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A prospective phase II study: High-dose pemetrexed as second-line chemotherapy in small-cell lung cancer

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ABSTRACT

Purpose: To investigate the efficacy and tolerability of high-dose pemetrexed as second-line chemotherapy in small cell lung cancer (SCLC).
Patients and methods: Patients with verified SCLC who had received one prior chemotherapy regimen, aged 18–75 years, WHO Performance Status 0–2, no clinical signs of brain metastases and measurable disease were eligible. Patients received pemetrexed 900 mg/m^2 IV every 3 weeks. Four courses were planned for all patients. Patients with relapse later than 3 months since last course of first-line chemotherapy were defined as "sensitive", those with relapse within 3 months as "refractory". Toxicity was graded using the CTCAE v3.0.
Results: 36 patients were accrued, 34 received study treatment. Median age was 61 (range 43–74), 18 (53%) males and 16 (47%) females. Mean number of courses administered was 2.5. One patient (3%) had partial response, three (9%) had stable disease and 29 (85%) progressed. One patient (3%) was not evaluable for response. Median TTP ($n = 33$) was 7.7 weeks ("sensitive": 8.4 weeks, "refractory": 5.1 weeks). Median OS ($n = 34$) was 17.6 weeks ("sensitive": 22.6 weeks, "refractory": 15.3 weeks). Of grade 3–4 haematological toxicity, anemia was observed in 2 (6%) patients, leukopenia in 6 (18%), granulocytopenia in 9 (27%) and thrombocytopenia in 3 (9%). Febrile neutropenia occurred in 6 (18%) patients. There were no treatment related deaths.
Conclusion: High-dose pemetrexed monotherapy to patients with recurrent SCLC yielded moderate toxicity, but limited treatment efficacy.

1. Introduction

A platinum compound in combination with etoposide is widely used as first-line chemotherapy for small-cell lung cancer [1–3]. Patients with limited disease (LD) also benefit from concurrent thoracic radiotherapy [4]. Response rates above 80% have been reported in patients with LD, and 40–50% in extensive disease (ED) [2,3]. The 5-year survival is 10–26% for LD, while few patients with ED survive more than 2 years [1–3].

Despite high response rates to first-line therapy, a majority of patients relapse within 1 year. Palliative radiotherapy is then a treatment option, but most patients have advanced disease and need systemic therapy. Reported response rates to second-line chemotherapy of 12–25% are lower than for first-line therapy [5–10]. However, a survival benefit has been observed after

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second-line treatment [11]. Patients who received oral topotecan had a significantly longer survival than patients who received best supportive care alone.

Important factors predicting efficacy of relapse treatment are response to first-line chemotherapy, time till relapse and WHO Performance Status at relapse [5,12,13]. Patients relapsing later than 3 months after first-line chemotherapy are considered to have "sensitive" disease and have a better prognosis than "refractory" patients who progress within 3 months [5,12].

Patients with recurrent SCLC often have significant comorbidity, poor performance status and poor bone marrow function after first-line chemotherapy. This limits the use of second-line therapy. Consequently, there is a need to explore the efficacy of drugs that might offer less toxicity than the regimens used today.

Pemetrexed is an antifolate registered for the treatment of malignant pleural mesothelioma and second-line treatment of non-small cell lung cancer (NSCLC). The most common side effects are myelosuppression, oral mucositis, diarrhea and skin rash [14]. Prophylactic treatment with corticosteroids reduces the frequency of rash. Since the drug is eliminated through the kidneys, a creatinine-clearance $\geq$40 mL/min is recommended [15]. Based on results from initial phase I/II trials, 500 mg/m^2 was defined as the standard dose [14,16]. Later, it was observed that toxicity was reduced in patients supplemented with vitamin B12 and folic acid [17]. New phase I trials were performed and the recommended dose for patients not heavily pretreated with chemotherapy was defined as 1000–1050 mg/m^2 provided vitamin supplementation [18,19].

Pemetrexed inhibits growth of cell lines from small-cell lung cancer [20]. Several agents effective in the treatment of NSCLC have shown efficacy in recurrent SCLC [8–10]. Pemetrexed has a favorable toxicity profile in second-line treatment of patients with NSCLC [21], a population comparable to patients with recurrent SCLC. In general, it is assumed to be beneficial to administer as high a dose of chemotherapy as possible. A trial investigating the efficacy of pemetrexed 500 mg/m^2 (standard dose) in recurrent SCLC [22] was already initiated when we planned our study. The aim of this study was to investigate the efficacy and tolerability of pemetrexed 900 mg/m^2 (high-dose) in patients with recurrent SCLC.

