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CLINICAL TRIAL REPORT

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A phase II study of 9-nitrocamptothecin in patients with advanced pancreatic adenocarcinoma

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Abstract *Purpose*: Preclinical and phase I clinical data suggest that 9-nitrocamptothecin (9NC) is an agent with potential anticancer activity. A phase II study was undertaken in order to evaluate the potential benefit of oral 9NC administration in patients with advanced pancreatic cancer. This was the first clinical study of 9NC in Europe. *Methods*: A total of 19 consecutive patients with locally advanced or metastatic adenocarcinoma were enrolled (8 males and 11 females, aged 37–73 years). The patients were given 9NC orally five times a week, once a day. The end-points of this study were toxicity, objective response rate, subjective response rate (i.e. pain control, performance status and body weight), and survival. *Results*: An objective response was documented in 4 of the 14 evaluable patients (28.6%), while a subjective response was observed in 13 patients (92.9%). Overall median survival was 21 weeks (31 weeks in the group of 14 patients evaluable for response), and the 1-year survival was 16.7% and 23.1%, respectively. Toxicity leading to temporary discontinuation of 9NC was encountered in seven patients (36.8%), all related to a prior dose increase, while milder toxicity was observed in eight patients (42.1%). *Conclusions*: 9NC administered orally to patients with advanced pancreatic cancer gave promising results, while the toxicity of the therapy was mild and readily overcome. A larger scale clinical trial should be organized in order to establish the potential benefit of 9NC in patients with pancreatic adenocarcinoma.

Keywords 9-NTC · Pancreatic cancer · Chemotherapy

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Introduction

The antineoplastic properties of camptothecin have been known for more than 30 years. However, the water-soluble sodium salt, introduced in the 1970s, showed disappointing results in clinical trials. Low antitumor activity and increased toxicity were observed [1]. Attempts to overcome these problems have led to the development of various camptothecin derivatives, which differ in potency against the targeted cellular molecule topoisomerase I, antitumor spectrum, toxicity profile, and pharmaceutical and pharmacological properties [2]. Therefore, each camptothecin derivative must be studied for efficacy against specific cancer types.

The water-insoluble camptothecin derivative, 9-nitrocamptothecin (9NC) has demonstrated impressive preclinical antitumor activity against a large spectrum of human cancer cells grown in culture and in the mouse model as xenografts [3]. Remarkably, 9NC is not a substrate for the P-glycoprotein multidrug transporter [4], and can be converted to equally active 9-aminocamptothecin (9AC) in human, dog and mouse tissue. However, 9NC itself can function as a potent topoisomerase I inhibitor as demonstrated in studies of cell-free systems that did not allow conversion of 9NC to 9AC [5]. Further, in preclinical studies in vivo, 9NC has proved to be more effective as an anticancer drug than the parent compound [6, 7].

In a recent study in the USA, 107 consecutive patients with advanced adenocarcinoma of the pancreas were enrolled to receive treatment with 9NC [8]. Of these patients, 60 were evaluable with a median survival of

8.7 months and included 31.7% responders, 31.7% with stable disease and 36.6% nonresponders. Here, we present the results of the first European phase II study of oral 9NC administered to patients with advanced adenocarcinoma of the pancreas.

Materials and methods

Patient enrollment

This was a prospective non-randomized clinical trial evaluating the effects of 9NC in 19 patients with inoperable, recurrent or metastatic, histologically proven adenocarcinoma of the pancreas, who were diagnosed and treated at the Hippocration Hospital, Athens, Greece, from 1996 to 1997. The number of patients enrolled was limited by the availability of 9NC at that time. Of the 19 patients, 8 were males (42.1%) and 11 were females (57.9%) with ages ranging from 37 to 73 years with a median of 64.0 years. Nine patients had had prior surgical treatment (47.4%) either palliative (five patients) or curative (four patients), while four patients had been unresponsive to previous chemotherapy.

