8-21.2)	0.345	0.557
Stage					
I-II	40	34 (20.6-40.4)	38 (30.1-45.9)	0.669	0.413
III	209	15 (12.7-17.3)	20 (18.1-21.9)	5.360	0.021
IV	143	10 (9.0-11.0)	14 (12.5-15.5)	2.508	0.113
Cycles					
2-3	184	10 (7.8-12.2)	12 (10.3-13.7)	5.106	0.204
4-5	148	18 (14.5-22.5)	20 (15.9-28.1)	0.053	0.818
≥6	60	22 (20.9-30.1)	24 (14.0-36.0)	1.121	0.290

CI, confidence interval; Sq, squamous cancer; GP, gemcitabine + platinum; TP, paclitaxel + platinum; DP, docetaxel + platinum; CAP, cyclophosphamide + doxorubicin + platinum; NP, navelbine + platinum.

Table IV. Toxicity of grades 3-4 of different platinum agents.

Variables	DDP, n (%)	NDP, n (%)	χ^2	P-value
Hematologic				
Anemia	8 (4.0)	3 (1.6)	2.036	0.154
Neutropenia	42 (20.8)	32 (16.8)	0.998	0.192
Thrombocytopenia	11 (5.4)	23 (12.1)	5.482	0.019
Non-hematologic				
Nausea/vomiting	73 (36.1)	16 (8.4)	48.862	<0.001
Anorexia	35 (17.3)	11 (5.8)	12.582	<0.001
Renal toxicity	0 (0.0)	0 (0.0)	N.A.	N.A.
Neurotoxicity	0 (0.0)	0 (0.0)	N.A.	N.A.
Weight loss	20 (9.9)	2 (1.0)	13.642	<0.001

DDP, cisplatin; NDP, nedaplatin; N.A., not accessible.

with NSCLC. For a number of years, DDP has been the major agent in these regimens. However, its relatively high rates of renal and gastrointestinal toxicities lead numerous patients in China to give up chemotherapy. Carboplatin and NDP are DDP analogs, with a relatively lower toxicity profile. As NDP has the same administration method and dosage as DDP, it has become the most popular platinum-based agent for NSCLC patients in China. Although numerous trials have compared the effect and survival benefit of DDP and carboplatin in NSCLC (18-21), only few trials have compared NDP with DDP. Cao *et al* (22) reported that NDP had similar response rates to DDP in the treatment of nasopharyngeal carcinoma. Yamashita *et al* (23) reported that the overall survival rates of NDP at 1, 2 and 3 years were lower than those of DDP (40, 13 and 13% vs. 56, 42 and 8%, respectively) in the treatment of esophageal cancer, but no significant difference was found between the two groups. However, in the study, the two groups had an unequal number of patients (12 on the NDP regimen vs. 29 on the DDP regimen). Therefore, the survival benefit of NDP has remained an unsolved issue thus far.

In the present study, the patients receiving NDP-based chemotherapy had higher survival rates than those treated with DDP. The MST was greater by 5 months, whereas the 1- and 2-year overall survival rates were also higher in the NDP group. The observed survival benefits of NDP can be explained as follows: Firstly, the two groups have similar baseline characteristics, except for the chemotherapy cycles. As patients receiving NDP-based treatment experience less toxicity and show good compliance with the chemotherapy regimen, these patients can complete more cycles of the chemotherapy. The chemotherapy cycle number was an independent predictive factor. More chemotherapy cycles can reduce the mortality risk for 46%. Scotti *et al* (24) also came to the same conclusion

that the number of chemotherapy courses persisted as a significant mortality predictor at multivariate regression analysis, with a reduced mortality risk for 5-6 chemotherapy cycles in comparison to 3-4 cycles (HR, 0.44). Secondly, the differential weight loss effect of NDP could also account for the observed survival benefit. More specifically, the rate of weight loss was much higher in DDP- compared to NDP-treated patients. Yang *et al* (25) reported that lung cancer patients undergoing weight loss had shorter MST than those not losing weight (6.4 vs. 9.2 months, P<0.001). Finally, the present study also showed that the type of platinum agent used was an independent predictive factor for the overall survival time and HR is 0.764. Preclinical and *in vitro* studies have found that the plasma concentration profile of unbound platinum following NDP infusion is similar to that of total platinum, and that the protein-binding affinity of NDP is lower than that of DDP (26). Thus, NDP has been demonstrated to have higher antitumor activity than DDP (2).

In the present study, male patients, patients <60 years of age, and patients with squamous cancer and stage III in the NDP group had a much longer survival time than patients with similar characteristics in the DDP group. In the further study, the distribution of chemotherapy cycles was significantly different in different platinum agent groups, which suggested that the chemotherapy cycles were the main reason that caused the different survival time. However, Yamamoto *et al* (27) observed that when NDP was used in advanced NSCLC patients, partial responses were observed in 13 (33%) of the 39 patients, while 12 of the 13 patients who responded had squamous cell carcinoma. Teramoto *et al* (28) also reported that NDP responded better in squamous cell carcinoma of the lung. Thus, further clinical trials are required to confirm these observations.

In conclusion, NDP-based chemotherapy prolongs the median survival time of NSCLC patients, compared to DDP-based chemotherapy. The observed survival benefit is due to the reduced toxicity of NDP, which allows patients to tolerate more cycles of chemotherapy. A slow toxicity and high life quality were the tendencies of the advanced cancer treatment currently. Thus, NDP may be a more reasonable choice than DDP in clinical practice. In addition, noteworthy information is also provided regarding the impact of gender, age and histological type, which may improve treatments by targeting specific patient populations.

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