Anti-Tumour Treatment

Neoadjuvant therapy in resectable pancreatic cancer: A critical review

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S U M M A R Y

Background: Pancreatic cancer is among the deadliest tumors. Due to intrinsic chemotherapeutic agents 7,8 The use of adjuvant chemoradiation therapy is highly controversial with a few randomized clinical trials showing conflicting results, ranging from a significant improvement 9 to only a small benefit, 10 to a detrimental impact on OS. 6 Altogether, available data show that surgery followed by adjuvant treatment yields disappointing outcome figures in patients with resectable pancreatic cancer. Due to the high mortality and morbidity risk of pancreatic surgery and, accordingly, to the narrow therapeutic window, the neoadjuvant approach has a strong theoretical rationale in this disease, but limited information on the efficacy of this strategy is available.

Data from randomized phase III trials have shown that adjuvant chemotherapy with 5-FU/FA 6 and with gemcitabine 4 provide a modest improvement in median survival of 1.9–4.7 months and of 6–10% in 2-year overall survival (OS) compared to pancreatic resection alone with no significant difference between these two chemotherapeutic agents. 7,8 The use of adjuvant chemoradiation therapy is highly controversial with a few randomized clinical trials showing conflicting results, ranging from a significant improvement 9 to only a small benefit, 10 to a detrimental impact on OS. 6

Altogether, available data show that surgery followed by adjuvant treatment yields disappointing outcome figures in patients with resectable pancreatic cancer. Due to the high mortality and morbidity risk of pancreatic surgery and, accordingly, to the narrow therapeutic window, the neoadjuvant approach has a strong theoretical rationale in this disease, but limited information on the efficacy of this strategy is available.

This review critically overviews the current knowledge, the rationale, the available data and information on neoadjuvant treatment in resectable pancreatic cancer.

Conclusion: Currently there is no straightforward evidence to support the routine clinical use of this strategy. Only a properly designed randomized trial testing combination chemotherapy regimens selected on the basis of their efficacy and activity against metastatic disease can address this issue.

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Introduction

Pancreatic cancer is an aggressive tumor and only 10–20% of patients are considered candidates for curative resection at diagnosis 1,2 because surgery is possible only in the absence of distant metastases, peritoneal carcinomatosis, and lack of involvement of celiac axis and superior mesenteric artery. Due to intrinsic chemo- and radio-resistance, surgical resection is considered as the only therapy that may have an impact on the natural history of this disease and may increase chance for cure. However, surgical resection alone results in a very modest median overall survival of around 20 months due to the high rate of relapse. 3,4 A recent report on long-term survival after pancreatectoduodenectomy gave a dismal outlook with low 5- and 10-year survival rates of 18% and 13%, respectively. 5 These data clearly demonstrate that surgery alone is unable to considerably improve survival of patients affected by pancreatic cancer and hence other complementary treatments such as chemotherapy and radiotherapy in a multimodal approach have been tested.

Rationale for preoperative therapy

Neoadjuvant treatment may offer several theoretical advantages over adjuvant approach. Pancreatic cancer should be considered as a systemic disease “ab initio” due to the presence of
micro-metastatic disease in lymph nodes, liver, peritoneum and lung at time of diagnosis, which is responsible for most of the early relapses after curative surgery. Pre-operative chemotherapy timely addresses the undetected part of the disease thus avoiding the delay of at least 2 months between diagnosis and start of post-operative chemotherapy, which usually occurs due to surgical waiting list and time for postoperative recovery for patients submitted to upfront surgery. Furthermore, a larger proportion of patients may receive the treatment compared to the adjuvant setting. In fact, about a quarter of patients submitted to curative resection do not receive the planned postoperative treatment due to the surgical complications, poor performance status, comorbidity, patient refusal, and early disease recurrence. In addition, the treatment itself may be tolerated much better, resulting in a higher rate of treatment compliance and improved dose-intensity. Another potential advantage is that neoadjuvant treatment may reduce intraoperative tumor spillage thus reducing the risk of peritoneal tumor cell implantation during surgery. The administration of chemotherapy before surgery also allows an in vivo assessment of tumor chemosensitivity. Finally, neoadjuvant treatment may also lead to more definitive surgical resections by reducing the risk of tumor infiltration of lymph nodes and of resection margins in the surgical specimen.

