

HIGHLIGHT ARTICLE

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

Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA.
January 20-22, 2011

Bryan W Chang¹, Muhammad Wasif Saif²

¹Department of Therapeutic Radiology, Yale University School of Medicine. New Haven, CT, USA.

²Division of Hematology/Oncology at Columbia University College of Physicians and Surgeons.
New York, NY, USA

Summary

Eight abstracts highlighting the continued evolution of the management of locally advanced pancreatic cancer were presented at the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium (Abstracts #195, #239, #259, #281, #287, #305, #307, #324). These studies address key issues including the role of novel targeted therapies, what chemotherapy regimen should be used in conjunction with radiotherapy, and whether locally advanced pancreatic cancer can be managed with chemotherapy alone.

What We Knew Before the 2011 ASCO GI Cancer Symposium

Locally advanced pancreatic cancer, in which the tumor has not metastasized but encases the celiac axis or superior mesenteric artery, is by definition unresectable and represents about 25% of pancreatic cancer cases at presentation. Patients with limited vascular involvement by tumor are considered to have borderline resectable disease and are often treated as locally advanced pancreatic cancer. Treatments range from chemoradiation to chemotherapy alone to induction chemotherapy followed by chemoradiation for patients who do not metastasize [1, 2, 3]. The median survival is limited to 10-12 months, leaving significant room for improvement.

What We Learned at the 2011 ASCO GI Cancer Symposium

Novel Agents for Locally Advanced Pancreatic Cancer

Phase I trial of gene-mediated cytotoxic immuno-

therapy in combination with chemoradiation for locally advanced pancreatic cancer

Bloomston *et al.* injected escalating doses of an adenoviral vector containing HSV-thymidine kinase gene into tumors of a dozen patients with locally advanced pancreatic cancer, followed by treatment with an anti-viral prodrug and standard 5-fluorouracil (5-FU) and radiation. (Abstract #195). No dose-limiting toxicities were seen and there were two partial responses [4].

A phase I study of erlotinib, bevacizumab, and external beam radiation therapy (RT) for patients with localized pancreatic carcinoma (PC)

Dr. Czito and the Duke University group completed a phase I dose-escalation trial of erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR), with bevacizumab, a monoclonal antibody inhibitor of vascular endothelial growth factor (VEGF) (Abstract #281). Borderline resectable and locally advanced pancreatic cancer patients were enrolled. Three of the 9 patients enrolled went to surgery, but only one underwent successful resection [5].

Discussion

The combination of gemcitabine with erlotinib has been shown to modestly extend survival in patients with metastatic pancreatic cancer in comparison to gemcitabine monotherapy [6]. Numerous other biological and targeted therapies have been studied in metastatic and locally advanced disease, without

Key words bevacizumab; erlotinib; Fluorouracil; gemcitabine; oxaliplatin; Pancreatic Neoplasms; Radiotherapy

Abbreviations FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin

Correspondence Muhammad Wasif Saif
Columbia University; College of Physicians and Surgeons and the Herbert Irving Cancer Center; 177 Fort Washington Avenue, Suite 6-435; New York, NY 10032; USA
Phone: +1-212.305.4954; Fax: +1-212.3050.3035
E-mail: mws2138@columbia.edu

Document URL <http://www.joplink.net/prev/201103/23.html>

benefit (Table 1). Gene-mediated cytotoxic immunotherapy is a fascinating and elegant concept and appears safe in phase I, but further studies are required to evaluate its true benefit in terms of efficacy. A recent phase III trial of an injectable adenoviral vector bearing tumor necrosis factor-alpha failed to show a survival benefit when added to conventional chemoradiation [7].

Erlotinib and bevacizumab are both felt to have enhance the antitumor effect of radiotherapy [15, 16], but efficacy in the Duke series does not seem overwhelming. A note of caution is in order as bevacizumab is known to cause wound healing complications after surgery [17], and two patients in this series had serious post-operative complications.

Which Chemotherapy to Combine with Radiotherapy

Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreatic cancer.

Huang *et al.* retrospectively reviewed records of 93 patients with locally advanced pancreatic cancer (Abstract #287). Patients treated with concurrent full-dose gemcitabine and radiation had improved overall survival compared with those who received chemoradiation with 5-FU, and 11% survived for 5 years. There was no difference in acute gastrointestinal toxicity [18].

