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Bi-weekly irinotecan is an effective and convenient regimen in the treatment of relapsed or refractory small cell lung cancer

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Abstract

Background Despite initial dramatic responses, metastatic small cell lung cancer (SCLC) invariably recurs. Irinotecan is one of the active agents for patients with recurrent SCLC. In the second line, weekly or three-weekly irinotecan regimens have been adopted, however, the optimal dose and schedule is not defined. In our institution, we use a bi-weekly regimen of irinotecan. In this study, we aimed to investigate the safety and efficacy of the bi-weekly irinotecan in the second- or third-line treatment of SCLC patients.

Methods The study population consisted of advanced stage SCLC patients who were followed at Hacettepe University Cancer Institute between January 2007 and March 2021 and received salvage irinotecan 180 mg/m^2 every two weeks, following progression after platinum-etoposide treatment.

Results One hundred patients were included. At diagnosis, nineteen patients (19%) had limited stage and 81 patients (81%) had extensive stage SCLC. Objective response rates (ORR) were 44.6% and 46.2% for patients who received irinotecan treatment in second line, and in third line, respectively. Seventeen percent of all the patients had grade 3 and above adverse events during irinotecan treatment. In our study, 45.8% of patients were able to complete at least 6 cycles of irinotecan treatment and 69.8% were able to receive at least 3 cycles of irinotecan treatment without any dose interruption or reduction.

Conclusions Irinotecan 180 mg/m^2 every two weeks appears to be safe and effective in the 2nd- and 3rd-line treatment of advanced stage SCLC. Bi-weekly administration allows G-CSF prophylaxis in between doses, leading to an uninterrupted administration.

Keywords Irinotecan, Small cell lung cancer, Tolerability, Bi-weekly administration

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Background

Small cell lung cancer (SCLC) accounts for 10–15% of all cases of lung cancer [1]. Although SCLC is highly responsive to initial platinum-based chemotherapy, practically all patients relapse, and prognosis remains poor.

First line response and time to progression from final exposure to first line chemotherapy to recurrence may predict response to second line treatment. By definition, sensitive patients are those who respond to initial treatment and relapse at least 90 days after the completion of first line treatment and resistant patients are those who progress within 90 days. Those who do not respond or progress during first line treatment are considered refractory patients [2–4].

Following the failure of platinum-based chemotherapy, CAV (cyclophosphamide, doxorubicin, and vincristine) regimen was shown to have moderate activity [5]. Topotecan and amrubicin are the most extensively investigated agents for treating recurrent SCLC. Topotecan has been shown to improve survival compared to supportive care [6] and to be as efficacious as CAV therapy [7].

Irinotecan, an inhibitor of DNA topoisomerase I, is also a potentially active agent for patients with recurrent SCLC. Patients with recurrent SCLC treated with irinotecan in the second line setting have a median progression-free survival duration (PFS) of 2–4 months and an overall survival (OS) duration of 4–6 months, according to a previous phase II trial and other observational studies of irinotecan [8–10]. In these studies, [8, 11, 12], patients were given 100—125 mg/m^2 weekly or 350 mg/m^2 on day 1 every three weeks of irinotecan. However, severe gastrointestinal toxicities and myelosuppression were frequently observed at these dose levels.

A patient with recurrent SCLC is usually fragile and the toxicity of these dosing schedules may be prohibitory. There is no literature on bi-weekly irinotecan therapy for patients with advanced-stage SCLC, and the available information is primarily based on data from patients with gastrointestinal cancer. We think that weekly administration may result in cytopenia, leading to dose interruptions. The inability to deliver colony stimulating agents in between doses is inconvenient. Higher doses used in the 3-weekly regimens may result in significant toxicities, especially in a group of patients usually with a high frequency of significant comorbidities and who are already sick with a fulminant cancer. Bi-weekly regimen appears to be feasible as it enables the clinician to administer colony stimulating agents if needed. It is advantageous for the patient to have some time between doses, so that he or she can recover from the toxicities of the previous dose.

Given these observations, we would like to present our single-center data on the efficacy and safety of bi-weekly irinotecan in the second- and third-line treatment of SCLC.

Methods

Patient selection

Our study aimed to assess the safety and efficacy of bi-weekly irinotecan monotherapy in the second and third lines of SCLC treatment. We analyzed the medical records of SCLC patients diagnosed and treated at the Institute of Oncology of the Hacettepe University Hospitals between January 2007 and February 2024. Patients were selected for the study based on the following criteria: (1) patients with a histological or cytological diagnosis of SCLC, (2) patients with refractory or relapsed SCLC following initial chemotherapy or chemoradiation, and (3) patients who were treated with bi-weekly irinotecan monotherapy (180 mg/m^2 on day 1 every two weeks) as a second line or third line chemotherapy.

This retrospective observational study was approved by Hacettepe University Ethics Committee (approval number 2022/18–17).

