Alleviation of tumor-related symptoms may be a more appropriate basis for judging drug efficacy in pancreatic cancer than is tumor shrinkage. Clinical benefit response (CBR), a new

Introduction

Because pancreatic cancer has no early signs or symptoms, it tends to be diagnosed at an advanced stage; 80% to 90% of patients present with disease that is not curable by surgery alone due to spread of the cancer to adjacent tissues or beyond [1]. Metastatic pancreatic cancer has proven to be one of the most chemotherapy-resistant tumors, and, until recently, it has been difficult to demonstrate any beneficial impact of systemic therapy on this disease. Sobering testimony to this is the fact that pancreatic cancer has the lowest 5-year survival rate (3%) of any cancer listed in the Surveillance, Epidemiology, and End Results (SEER) data base of the National Cancer Institute (NCI) [2]. A brief review of clinical trial results prior to 1995 will serve to place more recent results in proper perspective.

Historical Perspective

Phase II Trials

A wide range of response rates can be found in single-agent phase II trials in patients with advanced pancreatic cancer (as reviewed by Rothenberg et al) [3]. In evaluating these data, it is important to keep in mind that clinical trial methodology and criteria for objective response have evolved over time. Phase II trials conducted in the 1970s routinely included patients with different tumor types in a single trial. As a result, response rates reported in these studies were often based on a small number of patients with that particular cancer and were therefore subject to a high degree of statistical uncertainty. Trials performed prior to 1985 relied heavily on estimation of tumor size by physical examination, with responses defined as shrinkage of a palpable abdominal mass by 50% or more or a reduction in palpable liver span by 30% or more [3].

The inherent inaccuracy of these techniques, intraobserver and interobserver variability, and the influence of confounding factors on the size of the measured lesions all contributed to the initial reports of high response rates for drugs such as fluorouracil (5-FU), chlorambucil (Leukeran), and mitomycin (Mutamycin), as well as the failure to confirm these promising response rates in subsequent trials, especially when CT scans were used to determine tumor response. It is instructive to review how these factors have led to a substantial decrease in response rates reported for 5-FU during the past 35 years.

The earliest reports on the activity of 5-FU in pancreatic cancer showed response rates as high as 56% [4]. Subsequent trials, involving larger numbers of patients and relying on CT imaging to determine response, reported response rates of 0% to 19%, even when biochemical modulation or infusional schedules of drug administration were utilized [5-9]. In effect, no drug has met the criteria for significant antitumor activity (ie, an objective response rate of 20% or more) using radiographic definitions of response in the post-CT era.

Phase III Trials

Two kinds of comparative studies have been conducted in patients with advanced pancreatic cancer: those that compared active treatment to best supportive care (to determine whether chemotherapy made any difference in the outcome of these patients) and those that compared multiagent regimens to single-agent chemotherapy (to determine whether combinations of drugs with distinct mechanisms of action could improve outcome over that achieved with single agents). Of the three trials that compared active treatment to best supportive care, two demonstrated no significant difference [10,11], while one generated very provocative results suggesting a substantial survival
advantage in favor of a five-drug regimen (Mallinson regimen) [12]. A confirmatory trial was never done, and subsequent trials of the regimen failed to replicate the impressive results of this trial [13]. In fact, phase III trials comparing this or other promising multiagent regimens (such as streptozotocin, mitomycin, and 5-FU [SMF] or 5-FU, Adriamycin, and mitomycin [FAM]) to single-agent 5-FU failed to demonstrate any advantage of multiagent chemotherapy over 5-FU alone [13,14]. Despite a number of promising preclinical leads and provocative phase II study results, virtually no progress has been made in chemotherapy for metastatic pancreatic cancer during the past 30 years.