A phase II study of neoadjuvant gemcitabine/5-fluorouracil followed by 5-fluorouracil/oxaliplatin

concurrent with radiation in patients with locally advanced pancreatic cancer.

Dr. Lin and other researchers from University of Nebraska treated 29 borderline resectable patients with 6 weeks of induction chemotherapy followed by chemoradiation to 50-50.4 Gy with 5-FU and weekly oxaliplatin (Abstract #259). Almost half of the patients experienced grade 3-4 acute toxicity, but 7 underwent margin-negative resections. The median survival was 26 months for patients undergoing resection but 10 months for the entire population [19].

Concurrent chemoradiotherapy with gemcitabine and S-1 for unresectable locally advanced pancreatic adenocarcinoma: A phase I study

Ioka *et al.* treated 15 patients on a phase I protocol with escalating doses of S-1 and gemcitabine combined with 50.4 Gy (Abstract #305). Dose-limiting toxicities were found to be anorexia and neutropenia. The 2-year survival rate was 44.4% [20].

Phase II trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation (RT) in patients with resectable (R) or borderline resectable (BR) pancreatic cancer.

Dr. Kim *et al.* reported the results of a multi-institutional trial of neoadjuvant chemoradiation in resectable and borderline resectable patients (Abstract #239). The radiation dose was 30 Gy in 15 fractions. In the borderline resectable population, 19 of 30 patients had a margin-negative resection, and the median survival was 18 months [21].

Table 1. Selected trials of novel and targeted therapies for locally advanced pancreatic cancer.

Study	No. of patients	Treatment	Median survival (months)	Comments
TNFRade Chang <i>et al.</i> 2009 [7]	185	50.4 Gy + 5-FU (c.i.) vs. 50.4 Gy + 5-FU (c.i.) + TNFRade	8.7 11.1	Trial terminated in 2010 due to equivalent survival outcomes on interim analysis
S-1 Sudo <i>et al.</i> 2010 [8]	34	50.4 Gy + twice daily oral S-1	16.8	-
Bevacizumab Crane <i>et al.</i> 2009 [9]	82	50.4 Gy + capecitabine + bevacizumab -> Gemcitabine + bevacizumab	11.9	35% with grade III gastrointestinal toxicity
Sorafenib Anderson <i>et al.</i> 2010 [10]	27	Gemcitabine -> 50 Gy + gemcitabine + sorafenib -> Gemcitabine + sorafenib	16	Increased gastrointestinal toxicity
Farnesyl transferase inhibitor R115777 Rich <i>et al.</i> 2006 [11]	174	50.4 Gy + gemcitabine + paclitaxel vs. 50.4 Gy + gemcitabine + paclitaxel + R115777	49% ^a 34% ^a	Increased grade III gastrointestinal and pulmonary toxicities
Nelfinavir Brunner <i>et al.</i> 2008 [12]	12	50.4-59.4 Gy + gemcitabine + cisplatin + nelfinavir	NR	Complete resection in 6 of 10 patients
Erlotinib Moore <i>et al.</i> 2007 [6]	569	Gemcitabine + placebo vs. Gemcitabine + erlotinib	17% ^a 23% ^a	Randomized trial with modest overall survival benefit (P=0.02) Included metastatic and locally advanced pancreatic cancer patients
Erlotinib Duffy <i>et al.</i> 2008 [13]	17	50.4 Gy + gemcitabine + erlotinib -> Gemcitabine + erlotinib	18.7	-
Cetuximab Crane <i>et al.</i> 2010 [14]	69	Cetuximab + gemcitabine + oxaliplatin x2 months -> 50.4 Gy + capecitabine + cetuximab -> Cetuximab + gemcitabine	18.8	One year survival of 68%

c.i.: continuous infusion; NR=not reported

^a Overall survival at one year

Table 2. Recent trials of chemoradiation with gemcitabine or 5-FU for locally advanced pancreatic cancer.

