Pancreatic cancer treatment and research: an international expert panel discussion

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Background: Pancreatic cancer has proven extremely challenging to treat. A collaborative effort is needed to advance research and improve treatment. An expert conference was conducted to elicit perspectives regarding the current treatment and future research of pancreatic cancer.

Methods: The conference comprised an international panel of experts representing five European countries and the United States.

Results: Adjuvant radiotherapy is used more frequently in the United States than in Europe. In locally advanced disease, there is now more emphasis on early chemotherapy in both Europe and the United States. In metastatic disease, combination chemotherapy is commonly used in Europe and the United States. This varies by country.

Advancing pancreatic research will require improving biorepositories and developing a roadmap to prioritize therapeutic targets in different models. Small randomized phase II trials of both non-selected and enriched patient populations will help identify activity of new agents. Phase III trials should only be initiated in appropriate patients based on strong clinical and biological signals. Developing drugs in the adjuvant setting may be preferable to eliminate some of the challenges of drug development in the advanced disease setting.

Conclusion: Progress in research combined with encouraging improvements from the past offer hope for the future of pancreatic cancer patients.

Key words: ductal adenocarcinoma, pancreatic cancer, pancreatic neoplasm, research, therapeutic targets, treatment

Introduction

Despite notable declines in cancer-related mortality over recent decades, progress in pancreatic cancer has remained exceedingly slow [1]. With one of the highest mortality-to-incidence rate ratios, pancreatic cancer is the eighth leading cause of cancer-related death in men worldwide and the ninth leading cause in women [2]. The majority of patients are diagnosed with advanced disease and have a median survival with treatment of ~6 months [3, 4]. Even for those seemingly fortunate enough to have early-stage local and resectable disease, the 5-year survival is only 20% after resection.

Pancreatic cancer is well recognized as an extremely challenging disease on multiple fronts. The disease is usually detected at an advanced stage, carries a poor prognosis regardless of stage and is associated with debilitating symptoms. Fueling this paradigm is a set of underlying biological attributes uncommon to other cancers. Three key attributes—multiple molecular aberrations, intense desmoplastic stroma, and hypoxia—result in a cancer that is biologically and clinically aggressive. This aggressiveness leads to a host of negative consequences, including exceedingly short overall survival (Figure 1).

Advances in treating pancreatic cancer have been few and modest. In the advanced setting, the current standard of care was established over a decade ago when gemcitabine improved symptoms and prolonged survival in a phase III trial when compared with 5-fluorouracil (5-FU) [3]. However, building on gemcitabine as an anchor drug has been difficult. Recent phase III trials adding oxaliplatin, bevacizumab, or cetuximab to gemcitabine have been negative [5–7]. A modest breakthrough occurred when the addition of erlotinib to gemcitabine was shown to prolong survival compared with gemcitabine monotherapy [4].

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In the adjuvant setting, the Charité Onkologie (CONKO)-001 trial demonstrated the benefit of gemcitabine over observation [8, 9] and the European Study Group for Pancreatic Cancer (ESPAC) group has demonstrated a similar benefit for 5-FU plus leucovorin without a clear advantage for either 5-FU and leucovorin or gemcitabine [10, 11].

An expert conference was conducted in order to elicit perspectives regarding the current state of treatment, to discuss the issues, and to identify optimal areas in which to focus research. What are the problems? Are phase II data being over-interpreted? Have the wrong targets been pursued? Is inadequate drug delivery to blame? Is the biology of pancreatic cancer more complicated than previously thought? With this multifaceted challenge, a collaborative effort is justified to identify barriers hindering progress in improving outcomes in this disease.

**Methods**

The expert conference was conducted by an international consensus panel that comprised oncologists with an expertise in treating pancreatic cancer (MAT, JB, MD, DH, PH, DK, H-JS, AS, and EVC). Members of the panel, chosen on the basis of their knowledge in the field and their international recognition, represented six countries: five in Europe (France, Germany, Italy, Netherlands, and UK) and the United States. Panelists reviewed and discussed pertinent data from published trials and reports and from abstracts presented at selected oncology association meetings (American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology). The final manuscript was reviewed by all panel members and approved by each author.