**Leads From a "Negative Trial"**

Between 1991 and 1994, 25 investigational new drugs were evaluated in phase II trials for the treatment of pancreatic cancer. The median response rate in these trials was 0% (range, 0% to 14%) and the median survival was 3 months [3]. One trial conducted during this period focused on gemcitabine (2',2'-difluorodeoxycytidine [Gemzar]). Although the objective response rate to this drug was only 11% and median survival was 5.6 months, several important observations were made in this trial [15]. The 1-year survival rate was surprisingly high (23%), as the responses observed were durable (more than 4 to more than 20 months). The most striking aspect of this study, however, was the impact of gemcitabine on tumor-related symptoms. Of the five patients who had an objective response to gemcitabine, four were able to resume normal daily activities. Three of the five patients were also able to reduce their daily consumption of analgesics. An additional 14 patients who did not meet radiographic criteria for response experienced disease stabilization for 4 months or more, and, of these, 9 had an improvement in performance status.

These results raised the question, how could a cytotoxic agent produce any beneficial effect without substantial tumor shrinkage? Several possible explanations have been proposed. First, gemcitabine could have been acting merely as an analgesic. This explanation was not felt to be likely since analgesic requirements tend to increase as the patient develops tolerance, the tumor grows, and the pain becomes more severe. Patients in this trial experienced significant alleviation of tumor-related symptoms on a stable dose of gemcitabine, and that effect was not lost during the 1 week out of every 4 in which the patient did not receive chemotherapy.

Another possible explanation was that gemcitabine may have interfered with neurotrophic growth factors that are essential for the spread and invasion of the tumor into the celiac plexus, which lies directly behind the pancreas. Evidence to support this theory is currently lacking. Alternatively, minimal tumor shrinkage (i.e., less than the 50% shrinkage required to qualify as an objective response) may have been sufficient to relieve the compression or invasion of the celiac plexus by the tumor. In other words, the standard paradigm for the determination of antitumor activity may not be well suited for pancreatic cancer.

Further examination suggests that tumor shrinkage may be an especially inappropriate way of determining the antitumor effect of cytotoxic therapy in pancreatic cancer. It is important to recognize our current limitations in the noninvasive imaging of pancreatic cancer. Standard CT scanning does not reliably distinguish a pancreatic tumor from normal pancreatic tissue, tumor desmoplasia, or pancreatitis. Incomplete opacification of the small intestine makes it difficult to distinguish tumor from gut, as well. As a result, inclusion of noncancerous tissue may significantly overestimate tumor shrinkage (as in the case of inflammatory tissue being included in the tumor measurement) or underestimate tumor shrinkage (if fibrotic tissue was included in the tumor measurement).

**New Clinical End Point**

For these reasons, consideration was given to the development of clinical end points that could capture the impact of new therapies on the disability caused by the disease. The NCI and the FDA have jointly acknowledged that relief of tumor-related symptoms is a worthwhile goal of cancer treatment, which can serve as the basis for new drug approval [16]. Pancreatic cancer may represent the ideal setting for applying this approach to drug development, since there is a well-defined constellation of symptoms present in the majority of patients with advanced pancreatic cancer: pain in more than 72% of patients, weight loss in 92%, anorexia in 64%, and nausea in 50% [17].

Recently, instruments that measure quality of life with acceptable reliability and validity have become available for cancer patients [18-21]. These instruments should prove useful in assessing the impact of new therapies on this disease. With the well-defined tumor symptoms associated with
advanced pancreatic cancer, specific assessment of tumor-related symptoms can provide
information that may not be specifically covered by more general quality-of-life questionnaires.

