RESEARCH ARTICLE

Randomized Control Study of Nedaplatin or Cisplatin Concomitant with Other Chemotherapy in the Treatment of Advanced Non-small Cell Lung Cancer

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Abstract

Objective: To observe the short-term efficacy, long-term survival time and adverse responses with nedaplatin (NDP) or cisplatin (DDP) concomitant with other chemotherapy in treating non-small cell lung cancer. Materials and Methods: A retrospective, randomized, control study was conducted, in which 619 NSCLC patients in phases III and IV who were initially treated and re-treated were randomly divided into an NDP group (n=294) and a DDP group (n=325), the latter being regarded as controls. Chemotherapeutic protocols (CP/DP/GP/NP/TP) containing NDP or DDP were given to both groups. Patients in both groups were further divided to evaluate the clinical efficacies according to initial and re-treatment stage, pathological pattern, type of combined chemotherapeutic protocols, tumor stage and surgery. Results: The overall response rate (ORR) and disease control rate (DCR) in the NDP group were 48.6% and 95.2%, significantly higher than in the DDP group at 35.1% and 89.2%, respectively ($P<0.01$). In NSCLC patients with initial treatment, squamous carcinoma and phase III, there were significant differences in ORR and DCR between the groups ($P<0.05$), while ORR was significant in patients with adenocarcinoma, GP/TP and in phase IIIa ($P<0.05$). There was also a significant difference in DCR in patients in phase IIIb ($P<0.05$). According to the statistical analysis of survival time of all patients and of those in clinical phase III, the NDP group survived significantly longer than the DDP group ($P<0.01$). The rates of decreased hemoglobin and increased creatinine, nausea and vomiting in the NDP group were evidently lower than in DDP group ($P<0.05$). Conclusion: NDP concomitant with other chemotherapy is effective for treating NSCLC, with higher clinical efficacy than DDP concomitant with chemotherapy, with advantages in prolonging survival time and reducing toxic and adverse responses.

Keywords: Nedaplatin - cisplatin - non-small cell lung cancer - chemotherapy

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Introduction

Being one of the most malignant tumors commonly seen in clinic, lung cancer has the highest malignant severity and poor chemo-radio-therapeutic efficacy, becoming the primary factor for tumor-associated death, in which on-small cell lung cancer (NSCLC) accounts for 80%~85%, and local NSCLC could be excised by surgery if it could be diagnosed early. However, more than half NSCLC patients are in middle and advanced stages when diagnosed, who are in poor sensitivity to radiotherapy and apt to produce tolerance to chemotherapy with unsatisfactory therapeutic efficacy (Wagner et al., 2006; Jemal et al., 2008; Wagner et al., 2010). In recent years, the present status of treatment for NSCLC has been improved, with its primary therapeutic protocols being the combination of 2 drugs with chemotherapy based on platinum drugs on the stage (Maione et al., 2011). Cisplatin (DDP) is the first generation of platinum drugs, which has become the basic drug for treating advanced solid tumors like NSCLC, etc. (Rinaldi et al., 2006). However, its clinical application is limited due to severe gastrointestinal responses, renal toxicity and neurotixicity. Nedaplatin (NDP) is a new anti-tumor drug derived from DDP, which has similar action mechanisms to DDP, but also revealed stronger anti-tumor effect and lower toxic and adverse responses in animal research (Kameyama et al., 1990). This study analyzed and compared the efficacy and safety of NDP or DDP concomitant with chemotherapies in treating advanced NSCLC, hoping to provide references for the reasonable clinical application of NDP in the future.

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Table 1. General Data of Layered Groups of Both Groups