Data collection

Patient data, including age, sex, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), initial disease stage, treatment history, and type of relapse were collected from medical records. The relapse was considered sensitive if it occurred within 90 days of the completion of initial chemotherapy and refractory if there was no response to initial chemotherapy or relapse occurred within 90 days of completion. The disease stage at diagnosis was classified as limited or extensive, and tumor response was evaluated based on computed tomography findings using Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (v4.0).

Treatment

Irinotecan 180 mg/m^2 as a 90-min intravenous infusion was administered every 14 days. Granulocyte colony stimulating Factor (G-CSF) use was at the discretion of the treating physician.

Evaluation of clinical information

The assessment of response and toxicity was conducted in accordance with the Response Evaluation Criteria in Solid Tumors guideline, version 1.1 [13]. Given the retrospective nature of the study, specific efficacy evaluation schedules were not strictly defined within the framework of clinical practice. Nonetheless, chest computed

tomography (CT) evaluations were routinely conducted every 2 to 3 months as per our clinical practice. Toxicity assessments were performed following the Common Terminology Criteria for Adverse Events (v4.0). Detailed toxicity data were systematically collected from medical records, allowing comprehensive bi-weekly analysis of each patient's toxicity profile in accordance with the bi-weekly schedule regimen.

Statistical analysis

Categorical variables were presented as frequency and percentage. Continuous variables were presented as the mean and standard deviation for normally distributed data and median and interquartile range (IQR; 25th–75th percentile) for parameters which were not normally distributed.

PFS was calculated as the interval between the date of initiation of irinotecan treatment and the date of progressive disease (PD) or death. If none of these events have occurred, it was censored on the date of the patient's last date of contact. OS was calculated from the date of initiation of irinotecan treatment to the date of death and if the patient was alive, it was censored on the last day of contact. PFS and OS were analyzed by the Kaplan–Meier method.

We used SPSS version 25.0 (IBM Inc., Armonk, NY, USA) to perform statistical analyses. A p-value less than 0.05 was considered statistically significant, and all tests were two-tailed.

Results

Patient characteristics

One hundred patients with SCLC received irinotecan monotherapy between 2007 and 2024. Irinotecan was administered at 180 mg/m^2 on day 1 of every 2-week cycle. Eighty-eight of the patients were male, and twelve were female. The mean age was 59.3 years (STD, 9.4). Fifty-four (54%) patients had 0, and thirty-five patients (35%) had 1 ECOG performance status at the time of diagnosis. Sixty-one percent of our patients had at least one comorbidity. The comorbidities observed in our patient cohort included hypertension, type 2 diabetes mellitus, hyperlipidemia and coronary artery disease. Additionally, one patient had a history of dermatomyositis, and another had undergone surgery for papillary thyroid cancer. Seventy-four (74%) patients had received irinotecan monotherapy as a second line treatment, and 26 (26%) patients had received this treatment as a third line treatment. Of these twenty-six patients who received irinotecan as third-line treatment, 19 had previously received carboplatin-etoposide, 3 had received cisplatin-etoposide, 2 had CAV, 1 had oral temozolomide, and 1 had been treated with weekly paclitaxel.

Initially, 19% of patients had limited stage ($n=19$) and 81% had extensive stage ($n=81$) SCLC.

All patients received a platinum etoposide regimen as first line therapy. Patients were given cisplatin-etoposide as initial treatment in 62% of cases ($n=62$), while carboplatin-etoposide therapy was administered to 38%. Fifty nine percent of patients had sensitive relapse, while 41% had refractory relapse.

Baseline characteristics of patients are outlined in Table 1.

Efficacy and survival analysis

Patients receiving second line irinotecan treatment received a median of 5 cycles (min 1- max 23). The remaining patients received third line irinotecan with a median of 6 cycles (min 1- max 18).

The total number of treatment cycles administered to all patients amounted to 631. 47% of the patients received 6 or more cycles (as indicated in Fig. 1). Most patients discontinued treatment due to disease progression. Of note, 10% ($n=10$) stopped because of progression and/or inability to tolerate after only one cycle of irinotecan treatment, reflecting the aggressive nature of the disease. Of these, nine patients experienced disease progression. One treatment-related death was recorded (intestinal perforation).

Among the 100 patients assessed, none of the patients had complete response (CR), while partial response (PR) was seen in 33 patients (44.6%) in 2nd line and 12 patients (46.2%) in 3rd line, resulting in an objective response rate (ORR) of 44.6% (95% Confidence Interval [CI], 33.0–56.6%) and 46.2% (95%CI, 26.6–66.6%), respectively ($p=0.89$) (Table 2). The disease control rates (DCR) of 48.6% (95% CI, 36.8–60.5%) in 2nd line and 57.7% (95%CI, 36.9–76.6%) in 3rd line ($p=0.43$).

Notably, in 2nd-line irinotecan treatment, 35 patients had sensitive relapse and the ORR was 54.3% (95% CI, 36.6–71.2) among them, whereas among the 39 patients with refractory disease, 35.9% (95% CI, 21.2–52.8) showed an objective response ($p=0.16$). In addition, DCRs were calculated as 41.0% (95% CI, 25.6–57.9) and 57.2% (95% CI, 39.3–73.7), respectively ($p=0.11$) (Table 3).

