"Feasibility of radiotherapy with concomitant gemcitabine and oxaliplatin in locally advanced pancreatic cancer and distal cholangiocarcinoma: a prospective dose finding phase I-II study"

Laurent, S.; Monsaert, E.; Boterberg, T.; Demols, A.; Borbath, Ivan; Polus, M.; Hendlisz, A.; De Hemptinne, Bernard; Mahin, C.; Scalliet, Pierre; Van Laethem, J.-L.; Peeters, Marie-Rose

ABSTRACT

Patients and methods: Twenty-two patients with locally advanced pancreatic (n = 17) or biliary tract cancer (n = 5) were included. They received two cycles of gemcitabine/oxaliplatin followed by 5 weeks of RT in combination with a weekly fixed dose gemcitabine and an escalating dose of oxaliplatin from 40 up to 70 mg/m\(^2\). National Cancer Institute-Common Toxicity Criteria 3.0 was used to score weekly the treatment-related toxicity. Results: The patients treated at a dose of 40 mg/m\(^2\) of oxaliplatin had no dose-limiting toxicity. At 50 mg/m\(^2\), two patients developed grade 4 thrombocytopenia. Nine patients received 60 mg/m\(^2\), one developed grade 4 thrombocytopenia. Grade 4 thrombocytopenia in two patients and grade 3 diarrhea in one patient were observed with 70 mg/m\(^2\). Median time to progression was 8 months and median overall survival was 17 months. Conclusions: RT in combination with gemcitabine and oxaliplatin is feasible in patients with locally advanced pancreaticobiliary cancer. The reported time to progression underlines the potential activity of this regimen. The dose of 60 mg/m\(^2\) of oxaliplatin can be considered as the recommended dose.

CITE THIS VERSION

Feasibility of radiotherapy with concomitant gemcitabine and oxaliplatin in locally advanced pancreatic cancer and distal cholangiocarcinoma: a prospective dose finding phase I–II study

S. Laurent1, E. Monsaert1, T. Boterberg2, A. Demols3, I. Borbath4, M. Polus5, A. Hendlisz6, B. de Hemptinne7, C. Mahin8, P. Scalliet9, J.-L. Van Laethem3 & M. Peeters1*

1Department of Gastroenterology; 2Department of Radiotherapy, Ghent University Hospital, Ghent; 3Department of Gastroenterology, Erasme University Hospital, Brussels; 4Department of Gastroenterology, Université catholique de Louvain, Cliniques universitaires Saint-Luc, Brussels; 5Department of Gastroenterology, CHU Sart-Tilman, Liège; 6Department of Gastroenterology, Institut Jules Bordet; 7Department of Surgery, Ghent University Hospital, Ghent; 8Department of Radiotherapy, Institut Jules Bordet, Brussels and 9Department of Radiotherapy, Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: The prognosis of pancreaticobiliary tumors is poor. The aim was to assess the feasibility of radiotherapy (RT) and concomitant gemcitabine and oxaliplatin in locally advanced pancreatic cancer and distal cholangiocarcinoma.

Patients and methods: Twenty-two patients with locally advanced pancreatic (n = 17) or biliary tract cancer (n = 5) were included. They received two cycles of gemcitabine/oxaliplatin followed by 5 weeks of RT in combination with a weekly fixed dose gemcitabine and an escalating dose of oxaliplatin from 40 up to 70 mg/m². National Cancer Institute—Common Toxicity Criteria 3.0 was used to score weekly the treatment-related toxicity.

Results: The patients treated at a dose of 40 mg/m² of oxaliplatin had no dose-limiting toxicity. At 50 mg/m², two patients developed grade 4 thrombocytopenia. Nine patients received 60 mg/m², one developed grade 4 thrombocytopenia. Grade 4 thrombocytopenia in two patients and grade 3 diarrhea in one patient were observed with 70 mg/m². Median time to progression was 8 months and median overall survival was 17 months.

Conclusions: RT in combination with gemcitabine and oxaliplatin is feasible in patients with locally advanced pancreaticobiliary cancer. The reported time to progression underlines the potential activity of this regimen. The dose of 60 mg/m² of oxaliplatin can be considered as the recommended dose.

Key words: chemotherapy, cholangiocarcinoma, gemcitabine, oxaliplatin, pancreatic cancer, radiotherapy

introduction

Pancreatic cancer accounts for 3% of all cancers and is the fifth leading cause of cancer deaths in Western countries [1]. The incidence of cholangiocarcinoma is even lower, <1.5 per 100 000.

