Commentary: Chemotherapy for stage IB large cell neuroendocrine carcinomas of lung: Convention becomes conviction

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Thoracic oncologists and surgeons have long recognized that large cell neuroendocrine carcinomas (LCNECs) represent a more aggressive type of non–small cell lung cancer. Meanwhile, LCNECs are relatively resistant to cisplatin-based chemotherapy compared with small cell carcinoma. Because LCNECs are rare, prospective evidence of the benefit of chemotherapy is lacking, especially for early-stage disease. Furthermore, there is compelling evidence that cisplatin-based chemotherapy is harmful for all patients with stage IA non–small cell lung cancer and of little benefit for those with tumors up to 4 cm in size. Nevertheless, and similar to practice with small cell, it has been conventional practice to offer adjuvant cisplatin-based chemotherapy to patients with resected stage I LCNECs. This convention may now be pursued with greater conviction thanks to the efforts of Wakeam and colleagues.

These authors should be commended for using a large national database to study management-specific outcomes for a rare disease. Using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code 8013, they identified 1770 patients in the US National Cancer Database (NCDB) with resected stage I (node-negative) LCNECs, of whom 463 received adjuvant chemotherapy. Statistical methods were used to adjust for potential retrospective confounders. The authors found an overall survival benefit when adjuvant chemotherapy was delivered in patients with >2-cm tumors, with the strongest association for tumor size >3 cm. Study weaknesses include the retrospective design and weaknesses inherent in the NCDB, all of which are thoroughly discussed by the authors and are not repeated here.

Despite these weaknesses, this article and similar international and US retrospective efforts are likely to inform clinical practice in patients with LCNEC for years to come. LCNEC is rare, and we will never have prospective studies to guide treatment decisions. These data are particularly valuable for patients with LCNEC, in whom poor prognosis is paired with a concern for chemotherapy resistance. This is distinct from other high-risk categories of node-negative non–small cell lung cancers (eg, >2 cm invasive component, lymphatic or vascular invasion, high-grade/poorly-differentiated, visceral pleural invasion) in which the high-risk characteristic is less likely to have predictive implications.

It remains an unsatisfying, although reasonable, convention to use a cisplatin-etoposide combination for neuroendocrine lung cancers, whether of small cell or large cell subtype. This convention has not changed despite advances in our understanding of the genomic and transcriptomic landscape of LCNECs and the recognition that one-half of LCNECs are genomically distinct from small cell cancers (wild-type for RB, and having STK11 or KEAP1 co-mutations). These genomic distinctions have yet to inform drug selection for stage IV LCNEC and thus are not an argument for performing comprehensive molecular profiling of early-stage LCNECs unless there is a diagnostic dilemma.

It is time that we look beyond the previous randomized trials that suggest no benefit to adjuvant chemotherapy for resected node-negative non–small cell lung cancers, because high-risk features were not specifically accounted for.
for in these efforts. Wakeam and colleagues bring conviction to our convention to offer adjuvant chemotherapy for patients with resected stage IB LCNECs of the lung.

References


