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HIGHLIGHT ARTICLE

Adjuvant Therapy of Pancreatic Cancer

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Summary

Strong evidence exists for the use of adjuvant chemotherapy following surgical resection in pancreatic cancer, whereas the role of adjuvant chemoradiotherapy remains controversial. The optimal time to initiate adjuvant therapy has yet to be elucidated, but is usually started 2-10 weeks following resection. First line adjuvant chemotherapy is gemcitabine, as this drug has demonstrated the better efficacy in studies. Other chemotherapeutic agents and gemcitabine in combination with biologic agents are under investigation. Furthermore, predicting response to gemcitabine based chemotherapy and other adjuvant therapies will be invaluable in guiding the practitioner to choose the most appropriate adjuvant treatment. Once adjuvant therapy has been started, accurately quantifying response to therapy is also important. The adjuvant regimen may be appropriately modified if response is inadequate. This review is an update from the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting regarding recent developments in the adjuvant treatment of pancreatic cancer with regards to choice of adjuvant regimen, timing of adjuvant therapy, predicting response to therapy and measuring response to adjuvant therapy. We will present the findings from Abstracts #4039, #4042, #e14519, #4118, and #4024. In conclusion, multiple adjuvant therapeutic regimens are associated with incremental improvements in the management of pancreatic cancer. The timing of initiation of adjuvant therapy appears to be important in outcomes. Research is ongoing into markers that can predict response to adjuvant therapy.

What We Know Before the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting?

Only 10-20% of patients have classically resectable disease at the time of pancreatic cancer diagnosis. Surgical resection remains the only curative modality for pancreatic cancer. Nevertheless, the prognosis of patients after complete resection is poor, with 3-year disease-specific survival rate at 27% (95% confidence interval (CI): 23-32%) and median survival of 15-19 months [1, 2, 3]. Therefore, judicious use of efficacious adjuvant therapies is necessary to improve the survival of resected pancreatic cancer patients. There is now substantial high level evidence to support the use of adjuvant chemotherapy in resected pancreatic cancer [4, 5, 6, 7]. However, the role for adjuvant chemoradiotherapy remains more controversial.

Key words Chemotherapy, Adjuvant; Combined Modality Therapy; Deoxycytidine Kinase; gemcitabine; Pancreatic Neoplasms; Radiotherapy, Adjuvant; RRM1 protein, human; S100A2 protein, human; SLC29A1 protein, human

Abbreviations dCK: deoxycytidine kinase; EORTC: European Organization of Research and Treatment of Cancer; ESPAC: European Study Group for Pancreatic Cancer; hENT1: human equilibrative nucleoside transporter 1; RRM1: ribonucleotide reductase subunit 1; RTOG: Radiation Therapy Oncology Group

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There are numerous randomized controlled trials that support the use of adjuvant chemotherapy after resection of pancreatic cancer [4, 5, 6,]. The European Study Group for Pancreatic Cancer (ESPAC-1) trial demonstrated a survival benefit for adjuvant chemotherapy but not adjuvant chemoradiotherapy and even a possible detrimental effect for adjuvant chemoradiation [4]. The Charité Onkologie Clinical-001 (CONKO-001) study randomized patients with resected pancreatic cancer to gemcitabine for 6 months or observation [5]. Adjuvant chemotherapy showed a trend towards improved overall survival. The use of gemcitabine versus 5-FU was further defined by the ESPAC-3 trial, which demonstrated equivalent survival for both treatments, but more favorable safety profile with gemcitabine [6]. There was also a trend toward improved survival in the gemcitabine arm in patients with node positive disease or those with positive resection margins [6]. To further support the role of adjuvant chemotherapy, the Boeck *et al.* [7] meta-analysis demonstrated adjuvant chemotherapy provided a significant increase in median survival.

The role for adjuvant chemoradiation is less well defined as there are conflicting results from trials. Despite the controversy, the level of evidence is strong enough to support the use of adjuvant chemoradiotherapy in the management of resected pancreatic cancer in the United States. However, in Europe it is common practice for patients to receive adjuvant chemotherapy alone. There are three randomized controlled trials investigating the role of adjuvant

Table 1. Abstracts presented at the 2011 ASCO Annual Meeting: adjuvant treatment.

