RESEARCH COMMUNICATION

Weekly Topotecan for Recurrent Small Cell Lung Cancer - a Retrospective Anatolian Medical Oncology Group Study

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Abstract

Aim: To evaluate efficacy and tolerability of topotecan treatment for recurrent small cell lung carcinoma. Patients and Methods: A total of 62 patients were evaluated retrospectively. Statistical analysis was performed using GraphPad Instat (version 3.05). Results: DFifty five of patients (89%) were male and 7 (11%) were female. Median age was 56.7±9.3 (34-75). Forty eight of patients (80%) were extensive stage (ES) at the time of diagnosis. Fifty of the patients (80.6 *Medical Oncology Clinic*) **were given median 5.36 cycles of cisplatin-etoposide (2-8 cycles). Time to recurrence was 15.6±6.13 weeks in patients with limited stage (LS) and 6.3±3.82 weeks in extensive stage (ES) (p<0.0001). Overall survival was 14.0±6.08 months in ES and 17.9±6.88 months in LS. The difference between two groups was statistically meaningful (p=0.0447). The overall survival of the patients was 14.8±6.43 months (4.5-40 months). In terms of survival, there was no difference between males and females (p=0.1171). In 17 (27%) patients who were refractory to topotecan or in whom progression occurred other chemotherapies were used. Conclusion: Small cell lung cancer is chemosensitive, but recurrences occur in short time. Other chemotherapy regimens are used in progression. Topotecan is one of them. Patients who were young and in whom recurrences occur late had given better response to topotecan. Because of the retrospective nature of the study, we couldn't reach the records exactly and consequently, rate and duration of response couldn't be calculated. In recurrent SCLC topotecan is one of the treatment choices. But both hematological and non hematological side effects should be taken into consideration.**

Keywords: Small cell lung cancer - recurrence - chemotherapy - topotecan - toxicity

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Introduction

Lung cancer is the most common cancer in the world. Small cell lung cancer (SCLC) accounts for 15-20% of lung cancers. The most important risk factor for SCLC, which is responsible for 90% of cases, is tobacco smoking. SCLC has a unique biological behavior with high incidence of paraneoplastic syndromes and hematological dissemination (Chua et al., 2004; Ruckdeschel et al., 2004; Murren et al., 2005). It has an aggressive nature with early metastases. Although SCLC responds chemotherapy well (80-90%), survival is only around 8-14 months, but in a small group of patients (5-10%) long term survival is possible (Chua et al., 2004; Wolf et al., 2004; Hoschec et al., 2007; Niederle et al., 2008). Prognosis is poor especially in ES, and great majority of patients are in ES at the time of diagnosis (Janssen et al., 2001). Since nineteen eighties standard chemotherapy for SCLC is cisplatin-etoposide combination (Chua et al., 2004; Wolf et al., 2004; Ukena et al., 2008). Other chemotherapy regimens, especially in ES, are cyclophoshamide-adriamycin-vincristine (CAV), adriamycin / epirubicin- cyclophoshamide -etoposide (ACE / ECE) and ifosfamide-carboplatin-etoposide (ICE) (Sambrook et al., 2001; Chua et al., 2004; Wolf et al., 2004).

In spite of high response rates to chemotherapy, recurrences occur around 95% of patients especially in the first year (Huisman et al., 1999; Chua et al., 2004). Once recurrence occurs, prognosis is poor with a median survival around 2-4 months (Niederle et al., 2008). Response rate to chemotherapy regimens in recurrent disease is around 20% (Huisman et al., 1999). If disease is non-responsive to first line chemotherapy, or if recurrence occurs in first 60 days following the treatment, it is accepted as refractory to chemotherapy. The cases which recur after 60 days [some authors accepts 90 days (Chua et al., 2004; Hoschek et

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al., 2007)] are accepted as chemo-sensitive (Niederle et al., 2008). In chemo-sensitive patients, response rates to paclitaxel, topotecan and irinotecan rises to 40% (Wolf et al., 2004). With topotecan, in patients with ES, response rate of 63% and median survival time of 9.3 months were achieved (Hoschek et al., 2007).

