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Research Article

Irinotecan and Ifosfamide Combination is an Effective and Safe Option in Patients with Refractory Small Cell Lung Cancer: A Retrospective Cross-Sectional Study

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Abstract

Objectives: Recurrent and progressive small cell lung cancer (SCLC) has a very poor prognosis, and treatment options are limited. Combination of irinotecan with ifosfamide (I-I regimen) in SCLC has limited preliminary data. In this study, we aimed to evaluate the efficacy and toxicity of I-I regimen in patients with previously treated SCLC.

Methods: A total of 25 patients were retrospectively reviewed. Ifosfamide dose was 1500 mg/m^2/ per day, days 1-3, irinotecan 80 mg/m^2 per day days 1.8 and 15 every four weeks.

Results: Median age of patients was 55 years (range 42-80). Median chemotherapy cycles were 3 (range 1-7). The frequency of the second, third and fourth line treatments were 68%, 24%, and 8% respectively. Partial remission was obtained in 15 patients (60%) and complete remission in one patient (4%). Median progression free survival (PFS) and overall survival (OS) figures were 7.8 and 11.1 months, respectively. Granulocyte colony stimulating factor (G-CSF) was used in 40% of patients. Grade 3-4 anemia, leukopenia, and thrombocytopenia were seen in 20%, 36% and 12% of these cases, respectively.

Conclusion: Ifosfamide and irinotecan combination is an effective and a tolerable treatment option for patients with platinum refractory SCLC.

Keywords: Chemotherapy, ifosfamide, irinotecan, small cell lung cancer, survival

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Recurrent or progressive small cell lung cancer (SCLC) has a dismal prognosis. Second-line and beyond second-line chemotherapy is associated with improvement in the quality of life and survival regarding months.[1] Toxicity in this non-curative setting is an important consideration, as performance status quickly declines when disease progression occurs after first-line chemotherapy. Indeed, at the time of progression after first-line chemotherapy, most of the patients do not qualify for second-line treatment, and even with the standard topotecan in this setting, the median overall survival is only around eight months.[2] In this setting of refractory disease, where there is no hope for the cure, there is an obvious need for a proper chemotherapy protocol with low toxicity profile and significant efficacy.

The results of many studies in patients with non-small cell lung cancer (NSCLC) or SCLC have suggested that ifosfamide

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can be used as an active chemotherapeutic agent.[3–7] The use of irinotecan in the treatment of patients with SCLC has also been studied in various studies.[8–14] A combination of irinotecan and ifosfamide (I-I regimen) has been used successfully in Japan for refractory or progressive SCLC.[15]

We aimed to confirm the feasibility and toxicity of the I-I regimen in our cohort of Turkish patients with platinum-refractory SCLC. This paper is a retrospective report of the real-life data of our patients and the first study to demonstrate the results of the I-I regimen in patients outside of Japan.

Methods

This was a retrospective crossover study. In this study, 25 patients who underwent the I-I regimen at the outpatient chemotherapy units of participating centers between January 2004 and December 2014 were examined. Medical oncologists analyzed all data in the files of the eligible patients.

Patient Selection, Evaluation, and Treatment Details

All patients had histologically or cytologically proven SCLC and were older than 18 years, with an Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤2. All of them had a recurrence or progressive disease that was defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) criteria after at least one line of chemotherapy and then received the treatment protocol.[16] According to the institutional practice guidelines, first-line chemotherapy was always cisplatin and etoposide in the study cohort.

In the treatment protocol, ifosfamide dose was 1500 mg/m^2/per day with 1500 mg/m^2/day mesna coverage, days 1-3, irinotecan 80 mg/m^2 per day days 1, 8 and 15 every four weeks. Granulocyte-colony stimulating factor (G-CSF) was administered along with the decision of the treating physician.

The response evaluation of the patients was done according to RECIST version 1.1.[16] Patients who achieved a complete response (CR), partial response (PR), and stable disease (SD) in accordance with RECIST were defined as responders. In contrast, patients with progressive disease (PD) were identified as non-responders. The overall response rate (ORR) was defined as the responders, including only CR or PR. The laboratory and clinical adverse effects of treatment were calculated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[17]

Statistical Analysis

Primary statistical analysis included descriptive statistics of the patients' characteristics (gender, age, performance status, the line of treatment).

Progression-free survival (PFS) was calculated as the time from the beginning of treatment to the date of first disease progression or death. Overall survival (OS) was determined by measuring the time from diagnosis to death. All patients underwent PFS and OS analysis.

