

HIGHLIGHT ARTICLE

Updates of Adjuvant Therapy in Pancreatic Cancer: Where Are We and Where Are We Going? Highlights from the “2010 ASCO Annual Meeting”. Chicago, IL, USA. June 4-8, 2010

Jia Li¹, Man Yee Merl², John Chabot³, Muhammad Wasif Saif¹

¹Yale University School of Medicine and ²Yale-New Haven Hospital. New Haven, CT, USA.
³Columbia University. New York, NY, USA

Summary

Pancreatic cancer represents the 4th leading cause of cancer deaths in the United States. Surgical resection remains the only potential curative approach. Current standard adjuvant therapy is gemcitabine monotherapy for 6 months. This year several trials investigated other combinations with or without molecular target agents, with or without concurrent radiation attempting to optimize adjuvant therapy. Several abstracts presented at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting are highlighted here and will be further discussed in this review article. Abstracts #4012, #4059, and TPS226 added immunotherapy to adjuvant treatment. Abstract #4034 demonstrated lack of efficacy by adding either cetuximab or bevacizumab to known adjuvant therapies. Abstract e14625 combined S-1 to gemcitabine and abstract #4113 demonstrated a positive correlation between symptoms and CA 19-9 levels with the length of survival.

What Did We Know Before 2010 ASCO Annual Meeting?

The American Cancer Society estimated that approximately 42,470 new cases of pancreatic cancer were diagnosed in the United States in 2009 with 35,240 deaths [1]. Of the new cases, only approximately 20% would be considered resectable and would be given adjuvant chemotherapy. Results from the Charité Onkologie (CONKO-001) trial have shown that compared to placebo, adjuvant chemotherapy with gemcitabine demonstrated a median recurrence-free survival of 14 months, median overall survival of 22 months, and a survival rate of 20% at 5 years [2]. This landmark paper established the cornerstone of resected pancreatic cancer treatment.

What Did We Learn from 2010 ASCO Annual Meeting?

This review article will update you with the material presented at the 2010 ASCO Annual Meeting (Table 1) regarding adjuvant therapy of pancreatic carcinoma.

Incorporation of Immunotherapy into Conventional Chemotherapy or Chemoradiation

Completely resected pancreatic cancer represents a compelling model of minimal residual disease for which many investigators believe immunotherapy may be the treatment choice.

Hardacre *et al.* (Abstract #4059) presented the data of an allogeneic immunotherapy in addition to standard therapies such as gemcitabine based chemotherapy or 5-fluorouracil (5-FU) based chemoradiation in patients with resected pancreatic cancers [3]. A total of 62 patients were enrolled; the majority (81%) had lymph node positive disease. The current median progression free survival is 17 months, and one year overall survival rate reaches 96%. The survival benefit of adding hyperacute pancreas to standard therapy is very promising. A phase III multi-institutional (more than 50), open-label, randomized trial has been initiated.

Another pancreatic adjuvant trial (CapRi; Abstract LBA4012) tested chemoimmunoradiotherapy vs. 5-FU/leucovorin alone [4]. The former includes cisplatin, IFN-alpha concurrent with radiation (CRI); this regimen was developed by Picozzi *et al.* and tested in the ACOSOG trial [5]. There was no significant survival difference between the two arms (32.1 and 28.5 months, respectively); however, unplanned subset analyses favored CRI for R1 and N1 disease. In addition, the CRI treatment, as expected, significantly reduced the local recurrence rate from 55.6% to 29.3% (P=0.014). The chemoimmunoradiotherapy arm

Key words Chemotherapy, Adjuvant; gemcitabine; Immunotherapy; Pancreatic Neoplasms

Abbreviations ASCO: American Society of Clinical Oncology; CRI: cisplatin, IFN-alpha concurrent with radiation

Correspondence Muhammad Wasif Saif
Yale Cancer Center, Yale University School of Medicine, 333 Cedar Street, FMP 116, New Haven, CT, USA
Phone: +1-203.737.1569; Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

