Phase II Study of Induction Irinotecan + Cisplatin Chemotherapy Followed by Concurrent Irinotecan + Cisplatin Plus Twice-Daily Thoracic Radiotherapy

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유제한성 병기의 소세포 폐암에서 3주 간격으로 시행된 irinotecan과 cisplatin을 이용한 과다분할 방사선 동시 요법

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배 경: Irinotecan hydrochloride는 topoisomerase I inhibitor로서 소세포 폐암에 효과적인 약제로 알려져 있다. Irinotecan은 cisplatin과 더불어 방사선감작물질로 작용하기도 한다. 본 연구는 이전에 치료받은 경험이 없는 제한성 병기의 소세포 폐암 환자에서 irinotecan과 cisplatin(IP)의 방사선 동시화학요법의 효과를 평가하기 위하여 시행되었다

방 법: 2002년 12월부터 2004년 11월까지 충남대학교 병원에서 새로이 제한성 병기의 소세포 폐암으로 진단된 24명의 환자들을 대상으로 하였다. Irinotecan 60 mg/m^{2}을 제 1일과 제 8일째 투여하였고 cisplatin 60 mg/m^{2}을 제 1일째 투여하였으며 매 3주 간격으로 시행되었다. 제 3차 항암화학요법을 시작하는 날과 동시에 과다 분할방사선 치료(twice-daily thoracic irradiation; 45 Gy total)을 시작하였다. 예방적 전 뇌 방사선 조사(Prophylactic cranial irradiation)가 방사선 동시화학요법이 끝난 후 완전반응(complete response)을 나타낸 환자에서 시행되었다. 제 2차 항암요법과 제 6차 항암요법이 끝난 후에 흉부 전산화 단층촬영과 기관지경 등을 통한 병기의 재평가가 이루어졌다.

결 과: 병기의 재평가는 19명의 환자에게 이루어졌다. 중앙 추적관찰기간은 12.5개월이고 전체 99회의 항암치료가 시행되었다. 평균 한 환자당 5.2회의 항암치료가 시행되었다. 실제 용량강도는 cisplatin 19.6 mg/m^2/week과 irinotecan 38.2 mg/m^2/week이었다. 9명의 환자가 완전반응을 보였고 10명의 환자가 부분반응(partial response)을 보여서 전체 반응률은 95%였다. 3에서 4도의 혈액학적 독성은 백혈구 감소증(35% of cycles), 빈혈(7% of cycles), 혈소판 감소증(7% of cycles) 등으로 나타났다. 3에서 4도의 비 혈액학적 독성은 설사(5% of cycles)였다. 3에서 4도의 방사선 식도염(10% of patients)을 제외하고는 과다 분할 방사선 치료를 이용한 방사선 동시 화학요법의 기존의 방법과 독성 면에서는 큰 차이가 없었다. 치료와 관련된 사망은 관찰되지 않았다. 평가가 가능한 환자들에서 1년 생존율과 2년 생존율은 각각 89% (16/18)와 47% (9/18)였다.

결 론: 3주 간격으로 시행된 irinotecan과 cisplatin을 이용한 과다분할 방사선 동시 요법은 제한성 병기의 소세포 폐암 환자에서 부작용은 높지 않으면서 효과적인 치료법으로 고려될 수 있을 것이다.

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Key Words: Cisplatin, Irinotecan, Limited-disease, Small cell lung cancer, 3-week cycle, Chemotherapy-naïve, Twice-daily thoracic radiotherapy, Concurrent chemoradiotherapy.

