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Commentary: Durable activity of a tyrosine kinase inhibitor in lung cancer

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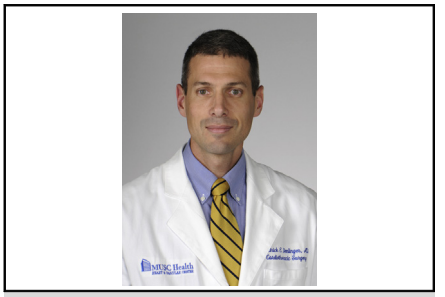

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CENTRAL MESSAGE

Surgery for locally advanced lung cancers following neoadjuvant gefitinib appears safe with surprisingly optimistic long-term outcomes.

Lung cancer treatment has progressed dramatically in the past decade with the emergence of tyrosine kinase inhibitors (TKI) targeting specific growth factor receptors and immune checkpoint inhibitors. After identifying that growth factor mutations, rather than simple overexpression, was a critical factor for the efficacy of TKIs, some of these agents became the preferred treatment for lung cancers. Epithelial growth factor receptor (EGFR) inhibitors, such as gefitinib and other newer agents, have replaced cytotoxic agents as the principal treatment for advanced-stage lung cancers for patients with activating mutations of EGFR based on improved efficacy and better side effect profiles.[1] TKIs have a substantial influence on progression-free survival while overall survival rates remain similar to standard cytotoxic chemotherapy.[2] It is well understood that the long-term treatment efficacy of TKIs is limited by cancers developing new point mutations or alternative escape pathways leading to TKI resistance and cancer progression.[3] For this reason, TKIs are not currently indicated in any curative-intent treatment strategies.

Zhang and colleagues[4] pushed the envelope to determine the efficacy of using gefitinib as neoadjuvant therapy followed by surgical resection of locally advanced lung cancer harboring EGFR activating mutations.[4] Most importantly, the treatment protocol appears safe with short-term surgical outcomes that were comparable to other neoadjuvant treatment protocols. Indeed, there were no 90-day mortalities and the median operative blood loss was 100 mL. Loose correlations between clinical response and pathological response open the door for interpretation. However, the direct relationship between pathological response and both progression-free and overall survival are logical and correlate with well-established outcomes associated with neoadjuvant treatments.[5]

The overall survival rate of 66% is quite impressive for a cohort of stage II through IIIA patients even when considering that some reports suggest lung cancer patients with mutant EGFR have improved outcomes relative to EGFR wild-type patients.[6] This is particularly true when considering that 27 of 33 patients included in the survival analysis were diagnosed with stage IIIA disease. One concern for the unusually favorable results is the potential for selection bias, and this concern is accentuated by the exclusion in

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the outcomes analysis of 2 patients who received neoadjuvant gefitinib but did not receive the entire treatment course or refused surgery. Another concern, as previous mentioned, is that under normal circumstances, TKIs typically remains efficacious for 12 to 18 months before tumors develop resistance mechanisms. Therefore, the prolonged survival among a cohort of patients with locally advanced disease is surprising. For these reasons, I agree with the authors' conclusions that TKIs should be further evaluated prospectively in neoadjuvant settings.

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