Ask ACCC's Community Resource Centers: *Pancreatic Cancer*

Adenocarcinoma of the pancreas, commonly known as pancreatic cancer, continues to have a high mortality despite decades of research and modern chemotherapy. In 2014 there is estimated to be 46,420 new cases of pancreatic cancer, with 39,590 deaths.[1] The five-year survival rate for patients with advanced pancreatic cancer is estimated to be 2 percent; overall survival for all stages is 6 percent.[1] Erkut Borazanci, MD, MS, Virginia G. Piper Cancer Center Clinical Trials program, discusses current standard of care and future research directions for pancreatic cancer.

Treatment Options

Once a diagnosis of pancreatic cancer is made, options for treatment vary depending on whether the disease is resectable, borderline resectable, unresectable, or metastatic. If resectable, clinicians recommend that most patients proceed to surgery with consideration of adjuvant chemotherapy and/or radiation therapy, depending on pathologic findings. In cases of borderline resectable or locally advanced disease, neoadjuvant therapy is often indicated in the hope of getting a patient to surgery.

Surgical resection of pancreatic cancer remains the best chance for cure. However, even in the setting of an R0, node-negative resection, the five-year survival ranges from 25 to 30 percent. Many patients with resected pancreatic cancer ultimately experience recurrence and develop metastatic disease. Current front-line treatment options in advanced or metastatic pancreatic cancer involve the use of combination chemotherapy regimens, such as 5-FU, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) or nab-paclitaxel plus gemcitabine.[2]

Once patients progress on initial chemotherapy, clinicians often suggest a clinical trial using a chemotherapy regimen consisting of a fluoropyrimidine-based or gemcitabine-based therapy, depending on what the patient received for initial therapy.[3]

One of our research institute's key foci has been treating pancreatic cancer. This focus led to the development of the nab-paclitaxel plus gemcitabine treatment regimen.[4] However, pancreatic cancer is very difficult to treat due to its effects on the digestive system, resulting in significant pain and pancreatic insufficiency, as well as the inherent resistance to drug delivery through the stroma of the pancreas.

A Multidisciplinary Approach

At Virginia G. Piper Cancer Center, Scottsdale, Ariz., we believe in a multidisciplinary approach in treating pancreatic cancer patients. This team includes dietitians, occupational and physical therapists, social workers, pharmacists, genetic counselors, nurses, nurse practitioners, and physicians. Each multidisciplinary team member plays a key role in treatment. For example, our dietitians help us to recommend a diet high in protein that tends to lower insulin levels, as we know that a patient's hemoglobin A1C impacts survival in pancreatic cancer.[5] One of the most common side effects of treatment involving agents such as oxaliplatin and nab-paclitaxel is peripheral neuropathy. Our occupational and physical therapists assist patients with a wide variety of exercises to help reduce the clinical impact of neuropathy and help patients attain maximal benefit from their chemotherapy. A dedicated social worker is vital in addressing patient's financial and social needs in addition to their stress of living with advanced pancreatic cancer.

Molecular Testing & Targeted Therapy

Once patients progress on initial therapy for pancreatic cancer, our next treatment decisions are based on available molecular profiling data on the individual's tumor. Data can be used from several sources:

- From commercial molecular profiling companies, such as Caris Life Sciences, Foundation One Medicine, or Paradigm
- From whole genomic sequencing through our partnership with Mayo Clinic Scottsdale and TGen (Translational Genomics Research Institute)
- Through the use of germline testing.

Tissue sources for this testing range from peripheral blood or cheek swabs for germline testing, to core needle biopsies obtained through interventional radiology (IR)-based procedures, to surgical specimens. Our clinicians and others have shown the benefit of molecular testing through improvements in progression-free survival (PFS) and overall survival (OS), particularly in patients who have progressed on several lines of therapy.[6,7]

More and more anti-cancer agents are coming to market each year, many of them targeted in nature. Examples include the agent Minnelide™, which targets heat shock protein 70 (HSP70) (ClinicalTrials.gov NCT01927965), which is up-regulated in times of cellular stress and explains resistance to HSP90 inhibitors.[2] Other agents designed to break down the pancreatic stroma, such as hyaluronidase, are being combined with nab-paclitaxel plus gemcitabine (ClinicalTrials.gov NCT01839487) and have shown promise in the pre-clinical setting.[2] A study using an agent targeting the JAK pathway, which has shown clinical utility in treating myelofibrosis and appears to be involved in the inflammation-driven mechanism of pancreatic cancer, is being studied in combination with nab-paclitaxel plus gemcitabine (ClinicalTrials.gov NCT01858883).