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Introduction

Lung cancer is the most common cause of cancer death worldwide[1,2]. Small cell lung cancer (SCLC) accounts for approximately 13 to 20% of all lung cancers diagnosed[3]. Although SCLC is usually sensitive initially to chemotherapy and radiotherapy,

it has a poor prognosis characterized by an aggressive clinical course, rapid tumor growth, and metastasis, which is often present at the time of diagnosis[4]. Approximately one-third of patients with SCLC represent limited-stage disease (LD). Combined modality treatment consisting of thoracic radiotherapy (TRT) and systemic chemotherapy is widely accepted as a standard for patients with LD-SCLC. A cisplatin or carboplatin plus etoposide (PE) regimen is the most frequently used chemotherapy regimen worldwide. Several new anticancer drugs have been shown to be active against SCLC. The most active of these drugs to date is irinotecan, a topoisomerase I inhibitor. A randomized phase III study of irinotecan plus cisplatin (IP) chemotherapy compared with PE reported a significant benefit in the survival of patients receiving IP for extensive-stage SCLC[5].

Radiotherapy also has a central role in the treatment of LD-SCLC[6,7]. Two meta-analyses dealing with the role of thoracic radiotherapy (TRT) in addition to chemotherapy suggested a benefit in both local control and overall survival[8,9]; they showed significant increases in survival and major reduction in thoracic recurrence in the combined-therapy group. However, the optimal sequencing, dosing, and timing have not been clearly defined[6,7]. Several randomized studies have addressed the importance of the timing of TRT, but their results are conflicting[10-13]. One of the phase III trials, reported from the Japanese Clinical Oncology Group (JCOG), compared concurrent versus sequential chemoradiation in combination with PE in 231 patients with LD-SCLC[10] and found that the median survival favored the concurrent approach (27.2 vs. 19.7 months, p = 0.097).

In the present study, we assumed that two cycles of induction chemotherapy of dose-intensified 3-week administrations of IP followed by an IP regimen with concurrent twice-daily TRT would further improve the outcome of chemotherapy-naïve patients with LD-SCLC. We sought to validate the efficacy and toxicity of IP chemotherapy with concurrent hyperfractionated TRT in chemotherapy-naïve patients with LD-SCLC.

Patients and methods

1. Eligibility criteria

The diagnosis of SCLC was confirmed by histologic or cytologic findings in all cases. Limited stage (LS) was defined as disease confined to one hemithorax and regional lymph nodes (including mediastinal, contralateral hilar, and bilateral supraclavicular nodes). Additional eligibility criteria were: at least one bi-dimensionally measurable or assessable disease; age ≥18 years; Eastern Cooperative Oncology Group performance status (PS) ≤2; leukocyte count ≥4,000/L; platelet count ≥ 100,000/L; bilirubin level ≤1.5 mg/dL; creatinine level ≤1.5 mg/100 mL and 24-h creatinine clearance >60 mL/min/m^2; absence of active infection; no prior chemotherapy or radiotherapy; no history of myocardial infarction in the last 6 months; no congestive heart failure or significant arrhythmia; and no prior second primary cancer. Patients with malignant pleural effusions were excluded. In addition to the assessments described above, each patient underwent the following: chest radiography and computed tomography scan of the thorax, abdomen, and brain; radionuclide bone scan; fiberoptic bronchoscopy; pulmonary function studies; and arterial blood gas measurements when signs or symptoms of respiratory insufficiency were present.

All patients provided written informed consent. The study was approved by the institutional review

board of Chungnam National University Hospital and was conducted in compliance with institutional review board regulations.

2. Chemotherapy

Chemotherapy was given in a 21-day cycle, as shown in Figure 1. For induction chemotherapy, the treatment consisted of three cycles of cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1 and 8. For patients who had not changed stage in response to induction chemotherapy, three cycles of IP chemotherapy were continued for concurrent chemoradiotherapy with the same schedule and doses. Cisplatin (60 mg/m^2) was diluted in normal saline to 150 mL and administered as a 60-min intravenous infusion on day 1. Irinotecan (60 mg/m^2) was diluted in 5% dextrose in water and administered as a 90-min intravenous infusion on days 1 and 8. Irinotecan was administered immediately after cisplatin on day 1. The dose of chemotherapy was reduced to 75% of the initial dosage for patients who experienced hematologic toxicity greater than grade 3 in the previous cycle. If the leukocyte count was below 3,000/mm^3, the absolute neutrophil count was below 1,000/mm^3, the platelet count was below 100,000/mm^3, or non-hematologic toxicities were greater than grade 2 on the first day of the next cycle, chemotherapy was withheld until the counts recovered.

