Pancreatic cancer—is the wall crumbling?

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In spite of advances made in the management of the other more common cancers of the gastrointestinal tract, significant progress in the treatment of pancreatic cancer remains elusive, more so with the recent negative results of several much anticipated randomized trials. Gemcitabine has been a standard treatment for advanced pancreatic cancer since it was shown a decade ago to result in a superior clinical benefit response and survival compared with bolus 5-fluorouracil (5-FU). Since then, clinical trials have explored the pharmacokinetic modulation of gemcitabine by fixed dose administration and the combination of gemcitabine with other cytotoxics or the biological ‘targeted’ agents. Against a background of numerous negative randomized trials of gemcitabine-based combination treatment, two trials have recently reported modest survival improvements with the use of combination treatment: the United Kingdom National Cancer Research GEMCAP trial of gemcitabine with the orally administered precursor of 5-FU–capecitabine and the National Cancer Institute of Canada Clinical Trials Group PA.3 trial in which the tyrosine kinase inhibitor erlotinib was used with gemcitabine. This review will summarize the results of several recent randomized trials of combination treatment in advanced pancreatic cancer and discuss their implications for clinical practice and for future research in this disease.

Key words: Adenocarcinoma, advanced, chemotherapy, gemcitabine, metastatic, pancreas

introduction

In spite of advances made in the management of the other more common cancers of the gastrointestinal tract, significant progress in the treatment of pancreatic cancer remains elusive, more so with the recent negative results of several much anticipated randomized trials. Worldwide, pancreas cancer is a significant problem with >230 000 cases diagnosed annually, mostly in developed countries and with a slight male predominance [1]. As the eighth most common cause of death from cancer, nearly as many deaths occur from this disease as are diagnosed each year reflecting the poor prognosis typically associated with pancreatic cancer. The median survival of this disease is between 3 and 4 months when patients are untreated. However, in spite of treatment, <5% of patients are alive at 5 years.

Pancreatic cancer presents several challenges which need to be considered when attempting to address this problem. It is insidious in onset and is often diagnosed late in the course of disease, often with metastatic spread. Patients frequently suffer from disease-related symptoms out of proportion to their tumor burden, the effects of symptoms such as pain and cachexia, so characteristic of pancreatic cancer, impacting negatively on performance status and limiting the safe delivery of active treatment which is also associated with toxicity.

Only a small proportion of patients (10%–15%) have limited stage disease amenable to surgical resection, but even with surgery, disease recurrence will occur in the majority, although improved outcomes from new approaches to adjuvant therapy are encouraging. Systemic treatment of pancreatic cancer is only of modest benefit, with the tumor having a propensity for being chemoresistant, while these patients are often sensitive to the adverse effects of more intensive treatments. The evaluation of the effects of treatment on the primary tumor can also be difficult due to the associated extensive desmoplastic reaction and fibrosis that characterizes these tumors independently of any effect of radiotherapy sometimes used in patients with localized disease.

This review will discuss the use of systemic therapy for advanced pancreatic cancer, focusing on the results of recent clinical trials. From the perspective of systemic treatment, the focus of clinical research has been in developing more effective treatment regimens by combining cytotoxic chemotherapy agents or biological-targeted therapies or both. Frustratingly, however, often promising trial results in small phase II trials have not translated into survival improvements in larger phase III randomized trials in the advanced disease setting, with the reasons for lack of success often poorly understood.

palliative chemotherapy in pancreatic cancer

Patients with metastatic or locally advanced inoperable pancreatic cancer are usually managed similarly. The benefit
of chemotherapy in addition to best supportive care in these patients has been established for some time, with patients receiving active treatment achieving a significantly better median overall survival (OS) of >6 months with better quality of life [2–4]. In general, however, chemotherapy should only be offered to carefully selected patients with reasonable performance status as patients with advanced pancreatic cancer are particularly susceptible to the side-effects of cytotoxic treatment.

The standard treatment for advanced pancreatic cancer for the past decade has been the deoxycitidine analogue gemcitabine (1000 mg/m² administered over 30 min) since it was shown to improve clinical benefit response (a composite parameter for evaluating symptomatic benefit of treatment derived from the measurement of pain, functional impairment and weight change) and survival compared with bolus 5-fluorouracil (5-FU) [5]. Although superior to bolus 5-FU, the efficacy of gemcitabine as a single agent is modest, with a median survival of only ~6 months in randomized trials and a 12-month survival of <20%. Side-effects associated with gemcitabine include myelosuppression, lethargy, an influenza-like syndrome, nausea and vomiting and peripheral edema of noncardiac and nonrenal origin.

