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HIGHLIGHT ARTICLE

Locally Advanced Pancreatic Cancer

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

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Summary

Treatment of locally advanced pancreatic cancer is palliative, based on chemotherapy and according to response, chemoradiotherapy can be applied. The authors summarize three abstracts (#LBA146, #256 and #303) presented on the 2013 ASCO Gastrointestinal Cancers Symposium, which were focused on treatment of locally advanced pancreatic cancer. A discussion is presented about the different chemotherapy or chemoradiotherapy regimens, that move away from gemcitabine-based treatment, and the effort to find less toxic, but efficient therapeutic combinations.

What We Knew Before the 2013 ASCO GI Cancers Symposium?

Locally advanced pancreatic cancer is defined by superior mesenteric artery encasement, aortic invasion, portal vein occlusion, and superior mesenteric vein involvement if not amenable to reconstruction. Treatment has palliative intent and systemic chemotherapy is the backbone. According to the results of the Action to Control Cardiovascular Risk in Diabetes 11 (ACCORD-11) trial, oxaliplatin plus irinotecan plus fluorouracil plus leucovorin (FOLFIRINOX) has become the gold standard of chemotherapy providing the longest overall survival (10.5 months) and progression free survival (6.4 months), compared to gemcitabine (6.9 and 3.4 months, respectively) [1]. However, patients receiving FOLFIRINOX suffered significant toxicity and this trial did not include patients with locally advanced disease. Other options for first-line chemotherapy include gemcitabine combinations with either erlotinib [2] (category 1 recommendation), cisplatin (category 2A), especially in hereditary forms of pancreatic cancer or BRCA mutations [3, 4], or capecitabine (category 2A) [5]. Alternatives include capecitabine monotherapy (category 2B) [6], and oxaliplatin plus fluorouracil plus leucovorin (FOLFOX)/capecitabine plus oxaliplatin (CapeOX) (category 2B) [7].

For patients who have received two to six cycles of chemotherapy with good performance status and have not developed metastatic disease, consolidation with chemoradiation is recommended, as long as the patient continues to have unresectable disease [8]. Starting with chemotherapy may help control progression to metastatic disease and also evaluate the aggressiveness of the tumor, helping to select the patients who may benefit from chemoradiotherapy. Radiotherapy is given concurrent with either gemcitabine, 5-FU or capecitabine [9, 10].

Key words Chemoradiotherapy; Chemoradiotherapy, Adjuvant; Drug Therapy; Neoadjuvant Therapy; Pancreatic Neoplasms

Abbreviations CapeOX: capecitabine plus oxaliplatin; FOLFIRINOX: oxaliplatin plus irinotecan plus fluorouracil plus leucovorin; FOLFOX: oxaliplatin plus fluorouracil plus leucovorin; mFOLFOX6: modified FOLFOX6

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What We Learnt at the 2013 ASCO GI Cancers Symposium?

SCALOP: Results of a Randomized Phase II Study of Induction Chemotherapy Followed by Gemcitabine (G) or Capecitabine (Cap) Based Chemoradiation (CRT) in Locally Advanced Pancreatic Cancer (LANPC.). (Abstract #LBA146 [11])

Somnath Mukherjee *et al*. performed a multicenter randomized phase II trial with 74 patients comparing the activity, safety, and feasibility of induction chemotherapy comprising 3 cycles of gemcitabine (1,000 mg/m^2 days 1, 8, 15 every 28 days) and capecitabine (830 mg/m^2 *bid* days 1-21 every 28 days) followed, in responsive patients, by one cycle of

gemcitabine-capecitabine and then two different schedules of chemoradiotherapy using gemcitabine (300 mg/m^2 once weekly on day 1) or capecitabine (capecitabine twice daily on days 1-5/week) and radiotherapy (50.4 Gy in 28 fractions, 5 days a week for 5.5 weeks) in patients with locally advanced, nonmetastatic, unresectable pancreatic cancer. This study showed that both arms reached the primary endpoint of 9-month progression free survival (63.0% *vs*. 51.4% for gemcitabine *vs*. capecitabine, respectively). Overall survival was found superior for the capecitabine chemotherapy arm (15.2 months *vs*. 13.4 months; P=0.025). Patients in the gemcitabine arm suffered more grade 3-4 hematologic (18.4% *vs*. 0%; P=0.007) and non-hematological toxicity (26.3% *vs*. 11.1%, P=0.095). As a result, capecitabine may be more effective and safer in combination with radiotherapy for treatment of locally advanced pancreatic cancer.

