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Original Article

CISPLATIN AND ETOPOSIDE WITH EITHER CONCURRENT OR SEQUENTIAL RADIATION THERAPY IN LIMITED-STAGE SMALL CELL LUNG CANCER

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ABSTRACT

Aim of the Work: To compare concurrent versus sequential thoracic radiation therapy in combination with cisplatin and etoposide in treatment of limited-stage small cell lung cancer.

Patients and Methods: Forty two patients with previously untreated limited-stage small cell lung cancer were randomized to receive chest irradiation either with the first cycle of chemotherapy in the concurrent arm (20 patients) or after the fourth cycle of chemotherapy in the sequential arm (22 patients). The total dose of radiation was 60 Gy, using daily seating of 2 Gy in 30 treatments over a period of six weeks. All patients received chemotherapy every 4 weeks, for total of 4 to 6 cycles in the form of cisplatin (100 mg/m2 intravenously) on day 1 and etoposide (100 mg/m2 intravenously) on days 1, 2 and 3.

Results: The overall response rate was higher in concurrent arm (90%) than in sequential arm (77.2%). Brain metastasis occurred as first site of recurrence in 22.7% of the patients in the sequential arm and 20% of the patients in the concurrent arm. Leucopenia was more frequent in the concurrent arm. Progression-free and overall survivals tended to be higher in the concurrent arm than those in the sequential arm (P =0.09 and 0.07, respectively).

Conclusion: Concurrent use of cisplatin and etoposide with radiation therapy in limited-stage small cell lung cancer is preferred than sequential treatment.

Key Words: lung cancer, limited stage, small cell, concurrent chemoradiation.

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INTRODUCTION

In 2008, an estimated 215,020 new cases of lung cancer were diagnosed in the United States, with 161,840 resultant deaths[1]. Small cell lung cancer (SCLC) accounts for approximately 15% of all newly diagnosed cases of lung cancer[2]. Small cell lung cancer is typically staged according to the Veterans Administration Lung Cancer Study Group (VALCSG) staging system. Disease confined to one hemithorax with the tumor encompassed in one radiation port is classified as limited-stage disease (LD); while disease that is any less confined, is classified as ED. At diagnosis, approximately 30% of patients with SCLC have LD[3].

Clinical stage, performance status, age, gender and paraneoplastic phenomena are the important prognostic clinical factors[4]. With its propensity for early hematogenous spread, SCLC is a systemic disease and is rarely cured with surgical resection[5]. Small cell lung cancer is responsive to chemotherapy, several chemotherapeutic agents, including doxorubicin, methotrexate, vincristine, cyclophosphamide, etoposide, cisplatin and carboplatin, produce single-agent response rates of 30% or greater in patients with SCLC. Combination regimens yield higher responses and superior survival compared with the use of single agents. The role of maintenance therapy did not reveal any survival advantage for prolonged treatment after four to six cycles of chemotherapy[6].

Currently, etoposide plus cisplatin (EP) is the regimen of choice for patients with LD because of the superior efficacy and the favorable toxicity profile[7]. The risk of central nervous system metastasis developing two years after successful treatment of SCLC is approximately 35% to 60%. Thus, prophylactic cranial irradiation was introduced, primarily for responsive LD SCLC[8].

Meta-analysis of thoracic irradiation for limited small cell lung cancer showed that thoracic irradiation helps in improving survival and local control in limited small cell lung cancer patients[9]. Because of the radiosensitivity of SCLC, modest doses of thoracic radiotherapy (45-50 Gy) were typically administered in daily fractions of 1.8 to 2.0 Gy. Subsequent data suggested that more aggressive thoracic radiotherapy can improve the long-term outcome of patients with LD-SCLC as well[10]. However, adoption of a twice-daily dose thoracic radiotherapy of 45 Gy as a routine treatment is limited by increased esophageal toxicity as well as scheduling inconvenience for patients[11]. The timing of thoracic radiotherapy has been the subject of several randomized trials, concurrent

and sequential approaches have been tried in integrating thoracic radiotherapy with chemotherapy. Some reported a survival benefit for early thoracic radiotherapy[12,13] whereas others did not[14,15].

Our study was designed to compare concurrent and sequential chemoradiotherapy in limited stage SCLC.