Efficacy and tolerability of topotecan in second line chemotherapy of SCLC has been shown in phase II and III studies (Heber et al., 2000). In second line, response rate of 14-37% in chemosensitive group and 2-6% in chemoresistant group were reported (Chua et al., 2004; Wolf et al., 2004; Hoschek et al., 2007). Major toxicities may be hematological or non-hematological, and should be taken into account (Wolf et al., 2004; O'Brien, 2006; Hoschek et al., 2007).

Materials and Methods

Records of 62 patients in 9 ATOD centres were evaluated retrospectively. Results are expressed as the mean ±SD or percentage. Statistical analysis was performed using GraphPad Instat (version 3.05). For comparisons of the differences between mean values of two groups, the unpaired Student's t test was used. All statistical tests and p values were two-sided, and $p<0.05$ was considered statistically significant.

Results

Of 62 patients, 55 (89%) were males and 7 (11%) were females. Median age in males (57.15± 9.62) and in females (52.86±5.46) was similar (p=0.23). At the time of diagnosis, 48 patients (80%) have ES disease. Fourteen (25.5%) of the males have LS disease and 41 (74.5%) have ES disease. All the females were in ES (p=0.2274).

In Table 1 the characteristics of the patients according to centers were given. There was no relation between median age and TTP, number of CT cycles, survival and the stage. Fifty of the patients (80%) had taken median 5.36 cycles (2-8 cycles) of cisplatin + etoposide combination.

The records of the patients who had given weekly topotecan (2.5 mg/m^2/week) were evaluated retrospectively.

Table 1. Patient Characteristics According to Centres

Centre	Patient	Male	Female	LS	ES	GR ¾ Toxicity	Mean CT Cycle
Diskapi	6	6	-	2	4	1/6	5.60
Ataturk	4	3	1	-	4	4/4	3.25
Gazi	3	3	-	-	3	0/3	3.00
Gaziantep	21	20	1	6	15	2/21	8.53
Demetevler	4	4	-	1	3	2/4	6.50
Numune	3	1	2	-	3	1/3	3.33
Diyarbakir	5	5	-	-	5	1/5	6.40
Kartal	11	10	1	2	9	6/11	7.63
Erciyes	5	3	2	3	2	2/5	8.80
Total	62	55 (89%)	7 (11%)	14 (22.5%)	48 (77.5%)	19/62 (30%)	5.88

*LS: limited stage, ES: extensive stage, Gr: grade, CT: chemotherapy

Median 6.97±4.33 weekly topotecan were given. Between males (6.8±4.3 weeks) and females (8.2±4.6 weeks) there were no difference in terms of duration of topotecan (p=0.396). Median number of topotecan was 7.06±4.64 weeks in ES and 6.64±3.15 weeks in LS (p=0.7523).

Two of the patients had inappropriate SIADH at the time of diagnosis, and symptom control had achieved in them after topotecan CT. At the time of diagnosis the most frequent site of metastasis was liver. The sites of metastasis are given in Table 2.

Tobacco history couldn't be found in all the files, but it was positive in all the patients who had been asked. Similar results were valid both for weight loss and LDH levels. Weight loss was found in majority of patients. LDH records were found in 11 file, of them 6 were increased. Median overall survival was 14.84±6.43 months (4.5-40 months). There was no difference between males (14.38±6.54 months) and females (18.43±4.24) in terms of overall survival (p=0.1171). But difference was statistically significant between the patients who were staged as LS (13.96±6.08 months) and ES (17.86±6.88 months) at the time of diagnosis (p=0.0447).

