Carzelesin phase II study in advanced breast, ovarian, colorectal, gastric, head and neck cancer, non-Hodgkin’s lymphoma and malignant melanoma: a study of the EORTC early clinical studies group (ECSG)

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Abstract Purpose: In a phase II trial, the activity of carzelesin, a cyclopropylpyrroloindole prodrug analog, was assessed. Methods: Carzelesin was used as second- or third-line chemotherapy in patients with breast, ovarian, head and neck cancer and non-Hodgkin’s lymphoma, and as first-line chemotherapy in patients with colorectal and gastric cancer and melanoma. The drug was given as a bolus infusion at a 4-weekly dose of 150 µg/m². A total of 140 patients were entered and a total of 285 courses were administered. Results: In general, the compound was well tolerated. Myelotoxicity was the most common toxicity. Grade 3 and 4 leukopenia was observed in 18.6% of the courses, neutropenia in 20.3%, thrombocytopenia in 16.2% and anemia in 8.7%. Double nadirs were seen in a total of 41 courses for neutrophils, in 40 for leukocytes and in 3 for platelets. Non-hematological toxicity was very mild. Only one partial response in a patient with melanoma was seen. Conclusions: At this dose and schedule carzelesin did not yield activity in the types of tumors studied.

Key words Carzelesin · Lymphoma · Solid tumors · Toxicity

Introduction

Carzelesin (U-80244) is a cyclopropylpyrroloindole (CPI) prodrug analog and is a semisynthetic compound based on cc-1065, a natural product isolated from the soil organism Streptomyces zelenis. CPI drugs are a class of compounds with unique DNA-interactive properties. These agents enter into the minor groove region of DNA and mediate the covalent bonding to the N⁵-position of adenine in A-T rich regions, thus forming DNA adducts in a sequence-selective fashion [5, 9].

Three new CPIs have so far been developed: adoz elesin, bizelesin and carzelesin. Adoz elesin, which possesses the active CPI moiety, is the analog most closely related to CC-1065. Bizelesin is a CPI dimer, and thus has the potential to form DNA interstrand crosslinks, a characteristic that distinguishes this compound from the classical CPI drugs [6, 7].

Carzelesin was designed to be an inactive prodrug that is activated through hydrolysis of the phenylurethane substituent to yield U-76073, followed by ring closure to form the active prodrug U-76074 [9, 12]. All three compounds have been found to be extremely potent in tumor cell lines and in transplanted tumors in
mice. Carzelesin shows activity against Lewis lung carcinoma, B16 melanoma, colon 38 carcinoma, colon CX1 adenocarcinoma, lung LX-1 tumour, and ovarian 2780 and prostatic DU-145 carcinoma [4, 8].

Carzelesin has been selected for clinical development in Europe under the framework of the EORTC. Clinical multicenter phase I studies with carzelesin have been reported. Patients receive the drug either as a single dose intravenously every 4 weeks or in a daily ×5 schedule repeated every 4 weeks [1, 13]. The Early Clinical Studies Group (ECSG) of the EORTC initiated phase II studies with carzelesin administered as a single bolus infusion every 4 weeks at a dose of 150 μg/m² in patients with breast, ovarian, colon, gastric and head and neck cancer, non-Hodgkin’s lymphoma (NHL) and melanoma.

**Materials and methods**

These studies opened in May 1995 and closed in February 1997.

**Eligibility**

All patients entered into these studies had to have histologically or cytologically verified advanced measurable malignant disease beyond resectability. Other eligibility criteria included: WHO performance status ≤2; age 18–75 years; adequate bone marrow, hepatic and renal function; neutrophils ≥2000/μl; platelets >100,000/μl; creatinine ≤140 μmol/l (1.6 mg/dl) (if borderline, a creatinine clearance had to be performed and to be ≥90 ml/min); serum bilirubin ≤26 μmol/l (1.5 mg/dl); and alkaline phosphatase, SGPT and SGOT not more than twice the upper limit of normal, unless related to liver involvement.

