

Meta-Analysis and Randomized Trials: Chemotherapy for Advanced Pancreatic Cancer

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Abstract

Pancreatic cancer has an extremely poor prognosis and prolonged survival is achieved only by resection with macroscopic tumor clearance. There is a strong rationale for a neoadjuvant approach, since a relevant percentage of pancreatic cancer patients present with non-metastatic but locally advanced disease and microscopic incomplete resections are common. The objective of the present analysis was to systematically review studies concerning the effects of neoadjuvant therapy on tumor response, toxicity, resection, and survival percentages in pancreatic cancer.

No common malignancy is as rapidly and inevitably fatal as pancreatic ductal adenocarcinoma (PDA). This grim fact has driven substantial research efforts into this disease in recent decades. Unfortunately, the investment has yet to result in a meaningful increase in 5-year survival. This has prompted many pancreatic cancer researchers and advocates to redouble their efforts, but also requires one to step back and ask why the previous efforts were lacking and to consider why pancreatic cancer is so difficult to treat. The difficulties are legion. PDA is characterized by an insidious clinical syndrome, but is rarely diagnosed at a time when surgical resection is feasible. We lack markers of early detection and screening programs remain unproven even in high risk populations.

The location of the tumor in the retro peritoneum, the advanced age of patients, and the systemic effects of disease limit the options for local therapy. Chemotherapy may provide a small benefit, but most efforts to improve on the current regimens consistently and stubbornly fail in advanced clinical trials. The molecular and cellular features of ductal pancreatic tumors are aggressive and underlay multiple levels of therapeutic resistance. Non-cell-autonomous features including stromal proliferation, reduced vascular density and immune suppression also contribute to therapeutic resistance. Growing awareness of these the fundamental features of PDA has begun to guide ongoing research efforts. Clinical trials are now specifically targeting these tumor properties and actively focusing on the therapeutic implications of tumor stroma. As reviewed here, reflecting on the fundamental question of why pancreatic cancer is so difficult to treat is a necessary and informative exercise that will aid our efforts to improve patient outcomes. These efforts will lead to improvements in clinical trial design, expand our focus to include the molecular and histologic implications of novel treatment paradigms, and ultimately change the lives of our patients.

Keywords

pancreatic cancer, chemotherapy resistance, Meta-Analysis

Introduction

In the modern era of cancer research, pancreatic ductal adenocarcinoma (PDA) has proven to be among the most unyielding of adversaries. The oncology community has expended its entire arsenal at this disease with little effect: the 5-year survival rate has ticked up to 6% over the past 40 years, but nearly all diagnosed patients ultimately succumb to the disease. An estimated 37,390 people will die of pancreatic cancer in the US in 2012 with a similar pattern in the rest of the developed world. Over 80% of them will be found to have unresectable tumors at diagnosis giving them an expected overall survival of just 6 months. There are few therapeutic options for these patients and the most efficacious are also the most burdensome. Those who do undergo surgery improve their overall survival compared with patients of a similar stage by about 10 months but must tolerate significant morbidity and face almost inevitable recurrence. Given the slow progress against this disease, one must ask the question 'why is pancreatic cancer so hard to treat'.

The particular problem of pancreatic cancer is multifactorial in its nature. The patient population in PDA is predominantly elderly and in poor overall health. There is no simple early detection method for pancreatic cancer and the earliest indications of disease are nonspecific.

The tumor itself has its own peculiarities. For example, it has become apparent that PDA metastasizes microscopically early in the disease course, limiting the effectiveness of local therapies such as surgery and radiation. At the cellular level, the actual neoplastic epithelial cells at the heart of the disease harbor some of the most profoundly oncogenic alterations known to biology, and these are found at unusually high frequencies in PDA. In addition to driving growth and promoting cell survival, these alterations alter the metabolism of pancreatic cancer to one that can better support the manufacture of new cellular components. Layered on top of these high penetrance mutations is a host of rare alterations that are found in effectively unique combinations in each patient. The extent of genetic alterations in pancreatic tumors bears witness to a genomic instability phenotype that appears to play a significant role in the biology of PDA and implies an ability to rapidly develop acquired resistance to therapies that do manage to provoke an initial response. In addition to features of the tumor epithelium, PDA harbors a dense, desmoplastic stroma that can serve to limit the delivery of agents to tumors and foreshadows an incredibly complex interplay of intercellular signals that confound our ability to study the disease *in vitro*. Certain cell types within this stroma construct an immune-suppressed microenvironment that prevents the local immune system from clearing the tumor.

Finally, PDA manifests as a syndrome, not just a mass, with systemic comorbidities that have a profoundly negative impact on quality of life.