Study Group	No. of patients	Treatment	Median survival (months)	P value ^a (CT vs. CRT)	Caveats
FFCD/SFRO (France) Chauffert <i>et al.</i> 2008 [23]	119	Gemcitabine vs. 60 Gy + 5-FU (c.i.) + cisplatin -> Gemcitabine	13 8.6	0.03	Terminated early due to toxicity of chemoradiotherapy regimen Phase III randomized
ECOG E4201(USA) Loehrer <i>et al.</i> 2008 [1]	74	Gemcitabine vs. 50.4 Gy + gemcitabine -> Gemcitabine	9.2 11	0.04	Under-enrolled phase III randomized
Osaka (Japan) Ioka <i>et al.</i> [24]	80	Gemcitabine vs. 50.4 Gy + gemcitabine	12.2 12.8	<0.02	Phase II randomized
University of Michigan (USA) Ben Josef <i>et al.</i> [25]	27	50-60 Gy + gemcitabine	23.1	NA	Phase I Intensity modulated radiation therapy to tumor only
University of Michigan (USA) Murphy <i>et al.</i> [26]	74	36 Gy + gemcitabine	11.2	NA	Retrospective
Tokyo (Japan) Ishii <i>et al.</i> 1997 [27]	20	50.4 Gy + 5-FU (c.i.)	10.3	NA	Phase II
Grenoble (France) Andre <i>et al.</i> 2000 [28]	32	45 Gy + 5-FU (bolus) + cisplatin -> 5-FU + cisplatin + leucovorin	9	NA	Phase II
Vienna (Austria) Kornek <i>et al.</i> 2000 [29]	38	55 Gy + 5-FU (bolus) + cisplatin	14	NA	Phase II
Italy Boz <i>et al.</i> 2001 [30]	42	59.4 Gy + 5-FU (c.i.)	9.1	NA	Phase II

c.i.: continuous infusion; ECOG: Eastern Cooperative Oncology Group; FFCD-SFRO: French Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique; NA: not applicable

^a Chemotherapy *versus* chemoradiotherapy

Discussion

One flawed randomized trial compared gemcitabine-based chemoradiation to 5-FU-based chemoradiation, showing a survival benefit for gemcitabine [22]. Selected series of patients treated with 5-FU and gemcitabine-based regimens are presented in Table 2. Recent studies such as the results presented by Huang *et al.* [18] have shown promising results for gemcitabine-based chemoradiation. Of note, severe acute toxicity with concurrent full-dose gemcitabine [31] has generally necessitated dose reductions of radiotherapy, as in the Kim *et al.* study [21], or use of limited-field radiotherapy [32], an approach used successfully by Ioka *et al.* [20]. Further study in homogeneous patient populations will be needed to better define the efficacy of these promising regimens.

Chemotherapy Alone for Locally Advanced Pancreatic Cancer

Pilot study of neoadjuvant FOLFIRINOX in unresectable locally advanced (LA) pancreatic carcinoma (PC)

Hosein *et al.* treated 12 patients with locally advanced pancreatic cancer using 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) off protocol (Abstract #324). Four patients were able to undergo margin-negative resections. The overall median survival was estimated at 20.7 months [33].

Phase I/II study of arterial infusion with 5-fluorouracil combined with systemic gemcitabine for unresectable pancreatic cancer

Dr. Tanaka together with a Japanese group studied the toxicity and efficacy of a chemotherapy-alone regimen including hepatic and pancreatic arterial-infusion 5-FU (Abstract #307). A number of metastatic patients were included. The partial-response rate was 68% [34].

Discussion

Trials of chemotherapy for metastatic disease have sometimes included locally advanced pancreatic cancer as well [6], which has led some investigators to treated locally advanced pancreatic cancer without radiation. While the regimen of the Tanaka *et al.* study appears safe, it requires further study for efficacy in a locally advanced pancreatic cancer population. FOLFIRINOX has been shown to dramatically improve survival in metastatic disease compared with gemcitabine alone [35]. The researchers from Miami and Sao Paulo [33] have reported some of the first results from use of this promising but rigorous regimen in patients with locally advanced pancreatic cancer. Both the median survival and the fact that a third of patients were rendered resectable are impressive, and further study is certainly warranted.

