

Research Letter

CLINICAL EXPERIENCE WITH ORAL TOPOTECAN IN RELAPSED SMALL CELL LUNG CANCER PATIENTS FOLLOWING IRINOTECAN-PLATINUM CHEMOTHERAPY

To,
The Editor, JPMER

Sir,

Single-agent oral topotecan is approved for use in patients with relapsed small cell lung cancer (SCLC). In most of the earlier studies involving the use of topotecan as second/third-line agent, patients were treated with etoposide-platinum combination as first-line chemotherapy.^{1,2} There is little data on the role of oral topotecan following initial treatment with irinotecan-platinum doublet. We therefore sought to assess clinical efficacy and tolerability of oral topotecan in relapsed SCLC patients following initial chemotherapy with irinotecan-platinum.

We carried out a retrospective analysis of relapsed SCLC patients treated with oral topotecan (2.3 mg/m²/day D1-D5 every 3 weekly) from July 2011 to June 2014 at our institute. Baseline demographic characteristics, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at topotecan initiation, and details of first-line chemotherapy and topotecan treatment were noted in a standard data extraction sheet. All patients had received irinotecan-platinum as first-line chemotherapy as per standard protocol followed at our center.^{3,4} Staging was done using both 7th edition of Tumor Node Metastases (TNM) classification of malignant tumors and the two-stage system (limited disease and extensive disease). Radiological responses were assessed using RECIST for both first-line chemotherapy and oral topotecan. Toxicity was graded as per Common Terminology Criteria for Adverse Events (CTC-AE) v3.0. Both overall survival (OS) and survival after initiation of topotecan were calculated. Time to progression (TTP) was calculated from initiation of irinotecan-platinum chemotherapy to end of topotecan treatment to classify patients as sensitive (TTP > 90 days) or refractory (TTP < 90 days) disease.

During the study period, a total of 15 patients received topotecan after prior therapy with irinotecan-platinum chemotherapy. Most were men who were smokers (n = 14, 93.3%). Mean age was 58.5 (SD < 10.9) years. Baseline TNM stages were stage IIIA (n = 2, 14.3%), stage IIIB (n = 2, 14.3%), and stage IV (n = 11, 73.3%). Baseline PS was ECOG = 0-1 in 10 (66.7%) and ECOG = 2 in 5 (33.3%) patients respectively. Responses to initial doublet chemotherapy (Graph 1A) were Complete Response (CR) in 6 patients (40%), Partial Response (PR) in 6 patients (40%), Stable Disease (SD) in 1 patient (6.7%), and Progressive Disease (PD) in 2 patients (14.3%). Ten patients received thoracic radiation and 6 received prophylactic cranial irradiation (PCI) after first-line chemotherapy. Oral topotecan was used as second-line and third-line therapy in 12 (80%) and 3 (20%) patients respectively. Time to progression after first-line chemotherapy was < 90 days and > 90 days in 6 and 9 patients respectively. Performance Status at topotecan initiation was ECOG 0-1 in 7 (46.7%) patients and ECOG ≥ 2 in 8 (53.3%) patients. Median number of topotecan cycles was 3 [interquartile range (IQR) = 1-6]. Median topotecan dose administered was 70% (IQR = 55-75%) of recommended.

Two patients on topotecan experienced intercycle delays of > 7 days.⁵ Incidence of grade 3/4 hematological toxicity was anemia 26.7% and neutropenia 6.7%. Among 10 patients with assessable responses to topotecan, PD was most commonly observed (n = 8), while SD and PR were noted in one patient each (Graph 1B). No patient experienced CR. Median OS was 409 days [95% confidence interval (95% CI) 283-535] from start of initial treatment and 106 days (95% CI 18-194) after initiation of topotecan. Patients with ECOG PS ≥ 2 at topotecan initiation had significantly worse survival [median 60 days (95% CI 10-109)] as compared with those with ECOG PS 0-1 [median 200 days (95% CI 106-294)] (Graph 1C). No significant differences were observed between patients with sensitive or refractory disease following first-line chemotherapy in relation to outcomes with oral topotecan use.