Together, these raw observations paint a grim picture of the battle against pancreatic cancer that has at times led to a sense of nihilism. In reality, there are many signs that the research efforts of the past few decades have altered the momentum of this battle. Each of the challenges listed above has, in recent years, been the subject of intense research, leading to new ideas that are now being developed in the lab and in the clinic. For example, an understanding of the dynamics of drug delivery in PDA has led to a focus on targeted agents with desirable pharmacological properties. Another approach is to target the tumor stroma directly in order to facilitate the delivery of genotoxic agents or relieve local immune suppression. Other agents take advantage of the hypoxic microenvironment conferred by the desmoplastic stroma, or specific metabolic dependencies. Furthermore, decades of failed trials have led to improvements in clinical trial design and in the diagnostic and interventional techniques used in patients. By addressing the manifold difficulties that underpin the challenge of pancreatic cancer, a new sense of optimism is apparent. These barriers are surmountable and the nascent efforts to address them will ultimately be reflected in improved patient outcomes.

Methods and Findings

Trials were identified by searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1966 to December 2009 as well as through reference lists of articles and proceedings of major meetings. Retrospective and prospective studies analyzing neoadjuvant radiochemotherapy, radiotherapy, or chemotherapy of pancreatic cancer patients, followed by re-staging, and surgical exploration/resection were included. Two reviewers independently extracted data and assessed study quality. Pooled relative risks and 95% confidence intervals were calculated using random-effects models. Primary outcome measures were proportions of tumor response categories and percentages of exploration and resection. A total of 111 studies ($n=4,394$) including 56 phase I–II trials were analyzed. A median of 31 (interquartile range [IQR] 19–46) patients per study were included. Studies were subdivided into surveys considering initially resectable tumors (group 1) and initially non-resectable (borderline resectable/unresectable) tumors (group 2). Neoadjuvant chemotherapy was given in 96.4% of the studies with the main agents gemcitabine, 5-FU (and oral analogues), mitomycin C, and platinum compounds. Neoadjuvant radiotherapy was applied in 93.7% of the studies with doses ranging from 24 to 63 Gy. Averaged complete/partial response probabilities were 3.6% (95% CI 2%–5.5%)/30.6% (95% CI 20.7%–41.4%) and 4.8% (95% CI 3.5%–6.4%)/30.2% (95% CI 24.5%–36.3%) for groups 1 and 2, respectively; whereas progressive disease fraction was estimated to 20.9% (95% CI 16.9%–25.3%) and 20.8% (95% CI 14.5%–27.8%). In group 1, resectability was estimated to 73.6% (95% CI 65.9%–80.6%) compared to 33.2% (95% CI 25.8%–41.1%) in group 2. Higher resection-associated morbidity and mortality rates were observed in group 2 versus group 1 (26.7%, 95% CI 20.7%–33.3% versus 39.1%, 95% CI 29.5%–49.1%; and 3.9%, 95% CI 2.2%–6% versus 7.1%, 95% CI 5.1%–9.5%). Combination chemotherapies resulted in higher estimated response and resection probabilities for patients with initially non-resectable tumors (“non-resectable tumor patients”) compared to monotherapy. Estimated median survival

Following resection was 23.3 (range 12–54) mo for group 1 and 20.5 (range 9–62) mo for group 2 patient

Results

Mean scale scores in the QLQ-C30 improved more often/deteriorated less frequently in the chemotherapy group than in the best supportive care group. More patients in the chemotherapy group (36%, 17/49) had an improved or prolonged high quality of life for a minimum period of months compared to those in the best supportive care group (10%, 4/41, $p < 0.01$).

Overall survival was significantly longer in the chemotherapy group (median 6 vs. 2.5 months, $p < 0.01$). Also, the quality-adjusted survival time was longer for patients randomized to chemotherapy (median 4 vs. 1 months, $p < 0.01$). The effects were seen both in pancreatic cancer.

Chemotherapy

Chemotherapy was applied as neoadjuvant treatment in 107 of the 111 studies (96.4%). Different combinations of chemotherapies/agents and dosages were tested, as 56 of the studies were phase I–II trials. The main agents were gemcitabine, 5-FU (and oral analogues), mitomycin C, and platinum compounds. In the trials that used only one regimen ($n=79$), 43 (54.4%) were performed using 5-FU or its oral analogues. 5-FU monotherapy was given in 14 (17.7%) of the studies. Thirty-six (45.6%) of the studies used a gemcitabine-based regimen, and of those, 18 (22.8%) studies applied gemcitabine monotherapy. 5-FU and gemcitabine combinations were used in 3 studies. Several studies compared different schemes or agents. Five studies were performed comparing gemcitabine with 5-FU or capecitabine, two studies comparing gemcitabine with cisplatin, two gemcitabine with 5-FU/cisplatin, and another three gemcitabine with 5-FU/mitomycin C. A further 16 studies included different agents and combinations (some for only few patients) Twelve trials included taxanes (docetaxel/paclitaxel) in different combinations or as monotherapy ($n=3$). Five of the 107 studies included antibodies or tyrosine kinase inhibitors (bevacizumab, cetuximab, erlotinib) in the chemotherapeutic regimen. There were 44 studies using single agents (alone or in comparison) and 48 studies using combination therapies. In 15 studies both single agents and combination therapies were utilized.