Conversely, neoadjuvant approach raises several concerns among detractors such as inaccuracy of staging and consequently the risk of overtreatment of very early disease; erroneous histology; diagnostic imprecision due to difficulties in distinguishing between intra-pancreatic bile duct adenocarcinoma and pancreatic adenocarcinoma; increase in operative morbidity and mortality; and the possibility that the disease might metastasize or become unresectable during the course of induction therapy. The first topic appears of little relevance in pancreatic cancer since systemic treatment is virtually recommended at any stage of disease, with the possible exception of stage I, which is exceedingly rare. Currently, the widespread and systematic use of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (EUS-FNA) considerably reduces the risk of inaccurate pathological diagnosis. Regarding surgical complications, no increase in morbidity or mortality after neoadjuvant therapy has been reported in previous trials.

On the other hand, the concern for disease progression during pre-surgical treatment is not negligible due to the low rate of curative resections performed among patients whose disease was deemed resectable at the time of start of neoadjuvant therapy both after induction chemoradiation (45–74%) and after induction chemotherapy (38–70%). However, advocates of neoadjuvant therapy claim these data as an advantage of this strategy, arguing that the patients who experience disease progression during induction treatment suffer from an extremely aggressive tumor, which cannot be cured by extensive surgery. It might be appealing to avoid the risk of surgical mortality and morbidity in this subset of patients, but not necessarily for patients experiencing only local progression during neoadjuvant therapy. But there is not randomized trial comparing different management strategies in order to confirm a detrimental impact of delaying surgery. Also, the proper goal of pre-operative therapy should be that of downstaging the disease thereby improving both cure rate and disease control, rather than improving patient selection for surgery.

Studies of neoadjuvant treatment in resectable pancreatic cancer

Since the early eighties, several clinical trials have evaluated the role of neoadjuvant radiotherapy, chemotherapy, or various combinations of these therapeutic modalities in resectable pancreatic cancer. For the purposes of this review, prospective, retrospective and cohort studies, meta-analyses and pooled analysis focusing on neoadjuvant therapy of treatment-naive patients with pancreatic adenocarcinoma were considered. Articles from which separate results of resectable, borderline and unresectable tumors or of pancreatic and periampullary tumors were not retrievable, were excluded. Studies to be considered for this review were identified by a Medline search of articles published between January 1992 and December 2011. The search strategy included the following key words: (“pancreas” or “pancreatic”) and (“cancer” or “neoplasm” or “carcinoma” or “adenocarcinoma”) and (“neoadjuvant” or “preoperative”) and (“radiation” or “chemotherapy” or “chemoradiation” or “target therapy”) and (“resectable”). No language restrictions were applied. Manual searching for eligible studies to capture missing studies that met our inclusion criteria was performed by reading through reference lists of relevant articles. Furthermore, the ClinicalTrials.gov database was explored to identify prospective ongoing trials.

Radiotherapy

The role of neoadjuvant radiation therapy in pancreatic cancer patients has been rarely addressed. A retrospective study evaluated the role of neoadjuvant radiotherapy compared to upfront surgery in 54 consecutive patients during the period of 1985–1989, in whom pancreatic cancer was deemed to be resectable by preoperative imaging technique. Out of 54 patients, 23 (43%) received preoperative radiotherapy before surgery (group A) while the remaining 31 (57%) went directly to laparotomy (group B). The indication for preoperative irradiation was determined by the consent of both the patients and their family. Surgery was possible in 17 patients (74%) in group A and 19 patients (61%) in group B. The median survival of all patients was 15 months in group A and 11 months in group B. No significant difference in OS was observed: 2- and 3-year survival rates were quite similar in both groups (30% vs. 24% and 22% vs. 19%, respectively). Similar results were observed in the subset of resected patients. In fact, there was no difference in 3- and 5-year rates between two groups (28% vs. 32%, and 22% vs. 26%, respectively). A lower rate of loco-regional recurrences was reported among patients receiving neoadjuvant irradiation albeit this had no impact on long term survival due to the prevalence of systemic failure.

While the retrospective nature and the small sample size do not allow drawing firm conclusions, these data confirm that the pattern of failure of pancreatic cancer, even at early stages, is characterized by a tendency to metastasize at distant sites. Accordingly, a local therapy might not be sufficient to have an impact on the natural history of the disease.

