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A new standard for malignant pleural mesothelioma

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Mesothelioma is an asbestos-related malignancy that begins in the pleural lining of the lung, pericardium, peritoneum, or testes. Early stage pleural mesothelioma can be resected but almost always recurs and many patients are diagnosed at an advanced stage of disease, at which point surgery has no role. Since 2003, the standard treatment for unresectable disease has been combination chemotherapy with cisplatin/pemetrexed.[1] Despite many attempts, until now no regimen has further improved survival. While addiction to oncogenes occurs in some cancers, most molecular alterations in mesothelioma occur in tumor suppressors and the corresponding drug target is less clear. Currently, research is underway to exploit some of the most common molecular aberrations and dependencies in mesothelioma.[2–4] For example, the important role of vascular endothelial growth factor (VEGF) signaling in mesothelioma has been known for many years,[5, 6] but studies of single-agent VEGF inhibitors were disappointing.[7–10]

It was in this context that the French Cooperative Thoracic Intergroup (IFCT) began randomizing 448 patients to cisplatin/pemetrexed with or without bevacizumab (an antibody to VEGF). As reported by Zalcman et al. in this issue of The Lancet, overall survival was improved among those who received cisplatin/pemetrexed/bevacizumab, 19 months versus 16 months with cisplatin/pemetrexed (hazard ratio of 0.77 and p=0.0167). Serious adverse events were more common on the bevacizumab arm (71% versus 62%) and more patients stopped first-line therapy due to toxicity in the bevacizumab arm, 24% versus 6% (p=0.02). It is worth noting that all-cause mortality rates were similar: 3% without bevacizumab versus 5% with bevacizumab, p=0.31. Somewhat unexpectedly, fewer patients on the bevacizumab arm went on to receive post-study chemotherapy, 62% versus 72%. Even with the differences in early discontinuation and post-study therapy favoring the arm without bevacizumab, overall survival was improved in the bevacizumab arm in this intent-to-treat analysis. Of note, while this trial was ongoing, a randomized phase II study of cisplatin/gemcitabine/bevacizumab versus cisplatin/gemcitabine in unresectable mesothelioma reported no statistically significant difference in progression-free survival or overall survival.[11]

The results of the IFCT trial warrant the routine use of bevacizumab in addition to cisplatin and pemetrexed for unresectable mesothelioma. In patients without contraindications to bevacizumab, it is appropriate to add bevacizumab to cisplatin and pemetrexed, acknowledging that toxicity and treatment discontinuation will be more common. However, despite the impressive results of this rigorously designed and executed phase III clinical

trial, many questions remain. For patients who cannot tolerate cisplatin, should bevacizumab be added to carboplatin/pemetrexed? What about patients over the age of 75 (who were excluded from the study)? Where does pemetrexed maintenance fit into this paradigm? Given the prior negative trial of bevacizumab added to cisplatin/gemcitabine, are these results specific to the combination of pemetrexed and bevacizumab?

We will likely never obtain definitive answers to all of these questions, particularly due to the relative rarity of mesothelioma. Even if patients and resources were more abundant, we must not spend time and effort on questions of limited impact. Rather, we need to refocus our efforts on opportunities not only to shift the survival curve but also to raise it, by aiming to cure more patients.[12] We must continue to forge ahead with the development and study of novel agents with strong biologic rationale and we must evaluate them in new clinical trial designs that optimize our ability to rapidly advance care, enroll patients, and answer valuable questions. One way to iterate advances more rapidly is to break free from the construct of studying ‘promising new drug X’ with cisplatin/pemetrexed versus cisplatin/pemetrexed. Using new drugs upfront either alone or with other novel agents could allow us to identify promising therapies with accompanying biomarkers more quickly and thereby translate findings rapidly into meaningful change for patients. While such work is ongoing, those who are not candidates for clinical trials or who do not have access to such opportunities but who do not have contraindications to bevacizumab should be offered three drug therapy as a new standard of care.

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