Programs	NDP group (n=294)	DDP group (n=325)	*P*
Age (year)			
Mean (S.D)	56.28 (8.950)	55.01 (9.003)	0.0787
Median	56.0	56.0	
Min~Max	22.0~78.0	21.0~81.0	
Height (cm)			
Mean (S.D)	166.61 (7.462)	167.99 (7.551)	0.0232
Median	167.0	170.0	
Min~Max	147.0~186.0	124.0~189.0	
Weight (Kg)			
Mean (S.D)	64.80 (11.926)	64.82 (11.277)	0.9777
Median	63.0	63.0	
Min~Max	38.0~112.0	40.0~115.0	
Gender[n (%)]			
Male	175 (59.5)	216 (66.5)	0.0800
Female	119 (40.5)	109 (33.5)	
Initial and re-treatment[n (%)]			
Initial treatment	248 (84.4)	274 (84.3)	1.0000
Re-treatment	46 (15.6)	51 (15.7)	
Pathological patterns [n (%)]			
Squamous carcinoma	103 (35.0)	117 (36.0)	0.8665
Adeno-carcinoma	191 (65.0)	208 (64.0)	
Clinical stages [n (%)]			
I	31 (10.5)	45 (13.8)	0.1301
II	38 (12.9)	52 (16.0)	
IIIa	55 (18.7)	64 (19.7)	
IIIb	43 (14.6)	56 (17.2)	
IV	127 (43.2)	108 (33.2)	
Smoking history [n (%)]			
No	158 (53.7)	160 (49.2)	0.2952
Yes	136 (46.3)	165 (50.8)	
Family history [n (%)]			
No	258 (87.8)	294 (90.5)	0.3016
Yes	36 (12.2)	31 (9.5)	
Chemotherapeutic protocols[n (%)]			
CP	12 (4.1)	9 (2.8)	1.0000
DP	40 (13.6)	19 (5.8)	
GP	110 (37.4)	103 (31.7)	
NP	48 (16.3)	101 (31.1)	
TP	84 (28.6)	93 (28.6)	
Chemotherapeutic cycles[(%)]			
Mean (S.D)	3.54 (1.529)	3.40 (1.271)	0.2020
Median	4.0	3.0	
Min~Max	1.0~16.0	1.0~8.0	
Operation[n (%)]			
No	202 (68.7)	224 (68.9)	1.0000
Yes	92 (31.3)	101 (31.1)	
Radiotherapy[n (%)]			
No	211 (71.8)	220 (67.7)	0.2940
Yes	83 (28.2)	105 (32.3)	

Materials and Methods

General data

A total of 619 patients with advanced NSCLC hospitalized in our hospital from October, 2009 to July, 2011 were selected, in which there were 391 males and 228 females aging from 21 years to 81 years with average age being (55.65±8.50) years. And in this study, there were 522 patients with initial treatment, 97 with re-treatment, 220 with squamous carcinoma, 399 with adeno-carcinoma and 426 with surgeries during treatment. According to pathological stages, 76, 90, 119, 99 and 235 patients were in phases I, II, IIIa, IIIb and IV, respectively.

Layered Groups

The selected patients were randomly divided into NDP group (n=294) and DDP group (n=325). Chemotherapeutic protocols (CP/DP/GP/NP/TP) containing NDP/DDP were administrated to both groups and there were no statistically significant differences in general data (P>0.05), as shown in Table 1. Methods

Chemotherapeutic protocols containing 75 mg/m^2 NDP/DDP were conducted to both groups, which included 500 mg/m^2 pemetrexed on d 1 (CP), 75 mg/m^2 Docetaxel on d 1 (DP), 1000 mg/m^2 gemcitabine on d 1 and 8 (GP), 25 mg/m^2 vinorelbine on d 1 and 8 (NP) as well as 175 mg/m^2 paclitaxel on d 1 (TP). All drugs were given in 3 d, 4 weeks as 1 cycle.

Observational indexes

Short-term efficacy, survival time and toxic and adverse responses in both groups were observed after the follow-up was ended on November, 23th, 2012. Moreover, the 2 groups were further divided to evaluate clinical efficacies according to initial and re-treatment, pathological patterns, types of combined chemotherapeutic protocols and tumor stages.

Efficacy evaluation criteria

Therapeutic efficacy was evaluated according to Response Evaluation Criteria of WHO (World Health Organization): (1) Complete response (CR): all nidi disappeared for >4 weeks; (2) Partial response (PR): the nidi shrank >50% for >4 weeks; (3) Stable disease (SD): the change of nidi was between PR and PD; (4) Progressive disease (PD): nidi increased >25% or new nidi appeared. Objective response rate (ORR)=[(CR+PR)/ total cases]×100% while disease control rate (DCR)=[(CR+PR+SD)/total cases]×100%.

Statistical data analysis

SPSS 10.0 software was adopted for all data analysis, whereas t-test was applied for the comparison of means of both groups and measurement date was expressed as mean±standard deviation (χ±s). P<0.05 was regarded as the difference was statistically significant.

