EDITORIAL

Pancreatic Cancer in 2014

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Pancreatic adenocarcinoma remains a therapeutic challenge. The American Cancer Society's estimates [1] for pancreatic cancer in the United States for 2014 are:

- about 46,420 people will be diagnosed with pancreatic cancer;
- about 39,590 people will die of pancreatic cancer.

The incidence of pancreatic carcinoma has markedly increased over the past several decades and now it ranks as the fourth leading cause of cancer-related death in the United States. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood. The landscape in treatment of pancreatic adenocarcinoma changed in 2010 with the comparison of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) *versus* gemcitabine for metastatic pancreatic cancer [2]. This raised enthusiasm that was tempered by fear for the increased toxicity of FOLFIRINOX. Also there are data evidencing that there is quality of life improvement with the administration of FOLFIRINOX. This new option has now extended on landscape of pancreatic cancer across all stages of cancer, including locally advanced disease, borderline resectable disease, and adjuvant treatment. Another treatment option appeared in 2013 based on the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT; NCT02021500) study that showed superiority of gemcitabine plus nab-paclitaxel over single agent gemcitabine [3]. In addition to overall survival as the primary end point, the study also showed superiority of the combination arm for the secondary efficacy end points. A difficult question immediately arises that which regimen should be chosen for first-line treatment of pancreatic cancer. There is no clear data to guide the decision for the treating oncologists [4]. The main factors to be considered for selection of the regimen in general include age, performance status, and patient's preference. In general, combination of gemcitabine and nab-paclitaxel seems to be more applicable to older population and relatively less robust performance status. However, other factors especially molecular biomarker of pharmcogenetic surrogates are needed to enhance our ability to select which regimen will give benefit and for which patients. In that direction, Yu *et al*. isolated and performed gene expression profiling of circulating tumor and infiltrating cells in unresectable pancreatic cancer patients [5]. Preliminary analysis suggests that cytotoxics profiling can predict response. Repeat pharmacogenomic profiling identifies key pathways associated with treatment resistance. Also, this model can be validating to other regimens and can evaluate regimens for second-line treatment. One such biomarker pending validation is the secreted protein acidic and rich in cysteine (SPARC) as earlier studies showed superior benefit of combination of gemcitabine and nab-paclitaxel regimen in patients with higher expression of SPARC [4].

On the side of targeted agents, including bevacizumab, cetuximab, and erlotinib has been dismal except a modest benefit with erlotinib [4, 6]. Though statistically significant in the erlotinib

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Abbreviations 5-FU/LV: 5-fluorouracil and leucovorin; FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX: 5-flouorouracil, leucovorin and oxaliplatin; HA: hyaluronic acid; JAK: Janus kinase; MM-398: irinotecan sucrosofate; MPACT: Metastatic Pancreatic Adenocarcinoma Clinical Trial; PARP: poly (ADP-ribose) polymerase; PEGPH: pegylated recombinant human hyaluronidase; PSCA: prostate stem cell antigen; SN-38: active metabolite of irinotecan; SPARC: secreted protein acidic and rich in cysteine

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study, this difference was not considered clinically significant. Recent data was also disappointing about IPI926, CO-101, AMG479, vismodegib and sorafenib. These disappointing results again underlined the difficulty of treating patients with pancreatic cancer. Currently, novel agents targeting numerous pathways are under study, such as histone deacetylases, insulin-like growth factor 1 receptor, mammalian target of rapamycin, transforming growth factor β type I receptor, PIK3/AKT, Notch, prostate stem cell antigen (PSCA), and SRC. A promising approach under evaluation in clinical studies is the development of pegylated recombinant human hyaluronidase 20 (PEGPH20). Preliminary data from a phase Ib study in combination with gemcitabine for the treatment of patients with stage IV metastatic pancreatic cancer showed a promise [7]. In this trial, both progression free survival and overall survival data suggest a potential clinical benefit of using PEGPH20 with gemcitabine in patients with high levels of tumor associated hyaluronan (hyaluronic acid; HA). Multiple regimens are under testing with PEGPH20 such as combination with nab-paclitaxel and gemcitabine, as well as, combination with 5-flouorouracil, leucovorin and oxaliplatin (FOLFOX) and FOLFIRINOX.

The breast cancer susceptibility genes *BRCA1* and *BRCA2* act as caretakers in the maintenance of genomic stability, partly by participating in homology-directed DNA repair. Poly (ADP-ribose) polymerase 1 (PARP1) is an enzyme that functions in the base excision repair pathway. These data and the preliminary results with a PARP inhibitor spawned the idea to use PARP inhibitors to treat *BRCA1/2* mutant pancreatic cancers [8, 9]. Initial data from studies including oniparib, veliparib have been promising. These data are very intriguing and warrant further investigation. There are ongoing prospective phase II studies with cisplatin-gemcitabine and veliparib *versus* cisplatin-gemcitabine alone and with single agent veliparib for second-line treatment in patients with pancreatic cancer.

NAPOLI 1 (NCT01494506) is a global, randomized, open label phase III trial testing MM-398 as a monotherapy and MM-398 in combination with 5-fluorouracil and leucovorin (5-FU/LV) compared with the shared control arm of 5-FU/LV [10]. MM-398 is a novel nanoliposomal encapsulation of irinotecan sucrosofate. MM-398 is designed to optimize the delivery of irinotecan by extending the duration of circulation in the body and preferentially activating the drug within the tumor to achieve higher levels of the active cytotoxic irinotecan (SN-38). In another phase II trial, known as the Ruxolitinib in Pancreatic Cancer Patients (RECAP; NCT01423604) trial, patients with metastatic pancreatic cancer who had failed first-line treatment with gemcitabine, or another chemotherapy agent if they were ineligible to receive gemcitabine, received capecitabine 2,000 mg/m^2 or 1,000 mg/m^2 twice a day and were randomized to receive either ruxolitinib 15 mg twice a day or a placebo [11]. Ruxolitinib is a potent and selective oral Janus kinases 1 and 2 (JAK1 and JAK2) inhibitor that was approved by the FDA in 2011 for the treatment of myelofibrosis. Glufosfamide *versus* 5-FU/LV is being tested in second-line metastatic pancreatic cancer [12].

Despite progress in the development of new cytotoxic and biological drugs for the treatment of pancreatic cancer the outcome remains grim. The conclusions from the recent 2014 ASCO Gastrointestinal Cancers Symposium are that we are awaiting for new chemotherapy combinations. Data are emerging for the benefit of second-line regimens. Also new targets are in development, as anticancer stem cell agents, immunotherapy and gene therapy, for this very deadly malignant tumor. Patients with any stage of pancreatic cancer should be considered candidates for clinical trials.

Conflict of interest The authors have no potential conflicts of interest

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