URL <http://www.serena.unina.it/index.php/jop/article/view/3610/3949>

demonstrated much lower incidence of severe toxicity compared to the historical data from ACOSOG Z05031 trial [5], which was closed early because of toxicity. More importantly, this trial demonstrated a positive correlation between response to single IFN-alpha treatment and longer survival. Whether the response to IFN is a prognostic or predictive marker needs to be investigated. Several concerns about this trial were brought up during the meeting. Lack of stratification may have biased these results and masked a positive effect of chemoradioimmunotherapy. Differences in the toxicity profile compared to the ACOSOG Z05031 trial [5] need to be explained.

Ras mutations occur commonly in the development of pancreas cancer. GI-4000 is an immunotherapy using targeted molecular immunogens (Tarmogens) to specifically activate immune response and attack cells expressing ras mutations. Whiting *et al.* (Abstract TPS226) are conducting a trial to evaluate the efficacy of gemcitabine with or without GI-4000 in the adjuvant setting [6]. The trial is designed for patients to receive weekly GI-4000 or placebo x3 followed by gemcitabine weekly x3 every 28 days for a total of 6 cycles. All patients are maintained on monthly GI-4000 or placebo for up to 5 years. This trial is ongoing with no results reported at this meeting. It would be interesting to see any additional benefit of an immunotherapy beyond gemcitabine alone.

Incorporation of Molecular Target Agents with Cytotoxic Agents

Combining molecular target agents with conventional cytotoxic agents remain a popular thought. Berlin *et al.* (ECOG 2204; Abstract #4034) presented an interesting randomized phase II trial to investigate the feasibility of cetuximab or bevacizumab in combination with

standard adjuvant chemotherapy followed by capecitabine-based concurrent chemoradiation [7]. Molecular agents were given throughout therapy. One-hundred and twenty-nine eligible patients were randomized to either arm (cetuximab or bevacizumab plus gemcitabine followed by capecitabine-based chemoradiation). Primary endpoint was toxicity; secondary endpoints were disease free survival and overall survival. No severe toxicities were observed in the study; however, more than 10% patients recurred during the adjuvant treatment period. Disease free survival or overall survival was not superior to historical data derived from gemcitabine monotherapy. Neither arm demonstrated enough clinical activity to warrant further study. Therefore, the investigators believe there is no role for cetuximab or bevacizumab as part of adjuvant therapy. Development of novel agents may be necessary to make a change.

Combination of Conventional Cytotoxic Agents

S-1 has been proved to be highly active in advanced or metastatic pancreatic cancer. A Japanese study group (Abstract e14625) presented a phase I/II trial of gemcitabine plus S-1 in the adjuvant setting [8]. All enrolled patients received i.v. gemcitabine (mg/m²/week) on day 1 and oral S-1 (mg/m²/day) twice daily from days 1 to 7 every 14 days for 12 cycles at the following dose levels of gemcitabine/S-1: 800/60 (level 0), 1,000/60 (level 1) and 1,000/80 (level 2). Thirteen patients were enrolled in the phase I part. Level 0 was determined to be maximal tolerated dose. A total of 55 patients were enrolled onto phase II part. Severe neutropenia is a concern in this gemcitabine/S-1 combination. Whether S-1 has similar promising anti-tumor effect in pancreatic cancer as in gastric cancer will have to be evaluated based on survival data.

Table 1. 2010 ASCO Annual Meeting: pancreatic cancer adjuvant therapy.