Statistical analysis was performed by using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated as proportions and medians. The Kaplan–Meier method was used for survival analysis.[18] The median PFS and OS were calculated, and survival curves were constructed. A p-value of less than 0.05 was required for statistical significance.

Results

Patient Characteristics

The median age was 55 years (range 42-80), and the majority of patients (96%) were male. The number of treatment cycles for patients ranged from 1-7. Median chemotherapy cycles were 3. The second-line treatment was the most common setting that the I-I regimen was used, and the frequency of the second, third, and fourth-line treatments was 68%, 24%, and 8%, respectively. Please refer to Table 1 for details.

Efficacy and Toxicity of Treatment

The PR was obtained in 15 patients (60%), and CR was obtained in one patient (4%). When pooled with the Ichiki series,[15] the resultant response rate becomes 57.6% and the complete response rate of 5.1%. Details are given in Table 2. The median PFS and OS figures were 7.8 and 11.1 months, respectively. See Figures 1 and 2 for the survival curves. G-CSF was used in 40% of patients. The toxicity was generally manageable, and grade 3-4 anemia, leukemia, and thrombocytopenia were seen in 20%, 36%, and 12% of these

Table 1. Patient and Treatment Characteristics

	n (%)	Median	Minimum	Maximum
All patients	25 (100)			
Age		55	42	80
Gender				
Male	24 (96)			
Total cycles of I-I regimen* received		3	1	7
The line of I-I regimen*				
2nd line	17 (68)			
3rd line	6 (24)			
4th line	2 (8)			

*: Combination of irinotecan and ifosfamide.

Table 2. Pooled results for tumor response with I-I regimen* in progressive SCLC**

	n	CR (%)	PR (%)	RR (%)
Ichiki, et al. (2003)	34	2 (5.9)	16 (47.1)	18 (52.9)
This paper, Karaagac, et al. (2019)	25	1 (4)	15 (60)	16 (64)
Pooled results	59	3 (5.1)	31 (52.5)	34 (57.6)

Ichiki, et al (2003) data corresponds to reference no 15. *: Combination of irinotecan and ifosfamide; **: Small cell lung cancer.

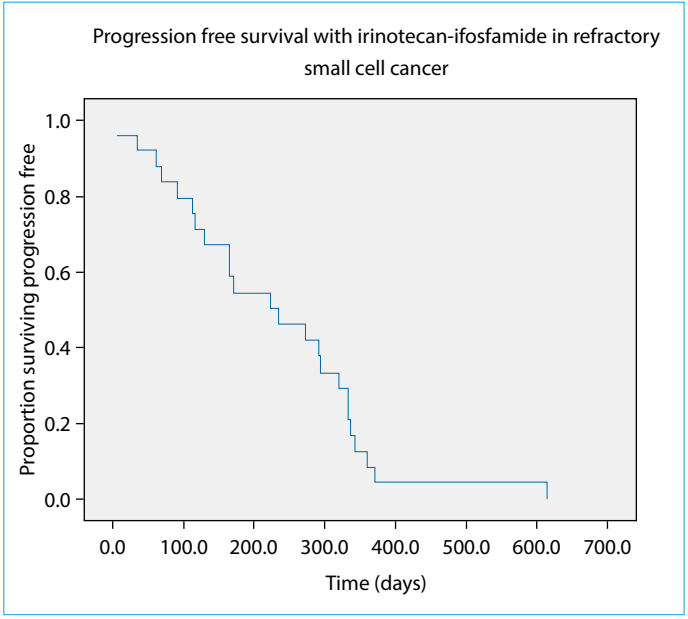

Figure 1. Progression free survival with irinotecan-ifosfamide small cell cancer. Median progression free survival is 7.8 months.

