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Oral second- and third-line lomustine–etoposide–cyclophosphamide chemotherapy for small cell lung cancer

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ABSTRACT

Purpose: There is no standard therapy for progressive or recurrent small cell lung cancer (SCLC). Lomustine, etoposide and cyclophosphamide oral chemotherapy were evaluated in a feasibility study of efficacy survival and toxicity.
Patients and methods: 71 patients were included in this study, 36 in second-line and 35 in third-line chemotherapy. They received lomustine (CCNU) 80 or 120 mg on D1 only, etoposide 100 mg from D1 until D6 up to D14 and cyclophosphamide 100 mg from D1 until D6 up to D14 every 4 weeks. The dosages of CCNU and duration of administration of the other two drugs were adapted to an original therapeutic risk level table on D1 and throughout treatment. Evaluation based on clinical status, response and weekly blood counts was performed before each cycle until progression.
Results: 70 patients were evaluable. They received between 1 and 20 cycles of treatment (mean = 3.7 for second-line and 3.0 for third-line treatment). Complete responses were observed for 3 patients in each line, and partial responses were noted in 13 patients in second-line and 8 patients in third-line, resulting in a total response rate of 27/70 = 38%. Median-survival time estimated from the start of second- or third-line treatment was the same in the two subgroups: 4.4 months, but the patients in two subgroups presented different clinical characteristics. Haematological toxicity was severe with three toxic deaths as frequently observed in this setting, but hospitalisations were uncommon during this fully oral treatment that provided a very good quality of life for these out-patients. Consumption of health care resources for this low-cost and ambulatory treatment was limited.
Conclusion: The similar efficacy with acceptable safety, the ease of administration in out-patients and the economical advantages justify comparison of this oral chemotherapy with conventional intravenous chemotherapy. A randomised phase II trial is on-going in France for second-line SCLC patients on this theme.

1. Introduction

Despite the high response rates to first-line chemotherapy, SCLC remains a frequently fatal disease. Less than 10% of patients are cured by first-line treatment. Some patients have no-response with immediate progressive disease. The majority of patients relapse after initial response. The evidence-based use of second-line chemotherapy was established by on a 20-year-old publication of a Cancer Research Campaign Trial [1]. Clinical benefit appeared to correlate with the type of first-line chemotherapy, in the response to this first-line treatment [2], with the treatment-free period [3] and with the performance status (PS) at relapse [4]. Many combinations have been investigated to treat patients with progressive or recurrent SCLC: intravenous chemotherapy [5–10] or combination of intravenous and oral chemotherapies [11–15]. Intravenous [16–18] or oral [19–21] monotherapies have been used, but no regimen has been shown to be superior to another. Reliable comparisons are difficult to perform on such small populations of selected patients. However, a review of second-line chemotherapy in SCLC suggests that combination chemotherapy is associated with higher response rates than monotherapy [22]. Patients obviously prefer oral treatment to intravenous administration [23]. The efficacy of prolonged daily use of oral etoposide has been demonstrated in refractory or relapsed SCLC [19,20]. Lomustine (CCNU) was extensively used for SCLC in the 1980s with good results [12,24], but was subsequently abandoned following the arrival of cisplatin and the incompatibility between lomustine and radiotherapy. In first-line treatment of extensive disease SCLC patients with performance status = 2, oral combination of etoposide and cyclophosphamide

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Table 1
Calculation of therapeutic risk level for first cycle by addition of points obtained from four criteria.

	0 point	1 point	2 points
Age	<70 years	>70 years	
PS	0 or 1	2	3
Weight	>70 kg	51–69 kg	<50 kg
Bone marrow status[a]	(1) No + (2) normal	(1) No + (2) N: 2.0–3.0, P: 120–180	(1) Yes + (2) N: 1.5–2.0, P: 100–120

[a](1) Grades 3–4 bone marrow hypoplasia due to previous intravenous chemotherapy. (2) Blood count results at the beginning of oral chemotherapy: N = neutrophils, P = platelets.

achieved significant results [25]. A feasibility study added lomustine to these two oral drugs in a first group of 13 patients and obtained objective responses for 5/7 second-line patients and 2/6 for third-line patients with a median overall survival of 6 months after starting oral chemotherapy [26]. This paper reports the complete results in 71 patients treated with this original combination between 1996 and 2007, as second-line or third-line treatment.

