Pancreatic Cancer: Incremental Success in Overcoming a Major Therapeutic Challenge

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Erlotinib (Tarceva) is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor initially approved by the US Food and Drug Administration for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen. In this report, we present the pivotal study that led to the approval of erlotinib in combination with gemcitabine (Gemzar) in patients with locally advanced/metastatic chemo-naive pancreatic cancer patients. The combination demonstrated a statistically significant increase in overall survival accompanied by an increase in toxicity. Physicians and patients now have a new option for the treatment of locally advanced/metastatic adenocarcinoma of the pancreas.

Treatments for pancreatic cancer have lagged behind those for other cancers. Following the 1997 approval of gemcitabine (Gemzar) for the treatment of pancreatic cancer, the research community faced a dearth of negative results spanning almost a decade. Improvements in therapy for pancreatic cancer have proved difficult, but the National Cancer Institute of Canada's (NCIC) pivotal study results led to the November 2005 US Food and Drug Administration (FDA) approval of the addition of erlotinib (Tarceva) to gemcitabine for the first-line treatment of advanced pancreatic cancer. This represents a small step forward in managing a tough-to-treat and highly deadly disease.

Treatment Toxicity and Quality of Life
While survival improvements are desperately needed for patients with advanced pancreatic cancer, quality of life should also remain an important goal. The NCIC study showed that those with a survival gain on the erlotinib/gemcitabine combination also experienced an increased risk of toxicity. In this issue of ONCOLOGY, Dr. Senderowicz and colleagues have provided a detailed report of the treatment toxicities experienced by patients on study, resulting in a higher number of patients in the erlotinib arm discontinuing treatment due to adverse events, patient refusal, or death. In addition, patients on the erlotinib arm showed an increased frequency of serious adverse events and grade 3 and higher treatment-related adverse events.

The NCIC trial highlights the importance of implementing adequate symptom management and taking into consideration the quality-of-life implications of treatment toxicities. While as a community we continue to push aggressively forward in developing improved treatments, we must at the same time provide care for the whole patient by actively monitoring and managing side effects.

Incremental Success
The results of the NCIC trial prompted much debate in the pancreatic cancer community on whether the modest survival benefit of erlotinib and gemcitabine is clinically relevant, even though the results are statistically significant. While in most other cancers this difference would be viewed as not having clinical relevance, the survival difference in this study is meaningful because of the poor outcome of advanced pancreatic cancer.

Moreover, the survival advantage of the erlotinib/gemcitabine arm is noteworthy in that numerous gemcitabine-paired combinations have failed to show a statistically significant survival advantage over gemcitabine alone. The NCIC trial was not only the first study to show such a survival benefit, it was also the first clinical trial with a targeted agent to show increased survival when combined with chemotherapy. This trial also provided a proof of principle for the study of targeted agents or combinations of targeted agents in treating pancreatic cancer.

The recent findings of two phase III cooperative group pancreatic cancer clinical trials were presented at the 43rd American Society of Clinical Oncology (ASCO) annual meeting in June 2007. Both the Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) trials showed no survival benefit for the combinations of gemcitabine and bevacizumab (Avastin) or...
gemcitabine and cetuximab (Erbitux), respectively. These results are a reminder of the difficulties of improving outcomes in pancreatic cancer. In oncology, science moves on an incremental basis. Achieving small increments in pancreatic cancer research such as the results of the NCIC trial are acceptable; however, we need ongoing cumulative increments in pancreatic cancer research if we are to achieve the kind of progress that has led to significant decreases in mortality associated with other forms of cancer.

Further Research
Although gradual progress has been made in the treatment of this disease, the prognosis of pancreatic cancer patients remains bleak. The NCIC trial not only resulted in a new treatment option for pancreatic cancer patients, it also highlights the importance of cumulative successes in the development of more effective treatments for pancreatic cancer.

The Pancreatic Cancer Action Network seeks to advance research not only by pushing for increased federal research funding but also by directly supporting innovative and progressive research with career development and pilot grant awards through a peer-reviewed grant system. To date, the Pancreatic Cancer Action Network has committed to funding 37 researchers with $3.5 million in research funds by June 2008. At the same time, the Pancreatic Cancer Action Network educates patients and families about available clinical trials, with the aim of empowering patients and expediting research progress.

For years treatments for pancreatic cancer have lagged behind other cancers. By supporting innovative pancreatic cancer research, it is our hope to accelerate achievements in pancreatic cancer research—both modest and momentous—in order to see more treatment options for this disease.

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