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Quantification of leptomeningeal metastases from solid tumors remains a challenging issue

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See the article by Nevel et al in this issue, pp. 675–683.

Leptomeningeal metastases (LM) from solid tumors are described in approximately 10% of patients with solid tumors. It is the third most common metastatic complication affecting the nervous system after brain metastases and epidural metastases. For both the assessment of the prognosis of LM patients and outcome to treatment, quantification of LM disease burden is important. By imaging alone this is quite difficult, as LM exhibit both solid and nonsolid growth patterns and can be present in multiple anatomical compartments.

In this issue of *Neuro-Oncology*, Nevel et al present their report on a retrospective quantitative assessment of disease burden in patients with LM from non-small-cell lung cancer (NSCLC).[1]

The purpose of their interesting study was to determine whether radiographic disease burden assessment and modern cerebrospinal fluid (CSF) analysis can be employed to predict survival. They reviewed charts and MRI scans of 171 patients with LM of NSCLC from a quaternary cancer center, the Memorial Sloan Kettering Cancer Center. Eighty-four patients (49%) had a targetable mutation. Radiographic involvement of LM was scored in 8 predefined locations on gadolinium-enhanced MRI scans in 76 bevacizumab-naïve patients with complete staging. In 16 patients, circulating tumor cells (CTCs) in CSF were quantified, and cell-free tumor DNA measurements in CSF were done in 21 patients. Extent of radiographic involvement of LM was found to be significantly correlated with shorter survival. CTC number in CSF was a borderline significant prognostic indicator ($P = 0.048$) for a shorter survival and cell-free DNA concentration in CSF showed a trend ($P = 0.06$) toward a statistical significant prognosticator for shorter survival. Therefore, both the extent of radiological involvement of LM and advanced CSF diagnostics appear to have value for the assessment of the prognosis of NSCLC patients with LM.

The study by Nevel et al is of particular interest, as the treatment of NSCLC patients is changing rapidly. Specific driver gene alterations in NSCLC patients have led to the development of targeted therapy with tyrosine kinase inhibitors. Epidermal growth factor receptor (EGFR) activating mutations and anaplastic lymphoma kinase (ALK) translocations are found in 25% of NSCLC patients, and in an additional minority of NSCLC patients BRAF or ROS mutations or MET or human EGFR 2 (HER2) amplifications are being detected.[2]

The use of EGFR and ALK inhibitors has significantly improved the clinical outcome of NSCLC patients, including those with central nervous system metastases, like LM. In the BLOOM study, the response rate was 62% (95% CI: 45–78%) with a response duration of 15.2 months (95% CI: 7.5–17.5 mo) in patients with LM from EGFR-mutated NSCLC patients treated with osimertinib, a third-generation, brain-penetrating EGFR inhibitor.[3] Similarly, the ASCEND-7 trial showed response of LM in patients with ALK-translocated NSCLC when treated with the ALK inhibitor ceritinib, even after prior failure to crizotinib.[4] Thus, for treatment monitoring, assessment of LM is becoming increasingly important.

For the radiographic part of assessing the LM disease burden, Nevel et al scored the MRI scans by using 8 predefined anatomic locations: cerebrum, ventricle, brainstem, cerebellum, cranial nerves, and cervical, thoracic, and lumbosacral spinal cord. Patients received one point per location of radiographically evident LM. An MRI review was done by 3 neuro-oncologists. When there was disagreement about the number of MRI sites of LM disease between the original radiology report and one of the neuro-oncologists, consensus was reached by the 3 neuro-oncologists.

The difficulties of the quantification of LM on MRI were nicely demonstrated by the Response Assessment in Neuro-Oncology (RANO) group on LM. In a report from this group, a complex RANO-LM scoring card was used to score LM of solid tumors in 22 patients at baseline and after treatment. The interobserver variability between the 19 raters

(neuroradiologists and neurologists) was so high that this scoring system clearly cannot be used as a response tool in LM. A new simplified RANO-LM score is now under construction. [5] Can the MR score of Nevel et al be used instead of the RANO-LM criteria? Their MRI score appears straightforward and was found to correlate with outcome. However, its interobserver variability and whether it is a useful tool to monitor LM response need to be determined and validated in independent datasets.

Besides, with MR imaging, LM can by assessed by CSF analysis. Classically, the diagnostic golden standard for LM was cytology, by demonstrating intra-CSF tumor cells. More advanced CSF techniques consist of CTC detection and cell-free DNA analysis. Furthermore, if a driver mutation is present in the parental tumor, driver mutation analysis in the CSF can be performed. This latter technique was successfully used in the BLOOM study as the EGFR mutant DNA copy number appeared to be a promising response evaluation tool for LM in EGFR-mutated NSCLC.[6] For CTC enumeration of epithelial tumors in CSF, 2 different techniques can be used ie, rare cell capture technology and immune flow cytometry assay which both apply antibodies against epithelial cell adhesion molecule (EpCAM). These CTC techniques show a sensitivity for the diagnosis of LM of 76–100% and a specificity of 84–100%.[7]

Nevel et al used the rare cell capture technology to detect CTC in CSF. They were the first to show that the CTC number in CSF has prognostic value (CTC ≥50/mL vs <50/mL) in a small patient group (n = 16). They also showed that the cell-free DNA concentration in CSF (>0.02 vs <0.02 ng/mL), as determined by targeted exome sequencing, shows a trend toward having a significant prognostic value in LM (n = 21).

An important benefit of CTC enumeration, cell-free DNA analysis, or driver mutation copy analysis in CSF is that these CSF assays are quantitative. Therefore, they have the future potential to obviate the need for subjective MR quantification of subtle leptomeningeal abnormalities and their changes upon therapy. Moreover, the value of all of these advanced CSF techniques depends on how well they correlate with patient benefit, represented by absence of clinical progression and overall survival. In other words, upon the validation of the surrogacy of both the laboratory and imaging endpoint, their prognostic value should be determined. This is one of the key elements of the Nevel study.

Can the MRI and CSF assessments be used to evaluate LM activity over time, to monitor disease outcome to treatment? To address this question, the authors propose a prospective study to validate the prognostic and therapeutic response value of radiographic and advanced CSF techniques in LM. This may help us to better and earlier understand the effect of novel treatments on this disease. In order to speed up this evaluation process, multicenter collaboration but more importantly standardized and accepted techniques for advanced CSF assays will be crucial.

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