The median PFS of our patients receiving bi-weekly irinotecan was 4.2 (95% CI, 3.2–5.2) months and the median OS was 6.8 (95% CI, 5.1–8.5) months (Fig. 2).

Figure 3 shows Kaplan–Meier curves for PFS and OS, according to the line of treatment irinotecan was given. The median PFS with irinotecan monotherapy was 3.9 (95% CI, 2.6–5.1) months for 2nd-line and 5.1 (95% CI, 2.8–7.4) months for 3rd-line treatment ($p=0.72$) (Fig. 3, section A). Additionally, the median OS from the initiation of treatment with both 2nd- and 3rd-line irinotecan

Table 1 Baseline characteristics of the study population

Characteristic	n (%)
Total number of patients	100
Age (years), mean	59.3 (STD, 9.4)
Sex	
Male	88 (88%)
Female	12 (12%)
Comorbidity	
Yes	61 (61%)
No	39 (39%)
ECOG	
0	54 (54%)
1	35 (35%)
2	11 (11%)
Smoking	
Yes	99 (99%)
No	1 (1%)
Smoking duration (py), median	40 (IQR, 30–50)
Stage at the diagnosis	
Limited disease	19 (19%)
Extensive disease	81 (81%)
Type of relapse	
Refractory relapse	41 (41%)
Sensitive relapse	59 (59%)
Sites of metastases	
Liver	39
Brain	12
Lymph node	46
Adrenal	27
Bone	43
Prior therapy	
Cisplatin-Etoposide	62 (62%)
Carboplatin-Etoposide	38 (38%)
Response to prior chemotherapy	
CR	12 (12%)
PR	73 (73%)
SD	5 (5%)
PD	10 (10%)
PCI	
Yes	36 (36%)
No	64 (64%)
Thoracic RT	
CRT*	22 (22%)
Consolidative TRT	22 (22%)
No Thoracic RT	55 (56%)
Treatment Line	
2nd	74 (74%)
3rd	26 (26%)

Abbreviations: *ECOG* Eastern cooperative oncology group, *py* Package-year; g/dL, *PCI* Prophylactic cranial irradiation, *TRT* Thoracic radiotherapy, *RT* Radiotherapy, *CRT* Chemoradiotherapy (*for limited disease and extended disease with only isolated single bone metastatic patients)

monotherapy were 6.0 (95% CI, 3.8–8.2) months and 12.4 (95% CI, 4.1–20.6) months, respectively ($p=0.15$) (Fig. 3, section B).

At the time of analysis, 92 patients experienced progression, 68 of whom were on 2nd line and 24 on 3rd line irinotecan therapy. Eighty-five of the patients died, 63 of whom received 2nd line and 22 had 3rd line irinotecan. Currently, 6 of the patients continue to receive irinotecan as 2nd line and 2 of them as 3rd line.

The median OS in the patients treated with 2nd line irinotecan with sensitive relapse and refractory relapse was 9.5 months (95% CI, 6.4 – 12.7 months) and 3.6 months (95% CI, 1.7 – 5.4 months), respectively ($p=0.002$) (Fig. 4).

The median OS of those with limited-stage disease calculated since the initiation of irinotecan treatment was 15.5 (95% CI, 11.6–19.3) months, and those with the extensive-stage disease was 5.4 (95% CI, 3.8–6.9) months ($p<0.001$).

In addition, the median OS was 12.4 (95% CI, 6.2–18.6) months in patients who received PCI and 5.7 (95% CI, 3.9–7.4) months in patients who did not ($p=0.02$). Among the patients with extensive-stage disease (except for 3 patients with isolated bone or adrenal metastases who received CRT), there was no significant difference in survival between patients who received consolidation thoracic irradiation and those who did not, though the figures appeared numerically apart (11.5 (95% CI, 5.2–17.9 vs. 4.5 (95% CI, 3.5–5.6) months, respectively, $p=0.13$). No significant OS difference was found between patients with ECOG performance status 0–1 and patients with 2 (7.3 (95% CI, 5.2–9.4 vs. 1.9 (95% CI, 0.17–3.8) months, respectively, $p=0.54$).

Safety and tolerability

Adverse events experienced by patients receiving irinotecan are summarized in Table 4. Among adverse events related to irinotecan monotherapy, the most frequent non-hematological adverse events were nausea/vomiting (all grades, 22%, $n=22$) and diarrhea (all grades, 21%, $n=21$). Febrile neutropenia developed in only one patient; however, grade 4 neutropenia was observed in only two patients. There was one treatment-related death (intestinal perforation).

As seen in Table 4, due to grade 3 and 4 neutropenia, nine patients skipped one cycle of irinotecan treatment and eight of them had 15% dose reduction. Among these patients, one had febrile neutropenia and had 20% dose reduction.