Clinical Benefit Response
Andersen and colleagues have developed a method of assessing clinical benefit response (CBR) in
pancreatic cancer patients that is based on changes in pain (measuring pain intensity and daily
analgesic consumption), Karnofsky performance scale (KPS) status, and weight [22]. In this system,
pain and KPS status are considered the primary measures of CBR, with weight serving as a
secondary (and tie-breaking) assessment in the event that both primary measures are stable.
In order to be useful, the criteria for CBR had to be stringent and clearly defined so that minor
changes in symptoms that could be due to natural fluctuations in the disease course would be
excluded. In order to accomplish this, changes in disease-related symptoms had to be marked and
sustained. Criteria for CBR consist of a 50% or greater improvement (ie, reduction) in pain (as
measured on a 100-mm visual analog scale) compared to baseline, a 50% or greater reduction in
daily analgesic consumption compared to baseline, an improvement in KPS status by 20 points or
more from baseline, or, in the absence of a positive change in either of these parameters, a gain in
dry weight of 7% or more from baseline.
In order for a patient to qualify as a clinical benefit responder, these changes had to last for at least
4 weeks and be unaccompanied by deterioration in any other parameter (Figure 1). Any negative
change in pain, analgesic consumption, or performance status, no matter what the magnitude,
rendered the patient a nonresponder, even if there were positive changes in another parameter.

Clinical Trials of Gemcitabine

These criteria were applied prospectively in two complementary clinical trials (one a phase II and the
other a phase III study) in patients with advanced, unresectable pancreatic cancer. What makes
these trials unique is that they were the first to utilize symptom-centered criteria as the primary end
point to determine the efficacy of a new cytotoxic agent—in this case, gemcitabine.
For a clinical trial to be designed around alleviation of tumor-related symptoms, eligibility criteria
must require that the patients be symptomatic upon entry. For both the phase II and phase III
studies, patients were required, at baseline, to have an impaired functional status, defined as a KPS
status of 50, 60, or 70; pain intensity of at least 20 (on a scale of 0 to 100); and/or daily analgesic
consumption of 10 morphine-equivalent milligrams. Patients who met none of the three criteria were
not eligible for these trials.
It is well known that KPS status and disability from tumor-related symptoms are poor prognostic
factors for survival from any cancer. Therefore, the requirement of impaired KPS and/or significant
tumor-related disability served to select a subset of patients who would be expected to have a
shorter survival compared with asymptomatic patients with the same extent of disease. For this
reason, direct comparison of the survival data from these trials with survival data from any other
trials that did not have the same selection criteria is not appropriate.

Phase III Trial Results
As has been previously reported, 160 patients with newly diagnosed, unresectable pancreatic cancer
were enrolled in the phase III trial [23]. Since establishment of a reliable baseline was critical for
proper analysis of the study results, patients had to have stable pain intensity and stable analgesic
consumption prior to the initiation of therapy. A total of 126 patients completed this pain
stabilization period and were then randomized to treatment with gemcitabine or 5-FU. Gemcitabine
(1,000 mg/m²) was administered intravenously as a 30-minute infusion once weekly for 7 weeks,
followed by 1 week of rest; thereafter, the drug was given once weekly for 3 consecutive weeks out
of every 4. Fluorouracil was administered intravenously at a weekly dose of 600 mg/m² as a
30-minute infusion.
Both treatment arms were well balanced in terms of gender, age, and disease stage, with more than
70% of patients having stage IV disease at diagnosis. The extent and severity of tumor-related
symptoms were also well matched between the treatment arms.
Fifteen patients (23.8%) treated with gemcitabine achieved a CBR, as compared with only three
patients (4.8%) treated with 5-FU. This difference is highly statistically significant (P = .0022 using
the two-sided test for difference in binomial proportions). The median duration of CBR for
gemcitabine-treated patients was 18 weeks, as opposed to 13 weeks for 5-FU-treated patients.
Gemcitabine was also superior to 5-FU in terms of the trial’s secondary end points. Median survival
for gemcitabine-treated patients was 5.65 months vs 4.41 months for 5-FU-treated patients. In
addition, the probability of survival at 1 year was 18% in the gemcitabine group, as compared with
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2% in the 5-FU group. The survival advantage for gemcitabine-treated patients was also statistically significant (P = .0024 by the log rank test). For those patients (in either arm of the trial) who achieved complete benefit response (CBR), the probability of survival at 1 year was 41%, compared to 4% for non-CBR achievers, indicating that CBR and survival probability track in the same direction. Few objective responses were observed in either treatment arm. There were 3 partial responders [5.4%] out of 56 patients with measurable disease who were treated with gemcitabine. In contrast, none of the 57 patients with measurable disease who received 5-FU were partial responders (P = .077).