Patients received standard intravenous hydration with 1,000 mL of 5% dextrose in normal saline or normal saline for 2 h before cisplatin administration. A standard antiemetic regimen of dexamethasone 20 mg and ondansetron 8 mg was administered intravenously before the administration of cisplatin.

3. Thoracic radiotherapy (TRT)

Conventional radiotherapy techniques were used in all patients and the radiotherapy targets were defined in accordance with the International Commission on Radiation Units and Measurements Report (ICRU 50) as follows. Radiotherapy was administered to post-chemotherapy volumes. The radiation field included the primary tumor and ipsilateral hilum and bilateral mediastinal lymph nodes, with 1- to 2-cm margins. Radiation was administered to the supraclavicular lymph nodes only if they were involved. The gantry angles for oblique fields ranged from 30° to 45° from a line perpendicular to the treatment table and included the ipsilateral supraclavicular volume only if persistent disease was present in this region. Three coplanar isocentric fields were used to cover the target volumes in order to minimize doses to the lungs and other tissues (spinal cord, esophagus, great vessels, heart, etc.). Tissue inhomogeneity corrections were made. The prescribed dose of the clinical target volume was normalized by approximately 90% of the isocenter dose. TRT was delivered with 6-10 MV photons using custom-made blocks. TRT was started on the first day of the 3rd cycle of the IP regimen. The total dose of TRT was 45.6 Gy in 38 fractions (120 cGy per fraction). Treatment was given twice daily on weekdays, at least 6 h apart.

4. Prophylactic cranial irradiation (PCI)

Four weeks after completion of the concurrent chemoradiotherapy, cancer clinical responses were evaluated by chest X-ray and computerized tomography, brain MRI, and bone scan. Patients who achieved a CR were given a PCI that consisted of 10 doses of 2.5 Gy to the midplane of the brain over a 2-week period for a total dose of 25 Gy.

5. Response and toxicity criteria

Tumor response was evaluated according to the WHO criteria[14] and was assessed by chest radiography and chest CT after every two cycles of chemotherapy and at 1, 3, and 6 months after completion of thoracic radiation therapy. Acute toxicity and late toxicity were classified in accordance with the guidelines of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0[15]. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

6. Data analysis and statistics

The duration of survival was measured from the first date of the initial treatment to the date of death or most recent follow-up.

Results

1. Patient characteristics

Twenty-four patients were enrolled in the study from December 2002 to November 2004. Two patients dropped out after two cycles of chemotherapy because of progressive liver cirrhosis and Eaton-Lambert syndrome. All patients were assessed for response and toxicity analysis. The regimen of one patient had been changed because of progressive disease. Two patients who had achieved complete response (CR) after induction chemotherapy opted to refuse further therapy. Nineteen patients completed the chemoradiation. The characteristics of the 19 eligible patients, all male, are listed in Table 1. The median age was 62 years (range, 45 to 71 years) for the limited-stage patients. Eighteen (95%) patients had an ECOG performance status of 0 or 1. The total numbers of cycles was 99.

Table 1. Baseline characteristics of the patients

Characteristic	No. of patients	%
Patients	19	
Males	19	100
Female	0	0
Median age, years (range)	62 (45-76)	
Smokers	16	84
Non-smokers	3	16
Median pack-years (range)	40 (15-60)	
PS*		
0	2	11
1	16	84
2	1	5
Total Cycles	99	

* Eastern Cooperative Oncology Group performance status.

2. Tumor response and survival

Tumor response estimated after two cycles of IP chemotherapy (Table 2) revealed six CRs (27%) and 15 partial responses (PRs) (68%), for an overall response rate of 95%; there was one progression. After concurrent chemoradiotherapy, there were nine CRs (47%) and 10 PRs (53%), giving an overall response rate of 100%.

