

2016 Gastrointestinal Cancers Symposium: update on pancreatic cancer

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As we continue to investigate promising new therapies and optimize treatment strategies for pancreatic cancer to improve outcomes for patients with this deadly disease, investigators from all over the world met at the 2016 Gastrointestinal Cancers Symposium in San Francisco, CA from January 20-22. Among other GI malignancies, there was a major focus on current controversies in the management of pancreatic cancer as well as novel treatment approaches that hold promise for the future. Here we discuss selected abstracts that may influence the treatment of pancreatic cancer in the future. We divide this editorial into the following sections: screening, adjuvant, metastatic (first-line, second-line) and novel agents.

Screening

Screening for early detection in asymptomatic patients at high risk for development of pancreatic cancer

Interim results of a study which evaluated the utility of endoscopic ultrasound (EUS) to detect early stage pre-cancerous or cancerous changes in the pancreas of high-risk patients were presented (NCT01662609). 52 patients with normal screening EUS underwent repeat EUS at 1 year; and those with abnormal EUS with findings of mass or cyst measuring ≥ 5 mm underwent fine-needle aspiration (FNA). Those with indeterminate or benign FNA underwent pancreatic CT with repeat EUS/FNA at 3 or 6 months respectively. Patients with mass/cyst ≤ 5 mm underwent repeat EUS/FNA after 3 months. For the 41 eligible for analysis, 67% had a normal EUS and 34%

had abnormalities warranting FNA. 2 patients with large cyst were found to have intra-ductal papillary mucinous neoplasms and underwent surgical resection. The patients found to have at least 1 sub-centimeter lesion continue to be routinely screened per protocol. The investigators advocate the use of EUS for screening of asymptomatic persons at high risk for pancreatic cancer [1].

Adjuvant

Biomarkers to direct adjuvant therapy in patients with resected pancreatic cancer

Results of a phase II prospective trial (NCT01188109) aimed to investigate outcomes of patients treated with adjuvant gemcitabine and cisplatin with stratification of results by tumor excision repair cross-complementing gene-1 (ERCC1) expression were presented. The study was based on the hypothesis that the additional benefit observed by combining cisplatin with gemcitabine in patients with advanced pancreatic cancer (APC) may be inhibited by high expression of ERCC1. 22 patients with stage IA to IIB pancreatic cancer who underwent initial surgical resection received adjuvant gemcitabine and cisplatin for 6 cycles. Tumor ERCC1 expression was evaluated using immunohistochemistry and separated into low and high expression groups for 20 patients (15 low and 5 high). Low compared to high ERCC1 found to be associated with improved relapse-free survival (RFS) (12.4 vs. 16.7 months; $P=0.68$ or overall survival) (OS) ($P=0.22$). The investigators concluded that low expression is present in the majority of patients and further investigation examining ERCC-1 as a biomarker in resected pancreatic adenocarcinoma is warranted [2].

Role of radiation in the adjuvant treatment of resected pancreatic cancer

Effect of adjuvant radiotherapy on outcomes following pancreaticoduodenectomy for pancreatic adenocarcinoma remains a hot topic of controversy. Investigators from the University of Pittsburgh presented a retrospective study that examined the role of adjuvant radiotherapy based on margin clearance, based on the data that increased margin clearance is

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associated with improved survival in resected pancreatic cancer. The study included 326 patients with margin clearance data (mm) following pancreaticoduodenectomy. Adjuvant radiation was delivered to 87 patients. RFS and OS was determined by Kaplan-Meier analysis and hazard ratios were calculated by Cox multivariate regression analysis. The investigators found that median RFS and OS were 14 and 25 months, respectively and adjuvant radiation was not associated with improved RFS (13 vs. 14 months) or OS (23 vs. 27 months), but increasing margin clearance was associated with both. Even when stratified by margin clearance, adjuvant radiation was not associated with improvement in outcomes [3].

Metastatic APC

First-line therapy for patients with metastatic or locally-advanced unresectable pancreatic cancer

Three studies are worth mentioning in this editorial: MAESTRO (NCT01746979), PANOVA (NCT01971281), and PEGPH20 (NCT01839487).

Maestro Eric Van Cutsem presented the results of the MAESTRO, an international, randomized, double-blind, placebo-controlled phase III trial that attempted to address the problem of hypoxia in pancreatic cancer, which is associated with poor prognosis. The study randomized patients with locally advanced unresectable or APC treated with gemcitabine to placebo or evofosfamide (TH-302), which is a hypoxia-activated pro-drug of bromo-isophosphoramidate mustard. The phase III study was triggered by the promising results of a phase II study that showed significantly improved progression-free survival (PFS) with the addition of evofosfamide to gemcitabine (NCT01144455). In the phase III study, 693 patients were randomized to treatment with evofosfamide + gemcitabine vs. gemcitabine alone. Median OS and 1-year survival trended toward improvement for patients receiving evofosfamide (8.7 months, 34.2% vs. 7.6 months, 29.8%, respectively; $P=0.059$), with a statistically significant improvement in PFS (5.5 vs. 3.7 months; $P=0.004$). Dose interruptions and reductions were more frequently observed in the combination arm but no new safety findings were identified. Although the study did not meet the primary endpoint of improvement in OS, a signal for overall antitumor activity was observed [4].

