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HIGHLIGHT ARTICLE

Locally Advanced Pancreatic Adenocarcinoma: Where Are We and Where Are We Going?

Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22-24, 2010

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Summary

Although many cancers have seen a decline in rates due to screening techniques, the lack of viable screening for pancreatic cancer yields a large number of patients presenting with locally advanced and metastatic disease. Interesting new data regarding the management of locally advanced pancreatic cancer was presented at the 2010 ASCO Gastrointestinal Cancers Symposium, January 22-24, Orlando, FL, USA. Crane *et al.* presented phase II data exploring induction chemotherapy followed by chemoradiotherapy with multiple agents including cetuximab, gemcitabine, oxaliplatin and capecitabine (Abstract #132). Phase II data was also presented examining the role of S-1, an oral fluoropyrimidine, in the locally advanced setting (Abstract #196). In the wake of several studies exploring the role of platinum compounds in combination with gemcitabine; Raftery *et al.* explored the combination of oxaliplatin and gemcitabine with concomitant radiotherapy (Abstract #220). As surgical resection still represents the only clear pathway towards cure, data was presented exploring the factors associated with patients who are converted from unresectable to resectable in the locally advanced setting (Abstract #218). The authors summarize and discuss the data from the meeting.

Introduction

Pancreatic cancer remains a major unsolved health problem, representing approximately 3% of new cancer diagnoses last year (42,470 new cases) and 6% of the total cancer deaths (35,240) in the United States [1]. Unfortunately most patients present with locally advanced or metastatic disease at the time of diagnosis leaving relatively few patients as candidates for upfront resection. Locally advanced disease is observed in 15-20% of all patients with pancreatic cancer, and is associated with a median survival of 6-10 months. Locally advanced pancreatic cancer is defined as surgically unresectable because of the encasement or occlusion of the superior mesenteric vein or portal vein confluence, or direct involvement of the superior mesenteric artery, celiac axis, inferior vena cava, or aorta. Four randomized control trials have compared the effectiveness of chemoradiation incorporating 5-fluorouracil with radiation alone or systemic chemotherapy [2, 3, 4, 5]. Three of these trials showed an improved median survival of 10.1-10.6 months for radiotherapy plus 5-fluorouracil alone or triple therapy (streptozocin, mitomycin C and 5-fluorouracil) compared with 5.7-6.3 months for radiotherapy alone or systemic chemotherapy with streptozocin, mitomycin C and 5-fluorouracil. Based on these data, chemoradiotherapy has been considered a standard therapy for locally advanced pancreatic cancer.

Locally advanced pancreatic adenocarcinoma represents a particularly troublesome area with several unanswered questions: What is the optimal regimen for locally advanced pancreatic adenocarcinoma? What is the role of the neoadjuvant approach? Is there a role for radiotherapy? Do we know how to incorporate targeted agents in this setting? The Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic (GERCOR) has provided continued work in this area to help provide some much needed answers. In 2007 Huguet *et al*. explored the role of chemoradiotherapy in patients achieving either disease stability or improvement following upfront chemotherapy. They found an improvement in progression free survival and overall survival between the chemoradiotherapy and the chemotherapy arms of 10.8 and 7.4 months (P=0.005) and 15.0 and 11.7 (P=0.0009) months,

Key words gemcitabine; Neoadjuvant Therapy; Pancreatic Neoplasms

Abbreviations GERCOR: Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic; NCCN: National Comprehensive Cancer Network; S-1: tegafur, gimeracil, and oteracil potassium

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Table 1. 2010 ASCO Gastrointestinal Cancers Symposium: treatment in locally advanced pancreatic cancer abstracts.