The inclusion criteria were measurable disease (CT scan), no history of other active malignancy within the last 5 years, Zubrod performance status grade 0–2 and expected survival of more than 2 months. Patients who had previously had surgery and/or chemotherapy were included in this study as long as they had measurable disease at the time of enrollment. Absolute granulocyte count ≥1500/μl, platelet count ≥1000,000/μl and hemoglobin ≥8.0 g/dl were also considered inclusion criteria. All patients also had to provide signed informed consent prior to entering the study. Patients who were excluded from the study showed at least one of the following conditions: uncontrolled infection at the time of entry, serious concomitant medical condition such as chronic obstructive pulmonary disease, chronic renal or hepatic failure, coronary artery disease, partial or intermittent intestinal obstruction, or were of child bearing potential and not practicing adequate contraception.

Drug and patient treatment

9NC was administered orally for 2 to 37 weeks (median 11.0 weeks). The drug was provided by the Stehlin Foundation for Cancer Research in gelatin capsules containing 1 and 0.25 mg. The starting dose of oral 9NC was 1.5 mg/m^2 per day, 5 days a week and was increased to 2.0 mg/m^2 per day. The dose was reduced or temporarily discontinued according to toxicity. Treatment and follow-up were conducted in our outpatient oncology clinic. Clinical examination, full blood count and chemistry were performed every week. Levels of CA 19-9 and CEA were measured every 3 to 6 weeks, and a CT scan was performed every 6 weeks.

Evaluation of patient response

Response was evaluated in patients who had completed at least two cycles (6 weeks) of chemotherapy [8]. Response was evaluated objectively and subjectively. An objective response (OR) was defined as 50% or more decrease in tumor size of all measured lesions in the CT persisting for at least 4 weeks, with no appearance of a new lesion, accompanied by 50% or greater decrease in CA 19-9 levels. Patients who did not achieve OR but had stable or progressive disease were classified as non-objective responders (NOR). Subjective response (SR) was evaluated according to clinical criteria including three parameters: pain, performance status and weight gain. SR was defined as improvement in pain intensity or decrease in analgesic consumption of ≥50% from baseline, an improvement in the Karnofsky index of ≥20 points or weight gain of >7% from baseline, lasting for at least 4 weeks. Patients who did not fulfill any of these three criteria were classified as non-subjective responders (NSR). Adverse reactions and toxicities encountered during this study were recorded before every cycle. Survival was measured from the time of enrollment and was estimated by the Kaplan and Meier method.

Results

Response could be evaluated in 14 patients (73.7%) who had completed at least 6 weeks of chemotherapy. An OR was observed in four patients (28.6%, 95% exact confidence limits 8.4%–58.1%) as indicated by an improvement in the CT scan and supported by a median percentage reduction in CA 19-9 levels of 89.7% (Fig. 1). Stable disease and/or disease progression was

