

EDITORIAL

Research in Pancreatic Cancer: An Update After ASCO 2012

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Metastatic pancreatic cancer remains a lethal disease with no improvements in combination regimens. The current FDA-approved cytotoxic treatment for advanced pancreatic cancer remains gemcitabine since 1997 [1]. Even though gemcitabine is tolerated well, its efficacy is marginal with median survival of 6 months. Combination chemotherapy with gemcitabine has shown no meaningful survival in metastatic pancreatic cancer. However, other options, such as gemcitabine combined with a fluoropyrimidine or a platinum agent and the combination of 5-fluorouracil, leucovorin, irinotecan, oxaliplatin (FOLFIRINOX), are also commonly used in patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-1 [2, 3, 4]. The results of the Partenarait de Recherche en Oncologie Digestive - Action to Control Cardiovascular Risk in Diabetes (PRODIGE4-ACCORD11) study that showed the improvement with FOLFIRINOX over gemcitabine in both progression-free survival and overall survival is now doubt a turning point and a step forward that we hope to see. A total of 342 patients with metastatic pancreatic cancer treated in this study showed a significant improvement in median overall survival (from 6.8 months with gemcitabine to 11.1 months with FOLFIRINOX). Progression-free survival was also improved, from 3.4 to 6.4 months. The authors concluded that these survival times were the best ever seen in metastatic pancreatic cancer. This progress in research has already trickled down to the clinic, evidenced by some long-term survivors in this disease population. Many targeted agents, including bevacizumab, cetuximab have been tested in pancreatic cancer and showed negative results. Only the combination of erlotinib (*Tarceva*, Genentech Inc., South San Francisco, CA,

USA) with gemcitabine showed a survival benefit and is approved for first-line treatment [5]. Though statistically significant, this difference was not considered clinically significant [6].

The toxicity associated with FOLFIRINOX is very concerning; especially grade 3 and 4 myelosuppression and fatigue. However, prophylactic use of granulocyte colony-stimulating factors (G-CSF) seems to help. It is very important to keep in mind that FOLFIRINOX regimen should be chosen for selected patients, such as younger than 75 years of age, have a good performance status (ECOG 0-1), and have low bilirubin levels (less than 1.5 times the upper limit of normal). Of note, only fewer patients had the head-of-pancreas lesions in the FOLFIRINOX study compared to that would be typically seen in a metastatic pancreatic cancer population. This may have led to fewer patients having indwelling pancreatic stents, which pose a risk for cholangitis with myelosuppressive regimens [7].

FOLFIRINOX regimen has been taken up in the USA but has also been modified by various centers, such as omitting the bolus 5-fluorouracil, decreasing the dose of irinotecan, etc. [8]. I will like to argue that no impact of these dose modifications on the efficacy is known at present. Though I agree that FOLFIRINOX demonstrated superiority over gemcitabine alone in the metastatic pancreatic cancer setting, it does not qualify, at least at present, to be considered the first-line therapy in all patients with metastatic disease. Currently, FOLFIRINOX is tested in locally advanced disease, and in the neo-adjuvant and adjuvant settings. Based on the encouraging results of the preliminary data, all investigators are anxiously awaiting the results of an ongoing phase III study of nab-paclitaxel in pancreatic cancer. Other new therapeutic agents under investigation include insulin growth factor-1 receptor antibody, and hedgehog inhibitors [9].

Complete data from trabedersen Phase I/II study in patients with advanced pancreatic cancer, malignant melanoma or colorectal cancer was presented at the annual meeting of 2012 American Society of Clinical Oncology (ASCO) in Chicago, IL, USA [10]. Trabedersen is an antisense compound that specifically inhibits expression of transforming growth factor beta

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Abbreviations ECOG: Eastern Cooperative Oncology Group; FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, oxaliplatin

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2 (TGF- β 2; a protein which is overexpressed in advanced tumors and which triggers key cancer pathomechanisms; i.e., suppression of antitumor immune response and metastasis). A total of 61 patients with advanced pancreatic adenocarcinoma (n=37), malignant melanoma (n=19), or colorectal cancer (n=5), and Karnofsky performance status equal to 80% or more, were treated with continuous i.v. trabedersen as second- to fourth-line therapy with escalating doses in two treatment schedules (1st schedule: 7 days on and 7 days off; 2nd schedule: 4 days on and 10 days off) for up to 10 cycles for both schedules. The study demonstrated trabedersen optimal treatment schedule as being 4 days on and 10 days off for a well-tolerated dose of trabedersen of 140 mg/m²/day. Therefore, in the phase II part of the study additional 14 pancreatic adenocarcinoma and malignant melanoma patients respectively were enrolled and treated with 140 mg/m²/day (4 days on and 10 days off). Trabedersen was safe and very well tolerated. Dose-limiting toxicities were maculopapular rash (one event, non-serious), moderate, reversible thrombocytopenia (two events, non-serious), and gastrointestinal hemorrhage (one event, serious). Only two severe adverse events (gastrointestinal hemorrhage and pyrexia) were considered as possibly related to the study medication. These two severe adverse events were both reversible. Survival analysis of all patients with advanced pancreatic cancer (any number of pretreatments; any schedule or dose) revealed a median overall survival of 4.9 months (n=37; 95% CI: 3.2-7.1 months) while a median overall survival of 13.4 months (n=9; 95% CI: 4.9-18.2 months) was found in pancreatic cancer patients who had received trabedersen second-line with a dose of 140 mg/m²/day (4 days on and 10 days off). One patient with advanced pancreatic cancer (liver metastasis) had a complete response and is still alive after 76.2 months (as of January 2012). Based on these promising results, future studies are warranted.

To move forward and cause a real impact in the outcome in patients with pancreatic cancer, we ought to improve our knowledge on pancreatic cancer cells, relationships between tumoral, endothelial and stromal cells. In addition, we need to treat pancreatic cancer patients separately based on their staging (resected, borderline resectable, locally advanced or advanced) as well as other biomarkers. The importance of pharmacogenomics in the outcome of therapeutic agents and development of reliable biomarkers is urgently needed. This is the only way to prove newer

agents to be cost-effective and highly efficacious in this very competitive and challenging environment of modern oncology. This is particularly crucial in a disease such as pancreatic cancer that has such a short life expectancy that the "window" for any given treatment may be quite small. Development of novel agents and approaches are urgently needed in conjunction with improvement in access to clinical trials for patients.

Conflict of interest The authors have no potential conflicts of interest

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