Panova Investigators from Spain presented the results of this study, which investigated a novel treatment approach using TTFIELDS, which uses alternating electrical fields to interfere with mitotic spindle formation and mitotic activity, delivered to the region of the tumor using non-invasive transducer arrays. This clinical study was based on promising preclinical data demonstrating decreased proliferation and clonogenic potential *in vitro*, and reduced tumor volume *in vivo*. The PANOVA trial enrolled 21 previously untreated APC patients who received TTFIELDS at 150 kHz with concurrent weekly gemcitabine. Median compliance with TTFIELDS was 78% (14 h/day, median duration 5 months). TTFIELDS and

concurrent gemcitabine was deemed tolerable and safe for APC patients as the usual gemcitabine-related toxicities were observed and no TTFIELDS-related serious adverse events were reported. Results demonstrated encouraging median PFS and OS (8.3 and 14.9 months, respectively) of evaluable tumors, 30% demonstrated partial response and another 30% had stable disease [5].

PEGPH20 Poor outcome in pancreatic cancer has been previously associated with stromal hyaluronan (HA) accumulation, which compromises chemotherapy perfusion. PEGPH20 is a PEGylated recombinant human hyaluronidase, and has been demonstrated to potentiate chemotherapy by depleting HA in tumors. Dr Hingorani from Fred Hutchinson Cancer Research Center, Seattle presented the interim results of the phase II, open-label, randomized study of PEGPH20+nab-paclitaxel+gemcitabine (PAG) vs. nab-paclitaxel+gemcitabine (AG) in previously untreated stage IV APC. At the time of this report 135 patients were treated resulting in significant improvements in PFS in patients with high HA tumor receiving PAG vs. AG (9.2 vs. 4.3 months, respectively; $P=0.05$) and a trend toward improved OS (12 vs. 9 months). Overall, PAG treatment was well tolerated per investigators [6].

Effectiveness versus cost of FOLFIRINOX and gemcitabine and nab-paclitaxel in APC

With the change in health system, investigators have also started looking at the cost versus benefit of treatment in cancer patients. One such study presented at the meeting compared the effectiveness and costs of the ACCORD-11 (FOLFIRINOX) and MPACT (AG) treatment regimens by using a Markov model to estimate the cost per life-year gained (LYG) and per quality-adjusted life-year (QALY) for each treatment regimen. The model projected a life expectancy of 9 months and 7 months for FOLFIRINOX and AG, respectively, and a higher QALY for FOLFIRINOX than AG (0.51 vs. 0.40), but at a slightly higher cost. The authors recognized that the toxicity profile associated with FOLFIRINOX could account for a significant portion of cost and management of side effects may significantly impact the overall costs of treatment [7].

Second-line therapy for patients with metastatic or locally-advanced unresectable pancreatic cancer

Recently FDA approved the first regimen for the second line treatment of APC: nanoliposomal irinotecan (nal-IRI, MM-398), with 5-fluorouracil and leucovorin (5-FU/LV). This approval was based on the results of the NAPOLI-1 study, which was a phase III study of Nal-IRI with or without 5-FU/LV, vs. 5-FU/LV in APC previously treated with gemcitabine-based therapy (NCT01494506) that treated 417 patients. Updated overall survival analysis of NAPOLI-1. In an initial report Nal-IRI+5FU/LV significantly improved OS (6.1 vs. 4.2 months; $P=0.012$). The updated survival and safety analysis presented at this meeting demonstrated that the median OS benefit

Table 1 Novel agents presented at the 2016 Gastrointestinal Cancers Symposium

Abstract#	Agent	Mechanism of action/target
196 [9]	BBI-608	Cancer stemness inhibitor
341 [10]	Demcizumab	Humanized anti-DLL4 antibody
334 [11]	Cabozantinib	c-Met inhibitor
371 [12]	Sonidegib	Smoothed receptor inhibitor
385 [13]	Atu027	Protein kinase N3 (PKN3) inhibitor
419 [14]	Apatorsen	Heat shock inhibitor

for nal-IRI+5FU/LV over 5-FU/LV was maintained (6.2 vs. 4.2 months; P=0.041) with 6-month survival estimates 53 vs. 38%, and 12-month survival estimates 26% vs. 16%, both in favor of nal-IRI+5FU/LV [8].

Novel agents

Many novel agents were tested in phase I and II studies such as few shown in Table 1.

It is clear from the meeting that we all continue to make progress in understanding the cancer cells, developing new agents based on our knowledge about cancer cells and their environment and we now have more agents to offer to our patients, especially those will better performance status. To our disappointment, MAESTRO study included both locally advanced and APC a lesson we learned many years ago from bevacizumab studies. The importance of pharmacogenomics in the outcome of therapeutic agents and development of reliable biomarkers cannot be under estimated, especially that many tumor types are now treated based on precision medicine.

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