Radiotherapy concomitant to mono-chemotherapy

Starting in the early 1990s, several trials addressed the feasibility and the efficacy of radiotherapy concomitant to chemotherapy as upfront therapeutic management of resectable pancreatic cancer (Table 1). Chemotherapy with 5FU (300 mg/m²/day) concomitant to radiation therapy (50.4 Gy given over 5.5 weeks) was administered to 28 patients with resectable pancreatic cancer. Combined treatment was poorly tolerated due to gastrointestinal toxicity requiring hospitalization in 9 (32%) patients. A total of 17 patients (61%) underwent to curative surgery. None of the patients showed partial response (PR). Perioperative complications occurred in 3 patients (18%) and 1 patient (6%) died postoperatively from myocardial infarction. These data suggested that neoadjuvant chemoradiation does not appear to increase the risk of pancreaticoduodenectomy morbidity and mortality. On the other hand, this small series raises
remarkable concern due to the high rate of initially resectable patients who were not submitted to curative surgery. The same group also tested a rapid fractionation chemoradiation (30 Gy in 2 weeks in combination with 5FU at the same dosage of the previous study), in the attempt to reduce the delay of surgery.20 The modified schedule was better tolerated and, only 3 patients (9%) out of 35 patients enrolled in this study experienced grade 3–4 toxicity. However, only 20 of 35 (57%) patients were submitted to pancreaticoduodenectomy, thus confirming the disappointing resectability rate of the previous study (61%). The median OS of the subset of resected patients was 25 months, while the median OS of non-resected patients was only 7 months. Altogether, these results do not appear to be promising when compared to the outcome of series submitted to surgery alone.

A retrospective study11 compared the role of preoperative vs. postoperative chemoradiation in patients treated with curative intent over a 5-year period at M. D. Anderson Cancer Center. Altogether, 142 patients having cancer of pancreatic head or peripancreatic region, whose tumors were deemed to be resectable on the basis of pre-treatment CT images, were included in this study. The patients’ selection for preoperative chemoradiation was based on a pre-defined protocol which required a pathologic confirmation of adenocarcinoma and the presence of a low density mass in the pancreatic head on CT scan. Conversely, patients not fulfilling these criteria immediately underwent surgery. A total of 91 patients were treated by preoperative chemoradiation using 5FU and a heterogeneous radiotherapy schedule, including intra-operative radiotherapy (IORT) in 68% of cases. Also in this series, the rate of pancreaticoduodenectomy was disappointingly low as only 52 (57%) patients underwent curative surgery. Among the remaining 51 patients who were referred to immediate surgery, 9 (18%) were found to have unresectable disease intra-operatively, 25 (48%) had pancreatic adenocarcinoma while 17 (33%) were found to have no-primary pancreatic tumors (duodenum, ampulla, distal biliary tract cancers). Adjuvant therapy was administered in 19 of the 25 patients with pancreatic adenocarcinoma as 6 of them had a delayed postoperative recovery or bad performance status after pancreaticoduodenectomy. No OS difference was reported between the subset of 41 patients completing the whole neoadjuvant protocol and that of 19 patients completing the whole adjuvant protocol. However, the results of this study are extremely difficult to interpret due to its retrospective nature, to the divergent group-allocation criteria, to the intra-group heterogeneous therapy and staging procedures, and to the lack of information on the outcome of the whole population.

