Cisplatin and etoposide alternating ifosfamide, vincristine, epirubicin in small cell lung cancer

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ABSTRACT

Objective: The aim of this study was to evaluate the effects and toxicity of alternating cisplatin+etoposide (EP) and ifosfamide+vincristine+epirubicin (IVE) combination regimen in patients with small cell lung cancer (SCLC).

Methods: We have treated 38 SCLC patients with 6 courses of alternating chemotherapy consisting of cisplatin 100 mg/m^2 on day one and etoposide 80 mg /m^2 on the first, second and third days in courses of first, third and fifth, alternating with ifosfamide 4 g/m^2, vincristine 2 mg/day and epirubicin 60 mg/m^2 intravenously on day one in courses of second, forth and sixth. The courses were administrated every 3 weeks. After the sixth course of chemotherapy the patients with limited disease (LD) who had a complete response (CR) received concomitant chest irradiation. None of the patients had prophylactic cranial irradiation. The study was conducted between January 1997 and July 1997 in the Department of Chest Disease at Ondojuz Mayis University Hospital, Samsun, Turkey.

Results: The mean age of the 3 female and 35 male patients was 59.5 (33-72) years. Eighteen of which had LD and 20 had extensive disease (ED). Twenty patients had Eastern Cooperative Oncology Group (ECOG) 1 and 18 had ECOG 2 performance status. Objective response (OR) was obtained in 26 (68%) of the patients. While 13 patients had a CR rate, 6 patients remained stable (16%). The OR rate was observed to be 100% (CR 61%, partial response [PR] 39%) in patients with LD, whereas it was 40% (CR 10%, PR 30%) in patients with ED. The median survival was 9 months in LD and 6 months in ED. Relapses after CR occurred in 11 patients with LD (local relapse in 8; one in the brain; one in the liver; one in the bone) and one patient with ED (in the brain). The observed toxicities were grade III-IV leukopenia 13%, grade III-IV nausea and vomiting 8%, and 39% alopecia.

Conclusion: We conclude that the described regimen is a well-tolerated, less toxic therapy for SCLC.

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Small cell lung cancer (SCLC) has a rapid clinical course. Although new drugs have been recently in the management of SCLC, it is still has a poor prognosis. The failure in chemotherapy to obtain a long-term remission is thought to be dependent on the presentation of resistant clones.[1] Goldie et al,[2] stated that simultaneous treatment with multiple chemotherapeutic agents with different effects could achieve an early improvement in tumor response. The drugs used in the standard therapies (with or without hematopoietic growth factors) are given in high doses. The marrow transplantation is performed after late-dose intensification chemotherapy. Each cyclophosphamide, adriamycin and vincristin (CAV) and cisplatin and etoposide regimens had improved response rates and survival advantages in SCLC.[3,4] Alternating combined chemotherapy could be started with CAV or cisplatin+etoposide (EP).[5,7] The analog chemotherapeutics with similar effects and less toxicity can also be used to reduce the side effects of these

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combined drugs. Epirubicin is used as an analog of doxorubicin and ifosfamide is used as an analog of cyclophosphamide in SCLC in many studies.[8-11] However, these are few studies in which these 2 drugs are used in an alternating regimen.[12] In our study we evaluated the effects and toxicity of alternating cisplatin-etoposide, and ifosfamide, vincristine and epirubicin regimens.

