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HIGHLIGHT ARTICLE

Adjuvant Therapy of Pancreatic Cancer

Highlights from the "2013 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 24-26, 2013

Chakra P Chaulagain[1], John Ng[3], Martin D Goodman[2], Muhammad Wasif Saif[1]

[1]Division of Hematology and Oncology and [2]Department of Surgery, Tufts Medical Center and Tufts University School of Medicine. Boston, MA, USA. [3]Weill Cornell Medical College and Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital. New York, NY, USA

Summary

There is no clear consensus on what type of adjuvant therapy should be used for patients with pancreatic cancer. Chemoradiation is the favored treatment modality by many in the United States while gemcitabine based chemotherapy is favored in Europe. Both of these approaches have been shown by large prospective, randomized trials to improve disease free intervals and in some studies overall survival. This year at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancer Symposium, the randomized phase III study presented by Uesaka *et al*. from Japan (Abstract #145) represents a newer paradigm of oral adjuvant S-1 chemotherapy in place of the traditional standard of care intravenous gemcitabine in terms of prolonging patients' survival. Another study by Fan *et al*. (Abstract #269) examined the value of targeted therapy using erlotinib with adjuvant chemoradiation and chemotherapy. We present the summary of these two studies and discuss the potential impact on our clinical practice on this highly lethal cancer.

What We Knew Before 2013 ASCO Gastro-intestinal Cancers Symposium?

Clinical trials for utilizing adjuvant chemotherapy are mostly from Europe. The European Study Group for Pancreatic Cancer (ESPAC)-1 trail in 2001 had a 2x2 fractional design of chemoradiation and chemotherapy. The chemotherapy (5-FU and leucovorin) *versus* observation arms showed an overall median survival of 20.1 months *versus* 15.5 months (P=0.009) [1]. The German Charité Onkologie Clinical (CONKO)-001 trial in 2007 was a phase III randomized trial comparing adjuvant gemcitabine *versus* observation alone. The median disease free survival was 13.4 months *versus* 6.9 months (P<0.001) with overall median survival of 22.8 months *versus* 20.2 months (P=0.005) [2, 3]. The ESPAC-3 trial in 2009 compared gemcitabine *versus* bolus 5-FU plus leucovorin [4]. It showed a median overall survival of 23.6 months *versus* 23 months which was not statistically significant. Despite the comparable survival, there were greater toxicities with 5-FU based chemotherapy. Univariate survival analysis in this study showed that positive margin, lymph node involvement, tumor size greater than 3 cm, and the grade of the tumor were all independent prognostic factors. The only subgroup analysis performed was on the completeness of resection (R0 *versus* R1) where there was no difference in the two groups. There was no comparison looking at other adverse prognostic indicators in the treatment arm.

The Radiation Therapy Oncology Group (RTOG) 9704 trial (July 1998 - July 2002) randomized patients after gross total resection of pancreatic cancer to receive either 5-FU or gemcitabine for 3 weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation therapy. Chemoradiation with a continuous infusion of 5-FU was the same for all patients [5]. There was no difference in the two groups except for patients with pancreatic head tumors where a non-statistically significant improvement in survival was noted with gemcitabine group (i.e., the median survival was 20.5 months in gemcitabine group *versus* 16.9 months in the 5-FU group; P=0.09). This trial helped to establish the use of adjuvant gemcitabine-based chemotherapy along with 5-FU-based concurrent chemoradiation. This approach currently represents a

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Abbreviations CONKO: Charité Onkologie; EGFR: epidermal growth factor receptor; EORTC: European Organization of Research and Treatment of Cancer; ESPAC: European Study Group for Pancreatic Cancer; JASPAC: Japanese Adjuvant Study Group of Pancreatic Cancer; RTOG: Radiation Therapy Oncology Group

Correspondence Chakra P Chaulagain
Division of Hematology and Oncology; Tufts Medical Center and Tufts University School of Medicine; 800 Washington Street, Box 245; Boston, MA 02111; USA
Phone: +1-617.636.7385; Fax: +1-617.636.8538
E-mail: cchaulagain@tuftsmedicalcenter.org

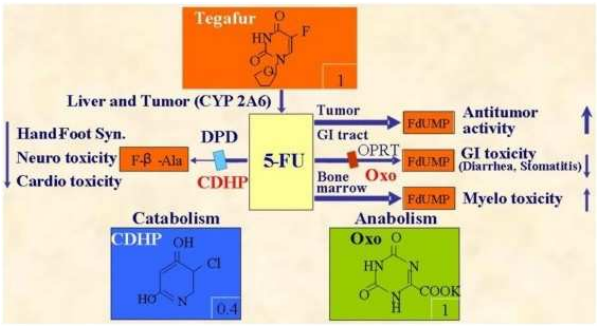

Figure 1. Composition and mechanism of action of S-1. S-1 is a new oral formulation of 5-FU combining tegafur (FT) with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (adapted from Saif MW *et al.*, 2009 [8]).

common clinical practice in the U.S.A. In general, both National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) encourage enrolling patients to clinical trials evaluating potential benefits of chemotherapy or combined modality therapy with chemoradiation.