2. Patients and methods

2.1. Patients

Between June 1996 and June 2007, all consecutive patients with SCLC treated by this oral chemotherapy were registered in our department. Baseline characteristics were recorded from the clinical file: gender, age and Eastern Cooperative Oncology Group (ECOG) performance status at the beginning of oral treatment, disease stage at diagnosis (limited or extensive disease). First-line chemotherapy, any second-line chemotherapy, tumour responses to these treatments and other treatments (surgery or radiotherapy) were recorded. The interval between the last day of intravenous chemotherapy and the first day of oral administration was calculated. Chest and abdominal CT-scan were performed for all patients who all showed metastatic disease at initial evaluation before beginning oral chemotherapy. The number of cycles and the quality and duration of responses to chemotherapy were recorded as complete or partial response (CR or PR) and no-response (NR) in patients with stable or progressive diseases. Follow-up is now sufficient as the dates of death are known for all but one of these patients, allowing the calculation of true survival. Toxicities were scored according to the WHO Hand-book for reporting results of cancer treatment.

2.2. Methods

The oral lomustine–etoposide–cyclophosphamide combination was administered to patients with histologically documented SCLC previously treated by one or two lines of intravenous chemotherapy (three lines for two patients). There was no age or PS limit but the therapeutic risk level had to be less than five. We make up the risk level on the basis of patients' four well-known criteria as risk factors for medullary vulnerability: age, PS, weight and past and present haematological status (Table 1). The dosage of lomustine at D1 (120 or 80 mg, as only 40 mg capsules were available) and the duration of 100 mg/day cyclophosphamide and 100 mg/day etoposide administration (ranging from 6 to 14 days) were based on the therapeutic risk level (Table 2). Drugs were taken on empty stomach in the afternoon. Antiemetics were administered at lunchtime on D1 to prevent the possible nausea induced by lomustine. Treatment cycles were continued every 28 days until progression or major toxicity. Evaluations were performed, before each cycle: clinical and radiological (more by chest X-ray than by CT-scan) assessment of response, according to WHO criteria, assessment of toxicity by weekly blood counts to adapt treatment. At D29, treatment was deferred from week to week until neutrophils >1.5 $\times 10^9$/l and platelets >100 $\times 10^9$/l. Treatment was not modified for patients with a neutrophil nadir between 1.0 and 2.0 $\times 10^9$/l and a platelet nadir between 30 and 150 $\times 10^9$/l. In other cases, dosages were adapted as shown in Table 3.

Table 3
Adjustment of the dosage of chemotherapy to weekly blood counts.

(a) Platelet nadir $\geq$ 150. $\times 10^9$/l
Lomustine, 40 mg increase (no more than 120 mg D1)

(b) Neutrophil nadir $\geq$ 2.0 $\times 10^9$/l
Increase the duration of cyclophosphamide and etoposide for 2 days

N.B.: Never perform (a) + (b) in the same cycle; when possible, perform (a) first, then, (b) 4 weeks later if still appropriate

(c) Platelet nadir $\leq$ 30 $\times 10^9$
Lomustine, 40 mg decrease

(d) Neutrophil nadir between 0.5 and 1.0 $\times 10^9$/l
Decrease the duration of cyclophosphamide and etoposide for 2 days

(e) Neutrophil nadir $\leq$ 0.5 $\times 10^9$/l
Decrease the duration of cyclophosphamide and etoposide for 4 days

N.B.: (c) + (d) or (c) + (e) should be performed as appropriate

3. Results

3.1. Patients characteristics and treatments

Patients characteristics before oral chemotherapy are shown in Table 4. The characteristics of previous lines of chemotherapy and their results are shown in Table 5. In three patients, second-line intravenous chemotherapy used before third-line oral chemotherapy was the same as first-line treatments which achieved CR with a long disease-free–treatment-free interval (one patient received PCDE with a PR, two patients received PE with one PR and one NR). In the other 32 patients, treatment was modified between first-line and second-line chemotherapy, using PE or CDE for 28 patients with very poor overall results (1 CR, 7 PR, 20 NR) and other treatments for four patients with no objective responses (topotecan for two patients, carboplatine–paclitaxel for one patient and

Table 2
Dosages and duration of administration of oral chemotherapy according to therapeutic risk level.

	Level					
	0	1	2	3	4	5
Lomustine day 1 (mg)	120	120	80	80	80	80
Cyclophosphamide and etoposide 100 mg day 1 to day:	14	12	12	10	8	6