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First-line Chemotherapy Options in Metastatic PDAC

Announcer:
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Dr. O'Reilly:
My name is Eileen O'Reilly. I'm a GI medical oncologist from Memorial Sloan Kettering in New York, and delighted to be here today to review frontline treatments for advanced pancreas cancer.

So I think the audience is aware that this disease is one of rising incidents. Most patients present with metastatic disease, and to date, chemotherapy has been the mainstay of treatment. And we have three main options in the frontline setting, NALIRIFOX, FOLFIRINOX or modified FOLFIRINOX, and gemcitabine and nab-paclitaxel.

So just a little bit of background on FOLFIRINOX versus NALIRIFOX. They both are combinations of irinotecan-based therapy, along with oxaliplatin and 5-FU. Two main differences of NALIRIFOX relative to FOLFIRINOX is the nano particle formulation of liposomal irinotecan that leads to higher circulation of the irinotecan and potentially higher levels at the tumor site. The other main difference between the two regimens is the lower dose of oxaliplatin, which may mitigate some of the cumulative neuropathy. And both of these now are widely used regimens.

So we'll just summarize the frontline studies that support the use of these different treatment combinations. The PRODIGE study, which was reported, gosh, almost 15 years ago now, looked at FOLFIRINOX relative to gemcitabine. The MPACT study reported in 2013 looked at gemcitabine and nab-paclitaxel relative to gemcitabine. And more recently, in 2023, we saw the readout of the NAPOLI-3 trial, which compared NALIRIFOX to gemcitabine and nab-paclitaxel in all in the frontline, untreated metastatic setting.

So just summarizing the highlights of these trials, if you look at the FOLFIRINOX relative to gemcitabine study, it was a significant difference in all the key primary endpoints of overall survival, progression-free survival, and response rate. The hazard ratios were in the 0.57 to 0.47 range, all supporting a substantial benefit from the combination cytotoxic regimen relative to gemcitabine.

Main toxicities from FOLFIRINOX are GI and hematologic, with diarrhea, nausea, need for growth factor support, being common considerations and fatigue for this particular program.

Moving to the MPACT study, again, comparing gemcitabine nab-paclitaxel to gemcitabine. This was conducted in a broader patient population, without limitation in terms of age relative to the FOLFIRINOX study. And more, perhaps real-world community-based setting and a global trial. And once more, the combination, the doublet of gemcitabine/nab-paclitaxel relative to gemcitabine demonstrated improvement in response, progression-free survival, and overall survival. For the most part, more hematologic toxicity evidence with this regimen. And in practice, commonly utilized versions are either an every-other-week schedule or a 2-week in a row, 1 off schedule, just to help with the cumulative impacts over time.

So moving to the NAPOLI-3, this was also a positive study with improvement in overall survival and progression-free survival. The

toxicity data speak more to GI toxicity, more diarrhea, electrolyte disturbances, fatigue, dehydration, and hematologic toxicity. So all of these regimens are now guideline approved and by many authorities approved for use in the frontline setting.

So as we think about choices of treatment, think about, you know, patient preferences, the toxicity profiles, GI perhaps with gemcitabine and nab-paclitaxel, the consideration of alopecia. And for NALIRIFOX and FOLFIRINOX, modified FOLFIRINOX, the need for a port and infusional therapy. And all of these are day-to-day considerations that are used for treatment selection.

So an important consideration in practice is managing the toxicity of NALIFIROX and modified FOLFIRINOX. So we talked about myelosuppression, GI toxicities being the main consideration, and key practical considerations are early dose adjustments, integration of hydration, and optimal anti-diarrheal strategies with Imodium, Lomotil, and using growth factors. All of these collectively help to reduce toxicities, to maintain the ability to administer treatment, and to maximize the benefit over time.

So moving to maintenance therapy for pancreas cancer. Precedent for this has been established in the BRCA setting. So BRCA1, BRCA2 mutations, either germline or somatic, occur in about 5 to 7% of people with pancreas cancer. And in 2019, the FDA approved olaparib as a maintenance treatment following 4 months of platinum-based therapy. And that has been shown to increase progression-free survival and is a nice option as an alternative to maintenance cytotoxic therapy for this subset of individuals.

So now moving to where the field is headed. A lot happening in the sense of targeted therapies for pancreas cancer, noting KRAS mutations and early data supporting targeting G12C and the other alleles in pancreas cancer. And a small subset of individuals with KRAS wild-type disease, there are also targeted options available for that subgroup. So just keeping in mind that it's very important to recommend both germline and somatic sequencing for patients with pancreas cancer.

Thank you very much for listening today. And just a reminder for our audience that there are detailed slides available for your reference which will support what we have reviewed. Thank you again.

Announcer:
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