Conclusions

The 2011 ASCO GI Cancer Symposium showcased a number of promising, early-phase results with a variety of therapeutic approaches. The search continues for a targeted therapy with clinically significant activity in locally advanced pancreatic cancer. Meanwhile, researchers are growing increasingly adept at safely and effectively combining gemcitabine-based

chemotherapy regimens with radiation. It is clear that some very good results can be obtained with gemcitabine-based chemoradiation, although the optimal approach is not yet clear. Finally, FOLFIRINOX has demonstrated intriguing activity in locally advanced pancreatic cancer, which will need to be confirmed. This regimen may also be useful as induction prior to chemoradiation for patients who do not metastasize early, as large retrospective series have shown that this is a beneficial way to deliver chemoradiation [3, 36]. There is also a need to investigate tailored or adaptive strategies to guide therapy for locally advanced pancreatic cancer. Such strategies could be guided by molecular tumor characteristics or by imaging, such as positron-emission tomography. Future trials should include provisions to aid in the development of flexible strategies that maximize therapeutic index and patient benefit.

Conflict of interest The authors have no potential conflict of interest

References

1. Loehrer PJ, Powell ME, Cardenes HR, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: e4201 [abstract]. *J Clin Oncol* 26, a4506 (2008).
2. Heinemann V, Labianca R, Hinke A, et al. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. *Ann Oncol*. 2007 Oct;18(10):1652-9. Epub 2007 Jul 28.
3. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007 Jan 20;25(3):326-31.
4. Bloomston M, Marsh C, Walker J, et al. Phase I trial of gene-mediated cytotoxic immunotherapy in combination with chemoradiation for locally advanced pancreatic cancer. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 195.
5. Czito BG, Willett C, Kennedy-Newton P, et al. A phase I study of erlotinib, bevacizumab, and external beam radiation therapy (RT) for patients with localized pancreatic carcinoma (PC). *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 281.
6. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *J Clin Oncol* 2005; 23(16S part I). Abstract No: 1.
7. Chang, K. J. Fisher W, Kenady D, et al. Multicenter randomized controlled phase III clinical trial using TNFerade (TNF) with chemoradiation (CRT) in patients with locally advanced pancreatic cancer (LAPC): Interim analysis (IA) of overall survival (OS) [abstract]. *J Clin Oncol* 2009; 27, Abstract 4605.
8. Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Hara T, Denda T, Tawada K, Imagumbai T, Araki H, Sakai M, Hatano K, Kawakami H, Uno T, Ito H, Yokosuka O. Phase II Study of Oral S-1 and Concurrent Radiotherapy in Patients with Unresectable Locally Advanced Pancreatic Cancer. *Int J Radiat Oncol Biol Phys*. 2010 Jun 2.
9. Crane CH, Winter K, Regine WF, et al. Phase II study of bevacizumab with concurrent capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Therapy Oncology Group RTOG 0411. *J Clin Oncol* 2009 Sep 1;27(25):4096-102.
10. Anderson S, Cardenes HR, Akisik F, et al. Phase I study of sorafenib (S) with gemcitabine (G)-based radiotherapy (G-RT) in patients (pts) with locally advanced unresectable pancreatic adenocarcinoma (LAUPC). *J Clin Oncol* 2010; 28:15s, (suppl; abstr 4139).
11. Rich T, Harris J, Abrams R, et al. Phase II study of external irradiation and weekly paclitaxel for nonmetastatic, unresectable pancreatic cancer: RTOG-98-12. *Am J Clin Oncol* 2004 Feb;27(1):51-6.
12. Brunner TB, Geiger M, Grabenbauer GG, et al. Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. *J Clin Oncol* 2008 Jun 1;26(16):2699-706.
13. Duffy A, Kortmansky J, Schwartz GK, et al. A phase I study of erlotinib in combination with gemcitabine and radiation in locally advanced, non-operable pancreatic adenocarcinoma. *Ann Oncol* 2008 Jan;19(1):86-91.
14. Crane CH, Varadhachary GR, Javle MM, et al. 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). *J Clin Oncol* 2010; ASCO Gastrointestinal Cancers Symposium. Abstract No. 132.
15. Prakash C, Huang S, Vallabhaneni G, et al. Mechanisms of Enhanced Radiation Response following Epidermal Growth Factor Receptor Signaling Inhibition by Erlotinib (Tarceva). *Cancer Res* 65: 3328-35, 2005.
16. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res* 59:3374-3378, 1999.
17. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical Wound Healing Complications in Metastatic Colorectal Cancer Patients Treated with Bevacizumab. *J Surg Oncol* 2005; 91:173-180.
18. Huang J, Robertson JM, Margolis JH, et al. Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreatic cancer. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 287.
19. Lin C, Kos BM, Sasson AR, et al. A phase II study of neoadjuvant gemcitabine/5-fluorouracil followed by 5-fluorouracil/oxaliplatin concurrent with radiation in patients with locally advanced pancreatic cancer. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 259.
20. Ioka T, Fukutake N, Ikezawa K, et al. Concurrent chemoradiotherapy with gemcitabine and S-1 for unresectable locally advanced pancreatic adenocarcinoma: A phase I study. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 305.
21. Kim EJ, Ben-Josef E, Griffith A, et al. Phase II trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation (RT) in patients with resectable (R) or borderline resectable (BR) pancreatic cancer. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 239.
22. Li CP, Chao Y, Chi KH, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. *Int J Radiat Oncol Biol Phys*. 2003 Sep 1;57(1):98-104.
23. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 19(9): 1592-99, 2008.
24. Ioka T, Nakamura S, Nishiyama K. A randomized phase II study of gemcitabine 1000 mg/m² and concurrent radiotherapy comparing gemcitabine alone for unresectable locally advanced

pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2010;78(3, Supplement):S102.

25. E. Ben-Josef, K. Griffith, I. R. Francis et al. Phase I radiation dose-escalation trial of intensity-modulated radiotherapy (IMRT) with concurrent fixed dose-rate gemcitabine (FDR-G) for unresectable pancreatic cancer. *J Clin Oncol* 2009; 27:15s (suppl; abstr 4602).

26. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int. J. Rad Oncol Biol Phys*, Vol. 68, No. 3, pp. 801-808, 2008.

27. Ishii H, Okada S, Tokuyue K, et al. Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma. *Cancer*. 1997 Apr 15;79(8):1516-20.

28. André T, Balosso J, Louvet C, et al. Combined radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) as palliative treatment for localized unresectable or adjuvant treatment for resected pancreatic adenocarcinoma: results of a feasibility study. *Int J Radiat Oncol Biol Phys*. 2000 Mar 1;46(4):903-1.1.

29. Kornek GV, Schratte-Sehn A, Marczell A, et al. Treatment of unresectable, locally advanced pancreatic adenocarcinoma with combined radiochemotherapy with 5-fluorouracil, leucovorin and cisplatin. *Br J Cancer*. 2000 Jan;82(1):98-103.

30. Boz G, De Paoli A, Innocente R, et al. Radiotherapy and continuous infusion 5-fluorouracil in patients with nonresectable pancreatic carcinoma. *Int J Radiat Oncol Biol Phys*. 2001 Nov 1;51(3):736-40.

31. Crane CH, Antolak JA, Rosen II et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. *Int J Gastrointest Cancer* 30(3):123-32, 2001.

32. Small W, Jr, Berlin J, Freedman GM, et al. Full-Dose Gemcitabine With Concurrent Radiation Therapy in Patients With Nonmetastatic Pancreatic Cancer: A Multicenter Phase II Trial. *J Clin Oncol* 26(6): 9427-7, 2008.

33. Hosein PJ, Kawamura C, Macintyre J, et al. Pilot study of neoadjuvant FOLFIRINOX in unresectable locally advanced (LA) pancreatic carcinoma (PC). *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 324.

34. Tanaka T, Nishiofuku H, Sho M, et al. Phase I/II study of arterial infusion with 5-fluorouracil combined with systemic gemcitabine for unresectable pancreatic cancer. *J Clin Oncol* 2011; 29(Suppl. 4):Abstract 307.

35. Conroy T, Desseigne F, Ychou M et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. *J Clin Oncol* 2010; 28:15s,(suppl; abstr 4010).

36. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer*. 2007 Jul 1;110(1):47-55.