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Radiation plus docetaxel and cisplatin in locally advanced pancreatic carcinoma: A non-comparative randomized phase II trial

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ABSTRACT

Background: We performed a randomized, non-comparative phase II study evaluating docetaxel in combination with either daily continuous (protracted IV) 5-fluorouracil or cisplatin administered weekly, concurrent to radiotherapy in the treatment of locally advanced pancreatic carcinoma. Results of the docetaxel plus cisplatin regimen are reported.
Methods: Forty chemotherapy-naive patients with locally advanced pancreatic carcinoma were randomly assigned to receive 5-fluorouracil and docetaxel or docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2/week, plus concurrent radiotherapy for 6 weeks. The radiation dose to the primary tumour was 54 Gy in 30 fractions. The trial's primary endpoint was the 6-month crude non-progression rate.
Results: 51 patients from 7 centres were included in the docetaxel–cisplatin treatment group. Six-month non-progression rate was 39% (95% confidence interval: 26–53). Median overall survival was 9.6 months (95% confidence interval: 2.4–60.7); 6 complete and 8 partial responses were obtained. Six patients survived more than 2 years after their inclusion in the trial. Grade ≥3 toxicity was reported in 63% of patients; no treatment-related death occurred. Severe toxicities were mainly anorexia (22%), vomiting (20%) and fatigue (24%).
Conclusions: Despite inadequate efficacy according to the main end point, this regimen gave a satisfactory rate of objective response (27%) with tolerable toxicity.

1. Introduction

The prognosis of pancreatic cancer is very poor due to it usually being detected at a locally advanced or metastatic stage. None of the patients presenting with an unresectable tumour, and only 20–30% of those having undergone surgery, will survive 5 years [1]. Furthermore, resection surgery is only possible in less than 20% of patients [2].

No consensus has yet been reached in the management of patients with unresectable locally advanced pancreatic cancer (LAPC). While two approaches are being explored, each has yielded only marginally significant benefits [3]. One relies on gemcitabine, administered predominantly as a single agent (1000 mg/m^2 weekly) or in combination with other cytotoxic agents [4,5]. Once the local disease has been brought under control with the

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systemic treatment, local radiotherapy is then proposed to the patient [6]. However, a recent trial has shown that results obtained using this sequential strategy of chemotherapy then radiotherapy may not be superior to chemotherapy alone [7]. While the importance given to radiotherapy in the treatment of pancreatic cancer does appear to be reducing, the development of new combinations of radiochemotherapy (RCT) needs maintaining. Indeed, results from small randomized trials using the alternative upfront approach concurrently combining RCT are encouraging [8–10]. Such regimens, essentially based on 5-fluorouracil (5-FU), have allowed a significant increase in median survival from 6–7 months to 10 months, thus supporting their superiority over chemotherapy or radiotherapy alone [8,10,11]. Another randomized trial recently demonstrated significantly increased survival rates offered by gemcitabine, another potent tumour sensitizing agent [12,13], when used in upfront radiochemotherapy as compared to gemcitabine alone (11.1 months versus 9.2 months) [14]. The results of this small phase III trial do not, however, concern the standard of care for patients with LAPC and alternative RCT schedules remain to be identified and tested in this population.

Paclitaxel has given variable results in combination with radiotherapy, yielding 33% of tumour responses in 18 evaluable patients with some problems of tolerance in two other studies [15–17]. Docetaxel on the other hand has well characterized radiosensitizing properties. Here in this phase II trial, we intended to determine the efficacy and toxicity of docetaxel combined with a second sensitizer, either 5-FU or cisplatin, when administered concurrently with radiotherapy in the treatment of histologically proven LAPC. At 6 months, 5-FU plus docetaxel proved inefficient with a 90% rate of disease-progression and was interrupted after the inclusion of 20 patients (results reported elsewhere) [18]. We report here the results of cisplatin–docetaxel (CP–DCT) RCT group of patients.

