Pulmonary Large Cell Neuroendocrine Carcinoma

A True High-Grade Neuroendocrine Tumor Needing Prospective Therapeutic Data

To the Editor:

We read with interest the article by Varlotto et al.[1] on large cell neuroendocrine carcinoma (LCNEC) of the lung. Based on Surveillance Epidemiology and End Results (SEER) database, the authors collected 1211 LCNEC cases (324 without radiotherapy) and compared the clinicopathologic and survival features of LCNEC with those of 8295 (1120 without radiotherapy) large cell carcinoma (LCC) cases and 35,304 (355 without radiotherapy) small cell lung cancer (SCLC) cases. Briefly, the conclusion of this article is that patients with LCNEC should be classified and treated as having a LCC rather than a SCLC.

We would here take the position that the results of this work do not entirely justify the final statements and may raise some confusion among oncologists.

First, diagnosis of LCNEC is difficult requiring a careful histopathologic and immunohistochemical examination on surgical specimens. Even in the hands of expert pathologists, a major agreement is achieved only in 40 to 50% of cases.[2] In a previous multi-institutional experience with LCNEC, we originally selected 122 cases.[3] Fifteen cases were subsequently excluded because LCNEC was combined with other tumor types, and 24 cases were finally excluded because they lacked an unanimous diagnostic agreement among expert pathologists.[3] For this reason, in our opinion, a centralized pathological review is necessary to confirm the diagnosis, a requisite that is lacking in the article by Varlotto et al.[1]

Second, molecular and biomarker analyses strongly support the fact that LCNEC is very similar to SCLC, from gene expression profiling to immunohistochemical expression of neuroendocrine (NE) markers, p53, Rb, bcl-2, Ki67/MIB-1, TTF-1, and several other biomarkers along with apoptosis and cell proliferation pathways.[4,5]

While LCNEC more often have a clinical and radiologic presentation resembling a non-small cell lung cancer (NSCLC)/LCC (i.e., as a peripheral mass), pooled analysis of therapy and survival data seem to confirm that LCNEC is an aggressive carcinoma with a poor prognosis in stage I (about 40% at 5 years) and receiving a significant benefit from pre-/postoperative chemotherapy with cisplatin-based regimens.[6,7] Response rate to platinum-based chemotherapy may reach about 80%, a figure more similar to SCLC than LCC/NSCLC.[6]

Curiously, all these data have not been considered in the discussion section in the article by Varlotto et al.[1]

The diagnosis of LCNEC requires immunohistochemical or electron microscopy confirmation of neuroendocrine differentiation. Data reported by Varlotto et al.[1] on the increase from 8 to 21% of LCNEC diagnoses among LCC likely reflect a wide and possibly not appropriate use of immunostains for NE markers in poorly differentiated NSCLC (i.e., have pathologists used nonspecific antibodies such as NSE or PGP9.5 to identify NE differentiation?).

In conclusion, to our eyes, there is a consistent body of evidence justifying the classification of LCNEC as a true high-grade NE carcinoma of the lung. Further supporting this fact, identical carcinomas have been recognized and recently accepted in the new World Health Organization classification of the digestive tract among NE tumors.[8]

On the other hand, prospective clinical data validating retrospective analyses concerning the most effective therapeutic approach for LCNEC are needed. By contrast, it is difficult to accept per se the conclusions of the work by Varlotto et al.[1] based on the absence of expert pathologic review of the SEER cases.

Finally, from a pathologic viewpoint, more stringent and objective criteria on quoting the NE differentiation (i.e., does a positive staining in more than 10% of tumor cells for only one NE marker represents a good cutoff in defining a LCNEC?) are clearly required.

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Disclosure: The authors declare no conflicts of interest.
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ISSN: 1556-0864/11/0610-1775