Abstract	Title	Number of patients	Study type
#132 Crane CH, *et al*. [8]	Multi-institutional phase II trial of induction cetuximab, gemcitabine, and oxaliplatin, followed by radiotherapy with concurrent capecitabine, and cetuximab, for locally advanced pancreatic adenocarcinoma (LAPC).	69	Prospective Phase II
#196 Shinchi H, Takao S. [9]	Phase II study of oral fluoropyrimidine anticancer agent (S-1) with concurrent external-beam radiotherapy for locally advanced pancreatic cancer.	50	Prospective Phase II
#218 Moskovic DJ, *et al*. [14]	Factors predicting outcomes in patients with locally advanced pancreatic cancer (LAPC).	142	Retrospective
#220 Raftery LL, *et al*. [15]	A phase I study of weekly oxaliplatin (Ox) and gemcitabine (Gem) during radiotherapy (RT) for unresectable pancreatic or biliary carcinoma.	18	Prospective Phase I

respectively [6]. A phase III study conducted with the addition of oxaliplatin to gemcitabine (*versus* gemcitabine alone) in the locally advanced setting has shown improvement in response rates and progression free survival but not in overall survival [7]. Although this trial failed to show a survival advantage; the improvement in response rates were marked (14.9% *versus* 27.4%), providing an approach for patients with "borderline-resectable" disease who may have the potential to become surgical candidates.

The following abstracts, presented at the 2010 ASCO Gastrointestinal Cancers Symposium, seek to add to our breadth of knowledge of the treatment of locally advanced pancreatic cancer (Table 1).

Update on Treatment in Locally Advanced Pancreatic Cancer

Abstract #132: Multi-institutional phase II trial of induction cetuximab, gemcitabine, and oxaliplatin, followed by radiotherapy with concurrent capecitabine, and cetuximab, for locally advanced pancreatic adenocarcinoma (LAPC) [8]

This phase II study evaluates the role of induction therapy with chemotherapy alone followed by chemoradiotherapy. Sixty-nine, treatment naïve patients were accrued between October 2005 and June 2009 and given induction therapy with gemcitabine and oxaliplatin. Figure 1 shows the treatment schema. After 4 doses patients were re-imaged with CT scans and those without progression of disease went on to receive radiation therapy with concurrent capecitabine. Cetuximab was administered on a biweekly basis starting on day 1 and continued throughout the treatment regimens with chemotherapy and chemoradiotherapy. The primary and secondary endpoints were 1-year overall survival and response and safety, respectively. The 1-year overall survival was 66.7% (95% confidence interval (CI): 60.2-73.2%) with a median survival of 19 months. Four patients who initially presented with disease that was deemed unresectable were "converted" into surgical candidates and underwent R0 resections. Major adverse events were constitutional, gastrointestinal, neuropathic, and hematologic. Sixty percent of patients experienced at least a grade-2 acneiform rash. Overall this regimen was tolerated reasonably well and was associated with encouraging responses.

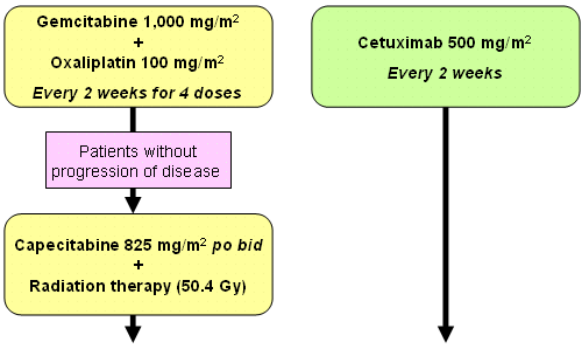

Figure 1. Induction chemotherapy followed by chemoradiotherapy for LAPC: treatment schema for abstract #132 [8].

Abstract #196: Phase II study of oral fluoropyrimidine anticancer agent (S-1) with concurrent external-beam radiotherapy for locally advanced pancreatic cancer [9]

Fluoropyrimidines have been a mainstay in the treatment of gastrointestinal malignancies for many years. Infusional formulations such as 5-fluorouracil can often time be cumbersome to administer. Several oral formulations have emerged and offer a multitude of potential benefits. S-1 is a new oral formulation consisting of 1 M tegafur, 0.4 M gimeracil and 1 M oteracil potassium. S-1 was developed by the scientific theory of both potentiating antitumor activity of 5-fluorouracil and reducing gastrointestinal toxicity induced by 5-fluorouracil [10, 11]. S-1 is widely used in Japan in both the adjuvant and metastatic setting as both monotherapy and in combination with gemcitabine. The key clinical sites and functional pathways of activity are noted in Figure 2.