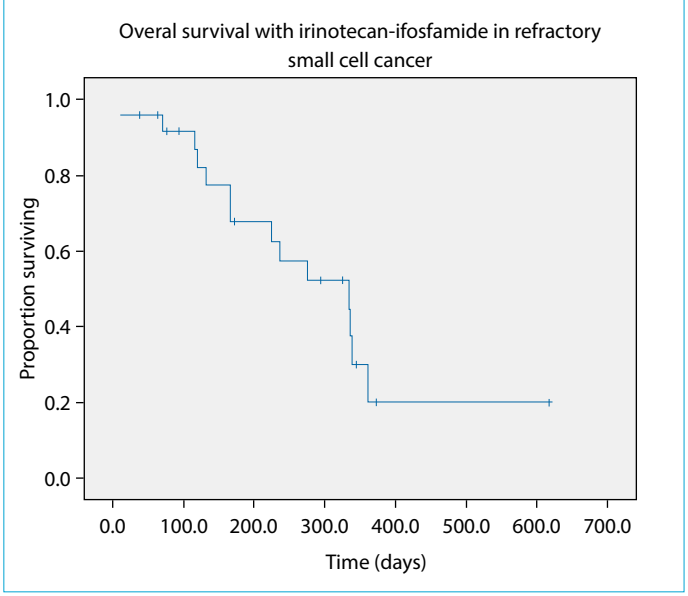

Figure 2. Overal survival with irinotecan-ifosfamide small cell cancer. Median overal survival is 11.1 months.

cases, respectively. No dose reduction was required in any patient. Treatment-related mortality did not occur.

Discussion

This was a unique study that included real-life data of I-I regimen from patients outside East Asia. Although the number of patients in our cohort was small, we observed that ifosfamide and irinotecan combination in SCLC was effective and tolerable after progression with cisplatin-based chemotherapy. Toxicity was manageable and acceptable. Treatment efficacy was not associated with the standard prognostic factors. In this regard, we conclude that this protocol is worth exploring further, as ifosfamide and irinotecan are two agents with the highest individual response rate in the refractory setting and, also, it has also been shown that nonplatinum combinations do not yield inferior survival in the management of SCLC when compared to platinum agents.[19] Proper clinical trials are needed to test this regimen in the refractory metastatic SCLC.

The median OS figure of 11 months achieved with this combination in refractory patients with SCLC in this study was among the highest reported so far in this setting. For example, topotecan used parenterally achieved a median overall survival of 25 weeks (i.e., around six months), and is the only approved agent in this setting. In parallel, the combination of cyclophosphamide, doxorubicin, and vincristine (CAV) again yielded a median overall survival of 24.7 weeks, around six months, as well.[2,20] Also, when our response data was pooled with the series of Ichiki, a response rate of 57% was achieved, and this rate compared very favorably with that of topotecan (24.3%) and CAV (18.3%) or oral topotecan (7%).[21] On the other hand, response rates with combination chemotherapy in the relapsed setting were higher than those by single agents and varied between 17% with single agents and 88% with combinations.[22,23]

Ifosfamide was used mainly with etoposide and a platinum agent in the management of chemo naive patients rather than chemorefractory patients with SCLC, and results showed that ifosfamide combinations were active but more toxic than the etoposide and platinum combination.[10,24] Therefore, it makes sense to use ifosfamide in the refractory SCLC setting in a combination, as is the case with irinotecan-ifosfamide, but without platinum, to maintain efficacy and to limit toxicity.

Myelotoxicity of this protocol was appeared to be manageable, although 40% of cases used myeloid growth factors. Grade 3-4 neutropenia of 36% with this protocol was not higher than the toxicity caused by topotecan (54%). Thus, the I-I regimen is a potent combination with manageable toxicity.

Up to now, no notable success was achieved with the use of biological treatments in refractory SCLC. For example, sunitinib, pazopanib and alisertib yielded response rates of only 8.7%, 0% and 15%, respectively.[25-27] Although significant improvements were achieved in the treatment of NSCLC with targeted molecular therapies such as erlotinib and crizotinib, this success has not been possible for SCLC.[28] Although many immunotherapy studies focused on NSCLC treatment and significant positive results were obtained, relatively few studies examined the effectiveness of immunotherapy for SCLC treatment, and the results were discouraging.[29] In addition to the limited developments in the treatment of SCLC, we believe that chemotherapy still has the potential to be combined with biological agents or immunotherapy to improve treatment outcomes.

Conclusion

Better therapeutics or more effective combinations are urgently awaited for patients with refractory SCLC. This combination of irinotecan and ifosfamide may be a step to improve treatment results for this group of patients, especially when treatment toxicity and treatment response is a priority. We conclude that the I-I regimen may substitute for topotecan or CAV regimens. Prospective clinical trials are urgently needed to test the utility of this combination further.

Disclosures

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Ethics Committee Approval: The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee (Ethics Committee approval number: 2019/2167). Patient informed consent was not required because this was a retrospective cross-sectional file scanning study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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