PATIENTS AND METHODS

Eligibility Criteria:

Patients age of up to 72 years with previously untreated, pathologically documented small cell lung cancer confined to the one hemithorax of origin, including hilar, mediastinal and supraclavicular nodes disease were entered in this prospective, randomized study through the closed envelop method. The eligibility criteria for patient entry included no active second malignancy and an Eastern Cooperative Oncology Group performance status of 0–2, adequate hematological function, defined as leukocyte count of at least 4000 /mm3, platelet count of at least 100,000 /mm3 and hemoglobin level greater than 11 g/dL, adequate liver function, adequate renal function with serum creatinine level of less than 1.5 mg/dL and adequate cardiac function defined as no symptomatic heart disease and no significant arrhythmia or myocardial infarction within the past 6 months. Patients with distant metastses, pericardial and pleural effusion found on chest x-ray were excluded, regardless of cytological findings, as were patients with contralateral hilar or supraclavicular adenopathy. Patients consent and approval of ethical committee were obtained.

Pretreatment Assessment:

The patients underwent staging evaluation before the initiation of treatment: A detailed history, careful physical examination and appropriate studies including fiberoptic bronchoscopy, complete blood cell count with differential count, renal, lung and liver functions. Radiological evaluation, is the key to establish the diagnosis of limited stage SCLC, chest radiograph, computed axial tomography of the chest extending through the liver and bilateral adrenal glands and contrast-enhanced MRI or CT of the brain are standards of care. Radionuclide bone scan are also typically obtained because of the frequency of bone metastasis.

Treatment plan:

Chemotherapy: Chemotherapy regimen was given every 4 weeks, for total of 4 to 6 cycles in the form of cisplatin (100 mg/m2 intravenously) on day 1 and etoposide (100 mg/m2 intravenously) on days 1, 2 and 3. Clinical examination, full blood cell count and serum biochemistry studies were carried out before every cycle. If the leukocyte count had decreased to below 3,000/mm3 or the platelet count to below 75,000/mm3 on the first day of next cycle, chemotherapy was withheld until the counts recovered. The dose of etoposide was reduced to 75% of the initial dosage for patients who experienced grade 4 hematologic toxicity in the previous cycle. Chemotherapy was terminated in patients with serum creatinine levels of 2.0 mg/dL or higher, serum bilirubin levels of 2.0 mg/dL or higher, after 6 weeks of the prior cycle.

Thoracic Radiotherapy:

Chest irradiation started with the first cycle of chemotherapy in the concurrent arm and after the fourth cycle of chemotherapy in the sequential arm. The target volume for thoracic radiotherapy, which was similar in both groups based on the pretreatment tumor volume, included the primary disease site, as defined by the chest CT scan, with 2 Cm margin around the mass, the ipsilateral hilum and the entire width of the mediastinum, 6cm below the carina in upper lobe lesions. For lower lobe lesions, the radiation portals were extended down to the diaphragm. The supraclavicular lymph nodes were included if there was involvement. The patients received 50 Gy using 6 MV linear accelerator or cobalt-60 machines. It was administered as standard radiation fractionation refers to schedules using daily treatments of 2 Gy, in 25 treatments over a period of five weeks, 5 times per week. This was achieved by using anterior and posterior opposed fields. Patients underwent treatment setup with radiotherapy simulators to mark field borders before treatment. The gross tumour was boosted to a total dose of 60 Gy with oblique portals using CT planning technique. The spinal cord was blocked to maintain its dose below 40 Gy.

After the end of treatment, the reassessment of the disease was done again by chest and brain CT, because of the high frequency of brain metastases. The patients who achieved complete response were given prophylactic cranial irradiation. This treatment consisted of 10 doses of 2.5 Gy to the midplane of the brain over period of two- weeks, for a total dose of 25 Gy. The treatment was planned using two lateral portals to encompass the whole of the brain.

Follow-up:

Physical examination, performance status assessment and laboratory investigation were repeated before each cycle during treatment. The response was determined by doing computed tomographic scan of chest after two and last cycles of combination chemotherapy. Patients were examined at the end of the treatment, every month for 6 months (after completion of therapy), every 2 months for 2 years thereafter and every 4 months after that.

Response Criteria:

The responses were assessed according to WHO criteria[16]. Complete response (CR) was defined as complete disappearance of all measurable malignant lesions for at least 4 weeks. Partial response (PR) was a reduction of at least 50% in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without any new malignant

lesion. No response was defined as stabilization or <50% reduction in measurable disease. Progression was defined as an increase of >25% of at least one lesion or the appearance of a new malignant lesion.

