The phase II trial of fractionated irinotecan plus carboplatin for previously untreated extensive-disease small cell lung cancer

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The phase II trial of fractionated irinotecan plus carboplatin for previously untreated extensive-disease small cell lung cancer

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The Master's thesis submitted to the

Department of Medicine

the Graduate School of Yonsei Universisty

in partial fulfillment of the requirements for the

degree of Master of Medicine

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December 2005

This certifies that the Master's Thesis

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December 2005

Acknowledgements

I would like to thank professor Joo Hang Kim who gave me the opportunity to participate in such a great project and always provided me with good and thorough ments with deep sincerity. In addition, I am in debt to professor Se Kye Kim and Chae Ok Yun who gave me many great advices during the study. Furthermore, I am greateful to Ju Hyuk Sohn who was helpful with meaningful discussion. Finally I express my greatest love to my parents who supported me with deep love and belief.

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ABSTRACT

The Phase II Trial of fractionated irinotecan plus carboplatin for previously untreated extensive-disease small cell lung cancer

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Irinotecan plus cisplatin has been previously documented to be effective in the treatment of extensive-disease small-cell lung cancer (ED-SCLC). This study was undertaken to investigate the efficacy and feasibility of combination chemotherapy of irinotecan and carboplatin in previously untreated ED-SCLC. From December 2002 to April 2005, 32 patients with previously untreated ED-SCLC were enrolled. Patients were treated with irinotecan (50mg/m^2 i.v. on day 1, 8, and 15) and carboplatin (target AUC=5 i.v. on day 1) every 4 weeks for up

to 6 cycles. Twenty-eight patients (87.5%) were male and the median age was 65 years. ECOG performance status was 0-1 in 18 (56.2%) and 2 in 14 (43.8%) patients. The median cycles of chemotherapy was 5.5 (range, 1-6 cycles). Twenty-nine patients were assessable for response evaluation. The overall response rate was 68.7% (1 CR, 21 PR) under the intent-to-treat analysis. After a median follow-up of 15.4 months, median time to progression was 6.4 months (95% CI: 5.4-7.4 months) and median overall survival was 12.7 months (95% CI: 2.3-23.1 months). The estimated 1-year survival rate was 47.1%. In terms of toxicities, Grade 3/4 neutropenia and thrombocytopenia occurred in 8 (25.0%) and 5 (15.6%) patients, respectively. Grade 3/4 non-hematologic toxicities included diarrhea (9.4%), anorexia (9.4%), infection (6.3%), and neutropenic fever (6.3%). There was one treatment-related death because of superimposed infection on bronchopleural fistula. The combination chemotherapy of irinotecan and carboplatin was effective and tolerable in previously untreated ED-SCLC. Based on the favorable results in this trial, further large scaled phase III studies are warranted.

Key words: extensive-disease small cell lung cancer, irinotecan, carboplatin

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I. INTRODUCTION

Small cell lung cancer (SCLC) comprises 20 % of the all lung malignancy and is classified into the limited and extensive stage depending on the extent of disease whether within or beyond the one hemithorax. For the last 15 years, chemotherapy with etoposide and cisplatin (EP) have been the standard treatment in extensive disease small cell lung cancer (ED-SCLC) with the median survival of 10-12 months [1].

Irinotecan, a camptothecin analogue that inhibits the nuclear enzyme, topoisomerase I, has been shown excellent antitumor activity against SCLC in monotherapy or in combination with cisplatin [2,3]. Irinotecan plus cisplatin was compared with EP in a randomized phase III trial resulting in a better survival in ED-SCLC [4]; however, it was not confirmed by the subsequent confirmative trial[5].

Cisplatin is the most active agent in the treatment of lung cancer; however, it gives rise to significant toxicities such as nausea, vomiting, nephrotoxicity, and neurotoxicity. On the other hand, carboplatin, another platinum derivative, has a similar activity to cisplatin but exhibits a more favorable toxicity profile and it is easier to administer [6,7]. Therefore, carboplatin is widely used as a practical substitute for cisplatin in various malignancies such as ovarian cancer or ED-SCLC [8,9].