In our study, a total of 462 cycles of irinotecan treatment could be administered without any dose delay/interruption/reduction/toxicity. Some patients received their treatment at other centers and therefore, exact dates

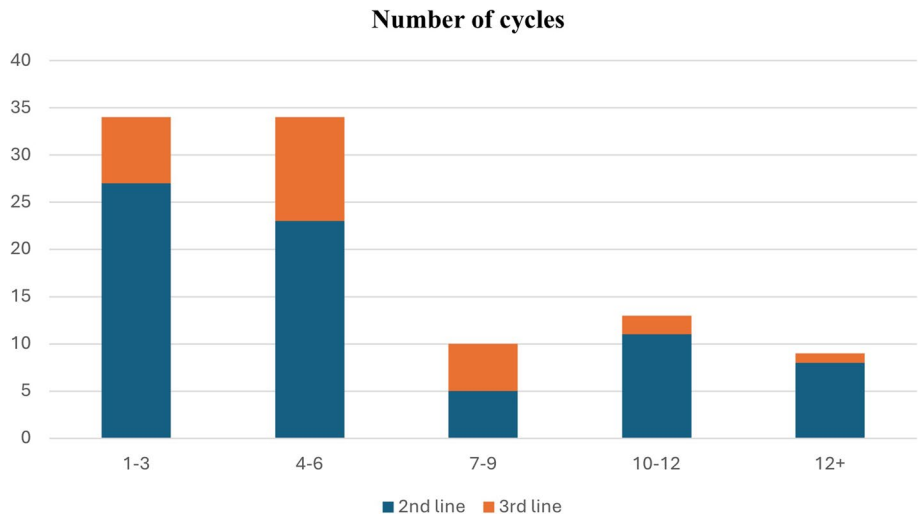

Fig. 1 Maximum number of cycles given per patient

Table 2 Response to irinotecan monotherapy

	2nd line, *n* = 74 (%)	3rd line, *n* = 26 (%)	All patients, *n* = 100 (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	33 (44.6)	12 (46.2)	45 (45.0)
SD	3 (4.0)	3 (11.5)	6 (6.0)
PD	22 (29.8)	9 (34.6)	31 (31.0)
NE	16 (21.6)	2 (7.7)	18 (18.0)
ORR	33 (44.6)	12 (46.2)	45 (45.0)
DCR	36 (48.6)	15 (57.7)	51 (51.0)

Abbreviations: *CR* Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease, *NE* Not evaluable, *ORR* Objective response rate, *DCR* Disease control rate

Table 3 Response to 2nd line irinotecan in subgroups of relapse

	Sensitive, *n* = 35 (%)	Refractory, *n* = 39 (%)	All patients, *n* = 74 (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	19 (54.3)	14 (35.9)	33 (44.6)
SD	1 (2.9)	2 (5.1)	3 (4.0)
PD	9 (25.7)	13 (33.3)	22 (29.7)
NE	6 (17.1)	10 (25.6)	16 (21.6)
ORR	19 (54.3)	14 (35.9)	33 (44.6)
DCR	20 (57.2)	16 (41.0)	36 (48.6)
Total	35 (100.0)	39 (100.0)	74 (100.0)

CR Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease, *NE* Not evaluable, *ORR* Objective response rate, *DCR* Disease control rate

of administration are not available. Of the 83 patients for whom all dates are available, 58 (69.8%) received 3 cycles and 38 (45.8%) received 6 cycles of treatment without any dose delays, interruptions or reductions. One patient received 20 cycles and one is still on therapy after 23 cycles.

Univariate and multivariate analyzes are shown in Table 5.

Discussion

Practically all patients with SCLC relapse after first line treatment. Unfortunately, most of SCLC patients with limited-stage disease will also share this fate. Though there are many active treatments in this setting, none of them yields durable remissions. Though the survival of patients can be improved to some extent, the main objective of these treatments is palliation.

The most commonly employed agent in this setting is topotecan, which may be given intravenously or orally [6, 14, 15]. In a randomized phase 3 study, single-agent intravenous topotecan was compared to CAV as a second-line treatment for SCLC patients who had relapsed at least 60 days after the completion of first-line treatment [7]. Both groups had similar response rates and survival (25.0 vs. 24.7 weeks), but intravenous topotecan had considerably lower rates of grade 4 neutropenia then CAV regimen (37.8% vs. 51.4%; $p = 0.001$). Topotecan is one of the well-established options for these patients, yet the obligation of IV infusions for 5 consecutive days and risk of thrombocytopenia may become prohibitive.

