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Lepto mets: loads of data

Larry Junck

Department of Neurology, University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, USA (L. J.)

Corresponding Author: Larry Junck, Department of Neurology, University of Michigan Rogel Cancer Center, 1914 Taubman Center #5316, Ann Arbor, MI 48109, USA (ljunck@umich.edu).

See the article by Le Rhun et al., pp. 1100–1112.

The literature regarding leptomeningeal metastases (LM) is a quagmire for several reasons. Clinical trials are few and are negative or inconclusive, partly because many patients with LM are poor candidates for trials due to low-performance status and rapid clinical decline. Ideas for potentially effective treatments have been few. The LM diagnosis is often challenging and sometimes uncertain, and the disease is hard to measure.[1] It is difficult to get drugs to the target—for systemic treatments because the CSF and CNS are protected by the blood-CSF and blood-brain barriers, and for intrathecal treatments because drugs in CSF have limited penetration into tissue.[2] Furthermore, LM is arguably not one disease but many, corresponding to the various primary cancers, some of which have several molecular subtypes.

In this issue of *Neuro-Oncology*, LeRhun and colleagues present the readers with a report that includes the largest number of patients with LM (254!) and contains the largest amount of data of any published article.[3] Their motivation was to analyze the 2017 guideline[4] from the European Association of Neuro-Oncology (EANO) and European Society for Medical Oncology (ESMO) classifying LM into type I (verified cytologically from CSF or histologically) and type II (cytologically unconfirmed, based on imaging features or even clinical features). Their conclusions are limited by the retrospective nature, the many hypotheses tested (some presumably unplanned), and lack of control or explanation for the treatments chosen. Nonetheless, within these constraints, the study provides many interesting and significant findings:

- Young age is predictive of survival ($P = .022$).
- Cytological confirmation is a negative predictor of survival (median, 2.3 vs 3.5 months, $P = .002$).
- Among patients without cytological confirmation, nodular vs non-nodular MRI findings are predictive of survival (median, 2.7 vs 5.0 months, $P = .014$).
- Among the most common primary tumor types, survival differs by tumor type (medians for type I and type II, breast, 2.4 and 4.5 months; lung, 2 and 2.9 months; and melanoma, 1.5 months and 2.2 months, respectively, $P = .018$).
- Systemic treatment was associated with better survival ($P = .001$ in the entire group). Subgroup analysis disclosed better survival with systemic treatment in type I (HR = 0.58, $P = .0004$), confirmed in multivariate analysis, but not in type II ($P = .46$).
- Intrathecal treatment was not associated with better survival in the entire group, but subgroup analysis showed better survival with intrathecal treatment in type I (HR = 0.70, $P = .018$), confirmed in multivariate analysis, but not in type II ($P = .56$).

Our knowledge of the course of disease for type II patients is somewhat limited because most literature on LM emphasizes patients with positive cytology, type I. The following comments pertain to the differences observed in this study between type I and type II:

- One possible explanation for the better outcomes with type II is that the diagnosis of LM may have been incorrect for some of these patients. The imaging diagnosis was made by local physicians, not confirmed centrally. This may have especially applied to patients without nodular disease on MRI, as the finding of only linear disease (type II-A) or the diagnosis of LM on clinical grounds without abnormal MRI findings (type II-D) may be less reliable.
- The apparent lack of benefit of intrathecal chemotherapy in type II patients could be accounted for by incorrect diagnosis of LM in some of these patients.
- Among type I patients, the cells floating in CSF are a ready target for intra-CSF drugs. In contrast, among some type II patients, nodular disease may have interfered with benefit of intrathecal chemotherapy, either because nodules obstruct CSF pathways or because the drug penetrates nodules poorly.[2]
- The authors speculate that the survival of type I patients may be worse because positive CSF cytology is a marker for

greater burden of disease. However, a simple calculation indicates that cells in CSF cannot themselves represent the burden. If the cell count were 50/mm^3 and cell size 20 μm, the total volume of tumor cells in CSF would be less than 0.03 cm^3. If tumor cells in CSF are an indicator of burden of disease, independent of MRI, it must be because they are associated with a much large volume of cells adherent to CNS structures, but still under the detection threshold of MRI.

- Perhaps further investigation or follow-up of type II patients by these authors could determine the number of probable correct and incorrect diagnoses of LM.

This article has many strengths. What are its major limitations? The imaging was not centrally reviewed, and its local review perhaps was not informed by Response Assessment in Neuro-Oncology (RANO) criteria.[1] Intrathecal chemotherapy was via lumbar puncture in 79%-88% in this study; in the United States, it is more commonly via ventricular catheter and scalp reservoir, which is an easier way to carry out a large number of treatments and is associated with more uniform drug distribution.[5] The patients in this study were seen over 24 years, and the treatments used in many may be different from those used today, eg, without osimertinib for patients with EGFR-mutant lung cancer[6] or checkpoint inhibitors for those with melanoma; also, few of the HER2+ breast cancer patients received intrathecal trastuzumab, which may extend survival with LM from HER2-positive breast cancer patients for up to several years per clinical reports[7] and per our experience.

The authors have succeeded in demonstrating that the EANO-ESMO classification of LM with vs without cytological confirmation is meaningful. How can we use this information going forward? When LM is diagnosed without positive cytology, one might maintain a glimmer of uncertainty about the diagnosis, depending on the strength of the clinical and imaging evidence. The finding that patients with positive cytology benefitted more from systemic and intra-CSF chemotherapy may be useful, regardless whether the lack of clear benefit in the others is due to misdiagnosis or other factors mentioned above. Finally, positive CSF cytology may deserve to be a stratification factor in clinical trials.

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