Several in vitro studies showed a synergistic effect between irinotecan and carboplatin in various cell lines [10]. Moreover, there were trials showing that irinotecan/carboplatin regimen was effective in heavily treated ED-SCLC patients [11,12]. Under the background of these previous studies, we have conducted a phase II trial of irinotecan plus carboplatin for previously untreated ED-SCLC with the recommended schedule from the other phase I trials [13,14].

II. MATERIALS AND METHODS

1. Patients

Patients with previously untreated SCLC, diagnosed histologically or cytologically, participated in this study. Patients were considered as eligible if they had extensive stage SCLC, defined as the extent of disease outside the unilateral hemithorax or as a disease with a malignant pleural effusion, with at least one unidimensionally measurable lesion, they were ≤ 75 years and had an Eastern Cooperative Oncology Group (ECOG) performance status(PS) of 0-2, and adequate organ functions, i.e. absolute neutrophil ≥ 1,500 /uL, hemoglobin ≥ 10 g/dl, platelets ≥ 100,000/uL, serum creatinine ≤ 1.5 mg/dl, total bilirubin ≤ 1.5mg/dl, and AST/ALT ≤ 3 times normal value. Patients who had symptomatic brain metastasis, prior treatment history for SCLC, and concurrent uncontrolled medical illness were excluded. All patients gave written informed consent before enrollment. The study was approved by the Ethical Review Committee of the center.

2. Treatment Schedule

Irinotecan was administered as a 90-min intravenous infusion at a dosage of 50 mg/m^2 on days 1, 8 and 15. Carboplatin was given at a dose of AUC

5mg × min/ml on day 1 in 500ml 5 % glucose over 2hrs. The carboplatin dose was calculated with Calvert's formula and the 24-h creatinine clearance rate[15]. Treatment was repeated every 28 days and continued for up to six cycles if there were not unacceptable toxicities or disease progression. No prophylactic recombinant human granulocyte colony stimulating factor (G-CSF) or loperamide was administered. Administration of irinotecan was skipped on day 8 or 15 if the leukocyte count was less than 1,500/uL, if the platelet count was less than 100,000/uL, or if there was diarrhea. G-CSF was administered when neutropenia was less than 500/uL. Platelet transfusion was done when platelet count less than 50,000/uL. Subsequently, after recovery the next course was started. Neither a dose reduction nor dose escalation was allowed.

3. Assessment

All patients underwent an evaluation of medical history, symptoms, physical examination, ECOG PS, and clinical tumor assessment at screening, each cycle and follow-up. Pretreatment laboratory evaluations consisted of complete blood count (CBC) with differentiation, serum chemistry profiles (total bilirubin, AST, ALT, alkaline phosphatase, and electrolytes) and urinalysis. Chest radiography, computed tomography (CT) of the chest, abdominal CT scan or ultrasound sonography and radionuclide bone scan were evaluated to determine the stage of

disease at screening. Chest X-rays, CBC with differentiation and a complete biochemical profile were obtained on day 1 of each cycle. CBC with differentiation was repeated on days 8 and 15. Response was assessed by plain chest x-ray before each course, with final response designation using chest CT scan after every third cycle, or whenever needed. In case of target lesion surrounded by lung parenchyma in chest X-ray, tumor response could be evaluated by chest X-ray.

4. Response and Toxicity Criteria

Objective response of a tumor to the current regimen was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [16]. A CR of target lesions was defined as the disappearance of all target lesions for a minimum of 4 weeks. A PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions for a minimum of 4 weeks, during which no new lesion could appear. PD was defined as at least a 20% increase in the sum of the longest diameter of the target lesion or the appearance of one or more new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. A CR of non target lesions was defined as the disappearance of all non target lesions. An incomplete response/stable disease was defined as the persistence of one or more non target lesion(s). PD

was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non target lesions. Toxicity evaluation was repeated before each cycle. Toxicities were scored according to the National Cancer Institute (NCI) common toxicity criteria version 2.0.

5. Statistical Methods

The primary end point of this study was the response rate and median overall survival time. Overall survival time (OS) was defined as the interval between the study treatment start date and the last date of follow-up (for patients still alive) or until death. The secondary end point of this study was the toxicity, response duration and time to progression (TTP). TTP was defined as the interval between the start date of treatment and the date of progression. If a patient was lost to follow-up, the patient was censored on the date of last contact. Response duration was defined as the interval between the date of response to the date of progression. Survival curves were estimated using the method of Kaplan-Meier. SPSS (version 12.0) was used to run the analysis.

