RESEARCH COMMUNICATION

Phase II Trial of Irinotecan plus Nedaplatin (INP) in Treating Patients with Extensive Stage Small Cell Lung Cancer

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Abstract

Purpose: We conducted a phase II study of combination chemotherapy with irinotecan (CPT-11) and nedaplatin (NDP), (INP regimen), to determine the effects and toxicities in patients with extensive stage small cell lung cancer (SCLC). Methods: From March 2005 to December 2010, 60 patients with histologically or cytologically confirmed extensive SCLC were enrolled into this study. All received treatment CPT-11 at a dose of 60mg/m^2 on days 1 and 8, and NDP 20mg/m^2 on days1-5, every 3-4 weeks as a cycle. Patients were treated until tumor progression or unacceptable toxicity. Results: Main toxicities included: myelosuppression, nausea or vomiting, diarrhea, elevation of alanine aminotransferase,and bilirubin. No treatment related death occurred in this study. Thirteen patients had complete response, forty-two had partial response, three remained stable, and two had progressive disease. Median progression-free survival was 13 months (95% confidence interval: 9-17) and median overall survival was 22 months (95% confidence interval: 19-25). Conclusion: INP is an effective and well tolerated regimen for treatment of extensive staged SCLC.

Keywords: Irinotecan - nedaplatin - chemotherapy - small cell lung cancer

Asian Pacific J Cancer Prev, **12**, 487-490

Introduction

Etoposide in combination with platinum-based chemotherapy has been the standard treatment for extensive staged small cell lung cancer (SCLC) (Evans et al.,1985). Other regimens like the combination of cyclophosphamide, adriamycin and vincristine (CAV) are equally effective (Roth et al.,1992) and have been employed in alternation with etoposide plus platinum for first-line therapy (Ueoka et al.,1998) or for treatment of relapse(Von Pawel et al.,1999).

More recently, a randomized phase III trial performed in Japan was terminated early,because of a superior survival in the irinotecan/cisplatin treatment arm when compared with standard etoposide/cisplatin (Noda et al.,2002). In addition, high efficacy of irinotecan-based chemotherapy has been demonstrated in two phase II trials in relapsed or refractory disease(Hirose et al.,2003; Naka et al.,2002).These data resulted in the initiation of further trials in SCLC. In North America, one randomized phase III trial comparing irinotecan/cisplatin to etoposide/cisplatin in a 2:1 randomization in 331 patients has recently been reported(Hanna et al.,2005).This trial confirmed lower myelotoxicity and a significantly increased frequency of diarrhea in the irinotecan arm, but failed to show a significant difference in overall survival.Furthermore, in Europe,a randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin in patients with extensive SCLC showed that irinotecan plus carboplatin active, less toxic and appears to improve prgression free survival (PFS) (Schmittel et al., 2008).

Nedaplatin (NDP) is an analogue of cisplatin,in vivo,with relatively low neurotoxicity and nephrotoxicity, and could play an important role in the treatment of patients with advanced lung cancer(Kameyama et al., 1990). A phase I study,in which 100 mg/m^2 of NDP was recommended, has demonstrated that the dose-limiting toxicity is thrombocytopenia (Ariyoshi et al.,1988). A phase II study on NSCLCsuggested NDP at a dose of 100 mg/m^2 every 4 weeks achieved a 14.7% objective response rate (RR) (Fukuda et al.,1990).Another study in Japan revealed that the combination of 60 mg/m^2 of irinotecan with 100 mg/m^2 of NDP was safe and feasible in treating patients with NSCLC., with antitumor activity not inferior to other cisplatin combinations (Oshita et al.,2003).

However, there are no data to date reported irinotecan and nedaplatin combination (INP) for extensive staged SCLC.We hypothesised that this combination is superior to current regimens in this setting. The aim of this phaseIIstudy was to obtain the safety and efficacy profile of INP in treating patients with extensive staged SCLC.