What Did We Learn at the 2013 ASCO Gastrointestinal Cancers Symposium?

Pancreatic cancer, a highly lethal disease remains a substantial public health problem and one of the leading causes of cancer deaths. This disease has been a fertile ground for testing new therapies with only slow progress without any groundbreaking results. More innovative treatment approaches are needed to improve survival in this patient population. This year in ASCO Gastrointestinal Cancer Symposium, Uesaka *at al*. (Abstract #145) presented the results of much anticipated phase III randomized trial of adjuvant chemotherapy with gemcitabine *versus* S-1 for patients with resected pancreatic cancer [6] (Japanese Adjuvant Study Group of Pancreatic Cancer; JASPAC-01 study). The study conducted in 33 centers in Japan showed that S-1 is as good as gemcitabine (non-inferior) or may be even better (superior) with tolerable side effect profile. S-1 has now emerged as a potential first-line alternative to gemcitabine in adjuvant setting for Japanese patients. Another interesting presentation was by Fan *et al*. (Abstract #269) on a phase II study looking at erlotinib combined with adjuvant chemoradiation and chemotherapy for resectable pancreatic cancer [7].

What Is Known About S-1?

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is an oral fluoropyrimidine designed with the aim of improving antitumor activity and reducing the toxicity of 5-FU. This novel molecule consists of tegafur, a prodrug of 5-FU combined with two 5-FU biochemical modulators: 5-chloro-2, 4-dihydroxypyridine (gimeracil or CDHP), a competitive inhibitor of dihydro-pyrimidine dehydrogenase and oteracil potassium which inhibits phosphorylation of 5-FU in the gastrointestinal tract thereby decreasing serious gastrointestinal toxicities such as nausea, vomiting, stomatitis and diarrhea [8] (Figure 1). This oral agent offers several advantages over 5-FU: ease of administration, less toxicities and no risk of complications associated with central venous access such as infection, thrombosis and bleeding.

Adjuvant Therapy with S-1 and Erlotinib in Pancreatic Cancer

A triple-arm phase III study from Japan and Taiwan (GEST study) randomized patients with unresectable advanced pancreatic cancer into gemcitabine plus S-1 *versus* S-1 *versus* gemcitabine. The results showed non-inferiority of S-1 to gemcitabine as the first-line treatment for advanced/metastatic pancreatic cancer [9]. This opened up the avenue for testing S-1 in the adjuvant setting and the JASPAC-01 study is the first large randomized phase III trial testing S-1 with or without gemcitabine after resection of pancreatic cancer.

Randomized Phase III Trial of Adjuvant Chemotherapy with Gemcitabine versus S-1 for Patients with Resected Pancreatic Cancer (JASPAC-01 Study) (Abstract #145) [6]

The aim of this phase III study was to determine non-inferiority of S-1 to gemcitabine on overall survival as adjuvant chemotherapy for resected pancreatic cancer. This study enrolled 385 patients (gemcitabine, n=193; S-1, n=192) between April 2007 and June 2011. The hazard ratio for S-1 to gemcitabine was 0.56 (95% CI: 0.42-0.74; P<0.0001 for non-inferiority and P<0.0001 for superiority). The reported 2-year survival rates were 53% (95% CI: 46-60%) for gemcitabine and 70% (95% CI: 63-76%) for S-1. The details are presented in Tables 1, 2, 3 and 4.

Table 1. Design of the Japanese Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) study [6].

Inclusion criteria:
- Histologically confirmed ductal adenocarcinoma of the pancreas, R0 or R1 resection
- Pathological stage I, II, or III with resection of the celiac axis
- Age older than 20 years
- No prior chemotherapy or radiotherapy within 3 years
- Adequate organ functions

Randomization:
- Gemcitabine (1,000 mg/m^2, divided on days 1, 8 and 15, repeated every 4 weeks, for 6 courses)
- S-1 (40-60 mg according to the body surface, twice a day, for 4 weeks, repeated every 6 weeks, for 4 courses)

Primary endpoint:
- Overall survival

Table 2. Incidence of grade 3-4 toxicities in the Japanese Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) study [6].

