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HIGHLIGHT ARTICLE

Adjuvant Therapy of Pancreatic Cancer

Highlights from the "2012 ASCO Annual Meeting". Chicago, IL, USA; May 31 - June 5, 2012

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Summary

Adjuvant therapy for pancreatic cancer remains controversial. However, both sides of the Atlantic Ocean agree that at least gemcitabine should be the pivotal agent offered to all patients. The role of radiation therapy remains somewhat inconclusive but chemoradiation, whether in the neoadjuvant or adjuvant setting is a standard option often utilized in the USA. This review is an update from the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago, IL, USA. We present the summary of the findings from Abstracts #4020, #4021, #4040 and #4049 and discuss the impact on this group of patients.

What Did We Learn at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting?

Proton Beam Therapy

In Abstract #4021, Hong *et al*. examined the role of short course chemoradiotherapy in the neoadjuvant setting for resectable pancreatic adenocarcinoma [1]. This study was a prospective, single institutional, phase I/II study with several dose levels of progressively shorter schedules; the final dose level was 5 Gy x 5 fractions (25 Gy total) concurrently with capecitabine (825 mg/m^2 *bid*). A total of 50 patients were enrolled in this study, and all patients received proton beam therapy targeting the pancreatic mass with elective nodal coverage. Surgery was performed 1-6 weeks after the chemoradiation, and patients were recommended to receive 6 months of adjuvant gemcitabine. Genotyping of 15 genes (including *K-ras*, *PIK3CA*, *BRAF*, *NRAS*, *TP53*, *IDH1*) was performed on 28 collected tumor samples (see genetic factors and Table 4). A summary of the results of their study is shown in Tables 1 and 2. The results of this phase I/II trial show excellent local control and little significant toxicity with this novel chemoradiotherapy strategy. It appears that, using proton radiotherapy, a shorter course of radiotherapy of one week with concurrent capecitabine could be well tolerated and enables the large majority of patients to undergo earlier surgical resection. Furthermore, the majority of the resections were able to achieve negative margins and favorable local control and survival outcomes. Finally, this study was able to gather and present genotype information regarding the collected tumors, which will hopefully provide further therapeutic insights into this disease.

A small study by Alvarez-Gallego *et al*. (Abstract #4040) of nab-paclitaxel with gemcitabine was also presented in neoadjuvant setting with two cycles prior to surgery in resectable and borderline resectable pancreatic cancer [2]. Only 16 patients were enrolled with preliminary results showing one complete pathological response and four near complete pathological response and complete resection rate of 89% (8/9 patients). A positive effect in the stromal composition in the resected tumors was also noted with the addition of nab-paclitaxel.

Is there a Role of Immunotherapy in Resected Pancreatic Cancer?

Due to the high rate of failure of standard of care adjuvant therapy, there has been an ongoing interest to evaluate the effectiveness of experimental cellular immunotherapy in adjuvant setting in patients with pancreatic cancer. Hardacre *et al*. in abstract #4049 presented the update of the open-label, dose-finding, nonrandomized phase II study of live, allogeneic, cellular immunotherapy with algenpantucel-L

Kew words Chemotherapy, Adjuvant; Immunotherapy; Pancreatic Neoplasms

Abbreviations CONKO: Charité Onkologie Clinical; RTOG: Radiation Therapy Oncology Group

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Table 1. Summary of results of short course chemoradiation with proton beam therapy followed by surgery.

	Phase I				Phase II
	Dose level 1	**Dose level 2**	**Dose level 3**	**Dose level 4**	**Dose level 4**
Radiation dose	3 Gy x 10 fractions daily	5 Gy x 5 fractions (week 1: Mo, We, Fr; week 2: Tu, Th)	5Gy x 5 fractions (week 1: Mo, Tu, Th, Fr; week 2: Mo)	5 Gy x 5 fractions (week 1: Mo-Fr)	5 Gy x 5 fractions (week 1: Mo-Fr)
Number of patients	3	3	3	6	35
Capecitabine (mg/m^2 *bid*; weeks 1-2: Mo-Fr)	825	825	825	825	825
Grade 3 toxicity	0	0	0	0	2 patients (6%): chest wall pain, colitis
Grade 4/5 toxicity	0	0	0	0	0

(HyperAcute Pancreas®, NewLink Genetics Corporation, Ames, IA, USA) plus standard adjuvant therapy with Radiation Therapy Oncology Group (RTOG)-9704: gemcitabine plus 5-FU based chemo-radiation for patients with resected pancreatic adenocarcinoma [3]. A total of 70 patients received standard adjuvant therapy plus algenpantucel-L and showed favorable survival advantage compared to historical control who did not receive algenpantucel-L. The major findings are summarized in Table 3. Of note, patients receiving higher dose of 300 million cells/dose tend to have better 1 year disease free survival (81% *vs*. 52%, P=0.02) and 1-year overall survival (96% *vs*. 80%, P=0.053) compared to patients who received lower dose of 100 million cells/dose.