Patients with breast cancer were allowed to have received one and only one prior chemotherapy regimen for advanced disease. A minimum of 4 weeks (6 weeks in the case of prior mitomycin C or nitrosourea) was required between the last dose and the study treatment. Prior (neo)adjuvant chemotherapy was allowed. A prior high-dose chemotherapy regimen with hematopoietic rescue was excluded. Prior hormonal therapy both adjuvant and/or for metastatic disease was allowed, provided that an interval of 1 week between the last hormonal treatment and study entry was observed. Patients with ovarian cancer and NHL had to have had at least one, but no more than two, prior chemotherapy regimens before entry into the study. The treatment-free interval had to be at least 4 weeks. Patients with head and neck cancer were not allowed to have received more than one chemotherapy regimen either given for neoadjuvant or for advanced disease with a minimum of 4 weeks between the last treatment and study entry. For patients with colorectal cancer no prior chemotherapy for advanced disease was allowed. Adjuvant chemotherapy (5-FU, leucovorin, levamisole) was allowed provided that the therapy-free interval was at least 12 months. For patients with gastric cancer, no prior chemotherapy was allowed. In patients with melanoma, no prior chemotherapy was allowed with the exception of prior adjuvant or local chemotherapy (extracorporeal circulation). If the measurable lesions were outside the treated limb, the treatment-free interval had to be at least 4 weeks. Otherwise the treatment-free interval had to be at least 6 months. Prior immunotherapy was allowed.

Institutional human research committee approval was obtained and appropriate informed consent was obtained from all patients.

**Formulation, dosage and treatment procedures**

Carzelesin was provided by The Pharmacia-Upjohn Company as a 0.25 mg (250 μg/ml) nonaqueous “PET-vehicle” in a 3-ml ampoule. The drug which was previously diluted to 50 ml with either 5% glucose or 0.9% sodium chloride, was given at a dose of 150 μg/m² as a single 10-min i.v. infusion every 4 weeks. After two full cycles only patients with tumour response or disease stabilization were allowed to continue treatment. Ancillary treatments were given as medically indicated.

Concerning dose modification, retreatment on day 28 was possible when the following criteria were met: (a) neutrophils ≥1.5 × 10⁹/l, (b) platelets 100 × 10⁹/l, (c) the values for the above-mentioned tests on day 28 were not lower than those measured on day 21 in view of the possibility of a double nadir as seen in phase I studies and (d) nonhematological toxicity had recovered to grade 2 or less. If the above criteria were not met on day 28 the treatment had to be delayed for 1 to 3 weeks. If there was no recovery on day 49 the patient had to be taken off study. Dose modifications were based upon the nadir values for white blood cells (WBC), granulocytes and platelets during the previous cycle. Whenever grade 4 toxicity lasting >7 days occurred in any of these tests, the dose for the next cycle had to be reduced by 25%.

**Response and toxicity criteria**

Follow-up studies included weekly complete blood counts and every 4 weeks full biochemistry, tumor markers and urine analysis. Tumors were evaluated every two full cycles. Standard WHO response criteria were used. Toxicities were graded according to the NCI Common Toxicity Criteria for cancer clinical trials. A double nadir is defined as a decline in WBC, neutrophil or platelet count after initial recovery to CTC grade 0 within the same course.

**Statistics**

Since for these tumor types (based upon selection criteria and prior chemotherapy) further development would only be of interest when activity in ≥20% of cases was shown, the Gehan design was chosen for this study. The trial for each tumor type consisted of two stages:

1. In the first stage 14 patients per tumor type would be entered. If there was no response (complete or partial), the trial would be terminated. This would ensure that if the drug was active in 20% or more of the patients the chance of erroneously rejecting the drug after the first 14 patients was 0.044.
2. If there was one response in the first 14 patients then one additional patient would be required. If two responses were observed then 6 additional patients would be required, if three responses, 9 patients, and if four or more responses, 11 patients. This would allow the response rate to be determined with a standard error of <0.10.

**Results**

The characteristics of the patients and their previous treatment are shown in Table 1.

**Breast cancer**

Of 19 patients with advanced breast cancer entered into the study, all were eligible. A total of 52 courses were administered. There were 12 delays, 10 due to hematological toxicity and 2 for non-drug-related reasons as well as 10 dose reductions due to myelotoxicity. No objective responses were observed in 16 evaluable patients. Six patients had stable disease, and the other ten progressed.