Results

Short-term efficacy

In NDP group, there were 12 CR, 131 PR, 137 SD and 14 PD, with ORR and DCR being 48.6% and 95.2%, while in DDP group, CR, PR, SD and PD were 10, 104, 176 and 35, with ORR and DCR being 35.1% and

Table 2. Clinical Efficacy Comparison of 2 Groups [n (%)]

Optimal efficacy	CR	PR	SD	PD	Total	ORR/%	DCR/%
NDP group	12 (4.1)	131 (44.6)	137 (46.4)	14 (4.8)	294	48.6**	95.2**
DDP group	10 (3.1)	104 (32.0)	176 (54.2)	35 (10.8)	325	35.1	89.2

Compared with DDP Group, **P<0.01

Table 3. Layered Efficacy Comparison of Two Groups

Programs	Groups	CR/n	PR/n	SD/n	PD/n	Total/n	ORR/%	*P*	DCR/%	*P*
Initial treatment	NDP group	12	112	112	12	248	50.00	0.000	95.16	0.003
	DDP group	10	80	150	34	274	32.85		87.59	
Re-treatment	NDP group	0	19	25	2	46	41.30	0.683	95.65	0.602
	DDP group	0	24	26	1	51	47.06		98.04	
Squamous carcinoma	NDP group	8	54	39	2	103	60.19	0.007	98.06	0.022
	DDP group	6	42	58	11	117	41.03		90.60	
Adeno-carcinoma	NDP group	4	77	98	12	191	42.41	0.029	93.72	0.080
	DDP group	4	62	118	24	208	31.73		88.46	
CP	NDP group	0	6	6	0	12	50.00	0.367	100.00	0.063
	DDP group	0	2	4	3	9	22.22		66.67	
DP	NDP group	1	16	20	3	40	42.50	0.570	92.50	0.376
	DDP group	0	6	10	3	19	31.58		84.21	
GP	NDP group	9	50	43	8	110	53.64	0.001	92.73	0.625
	DDP group	3	29	61	10	103	31.07		90.29	
NP	NDP group	2	19	27	0	48	43.75	0.862	100.00	0.058
	DDP group	3	43	46	9	101	45.54		91.09	
TP	NDP group	0	40	41	3	84	47.62	0.020	96.43	0.086
	DDP group	4	24	55	10	93	30.11		89.25	
I	NDP group	4	20	7	0	31	77.42	0.052	100.00	0.266
	DDP group	5	19	18	3	45	53.33		93.33	
II	NDP group	3	20	13	2	38	60.53	0.141	94.74	1.000
	DDP group	2	21	26	3	52	44.23		94.23	
IIIa	NDP group	1	37	15	2	55	69.09	0.006	96.36	0.174
	DDP group	1	27	29	7	64	43.75		89.06	
IIIb	NDP group	4	12	25	2	43	37.21	0.393	95.35	0.020
	DDP group	1	15	28	12	56	28.57		78.57	
IV	NDP group	0	42	77	8	127	33.07	0.057	93.70	0.464
	DDP group	1	22	75	10	108	21.30		90.74	

Table 4. Case Processing Summary

Groups	Total N	N of Events	Censored	
			N	Percentage (%)
NDP group	294	121	173	58.8
DDP group	325	116	209	64.3
Overall	619	237	382	61.7

Table 6. Case Processing Summary

Groups	Total N	N of Events	Censored	
			N	Percent (%)
NDP group	225	96	129	57.3
DDP group	228	92	136	59.6
Overall	453	188	265	56.5

Table 5. Means and Medians of Survival Time

Groups	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
NDP group	17.115	0.926	15.301	18.929	14.783	1.092	12.643	16.923
DDP group	21.391	2.049	17.375	25.408	13.502	2.327	8.941	18.063
Overall	20.219	1.458	17.361	23.077	14.783	1.155	12.519	17.048

[a]Estimation is limited to the largest survival time if it is censored

89.2%, respectively, showing that ORR and DCR were evidently higher in NDP group than in DDP group, and the differences were significant ($P<0.01$), as shown in Table 2.

Layered clinical efficacies

The 2 groups were further divided to evaluate clinical efficacies according to initial and re-treatment, pathological patterns, types of combined chemotherapeutic protocols and tumor stages. As shown in Table 3, ORR and DCR in NDP group were obviously higher than in DDP group in patients with initial treatment and squamous carcinoma ($P<0.05$ or $P<0.01$), while ORR was apparently higher in patients with adeno-carcinoma, GP/TP, and in phase IIIa ($P<0.05$ or $P<0.01$), and DCR was markedly higher in patients in phase IIIb in NDP group than in DDP group ($P<0.05$).

Survival time

Survival time of 619 patients was statistically analyzed, which indicated that mean survival time and medium survival time (MST) in NDP group were (17.115±0.926) months and (14.783±1.092) months, and were (21.391±2.049) months and (13.502±2.327) months in DDP group, respectively, demonstrating that MST was longer in NDP group than in DDP group, and the difference was significant ($P<0.01$) (Table 4, Table 5 and Figure 1).