Table 3. Summary of results of immunotherapy with algenpantucel-L in pancreatic cancer.

	1-year disease free survival	**1-year overall survival**
Overall study population	63%	86%
Dose response: 100M cells/dose	52%	80%
Dose response: 300M cells/dose	81%	96%
Historical control	45%	65%

Prognostic Factors for Resected Pancreatic Cancer Patients

The landmark Charité Onkologie Clinical (CONKO)-001 study established gemcitabine as the standard adjuvant chemotherapy after complete resection of pancreatic cancer as this randomized phase III trial showed significantly delayed development of recurrent disease after complete resection of pancreatic cancer compared with observation alone. This year at the ASCO Annual Meeting, Sinn *et al*. in Abstract #4020 presented the prognostic factors on the long-term survival in patients with pancreatic cancer who were enrolled in CONKO-001 study and followed for more than 5 years [4]. Of the 354 patients enrolled in CONKO-001, 53 (15%) patients were found to have overall survival greater than 5 years. As shown in Table 3, tumor grade (odds ratios: grade 3 *vs*. grade 1 equal to 0.07 and grade 3 *vs*. grade 2 equal to 0.38; P=0.017) and treatment with gemcitabine (odds ratio: gemcitabine *vs*. observation equal to 0.38; P=0.004) were the only two independent predictive factors for long term survival in multivariate analysis. Tumor size and lymph node status showed significance in univariate analysis but the significance was not seen in the multivariate analysis. Significance could not be demonstrated for resection margin, performance status, age, sex and CA 19-9 level at study entry. These results are summarized in Table 4.

Genetic Factors

Hong *et al*. in abstract #4021 also studied mutational analysis by genotyping of 15 genes including *K-ras* in 38 resected specimens. *DPC4* status was also analyzed in 30/38 resected specimens. As seen in Table 5, *K-ras* status and *DPC4* (also known as *SMAD4*) status did not appear to have a statistically significant impact on

Table 2. Summary of patient characteristic and results of short course chemoradiation with proton beam therapy followed by surgery.

Characteristic	**Result**
No. of patients who underwent pancreaticoduodenectomy	38
No. of patients who did not undergo pancreaticoduodenectomy due to metastatic disease	9
No. of patients who did not undergo pancreaticoduodenectomy due to unresectable tumor	1
Frequency of resected patients with positive margins	6/38 (16%)
Frequency of resected patients with positive nodes	28/38 (74%)
Median follow up	21 months
Local failure	4/48 (8%)
Median progression free survival (all patients)	10 months
Median overall survival (all patients)	18 months
Median progression free survival (resected patients)	14 months
Median overall survival (resected patients)	27 months

Table 4. Summary of long term survival predictors from CONKO-001 study.

Factors	Long-term survival		P value
	Yes	No	
Use of gemcitabine	68%	48%	0.006
Tumor grading			0.017
- G1	17%	3%	
- G2	64%	55%	
- G3	17%	40%	
Tumor size			0.004 [a]
- T2	15%	9%	
- T3	74%	84%	
Lymph node involvement			0.003 [a]
- N0	47%	25%	
- N1	53%	74%	

[a] P value statistically significant in univariate analysis only and not significant in multivariate analysis

overall survival or progression free survival. From this study, it appears that *K-ras* and *DPC4* status shows no correlation with survival outcomes.

Discussion

More than 80% of patients with pancreatic cancer present with locally advanced or metastatic disease and have a median survival of only 6 months and a 5-year overall survival of only 6%. Pancreatic cancer remains a highly lethal disease and more research in the tumor biology, genetics and innovative treatment approaches are needed to improve survival in this patient population.

The study by Hong *et al*. in Abstract #4021 is important at several levels [1]. First, by using a shorter chemoradiotherapy course (5 Gy x 5 fractions in consecutive days), their multi-modality approach allows resectable pancreatic cancer patients to get to surgery earlier than standard course chemoradio-therapy, which can take 5-6 weeks to complete. Furthermore, this regimen showed good tolerability. Chemoradiotherapy with 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) is often limited by the radiation dose tolerances of the bowel, liver, stomach, spinal cord, and kidneys. The dosimetric advantages achieved with proton beam therapy may be a key component of this regimen's excellent toxicity profile (Figures 1 and 2). While proton beam therapy, as a technique, has been limited by the relatively few number of proton centers and questions regarding its cost-effectiveness [5], this study offers yet another application of this emerging, alternative technology. Abstract #4021 demonstrates the promise that larger fractions of radiotherapy delivered in shorter courses, known as hypofractionated radiotherapy, and proton beam radiotherapy may be emerging techniques to add into the pancreatic cancer treatment toolbox. Neoadjuvant chemoradiation, with improved radiotherapy techniques, remain promising as part of the multi-modality approach towards pancreatic cancer.

