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Phase II study of weekly plitidepsin as second-line therapy for small cell lung cancer

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ABSTRACT

Objective: To evaluate the antitumor activity and safety profile of plitidepsin administered as a 1 h weekly intravenous (i.v.) infusion of 3.2 mg/m^2 to patients with small cell lung cancer (SCLC) who relapsed or progressed after one line of chemotherapy.
Patients and methods: This was a multicenter, open-label, single-arm, exploratory, phase II clinical trial. Treatment lasted until disease progression, unacceptable toxicity, patient refusal or treatment delay for >2 weeks. Objective response rate (primary efficacy endpoint) was evaluated according to response evaluation criteria in solid tumors (RECIST). The rate of stable disease (SD) lasting for at least 6 months and time-to-event variables were secondary endpoints of efficacy. Toxicity was assessed using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.
Results: Twenty pretreated SCLC patients (median age, 60 years) with extensive (n = 13) or limited-stage disease (n = 7) received a total of 24 treatment cycles (median, one cycle per patient; range, 1–2). Objective tumor responses were not observed and only one of the 17 evaluable patients had SD. With a median follow-up of 11.8 months, the progression-free survival and the median overall survival were 1.3 months and 4.8 months, respectively. The most troubling or common toxicities were fatigue, muscle weakness, lymphopenia, anemia (no patients showed neutropenia), and asymptomatic, non-cumulative increase of transaminases levels and alkaline phosphatase.
Conclusion: This clinical trial shows that a cycle of 1 h weekly i.v. infusion of plitidepsin (3.2 mg/m^2) was generally well tolerated other than fatigue and muscle weakness in patients with pretreated SCLC. One patient died due to multi-organ failure. The absence of antitumor activity found here precludes further studies of this plitidepsin schedule as second-line single-agent treatment of SCLC.

1. Introduction

Small cell lung cancer (SCLC) comprises approximately 13–15% of all lung cancers [1]. Chemotherapy combining cisplatin (or carboplatin) and etoposide with concomitant radiotherapy has become the standard first-line treatment option for patients with both extensive and limited SCLC [2,3]. This treatment achieves high response rates of 60–70% (with a complete response rate of 20–30%), but it is associated with a high recurrence rate and a median survival time of 8–10 months [4–6]. Although new agents have been evaluated in patients with SCLC who relapsed or progressed after one line of chemotherapy, prognosis is still considered to be poor regardless of disease stage, with an expected median survival of 2–3 months [5–8].

Plitidepsin is a naturally occurring cyclic depsipeptide isolated from the Mediterranean tunicate *Aplidium albicans* but currently produced by chemical synthesis. The primary mode of action of plitidepsin has not been fully elucidated; however, several mechanisms have been proposed, including oxidative stress resulting in cellular apoptosis [9], induction of apoptosis via activation of

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the Rac1-JNK pathway [10–12], epidermal growth factor receptor (EGFR) phosphorylation [13] and increased level of cell membrane phospholipids oxidation and DNA oxidation [14]. In addition, plitidepsin reduces growth and induces apoptosis in anaplastic thyroid cancer xenografts and human leukemia MOLT-4 cells through inhibiting the expression of several angiogenic genes and the secretion of vascular endothelial growth factor (VEGF) [15,16].

Six phase I studies with dosage schedules of daily × 5, weekly and every-two-week infusions, infusion times of 1 h, 3 h and 24 h, and dose levels ranging from 0.08 mg/m^2 to 8 mg/m^2 were conducted [17–22]. Evidence for objective remission and tumor control was found in patients with renal, colorectal, head and neck carcinomas, melanoma, as well as in patients with advanced neuroendocrine tumors, including SCLC (two patients had stable disease (SD) for ≥3 months) and medullar thyroid carcinoma (eight patients had SD for ≥3 months and one patient treated at plitidepsin dose of 3.2 mg/m^2 experienced unconfirmed partial response).The dose-limiting toxicities (DLTs) observed with most schedules included muscular toxicity, transient increase of transaminases (in many cases related with liver metastasis and biochemical abnormalities at baseline), fatigue, diarrhea, and cutaneous rash. Plitidepsin showed no severe bone marrow toxicity.

The objective of the current exploratory, open-label, phase II clinical trial was to assess the antitumor activity and safety profile of plitidepsin 3.2 mg/m^2 given as a weekly 1 h intravenous (i.v.) infusion to patients with SCLC who relapsed or progressed after first-line systemic therapy.

2. Patients and methods

This phase II clinical trial was conducted at four European and two Canadian medical centers. The protocol was approved by the institutional review board of each participating center, and written informed consent was obtained from each patient before registration.