More recently, neoadjuvant chemotherapy with gemcitabine concomitant to radiation has been tested in resectable pancreatic cancer.14 The rationale derives from in vitro studies in which this drug showed to have radiosensitization properties in pancreatic cancer cell lines.21 Eighty-six patients were enrolled in a large study cohort and received neoadjuvant gemcitabine at 400 mg/m2 once a week for 7 weeks concomitant to radiation therapy (30 Gy in 10 fractions in weeks 2 and 3).14 Pancreaticoduodenectomy was performed in 64 patients (74%). Median survival was 22.7 months for the whole study and 34 months for the 64 patients who underwent surgery. Fifty-seven patients (86%) had R0 resection, 40 (61%) had negative lymph nodes, and 13 (20%) of them underwent to vascular resection that may suggest a local progression of the disease during neoadjuvant treatment. Local failure developed in 7 patients (8%), while distant failure in 55 of cases (64%). Grade 3 and 4 toxicity in this trial consisted of granulocytopenia 30%, neutropenic fever 2%, fatigue 31%, anorexia 11%, nausea 16%, emesis 18%, stent occlusion 18% and increased transaminases levels 10%, but all the patients concluded the planned treatment and no toxic death occurred. Major surgical complications were observed in 6 patients (9%) and were not linked to preoperative treatment. This trial shows that this approach is safe and feasible while OS figures are difficult to interpret due to the lack of a comparative arm. Paclitaxel22 and tegafur23 were also tested concomitantly to radiotherapy in resectable pancreatic cancer patients. Paclitaxel (weekly 3-h infusion of 60 mg/m2 for 3-consecutive weeks) concomitant to radiotherapy (30 Gy; 3 Gy/Fx × 10 Fx) was administered to a small cohort of 35 patients without yielding promising results neither in terms of median survival (19 mo) nor in terms of toxicity (46% grade 3 toxicity; 11% hospitalization for dehydration due to grade 3 nausea and vomiting), when compared to the historical experience of the same group with 5FU-based neoadjuvant chemoradiation.22 Oral tegafur was administered at the dose of 1200 mg/d in combination with radiotherapy (45–50 Gy)33 to a cohort of 15 patients. Only 9 (60%) patients underwent to pancreaticoduodenectomy yielding a median survival of 23 months whereas the median survival for the whole population was 17 months. The small sample size and the use of IORT boost hamper the interpretation of results.

Polychemotherapy in combination with radiotherapy

Combination chemotherapy concomitant to radiation has also been tested (Table 2). 5FU (1000 mg/m2/d continuous infusion on days 2–5 and 29–32) and mitomycin C (10 mg/m2 on day 2) combined with 50.4 Gy of radiation were tested in a pilot study involving 34 patients with localized pancreatic adenocarcinoma.24 Only one third of patients (N = 11; 32%) underwent pancreatic resection.
Despite this very disappointing result, Eastern Cooperative Oncology Group (ECOG) conducted a phase II trial on 53 patients confirming the previous results: 24 patients (45%) were submitted to pancreatic resection. The median survival for the entire population was 9.7 months, which is inferior to that expected with surgery alone.

The results of 5FU-cisplatin combination were retrospectively reported. Altogether, 62 (61%) out of 102 patients with initially resectable pancreatic head adenocarcinoma treated with this combination in 10 years underwent pancreatic resection. The median survival for the resected patients and whole population was 23 months and 17 months, respectively, which appears worse than in series treated with adjuvant therapy. Similarly, a prospective phase II study with this combination failed to produce any promising result: out of the 41 treated patients, 26 (63%) underwent pancreatic resection, the median survival was 11.7 months for the resected patients and 9.4 months for the whole population suggesting a possible detrimental effect with this approach.

Chemotherapy

The very early systemic dissemination of pancreatic cancer endorses the rationale for an up-front use of systemic therapy. Accordingly, the administration of chemotherapy alone (Table 3) or followed by chemoradiation (Table 4) was also prospectively assessed.

An exploratory phase II trial randomized patients with resectable pancreatic cancer to receive either gemcitabine alone or gemcitabine-cisplatin combination in order to identify the most promising regimen for future study. Dose-intensity and toxicity profile were superimposable in both arms. No complete response was obtained in any arm; PR was observed in 4% of patients treated with combination chemotherapy and in none of those that received gemcitabine only. Nine patients (38%) in the gemcitabine arm and 18 (70%) in the combination arm underwent curative resection, without differences in terms of surgical complications. Histology showed that 12% of patients treated with gemcitabine and in 19% treated with gemcitabine plus cisplatin did not have a pancreatic adenocarcinoma. The median survival was poor: 9.9 months in gemcitabine arm and 15.6 months in combination arm. Given the small sample size and the high rate of diagnostic mistakes, these results are difficult to interpret but do not appear encouraging.