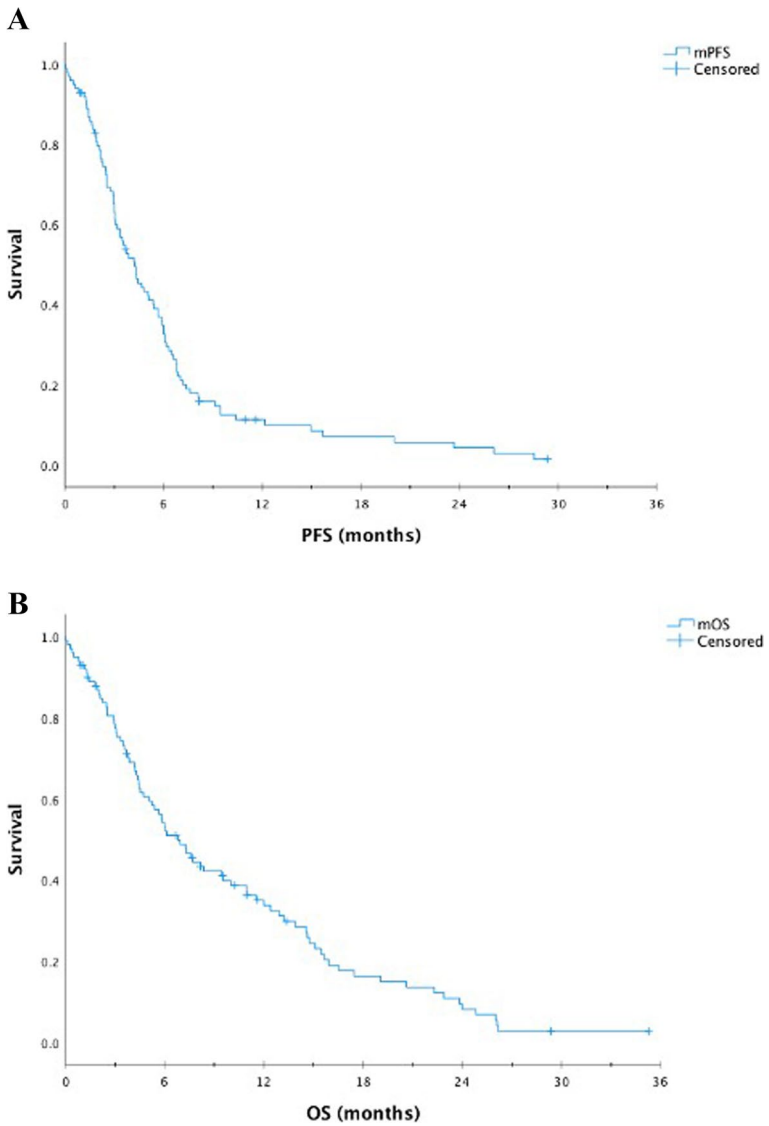

Fig. 2 **A** Progression-free survival (PFS) and (**B**) overall survival (OS) ($n = 100$)

As an alternative to topotecan, irinotecan as a second-line treatment has been evaluated in several clinical trials with limited patient numbers, with ORRs ranging from 16 to 47% [8, 16, 17]. In one study, 44 patients (17 with sensitive relapse and 27 with resistant or refractory disease) were treated with irinotecan 125 mg/m^2 weekly for 4 weeks in a row followed by 2 weeks off treatment. The response rate in patients with sensitive relapse was 35%, and the median survival time was 6.8 months [12]. In addition, Table 6 presents the survival data from key studies in the literature that involved second-line treatments for patients with sensitive and refractory SCLC. In our study, among our patients who received 2nd line irinotecan, 35 patients had sensitive, and 39 patients had refractory relapse. The ORR of these patients were 54.3% and 35.9%, respectively. In addition, DCRs were calculated as 57.1% and 41.0%, respectively. These figures compare favorably to the above-mentioned study.

Looking at the literature, the median survival in patients diagnosed with limited-stage SCLC is approximately 17 months, and the five-year survival rate is approximately 20 percent [33, 34]. Most patients diagnosed with extensive stage small cell lung cancer have a poor prognosis, and conventional chemotherapies using cytotoxic agents offer a median survival of approximately 10 months [35]. Although this situation is attributed to the disease being detected at an earlier stage, it can also be interpreted as a less aggressive disease biology compared to advanced