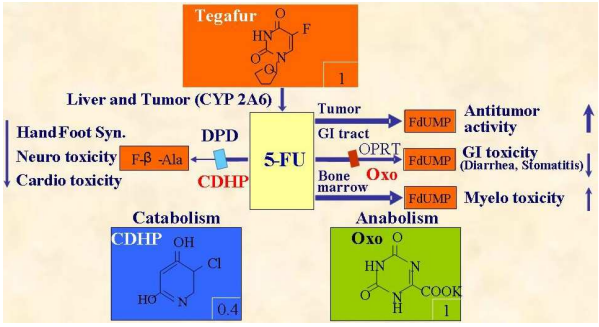

Figure 2. S-1: an oral fluoropyrimidine [24].

Ikeda *et al*. evaluated the combination of S-1 and concomitant radiotherapy in a phase I study; yielding a recommended treatment dose of 80 mg/m^2 [12]. The median survival for patients in this study (at varied S-1 doses) was 11.0 months. Although two patients reached dose-limiting toxicity in the 70 mg/m^2 dosing, no patients reached dose-limiting toxicity at the 50, 60, or 80 mg/m^2 dose [12].

Patients were deemed eligible if they had locally advanced pancreatic cancer, without evidence of distant metastatic disease, Eastern Cooperative Oncology Group (ECOG) 0-1, and adequate organ function. S-1 was administered at 80 mg/m^2 *po* twice-daily on days 1-21 along with radiation therapy. External beam radiotherapy (EBRT) was administered at 1.25 Gy/fraction twice daily over a period of 4 weeks for a total of 40 fractions (50 Gy). Following the initial chemoradiotherapy induction, a maintenance period of S-1 monotherapy was administered on a "14 day on, 14 day off" schedule at the previous dosage. This was continued until disease progression or cessation due to toxicity.

Of the 50 patients entered into the trial all but two completed the planned regimen of chemoradiotherapy. Forty-two patients (85%) had stable disease or better by Response Evaluation Criteria in Solid Tumors (RECIST) criteria [13] (Table 2). The regimen was tolerated quite well overall and was associated with only two instances of grade 3 toxicities and no grade 4 toxicities. This approach appears quite favorable and further phase III studies are warranted.

Table 2. Results: Abstract #196.

Response:	
- Partial response	17 (35%)
- Stable disease	25 (50%)
- Progressive disease	8 (16%)
Survival:	
- Median survival	14 months
- 1-year survival rate	60%
- 2-year survival rate	22%

Abstract #218: Factors predicting outcomes in patients with locally advanced pancreatic cancer (LAPC) [14]

Surgical resection remains the cornerstone of curability in patients in pancreatic cancer. Although a minority of patients will be candidates for upfront surgical resection; a number of patients with unresectable, locally advanced disease at presentation can be converted to an operable status. Moskovic *et al*. have sought to tease out the factors associated with this phenomenon in hopes of formulating a prediction schema which may help to guide initial management of locally advanced pancreatic cancer.

Multiple factors were evaluated for a patient cohort of 150 patients with locally advanced pancreatic adenocarcinoma. These included demographics such as age, race, gender; laboratory data such as CA 19-9 levels; as well as anatomic data looking at primary tumor location and presence of vascular invasion. The primary endpoint was rate of conversion to resectability and its correlative factors. Secondary endpoints were overall and progression free survivals and utilization of second-line chemotherapy. Eight patients were not evaluated in the final analysis as complete records were unavailable for those subjects.

In total 26 out of 142 (18.3%) patients were converted to resectability following chemotherapy with or without chemoradiotherapy. Although multiple variables affected the likelihood of survival; only anatomic variables had a significant effect on rates of resectability. All tumors which were eventually deemed "resectable" were located either in the head of the pancreas or in the uncinate process (P=0.0002). Tumors which remained unresectable were more likely to have either celiac artery invasion (P=0.001) or superior mesenteric artery invasion (P<0.001).

