Chemotherapy as initial treatment of locally advanced unresectable pancreatic cancer: a valid option?

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SUMMARY

Introduction — Radio-chemotherapy is the standard treatment for locally advanced unresectable pancreatic cancer (LAPC). Chemotherapy has been shown to be effective in the treatment of metastatic disease and we therefore evaluated its use as a first-line treatment for LAPC.

Patients and methods — We carried out a retrospective analysis of all consecutive patients treated for LAPC (N=33) between July 1997 and April 2005, analysing the results of first-line chemotherapy (CT group) and radio-chemotherapy (RCT group) in this setting.

Results — The first-line treatment was RCT in six patients (18.3%) and CT in 26 patients (78.8%). Secondary treatment was administered to nine patients of CT group with well-controlled disease: “closure” radio-chemotherapy for seven patients (26.9%) and secondary resection for three (12%).

After a median follow-up of 27 months, 23 patients died (69.7%). Overall survival was 13.8 months [95% CI: 10.1-19.4] for the whole population, 9.5 months [95% CI: 4.6-] for the RCT and 18.0 months [95% CI: 12.4-25.5] for the CT. Overall survival for the CT patients undergoing secondary surgery or “consolidation” radio-chemotherapy was 28.8 months [95% CI: 13.8-].

Conclusion — First-line chemotherapy is a valid option for LAPC treatment, making it possible to identify the patients who may benefit from secondary resection or radio-chemotherapy.

RÉSUMÉ

La chimiothérapie est-elle l’option thérapeutique de choix des adénocarcinomes pancréatiques localement évolutés non résécables ?

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Objectifs — La radio-chimiothérapie est le traitement standard des adénocarcinomes localement évolutés non résécables du pancréas (ALEP). La chimiothérapie a prouvé son efficacité en situation métastatique et nous avons voulu évaluer son utilisation en première ligne thérapeutique pour les ALEP.

Malades et méthodes — Nous avons réalisé une analyse rétrospective de 33 malades consécutifs traités pour un ALEP.

Résultats — Le traitement de première ligne était une radio-chimiothérapie chez 6 malades (18,3 %) (groupe RCT) et une chimiothérapie chez 26 malades (78,8 %) (groupe CT). Un traitement secondaire a pu être réalisé chez 9 malades du groupe CT avec une maladie bien contrôlée : radio-chimiothérapie de « clôture » chez 7 malades (26,9 %) et résection chirurgicale secondaire chez 3 (12 %).

Après un survi médian de 27 mois, 23 malades étaient décédés (69,7 %). La survie globale était de 13,8 mois [IC 95 % : 10,1-19,4] pour l’ensemble de la population, 9,5 mois [IC 95 % : 4,6-] pour le groupe RCT et 18 mois [IC 95 % : 12,4-25,5] pour le groupe CT. La survie globale des malades du groupe CT ayant pu bénéficier d’un traitement secondaire était de 28,8 mois [IC 95 % : 13,8-].

Conclusion — La chimiothérapie de première ligne est une option valide dans la prise en charge thérapeutique des ALEP.

Introduction

Pancreatic adenocarcinoma (PAC) accounts for about 3% of all cancers, but is the fifth most important cause of deaths from cancer in western countries. For all stages of this cancer, survival at five years is less than 5% [1, 2]. In France, about 5 000 new cases of PAC are observed every year [3].

Since the end of the 1980s, the gold standard treatment for locally advanced unresectable pancreatic cancer (LAPC) has been 5FU-based radio-chemotherapy. This was based upon several small therapeutic trials which have shown this combination to be more effective than either radiotherapy or chemotherapy alone [4-6]. However the survival of patients treated by radio-chemotherapy was poor with a median survival of around nine months (range: 6.5 to 10.4 months) and a two-year survival rate of about 12%. Conversely radio-chemotherapy may be toxic (mainly digestive toxicity) and imposes many constraints on the patient. In the ESPAC 1 trial, in patients undergoing adjuvant treatment following curative resection, excess mortality was reported in the group of patients treated by radio-chemotherapy. In addition, due to the dose and schedules of chemotherapy used in combination with radiotherapy, this treatment does not guarantee optimal systemic control of the disease in many patients, with 20 to 50% of patients developing hepatic or peritoneal metastases during their treatment [6-10]. Recent advances in systemic chemotherapy, with the development of...
gemcitabine and polychemotherapy based on platinum salts, have made it possible to obtain response rates of about 25%, tumor growth control rate of about 65% and median survival of six to nine months [11-14].