Similar results were also reported in another prospective phase II trial. In this single arm trial, 28 patients with cytologically proven resectable pancreatic head adenocarcinoma received four biweekly cycles of gemcitabine and cisplatin. Adverse events were mild and mainly consisted of grade ≤ 3 gastrointestinal and hematologic toxicity. At restaging, 2 patients had peritoneal metastases. At surgical exploration, one patient was found to have unresectable disease because of infiltration of the mesenteric axis. Twenty (71%) patients had an R0 resection and 5 (18%) an R1 resection. The median survival for the whole series was 26.5 months on intention-to-treat (ITT) analysis, while it was 19.1 months for patients who underwent successful resection.

Chemotherapy followed by chemoradiation therapy

Another approach tested in resectable pancreatic cancer patients was the sequential treatment, first using induction chemotherapy followed by chemoradiation therapy (Table 4).

The impact of sequential chemotherapy with gemcitabine and cisplatin, followed by gemcitabine-based chemoradiation was assessed in a phase II study on 90 patients with resectable pancreatic cancer, based on the better activity of this doublet compared to single agent gemcitabine in advanced disease. Again, only 52 patients (58%) underwent curative surgery and the median survival for the whole series was 17.4 months which appears inferior to the results reported with surgery alone in modern series.

In another phase II trial, 20 patients were treated with three cycles of gemcitabine (1000 mg/m² intravenously) and radiotherapy (36 Gy in 15 fractions delivered during the second cycle). Pancreatic resection was done in 17 (85%) patients. The median and 2-year OS for 17 patients treated with surgery were 26 months and 61%, respectively, while survival data for the whole population were omitted. Only three patients (15%) showed partial response and no complete response was observed at radiological exam. Five of the resected patients (29%) had vascular resection. At pathological analysis of pancreatic specimens, 1 (5%) did not contain residual tumor, and 3 (15%) had only microscopic foci of residual disease.

The results of chemotherapy, followed or not by chemoradiation, suggest that a poorly active combination chemotherapy which did not show superiority against single agent gemcitabine in the context of advanced disease has also a limited role in the neoadjuvant treatment of resectable pancreatic adenocarcinoma because of the low rate of downstaging, of the weak activity against microscopic disease and of the high rate of tumor progression. In fact, the apparent advantage in survival of chemoradiation over systemic chemotherapy followed by the same chemoradiation regimen may be related to the shorter duration of an ineffective therapy.

Targeted therapies in pancreatic cancer

During the last years the improvement in the knowledge of pancreatic cancer biology and the development of new drugs have made possible to test new targeted agents in PC. Several drugs like epidermal growth factor (EGFR) receptor inhibitors, vascular endothelial growth factor (VEGF) inhibitors, matrix metalloproteinase inhibitors, and insulin-like growth factor receptor (IGF-IR) inhibitors were

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### Table 2

Neoadjuvant trials of polychemotherapy in combination with radiotherapy.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Population</th>
<th>Rate of resectability N (%)</th>
<th>Node negative N (%)</th>
<th>R0 resection N (%)</th>
<th>Local failure N (%)</th>
<th>Distant failure N (%)</th>
<th>Median survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman24</td>
<td>5FU + MMC</td>
<td>50.4 Gy/S</td>
<td>53</td>
<td>24 (45)</td>
<td>19 (36)</td>
<td>11 (20)</td>
<td>12 (22)</td>
<td>36 (68)</td>
<td>9.7</td>
</tr>
<tr>
<td>Moutadier25</td>
<td>5-FU + CIS</td>
<td>45 Gy/S</td>
<td>61</td>
<td>40 (66)</td>
<td>30 (49)</td>
<td>37 (60)</td>
<td>2 (3)</td>
<td>41 (67)</td>
<td>20</td>
</tr>
<tr>
<td>Magnini26</td>
<td>5-FU + CIS</td>
<td>45 Gy/S or 15 Gy-SC</td>
<td>32</td>
<td>19 (59)</td>
<td>7 (22)</td>
<td>7 (22)</td>
<td>5 (16)</td>
<td>11 (34)</td>
<td>16</td>
</tr>
<tr>
<td>Turinii27</td>
<td>5-FU + CIS</td>
<td>45 Gy/S</td>
<td>102</td>
<td>62 (61)</td>
<td>47 (46)</td>
<td>57 (56)</td>
<td>18 (18)</td>
<td>65 (64)</td>
<td>17</td>
</tr>
<tr>
<td>Mornex28</td>
<td>5-FU + CIS</td>
<td>50 Gy/S</td>
<td>41</td>
<td>26 (63)</td>
<td>11 (27)</td>
<td>21 (80)</td>
<td>9 (22)</td>
<td>31 (75)</td>
<td>9.4</td>
</tr>
</tbody>
</table>