Follow-up was performed for all patients after 12

Table 2. Objective tumor response

Result	Induction IP chemotherapy		Concurrent chemoradiotherapy	
	No. of patients	%	No. of patients	%
Response				
Complete	8	27	9	47
Partial	15	68	10	53
Overall	23	95	19	
Progression	1	5		
1-year survival rate			16/18	88
2-year survival rate			9/18	47

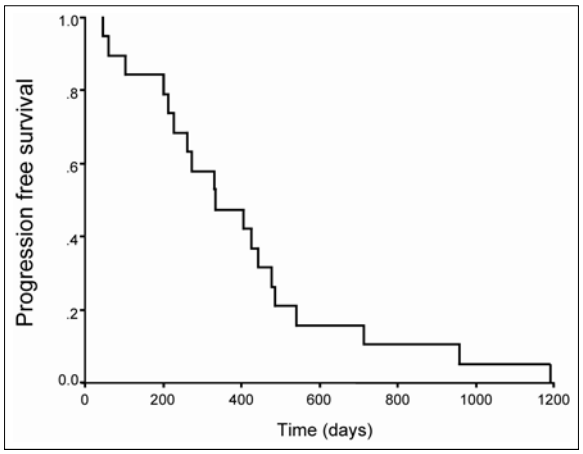

Figure1. Progression-free survival curve for the patients with two cycles of IP induction chemotherapy followed by concurrent chemoradiotherapy in LD-SCLC.

months (median follow-up time, 12.5 months). Four patients who did not receive TRT died of disease progression and one patient who did receive TRT died of uncontrolled seizure before 12 months. Radiation therapy was discontinued in two patients owing, respectively, to heart failure and treatment refusal. A third patient, with Eaton-Lambert syndrome, became progressively debilitated as a result of muscle weakness despite steroid therapy, and his performance status was poor. In a fourth patient, with liver cirrhosis, a very low platelet count after induction chemotherapy was slow to recover, and thus we decided that concurrent IP plus hyperfractionated thoracic radiotherapy was harmful to this patient. A fifth patient showed progressive disease after induction IP and consequently was not suitable for establishing the effectiveness of concurrent IP plus hyperfrac-tionated thoracic radiotherapy because he had already failed to respond to the IP regimen. Therefore, we excluded five patients from the survival estimates. The 1- and 2-year survival rates of the eligible patients were 94% (17/18) and 47% (9/18), respectively (Table 2). The median progression-free survival was 12 months (95% CI: 5.2 - 18.7 months) (Figure 1).

3. Toxicity

The toxicities of induction chemotherapy are described in Table 3. Myelosuppression was the

Table 3. Toxic effects during induction IP chemotherapy according to the NCI grade of toxicity

Toxicity	Grade (n = 22)									
	0		1		2		3		4	
	No.*	%	No.*	%	No.*	%	No.*	%	No.*	%
Hematologic										
Neutropenia	11	32	5	14	7	20	7	20	5	14
Anemia	15	41	10	27	10	27	2	5	0	0
Thrombocytopenia	21	73	4	14	2	7	1	3	1	3
Fever in absence of infection	34	94	0	0	1	3	0	0	1	3
Non-hematologic										
Diarrhea	30	81	0	0	3	8	3	8	1	3
Nausea/Vomiting	29	78	4	11	3	7	0	0	1	2
BUN	36	98	1	2	0	0	0	0	0	0
Cr	36	98	1	2	0	0	0	0	0	0
AST	34	93	2	5	1	2	0	0	0	0
ALT	33	92	3	8	0	0	0	0	0	0
TB	35	96	1	4	0	0	0	0	0	0
Pruritus	35	96	1	2	1	2	0	0	0	0

*number of events.