2. Methods and materials

2.1. Study design

Patients participating in this open, non-comparative, randomized (1:1), multicentre, two-arm phase II study were centrally randomized at the Gustave-Roussy Institute in Villejuif, France, using minimization stratification by centre, performance status and age. Patients were assigned to receive either 5-FU-docetaxel (arm A) or cisplatin-docetaxel (arm B) concurrent to radiotherapy. An interim analysis was planned after inclusion of 20 patients in each arm. This research was carried out in compliance with the Helsinki Declaration. The protocol (available on request) was approved by the Kremlin-Bicêtre Ethics Committee.

2.2. Patient population

Eligible patients were aged between 18 and 75 years and had pathologically confirmed unresectable LAPC. Unresectability, defined by a surgeon, was evaluated upon laparotomy or according to CT-scan and/or endoscopic criteria, including vascular involvement. Inclusion criteria were measurable disease, no prior chemotherapy, Karnofsky performance status (PS) higher than 70, adequate baseline bone marrow function (i.e., neutrophils > 1500/μL and platelets > 100,000/μL), normal serum creatinine levels (<120 μmol/L), and bilirubin levels < 25 μmol/L after biliary drainage. Excluded patients were those with metastases or with prior history of another primary tumour within the last 10 years, except adequately treated in situ carcinoma of the cervix uteri and basal or squamous cell skin carcinomas. Written informed consent was obtained according to French regulations.

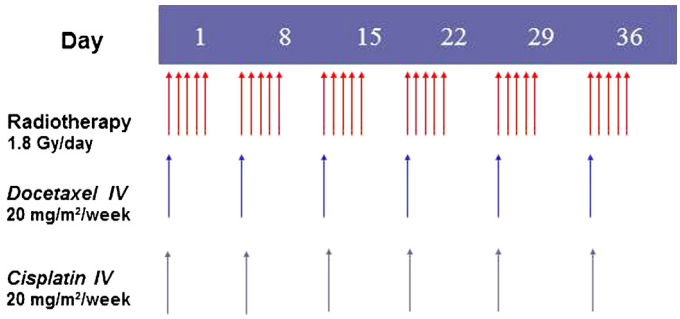

Fig. 1. Treatment schedule: docetaxel + cisplatin concurrent radiotherapy.

2.3. Treatment protocol

Patients were randomly assigned to receive cisplatin 20 mg/m^2/week and docetaxel (DCT) 20 mg/m^2/week treatment (Fig. 1). Treatment was administered for at least six weeks unless disease progression was documented, toxicity levels became unacceptable or patient refusal occurred. Premedication included adequate antiemetic therapy, dexamethasone (IV) before each docetaxel infusion, as well as granulocyte colony-stimulating factor (C-GSF) treatment in the event of severe haematotoxicity.

Dose adjustments were based on the worst toxicity observed during the previous cycle. Radiotherapy consisted of 54 Gy in 30 fractions (dose specified at the isocentre) with minimum photon energy of 6 MeV. The initial field covered the gross tumour volume and regional nodes, including the celiac axis.

2.4. Response and toxicity evaluation

Due to the difficulties encountered evaluating tumour response in LAPC, the main study endpoint was non-progression rather than objective response. Progressive disease (PD) was defined either as the appearance of a metastasis or protein-rich ascites or duodenal stenosis, and/or >30% increase in lesion size calculated as the sum of the two longest perpendicular diameters of the tumour. Tumours were evaluated by the local investigator using the modified RECIST scale at week 12 (i.e., 5 weeks after the end of treatment) and every 2 months thereafter until disease progression or the patient's death. No centralized review was made. Toxicities were graded according to the NCICTC scale (version 2.0) for chemotherapy, and according to the RTOG criteria for radiotherapy [19]. The trial registration number was NCT00112697 in the Current Controlled Trials database.

2.5. Statistical design

The primary endpoint was the 6-month crude non-progression rate (NPR). All eligible patients who started the study treatment were included in the primary endpoint analysis. A two-step Fleming design [20] was used and was detailed elsewhere [18]. Secondary endpoints included adverse events, progression-free survival (PFS), overall survival (OS), and objective response (OR) according to the RECIST criteria. Adverse events were evaluated before each cycle of treatment. Overall survival was defined as the time from randomization to the date of death or to the date the patient was lost to follow-up, and PFS as the time from randomization to disease progression or death, whatever its cause, or last follow-up. OS and PFS were estimated using the Kaplan–Meier method.