The prognosis is very poor with a 5-year survival of <5% for pancreatic cancer [2]. The only potentially curative therapy for early stages is radical surgical resection, resulting in 5-year survival rate between 18% and 24% [3, 4]. The median survival time after pancreatic resection varies between 13 and 20 months [5, 6]. Unfortunately, only a limited number of patients (<15%) are resectable at the time of diagnosis. More than 30% of all patients present with locally advanced non-resectable disease, usually due to invasion of the celiac vessels or the mesenteric artery, with a median survival time ranging from 5 to 11 months [7]. Moreover, a majority of patients have metastatic disease at the time of the diagnosis. The prognosis of cholangiocarcinoma is even worse with <6 months overall survival (OS). Most patients present initially with inoperable disease. For advanced pancreaticobiliary cancer, it has been shown that chemotherapy improves OS without impairing the patient’s quality of life [8, 9]. Gemcitabine is the standard treatment of advanced or metastatic pancreatic cancer.

However, objective tumor response is observed in only 6%–11%, and OS remains around 4–6 months [10]. Toxicity is variable and an initial phase I trial recommended a dose of 1200 mg/m² [11] in a 3 out of 4 weeks’ schedule. The pivotal trial in pancreatic cancer randomized 126 patients between gemcitabine and 5-fluorouracil (5-FU). Overall 23.8% of the patients treated with gemcitabine 1000 mg/m² per week...
experienced a clinical benefit compared with 4.8% for the 5-FU-treated patients [10]. The median survival was also significantly prolonged with gemcitabine. Subsequent phase III trials comparing gemcitabine to other agents confirmed these results [12, 13].

Oxaliplatin has also been investigated as a potential treatment for advanced pancreatic cancer. The combination with 5-FU is feasible with a response rate (RR) of 10% and a higher OS in the combination arm [14]. Moreover, oxaliplatin appears to enhance the activity of gemcitabine in vitro and thus may improve response to this agent [15, 16]. A phase II study testing the combination of gemcitabine and oxaliplatin was very promising in terms of clinical benefit, RR, progression-free survival (PFS) and OS [17]. However, more recently the result of the randomized phase III trial in comparison with gemcitabine alone was disappointing in terms of OS. The study failed to demonstrate a statistically significant advantage, probably due to its lack of power. However, this combination can be safely administered with clinical benefit and high RRs [18]. Therefore, it deserves further investigation.

A survival benefit has been demonstrated for chemoradiation over radiotherapy (RT) alone [19] in patients with locally advanced pancreatic cancer. This was confirmed by a recent review [20]. For patients with localized but unresectable malignancy, radiation therapy combined with fluorouracil, gemcitabine, or paclitaxel has shown modest improvement in survival and palliation of symptoms [21] over chemotherapy alone.

RT combined with gemcitabine has been increasingly investigated in locally advanced and adjacent setting of pancreatic cancer and was shown to be feasible, well tolerated, and active [22–24]. However, up to now, insufficient evidence is available to recommend chemoradiation in patients with locally advanced pancreaticobiliary cancer as a superior alternative to chemotherapy alone [20]. Intensification of this combination with platins could be attractive.

With limited benefit from available treatments, there is an urgent need for active modalities that improve response, subsequent respectability, and survival in this poor prognostic population. The integration of oxaliplatin into a full-dose gemcitabine and RT regimen could enhance local and systemic effects. This led us to investigate the combination of oxaliplatin, gemcitabine, and RT in locally advanced unresectable pancreaticobiliary tumors.

patients and methods

eligibility criteria

Eligible patients had a histologically proven and unresectable adenocarcinoma of the pancreas or cholangiocarcinoma with no evidence of metastatic disease as shown by thoracic and abdominal computed tomography (CT) scan. Patients unfit for surgery could also be included in the study, provided that they met all other criteria. Eligibility criteria included age ≥18 years; World Health Organisation performance status between zero and one; complete recovery from surgery in case of enteric and/or biliary tract by-pass operation, with a maximum delay after surgery of 8 weeks; life expectancy ≥6 months, and adequate hematologic, renal, and hepatic function. Written informed consent was obtained from all patients before initiation of therapy.