**Current practice**

**Review of available treatments**

Chemotherapy plays an integral role in the management of all stages of pancreatic cancer, with gemcitabine and fluoropyrimidines being the leading agents employed. The only targeted therapy proven effective to date, erlotinib, has shown a statistically significant benefit in combination with gemcitabine in patients with advanced disease [4]. The panel provided perspectives regarding current management of pancreatic cancer (Table 1).

**Adjuvant treatment**

**Chemotherapy.** The role of systemic therapy in the adjuvant treatment of pancreatic cancer is undisputed, and gemcitabine is the favored agent in both the United States and the Europe. Gemcitabine and 5-FU each produced an approximate doubling of 5-year survival rates in adjuvant trials (CONKO-001: 21%, gemcitabine versus 9%, observation; ESPAC-1: 29%, 5-FU and leucovorin versus 11%, observation) [9, 10], raising the question of whether a choice should be made between the two agents. However, because of a more favorable toxicity profile, more enthusiasm exists for utilizing gemcitabine.

Gemcitabine is a prodrug and requires a nucleoside transporter to gain access to the intracellular compartment. Emerging data link the absence of human equilibrative nucleoside transporter 1 (hENT1) expression to lack of a survival benefit with gemcitabine [12]. If a patient’s tumor does not express hENT1, one might argue that an optimally delivered fluoropyrimidine is a better option. However, this assay is not available yet for clinical decision making. It is agreed that using hENT1 as an enrichment tool must be further studied and validated.

**Radiotherapy.** The potential role of radiotherapy and its timing in the postoperative regimen varies worldwide. In the United States, chemotherapy alone and chemotherapy plus chemoradiation are accepted standards of care for postoperative adjuvant therapy. An analysis of the National Cancer Data Base showed that between the time periods of 1985–1994 and 1995–2003, use of adjuvant chemoradiation increased from 26.8% (n = 2 255/8 400) to 38.7% (n = 8 655/15 011).

**Table 1.** Summary of key perspectives from the expert panel on pancreatic cancer: current practice

<table>
<thead>
<tr>
<th>Perspectives on current practice in adjuvant therapy</th>
</tr>
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<tbody>
<tr>
<td>Adjuvant chemotherapy represents the standard of care.</td>
</tr>
<tr>
<td>Gemcitabine remains the agent of choice in the United States and Europe.</td>
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<tr>
<td>The potential use of human equilibrative nucleoside transporter 1 deserves further analysis.</td>
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<tr>
<td>Adjuvant radiotherapy is more commonly employed in the United States than in Europe.</td>
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<tr>
<td>Radiotherapy schedules vary among countries and centers.</td>
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<tr>
<td>Perspectives on current practice in metastatic disease.</td>
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<tr>
<td>Gemcitabine is the agent of choice in the United States and Europe with concomitant erlotinib more commonly employed in the United States.</td>
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<tr>
<td>Reimbursement for erlotinib varies throughout Europe.</td>
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<tr>
<td>Developing criteria to prospectively select appropriate patients for erlotinib is an important goal; K-ras may prove beneficial.</td>
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<tr>
<td>Combination chemotherapy is used more commonly in Europe than in the United States with gemcitabine–platinum combinations utilized in patients with good performance status.</td>
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<tr>
<td>No second-line therapy is standard, yet over half of patients receive second-line therapy.</td>
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</table>

**Figure 1.** Three key peculiarities associated with pancreatic cancer result in a cancer that is biologically and clinically aggressive, leading to multiple negative consequences.
21679) \( (P < 0.0001) \) and was more common at academic institutions \[13\]. However, some United States centers argue that its role in the postoperative adjuvant setting is unproven. The Radiation Therapy Oncology Group is planning an intergroup trial that will test both the value of radiotherapy and the value of erlotinib in resected patients, similar to the design of the French LAP 07 trial in locally advanced patients. Studies evaluating the role of radiotherapy in the locally advanced setting have proven challenging in the United States; the Eastern Cooperative Oncology Group (ECOG) 4201 trial of gemcitabine with or without radiotherapy failed to accrue its target sample size \[14\], possibly reflecting unwillingness of physicians to change long-standing clinical practices.