Gemcitabine must be metabolized to its active triphosphate metabolite (dfdCTP) which then causes cell death. The ratelimiting step in the activation pathway is phosphorylation by deoxycytidine kinase. Because of this, pharmacokinetic modulation of gemcitabine by fixed dose rate (FDR) administration (10 mg/m²/min) was developed to try to increase the plasma and intracellular levels of the active metabolite [6]. Although further development of FDR gemcitabine was supported by earlier phase trials, it has not been shown to be improve survival compared with standard administration regimens [7–9].

Despite these limitations, gemcitabine has become entrenched as the platform to which other agents have been added in the majority of subsequent clinical trials, and until recently its benefits have not been surpassed as a single agent. Against a background of numerous negative randomized trials of gemcitabine-based combination treatment, two trials have recently reported modest survival improvements with the use of combination treatment: the United Kingdom National Cancer Research Institute (UK NCRI) GEMCAP trial and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) PA.3 trial described below (see Table 1) [10, 11].

**combination gemcitabine-based chemotherapy**

The preliminary results of the 533-patient UK NCRI GEMCAP trial are the first to suggest that combination chemotherapy may be better than gemcitabine alone for the treatment of advanced pancreatic cancer [10]. Capecitabine, an orally administered precursor of 5-FU, is well absorbed in the gastrointestinal tract and preferentially converted by thymidine phosphorylase in tumor cells to the active metabolite [12]. It has single-agent activity in nonrandomized comparisons in this disease which appears similar to that of gemcitabine [13]. In the GEMCAP trial, the gemcitabine–capecitabine combination resulted in a median OS of 7.4 months, compared with 6.0 months for gemcitabine alone [hazard ratio 0.80, 95% confidence interval (CI) 0.65–0.98; P = 0.026], and an absolute improvement in 1-year survival of 7% (26% versus 19%) (Table 1). The GEMCAP regimen proved to be very well tolerated, with a similar incidence of grades 3 and 4 toxicity in both arms, except for more neutropenia (17% versus 11%) in the combination arm. The formal publication of this trial is awaited.

Although a modest improvement, similar results were not seen in a second trial of a similar combination. That study reported at the same time only demonstrated a trend towards a benefit in favor of the gemcitabine–capecitabine regimen over gemcitabine alone which was not statistically significant, possibly due to the study being underpowered (319 patients were included) [14]. A different schedule of

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**Table 1. Summary of the results of the UK National Cancer Research Institute GEMCAP and National Cancer Institute of Canada Clinical Trials Group PA.3 trials [10, 11]**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Overall survival</th>
<th>Hazard ratio (95% CI)</th>
<th>One year response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK NCRI GEMCAP [10]</td>
<td>Gemcitabine 1000 mg/m² weekly 3× every 4 weeks</td>
<td>7.4 months</td>
<td>0.80 (0.65–0.98, P = 0.026)</td>
<td>26% (14.2% (P = 0.008))</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine 1660 mg/m²/day for 21 days every 4 weeks (n = 267)</td>
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<tr>
<td></td>
<td>Gemcitabine 1000 mg/m² weekly for 7 weeks followed by 1 week rest, then 3× every 4 weeks (n = 266)</td>
<td>6.0 months</td>
<td>19%</td>
<td>7.1%</td>
</tr>
<tr>
<td>NCIC CTG PA.3 [11]</td>
<td>Gemcitabine 1000 mg/m² weekly for 7 weeks followed by 1 week rest, then 3× every 4 weeks (n = 285)</td>
<td>6.24 months</td>
<td>0.82 (0.69–0.99, P = 0.038)</td>
<td>23% (P = 0.023) 8.6% (P = ns)</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine 1000 mg/m² weekly for 7 weeks followed by 1 week rest, then 3× every 4 weeks (n = 284)</td>
<td>5.91 months</td>
<td>17%</td>
<td>8.0%</td>
</tr>
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</table>

CI, confidence interval; ns, not significant.
gemcitabine and capcitabine was used compared with the GEMCAP study, but treatment was similarly well tolerated. An exploratory subgroup analysis of patients with good performance status in this latter study did, however, suggest a significant overall and progression-free survival (PFS) benefit for these patients. Of note, the addition of 5-FU to gemcitabine has not been shown to improve survival [15, 16].