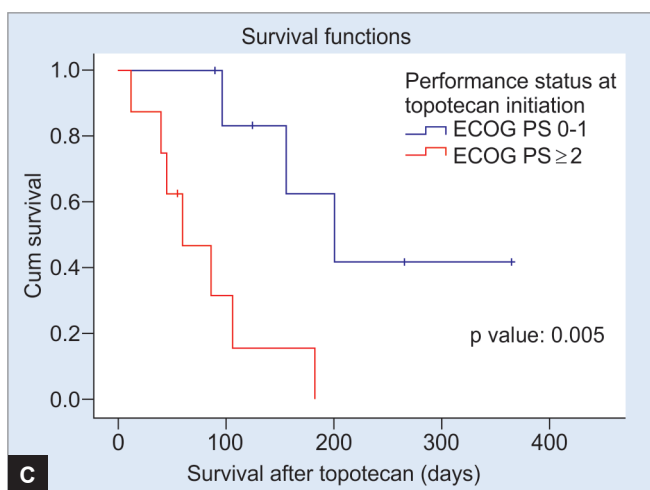
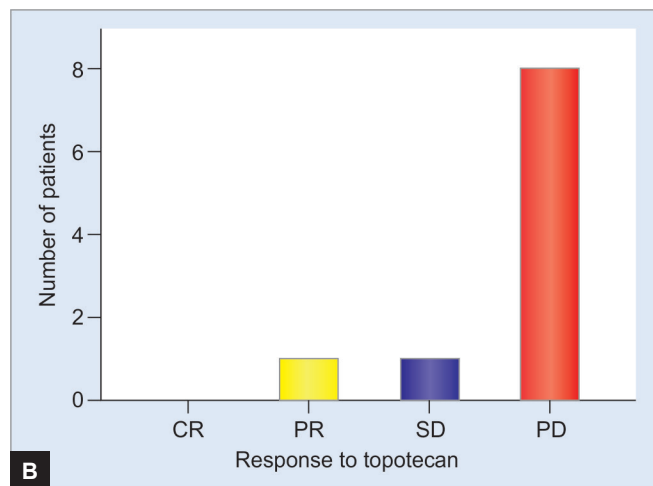
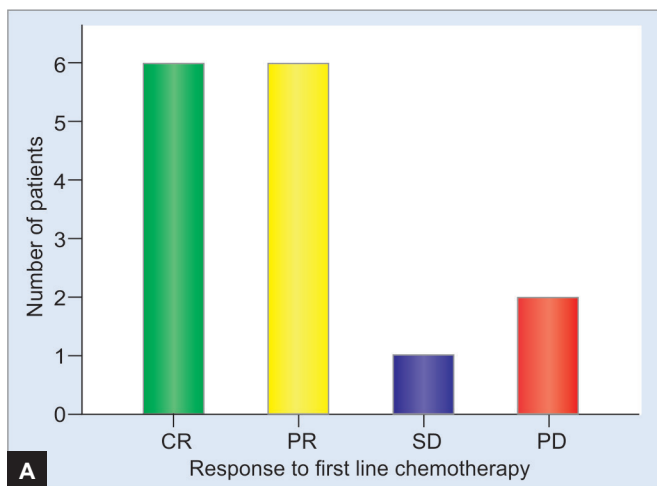
Despite inherent limitations in this study related to its retrospective design and small number of patients which precluded us from carrying out multivariate analysis for factors affecting radiological responses or survival, the lack of observed benefit was quite evident in the fact that 80% of patients experienced disease progression and that median survival following relapse was a little more than 3 months. The likely reason for this observation lies in the fact that irinotecan and topotecan are both topoisomerase inhibitors as compared with etoposide and topotecan, which belong to pharmacologically different classes of drugs. Most patients experiencing disease relapse in our study (prior irinotecan usage) therefore received an agent with a similar mechanism of action as they did in the first-line setting.

To the best of our knowledge, this is only the second study in published literature wherein role of oral topotecan in SCLC patients relapsing after prior irinotecan treatment has been assessed.⁶ A previously reported phase II study involved only 17 patients and lack of efficacy, in general, of oral topotecan in this setting was also documented therein.

In summary, our experience suggests that efficacy of single-agent oral topotecan following prior therapy with irinotecan-platinum chemotherapy is poor. Management options for such patients with relapsed disease include use of agent(s) not administered initially (especially etoposide) as well as novel targeted/immunotherapeutic agents.

References

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Graphs 1A to C: Radiological responses as per RECIST* to (A) initial irinotecan-platinum chemotherapy, (B) Oral topotecan, (C) Kaplan–Meier curves for survival after topotecan initiation showing significantly worse survival for those with ECOG performance status (PS) ≥ 2 as compared with those with ECOG PS 0-1; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

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