European countries have also hesitated to adopt adjuvant radiotherapy, although some agree that this should be further evaluated. Several studies are underway in the UK. In Europe, radiotherapy is generally considered only for patients with R1 resections or with locally advanced disease. In the setting of R1 resection, the specific treatment regimens vary in the length of gemcitabine monotherapy before the initiation of chemoradiotherapy. Some countries follow the European Organisation for the Research and Treatment of Cancer study regimen of administering gemcitabine alone for 2 months followed by chemoradiotherapy with gemcitabine \[15\]. In other countries, chemoradiotherapy is more commonly delayed for 6 months to allow occult metastases to reveal themselves before subjecting the patient to radiotherapy. Regardless of the number of cycles used, chemotherapy is most frequently initiated prior to chemoradiotherapy rather than after. For locally advanced disease, both prospective studies and a meta-analysis support the sequence of chemotherapy followed by chemoradiation \[16, 17\].

**metastatic disease**

first-line therapy. Gemcitabine (difluorodeoxycytidine) is a nucleoside analogue capable of inhibiting ribonucleotide reductase to deplete nucleoside pools and its phosphorylated metabolite is incorporated into DNA, causing chain termination. Gemcitabine is recognized and accepted as the current chemotherapeutic agent of choice in the treatment of advanced pancreatic cancer, as supported by the landmark phase III study of Burris et al. \[3\].

Erlotinib is an oral HER1/EGFR tyrosine kinase inhibitor. This tyrosine kinase is over-expressed in many pancreatic tumors and is associated with poor prognosis and disease progression. Blocking HER1/EGFR tyrosine kinase signaling decreases the growth and metastasis of human pancreatic tumor xenografts and improves the anticancer effects of gemcitabine. The PA.3 trial conducted by the National Cancer Institute of Canada showed significantly improved overall survival \[\text{hazard ratio (HR)} = 0.82\] in the patient group treated with gemcitabine (1000 mg/m² weekly × 3 out of 4) plus erlotinib (100 mg/day) over the group treated with gemcitabine plus placebo \[4\]. Both the US Food and Drug Administration and the European Medicines Agency have approved erlotinib for advanced disease. Usage varies across the United States and Europe. Because the survival improvement was small, gemcitabine plus erlotinib has not been deemed standard of care and single-agent gemcitabine is still acceptable \[18\].

It would be optimal to enrich for patients more likely to benefit from treatment with erlotinib. More benefit has been demonstrated in those patients who developed skin rash compared with those who did not \( (\text{HR} = 0.74, 95\% \text{ confidence interval} 0.56–0.98, P = 0.037) \) and the median survival rates for patients with grades 0, 1, and 2+ rash were 5.3, 5.8, and 10.5 months, respectively \[4\]. The AVITA trial \[19\], which tested gemcitabine plus erlotinib, with or without bevacizumab, has confirmed the correlation between rash and improved survival. The association with rash and survival observed in these retrospective analyses is now under prospective study and may become a valuable tool in identifying which patients will ultimately benefit from anti-EGFR therapy. Nonetheless, rash is not a factor that can be used to preselect patients for treatment.

