EDITORIAL

Is Personalization of Care Coming to Pancreatic Oncology?

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The results of a phase II trial evaluating adjuvant treatment using a novel way of administering gemcitabine with radiation in patients with resected pancreatic cancer are presented in this issue of the *Annals of Surgical Oncology*. The trial was designed to evaluate local tumor control as the primary endpoint, using historical local tumor control rates of less than 60 % derived from results reported from cooperative group trials and seeking to show a 2-year local tumor control rate of over 80 % with this novel regimen. The authors reported that the local tumor control rate was apparently improved, without impacting overall survival. Thus, although the primary endpoint was met, there was no identifiable improvement in outcome. As the authors have concluded, future trials should focus on improving systemic disease control due to the high rate of distant metastatic disease in these patients.

Adjuvant trials should be designed with overall survival as the primary endpoint. The use of local tumor control as a primary endpoint is problematic in pancreatic cancer for several reasons. Local tumor control is necessary but not sufficient to cure a patient of pancreatic cancer due to the competing risk of distant metastatic disease. Even if the local tumor is controlled, most patients will die of distant disease. As distant disease control is improved in the future with the development of novel systemic therapies, the impact of local tumor recurrence on overall survival could be greater. Until that happens, local tumor control will have a modest impact on overall survival even in the most highly selected patients. Another problem is the heterogeneity of patient selection and surgical quality in cooperative group trials as well as the lack of consistency in identifying and reporting local disease recurrence, which makes the historical local tumor control rate difficult to define. Although

clearly there have been many studies that have reported high rates of local tumor recurrence after pancreaticoduodenectomy, the use of chemoradiation is controversial. Patients with resected pancreatic cancer should be enrolled on the current Radiation Therapy Oncology Group (RTOG)-led adjuvant trial, RTOG/INT 0848. That trial randomizes patients to receive gemcitabine with or without erlotinib for five cycles followed by a second randomization to chemoradiation or a sixth cycle of chemotherapy. Off-protocol, the preferred standard treatment is initial gemcitabine for 4–6 cycles followed by consideration of chemoradiation. The sequencing strategy of chemotherapy followed by chemoradiation optimizes the impact of systemic therapy and reserves chemoradiation for those patients who are most likely to benefit.

Given what we know about the genomic heterogeneity of pancreatic tumors, personalization of care should have the highest priority. Thus far, surgical pathology specimens from randomized adjuvant trials have proven to be the best source of tissue for correlative studies in pancreatic cancer. Retrospective correlative studies have led to promising hypotheses that could lead to personalization of care. For instance, the relevance of human equilibrative nucleoside transporter 1 (hENT1) as a predictor of gemcitabine activity was discovered from translational studies of specimens from the RTOG 9704 adjuvant trial. Patients with low hENT1 expression did not appear to benefit from gemcitabine.¹ C0-101, lipid conjugated form of gemcitabine that enters the cell independently of hENT1, was designed to overcome this limitation and could be a pioneering drug in the path to personalization of care in pancreatic cancer. It is being evaluated in the Low hENT1 and Adenocarcinoma of the Pancreas (LEAP) trial, the first trial to use an integral biomarker in pancreatic cancer. Patients with low hENT1-expressing metastatic pancreatic cancer determined by immunohistochemistry were randomized to gemcitabine versus C0-101. The LEAP trial has completed accrual, and survival results are expected this year.

The discovery of predictive markers, promising targets, and effective targeted agents has lagged behind other disease sites in pancreatic cancer due to the difficulty in obtaining tissue for correlative studies. The lack of tissue obtained in patients with locally advanced and metastatic pancreatic cancer is the most significant hurdle in the path to personalization of care. Most cases of pancreatic cancer are diagnosed with fine-needle aspirate (FNA) specimens that contain barely enough cells to make a cytologic diagnosis, let alone to evaluate molecular predictors that can inform treatment decisions. The technical ability to detect molecular genetic alterations of significance in diagnostic samples with limited cellularity must be developed. This may be possible with next-generation sequencing (NGS) methods. Samples can be evaluated simultaneously for immunohistochemical expression of validated biomarkers as well as for genetic alterations by NGS. A system in which tissue samples for molecular testing are routinely acquired at the time of diagnostic biopsy is critical if we are going to be able to move forward with personalization of care in pancreatic cancer. At a minimum, cell blocks prepared from FNAs are needed for both immunohistochemical and NGS studies; ideally endoscopic core biopsies would replace FNAs altogether. The technology and expertise to obtain endoscopic core biopsies exist but are only slowly being adopted for patients with inoperable pancreatic cancer.² The catalyst for adoption of these methods by the gastroenterology community will come when clinical decision making depends on the quality of the specimen.

Candidate molecules such as hENT-1, SMAD-4, and stromal SPARC are currently being studied as predictive markers in clinical trials. Validation of a predictive marker in pancreatic cancer will create a medical need to obtain adequate tissue for molecular diagnostic studies and revolutionize the clinical culture in pancreatic oncology and will lead to more widespread access to specimens for translational research in the future. RTOG 1201 will evaluate the role of SMAD-4 expression in personalizing care in patients with locally advanced pancreatic cancer. The potential role of SMAD-4 as a predictor of local progression-related death was discovered in an autopsy study by investigators at Johns Hopkins University. Loss of SMAD-4 immunolabeling was highly correlated with widespread metastasis, while intact SMAD-4 expression was highly correlated with a locally destructive phenotype.³ This was supported by the report of a correlation of

the pattern of disease-related death and SMAD-4 expression in locally advanced pancreatic cancer in a cohort of patients treated on a phase II trial at The University of Texas MD Anderson Cancer Center.⁴ This trial could be the first step in the validation of SMAD-4 as a medically necessary biomarker in pancreatic cancer treatment.

In summary, Ippolito et al. reported significant improvement in local tumor control, but no improvement in the overall survival rate, using a regimen designed to enhance local tumor control. In the future, the most significant improvements in survival for all stages of pancreatic cancer will come from personalization of therapy. The evolution of molecular diagnostic techniques and endoscopic capabilities are coming at a time when the first biomarkers for personalization of care may be validated. The validation of any predictive marker, such as hENT-1, SPARK, or SMAD-4, in a clinical trial would lead to a requirement of adequate tissue for molecular diagnostic studies in routine care, a development whose impact would revolutionize the clinical culture. With high-quality specimens, we will be able to detect both protein expression and genomic alterations for improved sensitivity and specificity of biomarker detection. When that happens, cell blocks or core biopsies will be required to adequately treat every patient and personalization of care in pancreatic cancer will be a reality.

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