Table 4. Toxic effects during concurrent chemoradiotherapy according to the NCI grade of toxicity

Toxicity	Grade (n = 19)									
	0		1		2		3		4	
	No.*	%	No.*	%	No.*	%	No.*	%	No.*	%
Hematologic										
Neutropenia	9	16	7	12	20	35	17	30	4	7
Anemia	7	16	5	11	27	61	4	9	1	3
Thrombocytopenia	35	60	15	26	4	7	4	7	0	0
Fever in absence of infection	57	100	0	0	0	0	0	0	0	0
Non-hematologic										
Diarrhea	53	93	1	2	3	5	0	0	0	0
Nausea/Vomiting	57	100	0	0	0	0	0	0	0	0
BUN	57	100	0	0	0	0	0	0	0	0
Cr	57	100	0	0	0	0	0	0	0	0
AST	56	98	1	2	0	0	0	0	0	0
ALT	56	98	1	2	0	0	0	0	0	0
TB	57	100	0	0	0	0	0	0	0	0
Esophagitis	15	58	4	15	4	15	3	12	0	0
Pneumonitis	15	58	7	26	3	12	1	4	0	0

*number of events.

most common of both the hematologic and non-hematologic toxicities. Among the hematologic toxicities, neutropenia was the most common of grade 3/4 (19 cases, 35%), and anemia was the most frequent of grade 1/2 (30 cases, 55%). Fever in the absence of infection was reported in four cases (7%). There was one grade 4 case, in which further treatment was withheld. There were no treatment-related deaths. Hematopoietic growth factors were used only in the cases of neutropenic fever. Diarrhea was the most common grade 3/4 non-hematologic toxicity (5 cases, 9%).

The toxicities of concurrent chemoradiotherapy are described in Table 4. Among the grade 3/4 hematologic toxicities, neutropenia was most common (16 cases, 37%); among the grade 1/2 hematologic toxicities, anemia occurred most frequently (34 cases, 79%). Fever in the absence of infection was reported in one case (2%) but did not delay the treatment schedule. No deaths occurred. Hematopoietic growth factors were used only in the case of neutropenic fever. Among the non-hematologic toxicities were radiation-related toxicities such as esophagitis (6/19), radiation pneumonitis (7/19), and vesicles, itching, or pain on related skin (1/19 each). Late moderate to high-grade (≥grade 2) radiation-related toxicity was uncommon. Twelve patients experienced late low-grade (grade 1) radiation pneumonitis, and three experienced late low-grade (grade 1) radiation esophagitis.

4. Treatment delivery and dose-intensity

The median chemotherapy interval during the concurrent chemoradiotherapy was 21 days. The planned and actual dose intensities are shown in

Table 5. Dose Intensity (DI)

Treatment	Planned DI	Actual DI
	mg/m2/week (%)	
Irinotecan	40	38.2 (95.5)
Cisplatin	20	19.6 (98)

Table 5. The actual dose intensity as a proportion of the planned dose intensity was greater than 95%, and 100% of the patients (19/19) completed thoracic radiotherapy at 45 Gy.

Discussion

Most patients with LD-SCLC receive combined modality therapy with TRT and PE (or another platinum-containing regimen), which is widely accepted as the standard treatment[6]. The goal of treatment is to achieve complete clinical regression of the tumor at the initial response, determined 6 to 12 weeks after the start of therapy, which predicts median and long-term survival, response to second-line therapy, and potential for a cure. Patients who achieve complete clinical regression survive longer than those with a partial response, who in turn survive longer than those with no response. Complete remission is required for long-term survival. The IP regimen is significantly more effective than the PE regimen in ED-SCLC[5], and thus irinotecan has been actively introduced to improve the treatment results in SCLC[16-20]. Some studies have demonstrated that combining cisplatin with topoisomerase I inhibitors has an exclusively synergistic effect[21,22]. However, Hanna et al have reported no significant differences in patient outcomes between those treated with PE and those treated with IP[23], using an IP dose and schedule (cisplatin 30 mg/m2 i.v. and irinotecan 65 mg/m2 i.v. on days 1 and 8 every 21 days) that differed from those in Noda et al[5]. Even though dose intensification of cisplatin had not resulted in significant outcome differences in ED SCLC, Hanna et al changed the cisplatin dose from 60 to 30 mg/m2[23] based on a study by Ihde, which compared high-dose PE with standard-dose PE[24]. This trial was against to the positive results of Noda's study. They explained that differences in polymorphisms of UDP-glucuronosyltransferase (UGT1A1) between different in North American and Japanese may be related to pharmacogenomic differences. During concurrent IP chemotherapy with TRT in the treatment of LD-SCLC, irinotecan might act as a potential radiation sensitizer with cisplatin. Our data showed six CRs (27%) and 15 PRs (68%), for a 95% overall response, after two cycles of IP chemotherapy. After concurrent chemoradiotherapy, there were nine CRs (47%) and 10 PRs (53%), for an overall response rate of 100%.