Outcomes with FOLFIRINOX for Locally Advanced Pancreatic Cancer. (Abstract #256 [12])

Brian A Boone *et al*. studied retrospectively the outcomes of patients with locally advanced pancreatic cancer that received FOLFIRINOX as neoadjuvant treatment. Twenty-five patients were included, 52% with unresectable and 48% with borderline resectable pancreatic cancer. Nineteen percent of all patients showed major pathologic response and 73% some pathologic response. Twenty-nine percent of patients received additional chemotherapy and/or radiation therapy. At the end 88% of the patients with borderline resectable cancer, and 20% of them with unresectable disease underwent R0 resection. As a result FOLFIRINOX is a promising treatment in the neoadjuvant setting, to convert a patient with locally advanced pancreatic cancer to have resectable disease. Further evaluation of the use of this regimen in the neoadjuvant setting is warranted.

A Single-Center Experience of Modified FOLFOX-6 in Locally Advanced and Metastatic Pancreatic Adenocarcinomas. (Abstract #303 [13])

Bradley Thomas Sumrall *et al*. performed a retrospective review of 26 patients with locally advanced (n=7) or metastatic (n=19) pancreatic cancer, who received chemotherapy with modified FOLFOX6 instead of FOLFIRINOX.
FOLFIRINOX improves survival, but shows increased rate of hematological or no toxicity. So mFOLFOX6 was used as a more tolerable chemotherapy regimen.
The study analyzes the overall survival in these patients. Seventeen patients received mFOLFOX6 as first-line therapy, 6 as second-line and 3 as third-line treatment. Seven patients were treated with fluorouracil plus leucovorin plus irinotecan (FOLFIRI) after the study treatment. The median overall survival was 9 months and the mean survival was 10.6 months.
This small study shows similar overall survival between mFOLFOX6 and FOLFIRINOX, but with a safer toxicity profile with mFOLFOX6. Therefore, this regimen may become an option in patients with locally advanced or metastatic pancreatic cancer, especially those who are unable to tolerate FOLFIRINOX. Head-to-head comparison should be considered.

Discussion

Continued great efforts are applied to find more effective and less toxic treatment of locally advanced pancreatic cancer as it remains a disease with an extraordinarily poor prognosis. Chemoradiation with capecitabine in selected patients with localized unresectable disease appears to be less toxic and have a favorable survival compared to chemoradiation with gemcitabine. This backbone can be used towards further investigations into improvements in delivery of radiotherapy (i.e., hypofractionation, dose escalation intensity modulated radiotherapy or in combination with targeted radiosensitizers). FOLFIRINOX has showed its value in the metastatic pancreatic cancer, so a study about its effectiveness in the locally advanced pancreatic cancer, where there is still a possibility of converting a non-resectable tumor to resectable, is quite important. Boone *et al*. showed that it is possible to perform an R0 resection in a significant percentage of patients with locally advanced pancreatic cancer after induction chemotherapy with FOLFIRINOX [12].
In the everyday practice patients with locally advanced pancreatic cancer are not fit, with the majority having serious comorbidities and an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 2. mFOLFOX6 proved to have similar efficacy to FOLIRINOX, but a significantly safer toxicity profile making it an excellent alternative therapy for patients who cannot tolerate FOLFIRINOX.
So far these studies add to the growing evidence that it is time to move beyond gemcitabine and its combinations, as this therapy has reached a plateau. Fluoropyrimidine combined with two or three drugs or with radiotherapy is proving to be a more promising backbone in the treatment of locally advanced pancreatic cancer. Further investigation into the clinical use of tumor markers and the addition of targeted therapy to a fluoropyrimidine backbone is a reasonable next stage in furthering treatment of patients with locally advanced pancreatic cancer.

Conflicts of interest The authors have no conflicts to disclose

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