K-ras mutation occurs in 70%–90% of pancreatic cancers and RAS activation predicts for resistance to erlotinib in other malignancies. This suggests that only a small number of patients may benefit from erlotinib therapy. However, available data do not yet define a relationship between K-ras status and erlotinib efficacy in pancreatic cancer \[20\].

combination chemotherapy. Combination chemotherapy is utilized in both the United States and the Europe, except for the UK. Despite many negative phase III trials \[21–23\], gemcitabine–platinum combinations are still used particularly for those with good performance status. Gemcitabine plus capecitabine has also been extensively studied. The most recent phase III trial using a 3-week schedule of capecitabine demonstrated a clear benefit for progression-free survival but not overall survival \[24\]. These practices are supported by meta-analyses that demonstrated significantly superior survival for patients who received a gemcitabine–platinum combination versus gemcitabine alone \( (\text{HR} = 0.85; P = 0.01) \) and for patients with good performance status who received gemcitabine-based combination therapy \( (\text{regardless of agent}) \) versus gemcitabine monotherapy \( (\text{HR} = 0.76, P < 0.001) \) \[25, 26\]. Combination regimens with 5-FU (without gemcitabine) also appear promising \[27\].

second-line therapy. No standard second-line therapy exists for pancreatic cancer, yet over half of patients are eligible for and receive some form of second-line therapy. In the Fédération Francophone de Carcinologie Digestive 0301 trial, which compared gemcitabine followed by 5-FU–leucovorin plus cisplatin or the reverse sequence, 55%–68% of patients received second-line therapy \[28\]. In the United States, various regimens are utilized in the second-line setting, including gemcitabine plus erlotinib \( (\text{in erlotinib-naive patients}) \), gemcitabine plus oxaliplatin, capecitabine, and infusional 5-FU–leucovorin plus oxaliplatin. Evaluating the true benefit of second-line therapy is difficult. The CONKO-003 study began by comparing second-line 5-FU–leucovorin plus oxaliplatin versus best supportive care; however, the protocol was amended after 46 patients to include 3-FU–leucovorin in the control arm because of slow accrual and reluctance to accept best supportive care \[29, 30\]. Nonetheless, results from those 46 patients demonstrated a statistically significant survival advantage for
5-FU–leucovorin plus oxaliplatin and the final results demonstrated superiority of the regimen over 5-FU and leucovorin. This signal for efficacy and the unmet need of patients still able to receive second-line chemotherapy suggests that second-line therapy warrants further investigation [29]. Since the benefit of therapy was most pronounced in patients with good performance status (Karnofsky performance status 90%–100%) or who responded poorly to first-line gemcitabine, this approach may best be suited for a selected group of patients.

**perspectives on clinical trial design and the future of treating pancreatic cancer**

With the current state of pancreatic cancer treatment defined in Europe and the United States, the panel turned toward future research and management. Panelists discussed how to advance the development of new treatments for pancreatic cancer by responding to several currently pressing questions (Table 2).

**why have recent phase III trials failed?**

Numerous phase III trials in recent years have tested either new gemcitabine-based chemotherapy regimens or novel targeted agents, and most have uniformly failed to produce improved overall survival [5–7, 31–38]. These trials probably failed for many reasons. One reason might have been inadequate interpretation of phase II data and a lack of appreciation for unintentional but biased patient selection. Phase II trials should be interpreted carefully before proceeding to phase III. For example, some argue that axitinib should not have been tested at the phase II level and patient populations are appropriately selected.

A phase II signal of 50% improvement over standard of care may warrant continued drug development if patient selection factors are considered or a biological signal is identified. Randomized phase II design or replicate phase II trials will minimize the chance of bias. Predictive biomarkers should be explored in phase II trials in order to target therapy to the appropriate patients. Metastatic and locally advanced populations should be studied separately. The adjuvant setting is recognized as micrometastatic disease and should be considered for new drug development. Key targets of interest include K-ras, c-Met, and sonic hedgehog due to their roles in cancer stem cells. A virtual archive of annotated (molecular and clinical) tissue would facilitate research aimed at early detection and treatment.

**what is the best clinical setting for new drug development: metastatic or adjuvant?**

The traditional paradigm has been to study new drugs in combination with gemcitabine in the metastatic setting. However, resectable pancreatic cancer is now recognized as a condition in which most patients have micrometastatic disease. Testing novel agents in the adjuvant setting may be more useful than following the traditional paradigm.