Since 2000, the efficacy of such chemotherapy has made it possible to treat patients suffering from LAPC using first-line systemic chemotherapy. This enables patients to avoid the toxicity, cost and time of radiotherapy, while receiving potentially effective chemotherapy, and may allow identification of patients most likely to benefit from secondary local treatment (*consolidation* radio-chemotherapy or surgery in cases of a “good” response).

The aim of this study was to retrospectively analyze the results obtained in all the patients with LAPC followed consecutively at our center since 1997 as a function of the first-line treatment: radio-chemotherapy (RCT) or chemotherapy (CT).

### Materials and methods

#### Population

Since 1997, the medical files of all patients treated at our center have been registered prospectively in a computerized database listed with the French national data protection organization (the CNIL; Comité National d’Informatique et des Libertés). By May 2005, 1,455 patients had been treated for PAC. Diagnosis was based on histological data in all cases. At the time of the initial examination, 32 patients had operable, resectable tumors, 80 patients already had metastatic disease and 33 patients had a locally advanced adenocarcinoma (LAPC) (vascular invasion) contraindicating first-line surgical resection.

#### Data collected

We analyzed the medical files of the 33 patients with LAPC. We collected the following data: clinical and biological characteristics of the patients and histological and morphological characteristics of the tumor at diagnosis; biliary or digestive diversion (endoscopic or surgical) during follow-up; protocols of the courses of chemotherapy and/or radio-chemotherapy administered, with the dates on which treatment began and ended; best response and the date of that response; data of imaging results demonstrating progression; date of possible curative surgery; date of last follow-up or of death.

#### Evaluation of the tumor response

The tumor response to chemotherapy was evaluated at two-month intervals, by helicoidal scans with vascular contrast and the determination of tumor markers (CEA and Ca 19-9). We used the WHO response criteria: complete response (CR) was defined as the disappearance of all lesions; partial response (PR) was defined as a decrease of 50% or more in the product of the two perpendicular largest dimensions of each measurable lesion and progressive disease (PD) as a decrease of less than 50% or an increase of less than 25% of measurable lesion. We defined objective response rate (OR) as CR + PR + SD. In the absence of imaging for evaluating the tumor response, the disease was considered non-evaluable.

#### Survival analysis

Overall survival was defined as the time between histological diagnosis and the date of death or of the last follow-up. Progression-free survival was defined as the time between the first day of treatment and the date of the scan demonstrating progression of the diseases according to WHO criteria, or death of the patient. For the analysis, we assigned the patients to two groups, according to the first-line treatment received: radio-chemotherapy (RCT) and chemotherapy (CT). Data were censored on January 6th 2006.

#### Statistical analysis

All results are expressed as medians and ranges. The two groups were compared using Student’s t test for quantitative data, and χ² tests with Yates correction for qualitative data. Values of p below 0.05 were considered statistically significant. Cumulative survival curves were plotted according to the Kaplan-Meier method [15]. Log-rank correlation tests were used to compare survival in the two groups. We used STATA 8 software (College Station, Texas) for statistical analysis.

#### Results

##### Population

The clinical and biological characteristics of the patients at diagnosis are summarized in table I. The median age of the patients was 60 years (range: 37-83) and the sex ratio was 1.53 (20 men, 13 women). The inaugural symptoms were, in decreasing order of frequency: abdominal pain, loss of more than 10% of normal body weight, jaundice, digestive problems (vomiting, diarrhea, constipation). Twenty patients had Ca 19-9 values more than twice normal values on diagnosis, but only six had no associated cholestasis.

The histological and morphological characteristics of the tumors are summarized in table I. The tumor had developed in the head of the pancreas in 20 patients, in the isthmus in seven patients, in the body of the pancreas in five patients and in the tail of the pancreas in one patient. In all cases, the tumor was judged non-resectable during a pluridisciplinary meeting, due to vascular invasion (celiac trunk, superior mesenteric artery and vein). The median largest tumor dimension was 40 mm (range: 25-90). Biliary and/or digestive diversion had been carried out in 25 patients (76%): by surgical means in 11 cases (digestive diversion: 1; biliary-digestive diversion: 3; double diversion: 7) and by endoscopy in 14 cases (biliary prosthesis: 11; duodenal prosthesis: 3).

##### First-line treatment

One 81-year-old patient received no anti-tumor treatment and instead received palliative care from diagnosis, due to a rapid change in general condition. For the other 32 patients, the first-line treatment was either radio-chemotherapy (6 patients, RCT group) or chemotherapy (26 patients, CT group).