Table 7. Means and Medians of Survival Time

Groups	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
NDP group	16.348	1.025	14.339	18.357	14.619	1.235	12.198	17.040
DDP group	15.688	1.482	12.783	18.592	10.545	1.050	8.487	12.604
Overall	16.491	1.077	14.380	18.602	12.681	0.718	11.273	14.088

[a]Estimation is limited to the largest survival time if it is censored

Table 8. Adverse Responses of Each Group [n (%)]

Adverse responses	NDP group (n=294)	DDP group (n=325)
Leucopenia	66 (22.4)	91 (28.0)
Decreased hemoglobin	38 (13.0)*	67 (20.6)
Neutropenia	86 (29.3)	90 (27.7)
Thrombocytopenia	23 (7.8)	18 (5.5)
Increased creatinine	97 (33.0)*	138 (42.5)
Increased blood urea nitrogen	76 (25.9)	92 (28.3)
Increased glutamic-pyruvic transaminase	161 (54.8)	178 (54.8)
Increased glutamic-oxaloacetic transaminase	62 (21.1)	45 (13.8)
Elevated total bilirubin	41 (13.9)	26 (8.0)
Direct elevated bilirubin	29 (9.9)	21 (6.5)
Indirect elevated bilirubin	70 (23.8)*	54 (16.6)
Nausea	62 (21.1)**	112 (34.5)
Vomiting	27 (9.2)*	51 (15.7)
Constipation	3 (1.0)	10 (3.1)
Diarrhea	1 (0.34)	7 (2.2)
Fatigue	47 (15.9)	63 (19.4)

Adverse responses

Table 8 is showing the adverse responses of 2 groups, which demonstrated that the rates of decreased hemoglobin, increased creatinine, nausea and vomiting were markedly lower ($P<0.05$ or $P<0.01$) but indirect elevated bilirubin was evidently higher in NDP group than in DDP group ($P<0.05$).

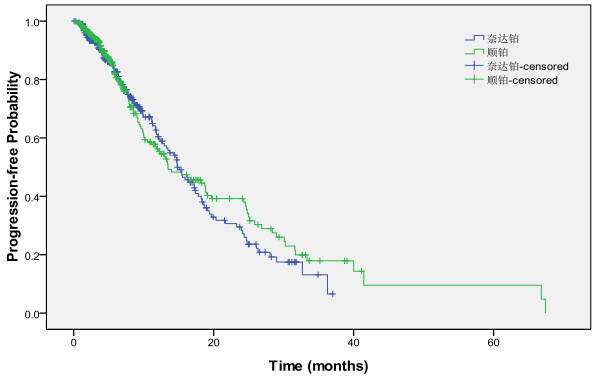

Figure 1. Kaplan-Meier Survival Curve of All Patients

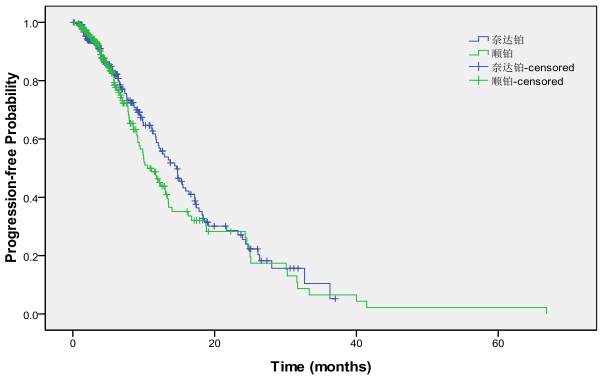

Figure 2. Kaplan-Meier Survival Curve of Patients in Clinical Stage > Phase III

Discussion

Incidences of lung cancer in China have been increasingly more serious for the past few years, in which NSCLC accounts for>80%, including large cell carcinoma, adeno-carcinoma and squamous carcinoma (Govindan et al., 2006; Liu et al., 2013; Kim et al., 2014). Surgery is one of the optimal therapeutic methods for early treatment, but it is difficult to perform because there is no specific or obvious clinical symptom in early stage (Yu et al., 2013; Oven Ustaalioglu et al., 2013; Mandal et al., 2013). When diagnosed, only < 20% NSCLC patients could receive surgeries and fewer with radiotherapy, and most are in advanced ones with distant metastasis who missed the optimal surgical opportunities except the systemic chemotherapies. Studies demonstrated that the third generation of cytotoxic drugs concomitant with cisplatins and chemotherapies were the optimal choices for treating middle and advanced NSCLC (Sugiyama et al., 2011; Terret et al., 2011), which played a critical and important role in controlling disease progression, alleviating clinical symptoms, improving patients' quality of life (QOL) and prolonging their survival time, etc.. However, appropriate chemotherapeutic protocols and drugs are extremely important due to frequently occurred distant metastasis and recurrence according to complex biological properties and poor immunity in old and weak patients.

