

PANCREATIC CANCER

CONKO conquers

The aggressive nature of pancreatic adenocarcinoma, its difficulty in being detected at early stages, and its propensity to develop resistance to chemotherapy makes of this cancer one of the deadliest types. Since gemcitabine became the first-line standard of care for metastatic pancreatic cancer nearly 20 years ago, only two combination regimens have been made available: nab-paclitaxel plus gemcitabine and the combination with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). Both combinations have shown improved overall survival and response compared with gemcitabine alone in phase III clinical trials. However, given that FOLFIRINOX is associated with severe toxicity and a high proportion of patients do not respond to treatment with gemcitabine, what are the options for patients who require second-line treatment?

The group led by Helmuth Oettle have conducted the CONKO-003 trial, a randomized, open-label, phase III study carried out in 16 institutions throughout Germany to assess the efficacy of a second-line regimen in patients with advanced-stage pancreatic cancer who have experienced progression while receiving gemcitabine monotherapy. “Various second-line therapies have been associated with improved survival outcomes in these patients,” explains Oettle “but only limited definitive phase III data support any particular regimen.” The trial included 168 patients who had experienced disease progression during treatment with first-line gemcitabine. The patients were randomly assigned to receive folinic acid and fluorouracil (FF) or oxaliplatin and FF (OFF). After a follow-up of 54.1 months, the median overall survival observed in the OFF group was 5.9 months compared with 3.3 months in the FF group. Reported adverse events were similar between both arms, although more patients assigned to received OFF experienced grade 1–2 neurotoxicity (38.2% patients compared with 7.1% patients in the FF group).

Oettle points out that an important limitation of this study is that “it was performed before FOLFIRINOX and nab-paclitaxel in combination with gemcitabine became first-line treatment options for patients with advanced pancreatic cancer.” Because second-line treatment with OFF was mainly developed to follow first-line gemcitabine monotherapy, overlapping toxic effects were not expected. However, today, second-line OFF could be suitable for patients who have undergone first-line therapy with gemcitabine as monotherapy or in combination with erlotinib (as this regimen, approved in 2005 as a first-line therapy for advanced pancreatic cancer, is not neurotoxic), and especially for patients progressing upon treatment with nab-paclitaxel in combination with gemcitabine, because the neurotoxicity observed in those patients is generally reversible.

Thus, this phase III trial confirms the OFF regimen as a standard of care for the second-line treatment of patients with advanced-stage pancreatic cancer.

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Original article Oettle, H. *et al.* Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J. Clin. Oncol.* doi:10.1200/JCO.2013.53.6995