2.1. Study sesign and endpoints

This multicenter, two-stage, open-label, single-arm, exploratory phase II study was designed to determine the efficacy and tolerability of plitidepsin 3.2 mg/m^2 administered as a weekly 1 h continuous i.v. infusion (given on days 1, 8, and 15 every 4 weeks) in adult patients with advanced SCLC who had relapsed or progressed after one previous line of systemic chemotherapy.

The primary endpoint of efficacy was objective tumor response rate defined as the sum of complete (CR) and partial (PR) responses. Secondary efficacy endpoints were the rate of SD lasting for at least 6 months and time-to-event variables: tumor response duration, time to progression (TTP), progression-free survival (PFS) and overall survival (OS). Treatment related toxicity was also evaluated.

2.2. Patient population

Patients were required to have unresectable histologically-proven SCLC with progressive disease (PD) documented within 6 months prior to registration and a presence of at least one measurable lesion. All patients had to have received no more than one previous line of systemic chemotherapy for SCLC, which must have been discontinued at least 3 weeks prior to the first administration of plitidepsin. Prior radiotherapy was allowed and a minimum of 4 weeks (8 weeks in case of extensive prior radiotherapy) had to elapse between the end of the prior radiotherapy and patient registration. Patients were ≥18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, had recovered from any toxicities derived from previous treatments, and had an adequate organ function as defined by neutrophil count ≥1.5 × 10^9/l, platelet count ≥100 × 10^9/l, hemoglobin ≥10 g/dl, creatinine clearance ≥40 ml/min, serum bilirubin ≤1.5 mg/dl, alkaline phosphatase (AP) ≤2.5× the institutional upper limit of normal (ULN) and up to ≤5× ULN in case of extensive bone metastases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× ULN and up to ≤5× ULN in case of liver metastases, and albumin ≥25 g/l, and normal left ventricular ejection fraction (LVEF).

Patients were excluded if they had received prior treatment with plitidepsin, more than one line of systemic chemotherapy or any experimental treatment 30 days prior to inclusion in the study; were pregnant or lactating women; had a history of other neoplastic diseases (with the exception of adequately treated non-melanoma skin carcinoma or carcinoma *in situ*); were not using adequate contraception methods; had known brain or leptomeningeal involvement, suffered from any other relevant medical condition; or had hypersensitivity to plitidepsin, mannitol, or to the reconstitution solution (Cremophor EL and ethanol).

2.3. Evaluations during the study

Pretreatment evaluations included medical history and physical examination, complete blood count with differential cell counts, serum biochemistry, electrocardiogram (ECG), LVEF, creatinine clearance calculation, serum tumor markers (neuron-specific enolase or chomogranin A), coagulation test and urine analysis. Radiological evaluation (chest X-ray, computer tomography (CT) scan or magnetic resonance imaging (MRI)) 4 weeks before start of study treatment was required. Radiological evaluation within 6 months prior to registration must have confirmed disease progression. Additionally, to assess the existence of bone metastasis, an isotopic bone scan was conducted within 3 months prior to registration (or within 4 weeks, in case of a recent increase in bone pain). While on treatment, a complete clinical examination was done every 2 weeks. Blood samples for hematological and biochemistry analyses were obtained weekly during the first 8 weeks of therapy and afterwards at least every 2 weeks (save for analyses of total protein, albumin, amylase, which had to be performed every 4 weeks). Creatinine clearance calculation, urine analysis, coagulation test, and tumor markers were assessed before every cycle administration. An ECG was to be obtained at the end of the first infusion and thereafter if indicated only, while LVEF measurement was to be repeated at 3–6 months after the start of treatment. All disease parameters were reassessed every 8 weeks by using appropriate imaging procedures for the assessment of measurable and non-measurable lesions.

2.4. Study treatment

Plitidepsin (Pharma Mar, Colmenar Viejo, Madrid, Spain) was infused at a dose of 3.2 mg/m^2 as a 1 h i.v. infusion, repeated on days 1, 8, and 15 every 4 weeks. Administration of treatment for 3 consecutive weeks followed by one resting week was considered one cycle. Treatment cycles were repeated until disease progression, unacceptable toxicity, patient refusal or treatment delay for >2 weeks. In the event of specific toxicities after the first infusion, the dose of plitidepsin was to be reduced in subsequent infusions first to 2.7 mg/m^2 and then to 2.3 mg/m^2.

Hematopoietic growth colony stimulating factors were allowed (except during the first cycle of treatment) in accordance with the consensus guidelines of the American Society of Clinical Oncology (ASCO) [23]. Prophylactic treatment for emesis, which consisted of glucocorticoids (dexamethasone 4–8 mg i.v.), H_1-receptor antagonists and serotonin (5-HT_3) receptor antagonists [24], was to be