* Abbreviations: 5-FU: 5 Fluorouracil; CIS: cisplatin; MMC: mitomycin C; S: standard fractionation regimen; SC: split course, NR: Non Resected.

b Resection margins were analyzed in 21 restected patients.

c Three patients with local recurrence also had distant recurrence.
tested in advanced disease with disappointing results.\textsuperscript{32–35} Nevertheless, several prospective clinical trials using targeted agents in the neoadjuvant therapy for resectable disease are ongoing.

A couple of phase II clinical trials are evaluating the role of tyrosine kinase inhibitor (TKI) erlotinib in combination with chemotherapy with or without radiotherapy in patients affected by stage I–II pancreatic cancer (NCT00733746 and NCT01389440). A multicenter study conducted by the American College of Surgeons (NCT00733746) is evaluating a combination of gemcitabine administered on days 1, 8, 15, 29, 36 and 43 in combination with oral erlotinib once daily on days 1–43 in patients with potentially resectable pancreatic cancer. In absence of disease progression or unacceptable toxicity at 3–6 weeks after completion of neoadjuvant therapy, patients will undergo surgery and after 5–10 weeks they will begin adjuvant chemotherapy with the same drugs administered using the same schedule of preoperative treatment. The primary endpoint of this study is the estimation of the proportion of patients alive at 2 years from the study enrolment. Secondary endpoints consist in evaluation of resection rate, the rate of R0, R1, and R2 resection and the toxicity profile of chemotherapy combined with targeted therapies. This study will also evaluate the role of molecular profiling by assessing the epithelial-mesenchimal (EMT) markers and EGFR intron 1 polymorphism, and will identify the genetic profile by RNA analysis, which could predict the resection rate, the rate of R0 resection and the rate of pathological complete response after neoadjuvant therapy to establish if this regimen merits further development.

A phase II study is evaluating the role of anti-VEGF monoclonal antibody bevacizumab in potentially resectable pancreatic cancer patients (NCT005557492). This is a 2-stage study of bevacizumab plus gemcitabine, administered as fixed dose rate, in combination with sequential rapid fractionation radiotherapy (30 Gy) in neoadjuvant setting. The purpose of this study is to determine the rate of R0 resection and the rate of pathological complete response after neoadjuvant therapy to establish if this regimen merits further studies in a phase III trial.

Considering the disappointing results of studies using targeted therapy in advanced pancreatic cancer,\textsuperscript{32–35} there is very little hope that these drugs could affect the natural history of this disease. However, using these drugs could possibly permit to understand their mechanism of action in vivo and ultimately could help to select a group of patients that might benefit from these therapies.

### Discussion

Despite the numerous theoretical benefits that it holds, there is currently no straightforward evidence to support the routine clinical use of neoadjuvant therapy in resectable pancreatic cancer. In fact, several single arm studies have reported a median survival ranging from 8 to 23 months and 2-year OS rate from 27% to 40%.\textsuperscript{12–17,22,26} These figures are of the same order of magnitude than those achieved in modern series of patients undergoing surgery alone.\textsuperscript{3,4} (median survival 18–20 months; 2-year OS 40–42%) and appear worse than those observed in series of patients treated with single agent chemotherapy\textsuperscript{3,4,7,8} (median survival 21–25 months, 2-year OS 41–48%) or with combination chemotherapy\textsuperscript{37–39} (median survival 25.4–32.1 months; 2-year OS 59–62%) as adjuvant treatment. A recent systematic review and meta-analysis of 111 controlled trials confirmed that neoadjuvant treatment does not seem to provide any benefit over the adjuvant therapy in resectable pancreatic cancer.\textsuperscript{40} However, inter-trial comparisons, which already have many serious limitations, in this particular case are also hampered by the fact that the typical population enrolled in adjuvant trials is better selected than in neoadjuvant trials. For example, patients in which metastatic disease is detected intraoperatively or at the time of post-surgical re-staging or those who die perioperatively are enrolled in neoadjuvant trials but are not eligible for adjuvant trials. Similarly, patients who do not recover after surgery or who refuse postoperative treatment are also excluded from adjuvant trials.