III. RESULTS

1. Patients

Between December 2002 and April 2005, 32 patients were enrolled in the trial. The demographics of these patients are listed in Table 1. Three patients were not assessable for response. After 1 cycle of chemotherapy, three patients refused the treatment because of financial difficulties or toxicity. The median age was 64 years (range, 39 to 73 years). Twenty eight patients were male and 18 patients had an ECOG PS of 0 or 1. Eighteen patients had more than 2 sites of metastasis.

Table1 . Characteristics of the Patients

	Number of patients (%)
Number of total patients	32
Median age (years)	64.5 (range, 39 to 73)
Sex	
Male	28 (87.5 %)
Female	4 (12.5%)
ECOG performance status	
0	2 (6.2%)
1	16 (50.0%)
2	14 (43.8%)
No. of distant metastasis	
1	14 (43.8%)
≥2	18 (56.2%)

Abbreviations: ECOG, Eastern Oncology Cooperative Group

2. Dose intensity and Delivery

A total 146 treatment cycles were administered, with a median of 5.5 cycles per patient (range, 1 to 6 cycles). Sixteen (50.0%) patients completed six cycles of chemotherapy. Table2 shows the reason for discontinuation of chemotherapy of 16 patients. Mean actual dose intensity of irinotecan was 31.4 mg/m^2/wk (range 21.7~ 37.5) and carboplatin was 1.2 mg × min/ml /wk. The relative dose intensity of irinotecan and carboplatin was 0.84 and 0.96, respectively. The percent of administration on day 8 and day 15 were 92.8% and 70.5 %. The major reason for the omission of chemotherapy on day 8 and day 15 was neutropenia.

Table 2. Treatment Summary

Delivered cycles	No. of patients (%)
1	3 (9.3%)
2	1 (3.1%)
3	6 (18.6%)
4	1 (3.1%)
5	4 (12.5%)
6	16 (50.0%)
Reason for discontinuation	(Total n=16)
Progression	7 (21.9%)
Toxicity	2 (3.1%)
Death	1 (3.1%)
Withdrew consent	5 (15.6%)
Physician’s decision	1 (3.1%)

3. Response to Treatment and Survival

All 32 patients were included in the analysis of tumor response and survival. There were 1 CR (3.1 %), 21 PR(65.6 %), 4 SD(12.5 %) , 3 PD(9.3 %) and 3 unassesable (9.3 %). The overall response rate was 68.7 % by the intent-to-treat analysis and 75.9 % by per protocol analysis. Most common lesion of relapse was thorax (78.1 %), followed by bone(20.0 %), brain(16.0 %) and liver(8.0 %). Fourteen(43.7 %) of 32 patients were treated as 2^{nd} line regimen chemotherapy after progression; 11 received etoposide/topotecan chemotherapy ; 1 received cyclophosphamide/adriamycin/vincristine ; 2 received ifosfamide/etoposide and 4 patients received palliative radiotherapy on thorax, brain or bone.

Median follow up duration was 15.4 months (range 3.8 ~ 32.1 months). Sixteen patients died. The median TTP was 6.4 months (95% Confidence Interval 5.4~ 7.4 months). The median OS was 12.7 months (95% Confidence Interval 2.3~23.1 months). The estimated 1- year survival rate was 47.1%. The median response duration was 4.5 months (range, 1.7 to 9.6 months). The Kaplan-Meier curves of TTP and OS of the patients are shown in Figure 1 and 2.

