Viewpoint

Moving from late to early stage disease: lessons learned from erlotinib in pancreatic cancer

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At the time the CONKO-005 trial was originally conceived, there was an inherent rationale to its design; it represented the next logical step in trying to move the needle in the treatment of early-stage pancreatic adenocarcinoma. Specifically, the study was intended to build upon the positive findings from CONKO-001, a landmark trial that established a 6-month course of adjuvant chemotherapy (gemcitabine) as the standard of care for resected pancreatic cancer (1); and was further supported by the positive results of the PA.3 study, a phase III trial from Canada demonstrating a survival benefit from the addition of erlotinib (an oral tyrosine kinase inhibitor) to gemcitabine in patients with previously untreated metastatic disease (2). At the time, this combination of gemcitabine plus erlotinib was the only gemcitabine-based doublet therapy to show a positive survival outcome in the advanced setting; no matter that the magnitude of benefit from the combination was quite modest, with a hazard ratio for death of 0.82 and Kaplan-Meier survival curves for the two treatment arms that appeared almost indistinguishable from one another. One could readily make an argument that the therapeutic benefit of a particular drug or regimen might potentially be amplified when administered in an earlier stage setting, when the total disease burden is lower. Furthermore, in the adjuvant context, any improvement would ideally translate not only into a prolongation of median survival, but also (and perhaps more relevantly) into a higher proportion of patients who could actually be cured of their disease.

Therefore, one certainly cannot fault the CONKO-005 investigators for pursuing this trial strategy. At the same time, however, we should perhaps not be surprised that the study results, reported in the October 2017 issue of the *Journal of Clinical Oncology* (3), were entirely negative. While our conceptual belief is that therapeutic agents approved for use for advanced or metastatic cancers will be similarly, if not more, effective, when applied in an earlier stage setting, our clinical track record has told an entirely different story—particularly when it comes to molecularly targeted therapies and gastrointestinal malignancies. One need only look at negative results from targeted agents tested in phase III adjuvant trials for colon cancer [the anti-vascular endothelial growth factor antibody bevacizumab (4) and the anti-epidermal growth factor receptor antibody cetuximab (5)] and hepatocellular carcinoma (the multikinase inhibitor sorafenib) (6) to appreciate this sobering reality. Reasons for these disappointing findings are not entirely understood, but may include differences in tumor biology between earlier and later stages of disease [the one exception where clinical benefit may be retained across disease stages is when the molecular target is the sole oncogenic driver of the disease, such as c-KIT in gastrointestinal stromal tumors (GIST); in this case, imatinib is markedly effective in both

early and late-stage settings (7)]. Thus, if one takes a drug (erlotinib) that was only marginally effective to begin with in a notoriously difficult-to-treat disease (pancreatic cancer), it may have been unrealistic to expect a successful study outcome when applied in the adjuvant setting.

The study authors do point to a trend toward long-term survival in favor of gemcitabine plus erlotinib (estimated 5-year survival rate of 25%, compared to 20% for gemcitabine alone), a product of the Kaplan-Meier survival curves separating only after the three-year mark. However, a biologic explanation for any markedly delayed beneficial effects of a signal transduction inhibitor, occurring long after discontinuation of the agent, is lacking; it seems far more likely that this survival difference was a chance finding, as it is difficult to reconcile with the totality of the study data. Furthermore, exploratory analyses did not uncover any particular subgroup that appeared to derive particular benefit to erlotinib, nor did the development of a therapy-related rash prove to be a useful pharmacodynamic indicator of clinical benefit. Even while we await findings from the planned analysis of archived tumor specimens to see whether there might be a molecular subset of patients who benefitted from EGFR inhibition, there does not presently appear to be any justification for using this combination in the adjuvant setting in any resected patient.

When taken together with the findings from the LAP07 trial, which similarly showed no benefit from adding erlotinib to gemcitabine as induction therapy for patients with locally advanced pancreatic cancer (8), it becomes increasingly clear that erlotinib has relatively little role overall in the treatment of pancreatic cancer, across all disease stages. This is especially true with the emergence of other more effective systemic regimens for this malignancy. It is worth noting that CONKO-005 was developed prior to the advent of other combinations, such as FOLFIRINOX and gemcitabine plus nab-paclitaxel, that have now become new front-line standards for the treatment of advanced disease—and are themselves the subjects of randomized phase III adjuvant trials (9,10). We eagerly await the final report from these studies to learn whether either of these regimens may supplant gemcitabine or the other current standard, gemcitabine plus capecitabine (11), in this adjuvant setting.

More broadly, treatment paradigms may gradually be shifting for resectable pancreatic cancer. In particular, recognizing the high propensity for metastatic dissemination of this disease and the need to carefully select those patients who are most likely to benefit from a major cancer operation, there is a growing interest in neoadjuvant therapy even in patients with technically resectable disease at initial presentation. Ongoing clinical trials are testing this strategy of delivering some or all systemic therapy preoperatively (12), and large propensity score matched analyses suggest a benefit of this approach over postoperative therapy (13). Finally, leveraging the available large quantity of tumor tissue in resected patients should hopefully lead to studies of adjuvant therapy that incorporate integral biomarkers to assign patients to different treatment arms according to pre-specified molecular features or subtypes of their tumor. While this still remains a somewhat aspirational goal, it may perhaps one day move us entirely away from the traditional randomized phase III study design.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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