End Points:

Overall survival, the primary end point of the trial, was measured from the date of entry into the study to the date of death from any cause. Treatment failure was considered if there was objective evidence of disease progression or death without clear-cut evidence of tumor progression. Failure was considered local when an intrathoracic relapse occurred after a complete response or when there was no complete response. The secondary objective was to evaluate the difference between the two arms in clinical response and toxicity during treatment.

Statistical analysis

The statistical analysis of data had been done by using SPSS program (Statistical Package for Social Science Version 13). The analysis of the data was done to test statistical significant difference between groups. Chi square test was used as a test of significance. Overall and progression- free survivals were calculated by using Kaplan Meier curve with the use of log- rank test.

N.B: P is significant if < or = 0.05 at confidence interval 95%.

RESULTS

From November 2005 to November 2008, 42 eligible patients with limited stage SCLC were enrolled into this study. Twenty two patients were randomly assigned to receive sequential treatment and 20 patients were assigned to receive concurrent treatment. The baseline characteristics were listed in Table 1 and they were well balanced between the two arms.

The response rates achieved during the whole treatment period of chemotherapy and thoracic irradiation; were summarized in Table 2. The overall response rate was higher in the concurrent arm (90%) than in sequential arm (77.2%) but there was no statistically significant difference between the two arms. The rate of progression was higher in sequential arm (13.7%) when compared with that in concurrent arm (5%). The distribution of the first treatment failure sites was shown in Table (3). Brain metastasis occurred as the first site of recurrence in 22.7% of the patients in the sequential arm and 20% of the patients in the concurrent arm. There was no statistically significant difference between both arms.

Table (4) showed the toxicity of treatment (grade 3 or 4) using WHO toxicity criteria. Leucopenia was more frequent in the concurrent arm (P=0.04). Thrombocytopenia occurred more frequent in the concurrent arm but the difference was statistically insignificant. Grade 3 acute esophagitis occurred in only one patient out of 22 patients in sequential arm and two patients out of 20 patients in the concurrent arm. There was only one patient developed pneumonitis in the concurrent arm.

After median follow-up of 18 months (6-42 months), progression-free survival in the concurrent arm was superior to that in the sequential arm. However the difference had not reached the statistically significant difference (hazard ratio = 0.33; 95% CI, 0.08 to 1.36; log-rank P =0.09). Median progression-free survival time was 9 months in sequential arm and 12 months in concurrent arm Figure (1).

Figure (2) shows the Kaplan-Meier curves for overall survival. The median overall survival time for patients was 15 months in the sequential arm (95% confidence interval (CI), 11.57 to 18.4 months) versus 18 months (95% CI, 10.11 to 25.89 months) in the concurrent arm. Overall survival time in the concurrent arm tended to be superior to that in the sequential arm, but the difference was statistically insignificant (hazard ratio = 0.27; 95% CI, 0.67 to 1.097; P = 0.07 by log-rank test).

Table 1: Baseline characteristics according to treatment arms.

	Sequential Arm (n =22)		**Concurrent Arm (n =20)**		**P value**
Characteristics	No. of Patients	%	No. of Patients	%	
Age(years)					
Median	61.5		59.5		0.09
Range	48-72		45-70		
Sex					
Male	14	63.6	13	65	0.59
Female	8	36.4	7	35	
ECOG PS					
0	7	31.8	8	40	0.39
1	12	54.5	11	55	
2	3	13.7	1	5	

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2: Tumor response according to treatment arms.

Response	Sequential Arm (n =22)		Concurrent Arm (n = 20)		P Value
	No. of Patients	%	No. of Patients	%	
Response					
Complete	5	22.7	8	40	0.23
Partial	12	54.5	10	50	0.77
Overall	17	77.2	18	90	0.27
Stable disease	2	9.1	1	5	0.61
Progression	3	13.7	1	5	0.34

Table 3: Sites of first treatment failure according to treatment arms.

Site	Sequential Arm (n=22)		Concurrent Arm (n =20)		P Value
	No. of patients	%	No. of patients	%	
Lung	3	13.7	2	10	0.72
Node	2	9.1	1	5	0.61
Liver	4	18.2	3	15	0.87
Bone	4	18.2	2	10	0.45
Brain	5	22.7	4	20	0.83
No progression	4	18.2	8	40	0.12

Table 4: Reported toxicities (grade 3 or 4) according to treatment arms.