Median time to recurrence was 6.26±3.59 (2-16) weeks in overall, and statistically different in patients who were LS (15.6±6.13) at the time of diagnosis and in the patients who were ES (6.3±3.82) ($p<0.0001$). No significant relationship was found between age with survival (p=0.15), and age with recurrence (p=0,095).

Table 2. Sites of Metastasis

Site of metastasis	Time of diagnosis	Recurrence
Liver	9	2
Contra lateral lung	4	7
Surrenal	8	3
Brain	2	6
Bone	2	2
Bilateral Lung	1	-
Pleura	1	-
Skin	1	-
Supraclavicular LN	2	-
Spleen	1	-
Kidney	1	-
Pancreas	-	1

Table 3. Topotecan Toxicities

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	No records	Gr ¾
Nausea/Vomiting	18	20	9	1	-	14	2%
Neutropenia	24	13	13	6	1	6	12.5%
Mucositis/Diarrhea	29	9	5	-	-	19	-
Neuropathy	30	9	2	-	-	21	-
Anemia	20	21	7	6	2	6	14.2%
Elevation in transaminase	5	6	1	1	1	48	14.2%
Fatique	16	8	12	6	-	20	14.2%
Trombocytopenia	8	6	4	3	-	41	14.2%
Alopecia	-	7	3	3	-	49	-
Constipation		3	1			-	-
Other*						-	11

*Headache in 2 patients, nephropathy in 2 , hyper bilirubinemia in 2, GGT elevation in 2, zona zoster in1, blurred vision in 1 and ALP elevation in 1.

There was a significant relationship between time to recurrence and overall survival (p=0.002). The patients in whom recurrence occurred late had lived longer. Time from recurrence to death was found longer in young patients (p=0,014).

There was no significant relationship between age and time to recurrence, CT cycles given, overall survival and the disease stage at the time of diagnosis. Median time from recurrence to death was 5.82±4.4 months in overall, 5.98±4.56 months in males and 4.71±3.04 months in females (p=0.479). Median time from recurrence to death was 5.07±3.97 months in patients with ES at the time of diagnosis and 8.58±4.96 months in LS (p=0.079). After the recurrence, time to death was 6.89±3.59 months in LS and 5.2±4.18 months in ES (p=0.28). There was a significant relationship between time to second recurrence and overall survival (p=0,002).

In 17 patients (%27) because of unresponsiveness to topotecan or progression under treatment, other chemotherapy regimens were tried. Three of the patients are still alive (32, 19 and 20 months).

Toxicities due to topotecan treatment are given in Table 3.

Discussion

In a study comparing best supportive care and topotecan use in recurrent SCLC, topotecan was found to be related with better quality of life and increased survival (Hoschek et al., 2007).

In EQ-5D life quality questionnaire, in which 68 patients (96%) in topotecan and 65 patients in best supportive care group had completed questionnaire, symptom control was found better in topotecan group (O'Brien et al., 2006). In another study, response rate to topotecan was 39% in 48 chemonaive patients and 17% in 362 patients who had taken chemotherapy before (Murren et al., 2005).

Because of the retrospective nature of the study, we couldn't reach the records exactly, therefore; response rate and duration couldn't be calculated. In a meta-analysis of 24 studies, response rate to second line chemotherapy in SCLC was reported as around 20% (Huisman et al., 1999). In a phase III study topotecan and CAV regimen in 211 patients with SCLC who had relapsed at least 60 days after completion of first-line therapy were evaluated. Response rate was 24.3% in topotecan group and 18.3% in CAV group. Survival analysis was similar in two groups (median survival 25.0 weeks for topotecan and 24.7 weeks for CAV, 1-year survival rate was around 14%). Side effects were less in topotecan group. Grade 4 neutropenia occurred in 37.8% of topotecan courses versus 51.4% of CAV courses (P<0.001). Grade 4 thrombocytopenia and grade 3/4 anemia occurred more frequently with topotecan, occurring in 9.8% and 17.7% of topotecan courses versus 1.4% and 7.2% of CAV courses, respectively (P<0.001 for both) (Pawel et al., 1999). In a phase II study in 170 patients with recurrent SCLC 1.25 mg/m^2 x 5 days topotecan was given and toxicity was found less (Huber et al., 2000).