Author	Kwon *et al*. (Abstract #4094) [22]	Fensterer *et al*. (Abstract #4039) [21]
Trial design	Phase II	Phase II
Adjuvant treatment following resection	Gemcitabine + cisplatin -> no progression -> chemoradiotherapy (50.4 Gy/28 fractions) with gemcitabine -> maintenance with gemcitabine	Gemcitabine+cetuximab
No. of patients	74	76
Disease free survival	62.1% at 12 months	33.5% at 18 months
Median overall survival	33.6 months	21.5 months
Conclusion	Promising efficacy and good tolerability	Gemcitabine+cetuximab not better than gemcitabine alone

chemoradiation in resected pancreatic cancer [4, 8, 9]. The Gastrointestinal Study Group (GITSG) study showed a survival benefit in patients who received bolus 5-FU with radiotherapy, but has been criticized for a sample size of 43 patients [8]. The European Organization of Research and Treatment of Cancer (EORTC) trial did not demonstrate a survival advantage for patients treated with adjuvant chemo-radiation compared to observation [9]. There was a trend toward survival in the chemoradiotherapy arm compared to observation in the subset of patients with pancreatic ductal carcinoma [9]. Radiation therapy in the EORTC trial was suboptimal as the dose was inadequate (40 Gy) and the radiation was delivered with a split course. The ESPAC-1 evaluated adjuvant concurrent chemoradiation therapy (bolus 5-FU/split-course radiation), chemotherapy alone (5-FU/ leucovorin), chemoradiation therapy followed by chemotherapy, and observation [4]. The results demonstrated that the chemotherapy-only arm had a significant benefit over the observation arm in median survival and the chemoradiation therapy arm showed worse median survival compared to the observation arm [4]. This study was criticized for a confusing 2x2 factorial design, possible selection bias and suboptimal radiotherapy (split course/poor quality control). An additional phase 3 trial, Radiation Therapy Oncology Group (RTOG) 9704, showed a benefit of adding gemcitabine to infusional 5-FU combined with radiotherapy at the cost of more grade 4 hematological toxicity [10].

Despite the lack of randomized controlled trials, evidence supporting the role of adjuvant chemo-radiotherapy in resected pancreatic cancer, several single institution and retrospective series demonstrate a benefit for adjuvant chemoradiotherapy [11, 12, 13, 14]. The Johns Hopkins-Mayo Clinic Collaborative Study demonstrated that adjuvant chemoradiation (5-FU based chemo- and radio-therapy to 50.4 Gy) following pancreaticoduodenectomy was associated with improved survival compared to observation alone in their two institutional trial of 1,092 patients [11]. Furthermore, a retrospective review of 472 patients at the Mayo Clinic found a survival benefit for adjuvant chemoradiation after R0 pancreaticoduodenectomy [12]. Several Surveillance, Epidemiology and End Results (SEER) analysis have also demonstrated efficacy for radiation therapy in pancreatic cancer [13, 14].

There may be a role for chemoradiation in the treatment of patients with R1 resections [15, 16]. A meta-analysis by Stocken *et al*. demonstrated a 25% significant reduction in the risk of death with chemotherapy with no significant reduction in the risk of death with adjuvant chemoradiation [15]. However, their subgroup analyses demonstrated that chemoradio-therapy was more effective than chemotherapy alone in patients with positive resection margins [15]. Similarly, the meta-analysis by Butturini *et al*. demonstrated a possible benefit to chemoradiation in patients with positive resection margins [16].