The patients in the RCT group received a median dose of 45 Gy (21.6 to 60 Gy). The chemotherapy administered during radiotherapy was 5-fluorouracil (5FU) only in three patients, cisplatin (CDDP) in one patient and a combination of 5FU and CDDP in two patients. At the end of this first-line treatment, the disease was stable in two patients, with the other four patients displaying PD (peritoneal carcinosis: 2; hepatic metastasis: 1; peritoneal carcinosis plus hepatic metastasis: 1). Palliative chemotherapy was administered to all patients displaying PD (gemcitabine in 3 patients and LV5FU in 1 patient), at a median of 34 days after the end of radiotherapy. Two of these four patients displayed clinical PD contraindicating the continuation of chemotherapy and the other two received second-line chemotherapy (FOLFOX for one and LV5FU-CDDP for the other). None of these patients received three lines of chemotherapy.

The patients of the CT group received a median of 3.5 courses of chemotherapy (1 to 3); 11 patients (42%) received a single line, 10 patients (38.5%) received two lines and five patients received three lines. The protocols of the first, second and third courses of chemotherapy are detailed in table II. The median number of chemotherapy cycles administered as first-, second- and third-line chemotherapy was 4 (1-16), 4 (1-13) and 4 (1-10), respectively. For first-line treatment, for all chemotherapy protocols, 31% of patients displayed a PR, 42% had SD, 19% had PD and 8% could not be evaluated. For second-line treatment, 19% of patients had a PR, 37.5% had SD of the disease, 32% PD and 2% CR.
12.5% PD and 31% could not be evaluated. “Consolidation” RCT, combining radiotherapy (45 to 60 Gy) and chemotherapy with 5FU, was administered to seven patients (27%), following the first line of chemotherapy in five patients, the second in one patient and the third in one patient. The response of the tumor to chemotherapy before RCT was PR in three patients (43%), with SD in the other four patients (57%). Information concerning metastatic evolution during follow-up was available for 23 patients of CT group: 5 patients died without metastases (thromboembolic complication or local disease evolution), 1 patient was alive with only local disease, 1 patient was alive without recurrence after surgery and 16 had at least one metastatic localisation (hepatic: 7; peritoneal: 7; lung: 4). Median time between initial diagnosis and metastases diagnosis at imagery was 12.14 months (range: 2.93-57.37 months).

**Surgery**

Secondary resection was discussed in patients with objective response or excellent TGC and could only be envisaged for the CT group. In this group, three of the 26 patients (11.5%) underwent curative surgery after an objective response to chemotherapy. Before treatment, the largest dimension of their tumor lesions was between 30 and 34 mm. Two patients underwent surgery after chemotherapy alone and one underwent surgery after chemotherapy followed by RCT. The characteristics of treatment received by each patient are summarized in table III.
Survival

Overall survival for the 145 patients followed for PAC since 1997 is presented in figure 1. Overall survival as a function of the stage of the disease at diagnosis was 24.2 months [95% CI: 19.0-48.7] for resectable PAC, 13.8 months [95% CI: 10.1-19.4] for LAPC and 6.4 months [95% CI: 4.4-7.2] for cancers metastatic at diagnosis.

Twenty-three of the 33 patients with LAPC (69.7%) died during follow-up. The overall survival of these 33 patients, evaluated after a median follow-up period of 27 months (6.8 to 98.6 months) was 13.8 months [95% CI: 10.1-19.4].

For the RCT group, overall survival was 9.5 months [95% CI: 4.6-] and progression-free survival was 1.05 months [95% CI: 0.4-].

For the CT group, overall survival was 18 months [95% CI: 12.4-25.5] and progression-free survival was 7.3 months [95% CI: 2.5-12.1] (figure 2). In this group, patients who underwent consolidation RCT had an overall survival of 28.8 months [95% CI: 13.8-] and a progression-free survival of 12.1 months [95% CI: 2.5-23.1]. For the three patients who underwent potentially curative surgery, progression-free survival was 55.9 months [95% CI: 13.1-] and the median overall survival could not be determined. These three patients were still alive at 30, 31 and 63 months after histological diagnosis, 2 of them have recurrent disease and are under chemotherapy.

Discussion

This study confirms the poor prognosis of LAPC. We found that survival was longer for patients given chemotherapy than for patients given RCT as first-line treatment. Progression of the disease was observed in four of the six patients treated by RCT as first-line treatment. The overall survival of the RCT group was 9.5 months, consistent with the overall survival reported in phase III studies evaluating RCT using 5FU bolus [4-6]. The overall survival of the CT group was 18 months and 28.8 months for the subgroup of patients able to undergo secondary local treatment. These results appear to be better than those obtained for patients with metastatic disease at diagnosis, for whom recent studies have reported a median survival of 9 months [12-14].

