Current Management of Pancreatic Cancer

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Today we are discussing pancreatic cancer, the most deadly cancer in the United States. According to the National Cancer Institute, the 5-year survival rate is about 6%, mostly due to the high rate of first diagnosis once the cancer has already metastasized—about 53% of all cases are diagnosed once the cancer has spread to other organs. The 5-year survival rate for local or regional pancreatic cancer is about 24%, but unfortunately this type of cancer is usually detected after the tumor has metastasized. Approximately 45,000 people were diagnosed with pancreatic cancer in 2013 and almost 38,500 died of the disease. It is the 12th most common cancer in the United States and the 4th most common cause of cancer deaths. According to the annual reports on cancer by the National Cancer Institute and the American Cancer Society that were recently issued, both pancreatic cancer incidence and death rates have increased in the last 10 years.

Pancreatic cancer remains difficult to treat. We are speaking with Eileen O'Reilly, MD, a medical oncologist and pancreatic cancer expert at Memorial Sloan-Kettering Cancer Center in New York City, where she treats patients and develops novel therapies for patients with different stages of the disease.

CANCER NETWORK: *Dr. O'Reilly, could you briefly describe the current neoadjuvant and adjuvant therapies used to treat pancreatic cancer?*

DR. O'REILLY: For the majority of people who undergo surgery, undertaken with a potentially curative intent, adjuvant therapy is the main consideration. An international standard at the current time is single-agent gemcitabine given for 6 months, which has been shown to decrease the risk of relapse and to enhance overall survival. Some institutions take an approach of offering neoadjuvant or preoperative therapy for those with resectable pancreatic cancer, with the goals of trying to affect the delivery of systemic therapy sooner rather than later and to get more modalities of treatment into more patients, hoping that that will impact longer-term outcomes. It is fair to say that neoadjuvant therapies are conducted in select centers, and there have been no randomized trials comparing preoperative with postoperative therapy to know which may be a superior approach. Having said that, I think with developments in treatments for metastatic disease and the advent of more effective systemic therapies, it is clear that there has been a resurgent interest in neoadjuvant therapy to integrate some of these newer, more active therapies into preoperative treatment. There is much more to come on this topic.

CANCER NETWORK: *Are there any major trials ongoing now in these two settings, either neoadjuvant or adjuvant, that you would like to highlight?*

DR. O'REILLY: Sure. Regarding adjuvant therapy, does adding a second agent to gemcitabine improve overall survival? In Europe, capecitabine is being added to gemcitabine and being compared with gemcitabine alone in the European Study Group for Pancreatic Cancer (ESPAC)-4 trial, which is substantially accrued at this

point. But the data will need to mature for a number of years before there is a definitive answer. In North America, the current ongoing national study is the RTOG 0848 trial. This study is a twofold trial that is looking at the addition of erlotinib (the oral tyrosine kinase inhibitor) to gemcitabine, and then second randomization to plus or minus fluoropyrimidine-based radiation. The study is actually being amended as we speak to remove erlotinib, as the signal from a locally advanced European study does not suggest a strong, or any, advantage from the addition of erlotinib in this setting. The trial as it stands will go on to complete recruitment with gemcitabine as the backbone followed by a randomization to chemoradiation.

In Japan, the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01 study has been recently reported and suggests that S-1, another oral fluoropyrimidine, had in a Japanese patient population not only met a non-inferiority design compared with gemcitabine but actually looked to be superior to gemcitabine in the adjuvant setting. Mature data are still awaited on this, but this is certainly interesting. What this means for a North American and Western population is unclear. Other studies in the United States with S-1 haven't suggested the ability to administer the same dose of S-1 nor the same signals seen in the Asian population. Other considerations that could be at play include diet and pharmacogenomic differences in different patient populations.

With regard to neoadjuvant therapy, the first North American multicenter trial has completed recruitment by the American College of Surgeons Oncology Group and those data are maturing. In Europe, the first study comparing neoadjuvant with adjuvant treatment looking at gemcitabine and oxaliplatin, is underway. Those are the highlights, and I'll mention one last adjuvant trial for which we don't have data yet but has completed recruitments (and it's a different tack altogether). It's incorporating the drug algenpantucel-L, which is a form of immune therapy in the adjuvant setting based on a smaller phase II study, which provided an interesting signal. This is using transplant rejection hyperacute immunity to enhance survival. Those data are also maturing, and we will hopefully have results, if not by the end of 2014, then a bit later than that.

CANCER NETWORK: *The last therapy approved for advanced pancreatic cancer by the US Food and Drug Administration (FDA), this past September [2013], was Abraxane, which is an injection of paclitaxel chemotherapy bound to albumin. Can you talk about how you use Abraxane, and what are the other current therapy options for metastatic disease?*

DR. O'REILLY: Albumin-bound paclitaxel, which is also called nab-paclitaxel, was recently approved in combination with gemcitabine for front-line treatment of metastatic pancreatic adenocarcinoma in patients with a relatively good performance status. This particular combination, in comparison with gemcitabine, showed an improvement in tumor response, disease control, and overall survival. In addition, it provides a backbone for adding new novel agents. Gemcitabine and now paclitaxel are becoming integrated as standard options in the front-line setting in pancreatic adenocarcinoma.