In our patients who had taken 1.5 mg intravenous topotecan weekly, hematological grade 3/4 toxicity was 13.6% and non-hematological grade 3/4 toxicity was 8.1%. Anemia, fatique, thrombocytopenia and neutropenia were pronounced side effects.

In phase II studies response rates to chemotherapy was around 24% in chemosensitive patients and only around 10% in chemoresistant patients. Median overall survival was 5-7 months (Perez et al., 1996; Ardizzoni et al., 1997). In a phase III study comparing best supportive care and topotecan in recurrent SCLC grade 3/4 neutropenia was seen in 61%, thrombocytopenia in 38%, anemia in 25% of the patients (O'Brien et al., 2006). In our study grade 3/4 toxicities for neutropenia, thrombocytopenia and anemia was 12.5%, 14.2% and 14.2% respectively.

In a meta-analysis of 5 studies of second line chemotherapy, Gars et al reported that in older age group (70 or older), efficacy and tolerability of topotecan was comparable with younger age group (Garst et al., 2005). SCLC responds chemotherapy well, but recurrence in a short time was common. In our patients, second line topotecan was given 6.97±4.33 weeks in median. Survival was found better in patients who were in LS than ES at the time of diagnosis (p=0.0447).

In a multi-centric study 141 patients with SCLC were randomized to best supportive care (70 patients) and topotecan arm (71 patients). In topotecan arm 7% partial response and 44% stable disease was achieved. Median overall survival was longer in topotecan arm (25.9 weeks versus 13.9 weeks). In topotecan arm toxicities were as follows: grade 4 neutropenia 33%, grade 4 trombocytopenia 7%, grade 3/4 anemia 25%. Some other toxicities in best supportive care arm versus topotecan arm were as follows: Grade 2 infections 12% versus 14%, sepsis 1% versus 4%, grade 3/4 nausea 0% versus 3%, diarrhea 0% versus 6%, dispnea 9% versus 3% and pain 6% versus 3%. In topotecan arm treatment related death rate was 6%. Thirthy days' mortality was 7% in best supportive care arm and 13% in topotecan arm (Huisman et al., 1999). In our study the results were similar (in order 12.5%, 14.2%). Grade 3/4 toxicities in our patients were similar with literature; 2% nausea-vomiting, 12.5% neutropenia, 14.2% anemia, 14.2% thrombocytopenia, 14.2% fatigue, 14.2% elevation in transaminases. Because of high toxicity of second line topotecan chemotherapy, patients should be followed up closely.

In our study time to recurrence was 15.6±6.13 weeks in the patients who were LS at the time of diagnosis and only 6.3±3.82 in whom were ES (p<0.0001). Time from recurrence to death was 6.89±3.59 months in LS and 5.2±4.18 months in ES (p=0.28). A strong relationship between time to recurrence and survival was determined (p=0,002). Patients who recurred late had lived more. More and more younger the patients, time from recurrence to death was longer (p=0,014). Overall survival was found better in patients who were LS at the time of diagnosis (17.86±6.88 months) than the patients who were in ES (13.96±6.08) (p=0.0447). In two of our patients with SIADH symptom control was achieved with topotecan chemotherapy.

In literature, topotecan is recommended in the second line chemotherapy of SCLC, and in first line, as a single

agent, in the patients whose performance status are poor (O'Brien et al., 2006; Hoschek et al., 2007).

In conclusion, topotecan is one of the choices in recurrent SCLC especially in patients with good performance status. Response rates to topotecan are better in patients who are young, who are LS at the time of diagnosis or in whom recurrence occurred late. High toxicity rates should be kept in mind.

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