Methods. The study was conducted between January 1997 and July 1997 in the Department of Chest Diseases at Ondokuz Mayis University Hospital, Samsun, Turkey. Thirty-eight patients who were proven to have SCLC histopathologically and received neither chemotherapy nor radiotherapy were included in the study. Blood counts, serum biochemical analysis, electrocardiography, and performance status (Eastern Cooperative Oncology Group [ECOG]) were evaluated before starting the treatment. Chest x-ray, computerized tomography of the lung, upper abdomen and cranium, bone scan and fiber optic bronchoscopy were performed. The patients were categorized by the disease status as limited disease (LD) and extensive disease (ED). Patients with one hemithoracic, mediastinal and supraclavicular lymph node involvement and one without malignant pleural effusion were included in the LD group. The cases not matching those criteria were included in the ED group.[13] The exclusion criteria included patients >75-years-old, ECOG>2, with white blood cells of <3000/mm^3, platelets <100000/mm^3, creatinine clearance <60 ml/min, bilirubin values of >2 gr/dl and with a previous history of malignancy. The alternating regimen was started with EP (100 mg/m^2/intravenous [iv] cisplatin on the first day and etoposide 80 mg/m^2/iv on the first to third days) that was repeated in the 3rd and 5th courses. Second chemotherapy course with IVE (ifosfamide 4 g/m^2/iv, vincristine 2 mg/iv, epirubicin 60 mg/m^2/iv and mesna) was started on the twenty-first day and repeated in the second, fourth and sixth courses. Chest x-rays, complete blood counts, serum biochemical analysis, and electrocardiography were performed before each cycle. The performance status was evaluated preceding and following each course of chemotherapy. All patients were evaluated for toxicity and their responses to the therapy. Therapy was stopped in patients who had no response after the third course. The treatment was delayed for one week if white blood cell counts were <3000/mm^3 or thrombocytes were <100000/mm^3. Six courses of therapy was introduced to the patients with any response. Complete response (CR) was accepted to be disappearance of signs and measurable lesions for at least 4 weeks after chemotherapy. Partial response (PR) was accepted to be 50% decrease of measurable lesions in perpendicular diameters, without any new lesions in at least 4 weeks. Increase of measurable lesions more than 25% or appearance of new lesions was progression (PD) and the remaining patients were included in stable disease (SD) group. The World Health Organization criteria were used to evaluate toxicity.[14] The Kaplan-Meier method of survival analysis was used for statistical evaluation.[15]

Results. A total of 38 patients (3 females, 35 males) were included in this study and 18 of which had LD and 20 had ED. The mean age was 59.5 (33-72) years. Performance according to ECOG criteria was one in 20 patients and 2 in 18 patients (**Table 1**). The patients with LD who had a CR was treated with thoracic radiotherapy (50Gy) on the third week following the last course of therapy. None of the patients had prophylactic cranial radiotherapy. Overall, 26 (68%) patients had objective response. Thirteen of which (34%) had a CR. Six patients (16%) remained stable. In the patients with LD, objective response ratio was 100% (CR 61%, partial response 39%) and in the ED patients, objective response was 40% (CR 10%, PR 30%) (**Table 2**). The mean survival period was 8 months for all the patients included in the study. It was 9 months for LD and 6 months for ED (**Figure 1**). Median progression time was 6 months and one-year survival ratio (rate) was 0.5% and 2-year survival rate was 0.6%. Grade III-IV leukopenia was seen in 13%, grade III-IV nausea and vomiting was seen in 7%, and alopecia was seen in 36% (**Table 3**). Relapse was seen in 11 patients with LD (local relapse in 8 patients; one in the brain, one in the liver and one in bone) and in one patient with LD (in the brain).

Discussion. The progressions in the therapy were very limited although various chemotherapy combinations and methods with new drugs were tried in SCLC to improve survival and response to the therapy. Complete response was 50-60% in LD and 15-30% in ED with or without thoracic radiotherapy and objective response was achieved in 90% of the patients. Nevertheless, the reported mean survival was 12 months for LD and less than 16 months for ED.[16,17] The first

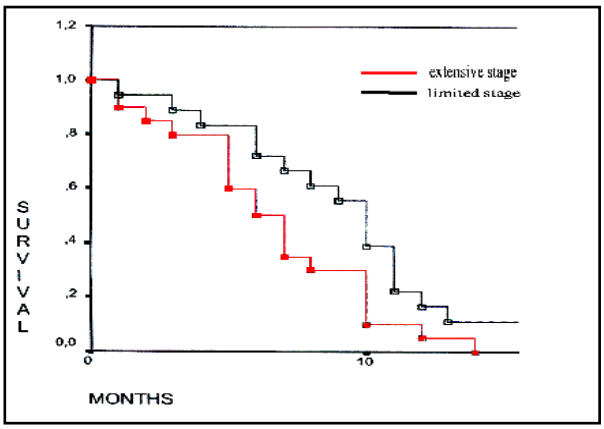

Figure 1 - Survival rates in limited and extensive stage of small cell lung cancer.

Table 1 - Patient characteristics.

Characteristics	Limited	Extensive	Total
N of patients	18	20	**38**
Male	16	19	**35**
Female	2	1	**3**
Age (year)	69.5	57.5	**59.5**
Median (range)	(33 - 72)	(33 - 71)	**(33 - 72)**
ECOG performance status			
0-1			**20**
2			**18**
Limited disease			**18**
Extensive disease			**20**

ECOG - Eastern Cooperative Oncology Group

Table 2 - Response ratios according to the stage of the disease.