Toxicity	Sequential Arm (n =22)		Concurrent Arm (n =20)		P value
	No. of patients	%	No. of patients	%	
Hematological					
Leucopenia	2	9.1	7	35	0.04*
Thrombocytopenia	1	4.5	4	20	0.12
Anemia	2	9.1	3	15	0.56
Nausea/vomiting	4	18.2	2	10	0.45
Esophagitis	1	4.5	2	10	0.49
Fever	1	4.5	1	5	0.95
Pneumonitis	0	0	1	5	0.29
Renal impairment	1	4.5	0	0	0.34

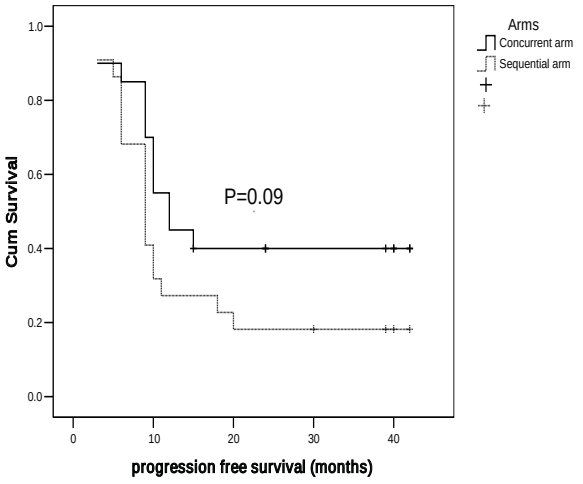

Figure 1: Progression-free survival.

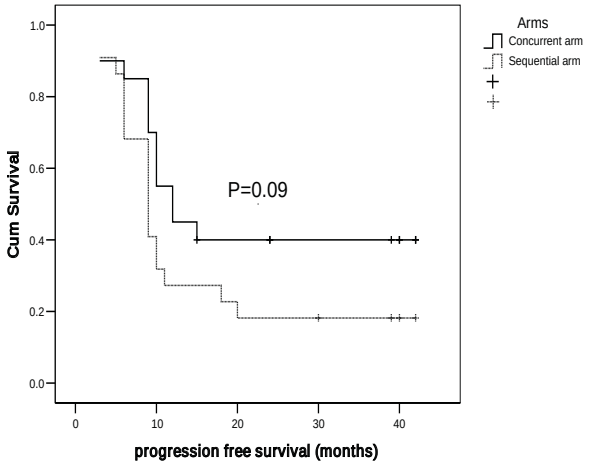

Figure 2: Overall survival.

DISCUSSION

Small cell lung cancer (SCLC) is characterized by a rapid tumour doubling time, a high rate of local tumour recurrence and the early formation of distant metastases. Chemotherapy is an important pillar of treatment in both stages of the disease. Despite the chemosensitivity of the disease, local recurrences occur in up to 90% of cases treated by chemotherapy alone[17]. Numerous clinical trials demonstrated the superiority of systemic chemotherapy plus thoracic radiation versus chemotherapy alone[18], meta-analyses of limited disease–SCLC treatment showed that additional local irradiation can significantly improve the local recurrence rate as well as the overall survival rate[19,20]. The combination of etoposide plus cisplatin is regarded as the standard form of chemotherapy in these patients[21]. Randomized trials of thoracic irradiation timing in LD-SCLC have been reported and some of them have shown the superiority of early thoracic irradiation over delayed thoracic irradiation[12,13], while other studies failed to show the superiority of early thoracic irradiation[14,15].

This study compared concurrent with sequential chemo-radiotherapy. The overall response rate was higher in the concurrent arm (90%) than in sequential arm (77.2%) but there was no statistically significant difference between the two arms. This result coincided with study done by Takada et al.[13] who found that there was a trend for a higher complete response rate in the concurrent arm than in sequential arm (P= 0.07)[13].

As regard progression-free survival the concurrent arm was superior to that in the sequential arm, however the difference was statistically insignificant (P=0.09). Overall survival in the concurrent arm also tended to be superior to that in the sequential arm. The difference was not statistically significant (P= 0.07), at median follow-up of 18 months, ranged (6-42). These results were coincided with Takada et al, who mentioned that comparison of overall and progression-free survivals in his study showed that concurrent radiotherapy was more advantageous than sequential radiotherapy and

the difference was not statistically significant. However, adjustment with Cox regression analysis suggested a greater benefit of concurrent radiotherapy than simple comparison[13]. Regarding our study the number of patients were smaller (42 patients), we used conventional fractionation of total dose 60 Gy in both arms while Takada et al. used twice daily fractionation of total dose 45 Gy.

