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EDITORIAL – PANCREATIC TUMORS

Perioperative Clinical Trials for Pancreatic Cancer in the National Clinical Trials Network

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In this issue of *Annals of Surgical Oncology*, Dr. Wei and colleagues report the final results of the American College of Surgeons Oncology Group (ACOSOG) Z5041 phase II trial of preoperative gemcitabine and erlotinib followed by pancreatoduodenectomy for patients with resectable pancreatic adenocarcinoma (PDAC).[1] ACOSOG investigators accrued 114 patients to this study during a 56-month period beginning in 2009. Unfortunately, due to slow accrual, the trial was terminated prematurely in 2013, before enrolling the number of patients required to power formal hypothesis testing. Since 2013, in contrast, the three subsequent studies of patients with localized PDAC that have been conducted within the National Clinical Trials Network (NCTN) of the National Cancer Institute (NCI)—Southwest Oncology Group (SWOG) S1505 and Alliance for Clinical Trials in Oncology A021101 and A021501—together briskly enrolled approximately 300 patients over a total of approximately 72 months, and each closed well ahead of schedule after meeting its accrual goal.[2–4] How can we explain this disparity, and what lessons can we learn from it?

Through today's lens, it may be tempting to assign full blame for Z5041's failure to accrue to its fundamental research concept—why would surgeons and medical oncologists enroll patients to a study of gemcitabine and erlotinib? However, when the study opened in 2009, the outcome of patients treated with either FOLFIRINOX and gemcitabine plus nab-paclitaxel for PDAC had not yet been reported, and single-agent gemcitabine still represented standard of care therapy in both the adjuvant and advanced disease settings.[5–9] Gemcitabine plus erlotinib was worthy of perioperative evaluation in this context, because it had recently been shown to prolong the survival of patients with advanced PDAC relative to gemcitabine alone in a large, phase III trial.[10] So, while the results of Z5041 clearly do not change clinical practice in 2019, this ACOSOG trial was a reasonably compelling investigation when it opened to accrual in 2009.

So why did Z5041 have trouble enrolling patients when subsequent NCTN trials of perioperative therapy for localized PDAC have accrued so well? Although multifactorial, two primary factors are likely paramount. First, preoperative therapy is generally viewed more favorably by surgeons today than it was in the early part of the decade, when the fear of losing a window for potential cure by delaying pancreatectomy was more widespread. Its administration is now even supported by national guidelines which state that systemic chemotherapy and/or (chemo)radiation are appropriate first-line alternatives to primary surgical resection for any patient with resectable PDAC and are preferred for patients with radiographically resectable tumors who also have clinical findings suggestive of more advanced cancer or physiologic debilitation.[11]

The other and perhaps even more significant source of the disparity is the profound change that occurred in the NCI's cooperative group system in the early part of the decade. ACOSOG Z5041 was conducted in the sunset of a system that, while historically successful, was increasingly characterized as competitive and ineffective.[12] In 2010, the NCI transformed the structure of its existing cooperative group program, reducing the number of its member groups and shifting the emphasis from competition to collaboration between them. Enrollment to clinical studies opened by one cooperative group, for example—historically

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limited to members of that group—became open to any NCTN investigator. Each new trial was to be promoted by all NCTN groups through involvement of liaisons and co-chairs that were assembled from each group. Furthermore, responsibility for oversight of all studies was granted to a national Pancreatic Cancer Task Force that was charged with establishing strategic priorities, evaluating and prioritizing trials with the greatest potential for impact, and maintaining a balanced research portfolio across the groups. Such systemic changes have increased not only the pool of patients eligible for pancreatic cancer trials, but also the number of passionate investigators enthusiastic about enrolling them to collaborative studies that are now aligned to a shared strategic mission.

Although other factors likely also exist, these two—changes in perception of the potential role of preoperative therapies and in the structure of the NCTN cooperative group system itself—are likely largely responsible for the increase in the enrollment rate to NCTN trials of perioperative therapy for PDAC observed since ACOSOG Z5041 closed prematurely in 2013. Two lessons emerge. First, both perceptions and realities of care of patients with PDAC are evolving rapidly. In this context, traditional studies of the effect of a single intervention on the survival outcome of a relatively large, heterogenous population are increasingly unacceptable, as the data from such studies may be irrelevant by the time they mature. Going forward, we must be ever more thoughtful in the design of clinical trials so that they are as rapidly informative as is reasonably possible by incorporating novel designs, early clinical and/or translational endpoints, and robust correlative studies.

Second, coordination and collaboration is essential. While PDAC is unfortunately all too common, the number of patients with potentially resectable cancer is small. The NCTN, which supports clinical trials at more than 2200 sites across the United States and Canada, boasts a highly coordinated and collaborative pancreatic cancer research program across its six member groups, and is composed of a significant number of surgical investigators and leaders. It is therefore extraordinarily well-suited to conducting perioperative trials for patients with PDAC. It will only become more so as we identify smaller and rarer biomarker-directed subpopulations to study. While this may have seemed a pipe dream only recently, the recent publication of the POLO trial, which demonstrated the favorable effect of targeted therapy in patients carrying a pathogenic germline BRCA mutation, highlights the fact that we are rapidly entering a new research era.[13] Robust enrollment to future perioperative studies in the NCTN will go a long way in helping us succeed within it.

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