Active Systemic Treatment of Pancreatic Cancer

Presented by Margaret Tempero, MD

Abstract

By 2020, pancreatic cancer is expected to be the second most common cause of cancer-related death, exceeded only by lung cancer. During her presentation at the NCCN 22nd Annual Conference, Dr. Margaret Tempero offered an update on the current state of systemic treatment of pancreatic cancer, focusing on resectable/borderline resectable, locally advanced, and metastatic disease.

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"Although cancer death rates have dropped dramatically, with amazing changes in age-adjusted mortality rates in the most common cancers, patients with pancreatic cancer are not enjoying such benefits," said Margaret Tempero, MD, Professor of Medicine, and Director, University of California San Francisco (UCSF) Pancreas Center, UCSF Helen Diller Family Comprehensive Cancer Center. Dr. Tempero also serves as Editor-in-Chief of *JNCCN* and as Chair of the NCCN Pancreatic Adenocarcinoma Panel.

Among the various reasons for poor outcomes in this aggressive disease are the lack of clear presenting symptoms, very early tumor invasion and metastases, and somewhat resistant nature to chemotherapy, she explained. Furthermore, patients with pancreatic cancer are "living in a sea of cytokines, which weaken them and make them more frail," Dr. Tempero added. To improve future outcomes, she noted the importance of continuing to study ways to target the *RAS* mutation, as well as its microenvironment, which makes it difficult for agents to penetrate the stroma.

Presented by Margaret Tempero, MD, Professor of Medicine and Director of the University of California San Francisco (UCSF) Pancreas Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California.

Dr. Tempero has disclosed that she has received consulting fees and honoraria from Champion Oncology, Inc., Cornerstone Pharmaceuticals, Inc., Eli Lilly and Company, EMD Serono, Inc., MCS Biotech Resources, LLC, NeoHealth Inc., Novocure, Opsona Therapeutics, Portola Pharmaceuticals, Inc., and Threshold Pharmaceuticals Inc.; and grant/research support from Celgene Corporation and Halozyme Therapeutics, Inc.; and she has served as a scientific advisor for EMD Serono, Inc., Gilead Sciences, Inc., and Pfizer Inc.

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Resectable/Borderline Resectable Disease

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma provide the criteria for both resectable and borderline resectable disease. "NCCN was the first organization to coin the term 'borderline resectable' and create some criteria around it," revealed Dr. Tempero. "Borderline resectable is a disease that is resectable but with a high chance of a positive margin," she said.

Dr. Tempero briefly reviewed some of the representative adjuvant therapy clinical trials conducted in pancreatic cancer, focusing primarily on the relatively recent phase III ESPAC-4 trial of gemcitabine/capecitabine[1] and the emerging use of neoadjuvant therapy.[1] A historical glance at the past 30 years of adjuvant therapy in this disease reveals little difference between regimens in overall survival (OS), until this past year, noted Dr. Tempero.

In the ESPAC-4 trial of patients with resected pancreatic ductal adenocarcinoma, adjuvant therapy with gemcitabine/capecitabine yielded a statistically significant improvement in survival compared with gemcitabine monotherapy, with a median OS of 28 months for patients randomized to receive gemcitabine/capecitabine.[1] As a result of these findings, "this regimen has now entered our guidelines as an important option for adjuvant therapy," she reported.

The CONKO-001 trial by Oettle et al[2] showed that, with a median OS of 22.8 months, gemcitabine delayed the development of recurrent disease versus observation alone, when used as adjuvant treatment. Gemcitabine monotherapy is considered "minimally active" in patients with advanced disease. "It can have a big impact in the adjuvant setting," noted

Dr. Tempero. "This should encourage us to get more aggressive with our combination therapies in the adjuvant setting."

As for chemoradiotherapy (CRT) after resection, the results have not been positive. According to a study by Neoptolemos et al,[3] adjuvant chemotherapy was linked to a significant surgical benefit in this setting, but adjuvant CRT had a "deleterious effect" on survival. "CRT after resection was not a good thing," she added. However, Dr. Tempero noted that this study was criticized by radiation oncologists due to "lack of quality control."

Placing these findings into perspective, Dr. Tempero indicated that adjuvant therapy works, and oncologists can build on the use of gemcitabine and optimally administered fluorouracil (5-FU). She stressed that these trials contain highly selected patients, "not the patients we see in the clinic every day." The role of radiation therapy remains unclear in this setting, but is under study in the phase III RTOG 0848 trial in combination with erlotinib (ClinicalTrials.gov identifier: NCT01013649).