Researchers are also studying the use of older chemotherapies in combination. For example, thanks to Dr. Michael Barrett's profiling work through our partnership with TGen, our team noticed that there may be a BRCA-like phenotype in some patients with pancreatic cancer. This finding led to the development of a Phase IB/II study of patients with newly-diagnosed metastatic pancreatic cancer combining cisplatin plus nab-paclitaxel plus gemcitabine (ClinicalTrials.gov NCT01893801).

A recent clinical trial at Virginia G. Piper Cancer Center involved the use of the investigational agent, MM-398, a nanoliposomal encapsulation of irinotecan. This agent showed an improvement of OS when combined with 5-FU in patients with pancreatic cancer on second line therapy for patients who progressed on gemcitabine.[8]

Immunotherapy

In the past few decades, treatment of solid tumor malignancies has largely ignored the use of immunotherapies. Recently, the use of agents targeting proteins, such as CTLA-4, have been developed for the treatment of melanoma, showing—in a subset of patients—long lasting responses.[9] Other agents targeting the programmed death 1 (PD-1) receptor, which is also involved in dampening the immune system in response to cancer, have also shown efficacy in melanoma patients with prior CTLA-4 treatment.[10]

Not only have these treatments shown promise in other immune responsive malignancies, such as renal cell carcinoma, they are also being studied in solid tumor malignancies, such as pancreatic cancer. One such trial at Virginia G. Piper Cancer Center involves PD-1 blockade (ClinicalTrials.gov NCT02054806). Furthermore, a pancreatic cancer specific trial using a combination of low-dose cyclophosphamide and two pancreatic cancer vaccines called GVAX and CRS 207 has also been brought to the clinic (ClinicalTrials.gov NCT02004262). It is currently in Phase IIB and an early Phase IIA study and has shown great promise by using the body's own immune system to home in on pancreatic cancer.

Case Study

An otherwise healthy 65-year-old woman was diagnosed in September 2013 with pancreatic cancer with liver metastasis. She was initially treated with the chemotherapy combination FOLFIRINOX. Despite obtaining a significant partial radiographic response after 4 cycles, the patient subsequently developed febrile neutropenia, requiring ICU admission in November 2013. The patient developed multi-organ failure and eventually recovered but required physical therapy.

On initial consultation with our clinic at the end of December 2013, we found that the patient had a family history of ovarian cancer, along with a background of Eastern European Jewish ancestry. The patient's repeat imaging exams and CA 19-9 tumor marker showed minimal disease and the patient elected to undergo expectant observation. During this time, the patient underwent genetic counseling that revealed a BRCA1 germline mutation.

The patient subsequently developed disease progression and was placed on an oral PARP inhibitor targeting her germline BRCA mutation. The patient had initial stable disease that eventually progressed and, as of July 2014, is undergoing therapy with gemcitabine chemotherapy. If the patient were to progress on this current therapy, the patient might consider enrolling in a pancreatic cancer vaccine trial examining the benefit of the agent CRS 207, an attenuated *Listeria monocytogenes* vaccine that expresses the pancreatic-tumor-associated antigen mesothelin.

This case highlights several unique aspects of pancreatic cancer, including germline mutations that can lead to potential treatment options for a patient with pancreatic cancer and how clinical trials can help difficult-to-treat cancers, including pancreatic cancer. It must be noted that the median overall survival for patients with stage IV pancreatic cancer is around 6 months, and this patient is alive at 10 months and has an excellent performance status to consider a clinical trial.

Going Forward

The reason why clinicians focus on the possibility of germline mutations is that they can now exploit these mutations through the use of agents, such as poly ADP ribose polymerase (PARP) inhibitors, for patients that carry mutations in the BRCA genes, PALB2, or APC genes (ClinicalTrials.gov NCT01286987). Other ways to exploit these types of mutations are by treating patients with DNA-damaging agents, such as gemcitabine, irinotecan, platinum agents, and a less commonly used agent, such as mitomycin C. Furthermore, knowing if a patient is a carrier for known germline mutations for pancreatic cancer can allow his or her

family members to be more vigilant about symptoms for pancreatic cancer and perhaps consider closer monitoring.

Pancreatic cancer remains a difficult disease to manage and treat, but clinicians have seen some success against the disease. Through better management of the disease and its innate side effects and more research into the mechanisms of how pancreatic cancer grows, researchers are hopeful they can turn the tide of this disease and improve the lives of pancreatic cancer patients and their families. OI

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