Although we agree that the definition of local control in SCLC is ambiguous, if the definition of local control for NSCLC also applies for SCLC, the local control rate was 63%[25]. For the response status of CR after concurrent chemoradiotherapy, the local control rate was 89%. Local control was used to evaluate the effectiveness of TRT.

The 1-year survival rate of eligible patients was 88%, and many more CRs converted after concurrent chemoradiotherapy resulting in a relatively higher 1-year survival rate. Recently, Han et al. designed two cycles of IP induction chemotherapy followed by concurrent PE chemotherapy with twice-daily TRT for the treatment of LD-SCLC. They reported three CRs (9%) and 31 PRs (88%), for an overall response rate of 97% after 2 cycles of IP induction; concurrent chemoradiotherapy resulted in 18 CRs (43%) and 16 PRs (57%), for an overall response rate of 100%. They also reported 1- and 2-year survival rates of 85.7 and 53.9%, respectively. Our data were similar, with 1- and 2-year survival rates of 88 and 47%, respectively. On the basis of our data and the results of many other studies, we suggest that irinotecan-containing regimens are feasible to one of the most promising strategies for improving the survival of LD-SCLC patients.

Despite controversy regarding the optimal timing of concurrent radiotherapy, a recent meta-analysis report recommended early (beginning within 9 weeks of the initiation of chemotherapy and before the third cycle of chemotherapy) chemoradiotherapy, which had a significant survival gain benefit at 2 years but not at 3 years[7]. Another meta-analysis concluded that early radiotherapy (beginning within 30 days of the initiation of chemotherapy, except concurrent chemoradiotherapy) was associated with better 5-year survival but not improved 2-year survival, especially when the overall treatment time of chest radiotherapy was less than 30 days[26]. A consensus conclusion of the two meta-analyses was that early chest radiotherapy could be more effective. We designed a concurrent IP chemotherapy with hyperfractionated early TRT[7] after two cycles of induction IP treatment.

A total of 99 cycles were given, and the actual dose intensities were more than 95% of the planned dose intensities. Given the benefit of TRT in addition to chemotherapy for both local control and overall survival in LD-SCLC[8,9,27,28], an optimal TRT fractionation scheme of twice-daily fractionation (hyperfractionation) is theoretically advantageous for SCLC characterized by a rapidly proliferating malignant tumor. Two studies have revealed that concurrent chemoradiotherapy with a radiation dose to 45 Gy delivered twice daily with the first cycle of cisplatin and etoposide significantly increased the 2- and 5-year overall survival rates compared with once-daily protocols[7,29].

In contrast, another study failed to show a beneficial effect of hyperfractionated TRT in overall survival[30]. Early twice- daily radiotherapy with concurrent chemotherapy improved overall survival, but late twice-daily radiotherapy with early chemotherapy did not improve overall survival. Twice-daily radiotherapy commonly resulted in radiation esophagitis. Radiation-related toxicity such as esophagitis is worse with combination treatment, but can be minimized with appropriate patient selection. Patients should be selected to allow radiotherapy to be given in full doses and in a manner that does not sacrifice too much lung function or a patient's quality of life.