Materials and Methods

Patients and methods

To be included in the study, patients had to have cytologically or histologically confirmed SCLC; extensive

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disease (defined by distant metastasis, contralateral hilar-node metastasis, or both; those with pleural effusion alone were excluded); no prior radiotherapy, chemotherapy, or surgery; measurable lesions; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; a life expectancy of at least three months; an age of 70 years or less; and adequate organ function. Staging of the tumor was based on the results of physical examination, chest radiography,computed tomography (CT) of the chest,brain,and abdomen, radionuclide bone scanning, and other tests as needed. Adequate organ function (adequate function of the bone marrow, liver, and kidney) was defined as indicated by a leukocyte count of at least 4000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a hemoglobin level of at least 9.5g per deciliter (5.9 mmol per liter), aspartate aminotransferase and alanine aminotransferase levels no higher than 100 IU per milliliter, a serum creatinine level no higher than 1.2 mg per deciliter (106 μmol per liter), and a creatinine clearance of at least 60 ml per minute.

The exclusion criteria were infection, diarrhea, ileus, interstitial ,pneumonitis, pulmonary fibrosis, uncontrolled diabetes mellitus, myocardial infarction within the preceding three months, massive pleural or peritoneal effusion, symptomatic brain metastases requiring whole-brain irradiation or administration of corticosteroids, a paraneoplastic syndrome, an active synchronous cancer, and pregnancy or breast-feeding.

Treatment protocol

A cycle of INP is as follows: irinotecan 60mg/m^2 on days 1 and 8, and NDP 20mg/m^2 on days1-5, repeat every 3-4 weeks. Antiemetic treatment was granisetron 3mg by intravenous bolus infusion prior to chemotherapy. Routine blood test, blood biochemistry and tumor markers were reviewed weekly during and after chemotherapy. If leukocyte count fell below 2000 per cubic millimeter or neutrophil count fell below 1000 per cubic millimeter, recombinant human granulocyte colony-stimulating factor was administered until the leukocyte or neutrophil count was restored.

Evaluations

All patients underwent weekly evaluations that included an assessment of symptoms, a physical examination, chest radiography, a complete blood count, blood-chemistry studies (including measurements of aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase, bilirubin, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes, and calcium), and urinalysis. Tumor assessment was evaluated after every two cycles of INP. Tumor response was evaluated according to World Health Organization criteria and was assessed by CT or MRI and by the same tests used initially to stage the tumor (Gehan et al., 2000). A complete response (CR) was defined as the disappearance of all clinical and radiologic evidence of tumor for at least four weeks; a partial response (PR) was defined as a decrease of 50 percent or more in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least four weeks; and progressive disease (PD) was defined as an increase of more than 25 percent in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate stable disease (SD).

Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1981).

Our end point was overall survival from the data documenting pathological diagnosis to Dec 2010. Survival data were obtained from the hospital follow-up team. Records with no reply were followed by local Ministry of Public Security.

Statistical analysis

The study data were analyzed through the STATA 8.0 software(Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA). The Kaplan–Meier method was used for plotting survival curves.

Results

Sixty patients,36 men and 24 women, were enrolled into this study. Characteristics of patients are presented in Table 1.

Toxicity

All 60 patients were assessable for toxicity. Main toxic effects are shown in Table 2. No treatment related death occurred in this study.The most common toxicity was mylosuppression (83.3%),nausea or vomiting (95%),diarrhea (83.3%),elevation of alanine aminotransferase(91.7%), and bilirubin(80%). Other side effects included: anemia,fever, peripheral neuropathy and creatinine elevation.

Table 1. Characteristics of the Patients

Characteristic		No (%)
Age (yr)Median (Range)		61 (43-75)
Sex	Male	36 (60.0)
	Female	24 (40.0)
ECOG performance status*	0	8 (13.3)
	1	47 (78.3)
	2	5 (8.3)
Weight loss during	<5%	43 (71.7)
previous 6 mo	5–10%	14 (23.3)
	>10%	3 (5.0)
Lymph-node metastasis		
Contralateral mediastinal	Absent	41 (68.3)
	Present	19 (31.7)
Supraclavicular	Absent	52 (86.7)
	Present	8 (13.3)
Distant metastasis†	Absent	3 (5.0)
	Present	57 (95.0)
	Liver	14 (23.3)
	Lung	17 (28.3)
	Brain	5 (8.3)
	Bone	8 (13.3)
	Adrenal gland	7 (11.7)
	Bone marrow	6 (10.0)