Cisplatin has some single-agent activity in advanced pancreatic cancer, with a response rate of 21% observed in one study [17]. In phase II studies, the combination of gemcitabine and cisplatin appeared to have promising activity [18–21]. A recently reported randomized trial, however, only found a trend towards an improvement in survival with the combination compared with gemcitabine alone, which did not reach statistical significance (7.5 versus 6.0 months, \( P = 0.15 \)) [22]. Another randomized study with only 107 patients was also unable to show a statistically significant benefit for the combination (median OS of 30 and 20 weeks for combination and monotherapy, respectively, \( P = 0.43 \)), although the response rate was markedly improved (26.4% versus 9.2%, \( P = 0.02 \)) with the gemcitabine–cisplatin combination compared with gemcitabine alone [23]. The newer platinum compound oxaliplatin has also been tested in this setting. In combination with gemcitabine given by 30-min infusion, a response rate of 11% and OS of 6.2 months was observed [24]. The combination appeared to be more active still with FDR gemcitabine, with a response rate of 30.6%, and 40% of patients reported as having a clinical benefit from treatment [25]. The PFS and OS in this study were 5.3 and 9.2 months, respectively, with 36% of patients surviving at 1 year. However, two separate randomized trials comparing the FDR gemcitabine–oxaliplatin combination to standard gemcitabine have reported negative results [9, 26]. In a trial jointly conducted by the French Multidisciplinary Clinical Research Group in Oncology (GERCOR) and the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD), median OSs of 9.0 and 7.1 months (\( P = 0.13 \)) for the combination and gemcitabine alone arms, respectively, were reported, although other secondary efficacy end points of PFS, response rate and clinical benefit response were superior with the combination arm [26]. It should be noted that radiotherapy was recommended for patients with locally advanced disease who had stable disease or a response after 3 months of chemotherapy. More recently, the US Eastern Cooperative Oncology Group protocol E6201 reported median OSs of 5.9 months (combination arm) and 4.9 months (\( P = 0.16 \)), and a 1-year survival difference of 4% for the comparison of gemcitabine–oxaliplatin versus gemcitabine alone [9].

Considering the trend towards a clinically useful benefit observed in these trials, the results of two of the platinum combination studies—gemcitabine with cisplatin or oxaliplatin [22, 26]—have been combined in a pooled univariate analysis that was able to demonstrate that both PFS and OS were improved by gemcitabine–platinum combination treatment (hazard ratio 0.75 and \( P = 0.0030 \) for PFS and hazard ratio 0.81 and \( P = 0.031 \) for OS) [27]. In a subgroup analysis, the benefit from combination treatment appeared to be greatest in performance status zero patients although this was only statistically significant for PFS but not OS. Whereas a Cochrane meta-analysis of trials in advanced pancreatic cancer did not find a significant difference in 1-year survival with the use of gemcitabine-based combination chemotherapy compared with gemcitabine alone, a subgroup analysis did show a reduction in 6-month mortality with the use of gemcitabine–platinum combination chemotherapy compared with gemcitabine alone [28]. It should be noted that neither GEMCAP nor the NCIC CTG PA.3 trial which is discussed later were included in the meta-analysis.

Other cytotoxic agents which have not improved survival when added to gemcitabine include the topoisomerase inhibitors, irinotecan and rubitecan, and the antifolate, pemetrexed [29–31]. The addition of docetaxel, a taxane, to gemcitabine has promising activity, but the combinations tested so far have shown unacceptable myelotoxicity [32–34].

**Biological agents in pancreatic cancer**

As is the case across much of oncology this decade, the focus of research in the treatment of pancreatic cancer has shifted from traditional cytotoxic agents to the novel targeted agents which antagonize the pathways that support the development, survival and progression of cancer cells. Pancreatic cancer also has particular biological characteristics which suggest that this class of agents may eventually prove to be useful, for example: its tendency for invasiveness and early local and/or distant spread suggests that pancreatic tumors are particularly able to evade the normal mechanisms which prevent cancer progression; the frequent occurrence of chemoresistance, either at the outset or developing quickly after the commencement of treatment, suggests aberrant cell survival and resistance to apoptosis and the marked associated desmoplastic reaction often seen with these tumors suggests the ability to effect change in surrounding stromal cells which may result in a more favorable environment for the survival of malignant cells.

Two pathways thought to be relevant in the biology of pancreatic tumors and which have been the subject of several clinical trials in pancreatic cancer following positive results in other tumors are the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways. The EGFR, via a cascade of downstream signaling events triggered by its activation, mediates cellular processes such as cell division and survival; overexpression has been shown to occur in several epithelial tumors and to correlate with worse outcome. VEGF on the other hand is a key regulator of angiogenesis, believed to be a necessary requirement for the progression and spread of cancer cells beyond a small focus of malignant but otherwise isolated cells.

