Title

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CLINICAL VIGNETTE

An Exceptional Response in a Patient with Pancreatic Adenocarcinoma

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Case

A 74-year-old male presented with a persistent abdominal wall bulge and discomfort initially thought to be due to an incisional hernia. He also reported 15-pound weight loss and mild fatigue in the preceding six months. CT scan of the abdomen and pelvis with contrast revealed extensive peritoneal carcinomatosis with large tumor deposits in the hernia and a 4.8 cm mass in the pancreatic tail. Subsequent core needle biopsy of peritoneal tumor confirmed the diagnosis of pancreatic adenocarcinoma. Genetic testing revealed a pathogenic germline *ATM* Y2019C mutation, which increases risk of pancreatic cancer. He was diagnosed with stage IV pancreatic adenocarcinoma and enrolled in the NAPOLI-3 trial at UCLA. This randomized open-label phase 3 trial randomizes patients to NALIRIFOX (irinotecan liposome, oxaliplatin, fluorouracil, and leucovorin) versus standard care of nab-paclitaxel and gemcitabine. He was randomized to the standard of care arm and received six cycles of gemcitabine and nab-paclitaxel, which resulted in a partial response. However, progression was noted on follow-up scans about 5.5 months after beginning therapy. Next-generation sequencing of the original tumor specimen revealed *SMAD4*, *ATM*, and a *KRAS* G12R mutation with tumor mutational burden of 1.6 m/MB,

Treatment was switched to 5-fluorouracil (5-FU)/ leucovorin(LV) and liposomal irinotecan (nal-IRI, or Onivyde). The liposomal irinotecan was dose reduced because he had a *UGT1A1* polymorphism, which hinders the ability to clear the active metabolite of irinotecan. The patient achieved a complete response with good tolerance of treatment, and approximately 45 months later, continues on 5-FU/LV + dose-reduced nal-IRI.

Discussion

Stage IV pancreatic adenocarcinoma unfortunately remains a particularly challenging disease to treat. Single-agent gemcitabine remained the standard of care for many years and provided some benefit as palliative-intent therapy with only a modest improvement in survival.[1] In 2013, a phase I-II trial evaluated the combination of nab-paclitaxel (Abraxane) and gemcitabine in patients with metastatic pancreatic cancer. The study demonstrated that the addition of nab-paclitaxel to gemcitabine significantly improved overall survival (OS) (8.5 months vs 6.7 months with gemcitabine alone) and progression-free survival (PFS) (5.5 months vs 3.7 months) compared to gemcitabine alone.[2] This was a landmark trial because of improvement in OS and PFS pancreatic adenocarcinoma treatment. However, improvement was a meager 1.8 month (55 days) in both median OS and PFS, at the cost of increased fatigue and peripheral neuropathy. In an accompanying correspondence to the Journal, Leonard B Saltz and Peter Bach commented, "This title strikes us as inappropriately rosy, given the modest benefits and substantial toxic effects observed.... The chance of being alive at 2 years was increased from 4% to 9%. Meanwhile, an additional 10% of patients had grade 3 (severe) fatigue."[3] This became the standard of care comparator, and our patients first-line response was consistent with the published data for a 5.5-month PFS.

More recent attempts to improve response have studied addition of nal-IRI to treatment regimens. The NAPOLI-1 trial was a Phase III, multicenter study that evaluated the efficacy of nal-IRI in combination with 5-FU/LV in patients with metastatic pancreatic adenocarcinoma who had progressed on gemcitabine-based therapy. The trial demonstrated a significant improvement in overall survival (6.1 months vs 4.2 months) and progression-free survival (3.1 months vs. 1.5 months) for the combination therapy compared to 5-FU/LV alone. The combination also resulted in a higher objective response rate (16.2% vs. 1.0%) but was associated with increased toxicity, notably diarrhea and neutropenia.[4] These findings supported liposomal irinotecan as a viable treatment option for this patient group, which was the treatment our patient received.

NAPOLI-3 trial expanded upon NAPOLI-1, with adding oxaliplatin to the 5-FU/LV and nal-IRI. Published results have led to the approval of NALIRIFOX on Feb 13, 2024. The NAPOLI-3 trial evaluated the efficacy of nal-IRI combined with 5-FU/LV and oxaliplatin in patients with previously untreated metastatic pancreatic cancer. The trial found that this combination, compared to standard chemotherapy, significantly improved overall survival (11.1 mo vs 9.2 mo) and progression-free survival (7.4 vs 5.6 mo).[5] Like the trial ten years prior that established gemcitabine and nab-paclitaxel as the standard of care, this trial reported the exact same 1.8 month incremental improvement in PFS. Since single-agent gemcitabine provides a modest clinically meaningful benefit, there is still a need for more effective therapies with long-term improvement.

It is not clear why our patient is an excellent responder who remains on 5-FU/LV + nal-IRI therapy 45 months later. Most patients progress a few months after starting second-line

therapy, detected on the first or second surveillance imaging scan. One analysis of 10 pancreatic cancer patients examined exceptional responders found and noted a lower number of nonsynonymous mutations may correlate to exceptional outcomes in patients with pancreatic cancer. “Exceptional responders had significantly fewer nonsynonymous mutations than controls (2.25 vs 5.17; P = .014). A mutation count of less than 3 was associated with significantly better progression-free survival (17.2 vs 2.3 months; P = .002) and overall survival (29.4 vs 4.6 months; P = .013).”[6] This patient’s Tumor Mutational Burden was 1.6 m/MB. This typically accounts for the number of nonsynonymous mutations and seems to be consistent with those observations. More studies are clearly needed, as studies on exceptional responders are limited by small number of patients.

Summary

Patients with stage IV pancreatic cancer are often painfully aware of the poor prognosis of the disease. Clinic discussions often focus on balancing quality of life with the prospect of life extension. Most patients will derive little long-term benefit from the addition of chemotherapy, and they are even less likely to do so after first-line therapy has stopped working. However, the exceptional responders may derive dramatic benefits without significantly compromising their quality of life. When embarking on therapy, we hope that our patients will achieve this goal, but we know it is a rare outcome. As providers, we are obligated to set realistic expectations, balancing potential side effects to protect patients near their end of life. Hopefully, future research will identify biomarkers that will help predict which patients will likely benefit and spare many others who may suffer from unnecessary toxicities.

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