The optimal time to initiate adjuvant chemotherapy after pancreatic cancer surgery is unknown. Adjuvant chemotherapy or chemoradiotherapy has been started from 2 to 10 weeks after surgery, with most trials starting adjuvant therapy within 8 weeks [1, 2, 5]. Once adjuvant chemotherapy has been initiated, predicting the response of patients has been the subject of intensive research. The calcium-binding protein S100A2 has been validated in a retrospective cohort of patients treated with pancreatectomy for pancreatic cancer as an independent predictor of survival, with high expression correlated with disease progression and poor outcome [17, 18]. Additionally, with gemcitabine-based chemotherapy being a mainstay of therapy, markers of the efficacy of gemcitabine such as expression of the human equilibrative nucleoside transporter 1 (hENT1), deoxycytidine kinase (dCK) and ribonucleotide reductase subunit1 (RRM1) proteins have been tentatively identified *in vitro* and *in vivo* [19].

Despite the use of adjuvant chemotherapy or adjuvant chemoradiotherapy after surgical resection, survival still remains poor. Future studies in pancreatic cancer will help to further define the role of adjuvant chemoradiotherapy, elucidate the most efficacious chemotherapeutic and biologic agents, optimize dosing and timing of chemotherapy/radiation therapy and individualize treatment based on predicting response to chemotherapy and radiation therapy.

What Did We Learn at ASCO 2011 Annual Meeting?

Chemotherapy versus Chemoradiotherapy

Drudi *et al*. (Abstract #4042) [20] conducted a pooled analysis of all randomized controlled trials from 1966-2010 investigating the role of adjuvant treatments,

including both adjuvant chemotherapy and adjuvant chemoradiation, in resected pancreatic cancer patients. The purpose of the analysis was to determine if adjuvant treatment, adjuvant chemotherapy or adjuvant chemoradiation confer a survival benefit at 5 years compared with no adjuvant treatment. There were a total of 2,410 pooled patients from 12 randomized controlled trials; 1,337 patients were treated with adjuvant treatment (1,008 with adjuvant chemotherapy and 329 with adjuvant chemoradiation), and 1,073 received no adjuvant treatment. The authors demonstrated significant 5 year survival benefit for adjuvant treatment and adjuvant chemotherapy (odds ratio equal to 0.62, P=0.001 and odds ratio equal to 0.63, P=0.021, respectively), but not for adjuvant chemoradiation (odds ratio equal to 0.92, P=0.71). This pooled analysis demonstrated that adjuvant chemotherapy improves 5-year survival in resected pancreatic cancer patients but not adjuvant chemoradiotherapy. This study served to further strengthen the role of adjuvant chemotherapy in the management of resected pancreatic cancer. These results concur with the results of previous meta-analyses demonstrating a survival benefit for adjuvant chemotherapy [7, 15].

Cetuximab plus Gemcitabine

The addition of cetuximab to adjuvant gemcitabine was investigated in an open label, multi-center, phase II trial reported by Fensterer *et al*. (Abstract #4039) [21]. Patients underwent R0 or R1 resection for pancreatic cancer, then were treated with adjuvant chemotherapy consisting of 6 cycles of gemcitabine with weekly cetuximab for 24 weeks. There were 76 patients enrolled, and 73 patients received at least one dose of cetuximab. Median age was 64 years; 22.4% had R1 resection and 69.1% had K-*ras* mutation. Median disease free survival was 11.9 months, and the disease free survival rate at 18 months was 33.5%, failing to demonstrate superiority over 35% as hypothesized by the authors. Median overall survival was 21.5 months (95% CI: 16.9-28.2 months). Grade 3 or 4 toxicities were neutropenia in 11% of patients, thrombocytopenia in 8.2%, dermatologic in 6.9%, and allergic reaction in 6.9%. The authors conclude that the addition of cetuximab to gemcitabine in the adjuvant treatment of pancreatic cancer does not improve disease free survival over the use of gemcitabine alone (Table 1).