Radiotherapy

In 104 of the 111 studies (93.7%) patients received neoadjuvant radiotherapy. In three studies the exact radiation dose was not given. Doses applied ranged from 24 Gy to 63 Gy. In 52 of the 104 studies that included radiotherapy the patients received doses between 45 and 50.4 Gy. In 14 studies different doses and radiation schedules were compared. Most patients received 1.8 Gy/fraction (50/104 studies), 2 Gy/fraction (15/104), or 3 Gy/fraction (10/104). In 13 studies intraoperative radiation (IORT) was applied with doses between 10 and 30 Gy. Since in most of those studies only few patients received IORT, this aspect was not further analyzed.

Tumor Response

Tumor response frequency for neoadjuvant chemo- and/or radiation therapy was evaluated in the different studies according to either radiographic or clinical response evaluation before exploration or histopathological response after resection. Six studies (5.4%) explicitly stated that the RECIST criteria were utilized. In 44 studies (39.6%) the criteria to assess tumor response were clearly stated, whereas in 61 studies (55%) criteria were either not clearly defined or not stated. For the whole study population the estimated fraction of patients with complete response was 3.9% (CI 3%–4.9%) and with partial response 29.1% (CI 24.5%–34%). Stable disease was averaged to 43.9% (CI 37.9%–50%) in all patients and tumor progression under therapy occurred by estimation in 20.8% (CI 17.3%–24.6%) of the patients.

Discussion

This comprehensive review of neoadjuvant therapy in pancreatic cancer aimed to evaluate the key issues, including aspects of response and survival, and to highlight current problems and drawbacks. Neoadjuvant protocols have been analyzed with increasing frequency, as they offer a number of hypothetical advantages over adjuvant (postoperative) therapy, such as shorter therapy and higher therapy completion rates, tumor down-staging with higher (R0) resection rates, and importantly better patient selection. Thus, neoadjuvant treatment and reassessment may identify those patients (both initially resectable and non-resectable) presenting with rapid progressive or disseminated disease at restaging who therefore have a very poor prognosis and for whom surgery is unlikely to provide any benefit. On the other hand, there is the potential risk for tumor progression during neoadjuvant therapy, i.e. patients with initially resectable tumors might present with local or distant tumor progression at restaging, which might not have occurred in the setting of an initial tumor resection.

In addition, neoadjuvant treatment protocols usually require histological confirmation before initiation of therapy, resulting in additional invasive diagnostic measures. Clearly, only randomized controlled trials can clarify which of the hypothetical advantages/disadvantages are real and which ones are not.

There is only one phase III randomized controlled trial being carried out comparing neoadjuvant therapy and surgery with surgery alone (NCT00335543). This multicenter trial has been recruiting patients since June 2003 and has currently enrolled less than a third of the originally planned 254 patients. Due to the exceedingly slow recruitment, the study will be terminated before reaching the target population.

In the future, phase III trials have to be carried out using already established protocols comparing neoadjuvant therapy followed by exploration and possibly resection, with immediate exploration and resection if possible (and additional standard palliative or adjuvant therapies in both arms). As our data point out, this would be especially relevant in the group of borderline resectable/unresectable tumors. As a prerequisite for such trials, standard definitions of resectability and objective computed tomography criteria should be applied.

Conclusion

The present analysis provides the most comprehensive review regarding neoadjuvant therapies in resectable and non-resectable pancreatic cancers to date—thus, the best actual available evidence for response rates, treatment toxicities, resection rates, morbidity and mortality, and survival estimates. The most important findings are that in the group of resectable tumor patients, resection and survival rates after neoadjuvant therapy are similar to the ones observed in primarily resected tumor that are treated by adjuvant therapy. Thus, in this group of patients, the current data do not point to an obvious advantage of neoadjuvant therapy. In contrast, in patients initially staged locally advanced/unresectable, approximately one third of the patients can be resected following neoadjuvant therapy with comparable survival rates as patients who were staged as resectable before treatment. Due to the heterogeneity of applied protocols, data regarding the optimal chemotherapeutic and radiotherapeutic regimen cannot be extrapolated; however, the data suggest that combination chemotherapies result in higher response rates, which is reflected by higher resection rates at least in the group of initially non-resectable tumor patients. Future trials have first to clearly establish the role of neoadjuvant therapy specifically in locally advanced/unresectable tumors and subsequently to define optimal treatment protocols. In addition, common definitions for resectability/non-resectability as well as for response evaluation should be applied. As of now, the available data strongly suggest that patients with locally advanced/unresectable tumors should be included in neoadjuvant protocols and subsequently be re-evaluated for resection, which is possible in a relevant number of patients.

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