Stage	CR n (%)	PR n (%)	SD n (%)	PD n (%)
Limited disease	11 (61)	7 (39)	- -	- -
Extensive disease	2 (10)	6 (30)	6 (30)	6 (30)
Total	**13 (34)**	**13 (34)**	**6 (16)**	**6 (16)**

CR - complete response, PR - partial response, SD - stable disease, PD - progressive disease

Table 3 - Toxicity related to the therapy.

Toxicity	Grade I - II n (%)	Grade III-IV n (%)	Total n (%)
Hematological			
Leukopenia	7 (18)	5 (13)	12 (31)
Anemia	11 (29)	1 (3)	12 (31)
Non-hematological			
Nausea or vomiting	15 (39)	3 (8)	18 (47)
Alopecia	14 (37)	1 (3)	15 (39)
Serum creatinine increase	2 (5)	- -	2 (5)

chemotherapy regimen used for combined chemotherapy in the 1970's was CAV therapy. This therapy has achieved a complete remission of 80-90% and 8-10 months of mean survival. Complications related to therapy such as grade IV neutropenia, pulmonary toxicity and neuropathy are met frequently. The following regimen such as EP has achieved an objective response in 90% (10-50% was CR). Neutropenia, nephrotoxicity, ototoxicity and peripheral neuropathy were also reported with this therapy. Although neuropathy incidence was similar with CAV therapy, neutropenia was less frequent.[11] There are studies supporting[18] and not supporting[7,19] the Goldie et al[2] hypothesis of drug failure due to resistant clones. Ghaemmaghami and Jett[9] compared alternating CAV and EP therapy (which was developed to prevent tumor resistance) with CAV or EP therapies alone and favored the survival advantage of alternating CAV and EP regimens. Some other authors claimed that alternating regimens resulted in similar survival rates[7] or had no effect in ED disease.[8,9] Alternated therapies did not match with Goldie et al[2] model. Although EP therapy is a beneficial regimen for the patients previously treated with CAV,[20] the vice versa is not true.[8,9] These 2 regimens are absolutely non-cross. Another reason of failure in alternating therapy is thought to be the long time intervals between courses. The same drugs in more concentrated doses and with short time intervals between courses could perhaps increase the response rates.[21] In SCLC, the analogs were also tried to reduce side effects of combined drugs. In some studies, toxicity and response rates are evaluated in CAV therapy by using ifosfamide and epirubicin instead of cyclophosphamide and doxorubicin.[22,23] In the study comparing cisplatin-etoposide with cyclophosphamide-epirubicin-vincristine (CEV), 67.7% objective response (of which 16.1% was CR) was found in the group using CEV.[22] The objective response rate (CR 54%, PR 29%) was found to be 83% in the therapy of cisplatin-oral etoposide and ifosfamide-vincristine-epirubicin. In LD, objective response was 85% and in ED it was 82%. The mean survival was 15 months in LD and 9 months in ED. Main toxicity was myelosuppression.[12] In both studies, the thoracic radiotherapy was also performed.[12,22] High incidence of intrathoracic relapses in limited SCLC is a result of manifestation of chemoresistant tumor cells. Chemoresistant cells starts to evolve in the primary site of the disease especially in patients with large tumors. In randomized trials with alternated combined chemotherapy regimens, cross-resistance problems are met. Due to limited cross-resistance between chemotherapy and high dose radiotherapy, radiotherapy is performed to reduce chemoresistance. Despite high response rates in limited SCLC with combined chemotherapy regimens, high rates of local-regional relapses and brain metastases are seen in 50-80% of patients. In LD, patients who had CR for therapy,

thoracic radiotherapy increases local control. Results of prospective randomized trials suggest that combined modality therapy produces a modest but significant improvement in survival compared with chemotherapy alone. Two meta-analyses showed an improvement in 3-year survival rates in approximately 5% for those receiving chemotherapy and radiation therapy compared to those receiving chemotherapy alone.[23,24]

In our study, objective response was seen in 26 (76%) patients. Thirteen (34%) of these patients had CR. Six (16%) patients remained stable. Objective response rate in LD was 100% (CR 61%, PR 39%) and in ED objective response was 40% (CR 10%, PR 30%). In 11 patients with ED (local relapse in 8 patients; one in the brain, one in the liver and one in the bone) and in one patient with LD (one in the brain) relapses were observed following CR.

Studies to improve survival in SCLC are in succession all around the world. In our study, high response rates were achieved. However, a significant advantage in survival could not be achieved. Nevertheless, this chemotherapy regimen can be accepted due to its low toxicity. Additional studies are required.

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