Identifying drugs of interest should start in the preclinical setting with appropriate characterization of targets. The targets that might be explored include those within the malignant epithelial compartment as well as the stromal compartment. Examples of the former might include critical cellular signaling pathways. Examples of the latter might include stromal networks that promote invasion and metastases. Either appropriate cell lines, or primary tumor xenografts, established as either s.c. or orthotopic xenografts or selected transgenic models, might be appropriate depending on the target of interest. Once a target and drug of interest are established, initial studies assessing safety and perhaps even efficacy might be done in a metastatic setting. To minimize patient resources required, validated surrogate end points for survival should be developed. ‘Window of opportunity’ trials of new drugs are difficult to do in the metastatic setting because these patients are frail and may deteriorate quickly. Thus, in this setting, new drugs should probably be tested within a chemotherapy backbone such as a randomized phase II setting to predict for possible success in phase III. Therefore, very large signals should be identified at the phase II level before proceeding with phase III trials. Small but statistically significant differences may secure agency approval but may not have a major clinical benefit. A rush to bring compounds into phase III testing without extensive phase I/II modeling has been a major obstacle to success.

Patient selection is another issue in clinical drug testing. Investigators must be cognizant of the population evaluated in phase II before translating results to phase III. For example, encouraging 8.8 months median survival observed in the phase II trial with bevacizumab did not translate to a successful phase III trial [6, 40]. One possible reason for this discrepancy is that the patient population enrolled in the phase II trial was highly selected since the phase II trial excluded patients with a history of thrombosis and a high proportion of patients had an ECOG performance status of 0 or 1. Seemingly, minor changes in eligibility criteria may lead to significant bias in subsequent studies.

With respect to patient subgroups, patients with metastatic disease should be investigated separately from those with locally advanced disease. Obviously, survival is prolonged in patients with locally advanced disease compared with those who have distant metastases and a differential effect of treatment is observed in clinical trials of both chemotherapy and targeted therapy between the two populations [4, 26, 35].

Finally, we need a better understanding of factors that affect prognosis and predict outcome in order to appropriately stratify patients in studies and enrich for populations most likely to benefit. A major investment must be made to identify those new biomarkers.

**Table 2. Summary of key perspectives from the expert panel on pancreatic cancer: clinical trial design and future treatment**

<table>
<thead>
<tr>
<th>Clinical trial design and the future of pancreatic cancer treatment</th>
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as gemcitabine or a combination regimen such as fluorinated pyrimidine and oxaliplatin. However, patients with locally advanced disease have a somewhat more indolent course and might be good candidates for ‘window of opportunity’ trials including those in which posttreatment tissue might be desired. From a safety perspective, this is best done through a endoscopic ultrasound-directed fine needle aspiration.

It is reasonable to initiate testing of new drugs in end-stage disease in the first- or second-line setting. If a strong signal is identified, initiating a phase III trial in the adjuvant, rather than metastatic, setting may be preferable for several reasons. It is important to remember that the benefit of 5-fluoruracil and gemcitabine in the adjuvant setting is considerably greater than that observed in the setting of advanced disease [9, 3]. This suggests differences in drug sensitivity or drug delivery or both. Investigating new drug combinations in this setting affords little additional risk to patients who are often managed variably across centers and countries. Since the primary tumor is no longer intact, the difficulty of penetrating the stroma is minimized. The stroma may still be a significant barrier for drug delivery in advanced pancreatic tumors but this may be less of an issue in micrometastatic disease. Mounting a comprehensive effort in the adjuvant setting would require a global consortium. A large international rolling adjuvant program using successive cohorts would be preferable to independent small studies.

Opponents to this method counter that evaluating new drugs in the adjuvant setting is unduly time consuming. However, proponents point out that the new drug could advance directly from a robust phase II trial to a randomized phase III adjuvant trial with a smaller patient cohort if the benefit is predicted to be substantial. This strategy was employed in CONKO-001, where it was clearly shown that disease-free survival predicted for overall survival. Also, the signal event—relapse—occurs relatively quickly, so although accrual may take time, the time-to-signal event does not.

can targets of interest be prioritized?