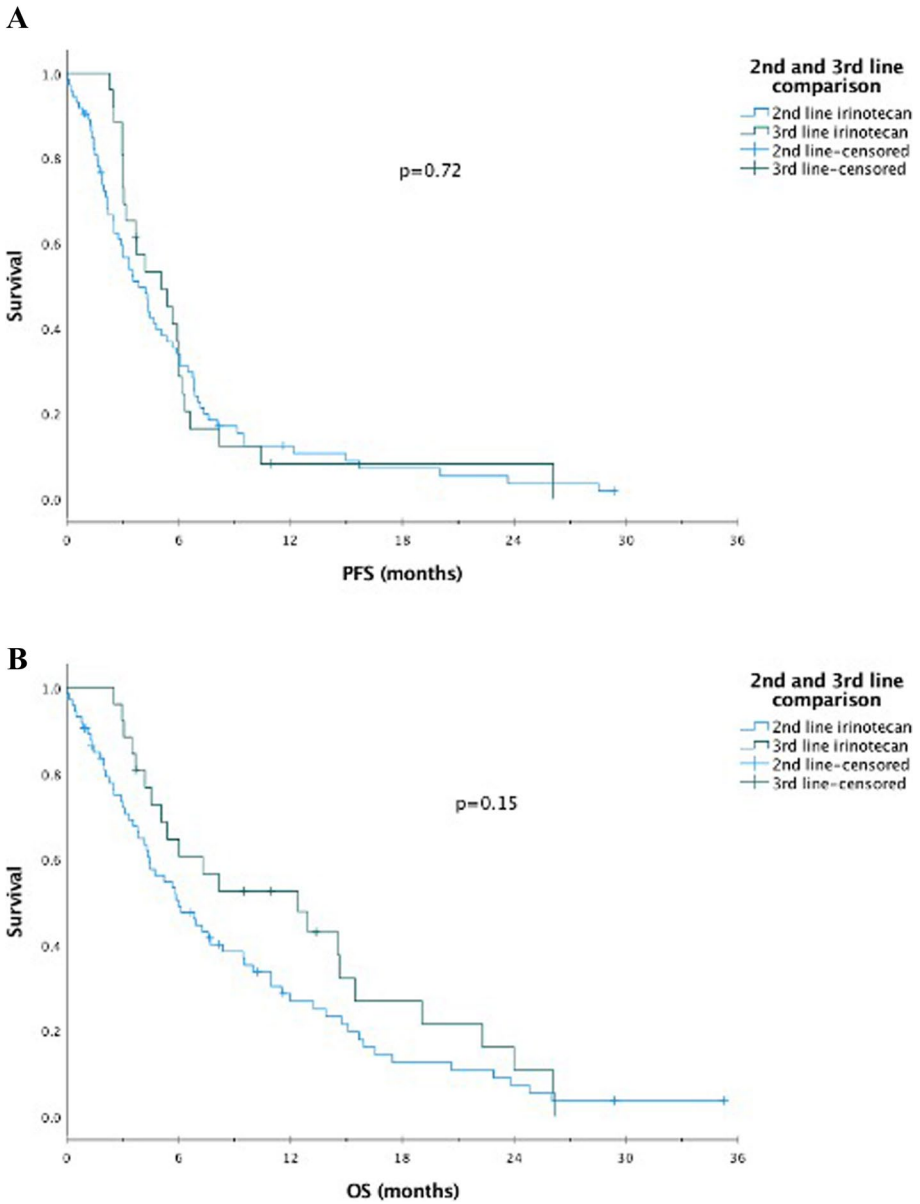

Fig. 3 Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) from the initiation of treatment with 2nd- and 3rd-line irinotecan monotherapy. (section A is demonstrating PFS for 2nd and 3rd line; section B is demonstrating OS for 2nd and 3.[rd] line treatment respectively)

stage disease. We observed a median OS of 15.5 months in patients diagnosed with limited-stage SCLC, and 5.4 months in those with extensive stage disease, consistent with the literature ($p < 0.001$).

In our study, the median PFS of all patients receiving irinotecan monotherapy was 4.2 months and 3.9 months for 2nd line irinotecan. These outcomes are comparable to previous PFS reported in patients with SCLC who received second-line therapy with other cytotoxic agents [17, 36, 37]. The median OS in irinotecan-treated patients was 6.8 months, which is in accordance with previous reports in the literature [12, 17, 38]. In addition, we also studied the contribution of treatment lines to OS. The reason for the increased OS seen in patients receiving 3rd-line irinotecan (although not statistically significant) suggested that the disease may have a less aggressive course in patients who received third-line treatment and that there could be a survival bias. Furthermore, ORR was 44.6% in 2nd line treatment and 46.2% in 3rd line, respectively. In the phase 2 trial by Masuda et al., the ORR in 2nd line irinotecan monotherapy was found to be 47%, which is similar to the ORR in our study [8].

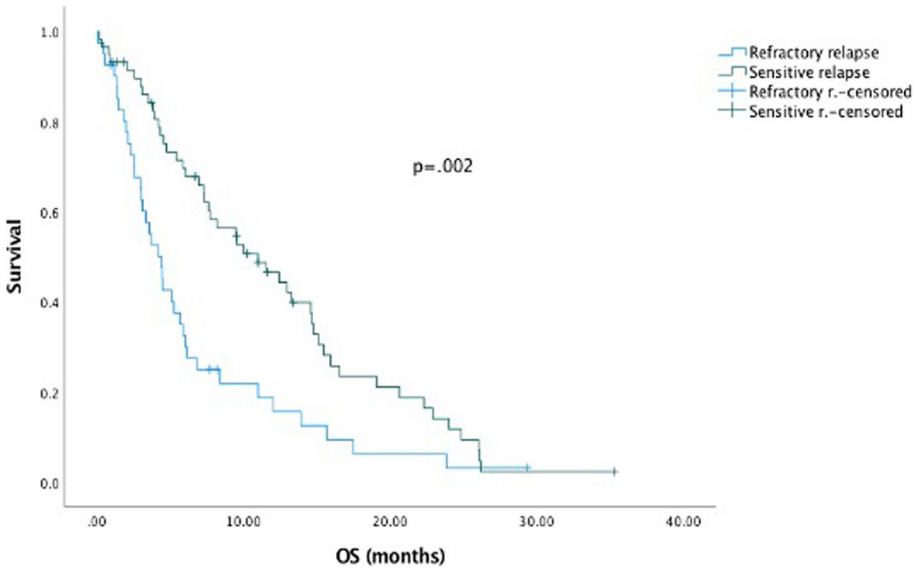

Fig. 4 Survival difference between sensitive and refractory relapse in 2nd line irinotecan treatment