Exclusion criteria were as follow: previous chemotherapy or RT; previous or coexistent malignant disease except non-melanoma skin cancer or adequately treated cervical carcinoma in situ; presence of distant metastases; active infection; inadequate liver function (bilirubin > 3 mg/dl, aspartate aminotransferase > 10 times normal) after derivative surgery or endoscopic biliary drainage; inadequate renal function (creatinine > 1.5 mg/dl); pregnancy or breast feeding; use of any other investigational agent within the month before enrollment into the study; patient with grade 2 or more neuropathy.

pretreatment evaluation

Pretreatment examinations were carried out within 4 weeks before the start of treatment and included complete history, physical examination, evaluation of weight loss in kilogram and percent of usual body weight, evaluation of jaundice, liver function, bone marrow reserve, renal function and CA 19.9 dosage, endoutrasosonography, upper abdominal CT or magnetic resonance imaging (MRI), chest CT, or standard chest X-ray for staging. Special attention was paid to the relationship between tumor and vessels. The inclusion of every patient in the trial was based on a multidisciplinary decision. All patients with jaundice underwent a careful and complete drainage of the bile ducts.

surgery

Patients eligible for curative surgery were not entered into this study unless they refused or were unfit for surgery. On the other hand, patients who underwent a derivative procedure (surgical or other) could be included in the study. Patients undergoing a surgical attempt resulting in R2 resection could also be entered. If the tumor became operable, surgery was proposed 6 weeks after the completion of therapy.

study objectives and definition of dose-limiting toxicity

The aim of this study was to determine the maximal tolerated dose of oxaliplatin combined with 300 mg/m² of gemcitabine weekly and RT 45 Gy and to evaluate the feasibility of this combination in patients with locally advanced and unresectable, but non-metastatic pancreaticobiliary cancer.

Dose-limiting toxicity (DLT) was defined as grade 3 acute gastrointestinal (GI) toxicity or any acute grade 4 toxicity following National Cancer Institute—Common Terminology Criteria of Adverse Events (NCI-CTC) version 3.0.

Originally, five patients were planned at each dose level. A consensus process has been determined as follows: when DLT was reached for a patient, the chemotheraphy was delayed until recovery. Afterwards, the dose of chemotherapy was reduced to 50% of the starting dose for the next administration. The steering committee could decide to go to a higher dose level if the patient did not experience a new DLT in a given level.

treatment regimens

The first two cycles of combined gemcitabine and oxaliplatin were given without RT (Figure 1). The regimen consisted of oxaliplatin (Gemzar®, purchased from Eli Lilly, Belgian Affiliate), 1000 mg/m², administered as...
a 100-min i.v. infusion, followed by oxaliplatin (Eloxatin®, provided by Sanofi-Aventis), 100 mg/m², administered i.v. as a 2-h infusion. The doses were based on the initially calculated body surface area.

This was followed by combination therapy consisting of RT to a total dose of 45 Gy (25 fractions of 1.8 Gy in 5 weeks). During the irradiation, gemcitabine, given a dose of 300 mg/m², and oxaliplatin at escalating doses (40–70 mg/m²) were administered weekly, respectively, at days 1 and 2 (Figure 2). Gemcitabine was infused over 30 min, 1–4 h before irradiation. Oxaliplatin was infused over 2 h.

RT was delivered on a linear accelerator, using megavoltage photon beams of 6 MV or more. Usually 15 MV or higher were necessary. SAD technique was recommended, with an isocenter distance of 100 cm. Most patients were treated with three or four fields and three-dimensional (3D) conformal planning was highly recommended.

A CT in treatment position was obtained with joined slices, allowing 3D reconstruction on a treatment planning system. The gross target volume (GTV) included all macroscopic tumor, including enlarged lymph nodes. The GTV was expanded with 1 cm and the lymph node regions to obtain a clinical target volume. Planning target volume (PTV) expansion was done according to the institute’s standard guidelines.

The reference dose per fraction was 1.8 Gy at the isocenter, according to International Commission on Radiation Units and Measurements (ICRU) report 50 (1.8 Gy per fraction, 5 days per week). The total prescribed dose was 45 Gy at the isocenter. The PTV was included at least in the 95% isodose of the reference isodose. The maximum dose did not exceed 107% of the reference dose. Less than 50% of the total renal parenchyma received a dose of 20 Gy or more. The mean dose to the liver did not exceed 30 Gy.