Figure 1. Overall survival curve

1yr survival rate: 47.1 %, median overall survival: 12.7 months

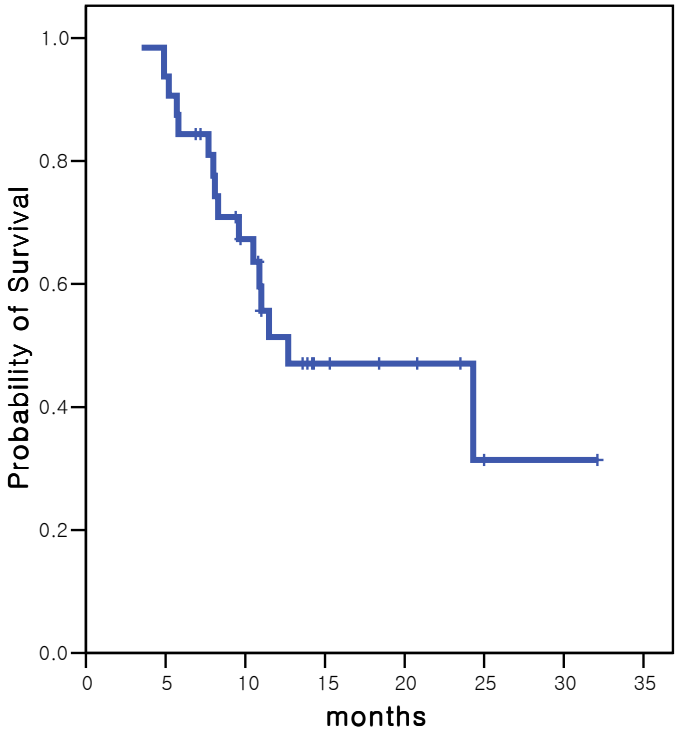
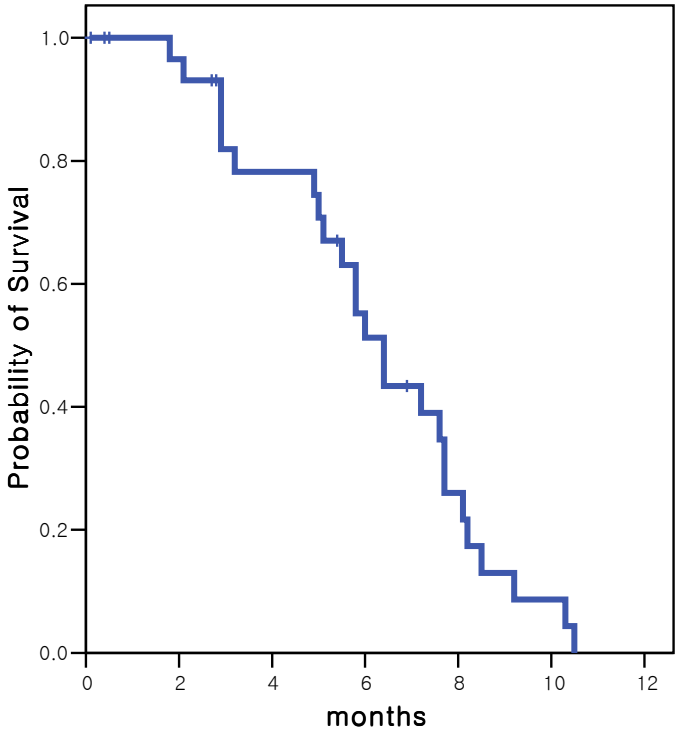


Figure 2. Time to progression curve

Median time to progression: 6.4 months



4. Toxicity

All 32 patients were included in the toxicity analysis. Table 3 lists the maximum toxicity experience during treatment. The most frequent toxicity was myelosuppression. Grade 3/ 4 neutropenia and thrombocytopenia were observed in 8(25.0 %) and 5(15.6 %) patients, respectively. Nine patients received G-CSF support. Five patients received platelet transfusion and 12 patients received transfusion of erythrocytes. Majority of non-hematologic toxicities were modest. Grade 3 /4 diarrhea was occurred in 3(9.4 %) patients. Grade 3 /4 neutropenic fever was reported 3 (9.4 %) patients and Grade 3 /5 infection was reported in 2(6.3 %) patients and they were recovered from infection except one patient. Treatment-related death was respiratory failure following bronchopleural fistula and pneumonia.

