SESSION 7: PANCREATIC CANCER

Pancreatic Cancer: How to Select the Optimal Systemic Therapy for Patients with Metastatic Disease

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Chemotherapy currently remains the mainstay of treatment for metastatic pancreatic cancer. Over the past several years, two combination chemotherapy regimens have emerged as new standards of care for first-line treatment, both based on positive results from large randomized phase III trials. The French PRODIGE 4/ACCORD 11 trial (1) demonstrated the superior efficacy of FOLFIRINOX (biweekly bolus plus infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) compared to single-agent gemcitabine, with a hazard ratio for death of less than 0.6. Recognizing that this patient population was particularly robust (ECOG performance status 0-1), the median survival rate of close to one year (11.1 months) was particularly notable, especially in a purely metastatic cohort. Moreover, despite higher rates of treatment-related toxicity for patients receiving FOLFIRINOX, a quality-of-life assessment built into the trial revealed that time to patients receiving FOLFIRINOX maintained their quality of life longer than those receiving gemcitabine (2). Meanwhile, the MPACT trial (3), an international phase III study, randomized patients with metastatic disease to receive either gemcitabine alone or the combination of gemcitabine plus albumin-bound paclitaxel (Abraxane, Celgene Corp.), and demonstrated that the combination regimen was associated with a statistically significant improvement in survival (HR 0.72), with a manageable and predictable toxicity profile. At this point, absent a prospective randomized trial that directly compares these two regimens head-to-head, we are left without clear direction as to how best to choose one versus another. Specifically, there remains no validated biomarker that helps us in this selection process; prior studies have failed to demonstrate the predictive utility of markers such as hENT1 (4) and SPARC (5). For now, practical considerations such as medical co-morbidities, age, organ function, convenience, and patient preference are what we are left using in making these decisions.

Sequencing of chemotherapy, analogous to what is commonly done in colorectal cancer and other malignancies in which a multiplicity of therapeutic options exists, is an approach that can now be increasingly used for patients with metastatic pancreatic cancer. However, it is important to recognize that there remains no universally accepted standard of care for patients who have progressed on first-line therapy. Data are mixed, for example, on the use of a fluoropyrimidine/oxaliplatin combination following progression on front-line gemcitabine (6,7). Recently, a phase III trial (NAPOLI-1) (8) evaluating a nanoliposomal formulation of irinotecan, MM-398 (Merrimack Pharmaceuticals), showed positive results when given in combination with 5-FU for patients with metastatic pancreatic cancer who had progressed on a gemcitabine-based regimen. This agent is currently under FDA review and may represent the first drug specifically approved for the second-line treatment of this disease.

Aside from cytotoxic agents, other novel drugs with varying mechanisms of action have shown promising results in early clinical studies of pancreatic cancer. Certainly, immunotherapies have

revolutionized the way we treat a variety of cancer types, and while pancreatic cancer has traditionally been considered a 'non-immunogenic' malignancy, a number of studies have been and are currently exploring ways to harness the host immune system in this disease, including vaccine-based approaches (CRS-207, an attenuated mesothelin-expressing Listeria vaccine; Aduro Biosciences) (9), immune checkpoint inhibitors, and BTK inhibitors. The dense desmoplastic reaction that characterizes pancreatic cancer may represent another exploitable target; promising preliminary results have recently been reported with a recombinant enzyme, hyaluronidase, that disrupts this tumor-associated stroma (PEGPH20, Halozyme) (10). Finally, while small molecules that inhibit EGFR or components of the KRAS signaling axes have shown fairly modest efficacy in pancreatic cancer to date, other agents such as ruxolitinib (Jakafi, InCyte) and PARP inhibitors have shown that targeting the JAK-STAT pathway and the PARP enzyme may represent promising strategies in carefully pre-selected patient populations (11,12).

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