

Raising the Bar in Advanced Pancreatic Cancer

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Pancreatic cancer remains one of our greatest clinical challenges. In the last 5 years we have witnessed the introduction of new agents into our armamentarium, which has fortunately translated into incremental improvements in overall survival. We have level 1 evidence for the use of FOLFIRINOX and nab-paclitaxel in the first-line setting; however, the generalizability of randomized studies in the second-line setting has been less compelling. The use of oxaliplatin and 5-fluorouracil (5FU) post-gemcitabine progression was shown to improve survival in the CONKO-003 trial but failed to do so in the PANCREOX trial. Nano-liposomal irinotecan in combination with 5FU in pre-treated patients yielded an improved survival in the NAPOLI-1 trial, presenting an option in this setting. However, these trials were largely conducted in an era of first-line gemcitabine monotherapy, which is no longer a standard practice. Better evidence with contemporary first-line regimens is needed in order to define the optimal post-progression strategy in advanced pancreatic cancer.

Keywords

Pancreatic cancer, second-line, post progression, advanced disease

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The challenge of treating pancreatic cancer is exemplified by its high case fatality—for the estimated 53,000 people who will be diagnosed with pancreatic cancer in the US in 2017, over 43,000 will die of the disease.¹ Due to the typically late presentation of pancreatic cancer, only 15–20% are considered resectable with the remaining majority deemed to be advanced with either locally advanced or distant metastatic disease.

Chemotherapy remains the backbone of treatment for advanced pancreatic cancer. It has now been 20 years since gemcitabine has been established as the preferred first-line approach with the demonstration of superiority over 5-fluorouracil (5FU) based on an improvement in clinical benefit response and a modest improvement in survival.² In 2011, we learned that the combination of infusional 5FU, irinotecan, and oxaliplatin (FOLFIRINOX) significantly improved survival in the first-line setting when compared with gemcitabine, with a median overall survival of 11.1 months compared with 6.8 months.³ Two years later, the multinational Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) reported a median survival of 8.5 months with the addition of nab-paclitaxel to gemcitabine when compared with 6.7 months using gemcitabine alone ($p < 0.0001$).⁴ As a result, we now have more efficacious options to offer for suitably selected patients in the first-line setting.

Meanwhile, the options for patients post-progression remained limited. In 2014, Oettle and colleagues published the results of the German Charité Onkologie 003 (CONKO-003) phase III trial which evaluated the efficacy of second-line oxaliplatin in combination with 5FU and folinic acid (FF) versus FF alone.⁵ In this study, patients with progression on first-line gemcitabine monotherapy were randomized 1:1 to receive weekly infusional FF for 4 of every 6 weeks ($n=84$), or the same with the addition of oxaliplatin 85 mg/m² intravenously on weeks 1 and 3, herein referred to as the OFF regimen ($n=76$). Despite the intended 1:1 randomization, there was an unexplained imbalance of subject numbers across the arms—77 patients were allocated to OFF with one exclusion, and 91 patients were allocated to FF with seven exclusions. After a median follow-up of 54.1 months, CONKO-003 demonstrated a median survival of 5.1 months in the OFF group versus 3.3 months in the FF group ($p=0.10$). The Canadian PANCREOX phase III trial attempted to validate the efficacy of oxaliplatin in this second-line setting by comparing the combination with infusional FF administered in the more commonly used biweekly modified (m)FOLFOX6 schedule ($n=54$) and biweekly infusional FF per the de Gramont schedule ($n=54$).⁶ No improvement was seen in the primary endpoint of progression-free survival with a median of 3.1 months versus 2.9 months ($p=0.99$). Interestingly, median survival favored the infusional FF arm (6.1 months versus 9.9 months, $p=0.02$). Importantly, the withdrawal rate due to adverse events in the absence of progression was much greater for the mFOLFOX6 arm (20% versus 2%).

The reasons for the discrepant results of CONKO-003 and PANCREOX are not entirely clear as both studies included patients with prior gemcitabine therapy; however, there were some notable differences—eligibility for CONKO-003 required demonstration of progression while on gemcitabine therapy whereas PANCREOX permitted inclusion of patients with progression either during or following gemcitabine; OFF appeared to be better tolerated than mFOLFOX6; and similar proportions of patients in both CONKO-003 arms received further therapy while patients receiving mFOLFOX6 on PANCREOX were less likely to receive further therapy compared with the control arm (25% versus 7%).

Another important trial that emerged in this setting is the recently reported multinational NAPOLI-1 study which randomized 266 gemcitabine-treated patients with metastatic pancreatic cancer to nano-liposomal irinotecan plus FF versus FF alone.⁷ The combination arm was associated with an improved median survival of 6.1 months versus 4.2 months (p=0.012), presenting a new option for this patient population.

So, where does this leave us? Given the discrepant results of CONKO-003 and PANCREOX, the benefit of second-line oxaliplatin in patients receiving prior gemcitabine monotherapy remains uncertain. Furthermore, the standard for first-line therapy has now evolved beyond gemcitabine monotherapy to the combination of FOLFIRINOX or gemcitabine and nab-paclitaxel; thus, the optimal second-line strategy for patients previously treated with these contemporary regimens has not been investigated. The 2016 American Society of Clinical Oncology Clinical Practice Guideline for Metastatic Pancreatic Cancer⁸ advises us that multiple options be considered for patients treated with gemcitabine plus nab-paclitaxel with a preserved Eastern Cooperative Oncology Group performance status including 5FU and oxaliplatin, nano-liposomal irinotecan, or 5FU, while patients treated with FOLFIRINOX may be offered gemcitabine plus nab-paclitaxel; however, these recommendations were based on informal consensus and low quality of evidence, thus limiting the confidence of applying them to standard practice. More robust evidence is needed, based on trials investigating a sequential treatment strategy, in order to define the optimal post-progression strategy for patients with advanced pancreatic cancer. □

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