DDP is the first generation of anti-tumor drugs with non-specific cycle in cisplatins that came to market in USA in 1979, which could dissociate chlorine in low chlorine environment after being administrated to form hydrated cation of cisplatin, and combine with N7s on DNA binding sites A and G to form covalent bond. After combination, the formation of intra-strand and inter-strand cross-links as well as the those of DDP and DNA-protein molecules reversed or un-winded DNA strands, which inhibit the republication of DNA, leading to cellular apoptosis (Arriagada et al., 2004; Scagliotti et al., 2008). One study compared the efficacy and safety of DDP or carboplatin (CBP) in the treatment of NSCLC, revealing that the short-term efficacy of DDP was markedly better than CBP, but there was no significant difference in improvement of survival time, whereas the analysis

of subgroups showed that DDP had better survival advantages than CBP when concomitant with the third generation of chemotherapeutic drugs (Hotta et al., 2004). However, another study indicated that CBP was superior to DDP in treating patients administrated with the third generation of cytotoxic drugs and those with squamous carcinoma, and it was predicated to be associated with the stronger renal toxicity and gastrointestinal responses, which severely influenced patients' QOL, especially those with renal dysfunction and poor compliances, tolerance and general condition, and inhibit the effective application of DDP in clinic.

NDP is the second generation of anti-tumor agent in cisplatins and has similar actions to DDP, that is, it could react with DNA nucleosides, produce compound of nucleosides-cisplatins and blockage the republication of DNA to achieve its anti-tumor effect (Alberto et al., 2009; Teramoto et al., 2012). However, NDP has become increasingly more important in treating NSCLC in that it has no complete cross-tolerance, but is 10 folds in water-solubility than DDP. One study indicated that ORR and DCR of NDP concomitant with docetaxel in the treatment of advanced NSCLC were 50.0% and 75%, respectively, in which patients with squamous carcinoma had evidently higher ORR and less adverse responses with slight non-hematological adverse responses and good tolerance than those with adeno-carcinoma, suggesting that NDP concomitant with docetaxel were more effective and tolerable in advanced NSCLC patients with squamous carcinoma than those with adeno-carcinoma (Yang et al., 2012). However, another clinical research of NDP/gemcitabine comparing with CBP/gemcitabine in treating advanced NSCLC showed that there were no significant differences in MST and ORR in 2 groups, and the main toxic and adverse responses contained leucopenia, anemia and thrombopenia, etc., which had no statistically significant difference (Niioka et al., 2007).

This study compared and analyzed the differences of efficacy and safety between NDP and DDP concomitant with CP, DP, GP, NP and TP in treating advanced NSCLC, which indicated that NDP group was evidently higher than DDP group in ORR and DCR in that ORR and DCR were 48.6% and 95.2% in NDP group, but were 35.1% and 89.2% in DDP group, respectively, and NDP group was obviously higher than DDP group in ORR and/or DCR of patients with initial treatment, squamous carcinoma, GP/TP and in stage IIIa/IIIb, demonstrating that NDP concomitant with chemotherapy were more appropriate for patients with initial advanced lung squamous carcinoma. Survival time of 619 patients was also statistically analyzed in this study, which found that MST was markedly longer in NDP group than in DDP group. For adverse responses, the main toxic and adverse responses in NDP group were hepatorenal functional injury and hematological toxicity with slight gastrointestinal responses, significantly lower than DDP group in the rates of reduced hemoglobin, increased creatinine, and nausea and vomiting.

To sum up, NDP concomitant with chemotherapy is more effective than DDP in the treatment of advanced NSCLC, and is more appropriate to patients with lung squamous carcinoma. Additionally, hematological toxicity and gastrointestinal responses in NDP group were alleviated more significantly than in DDP group with favorable tolerance, which improved their compliances. According to comprehensive consideration of clinical efficacy, rates and severity of adverse response and patients' tolerance, NDP is more easily to be accepted by physicians and patients, which has extensive clinical applicable prospect in treating patients with advanced NSCLC, especially those with lung suqamous carcinoma, deserving to be further concerned in clinic.

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