Table3 . Toxicity Profiles

Hematological toxicities (n=32)						
NCI-CTC grade	G 1	G 2	G 3	G 4	G 5	G3-5 (%)
Neutropenia	7	6	6	2	0	8 (25.0%)
Leukopenia	2	8	4	0	0	4 (12.5%)
Anemia	10	4	4	0	0	4 (12.5%)
Thrombocytopenia	5	5	4	1	0	5 (15.6%)
Nonhematological toxicities (n=32)						
NCI-CTC grade	G 1	G 2	G 3	G 4	G 5	G3-5 (%)
Anorexia	5	3	3	0	0	3 (9.4%)
Nausea	4	3	2	0	0	2 (6.3%)
Vomiting	3	0	1	1	0	2 (6.3%)
Diarrhea	5	3	2	1	0	3 (9.4%)
Constipation	1	2	0	0	0	0 (0%)
General weakness	4	2	1	0	0	1 (3.1%)
Hyperbilirubinemia	1	0	1	0	0	1 (3.1%)
AST elevation	3	0	1	0	0	1 (3.1%)
ALT elevation	1	0	1	0	0	1 (3.1%)
Alopecia	5	2				

Pain	7	4	0	0	0	0 (0%)
Infection	1	2	1	0	1	2 (6.3%)
Neutropenic fever	0	0	1	2	0	3 (9.4%)

Abbreviations: NCI-CTC, the National Cancer Institute's Common Toxicity Criteria

IV. DISCUSSION

Small cell lung cancer (SCLC) is one of those cancers which responds to chemotherapy very sensitively. But it metastasizes at the early stage of the disease to be called an aggressive malignancy. Over 20 years, many studies have been done for extensive-disease small cell lung cancer(ED-SCLC), including non-cross resistant alternating regimen, high-dose and dose-intensive chemotherapy with granulocyte-colony stimulating factor (G-CSF) and maintenance therapy [17-19]. But there is only a little improvement in median survival time and still the combination of etoposide and cisplatin is regarded as the standard chemo-therapeutic regimen for SCLC[1]. Therefore, necessity of new novel drug has been brought up for the better treatment outcome of ED-SCLC. Recently, taxane, gemcitabine, topotecan [20-22] and irinotecan have been tried to SCLC. Among them, only irinotecan showed the improvement of survival [4].

Noda et al. from Japan Clinical Oncology Group(JCOG) reported results of a phase III trial (JCOG9511) combinating irinotecan and cisplatin. Comparing to the combination of etoposide /cisplatin combination, irinotecan/cisplatin combination treated group showed significant increase in response rate , progression-free survival and overall survival in previously untreated ED-SCLC. In the Japanese design, the object was 77 ED-SCLC patients who were

previously untreated. They recieved 60mg/m2 of irinotecan on days 1,8, and 15 with 60mg/m^2 of cisplatin on day 1, repeated in every 28 days. Overall response rate was 84.4 % and median TTP, OS was 6.9 months, 12.8 months respectively.

For the rationale to examine a regimen that is equally active and more tolerable in ED-SCLC, we performed a phase II trial on 32 patients using irinotecan 50 mg/m^2 (day 1, 8 and 15) and carboplatin (day 1) with a target AUC 5mg × min/ml by Calvert formula. The trial produced an overall RR of 68.7 %, a median TTP of 6.4 months, a median OS of 12.4 months, and an estimated 1-year survival rate of 47.1 %. In terms of response rate, our result was at least comparable to that of irinotecan/cisplatin treated group in Japanese study and similar to those established therapies using etoposide/cisplatin in ED-SCLC[14].

The principal toxicity in irinotecan/carboplatin regimen was myelosuppression, especially neutropenia. Grade 3/ 4 neutropenia and thrombocytopenia was observed in 8 (25.0 %) patients and 5 (15.6 %) patients, respectively. Neutropenia was the main cause of treatment omission, but it was easily recovered by temporary G-CSF support and prophylactic administration of G-CSF was not considered. In contrast, Noda et al. reported a Grade 3 /4 neutropenia of 65.3 % and thrombocytopenia of 5.3 %. Even though our regimen used lower dose intensity of irinotecan than Noda's, carboplatin has

much more potency of myelosuppression rather than cisplatin, which means our regimen is more profitable for hematologic toxicities. In the point of view that thrombocytopenia is the major dose-limiting toxicity of carboplatin, relatively high incidence of thrombocytopenia in this study might be due to carboplatin.