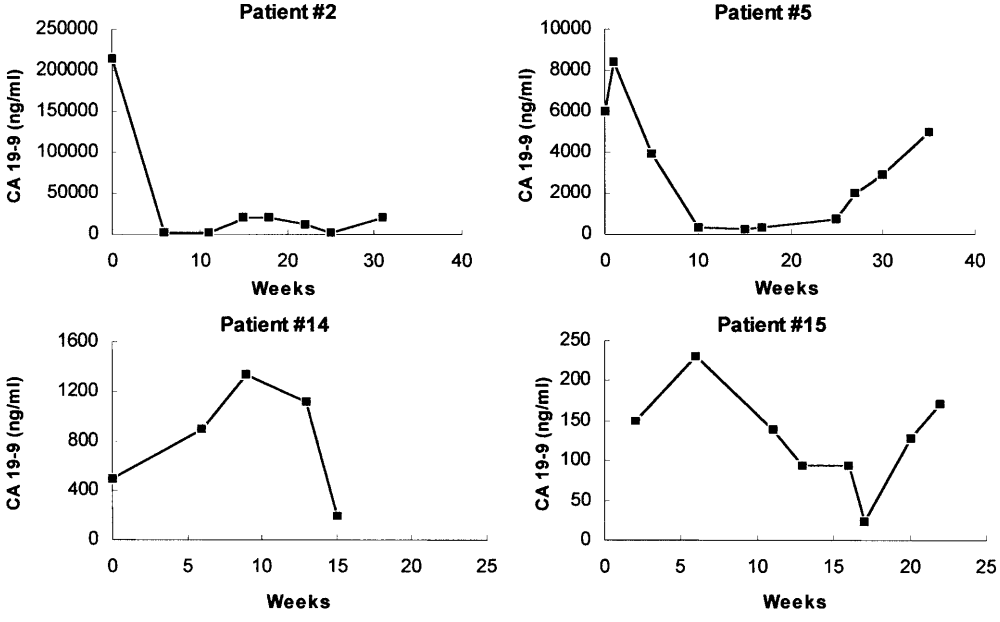

Fig. 1 CA 19-9 levels in four patients responding to 9NC. A decrease in CA 19-9 levels is apparent in all patients. In patients no. 5 and no. 15, CA 19-9 levels rose late in therapy, indicating recurrence

observed in ten patients (71.4%). An overall subjective response was observed in 13 patients (92.9%, 95% exact confidence limits 66.1–99.8%). In all of them, pain was relieved and the dose of analgesics reduced, while improvement in performance status (Karnofsky score) was observed in four patients (30.8%) and weight gain of ≥7% in only one patient (7.8%). Overall median survival was 21 weeks (2–85 weeks), while four patients (21.1%) were still alive 12 months after termination of the treatment. Overall 1-year survival was evaluable in 18 patients and was 16.7% (95% exact confidence limits 4–41%). In the group of the 14 patients who were evaluable for response, median survival was 31 weeks (6–85 weeks) and 1-year survival was 23.1% (95% exact confidence limits 5–54%).

Toxicity due to the drug administration was observed in 15 patients (78.9%), and was manifested as anemia in 11 patients (57.9%), neutropenia in 9 patients (47.4%) and gastrointestinal irritation (nausea and/or vomiting and/or diarrhea) in 6 patients (31.6%). Anemia was mild in most of the patients (grade 1 in nine patients, grade 2 and grade 3 in one patient each). The severity of neutropenia varied among the patients (grade 1 in two, grade 2 in four and grade 3 in three). Thrombocytopenia (grade 4), gastrointestinal hemorrhage (grade 3), alopecia (grade 1) and cardiac ischemia (grade 4) were observed in one patient (5.3%) each. Due to 9NC toxicity, drug administration was interrupted in seven patients (36.8%), but was restarted in all of them, while no life-threatening complications were encountered. In all seven patients, an increase in the 9NC dose from 1.5 to 2.0 mg/m^2 per day preceded the toxicities that led to the temporary discontinuation of the therapy.

Discussion

Chemotherapy for locally advanced or metastatic adenocarcinoma of the pancreas has poor results. Complete responses are rare while partial response rates are about 20% [9, 10, 11]. The partial response rate in our study was 28.6% (8–50%, 95% confidence intervals). In comparison with other studies, however, median survival was not prolonged and 1-year survival was still low at 16.7% [12, 13, 14]. For evaluation of response, a very important criterion is the duration of drug administration. In five patients the minimum evaluation period of 6 weeks was not completed due to rapid clinical deterioration and subsequent death. Response rate and survival improved in the other 14 patients, but still the increase in survival was not of a substantial magnitude. The drug appeared to be effective in patients with disease localized to the pancreas, since a significant reduction in the pancreatic mass was observed in all the responders.

The subjective response to 9NC is an aspect of the therapy that cannot be overlooked. Clinical improvement estimated in terms of pain reduction and a decrease or discontinuation of analgesic drugs was as high as 68.4%. Still, weight gain and improvement in Karnofsky score did not accompany this clinical benefit in most cases. Toxicity, while observed in almost 80% of patients and leading to temporary discontinuation of therapy in about 40%, was mild and not fatal in any patient, and was successfully overcome with a decrease in drug dose.

The number of patients in our study was relatively small and these preliminary results are open to debate. However, the results are in good agreement with the results reported for the USA study [8]. Still, the route of administration (oral), the advantages of outpatient treatment, the readily overcome side effects, and the response rate support further investigation of 9NC in a larger randomized trial either in a single-drug or a multidrug regimen.

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