*ECOG denotes Eastern Cooperative Oncology Group; †Some of the patients had distant metastasis to more than one site

Table 2. Toxicity Characteristics for the Patients

Toxicity	Grade 1	2	3	4
Hematologic				
Neutropenia	28 (46.7)	17 (28.3)	7 (11.7)	2 (3.3)
Leukopenia	23 (38.3)	19 (31.7)	6 (10.0)	2 (0.3)
Anemia	29 (48.3)	10 (16.7)	5 (8.3)	0 (0.0)
Thrombocytopenia	24 (40.0)	20 (33.3)	5 (8.3)	2 (3.3)
Nonhematologic				
Diarrhea	22 (36.7)	19 (31.7)	8 (13.3)	1 (1.7)
Nausea or vomiting	13 (21.7)	24 (40.0)	10 (16.7)	0 (0.0)
Decrease in arterial oxygen pressure	15 (25.0)	7 (11.7)	1 (1.7)	1 (1.7)
Increase in ALT	28 (46.7)	17 (28.3)	7 (11.7)	2 (3.3)
Increase in AST	24 (40.0)	8 (13.3)	0 (0.0)	0 (0.0)
Fever	13 (21.7)	6 (10.0)	2 (3.3)	0 (0.0)
Increased bilirubin	22 (36.7)	24 (40.0)	2 (3.3)	0 (0.0)
Increased creatinine	9 (15.0)	3 (5.0)	0 (0.0)	0 (0.0)
Periph neuropathy	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are No and % values; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Response Rates of Treatment

All patients were assessable for response.Thirteen patients (21.7%) had CR,42(70%) had PR, 3 (5%) had SD and 2(3.3%) experienced PD.

Survival

As of December 2010, when the final analysis was conducted, the median overall survival of our patient cohort was 22 months(95% confidence interval, 19-25) and the median progression-free survival was 13 months (95% confidence interval, 9-17) (Figures 1 and 2).

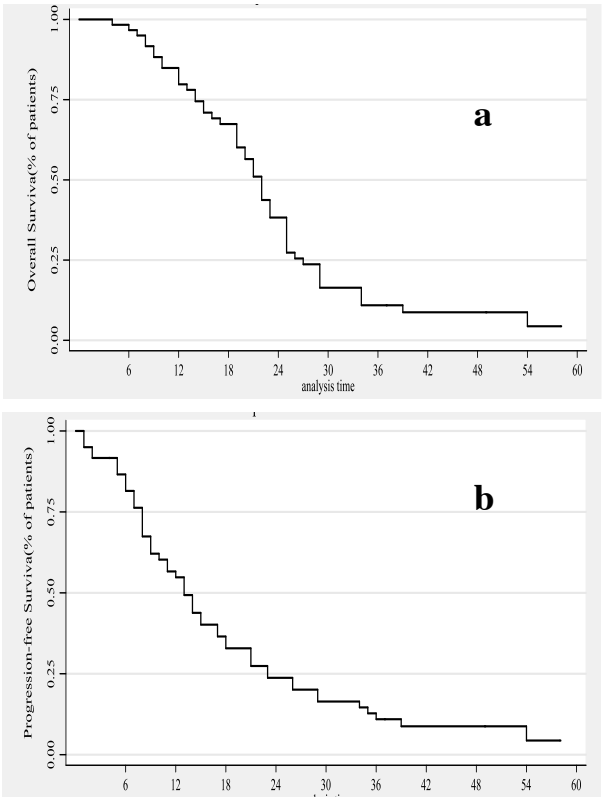

Figure 1. a) Overall and b) Progression-free Survival
Kaplan Meir survival estimates curves for 60 Extensive-Stage Small Cell Lung Cancer Patients

Discussion

The current well documented chemotherapy for extensive SCLC is a combination of etoposide and cisplatin or an alternate with other combinations consisting cyclophosphamide, doxorubicin, or vincristine,etc.These regimens yield a median survival of 8 to 10 months and a 2-year survival rate of 10 percent(Evans et al.,1985;Ihde et al.,1994;Sundstrom et al.,2002). In our present phaseIIstudy, 60 patients with extensive SCLC who were treated with INP had a median overall survival of 22 months, median progression free survival of 13 months and overall response rate of 91.7% that were superior to previous studies(Noda,et al.,2002; Hanna,et al.,2005; Schmittel,et al.,2006).