Blockade of the EGFR pathway with the tyrosine kinase inhibitor erlotinib, used in combination with gemcitabine, has been shown to improve survival compared with gemcitabine alone in the NCIC CTG PA.3 trial [11]. The median OS in the erlotinib-containing arms was 6.24 months compared with 5.91 months in those patients who received gemcitabine plus placebo, quite a small difference in the medians although the overall reduction in risk of death (hazard ratio 0.82, 95% CI 0.69–0.99, \( P = 0.038 \) (Figure 1) and improvement in the 1-year...
survival with combination treatment was more notable (23% versus 17%, \( P = 0.023 \)) (Table 1). This survival benefit comes at the cost of a slight increase in the incidence of grades 3 and 4 skin rash (6% versus 1%) and diarrhea (6% versus 2%). As has been observed in trials in other tumor types, EGFR positivity by immunohistochemistry was not found to correlate with survival outcome, whereas the occurrence of the skin rash was shown to predict for a better survival. EGFR antagonism can also be achieved using mAbs. However, the results of a randomized trial of gemcitabine with or without the anti-EGFR antibody cetuximab (US Southwest Oncology Group protocol S0205) disappointingly failed to improve OS [35]. Why the small molecule tyrosine kinase inhibitor was active in contrast to the mAb is not known.

Unfortunately, targeting VEGF has also not been successful, despite initial promise, given the putative role of angiogenesis in the propagation of pancreatic cancers and the benefit from adding the anti-VEGF antibody bevacizumab to chemotherapy in several other tumor types, most notably advanced colorectal cancer. The data and safety monitoring board of the US Cancer and Leukemia Group B (protocol C80303) concluded from an interim analysis that the addition of bevacizumab to gemcitabine was unlikely to result in a survival improvement, even with further maturity of the study [36]. This result did not prevent completion of a similar, almost mature, Roche sponsored trial (known as AVITA) in pancreatic cancer. Originally published by the American Society of Clinical Oncology [11].

The rapid deterioration of patients which often occurs after failure of first-line therapy and the unwillingness by many clinicians to offer further treatment to these patients who are often unwell, in pain and are likely to have impairment of liver function, as a consequence of which relatively few patients receive second-line treatment. Preliminary results of a randomized trial of an oxaliplatin-based regimen in this setting have reported a survival improvement compared with best supportive care alone [43]. A clear improvement in median survival (4.8 versus 2.3 months, \( P = 0.0077 \)) was observed. The study design has been modified as the best supportive care arm was no longer considered to be acceptable; the study is now continuing with 5-FU and leucovorin as the comparator treatment instead. In the second-line setting, FDR gemcitabine plus oxaliplatin has also been reported to result in a response rate of 23.3% and an OS of 4 months [44].

**unresectable locally advanced disease**

It is a common and widely accepted practice to treat patients with unresectable locally advanced disease with radiotherapy, frequently with the concurrent administration of a fluoropyrimidine as a radiosensitizer in addition to systemic palliative chemotherapy. The benefit of this treatment strategy has, however, never been conclusively proven by data from large randomized trials. Most of the small numbers of randomized trials carried out so far [45–48], some of which have shown a benefit for combined modality therapy, have enrolled relatively small numbers of patients, have been heterogeneous in the treatment regimens tested and were conducted before more sensitive staging modalities such as computed tomography were widely available.

Bearing in mind these limitations, two recent systematic reviews were unable to demonstrate that chemoradiotherapy was better than chemotherapy alone in this subset of patients [28, 49]. Instead, the addition of radiation to chemotherapy increased treatment-related toxicity. Further well-designed trials, such as the current French Intergroup Study (LAP-07), are required before a conclusion can be drawn as to the role of radiotherapy in locally advanced disease. Such trials should specify rigorous staging to exclude occult distant metastases and must be on the basis of modern radiotherapy techniques, such as the use of three-dimensional planning and conformal treatment.

Disease extent (locally advanced versus metastatic disease) has consistently been observed in randomized trials involving patients with pancreatic cancer to be an independent predictor of outcome. Ideally, these patients should be enrolled in separate trials; and if not, stratification for disease extent is mandatory to reduce the risk of false results from an imbalance in the number of patients with locally advanced disease between the study arms.