Pancreatic adenocarcinoma has been shown to be susceptible to immune stimulation and immunotherapy designed to target pancreatic tumor-associated antigens (TAAs) has been an important area of research. Immunotherapy is based on recruiting and activating cytotoxic T cells that recognize the tumor-associated antigens in the pancreatic cancer cells and induce cellular cytotoxity [6]. Pancreatic cancer cells that develop gemcitabine resistance would still be suitable targets for immunotherapy [6] and there is an increasing interest to evaluate the effectiveness of upfront use of multimodality approach with chemoradioimmunotherapy to treat this aggressive cancer.

Hyperacute immunotherapy with algenpantucel-L is based on the hypothesis that alfa-galactosyltransferase (alpha-GT) epitopes in human cancer cells trigger a powerful immune response called "hyperacute rejection", characteristically targeting xenotransplanted tissue, in this case against the modified cancer cells [7]. This inflammatory reaction/immune response is thought to be responsible for generating immunity against tumor antigens. Algenpantucel-L was well tolerated with no dose limiting toxicities and the commonly observed adverse reaction is inflammation at the injection site, which typically resolves within a week. Based on positive data from this phase II clinical trial, NewLink Genetics (Ames, Iowa, USA) in May, 2010 started enrolling a nationwide phase III clinical trial of HyperAcute Pancreas® immunotherapy in patients who have successfully undergone pancreatic surgical resection [8]. The FDA has granted both Fast Track designation and Orphan Drug designation for this program and the phase III trial aims at enrolling up to 722 previously untreated patients with stage I or II surgically-resected adenocarcinoma of the pancreas by

Table 5. *K-ras* mutational analysis, *DPC4* status and survival outcomes.

Mutation analyzed	*K-ras* status	*DPC4* status
Unmutated tumors	Wild type: 6/38 (15%)	Preserved: 11/30 (37%)
Mutated tumors	Mutated: 27/38 (71%)	Deleted: 19/30 (63%)
Impact on survival:		
- Progression free survival	P=0.729	P=0.950
- Overall survival	P=0.388	P=0.908

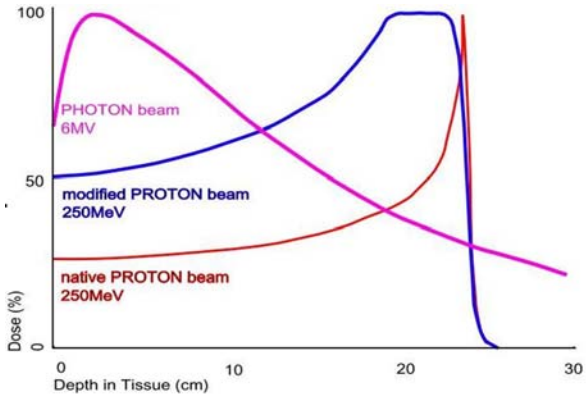

Figure 1. The dose distributions of photons and protons, including the characteristic Bragg Peak of the single proton beam profile.