Noda,et al investigated irinotecan-plus-cisplatin combination in extensive SCLC and reported a significant survival benefit , as well as a high response rate of 84.4%(Noda,et al.,2002). However,in North America, Hanna,et al reported that the response rate was 48%(Hanna,et al.,2005).Later in Europe, Schmittel,et al compared irinotecan plus carboplatin(IP) with etoposide plus carboplatin(EP) in extensive staged SCLC, response rates were 67% and 59% respectively(Schmittel,et al.,2006). Median PFS was 9 months (95% CI 7.1–10.9) in IP arm and 6 months (95% CI 4.1–7.9) in EP arm (P = 0.03) (Schmittel et al., 2006).The reason for high response rate and long survival observed in our study could be the addition of nedaplatin and its asssociated low toxic effcts.

A marked synergistic interaction was observed when tumor cells were simultaneously exposed to NDP and irinotecan (Kanzawa et al.,2001). The topoisomerase I inhibitory effect of irinotecan has been reported to be enhanced tenfold in the presence of NDP in an analysis of the effects of NDP and SN-38 on the activity of DNA topoisomerase I using nuclear protein extract of SBC-3 cells(Kanzawa et al.,2001). In that study, neither the catalytic activity of topoisomerase I nor its susceptibility to topoisomerase I inhibitors was affected by pretreatment with NDP. Anti-tumor effect of NDP and irinotecan combined together may correlate with the influence of NDP on the irinotecan-induced inhibition of topoisomerase I. In our study, it is very interesting to note that the combination of NDP and irinotecan resulted in high response rate but did not induce severe toxicities, which differing from other cisplatin or carboplatin containing regimens. INP did not result in neurotoxicity and nephrotoxicity, in contrast to cisplatin and irinotecan. Moreover, myelosuppression of INP regimen was mild, compared with carboplatin and irinotecan.

In this study, nausea or vomiting, elevation of alanine aminotransferase and bilirubin,and myelosuppression were frequent toxic effects of INP chemotherapy.A high incidence of grade 3 or 4 diarrhea was observed in our patient cohort. Therefore,during initial cycles of chemotherapy, diarrhea should be carefully prevented. All cases of grade 1 to 4 diarrhea occurred during the first and second cycles of INP treatment, according to our practice,early suspension of chemotherapy could prevent death caused by diarrhea.

Another possible reason why INP regimen

demonstrated superior response rate and survival may be related to pharmacogenomic differences that exist between caucasian and oriental people(Lampe et al.,1999).Specifically,differences in polymorphisms of UDP-glucuronosyltransferase (UGT1A1), an enzyme that metabolizes irinotecan, are observed between patient populations(Ando et al.,2000). For example,low rates (2%) of Gilbert's syndrome, which results in a decreased level of gene transcription of UGT1A1, are recognized in Asian compared with European or African populations(Beutler et al.,1998).This variety in metabolism of irinotecan may result in differences in toxicity, compliance, and chemosensitivity. In Chinese population,the homozygous carriers of (TA)7 allele is low, could explain lower toxicity (Zhang et al., 2007).

In conclusion, we suggest that INP regimen (a combination of 60 mg/m^2 of irinotecan on days 1 and 8, with NDP 20mg/m^2 on days1-5) is safe and feasible in extensive staged SCLC,with high response rate and long survival,and deserved to be further investigated by randomized clinical trials.

Acknowledgements

Dr. Xin-En Huang was supported in part by a grant from the Department of Personnel of Jiangsu Province (Liu Da Ren Cai Gao Feng Project 2#); Organization Department of Jiangsu Provincial Party Committee, Talent Work Leading Group of Jiangsu Province (333 High-level Talents Training Project); Special funds for research projects of Jiangsu Cancer Hospital and Research Institute (ZK200805); Kang Lai Te clinical research funds of Department of Health of Jiangsu Province (P200908).