Table 4 Adverse events associated with irinotecan therapy ($n = 100$)

Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	43	19	1	0
Neutropenia	11	10	7	2
Thrombocytopenia	8	8	4	0
Diarrhea	12	8	1	0
Nausea/Vomiting	13	7	2	0
Weight Loss	10	2	0	0

Regimens, including topotecan, irinotecan, temozolomide, docetaxel, CAV, amrubicin and others, have activity on the second or further lines SCLC treatment and are included in the guidelines [39]. When we evaluate the OS figures, the survival rate is around 6.8–8 months with topotecan [6, 40], 6 months with CAV [7], and around 6 months with amrubicin [41]. These findings are consistent with the median OS in our study, which is 6.8 months. Lurbinectedin was also found to be effective in terms of safety and tolerability

Table 5 Univariate and multivariate cox regression analyses for overall survival

Variable	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (< 65* vs. ≥ 65)	1.50	0.9–2.5	0.65	1.4	0.8–2.5	0.24
Sex (female* vs. male)	0.9	0.4–1.6	0.64	0.7	0.3–1.5	0.35
Comorbidity (no* vs. yes)	1.5	0.9–2.4	0.07	1.4	0.8–2.4	0.22
ECOG (0–1* vs. 2)	1.2	0.6–2.4	0.54	0.7	0.3–1.6	0.39
Stage at diagnosis (Limited* vs. Extensive)	3.1	1.7–5.9	**< 0.001**	1.6	0.4–6.1	0.49
Type of relapse (Sensitive* vs. Refractory)	1.9	1.3–3.1	**0.002**	**1.7**	0.9–3.1	**0.05**
Distant metastasis (no* vs. yes)	2.9	1.7–5.1	**< 0.001**	1.8	0.6–5.8	0.31
PCI (yes* vs. no)	1.70	1.1–2.7	**0.02**	1.4	0.8–2.5	0.26
Treatment line (2nd* vs. 3rd)	0.7	0.4–1.1	0.15	1.1	0.6–2.1	0.77
Smoking duration (< 40 py* vs. ≥ 40 py)	1.1	0.7–1.8	0.58	1.2	0.7–2.1	0.47

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *py* Package-year, *PCI* Prophylactic cranial irradiation, *TRT* Thoracic radiotherapy, *RT* Radiotherapy

* Reference variable

Table 6 Survival data from the studies on second-line single and combination chemotherapy in patients with sensitive and refractory small cell lung cancer

Study	Study Design	Total patients (s/r)	Treatment	PFS/TTP (months) (s/r)	OS (months) (s/r)
Gronberg et al. [18]	phase 2 multicenter	34 (25/9)	Pemetrexed	1.8 (2/1.2)	4.1 (5.3/3.6)
Hoang et al. [19]	phase 2	27 (15/12)	Gemcitabine	1.5 (1.5/1.3)	6.4 (8.8/4.2)
Smit et al. [20]	phase 2	24 (0/24)	Paclitaxel	2.1	3.3
Pietanza et al. [21]	phase 2	64 (48/16)	Temozolamid	1.6 (1.6/1.0)	5.8 (6/5.6)
Kosmas et al. [22]	phase 2	33 (13/20)	Paclitaxel + Ifosfamide + Cisplatin	5	7
Ardizzoni et al. [23]	phase 2 multicenter	100 (68/42)	Topotecan + Cisplatin	(4.7/3)	(6.4/6.1)
Rocha-Lima et al. [24]	phase 2	71 (35/36)	Irinotecan + Gemcitabine	(3.1/1.6)	(7.1/ 3.5)
Schuette et al. [25]	phase 2	35 (20/15)	Irinotecan + Gemcitabine	3.4	5.8 (4.5/8.7)
Nakanishi et al. [26]	phase 2	21 (0/21)	Cisplatin + Irinotecan	NA	8
Ichiki et al. [27]	phase 2	34 (24/10)	Irinotecan + Ifosfamide	4	7.2
Masuda et al. [28]	phase 2	24	Irinotecan + Etoposide	4,6	9
Groen et al. [29]	phase 2	34 (0/34)	Carboplatin + Paclitaxel	NA	7.7
Dazzi et al. [30]	phase 2	41 (22/19)	Gemcitabine + Paclitaxel	2.7	5.5
Sonpavde et al. [31]	phase 2	46 (32/14)	Paclitaxel + Doxorubicin	3.5	6.2
Hainsworth et al. [32]	phase 2	30 (13/17)	Vincristin + Gemcitabine	NA	5 (7/4)

Abbreviations: *PFS* median progression-free survival, *TTP* median time-to-progression, *OS* median overall survival, *s/r* Sensitive relaps/refractory relaps

in a recent study conducted for SCLC patients with a chemotherapy-free interval of more than 180 days, and median PFS was observed as 4.6 months and overall survival was approximately 16.2 months [42]. Additionally, in recent studies, tarlatamab has demonstrated significant activity with promising survival data in patients with previously treated small cell lung cancer [43]. Although new agents such as tarlatamab and lurbinectedin are promising, drugs such as irinotecan will remain important for a while, especially for countries with limited resources.

