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To add IT chemotherapy, or not to add, that is the question

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See the article by Le Rhun et al in this issue, pp. 524–538.

Leptomeningeal disease (LMD) can be a devastating diagnosis affecting approximately 10% of patients with metastatic cancer.[1] It can affect multiple levels of the neuroaxis, causing significant morbidity. There are generally no effective therapies and median survival is measured on the order of months even with treatment. With conventional imaging and cerebrospinal fluid (CSF) tests, definitive diagnosis may still be difficult. Few trial options exist as the majority of clinical trials exclude such patients. For these reasons, Le Rhun and colleagues should be commended for undertaking a multicenter, randomized trial in a disease population that clearly deserves greater attention.[2]

There is no standard of care in the management of LMD. How can we best treat LMD in the setting of active systemic disease? When is palliative radiation indicated? What systemic therapies can sufficiently penetrate CSF to effectively manage disease? When should we add intrathecal (IT) chemotherapy? This last question is the primary focus of the aforementioned DEPOSEIN trial.[2] Breast cancer patients with newly diagnosed LMD were randomized to receive either systemic chemotherapy alone or systemic chemotherapy with IT liposomal cytarabine. Median progression-free survival related to leptomeningeal metastases was longer in the IT treated group and quality of life until progression did not differ between groups. Overall survival did not reach statistical significance, although 15 of the 37 patients randomized to the control arm crossed over to receive IT therapy at LMD progression. Systemic therapies were based on the treating physician's choice and may not have been completely balanced for CNS penetration between the two arms. Focal radiation was administered to patients in either arm with nodular disease 5 mm or greater in diameter, as IT-delivered chemotherapy can only achieve therapeutic levels in tissue 2–3 mm beyond the subarachnoid space.[3] It is important to note that liposomal cytarabine is no longer commercially available.[4]

Nonetheless, we can take away important lessons from this study. Since LMD often occurs in patients with active systemic disease, ideally active agents with good blood–brain barrier penetration could be used to treat both the systemic and leptomeningeal disease. Recently published results from studies of the novel taxane derivative ANG1005 in LMD from breast cancer[5] and the targeted agent osimertinib in LMD with epidermal growth factor receptor (EGFR) mutation–positive non-small-cell lung cancer[6] suggest that select patients might be treatable with systemic therapy alone. However, since many systemic cancer therapies have difficulty crossing the blood–brain barrier and achieving effective concentrations in the CSF, combined systemic and IT therapy might be a reasonable approach to treat LMD in some situations. Whether the addition of IT chemotherapy to systemic therapy can improve outcomes in other LMD populations and with other IT agents remains to be determined. We need better agents to administer into the CSF. With the discontinuation of liposomal cytarabine, the most commonly used agents include methotrexate, cytarabine, and thiotepa—all drugs with limited benefit in prior studies of LMD from a variety of solid tumors and with inconvenient twice weekly administration during induction.[1] Results from early phase clinical trials of IT trastuzumab for human epidermal growth factor receptor 2–positive breast cancer suggest promise.[7,8] A study of i.v. and IT nivolumab for patients with LMD from melanoma or lung cancer is ongoing (NCT03025256).[9]

Another important takeaway from the study is the need for validated response assessment. The authors defined their own response criteria, as no standardized criteria existed at the time this study was developed. Although the leptomeningeal metastasis working group of the Response Assessment in Neuro-Oncology later proposed preliminary LMD response criteria,[10] subsequent validation studies (also led by Dr Le Rhun) demonstrated the limitations of these preliminary criteria.[11] A new scorecard for LMD response assessment has been proposed[11] which will also require further validation.

Finally, this clinical trial shows us that modern-day randomized studies of LMD are feasible, although thoughtful design is required. Select patients with LMD can participate meaningfully in clinical trials and should not be uniformly excluded from systemic therapy trials. Better treatments are desperately needed for LMD patients. While imperfect, this study represents an important step in our community's continued attempts to bring new therapies to patients with LMD.

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