References

Ando Y, Saka H, Ando M, et al (2000). Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res*, **60**, 6921-6.

Ariyoshi Y, Ota K, Wakui A, et al (1988). Phase I study of (glycolato-O,O')diammineplatinum(II) (254S). *Proc Am Soc Clin Oncol*, **7**, 59

Beutler E, Gelbart E, Demina A(1998). Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promote; a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci USA*, **95**, 8170-4.

Evans WK, Shepherd FA, Feld R, et al (1985). VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol*, **3**, 1471-7.

Fukuda M, Shinkai T, Eguchi K, et al(1990). Phase II study of (glycolate-O,O')diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. *Cancer Chemother Pharmacol*, **2**6, 393.

Gehan EA, Tefft MC (2000). Will There Be Resistance to the RECIST (Response Evaluation Criteria in Solid Tumors)? J Natl Cancer Inst, 92, 179-81.

Hanna NH, Einhorn L, Sandler A, et al (2005). Randomized, phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients with previously untreated, extensive-stage small cell lung cancer. Proc ASCO, LBA 7004.

Hirose T, Horichi N, Ohmori T, et al (2003). Phase II study of irinotecan and carboplatin in patients with the refractory or relapsed small cell lung cancer. *Lung Cancer*, **40**, 333-8.

Ihde DC, Mulshine JL, Kramer BS, et al (1994). Prospective randomized comparison of high-does and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol*, **12**, 2022-34.

Kameyama Y, Okazaki N, Nakagawa M, et al (1990). Nephrotoxicity of a new platinum compound, 254S, evaluated with rat kidney cortical slices. *Toxicol Lett*, **52**, 15.

Kanzawa F, Koizumi F, Koh Y,et al (2001). In vitro synergistic interactions between the cisplatin analogue nedaplatin and the DNA topoisomerase I inhibitor irinotecan and the mechanism of this action. *Clin Cancer Res*, **7**, 202.

Lampe JW, Bigler J, Horner NK, et al (1999). UDP-glucuronosyltransferase (UGT1A1*28 and UGT1A6*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. *Pharmacogenetics*, **9**, 341-9.

Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207-14.

Naka N, Kawahara M, Okishio K, et al (2002). Phase II study of weekly irinotecan and carboplatin for refractory or relapsed small-cell lung cancer. *Lung Cancer*, **37**, 319-23.

Noda K, Nishiwaki Y, Kawahara M, et al (2002). Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small lung cancer. *N Engl J Med*, 346, 85-91.

Oshita F, Yamada K, Kato Y et al(2003). Phase I/II study of escalating doses of nedaplatin in combination with irinotecan for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol*, **52**, 73-8.

Roth BJ, Johnson DH, Einhorn LH, et al (1992). Randomized study of cyclophosphamide,doxorubicin, and vincristine versus etoposide and cisplatin versus alternationof these two regimens in extensive small-cell lung cancer: a phase III trial ofthe Southeastern Cancer Study Group. *J Clin Oncol*, **10**, 282-91.

Schmittel A, Fischer von Weikersthal L, Sebastian M, et al (2006). A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Ann Oncol*, **17**, 663-7.

Sundstrom S, Bremnes RM, Kaasa S, et al (2002). Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years follow-up. *J Clin Oncol*, **20**, 4665-72.

Ueoka H, Kiura K, Tabata M, et al (1998). A randomized trial of hybrid administration of cyclophosphamide, doxorubicin, and vincristine (CAV)/cisplatin and etoposid (PVP) versus sequential administration of VAV-PVP for the treatment of patients with small cell lung carcinoma: results of long term follow-up. *Cancer*, **83**, 283-90.

Von Pawel J, Schiller JH, Shepherd FA, et al (1999). Topotecan versus cyclophosphamide, doxorubicine, and vincristine for the treatment of recurrent small cell lung cancer. *J Clin Oncol*, **1**, 658-67.

Zhang A, Xing Q, Qin S, et al (2007). Intra-ethnic differences in genetic variants of the GT-glucuronosyltransferase 1A1 gene in Chinese populations. *Pharmacogenomics J*, **7**, 333-8.