An important consideration in assessing the value of a palliative therapy in cancer patients is that the therapy be well tolerated. It would be difficult to justify the use of an agent that simply substitutes drug-induced toxicities for disease-related symptoms. Toxicity data from the phase III trial revealed that, at the doses and schedules employed, both drugs were well tolerated. Grade 4 hematologic toxicities and grades 3 and 4 nonhematologic toxicities were rare in both arms. Of grades 3 and 4 toxicities, those that occurred in more than 10% of patients included grade 3 neutropenia and elevations of alkaline phosphatase levels in gemcitabine-treated patients; no grade 4 toxicities were seen in more than 10% of patients [data on file, Eli Lilly and Company, Indianapolis, Indiana and ref 23].

Phase II Trial Results

The phase II study enrolled 63 patients with pancreatic cancer that had progressed despite prior treatment with 5-FU [24]. To be eligible for the trial, patients had to have a significant degree of tumor-related symptoms, as defined above. The dose and schedule for gemcitabine were identical to those used in the phase III trial.

In the phase II study, 17 patients (27.0%) experienced a CBR to gemcitabine. Those patients who experienced a CBR did so quickly: The median time to onset of a CBR was 3 weeks. This is an attractive feature for a treatment designed primarily for palliation. The median duration of CBR was 14 weeks, a clinically meaningful period of time for this group of patients. Median survival of all patients treated in this trial was 3.85 months. Objective responses were seen in 6 (10.5%) of the 57 patients with measurable disease.

The toxicity profile for gemcitabine in this study was similar to that reported in the phase III study. Of grades 3 and 4 toxicities, those that occurred in more than 10% of patients included grade 3 neutropenia and grade 3 elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase levels; no grade 4 toxicities occurred with an incidence of more than 10% [data on file, Eli Lilly and Company, Indianapolis, Indiana]. Although not a comparative trial, this study was the first to demonstrate significant activity (as measured by CBR) for any therapy as a second-line treatment in advanced pancreatic cancer.

Summary and Future Directions

Attempts to develop effective therapy for advanced, unresectable pancreatic cancer have met with little success over the past 30 years. New cytotoxic drugs, novel biologic agents or biologic-response modifiers, new surgical and radiotherapeutic techniques, or a combination of these modalities have all failed to have any appreciable impact on this disease. This has led to a sense of therapeutic nihilism for patients with metastatic pancreatic cancer [25].

A new therapeutic paradigm has been proposed for patients with diseases such as advanced pancreatic cancer, in whom there is a high prevalence of debilitating symptoms and for whom no curative therapy exists. This paradigm focuses on the alleviation of tumor-related symptoms as a meaningful, worthwhile goal of treatment.

Gemcitabine is the first cytotoxic drug to be evaluated using alleviation of tumor-related symptoms as the primary goal of treatment. The results of two complementary trials indicate that gemcitabine is useful in this setting, making it the first new therapy for advanced pancreatic cancer in more than 30 years.* Gemcitabine has an impact not only on the alleviation of tumor-related symptoms but also on prolongation of survival. It has a relatively mild toxicity profile that makes it appropriate for use in a cancer for which no curative therapy exists.

These results suggest that gemcitabine can serve as a model for the development of more effective therapies for patients with pancreatic cancer in the future. Studies to evaluate gemcitabine in patients with earlier stages of pancreatic cancer, as well as in combination with surgery, radiation, and other cytotoxic drugs, have been initiated. These trials will help further define and extend the utility of this important new drug in treating one of the most virulent of all cancers.

*Editor's Note: Subsequent to the roundtable discussion, gemcitabine received FDA approval for...
the treatment of advanced and metastatic pancreatic cancer.


Links:
[1] http://www.diagnosticimaging.com/review-article