2. Patients and methods

2.1. Design

The study was designed as an open, multi-center phase II trial and was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Medicines Agency, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2. Eligibility criteria

Eligible patients had histological or cytological proven SCLC, received one prior chemotherapy regimen (re-induction therapy with the first-line regimen at first relapse was allowed), age 18–75 years, given written informed consent, WHO Performance Status 0–2, no clinical symptoms of brain metastases, platelets $\geq 100 \times 10^9$/L, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, creatinine-clearance $\geq$45 mL/min (calculated using the Cockroft–Gault formula), bilirubin $<1.5 \times$ ULN, ALT and ALP $<3 \times$ ULN (in case of liver-metastases: $<5 \times$ ULN) and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Pregnant or lactating women or patients with other active malignant disease were not eligible.

2.3. Therapy

All patients were supplemented with folic acid 0.4 mg PO once daily and Vitamin B12 1 mg IM every 9 weeks, starting at least 5 days before the first course of chemotherapy and lasting until 3 weeks after the last course. Dexamethasone 4 mg $\times$ 2 BID (or an equivalent dose of another corticosteroid) was given the day prior to, the treatment day, and the day after every course of study treatment. Pemetrexed 900 mg/m^2 was administered IV over 10 min every 3 weeks. Four courses were planned for all patients.

Prior to each course, ANC had to be $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, creatinine-clearance $\geq$45 mL/min and any grade 3–4 non-hematological toxicity had to be resolved. If not, treatment was delayed 1 week. The dose of the following course was reduced by 25% in case of nadir ANC $<0.5 \times 10^9$/L, a neutropenic infection or any grade 3–4 toxicity following the preceding course. A 50% dose reduction was to be performed in case of nadir platelets $<50 \times 10^9$/L or grade 3–4 mucositis. Any dose reductions were maintained for all subsequent courses. If a patient qualified for a third dose reduction, or had a treatment-related delay of more than 42 days following the preceding course, the study treatment was discontinued.

2.4. Endpoints and evaluation

The primary endpoint was overall response rates (ORR). The secondary endpoints were overall survival (OS), time to progression (TTP) and toxicity.

A baseline CT scan of the thorax and upper abdomen was performed within 1 week prior to chemotherapy. Hemoglobin, leucocytes, ANC and platelet count were assessed on day 8 and 15 of every treatment cycle. All patients were evaluated for response with a CT scan 3 weeks after the fourth course of chemotherapy (earlier if progression was suspected) using the RECIST-criteria. A CT scan was performed every 8 weeks until progression. All patients were observed for one year or until death. No central review of the CT-scans was performed. Toxicity was assessed at every visit and was graded using the CTCAE v3.0. We estimated overall survival and time to progression using the Kaplan–Meier method.

2.5. Statistical considerations

Patients with relapse later than 3 months after the last course of first-line chemotherapy were defined as "sensitive", those with relapse within 3 months as "refractory". A two-stage Simon design was used to define sample size in each group using a one-sided alpha of 10% and a power of 90% [23].

For "sensitive" patients, a rate of non-progressive disease (non-PD) of 40–60% was considered to be of clinical significance. 18 patients were to be enrolled in the initial phase of inclusion. If $\geq$8 patients showed non-PD [complete response (CR) + partial response (PR) + stable disease (SD)] at evaluation 3 weeks after the last course of chemotherapy, 28 additional patients were to be included in this group. However, enrolment was to continue until it was possible to conclude whether the target number of patients with non-PD in the initial phase of enrolment was reached. The study treatment would be considered worth further investigation in this patient population if $\geq$23 of 46 patients showed non-PD.

For "refractory" patients, a rate of non-progressive disease of 10–25% was considered to be of clinical significance. 21 patients were to be enrolled in the initial phase of inclusion. If $\geq$3 patients responded to therapy (CR + PR) at evaluation 3 weeks after last course of chemotherapy, 29 additional patients were to be included in this group. However, enrolment was to continue until it was possible to conclude whether the target number of patients with treatment response in the initial phase of enrolment was reached. The