In our study, myelosuppression was the most common toxic effect, and neutropenia (35% of cycles) was the most common grade 3/4 toxicity. Almost all patients were able to continue the schedule. No treatment-related deaths occurred. The prevalance of grade 3/4 diarrhea was quite acceptable (5 cases in 98 cycles, 5%). Esophagitis occurred often in the patients who received hyperfractionated TRT. However, only one patient skipped chemotherapy on day 8 and delayed the next chemotherapy scheme 3 days later. All patients tolerated concurrent chemoradiotherapy. In regard to radiation-induced pneumonitis, one patient suffered from dyspnea, received prednisolone (1 mg/kg of body weight, once daily for 2 weeks and then tapered), and was discharged with symptom improvement. In spite of a favorable 1-year survival rate and tolerable side effects, that eligible patients were small numbers and only male was weak point. But, it is possible that two cycles of IP induction chemotherapy followed by concurrent chemoradiotherapy composed of hyperfractionated TRT with four cycles of an IP regimen is useful regimen in LD-SCLC.

Based on this study, we suggest that treatment with two cycles of IP induction chemotherapy followed by concurrent chemoradiotherapy composed of hyperfractionated TRT with four cycles of an IP regimen is useful effective in LD-SCLC, with a favorable 1-year survival rate and tolerable side effects. Concurrent twice-daily TRT with combination chemotherapy containing irinotecan and

cisplatin may be the most powerful treatment for LD-SCLC patients, given that the dose intensity of irinotecan can be reached close to the planned dosage with tolerable side effects. We expect that this protocol will improve the current long-term survival rate, but this needs to be studied further.

Summary

Background: Irinotecan hydrochloride, a topoisomerase I inhibitor, is effective against small-cell lung cancer. Irinotecan also can act as a potential radiation sensitizer along with cisplatin. To evaluate efficacy and toxicity of irinotecan plus cisplatin (IP) with concurrent thoracic radiotherapy, we conducted a phase II study of IP followed by concurrent IP plus hyperfractionated thoracic radiotherapy in patients with previously untreated limited-stage small-cell lung cancer.

Methods: Twenty-four patients with previously untreated small-cell lung cancer were enrolled onto the study since November 2004. Irinotecan 60 mg/m^2 was administered intravenously on days 1 and 8 in combination with cisplatin 60 mg/m^2 on day1 every 21 days. From the first day of third cycle, twice-daily thoracic irradiation (total 45 Gy) was given. Prophylactic cranial irradiation was given to the patients who showed complete remission after concurrent chemoradiotherapy. Restaging was done after second and sixth cycle with chest CT and/or bronchosocpy.

Results: Up to November 2004, 19 patients were assessable. The median follow-up time was 12.5 months. A total of 99 cycles (median 5.2 cycles per patient) were administered. The actual dose intensity values were cisplatin 19.6 mg/m^2/week and irinotecan 38.2 mg/m^2/week. Among the 19 patients, the objective response rate was 95% (19 patients), with 9 patients (47%) having a complete response (CR). The major grade 3/4 hematological toxicities were neutropenia (35% of cycles), anemia (7% of cycles), thrombocytopenia (7% of cycles). Febrile neutropenia was 4% of cycles. The predominant grade 3/4 non-hematological toxicities was diarrhea (5% of cycles). Toxicities was not significantly different with concurrent administration of irinotecan and cisplatin with radiotherapy, except grade 3/4 radiation esophagitis (10% of patients). No treatment-related deaths were observed. The 1-year and 2-year survival rate of eligible patients was 89% (16/18) and 47% (9/18), respectively.

Conclusion: Three-week schedule of irinotecan plus cisplatin followed by concurrent IP plus hyperfractionated thoracic radiotherapy is an effective treatment for limited disease small-cell lung cancer, with acceptable toxicity.

Conflict of interest: None declared

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