Gemcitabine, Cisplatin with Radiation

Kwon *et al*. (Abstract #4094) [22] conducted a phase II trial of adjuvant gemcitabine and cisplatin chemotherapy followed by chemoradiation with gemcitabine and 5,040 cGy of radiation, then 4 cycles of maintenance gemcitabine. There were 74 patients with stage IB-IIB pancreas cancer who had undergone resection enrolled between 2005 and 2009. The median age was 61 year and the median follow-up was 45 months (range: 10.2-64.6 months). Of the patients enrolled, 57 completed chemotherapy followed by chemoradiation. One-year disease free survival (DFS) rate was 62.1%, median disease free survival was 17.4 months, and median overall survival was 33.6 months. The majority of recurrences (66.2%) were distant metastases. Increasing stage and involved lymph nodes were associated with reduced disease free survival (P<0.001 and P=0.01, respectively). Fifty-three of 74 patients (71.6%) had grade 3 or 4 hematologic toxicity, with 4 patients experiencing febrile neutropenia. These finding suggest promising efficacy with acceptable toxicity for adjuvant multimodality therapy (Table 1).

Relationship Between Time to Adjuvant Chemotherapy and Survival

Pisa *et al*. (Abstract #e14519) [23] evaluated a cohort of 29 consecutive patients with resected nonmetastatic pancreatic cancer who received adjuvant chemotherapy with gemcitabine to attempt to identify a relationship between time to adjuvant chemotherapy and survival [7]. The median time to adjuvant chemotherapy was 47 days (range: 22-183 days), and the most common reason for delay of adjuvant chemotherapy was post-operative complications. No difference in age, gender, stage or palliative chemotherapy used at progression was identified between patients who started adjuvant chemotherapy within 56 days (8 weeks) of surgery *versus* those who started adjuvant chemotherapy after 56 days post-surgery. Median overall survival was 26.4 months in those who started adjuvant chemotherapy within 56 days of surgery *versus* 14.8 months in those who started adjuvant chemotherapy more than 56 days after surgery (P=0.015). No significant difference was seen in median progression free survival between the groups. No patients died of toxicity or post-operative complications. This underscores the need to keep time to adjuvant chemotherapy under 8 weeks after surgery, as has been the case in most clinical trials.

Prognostic Markers

S100A2 Expression as a Prognostic Marker

Tompero *et al*. (Abstract #4118) [24] performed a secondary analysis of a subset of patients with head of pancreas lesions treated adjuvantly on RTOG 9704 in an attempt to validate S100A2 expression as a prognostic marker in 150 specimens from patients receiving adjuvant chemotherapy for pancreatic cancer. Tissue microarray was used to quantify S100A2 expression, and patients were then stratified into four groups based on the level of expression. For high *vs*. no/low expression of S100A2, disease specific survival was not significantly different at 1 or 2 years (P=0.09; Table 2). While S100A2 was not validated as a

Table 2. Disease specific survival by S100A2 expression levels in patients receiving adjuvant therapy for pancreas cancer.

	No. of patients	Disease specific survival	
		1 year	2 years
S100A2 expression:			
- High intensity	72	73%	29%
- Low/no expression	78	76%	46%

P=0.09

prognostic marker in this cohort of patients, the authors recommend further study to try to resolve the conflicting data about the role of S100A2 as a prognostic biomarker.

hENT1, dCK, and RRM1

Marechal *et al*. (Abstract #4024) [25] conducted a study using expression of hENT1, dCK, and RRM1 in 434 patients receiving adjuvant gemcitabine after curative-intent resection of pancreatic cancer in an attempt to associate expression of these proteins with efficacy of gemcitabine. Among patients not treated with gemcitabine-based chemotherapy, hENT1, dCK, and RRM1 expression was not associated with overall survival. In contrast, among the patients treated with gemcitabine, hENT1 and dCK expression levels were associated with changes in overall survival after adjusting for tumor grade, size, lymph node involvement and resection margin. In tumors with high hENT1, gemcitabine was associated with better overall survival (HR: 0.44; 95%CI: 0.28-0.69; P<0.001); in tumors with high dCK, gemcitabine was associated with better overall survival (HR: 0.57; 95% CI: 0.41-0.78; P=0.001). In tumors with low hENT1or dCK levels, gemcitabine was not associated with improved overall survival. These findings suggest that expression levels of hENT1 and dCK may predict response to gemcitabine-based chemotherapy after curative-intent surgery.

Conflict of interest The authors have no potential conflicts of interest

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