Interesting targets have been identified but prioritizing those targets remains difficult. Twelve core-signaling pathways in pancreatic cancer were recently elucidated (Table 3) [41]. Of these, key targets of interest may include K-ras, c-Met, and sonic hedgehog because of their role in cancer stem cells, potentially an important avenue of research [42].

All potential targets require more thorough preclinical investigation both alone as well as in combinations. Human pancreatic cell lines and s.c. xenograft models may not be the most optimal tools. Importantly, a clear plan for credentialing interesting targets needs to be developed. Showing efficacy of new targeted therapeutics in multiple models including primary tumor explants will increase the level of confidence. Targets within the microenvironment might best be explored in transgenic mouse models.

what is the ideal biorepository?

Because so few patients undergo resection, access to clinically annotated tumor tissue for research is a worldwide problem. Creating an archive of well-annotated (clinical and molecular) tissue that can be viewed and explored virtually would be a major step forward. Similarly, creating a related large DNA (germ line) and serum and/or plasma bank could accelerate research on interesting leads now emerging from genome-wide association studies in the United States. Expansion of tissue as primary tumor explants would also be useful for discovery research and could potentially be exploited for therapeutic target validation studies.

All of these efforts would need to rely on a network of centers with appropriate infrastructure including informatics capability, standardized procedures, and quality control measures.

without early detection does hope for the future exist?

Despite the seemingly grim outlook for pancreatic cancer management, potentially valid targets and corresponding agents exist. Furthermore, chemotherapy has shown efficacy in this disease and is an avenue that, with continued exploration, will yield additional benefits. A better understanding of pancreatic cancer biology and an innovative approach to clinical development will move this field forward. Breakthrough treatments of chronic myelogenous leukemia and gastrointestinal stromal tumors at one time appeared out of reach. Exciting advances in these challenging tumors [43–45] provide hope for the future of pancreatic cancer patients.

conclusions

Pancreatic cancer continues to pose a significant challenge to physicians and investigators. Small but encouraging steps have been made in improving outcomes with therapy.

Some variations occur between Europe and the United States in the management of pancreatic cancer, particularly with the application of adjuvant radiotherapy and the use of combination chemotherapy or erlotinib in advanced disease. However, targeting treatment to the individual patient remains a goal worldwide and patient, tumor, and drug-related factors are beginning to be identified to foster that goal.

Advancing the field of pancreatic cancer management will require efforts on several fronts. Protocol-directed virtual
biorepositories with appropriately annotated samples will improve access to tissue. Much more preclinical work is required to select and prioritize appropriate targets. Small randomized phase II trials of enriched patient populations will help identify potentially useful new drugs. Only drugs that produce a substantial survival benefit in phase II trials should move into phase III development. Finally, developing drugs in the adjuvant setting should be considered as an alternative to the cohort paradigm. Progress on each of these fronts, together with small but encouraging improvements from the past, offers hope for the future of pancreatic cancer patients.

addendum

Subsequent to this consensus conference and prior to publication, results of the ACCORD study [46] were made public at the annual ASCO meeting in Chicago. This randomized, phase III study in patients with metastatic pancreatic ductal adenocarcinoma having a good performance status compared standard therapy with gemcitabine to a combination of 5-FU, oxaliplatin, and irinotecan (FOLFIRINOX). The FOLFIRINOX arm produced a significant improvement in progression-free survival (6.4 versus 3.3 months, HR = 0.47) and overall survival (11.1 versus 6.8 months, HR = 0.57) but also produced significant myelosuppression (42% of patients required growth factor support) and grade 3 or 4 fatigue (23%). The panel has reviewed these data and concurs that FOLFIRINOX is an excellent option for selected patients but cannot be considered standard of care for all. However, these data does support the development of first-line regimens based on a fluorinated pyrimidine (without gemcitabine) including regimens with selected targeted drugs.

disclosure

JB has done advisory boards for Amgen, Clavis, Merck, Roche, Bristol Myers Squibb AstraZeneca, Abbott, and Seattle Genetics.

references