### gemcitabine and oxaliplatin dose adjustments before and during combination therapy

- The dose modifications were followed on the base of weekly absolute neutrophil count and platelets count, within 48 h before infusion of gemcitabine/oxaliplatin and clinical assessment of non-hematologic toxicity.
- For cumulative, characteristic peripheral sensitive neuropathy more than grade 2, oxaliplatin was discontinued.
- The decision to hold both RT and chemotherapy instead of only chemotherapy was left to the investigator’s discretion.
- If toxicity required a treatment break of RT, both RT and chemotherapy were held until toxicity has declined to grade 2 or less.
- In case of grade 3 acute GI toxicity or any acute grade 4 toxicity (DLT), chemotherapy was delayed until recuperation and restarted at 50% of the starting dose for the next administration. If the combination therapy should be delayed for >2 weeks, the treatment administration was definitely discontinued.
- If chemotherapy alone or in combination with RT was omitted due to toxicity for a total of ≥2 weeks in three out of five consecutive patients, the dose of gemcitabine was de-escalated to 200 mg/m² and oxaliplatin to 30 mg/m².

### follow-up assessment of response to chemoradiation and subsequent surgery

Tumor evaluation by chest and abdominal CT and measurement of CA 19.9 in serum were carried out at baseline, before any treatment, and 1 month after stopping the chemoradiation. At that moment, operability was discussed at the multidisciplinary meeting. Follow-up was carried out every 3 months for a total period of 2 years. Determination of disease progression was based on imaging and not on an increase in CA 19.9 alone. Therapy-related complications were recorded. Evidence of progressive disease, patient’s request, unacceptable toxicity, or if the responsible physician thought that a change of therapy would be in the best interest of the patient were potential reasons for protocol discontinuation.

The study was approved by the ethical committee and monitored by a steering committee composed of delegates from the participating centers.

### results

#### patient characteristics

Twenty-four patients were enrolled over a period of 24 months in four Belgian centers. Two patients prematurely discontinued the treatment. One had a lymphoma as final diagnosis and the other one stopped the treatment for personal convenience without major toxicity. Patient characteristics are summarized in Table 1. Median age was 60.5 years (range 43–72). Baseline performance status was zero in 16 patients and one in six patients. Male : female ratio was 12 : 10. Seventeen patients had locally advanced pancreatic tumors and five patients had inoperable bile duct tumors.

#### dose escalation and DLTs

The number of patients assigned to each dose level is listed in Table 1.

Five patients were treated at the first dose level (40 mg/m²). No DLT was recorded in these patients and so the dose of oxaliplatin was escalated to 50 mg/m² in four patients. Two of them developed DLT (grade 4 thrombocytopenia). The fifth patient had a lymphoma and was excluded from the study and never received therapy. The steering committee decided to proceed to the next dose level based on the fact that thrombocytopenia is frequently seen with gemcitabine and more importantly, there was no clinical impact (i.e. bleeding) of this side-effect.

A cohort of nine patients was treated at a dose of 60 mg/m² and only one developed DLT. Four patients were treated at a dose of 70 mg/m², two developed a DLT.

#### acute adverse events and dose intensity

The number of patients developing adverse events is summarized in Table 2. The safety results are presented for 22 patients. Grade 1/2 and grade 3/4 adverse events according to
the NCI-CTC (version 3.0) are shown in Table 2. The most frequent grade 1/2 toxic effects were thrombocytopenia (64%), nausea (59%), and fatigue (50%). These side-effects did not result in any treatment interruption or dose modification. The most frequent grade 3 adverse event was neutropenia (50%). One patient had grade 3 neuropathy (4%) at dose level 1. Five patients (23%) experienced a grade 3 thrombocytopenia, one at each dose levels 2, 3, and 4. Grade 3 diarrhea was observed in one patient (5%) at dose level 4. Grade 4 thrombocytopenia occurred in five patients (23%), two at dose level 2, one at dose level 3, and two at dose level 4. The treatment was adapted in function of the adjustments previously described. One patient (5%) experienced grade 4 nausea and vomiting at dose level 4. No other major toxicity was observed.

Other serious adverse events occurring during the treatment period and not considered to be DLTs were seen in four patients. One patient developed cholangitis, the second one a mycotic oesophagitis, the third one a sepsis and infectious ascites, and the fourth one a pneumonia.

All patients received the prescribed radiation dose without interruption. The patients received at least 70% of the planned dose of chemotherapy. Three patients (14%) received the full dose, one at dose levels 2, 3, and 4.

response assessment and patient’s outcome

Efficacy was assessed by CT/MRI. Partial response was obtained in three patients and complete response in one patient. One of the partial responses was obtained in an inoperable biliary tract adenocarcinoma. The median time to...
progression was 8 months with a median OS of 17 months. Follow-up was carried out until January 2008. To date, six patients are still alive.

surgery
After the combined treatment, surgery became possible in four patients. A R0 resection was obtained in three patients with pancreatic cancer.

discussion
Improved treatments for locally advanced unresectable pancreaticobiliary tumors are urgently needed as demonstrated by their limited prognosis and the frequency of their presentation. The challenge of clinical research is well reflected by the controversies resulting from available studies and the difficulties in designing and performing clinical trials in those patients.