The other main option for good performance status patients, which is not FDA-approved because of the nature of how the study was designed, is the combination called FOLFIRINOX, which consists of oxaliplatin, leucovorin calcium, fluorouracil,

and irinotecan. Similarly to gemcitabine and paclitaxel, it showed improved tumor control and overall survival benefit over gemcitabine alone. These two options, FOLFIRINOX and gemcitabine plus nab-paclitaxel, have not been compared head-to-head, and the way we think about it is that for the first time in the treatment of metastatic pancreatic cancer, we now have the luxury of some choices. Both of these options are aimed at the higher end of the performance status of the patient population, particularly for FOLFIRINOX. The data from that trial were conducted in patients with an Eastern Cooperative Oncology Group (ECOG) 0 or 1 Performance Status compared with the broader population of the nab-paclitaxel/gemcitabine study.

Many clinical trials are building on gemcitabine and nab-paclitaxel, as this is probably going to be an easier platform to build upon compared with FOLFIRINOX, given the relative intensity and toxicity profile of FOLFIRINOX. Having said that, my personal bias for people with an excellent performance status, outside of a study setting, based on the comparison of the data (which is fraught with limitations in terms of the nuances of the trial design), is in favor of FOLFIRINOX.

CANCER NETWORK: *What about immunotherapies? Is there evidence that pancreatic cancer could be amenable to some of the newer immunotherapy antibodies or T-cell immunotherapies that are in development?*

DR. O'REILLY: The question of immunotherapy for pancreatic cancer is certainly an emerging one. I mentioned algenpantucel-L as being studied in the adjuvant setting and now also in locally advanced pancreatic cancer. There certainly is the hope that based on data from anti–PD-1, anti–PD-L1, and anti–CTLA-4 agents in other malignancies that would not be considered strongly immunogenic (such as lung cancer and renal cancer, where signals have been seen), that that may translate to a broader range of solid tumor malignancies that can be treated. There is limited data yet with checkpoint inhibitors in pancreatic cancer, but studies are underway evaluating both PD-L1 and PD-1 antibodies and anti–CTLA-4 therapies, both as single agents and in combination, so there is certainly hope that in the next 6 months we will have more data accrued to know whether this is an avenue worthy of continued development.

A couple other immune therapy approaches to mention are relatively early in development. One is the adoption of a CAR, or chimeric antigen receptor, approach targeting mesothelin. The first studies are underway in a select group of patients to see if this approach may have utility in solid tumors and particularly in pancreatic cancer. And in metastatic disease, a small randomized phase II trial of a *Listeria* vaccine, CRS-207, combined with GVAX, a vaccine developed at Johns Hopkins for an extended period of time has shown an interesting signal in refractory pancreatic cancer patients. A larger randomized phase II study has been designed to evaluate the robustness of that early signal. These approaches are very interesting, and I think the field is keeping a close watch on what is happening in this field for pancreatic cancer.

CANCER NETWORK: *Have there been advances you can highlight in identifying pancreatic cancer targets? Are there any targeted agents that are still preclinical or are now starting to be tested in early-stage trials that you can discuss?*

DR. O'REILLY: The area of targeted treatment in pancreatic cancer is one that has had a long tradition but not one with a huge amount of success. There is actually one approved targeted treatment, erlotinib, but the clinical significance and the value of that has been hotly debated in the field—having said that, an area that has been emphasized is the whole tumor microenvironment, as well as the interaction of the tumor and the stroma, and the coexistence of the two in pancreas cancer. A number of ongoing and recent approaches have targeted this area in pancreatic cancer. For example, some of the immune therapies that we touched on, that's partly how some of those agents are thought to work, by targeting the microenvironment.

But other approaches include pegylated PH20, which is a hyaluronidase, a degradation agent that has shown some activity, both preclinically and in an early phase Ib trial, and is now being tested in combination with gemcitabine and nab-paclitaxel, and will also be looked at in combination with FOLFIRINOX. That is an interesting area for which there is potential promise. Another area of research is Hedgehog inhibition. Despite some strong preclinical rationale and support, the translation of that area of targeting to the clinic has been disappointing. A series of randomized phase II trials have matured, and have not shown utility and have even suggested that there may be a negative impact. That research is going back to the preclinical setting to better understand what's been observed clinically.

One area that we are really interested in are the patients with *BRCA* mutations, which are present in a small subset of people with pancreatic cancer, where there may be susceptibility to DNA-damaging agents and where PARP inhibitors are being experimentally implemented. That is probably about 5% to 7% of pancreatic cancers, but certainly in that subgroup, a possibility of more directed tumor-targeting. A very small number of pancreatic cancer patients will have *HER2* or *BRAF* mutations, where known agents for those molecular targets are available and may have potential value.

CANCER NETWORK: *Thank you so much for joining us today, Dr. O'Reilly.*

DR. O'REILLY: You are very welcome. Thank you.

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