Poor prognostic indicators for patients with SCLC include poor performance status (PS), advanced disease, male gender, and advanced age [44]. PS, age and gender did not significantly affect survival, in our study. PCI demonstrated increased survival rates in patients with SCLC who had complete response to chemotherapy in many studies [45, 46] and our finding compatible with these studies. Besides, we compared patients receiving consolidative thoracic radiotherapy (TRT) with the group not receiving radiotherapy and could not obtain a statistically significant survival gain, as well. Ultimately, it should be noted that these factors we used in our analyses are not predictive markers beyond being prognostic for our bi-weekly irinotecan therapy.

Given the advanced age and comorbidities of our patient cohort, we chose a bi-weekly dosing regimen of 180 mg/m^2 to balance efficacy with tolerability. This dosing is also in line with other gastrointestinal cancer treatment schedules [47, 48], where irinotecan has been well tolerated.

Furthermore, the usage of our bi-weekly irinotecan (180 mg/m^2) regimen was also based on previous studies using cisplatin-irinotecan regimens administered on days 1, 8, and 15 [49]. We observed that weekly dosing was difficult for patients to tolerate due to side effects. Moreover, in a study by Sevinc et al. [9], patients receiving 300 mg/m^2 of irinotecan every three weeks were able to tolerate the treatment.

In a phase 2 study conducted by Le Chevalier, T. and colleagues, 350 mg/m^2 of irinotecan (d1, q3 weeks) was administered to 32 patients diagnosed with SCLC after first-line chemotherapy, and grade 3/4 adverse effects of 58% neutropenia, 37% diarrhea, and 22% nausea/vomiting were observed [16]. In our study, however, patients receiving bi-weekly irinotecan therapy exhibited much lower rates (9% neutropenia, 1% diarrhea, and 2% nausea/vomiting as grade 3/4 adverse effects), indicating a better safety profile.

A meta-analysis of topotecan use in patients diagnosed with relapsed SCLC showed that hematological side effects were predominant, with grade 3/4 neutropenia, anemia and thrombocytopenia occurring in 69%, 24% and 41%, respectively [50]. Compared to this treatment method, which has a high side effect profile, we see that the bi-weekly irinotecan treatment method is a more tolerable and sustainable regimen. Allowing patients to use G-CSF in the biweekly irinotecan regimen may also reduce the frequency of hospital admissions by ensuring that patients can receive their treatment without interruption. As evidenced by the fact that our bi-weekly irinotecan treatment is a more convenient regimen, almost half of our patients, whose records we

can fully access, receive their 3-month treatment without any disruptions and the fact that grade 3/4 hematological side effects are less common.

This study has several limitations. First, it is a retrospective analysis conducted at a single institution. The assessment of efficacy lacked strict definitions due to the retrospective nature of the study, as response and tolerability assessments were done as part of the routine clinical follow-up of the patients. Consequently, radiological evaluations did not include formal reporting according to RECIST. Regarding tolerability, we were able to obtain each toxicity profile every two weeks owing to the bi-weekly schedule regimen, yet it is possible that some adverse events, especially those not involving a laboratory abnormality, may have been missing from the patient charts.

Conclusions

Bi-weekly irinotecan monotherapy (180 mg/m^2 every 2 weeks) appears to be an active and tolerable regimen in the treatment of recurrent SCLC. Efficacy outcomes are comparable to other available cytotoxic regimens, yet every-2-week administration may be more convenient both for the patient and the clinic. Our data suggests that this schema may be a valid option for the treatment of recurrent SCLC.

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Authors' contributions
Feride Yilmaz: Conceptualisation; data curation; formal analysis; investigation; methodology; validation; visualisation; writing – original draft. Serkan Yasar, Omer Denizhan Tatar,: Conceptualisation; data curation; investigation; methodology; validation; visualization. Hasan Cagri Yildirim and Deniz Can Guven: Conceptualisation; data curation; methodology; writing – review and editing. Arif Akyildiz: Conceptualisation; data curation; methodology; supervision; writing – review and editing.Elvin Chalabiyev: Conceptualisation; methodology; supervision; validation; review and editing. Burak Yasin Aktas, Zafer Arik and Mustafa Erman: Conceptualisation; data curation; methodology; supervision; validation; review and editing.

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Availability of data and materials
The institutional review board (Hacettepe University Ethics Board) waived the requirement for written informed consent for this study due to its retrospective design. Consequently, supporting data are not available, given the sensitive nature of the research.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and its amendments, and with Good Clinical Practice guidelines. Ethical approval (approval number 2022/18–17) for this study was obtained from Hacettepe University Ethics Committee, Turkey. The need for written informed consent for this study was waived by the institutional review board (Hacettepe University Ethics Board) due to its retrospective design.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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