Radiological response assessment, at least by conventional anatomical imaging techniques such as computed tomography, can be less than straightforward due to the extensive desmoplastic reaction and fibrosis which can occur with pancreatic cancers. For this reason, evaluating treatment effect, particularly in patients with localized disease, can be difficult.

**second-line treatment**

There is no standard second-line treatment for patients with pancreatic cancer, and there have been few clinical trials in this setting. Difficulties which contribute to this situation include
discussion and conclusions

The impact of the results of the GEMCAP and PA.3 trials on standard practice is uncertain. The improvements in survival observed in both trials are considered by some to be too small to justify the additional cost, either financially or in terms of the risk of toxicity from combination treatment. It is likely that single-agent gemcitabine will continue to be used as standard treatment in many centers worldwide and that the uptake of gemcitabine in combination with either capecitabine or erlotinib will depend on factors such as local availability and physician and patient preference. Particularly in the case of erlotinib use, economic factors may also be important. For these reasons, we believe it acceptable that either of the two combination regimens or indeed single-agent gemcitabine be adopted as the control arm for future randomized trials [50]; however, whether the major regulatory bodies around the world are in agreement with this position is not clear at the present time. In the meanwhile, new treatments for advanced disease need urgent evaluation in randomized trials as the current options are not sufficient. These new studies should include approaches to evaluate the reasons for the success or failure of these experimental therapies so that we can learn from each trial how better to inform subsequent studies.

Further research in the treatment of pancreatic cancer should therefore be underpinned by an improved understanding of the biology of this disease, in particular of the processes at a cellular, molecular and genetic level which drive the pathways mediating tumor progression and treatment resistance; this in turn may give rise to the identification of new targets which may be used for therapeutic purposes. A better understanding of how tumors interact with the host environment, such as to induce desmoplasia, may also suggest how this environment may be manipulated to become less favorable for tumor growth. This should be accompanied by a shift away from studies based on trial-and-error testing towards research which is on the basis of scientific knowledge involving a sound rationale with drugs thought to impact on known targets.

Key to this development is the meticulous creation of biobanks in which demographic, clinical, treatment and outcome information are linked to collections of primary and secondary tumor biopsies as well as normal tissues and blood from each patient and can be made available to researchers for detailed analysis. Research into molecular markers which may be prognostic or predictive for outcome, in addition to helping clinicians tailor treatments to the needs of patients, may give initial clues as to the pathways which are of importance and which warrant further examination. The small overall benefit observed from the addition of erlotinib to gemcitabine in the PA.3 trial supports the need for better patient selection for treatment with the targeted therapies [50]. It would be clinically useful to be able to identify the subgroup of patients among the overall cohort who benefited more from treatment with erlotinib.

The development of better tumor models may also lead to more effective and efficient development of treatments. While cell lines and xenograft models may be useful in the initial development of treatments, neither tool is truly reflective yet of the human patient. For example, the role of human immune function is not considered in these models. Furthermore, our understanding of the mechanisms by which various agents actually achieve a therapeutic outcome in vivo is still limited, and our expectations of the efficacy of these agents are often somewhat simplistic. For example, blockade of a single step in a signaling pathway may not lead to tumor control because there is often more than one pro-oncogenic pathway involved. These pathways interact in complex ways, and there may be significant redundancy. Initially effective blockade may also be overcome as tumors, by nature genomically unstable, evolve to no longer be dependent on the inhibited pathway. We should therefore strive for knowledge which recognizes the complexity of the factors at play.

The development of techniques to better evaluate the actions of targeted agents in patients may be useful for confirmation that the correct target has been affected and allow the effects of treatment to be studied better in vivo. This may include minimally invasive and safer techniques for obtaining pancreatic tumor samples from patients or noninvasive imaging modalities which allow measurement of signaling pathway activity or tumor metabolic function, whereas the prevalent response assessment techniques depend heavily on measuring changes in apparent tumor volume which may not be accurately reflective of the likelihood of overall treatment benefit [51].

Finally, the plethora of new drugs affecting an ever increasing number of targets within tumor cells or stromal tissue offers much hope for the future. However, unless these drugs can be much more readily made available to the academic community to evaluate potential synergistic active combinations, in preclinical models, we are destined to further disappointment in tackling this disease. Now more than ever is the time for collaboration between clinicians, scientists, the pharmaceutical industry and regulators to ensure that innovative drug combinations can be explored preclinically and clinically without having to traverse minefields of contracts between the competing priorities of multiple pharmaceutical and biotechnology companies. Such an initiative needs to be led by regulators and the major funding agencies if this type of long-term collaboration is to be fostered in the interests of future patients.

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