With regard to non-hematologic toxicity, Grade 3/ 4 nausea and vomiting was 6.3 % in our trial and 13.3 % of Noda's. Diarrhea is another dose limiting toxicity of irinotecan treatment. Grade 3 / 4 diarrhea was reported in 3 (9.4 %) patients of our trial and 12 (16.0 %) patients in Noda's. High dose loperamide treatment seemed to reduce the incidence of diarrhea. Neutropenic fever was observed in 3(9.4 %) patients and all of them recovered easily after using intravenous antibiotics and G-CSF support. One patient experienced a varicella-zoster infection and one patient died of respiratory failure following broncho-pleural fistula and pneumonia. These non-hematologic toxicities were mild and comparable to those of recently published combination chemotherapy in ED-SCLC.

Approximately 44 % of our patients was in ECOG performance status 2 and 56 % of our patients had more than two metastatic sites. Direct comparing between patients enrolled in JCOG group & in our study may not be meaningful, but our patients were in more poor status than Japanese patients. In spite of progressed disease, patients could maintain their performance status during the

treatment course, and could receive second line treatment. Fourteen (43.7 %) of 32 patients were treated with combination chemotherapy and 4 patients received palliative radiotherapy on thorax, brain or bone. It can be interpreted as new combination is more tolerable in ED-SCLC patients.

In conclusion, the efficacy of fractionated irinotecan plus carboplatin was not inferior to irinotecan plus cisplatin, and this combination was less toxic in previously untreated ED-SCLC patients. Palliation of disease and improvement in quality of life as well as survival are the important goals of treatment in ED-SCLC. From this point of view, the regimen of fractionated irinotecan plus carboplatin would be a promising substitute for irinotecan/cisplatin, especially in patients with poor performance status or old age.

V. CONCLUSION

The combination chemotherapy of irinotecan and carboplatin was effective and tolerable in previously untreated ED-SCLC. Based on the favorable results in this trial, further large scaled phase III studies are warranted.

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ABSTRACT (IN KOREAN)

치료받지 않은 확장 병기 소세포 폐암에서

Irinotecan 및 Carboplatin 병용 화학 요법에 관한 2상 연구

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최혜진

확장 병기 소세포 폐암에서 Irinotecan 과 Carboplatin 병합 화학 요법은 효과가 있다고 알려져 있다. 이 연구는 치료 받지 않은 확장 병기 소세포 폐암에서 Irinotecan 과 Carboplatin 병합 화학 요법에 대한 효과와 그 가능성을 연구하고자 하였다. 2002년 12월부터 2005년 4월까지 치료받지 않은 소세포 폐암 환자 32명이 등록되었다. Irinotecan (50mg/m^2, 정맥 주사, 제 1, 8 및 15일 투여) 과 Carboplatin(목표 AUC=5, 제 1일 투여)을 매 4주마다 총 6주기까지 투여하였다. 환자 중에 남자가 28명(87.5 %)이었고, 환자들의 중간 나이는 65세였다. ECOG 수행지수는 0-1이 18명(56.2 %) 이었다. 화학 요법은 평균 5.5

주기(범위, 1-6 주기) 시행되었다. 29명의 환자가 반응 평가가 가능하였으며, 반응률은 68.7% (완전 반응 1명, 부분 반응 21명)이었다. 평균 15.4 개월의 추적 관찰 결과, 무진행 기간은 6.4개월(95% 신뢰구간: 5.4-7.4개월)이었고, 총 생존 기간은 12.7개월(95% 신뢰구간: 2.3-23.1개월)이었다. 예측 1년 생존률은 47.1%였다. 독성을 살펴보면, 3/4도 백혈구 감소증과 혈소판 감소증이 각각 8명(25.0%)과 5명(15.6%)에서 나타났다. 3/4도 비혈액 독성으로는 설사(9.4%), 오심(9.4%), 감염(6.3%) 그리고 호중구감소열(6.3%)이 있었다. 치료와 관련된 사망은 1명이 있었으며, 기관지늑막루에 병발된 감염으로 사망하였다. 치료 받지 않은 확장 병기 소세포 폐암에서 Irinotecan과 Carboplatin 병합 화학 요법은 효과가 있으며, 독성은 수용 가능하였다. 이를 바탕으로 앞으로 3상 연구가 필요하다고 생각된다.

핵심되는 말: 확장 병기 소세포 폐암, irinotecan, carboplatin