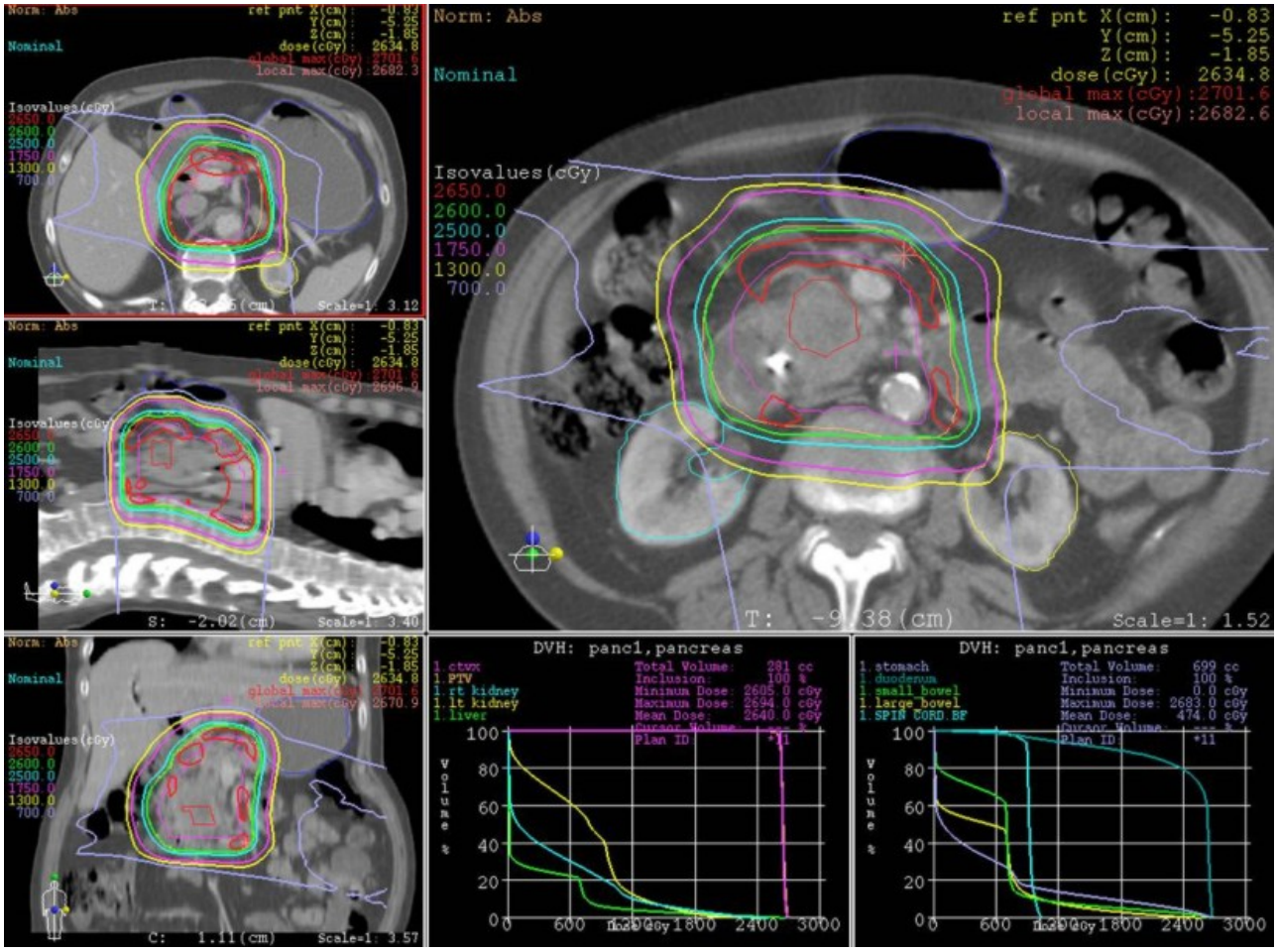

Figure 2. Treatment plan isodose distributions and dose volume histogram from Abstract #4021 [1] (courtesy of TS Hong).

incorporating the vaccine with current standard of care either CONKO-001 or RTOG 9704 regimens. Patients will be treated for approximately six months followed with imaging for five years. This year at the ASCO Annual Meeting, Hardacre *et al*. in Abstract #4049 presented that a higher dose of 300 million cells/dose may have better survival outcomes compared to lower dose of 100 million cells/dose and the phase III study will likely clarify whether a larger dose translates into a better survival outcomes [3]. Once completed this large, prospective phase III randomized controlled trial will further define the role of immunotherapy in pancreatic cancer.

There has been growing interest in novel biomarkers, both for early detection and better therapeutic targeting of pancreatic cancer cells. *K-ras* is a genetic biomarker which is often mutated in patients with pancreatic cancer. Hong *et al*. in abstract #4021 could not detect a survival difference between pancreatic cancer with wild type *vs*. mutated *K-ras* [1]. This is an active field of investigation why majority of pancreatic cancers have mutation in *K-ras* and its clinical significance. In an autopsy series of patients with advanced pancreatic cancer, loss of *DPC4* was highly correlated with disseminated metastasis [9]. A previous report of 101 patients demonstrated increased local recurrence in pancreatic cancer with *DPC4* loss than with intact status (34.4% *vs*. 13.7%, P=0.012), but there was no difference in the rates of distant recurrence with intact *vs*. loss of *DPC4* expression (62.8% *vs*. 55.7%, P=0.45) [9]. Hong *et al*. in Abstract #4021 demonstrated that *DPC4* status has no impact on survival outcomes from their study [1]. Future trials, including an upcoming RTOG trial which will stratify patients by these genetic markers, would clarify their significance in the clinical setting.

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Conflict of interest The authors have no potential conflicts of interest

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