Two trials that may shed more light on the role of adjuvant therapy for pancreatic cancer in the future are the ACCORD study (NCT01526135; surgery followed by either FOLFIRINOX [5-FU, leucovorin, irinotecan, and oxaliplatin] or gemcitabine) and the APACT study (NCT01964430; surgery followed by either gemcitabine/nanoparticle albumin-bound [nab]-paclitaxel or gemcitabine monotherapy).

Turning to neoadjuvant therapy, Dr. Tempero briefly discussed the A021101 pilot study at the University of California San Diego (NCT01821612). Patients enrolled in this single-arm phase II study received neoadjuvant chemotherapy (FOLFIRINOX) and capecitabine-based CRT followed by resection and adjuvant chemotherapy (gemcitabine) for borderline resectable disease. She called the results "good" with "great quality control," and noted, "If I had been in charge of this trial, I would have put more chemotherapy upfront, as you don't know that the patient after surgery is going to be strong enough to get additional therapy."

Clinical trials in the pipeline are attempting to determine the role of CRT with substantial chemotherapy before resection and to identify benchmarks for FOLFIRINOX and gemcitabine/nab-paclitaxel before surgery. "Once we have benchmarking data, we can really sail in the neoadjuvant setting," Dr. Tempero predicted.

Locally Advanced Disease

Patients with locally advanced unresectable pancreatic disease have significant vascular involvement that precludes resection.

The question of sequencing CRT after chemotherapy for locally advanced disease was initially explored by French investigators, producing what Dr. Tempero called "somewhat provocative" results. The patients who were offered CRT after stopping chemotherapy seemed to do a bit better, but she noted mixed results in the literature on this issue. For instance, in the LAP07 trial, Hammel et al[4] found no significant difference in OS with CRT versus chemotherapy alone in this patient population. "They could not prove that radiation therapy added to chemotherapy in locally advanced disease was an important maneuver," acknowledged Dr. Tempero.

"In my mind," she continued, "in locally advanced disease, the most important component of treatment is the chemotherapy. I don't mind that patients get radiation therapy, but I have a lot of patients who have had a durable remission for years after just chemotherapy alone."

Metastatic Disease

With a median OS of approximately 3 months in patients with metastases without treatment, identifying effective options in this setting is essential. This is especially true given the fact that some patients could move into the neoadjuvant and adjuvant settings.

The use of FOLFIRINOX has produced some "amazing" benefit in patients with metastatic pancreatic cancer, stated Dr. Tempero. For instance, Conroy et al[5] reported that, compared with gemcitabine alone, FOLFIRINOX was associated with a survival advantage. "This is the first time we saw this magnitude of benefit, with a hazard ratio below 0.6 in this disease," she declared.

However, she readily admitted that FOLFIRINOX is a tough regimen for patients to tolerate, with dominating toxicities of myelosuppression, diarrhea, and neuropathy. To handle this therapy, Dr.

Tempero noted, patients require a good performance status, and an age cutoff of approximately 75 years is reasonable. Researchers have made efforts to make this regimen easier to tolerate, although Dr. Tempero noted that there is no clinical trial evidence to support their recommendations. For instance, omitting bolus 5-FU and reducing doses across the board have been helpful. Dr. Tempero also suggested the use of "chemotherapy holidays" for patients to help them rebuild their strength before resuming therapy.

Another regimen that has yielded an advantage in this patient population is nab-paclitaxel combined with gemcitabine. In a global trial by Von Hoff et al,[6] the combination therapy significantly improved OS, progression-free survival, and response rates, with a "respectable" hazard ratio. Although this combination is a bit easier to manage than FOLFIRINOX, Dr. Tempero admitted, "it is still not a walk in the park." With increased rates of both peripheral neuropathy and myelosuppression, alternate schedules may be needed for patients having difficulty tolerating it.

When selecting a treatment option, Dr. Tempero mentioned several considerations: patient preference, comorbidities, treatment goal, compatibility with investigational agents, and predictive biomarkers. "[My patients and I] have a conversation about the goals of treatment and the toxicities," she said. In addition, patients may have strong opinions regarding certain side effects, helping to narrow the choice of treatment.

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