In agreement with our study Law et al.[22] showed that the group treated with concomitant chemoradiation had an improved outcome with acceptable short- and long-term toxicities. Although the improved outcome may in part have been due to selection bias, with the group received concomitant treatment being younger, fitter and having less bulky disease, this survival advantage persisted in the multivariate analysis when age and performance status were taken into account[22]. Meta-analysis of 7 randomized trials comprising 1524 patients showed a small 2-year survival benefit favoring early thoracic radiation and the magnitude of the survival benefit remained similar at 3 years[19].

Spiro et al.[23] showed that there was no evidence of difference in survival between patients who received early or late thoracic irradiation, while the NCIC trial[12] reported significant advantage of early thoracic irradiation regarding progression-free and overall survivals. Despite both trials used similar protocol of chemotherapy which was consisted of cyclophosphamide, doxorubicin and vincristine (CAV) alternating with etoposide and cisplatin (EP) and the radiotherapy total dose used was 40 Gy in 15 fractions over 3 weeks. The explanation was that in the NCIC trial, CT scan of the thorax was not routinely available at that time and, therefore, not mandatory done [23]. In contrast to The Cancer and Leukemia Group B trial which compared radiotherapy starting with cycle 1 of chemotherapy and radiotherapy starting with cycle 4[18]. This trial also used cyclophosphamide-based chemotherapy but they found the best survival when the radiotherapy began with cycle 4. Others, particularly in Europe[14,24] found that sequential strategies were superior to concurrent treatment, which was associated with excess toxicity and the decrease in dose-intensity because of the accelerated toxicity of the combined-modality therapy. Cyclophosphamide-based or doxorubicin-based chemotherapy used in these studies, which may explain the inability to integrate concurrent thoracic radiotherapy successfully. While an EP-based concurrent regimen did not increase pulmonary toxicity or lead to the radiation recall phenomenon[13].

Brain metastasis occurred as the first site of progression in 22.7% of the patients in the sequential arm and 20% in the concurrent arm. There was no statistically significant difference between both arms. Coinciding with Takada et al, brain metastasis was experienced as the first progression site in 27% of the patients in the sequential arm and 19% in the concurrent arm. They suggested the hypotheses that local control is achieved earlier in the concurrent arm, preventing distant dissemination beyond the confines of the radiation field[13]. Law et al.[22] also found that brain metastasis occurred in 17% of the patients in the sequential arm and 10% in the concurrent arm[22]. Murray et al reported that the patients in the late thoracic irradiation arm had a higher risk of brain metastases, the difference were statistically significant (P=0.006)[12].

As regard toxicity in our study, leucopenia was more frequent in the concurrent arm (P=0.04), thrombocytopenia also occurred more frequent in the concurrent arm but the difference was statistically insignificant. Grade 3 acute esophagitis occurred in only one patient out of 22 patients in sequential arm and two patients out of 20 patients in the concurrent arm. There was only one patient developed pneumonitis in the concurrent arm. In consistent with study done by Takada et al, who reported that myelosuppression was common in both arms but more severe in the concurrent arm. Leukopenia was much more frequent in the concurrent arm. Thrombocytopenia was infrequent and mild in both arms. Grades 3 or 4 esophagitis occurred in 10 patients out of 112 patients in the concurrent arm and four patients out of 110 patients in the sequential arm, but none of these patients developed permanent stricture. There were no marked differences in nonhematologic toxicity between the two arms[13]. Also consistent with our study Law et al.[22] observed that grade 4 haematological toxicity was higher in patients received concomitant radiotherapy than patients received sequential radiotherapy and the difference was statistically significant. Grade 3 acute esophagitis occurred in less than 10% in both arms and late esophageal toxicity was observed in only one patient with the sequential regimen and none with concomitant treatment. There were no cases of grade 3 or greater pneumonitis[22].

The rate of esophagitis depends on the irradiated volume of the esophagus and the total radiation dose, the fractionation and the type of applied chemotherapeutic agents. So it is difficult to compare the rates of esophagitis of different studies. Turrisi et al., who compared conventional with hyperfractionated schedules using total dose of 45Gy, reported a rate of grade III/IV esophagitis in a hyperfractionated accelerated radiation schedule of 32%[25].

CONCLUSION

Concurrent use of cisplatin and etoposide with radiation therapy in limited-stage small cell lung cancer is preferred than sequential treatment.

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