EDITORIAL

Therapeutic Advances in Pancreatic Cancer: Miles to Go Before We Sleep

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Pancreas adenocarcinoma maintains its dastardly reputation as among the most lethal of cancers (1). Following decades of negative studies, new drug combinations are shifting the treatment landscape for this disease. In 2010, the Actions Concertées dans les Cancer Colo-Rectaux et Digestif (ACCORD) 11 study known as Partenariat de Recherche en Oncologie Digestive (PRODIGE) 4 found Oxaliplatin; Irinotecan; Leucovorin; and Fluorouracil (FOLFIRINOX) statistically improved response rate (RR), progression-free survival (PFS), and overall survival (OS) over single-agent gemcitabine (2). Shortly thereafter, Van Hoff et al. published the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) phase III study; combining nab-paclitaxel with gemcitabine statistically improved RR, PFS, and OS compared with gemcitabine alone (3). More recently, a three-arm phase III study, NAPOLI-1, comparing single agent MM398 (nanoliposomal irinotecan), infusional 5-fluorouracil (5FU), and MM398 plus infusional 5FU (MMF) found improved outcomes with the combination in patients with refractory metastatic pancreatic cancer (4). Charité Onkologie (CONKO)-003, confirmed that OFF (oxaliplatin, folinic acid and fluorouracil) was superior to 5FU in patients with refractory metastatic pancreatic cancer (5).

In this issue of the Journal, Goldstein and colleagues (6) update the long-term results from the MPACT study confirming a survival advantage of 2.1 months with nab-paclitaxel plus gemcitabine over gemcitabine alone, a finding independent of performance status or the presence of liver metastases. Among the nab-paclitaxel plus gemcitabine patients, 4% survived 36 months or longer, compared with 0% in the gemcitabine arm. No baseline characteristics helped predict long-term survival. Toxicities were more common in the combination arm: Notably peripheral neuropathy (grade 3) in 17% of patients on the experimental arm meant that over half were never resumed on nab-paclitaxel.

How do these results impact the choice for first line treatment of patients with metastatic pancreatic cancer?

There is no Phase III trial comparing the efficacy of nab-paclitaxel plus gemcitabine vs FOLFIRINOX. Historical cross-comparisons seem to give FOLFIRINOX an edge. However, the validity of direct comparison is hampered given the populations studied and the toxicity profiles differed. Now that we have a network of active multidrug regimens, a sequential approach with nab-paclitaxel plus gemcitabine first followed by MMF or OFF upon progression is a feasible and potentially less toxic approach and one that will facilitate the addition of novel agents to established chemotherapy backbones.

With this in mind, how can we improve the selection of patients who will benefit from the addition of nab-paclitaxel to gemcitabine?

Cost-effectiveness and individualized therapy based on molecular markers is increasingly possible. The recent draft guidance from the UK’s National Institute for Health and Care Excellence (NICE) advised the National Health Service not to fund nab-paclitaxel because of its limited benefit and added toxicity compared with gemcitabine (7). Selection of patients most likely to benefit could make this a better investment.

Understanding the relevance of genomic heterogeneity in patients with pancreatic cancer lags behind what is known in a number of other solid tumors, and specific mutations have generally not been of clinical utility in making treatment decisions. This means that we continue to rely on standard histologic and biologic prognostic determinants to risk-stratify these patients. Two such prognostic factors include Carbohydrate Antigen 19-9 (CA 19-9) levels and the neutrophil-to-lymphocyte ratio (NLR). CA 19-9 is a sialylated Leantigen not present in 15% to 20% of individuals with Le phenotype who are unable to synthesize the antigen. It is overexpressed in the bloodstream by 69% to 92% of pancreatic cancer patients (8). High expression of the antigen is a negative prognostic factor. In this trial (6), CA 19-9 levels were measured every eight weeks. Patients were divided into two cohorts depending upon levels above (high) or below (low) the median baseline of 2470U/mL. The two-year survival for individuals with high CA 19-9 levels treated with nab-paclitaxel was 55% compared with 15% for those receiving gemcitabine. The hazard ratio (HR) for overall survival among patients with high levels who received nab-paclitaxel compared
with those receiving gemcitabine alone was 0.612 ($P < .001$), and the hazard ratio for the population with low levels was 0.833 ($P = .113$). In the cohort treated with gemcitabine alone, OS was statistically significantly longer in the low CA 19-9 than the high CA-19-9 cohort. This analysis suggests that the two-drug combination is more likely to benefit the cohort of patients with high CA 19-9 levels than is gemcitabine alone. This is a finding of clinical relevance to treating physicians.

The NLR, a putative marker of systemic inflammatory response, has been examined in retrospective analyses and a ratio of greater than five has been predictive of poor outcomes in populations with advanced pancreatic adenocarcinoma. In this trial (6) a baseline NLR of greater than five was a negative prognostic factor, with a hazard ratio of 0.57 ($P < .001$). The median survival was 9.1 months vs 5.0 months when data from both arms were pooled (HR = 1.8, $P < .001$). In both the populations with NLR below and above five, longer OS was noted in the nab-paclitaxel arm (NLR < 5: 10.9 vs 7.9 months, HR = 0.67, $P < .001$; NLR > 5: 5.6 vs 4.3 months, HR = 0.81, $P = .079$). Perhaps NICE would be more willing to invest in more intensive treatment if the CA 19-9 and NLR were unfavorable, indicating limited benefit of gemcitabine alone.

A number of other molecular biomarkers remain under evaluation for defining subgroups of patients most likely to benefit. SPARC (secreted Protein Acidic and Rich in Cysteine) expression in pancreatic stroma is associated with poor outcome (9). Nab-paclitaxel may target stromal SPARC facilitating intratumor accumulation of paclitaxel (10) or the nab formulation may improve pharmacologic delivery of paclitaxel to the tumor bed (11). Identification of predictive biomarkers may have utility in stratifying patients for treatment and help us choose who is most likely to benefit among the various regimens showing activity in this disease. And finally, physicians and their patients have choices in the management of pancreatic adenocarcinoma. However, in the management of this disease in particular, we “have miles to go before we sleep.”

Notes
The authors declare the following relevant conflicts of interest within the last 36 months: TBS is a consultant for Celgene and Lilly. RG is a consultant (DSMB) for Lilly.

References