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EDITORIAL – PANCREATIC TUMORS

Neoadjuvant Chemotherapy for Localized Pancreatic Cancer: Too Little or Too Long?

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For a "systemic" disease such as pancreatic cancer, neoadjuvant chemotherapy is a logical approach that thus far has been limited largely by a lack of effective systemic agents. For example, when considering treatment sequencing for patients with resectable disease, the concept of offering a treatment with an objective response rate of less than 10 % (as for gemcitabine alone) has been unacceptable to most clinicians. (Chemo)radiation has therefore been the backbone of most neoadjuvant approaches, with the goal of improving local/regional disease control (preventing local recurrence) and avoiding operation in those with progressive disease found on post-treatment, preoperative restaging. A few neoadjuvant studies to date have included relatively short courses of chemotherapy—without any obvious improvement in outcomes compared with chemoradiation alone.[1] To further complicate treatment sequencing controversy, surgeons have cautioned that many patients (and referring physicians) want their tumors resected tomorrow and can find a surgeon who will accommodate them. Concerns about increased perioperative morbidity (following neoadjuvant therapy) still exist but have been allayed by several studies, including a recent NSQIP analysis.[2] Importantly, an "effective" neoadjuvant chemotherapy regimen could theoretically improve long-term outcomes by successfully treating (possibly even eradicating) micrometastatic disease in the setting of an immune-competent host who is not attempting to recover from a large operation. The duration of neoadjuvant chemotherapy is a critical variable. If the right drug is selected for the right patient, treatment will need to be long enough to effectively treat micrometastatic disease. If the wrong drug(s) is selected (we only learn this in retrospect when restaging is performed), treatment should be short enough to avoid losing a window of resectability due to local disease progression. This is an important consideration in patients with resectable and borderline resectable disease (in contrast to those patients with locally advanced pancreatic cancer—thus the importance of accurate pretreatment staging). At present, there is little evidence to support any specific neoadjuvant treatment duration, although opinions exist that are based largely on personal experience, extrapolation from other solid tumor sites, and translational laboratory science.

Rose and coauthors from Virginia Mason Medical Center are to be commended for demonstrating that patients are willing and able to undergo almost 6 months (on average) of neoadjuvant chemotherapy with good results, both short-term and long-term . To what degree this was the result of the well-known experience and talent of this multidisciplinary group will be reflected in the ability of others to duplicate these results. Although patients were not treated on a clinical trial, they were maintained in a prospective registry, which is a practice that should be encouraged. The major strength of the study was the relatively large ($n = 64$) and homogeneously staged patient population, all radiographically "borderline resectable" by the SSO/AHPBA consensus criteria and with no evidence of metastatic disease by pretreatment staging that included laparoscopy with peritoneal washings—which did introduce an added selection bias as most such reports have not included laparoscopic staging. The outcomes in this study are not entirely due to increased "selection" provided by the extended duration of therapy. There clearly was a treatment effect demonstrated at the site of the primary tumor. Almost half of patients underwent resection of the primary, with R0

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resection rates comparable to borderline resectable series that included neoadjuvant chemoradiation.[3] Radiographic response rates (30 % partial and 12.5 % complete) were impressive; these are superior to most neoadjuvant studies in which few reported patients had responses by RECIST criteria. The pathologic complete response rate of 10 % is also impressive. Overall, these results suggest that gemcitabine and docetaxel is certainly more effective than gemcitabine alone and possibly more effective than preoperative chemoradiation in some patients. However, 8 of 64 patients (13 %) evidenced local disease progression either during or after induction therapy or at the time of operation and did not undergo successful pancreatectomy. If restaging after three cycles (for example) of chemotherapy had identified those patients with nonresponding disease and they had then transitioned to chemoradiation, could some of these 8 patients have undergone successful surgery? The study did not address the important question of whether the inclusion of chemoradiation (in addition to chemotherapy) in neoadjuvant regimens is beneficial; most patients who underwent resection received chemoradiation postoperatively.

Since the initiation of this study in 2008, the playing field has changed. FOLFIRINOX has been associated with objective response rates of approximately 40 % in the advanced setting and is being examined in the neoadjuvant setting in several prospective studies. However, the toxicity profile of FOLFIRINOX may preclude its use in many patients, especially if neoadjuvant FOLFIRINOX is attempted at low volume institutions by less-experienced physicians. The promising results and acceptable toxicity seen with gemcitabine and nab-paclitaxel in the advanced setting reinforce the potential role of taxols in the neoadjuvant setting.[4] Hopefully, with such combination therapies of greater efficacy, a larger percentage of patients will complete all intended therapy. The 48 % of patients who completed all therapy (to include surgery) reported by the Virginia Mason group remains a low number. Further refinements in the treatment, its duration, and the sequencing and application of chemoradiation remain important research questions in patients with borderline resectable pancreatic cancer.

Lastly, ACOSOG 5041 (NCT00733746) is the first U.S. cooperative group study of neoadjuvant chemotherapy (gemcitabine and erlotinib) in patients with potentially resectable disease. Results have not yet been reported, but the fact that it has successfully accrued patients demonstrates that our medical community may be ready for a randomized trial. While there may never be equipoise in this country for a study of neoadjuvant therapy versus surgery-first treatment sequencing, there may be equipoise for a study of different neoadjuvant approaches, such as neoadjuvant chemotherapy alone versus chemoradiation or short versus long duration neoadjuvant chemotherapy. The complex relationships between the tumor, the chosen therapy, and the antitumor response of the host (patient) make optimal treatment sequencing for pancreatic cancer a difficult challenge. With continued emphasis on accurate pretreatment staging and novel treatment sequencing, as demonstrated in the manuscript by Rose and colleagues, patient survival will improve, even if not as fast as our patients deserve.

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