Abstract# Author	Study design	Testing drug	No. of patients	Local recurrence rate	Overall survival	Side effects	Comments
#4059 Hardacre, <i>et al.</i> [3]	Phase II	Hyperacute pancreas (HAPa) plus gemcitabine or 5-FU chemoradiotherapy	62	Not reported	1-year rate: 90%	Erythema, induration at the injection sites	Addition of HAPa to gemcitabine or 5-FU based adjuvant therapy is promising; phase III is ongoing.
LBA#4012 Marten, <i>et al.</i> [4]	Phase III	Cisplatin plus IFN-alpha concurrent with radiation (CRI) vs. 5-FU alone	110	CRI: 29.3% 5-FU alone: 55.6%	Median: CRI: 32.1 months 5-FU alone: 28.5 months	Neutropenia, diarrhea	In addition to reduce the risk of local recurrence, CRI offers the longest ever reported survival
TPS226 Whiting, <i>et al.</i> [6]	-	Weekly GI-4000 or placebo x3 followed by gemcitabine	Target accrual: 200	Not reported	Not reported	Not reported	-
#4034 Berlin, <i>et al.</i> [7]	Phase II	Cetuximab or bevacizumab with gemcitabine followed by capecitabine concurrent with radiation	129	Recurrent disease while on therapy: Cetuximab: 9% Bevacizumab: 13%	2-year rate: Cetuximab: 35% Bevacizumab: 37%	Grade 3-4 hematological toxicities	The two molecular target agents seem not to have activity against pancreatic cancer
e14625 Ishii, <i>et al.</i> [8]	Phase I/II	Gemcitabine and S-1	Phase I: 13 Phase II: 55	Not reported	Not reported	Hematological toxicity remains the issue, especially neutropenia.	Only toxicity data are available. Survival data are pending

HAPa: hyperacute pancreas

CRI: cisplatin plus IFN-alpha concurrent with radiation

Role of CT Scan, Symptoms And Tumor Marker CA 19-9

A retrospective review conducted by Vaccaro *et al.* (Abstract #4113) assessed the use of CT scan, symptoms and tumor marker CA 19-9 as surveillance tools to detect early recurrent disease [9]. Data from a total of 476 patients with pancreatic cancer resections from 1998 to 2008 were reviewed. Only 15% of recurrences were observed on CT scan in the absence of symptoms. However, 85% of recurrences were associated with symptoms and/or rising tumor marker levels. Asymptomatic patients with a normal CA 19-9 had a significantly prolonged overall survival compared to either asymptomatic or symptomatic patient with rising CA 19-9 (18 vs. 10 vs. 5 months, respectively; $P < 0.0001$).

Discussion

The optimal adjuvant approach for patients with resected pancreatic cancer remains unclear. The National Comprehensive Cancer Network (NCCN) guidelines offer a variety of approaches including systemic chemotherapy with agents such as gemcitabine, 5-fluorouracil, capecitabine or gemcitabine followed by 5-fluorouracil based chemoradiotherapy [10]. Whether one is superior to the other needs to be validated in large randomized trials.

Intensive research is currently being conducted to evaluate the role of immunotherapy in the adjuvant setting. The rationale favoring immunotherapy in the adjuvant setting lies on the theory of eradicating any microscopic disease after a complete resection. The IFN- α containing regimen showed the longest ever reported over survival; final survival data from other groups are pending. Overall, immunotherapy represents an appealing approach. More randomized trials are certainly needed to confirm the results and further clarify the role of radiation in this setting. Several trials included radiation therapy concurrent or after chemotherapy; however, the survival benefit of radiation remains unclear.

GI-4000 approach focuses on selectively targeting pancreatic cancer cells expressing a *ras* mutation. It is well known that the vast majority of pancreatic cancers have mutated *ras*. This yeast derived immunogen induces an endogenous T-cell response which may confer a role in both the active therapeutic as well as the preventative setting.

EGFR and VEGF, two commonly used monoclonal antibodies (cetuximab and bevacizumab) with demonstrated anti-tumor effects in other solid tumors such as head, neck and colorectal, appear to have no

activity in resected pancreatic cancer. These results reinforce the message that development of novel agents is critical to provide durable benefit and tolerable toxicity.

Conflict of interest The authors have no potential conflicts of interest

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