Younger age, lower CA 19-9, and maintenance chemotherapy all correlated with a statistically significant improvement in progression free survival. Older age, higher CA 19-9, and lack of maintenance therapy trended towards lower overall survival and progression free survival but did not reach significance. The findings of this abstract can help to guide a plan of care for patients with locally advanced pancreatic cancer and offer some prognostic methodology as well.

Abstract #220: A phase I study of weekly oxaliplatin (Ox) and gemcitabine (Gem) during radiotherapy (RT) for unresectable pancreatic or biliary carcinoma [15]

Gemcitabine has been shown to be a potent radiosensitizer in pancreatic cancer cells [16]. Although the standard weekly dosing of gemcitabine is 1,000 mg/m^2; phase I studies have demonstrated a significant increase in hematologic and hepatic dose-limiting toxicities at this dosing level [17]. In turn, when gemcitabine is given concomitantly with radiation, the dosing ranges are typically on the order of 100-400 mg/m^2. The combination of gemcitabine and oxaliplatin has been studies in the locally advanced and metastatic setting in the GERCOR and the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD) trials [7]. While this study did not demonstrate a significant improvement in overall survival; significant improvements were seen in response rates and progression free survival. The abstract discussed here offers phase I data examining the role of the combination of gemcitabine and oxaliplatin in the locally advanced setting when combined with radiotherapy.

Patients were allocated into 4 treatment arms based on a 3x3 design. Four dosing levels were tested with gemcitabine doses ranging 100-200 mg/m^2 and oxaliplatin doses ranging 30-60 mg/m^2. The chemotherapy was administered on a weekly basis (for a maximum of 6 doses) along with daily radiation of 180 cGy/fraction for a cumulative dose of 50.4 Gy.

The highest dosing cohort (gemcitabine 200 mg/m^2 plus oxaliplatin 60 mg/m^2) had no dose-limiting toxicities. Major side effects included leukopenia,

nausea and hyperglycemia. Overall survival was 10.8 months with a 95% CI of 7.1-16.7 months and progression free survival was 9.6 months with a 95% CI of 4.6-11.1 months. This dosing level cohort has been expanded for further testing. Phase II/III studies are warranted to explore this approach further.

Discussion

Optimal therapy for patients with locally advanced pancreatic cancer remains elusive. Early clinical data presented at the 2010 ASCO Gastrointestinal Cancers Symposium offer a multitude of venues for further research. The National Comprehensive Cancer Network (NCCN) guidelines recommend gemcitabine monotherapy *versus* gemcitabine based chemoradiotherapy [18]. The position of the NCCN remains that the best approach for all patients with cancer is clinical trial.

As surgical resection remains a key component of the curative strategy; a neoadjuvant approach in the locally advanced setting represents a viable pathway to long term survival. A recent meta-analysis by Morganti *et al*. showed evidence that patients who do not progress after induction therapy may benefit from radical surgical approaches in skilled surgical settings [19]. In Japan the availability of S-1 allows for its use in concert with gemcitabine based chemoradiotherapy in efforts to convert patients to resectability [20, 21].

Other agents, such as irinotecan, which has shown activity in a variety of gastrointestinal tumors has been used as a radiosensitizer in patients with locally advanced pancreatic adenocarcinoma. Phase I data from de la Fouchardière C, *et al*. has shown activity with median survival times of 12.6 months [22].

Gene therapy also shows interesting promise as an adjunct in the neoadjuvant approach. Early data with the use of TNFerade® (GenVec Inc., Gaithersburg, MD, USA) has shown promise when used with radiotherapy with or without chemotherapy. TNFerade® delivers and modulates tumor necrosis factor alpha via a replication deficient adenovirus under the influence of a radiation-inducible gene promoter [23].

Targeted therapy has found a home in the age of personalized medicine. Moskovic *et al*. [14] offers an excellent framework for the "tailoring" of therapies based on individual patient/tumor nuances. As our knowledge advances in the fields of tumor biology and molecular analysis we begin to unravel the heterogeneity within pancreatic adenocarcinoma and can more accurately treat and potentially cure the disease.

Conflict of interest The authors have no potential conflicts of interest

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