There is no consensus on the management of locally advanced pancreatic cancer. Ninety percent of patients have unresectable disease at diagnosis, of which 40%–50% have locally advanced disease [25]. Both chemotherapy and chemoradiation improve the 1-year survival in patients with advanced inoperable pancreatic cancer [26].

Gemcitabine remains the standard therapy for advanced pancreatic cancer. With the exception of adding erlotinib to gemcitabine, no other combination showed a significant improvement in OS [27].

Preclinical data and available clinical trials support the use of gemcitabine as a radiosensitizing agent [23, 28]. The combination of additional agents with gemcitabine and radiation appears to be feasible. Although toxicity of chemoradiation is occasionally severe [7], improvement in response and survival is encouraging [29].

A recent meta-analysis supports the use of gemcitabine–platinum combination chemotherapy over gemcitabine alone [30]. In advanced-disease trials, a gemcitabine–platinum-containing doublet has consistently demonstrated improved RR, PFS, and clinical benefit compared with gemcitabine alone [18, 31, 32]. It seems logical that the combination of radiation therapy with gemcitabine–platinum chemotherapy may improve the treatment of locally advanced tumors. The strategy of using chemotherapy followed by chemoradiation seems effective in locally advanced pancreatic carcinoma [33] but until now, this strategy failed to prove its superiority in comparison to chemotherapy alone.

The combination of RT and gemcitabine and oxaliplatin has recently been investigated in a phase I study in (un)resectable or metastatic pancreatic carcinoma. This study showed an acceptable tolerance [34]. A concomitant administration of weekly oxaliplatin, fluorouracil continuous infusion, and RT after 2 months of gemcitabine and oxaliplatin induction in patients with locally advanced pancreatic cancer was also carried out by the GERCOR with encouraging results [35].

Our study was initially designed to determine the optimal dose of oxaliplatin that could be safely added to a 300 mg/m² weekly dose of gemcitabine, as previously reported, and radiation therapy in patients with unresectable pancreatic or biliary tract cancer without evidence of metastatic disease. We designed this trial with escalating doses of oxaliplatin, given once a week during the RT period. Two cycles of gemcitabine and oxaliplatin were given upfront. A moderate radiation dose was used to allow full systemic doses of oxaliplatin and gemcitabine.

All patients completed their RT. Dose intensity for chemotherapy was calculated and the patients received at least 70% of planned chemotherapy doses. The safety profile of the combined modality was found favorable and treatment-related toxicity manageable in most patients. The most frequent grade 4 toxicity was thrombocytopenia, which is consistent with the data recently published in another phase I study [34]. Other grade 4 toxic effects were very uncommon. Based on the fact that only one out of nine patients in the 60 mg/m² dose level showed a DLT and two out of four in the 70 mg/m², the dose of 60 mg/m² was selected for further trials. Since the RT-specific toxicity was low with no need for treatment modifications, increasing the radiation dose with the same chemotherapy regimen also seems a feasible option for future trials.

Although this study was designed to determine the appropriate dose of oxaliplatin and evaluate safety, favorable response was seen in 18% of the patients. Three of those patients had a R0 resection. A partial response was observed in three patients and a complete response in one patient reflecting an overall RR of 18%.

In conclusion, the combination of oxaliplatin, gemcitabine, and radiation therapy in locally advanced pancreaticobiliary tumors is feasible. The recommended dose of oxaliplatin for further trials is 60 mg/m². Further investigations are needed to better define the efficacy and the place of this new chemoradiation regimen in the therapeutic arsenal of locally advanced pancreaticobiliary cancer.

In addition to the results found in the published study from Desai et al [34], this combined regimen could be one of the most active in the neoadjuvant approach of biliary tumors and deserves further investigations.

funding
Eli Lilly and Sanofi-Aventis.

acknowledgements
The authors are grateful to the study nurses Tine Derre, Peggy De Clercq, Anja Carlier, and Nancy Van Damme and to the patients. Disclosure of potential conflicts of interest: Marc Peeters has served as an advisory board member for Eli Lilly.

references


