Cabazitaxel Versus Topotecan in Patients with Small-Cell Lung Cancer with Progressive Disease During or After First-Line Platinum-Based Chemotherapy

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Introduction: Patients with small-cell lung cancer (SCLC) typically respond well to initial chemotherapy. However, relapse invariably occurs, and topotecan, the only approved second-line treatment option, has limited efficacy. Taxanes have activity in SCLC, and cabazitaxel is a second-generation taxane with potential for enhanced activity in chemorefractory malignancies.

Methods: Patients with SCLC who relapsed after initial platinum-based chemotherapy were randomly assigned to receive cabazitaxel 25 mg/m^2 every 21 days or topotecan 1.5 mg/m^2 on days 1–5 every 21 days. Two patient subgroups, defined by chemosensitive and chemo-resistant/refractory disease, were assessed in combination and separately.

Results: The safety profile of cabazitaxel and topotecan was consistent with previous studies, and despite considerable toxicity in both arms, no new safety concerns were identified. Patients receiving cabazitaxel had inferior progression-free survival compared with topotecan (1.4 versus 3.0 months, respectively; two-sided $p < 0.0001$; hazard ratio = 2.17, 95% confidence interval = 1.563–3.010), and results were similar in both the chemosensitive and chemorefractory subgroups. No complete responses were observed in either arm, and no partial responses were observed in the cabazitaxel group. The partial response rate in the topotecan arm was 10%. Median overall survival was 5.2 months in the cabazitaxel arm and 6.8 months in the topotecan arm (two-sided $p = 0.0125$; hazard ratio = 1.57, 95% confidence interval = 1.10–2.25).

Conclusion: Cabazitaxel, a next-generation taxane, had inferior efficacy when compared with standard-dose topotecan in the treatment of relapsed SCLC. Topotecan remains a suboptimal therapy, and continued efforts to develop improved second-line treatments are warranted.

Key Words: Cabazitaxel, Phase 2, Small-cell lung cancer, Relapse, Topotecan.

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Small-cell lung cancer (SCLC) constitutes 12%–14% of all lung cancers, and is characterized by a rapid doubling time, a high growth fraction, and early development of systemic metastases.[1,2] While initially quite responsive to chemotherapy, resistance invariably develops. As a result, SCLC has a poor prognosis, with a median survival without treatment of 2 to 4 months.[3] With treatment, disease extent is considered the most reproducible prognostic factor. Two-year survival rates range from 20% to 40% for limited-stage disease (restricted to one lung or local tissues/lymph nodes) and 5% or less for extensive-stage disease (metastatic to contralateral lung or other sites).[1–3]

Platinum-based chemotherapy is first-line standard of care for SCLC. Etoposide with cisplatin or carboplatin is the most commonly used regimen,[2–4] although irinotecan plus carboplatin is an alternative option.[2,5] Despite high response rates to first-line chemotherapy, most patients with SCLC experience rapid relapse.[6] Patients with relapsed SCLC can

be categorized into two groups: those who relapse during or within 3 months of first-line therapy are considered chemorefractory (or resistant), and have a response rate to second-line chemotherapy of less than or equal to 10%; those who relapse after 3 months or more have chemosensitive disease, and have a response rate to second-line chemotherapy of ~25%.[2] Although several chemotherapies have demonstrated single-agent activity in relapsed SCLC, topotecan is currently considered to be the standard treatment.[2,7] In phase III trials in relapsed SCLC, topotecan treatment resulted in longer overall survival (OS) compared with best supportive care (26 versus 14 weeks)[8] and better symptom control versus a cyclophosphamide–doxorubicin–vincristine regimen.[9] Across several studies of patients with relapsed SCLC, median survival time has ranged from 14 to 35 weeks.[7] Therefore, new second-line therapies are needed to improve survival in patients with relapsed SCLC.

