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HIGHLIGHT ARTICLE

Second-Line Therapy in Pancreatic Cancer

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

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Summary

At the time of diagnosis most of patients present with advanced or metastatic pancreatic cancer, thereby precluding surgical resection. While the standard of care in the first line setting is established, there are limited data to support a standard second-line chemotherapy regimen. The authors summarize two interesting studies (Abstract #263 and Abstract #287) presented at the 2013 ASCO Gastrointestinal Cancers Symposium. These studies concern two phase II trials about second-line chemotherapy in pancreatic cancer. The first one evaluated the role of fluoropyrimidine as monotherapy *versus* fluoropyrimidine in combination with irinotecan (Abstract #263) and the second one compared the fluoropyrimidine treatment with the continuation of gemcitabine as monotherapy (Abstract #287).

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

Pancreatic cancer is one of the most aggressive types of malignancy, with the majority of patients exhibiting surgically unresectable disease at the time of diagnosis [1]. Although the standard of care in the first line setting is established, there are limited data to support a standard second-line chemotherapy regimen [2]. In daily practice, second-line therapies are regularly used in gemcitabine-pretreated patients with pancreatic carcinomas, but the efficacy and benefit in terms of survival or quality of life have never been validated [2]. For these patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable options [3, 4, 5]. The only established therapy is the combination of 5-flouorouracil, leucovorin and oxaliplatin (FOLFOX), according to the results from the phase III Charité Onkologie Clinical (CONKO)-003 trial [3]. The presented results of this study showed significant improvements in both median progression-free survival (13 *vs*. 9 weeks; P=0.012) and median overall survival (20 *vs*. 13 weeks; P=0.014) when oxaliplatin was added to 5-fluorouracil/leucovorin making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy [6]. Finally, the XELOX regimen (oxaliplatin plus capecitabine) showed comparable efficacy to FOLFOX regimen, while offering the advantage of oral fluoropyrimidine treatment [4].

Key words 5-fluoropyrimidine; Drug Therapy, Combination; irinotecan; Pancreatic Neoplasms; S 1 (combination)

Abbreviations FOLFOX: 5-flouorouracil, leucovorin and oxaliplatin; IRIS: S-1 plus irinotecan

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What We Learnt at the 2013 ASCO Gastro-intestinal Cancers Symposium?

In the 2013 ASCO Gastrointestinal Cancers Symposium, there were two abstracts from Japan concerning phase II trials for the second-line therapy in patients with gemcitabine-refractory pancreatic cancer.

Randomized Phase II Trial of S-1 versus S-1 Plus Irinotecan (IRIS) in Patients with Gemcitabine-Refractory Pancreatic Cancer (Abstract #263) [7]

Mizuno *et al*. performed a randomized phase II trial and examined the activity of an oral fluoropyrimidine derivative, S-1 *versus* S-1 plus irinotecan (IRIS) as a second-line treatment of pancreatic cancer. A total of 137 patients were enrolled in the trial but 127 patients were eligible. All patients had confirmed progressive disease after gemcitabine treatment, and performance status 0-1. Sixty patients received IRIS (Arm A) and 67 patients received S-1. The primary endpoint was to compare progression-free survival in two patients groups. This study demonstrated that IRIS showed a

significant improvement in response rate (18.3% *vs.* 6.0%; p=0.0311) when compare to S-1, although showing no statistically significant improvement in median progression-free survival (107 *vs.* 58 days, respectively; P=0.175) and median overall survival (208 *vs.* 176 days, respectively; P=0.134). IRIS also showed favorable hazard ratio, in both progression-free survival (HR=0.767) and overall survival (HR=0.749). Both IRIS and S-1 were well tolerated.

Randomized Phase II Study of Best Available Fluoropyrimidine Compared with Continuation of Gemcitabine (Gem) Monotherapy in Patients with Gem-Refractory Pancreatic Cancer (Abstract #287) [8]

Ioka *et al*. examined the activity of fluoropyrimidine regimen (5-fluorouracil, tegafur uracil, and S-1) in patients who were treated with standard dose of gemcitabine and were diagnosed with disease progression. Forty patients (Arm A) received fluoropyrimidine (67.5% S-1, 29.0% tegafur uracil, and 12.5% 5-fluorouracil) and 40 patients continued to treat with the standard dose of gemcitabine (Arm B). In all endpoints there was significant improvement with fluoropyrimidine administration. In Arm A versus Arm B, the response rate and disease control rate were 10% *vs*. 0% and 50% *vs*. 17.5%, respectively. Also, median progression free survival and overall survival times were 113 days *vs*. 50 days (P=0.105) and 226 days *vs*. 161 days (P=0.038), respectively.

Discussion

Pancreatic cancer remains a highly chemoresistant malignancy carrying an extremely poor prognosis. While the first line treatment is established, there is limited data available to guide treatment decisions in patients whose disease has progressed following gemcitabine treatment. Many small studies have shown some hints of activity, with oxaliplatin-fluoropyrimidine combinations appearing the most promising [3, 9].

The two studies presented at the 2013 ASCO Gastrointestinal Cancers Symposium by Mizuno *et al*. [7] and Ioka *et al*. [8] focus on second-line treatment in patients with pancreatic cancer. Both studies evaluated the efficacy of fluoropyrimidine in gemcitabine-refractory patients either as monotherapy or in combination with other regimens. Ioka *et al*. showed that fluoropyrimidine administration statistically improves overall survival, progression-free survival and response rate compared to the continuation of gemcitabine [8]. On the other hand, Mizuno *et al*. reported that the combination of fluoropyrimidine plus irinotecan is better than the S-1 alone with significant advantage in response rate but without statistically significant improvement in progression-free survival and overall survival [7]. Concerning the safety, Mizuno *et al*. showed that both regimens were well-tolerated [7].

In conclusion, the main findings presented in studies concerning the second-line therapy show that gemcitabine has no role as second-line therapy and fluoropyrimidine-based therapy may be the standard approach for second-line therapy. Its combination with irinotecan seems promising but further study is required with larger randomized controlled trials.

Conflicts of interest No conflicts to disclose

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