Our study is retrospective, and so, results are limited. The fact that RCT was the first-line treatment in only six patients is explained by historical consideration. At the end of 90’s, treatment strategies for LAPC in our center have changed for two main reasons: first, many patients developed distant metastases during RCT, and, second, control of abdominal pain was allowed by the development of morphine alcaloids without use of radiotherapy. As early as 2000, our treatment strategy began by chemotherapy in all patients with LAPC. Nevertheless, our results suggest that chemotherapy may be the best option in first-line for LAPC.

### Table III – Characteristics of treatment received by patients who had a secondary resection.

Détail des traitements reçus par les malades ayant été opérés secondairement.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
<th>Delay between diagnosis and surgery</th>
<th>Type of surgery</th>
<th>Results of surgery on pathological examination</th>
<th>Adjuvant treatment</th>
<th>Delay between surgery and relapse</th>
<th>Last follow-up (status and delay since diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 years</td>
<td>Gemcitabine, 7 cycles, partial response</td>
<td>-</td>
<td>8 months</td>
<td>CDP</td>
<td>pT3N0 (0/10) R0</td>
<td>-</td>
<td>36 months</td>
<td>Recurrence at 44 months and Alive at 63 months</td>
</tr>
<tr>
<td>62 years</td>
<td>Gemcitabine, 8 cycles, partial response</td>
<td>RCT (45 Gy and 5FU)</td>
<td>12 months</td>
<td>CSP</td>
<td>pT4N0 (0/27) R0</td>
<td>-</td>
<td>2 months</td>
<td>Recurrence at 14 months and Alive at 30 months</td>
</tr>
<tr>
<td>39 years</td>
<td>GemOx, 5 cycles, stable disease</td>
<td>-</td>
<td>4 months</td>
<td>CSP</td>
<td>pT2N0 (0/46) R0</td>
<td>GemOx 6 cycles</td>
<td>No relapse</td>
<td>Alive without recurrence at 31 months</td>
</tr>
</tbody>
</table>

RCT: radio-chemotherapy
CDP: cephalic duodenopancreatectomy
CSP: caudal splenopancreatectomy

Two phase III clinical trials have compared RCT and chemotherapy as first-line treatments for LAPC. In 1977, the Eastern Cooperative Oncology Group (ECOG) Study compared weekly bolus 5FU with RCT (40 Gy plus weekly bolus 5FU) followed by bolus 5FU in patients with LAPC; median survival was similar in the 2 groups (CT: 8.2 and RCT: 8.3 months). Toxicity was higher in RCT group [16]. A Gastrointestinal Tumour Study Group (GITSG) trial, compared SMF (streptozocine, mitomycin and bolus 5FU) chemotherapy with RCT (54 Gy and bolus 5FU) followed by SMF; median survival seemed higher in the RCT group (42 vs 32 weeks) with a tendency towards higher toxicity [6]. These two trials were in favor of RCT, however they were small and carried out more than 20 years ago using chemotherapy protocols which were not demonstrated to be effective [17], whereas current chemotherapy protocols based on platinum salts and gemcitabine have been shown to be more effective [12-14]. As for chemotherapy, the RCT regimens used in these trials cannot be compared with present regimens. Now, currently conformational radiation is used and concomitant chemotherapy includes continuous 5FU and cisplatin or gemcitabine [10, 18, 19]. In the future, development of new drugs could improve the results of RCT. Encouraging results were observed in squamous-cell carcinoma of the head and neck treated with a strategy based on the use of optimal chemotherapy, resulting in tumor control in almost two thirds of patients [12, 13] and combined with local treatment carried out in cases of good TGC seems a valid option. Nevertheless, in our study, only one third of patients had been able to have a “consolidation RCT” with such a strategy. Interestingly, in a phase III study, Louvet et al. have reported a similar rate after gemcitabine or GemOx in first-line treatment (respectively, 33.3% and 40%) [14].

Our study, as previous studies [10, 23], confirms that in cases of a objective response and significant regression of tumor volume, patients may undergo potentially curative surgery. In other cases, “consolidation” RCT after chemotherapy may allow patients a break from treatment, thereby improving their quality of life.

The place of RCT in the treatment of patients with LAPC could therefore be re-evaluated, as it was the case for adjuvant treatment for which Neoptolemos et al. showed that survival was higher for chemotherapy than for RCT [24]. Radio-chemotherapy may be a very attractive option for patients with good TGC, after initial chemotherapy. Only prospective trials could answer to this important question.

REFERENCES