Toxicities	Gemcitabine	S-1
Fatigue	4.7%	5.4%
Anorexia	5.8%	8.0%
Leukopenia	38.7%	8.6%
Thrombocytopenia	9.4%	4.3%
Anemia	17.3%	13.4%
Elevated AST	5.2%	1.1%

Discussion

This relatively large multicenter phase III study from Japan in patients with stages I-III pancreatic cancer clearly showed both non-inferiority and superiority of S-1 to gemcitabine in the adjuvant setting. Though the trial was designed to show non-inferiority only, the authors were able to show superiority as well. The toxicities were comparable in both arms with less myelosuppression in patients receiving S-1. The results are potentially practice changing (at least in Japanese patients) as the findings have challenged the long standing traditional gold standard of gemcitabine as the choice of adjuvant chemotherapy. The results will likely influence the clinical trial designs beyond Asia with potential for similar clinical studies in other population in Europe and North America. A longer follow up (e.g. 5 years) is warranted to see if the superiority of S-1 to gemcitabine lasts beyond 2 years and translates into long term survival.

Pancreatic cancer community throughout the world is curiously waiting to see the final publication of this study which will help understand the details on study design, setting, participants, study methodology used, outcome measures and the results and their relevance to patients with pancreatic cancer.

The ESPAC-3 study showed similar survival outcome between 5-FU *versus* gemcitabine in the adjuvant setting though the safety and dose intensity favored gemcitabine. This study, however, helped to bring back 5-FU and other fluoropyrimidines such as capecitabine and S-1 on the stage for further assessment in clinical trials. While discussing applicability of S-1 in the U.S. population, it is important to recollect that multinational clinical studies of another oral fluoropyrimidine capecitabine in gastrointestinal cancers has shown significantly worse toxic-effect profile (mainly diarrhea) in patients recruited from the U.S. than in those from Asia. In general early clinical studies of S-1 in the U.S.A. showed diarrhea as the dose-limiting toxicity whereas the Japanese studies showed myelosuppression as the dose-limiting toxicity. This differential tolerability between populations is likely to be due to polymorphisms in the CYP2A6 gene [10]. One important question to be addressed in the future clinical trials is whether or not a reduced dose of S-1 will cause less severe diarrhea while retaining therapeutic efficacy. At this point, gemcitabine remains the agent of choice both in Europe and North America as adjuvant chemotherapy in resected pancreatic cancer.

Table 3. Reasons for treatment discontinuation in the Japanese Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) study [6].

Reasons	Gemcitabine	S-1
Recurrence	27%	9%
Toxicity	48%	40%
Patient's refusal	5%	3%
Others	2%	0

Table 4. Summary of results of the Japanese Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) study [6].

	Gemcitabine	S-1
Total patients enrolled (n=385)	193	192
Analyzable patients	191	187
2-year overall survival	0.53	0.70
Hazards ratio, HR 95% CI	0.56 (0.42-0.74)	
P value for non-inferiority and superiority	<0.0001	

Phase II Study of Erlotinib Combined with Adjuvant Chemoradiation and Chemotherapy for Resectable Pancreatic Cancer (Abstract #269) [7]

Fan *et al*. presented their phase II study results investigating the role of erlotinib in the treatment of resectable pancreatic cancer [7]. Epidermal growth factor receptor (EGFR) targeted therapy is of interest because EGFR amplification and over-expression have been described in up to 80% of pancreatic tumors. In this phase II trial, the activity and toxicity of erlotinib

Table 5. Summary of the phase II study of erlotinib combined with adjuvant chemoradiation and chemotherapy [7].

Patient characteristics:	
No. of patients	50
Pancreatic head tumors (out of all tumors)	79%
Nodal involvement	22%
Positive margins	17%
Treatment outcomes:	
Median recurrence free survival: median 95% CI	15.6 months (14.1-17.1)
Local recurrence free survival: median 95% CI	21.1 months (17.1-25.1)
Overall survival: median 95% CI	24.4 months (17.1-31.6)
Local recurrence	19%
Synchronous recurrence	8%
Chemoradiation toxicities:	
Grade 3 toxicity	31%
Grade 4 toxicity	2%
Treatment break/early stop	31%
Post-chemoradiation chemotherapy toxicities:	
Grade 3 toxicity	35%
Grade 4 toxicity	8%
Dose reduction	30%

CI: confidence interval

combined with chemoradiation and chemotherapy was evaluated in the adjuvant setting. The study enrolled 50 patients with resected stage I/II pancreatic adenocarcinoma. Adjuvant erlotinib and capecitabine were given concurrently with radiotherapy (delivered to 50.4 Gy via intensity-modulated radiation therapy) followed by 4 cycles of erlotinib and gemcitabine.
The median follow-up time was 18.2 months. A summary of their results with clinical characteristics and gradable toxicities are shown in Table 5.

Discussion

Factors that were associated with better outcomes included tumors less than 3 cm, cutaneous reaction to erlotinib, and CA 19-9 levels less than 32.3 U/mL. The authors concluded that their results suggested that erlotinib combined with adjuvant chemoradiation and chemotherapy provided excellent local disease control with reasonable tolerability. This approach deserves further testing in a phase III trial.

Conflict of interests None

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