Apart from difficulties in the interpretation of trials results, hypothetical causes of disappointing results of the neoadjuvant approach include methodological issues and strategy issues. Retrospective series, single arm trials without a control or a calibration arm, randomized phase II trials with limited sample size, the lack of a confirmed pathological diagnosis, the incomplete data reporting, different enrolment timings, divergent study design and entry criteria, and population heterogeneity do not allow to properly explore the role of neoadjuvant therapy in resectable pancreatic cancer.

To answer the question on the role of neoadjuvant therapy in resectable pancreatic cancer and to produce an evidence-based rationale supporting the routine use of this strategy, there is no alternative to properly designed randomized trials. Patients should
be randomized to receive exactly the same treatment for the same amount of time before and after surgery to avoid interpretative bias related to different treatment duration or treatment regimen.

From the therapeutic strategy point of view, the choice of local therapy such as chemoradiation, or of chemotherapy regimens which achieve a low rate of tumor shrinkage against advanced disease unlikely may have a remarkable impact against early micro-metastatic disease. In fact, single agent gemcitabine and 5FU obtained a very low objective response of around 10%\(^\text{41-42}\) while chemotherapy combination yielded 9–28% of responses in advanced disease.\(^\text{43-47}\)

Interestingly, the response rate was increased by using more than two chemotherapeutic agents in advanced pancreatic cancer: triplets including gemcitabine, a fluoropyrimidin and either a platinate agent (18–41%)\(^\text{48-51}\) or docetaxel (29%),\(^\text{52}\) FOLFOXIRI triplets including gemcitabine, a fluoropyrimidin and either a gemcitabine or cisplatin)/(gemcitabine-lipiodol-irinotecan; 72–32%)\(^\text{53,54}\) and G-FLIP (gemcitabine-5FU-irinotecan-cisplatin; 26%\(^\text{55}\) regimens showed promising results in phase II series.

Similarly, four drug combinations, PEGF (cisplatin, epirubicin, 5FU, gemcitabine)\(^\text{56-60}\) PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) and PDXG (cisplatin, docetaxel, capecitabine, gemcitabine) and PDXG (cisplatin, docetaxel, capecitabine, gemcitabine) yielded a radiological response rate in the range of 38.5–51%. The reliability of the response rate was also supported by a concordant biochemical response rate. In effect, a major biochemical response (i.e. CA19.9 reduction at nadir relative to baseline value reduction \(>90\%\)) was observed in 30% of patients treated with quadruplets versus 7% with single agent gemcitabine.\(^\text{61}\) The superiority of this four-drug combination over other regimens was also suggested by a recent survey on treatment trends and outcomes of 650 patients with stage III and on 943 patients with stage IV pancreatic adenocarcinoma.\(^\text{62,63}\) Based on these data and considerations, 3- or 4-drug regimens are suitable candidates and deserve a prospective assessment in the neoadjuvant setting.

Conclusion

More than two decades of active research have not as yet defined the role of neoadjuvant therapy in resectable pancreatic cancer. However, evidence collected so far depends on retrospective data, small case series and approaches that did not balance the different characteristics of patients suitable for surgery before or after neoadjuvant chemotherapy. Only the use of the most active combination chemotherapy regimens within a properly designed randomized controlled trial can properly address the issue of the benefits of the neoadjuvant strategy with respect to the conventional adjuvant approach. A multicenter prospective randomized three arms phase II–III trial (NCT01150630) is currently underway in Italy with the goal of defining the role of either perioperative or postoperative PEXG regimen as compared to adjuvant gemcitabine in the therapeutic management of patients with resectable pancreatic cancer.

Conflict of interest

There are not financial or commercial interests or relationships that may pose conflict of interest.

Author contributions

Dr. Michele Reni conceived the paper, contributed to drafting the article and critically reviewed the data and the final version. Dr. Stefano Cereda and Dr. Santosh Anand contributed to the analysis and interpretation of data. Dr. Carmen Belli drafted the article and revised it critically for important intellectual content. All authors approved the final version.

This article is dedicated to the memory of Steve Jobs whose life was unfortunately cut short by Pancreatic Cancer.

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