The first-generation taxanes, docetaxel and paclitaxel, have shown activity as first- or second-line single-agent treatments in SCLC.[10–12] In a phase II study of paclitaxel in patients with extensive-disease SCLC, 11 patients (34%) had a partial response (PR) and six patients (19%) had stable disease.[10] In another phase II study of paclitaxel, the overall response rate was 53%.[12] In a phase II study of docetaxel in previously treated patients with SCLC, seven patients (25%) had a PR and seven patients (25%) had stable disease.[11]

Cabazitaxel is a second-generation taxane that has demonstrated activity in the second-line treatment of chemotherapy-resistant solid tumors.[13,14] In particular, in the pivotal phase III TROPIC trial in patients with metastatic castration-resistant prostate cancer progressing after docetaxel therapy, cabazitaxel plus prednisone had superior efficacy versus mitoxantrone plus prednisone, including significantly longer OS and progression-free survival (PFS),[13] leading to regulatory approval worldwide. Interestingly, unlike other taxanes, cabazitaxel crosses the blood–brain barrier,[15] which could be therapeutically beneficial in cancers, such as SCLC where brain metastases are common. The paucity of therapeutic options and activity of taxanes in SCLC, the ability of cabazitaxel to cross the blood–brain barrier, and the activity of cabazitaxel in chemorefractory tumors provide a compelling rationale to assess cabazitaxel as a treatment for SCLC.

This phase II study evaluated the efficacy of cabazitaxel versus topotecan in patients with SCLC that had progressed during or after first-line platinum-based chemotherapy.

PATIENTS AND METHODS

Study Population

Eligible patients had histologically/cytologically documented locally advanced or metastatic SCLC that relapsed during or after first-line platinum-based chemotherapy. Patients were aged greater than or equal to 18 years, had measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1[16] and an Eastern Cooperative Oncology Group performance status less than or equal to one. Patients were required to have received no more than one prior chemotherapy regimen, and to have adequate hematologic and organ function. Exclusion criteria included: prior topotecan or taxane treatment; prior chemotherapy, radiotherapy (except for bone pain palliation), or surgery within 28 days; treatment with any investigational drug within 30 days; uncontrolled metastases of the central nervous system; known leptomeningeal metastases; other invasive neoplasm requiring ongoing therapy; unresolved adverse event (AE) of grade greater than one (except alopecia) resulting from prior anticancer therapy (according to National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.03);[17] or myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association Class III or IV congestive heart failure, stroke or transient ischemic attack within 6 months before study enrollment.

The study was conducted according to the Declaration of Helsinki with approval from ethics committees at each institution. Patients provided written informed consent.

Study Design

This was a phase II, open-label study (ARD12166; NCT01500720, ClinicalTrials.gov). Patients were randomly assigned (1:1) to receive cabazitaxel or topotecan. Patients were divided evenly into two subgroups depending on whether their disease had progressed (by RECIST 1.1) either greater than or equal to 90 days after completing first-line chemotherapy (chemosensitive subgroup) or during or up to 90 days after completing first-line chemotherapy (chemorefractory subgroup). Patients were also stratified by the presence of brain metastases and serum lactate dehydrogenase (LDH) concentration.

The primary endpoint was PFS, defined as time from randomization to documented tumor progression or death from any cause, whichever came first. Secondary endpoints included disease progression-free rate at week 12, response rate, duration of response, OS, and safety. Progression and response were defined per RECIST 1.1.

Study Treatment

Cabazitaxel 25 mg/m^2 was administered as a 1-hour intravenous (IV) infusion on day 1 every 21 days. Topotecan 1.5 mg/m^2 was administered as a 30-minute IV infusion on days 1–5 every 21 days. For cabazitaxel, premedication included an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent), a steroid (dexamethasone 8 mg or equivalent) and an H2 antagonist (ranitidine 50 mg or equivalent). Premedications were administered by IV infusion at least 30 minutes before each cabazitaxel dose. If IV antihistamines were not available, premedication for hypersensitivity could be administered per local practice. Antiemetic prophylaxis with ondansetron, granisetron or dolasetron, or per local practice for topotecan, was permitted. Supportive care with granulocyte colony-stimulating factor (G-CSF) could be considered in both treatment arms, in accordance with ASCO guidelines.[18]

Safety Assessments

The safety population was defined as all randomized patients who received at least one dose of cabazitaxel or topotecan during the treatment period. Patients had a full health evaluation before treatment initiation. On-study safety assessments