Correspondence

To the editor:

Intrathecal MTX for DLBCL: from an inappropriate prophylactic tradition to a medical error?

Whether intrathecal methotrexate (MTX) should be administered to diffuse large B-cell lymphoma (DLBCL) patients to prevent central nervous system (CNS) relapse is highly controversial. In a recent issue of Blood, Boehme et al provided further evidence for the inefficacy of this prophylactic procedure.1 They should be congratulated for this information that is very useful for our daily practice and for patients. One could argue that CNS relapse was not the primary end point of the RICOVER study and that the retrospective analysis was possible because of protocol violations resulting in 42.9% of patients with bone marrow or upper neck involvement not receiving the intrathecal MTX planned in the study design. However, the data are strong and similar to the recent analysis of 899 patients included in the Southwest Oncology Group studies.2

First, the authors confirmed that CNS relapse in DLBCL patients is a rare event (<5%) in the rituximab era, a “low” rate that could be considered as an intrinsic limitation of any prophylactic treatment. Second, they also confirmed that a high proportion of CNS relapses are observed concurrently with systemic relapses or refractory diseases and, thus, reflect failure to control systemic disease rather than the consequences of disease’s sanctuary for which a prophylactic measure should be taken. In this regard, it would be interesting to know the number of isolated CNS relapses developing in patients in CR treated or not with intrathecal MTX. Third, and most importantly, intrathecal MTX had no effect on the low rate of CNS relapses observed in DLBCL patients with BM or upper neck involvement treated with R-CHOP14. Whether intrathecal MTX should be administered to patients at high risk to develop CNS relapses (elevated lactate dehydrogenase, poor performance status, and >1 extranodal site) was not answered in this study. But the rate of 43% of CNS relapses that was observed in this population despite intrathecal prophylaxis, in line with previous retrospective analysis,3 is very disappointing.

Another matter of debate is whether intrathecal MTX is associated with short- and long-term toxicity. The interest of this question could appear to be modest in the field of DLBCL, where this procedure must be abandoned. However, the question is pertinent in other settings where intrathecal prophylaxis has been proven to be beneficial (eg, Burkitt lymphoma, acute lymphoblastic leukemia). The RICOVER trial offers a unique opportunity to address this issue. What is the rate of myelotoxicity, neurotoxicity, renal failure, and mucositis in patients receiving or not intrathecal MTX? Our daily practice suggests that intrathecal MTX may add toxicity to standard polychemotherapy regimen, and, indeed, this was recently shown in 352 children with anaplastic large-cell lymphoma, where 6 cycles of MTX 1 g/m² plus intrathecal MTX were significantly more toxic (myelotoxicity, infections, stomatitis) that 6 cycles of MTX 3 g/m².4 If the toxicity for patients having received intrathecal MTX in the RICOVER trial is increased and/or if a single patient is suffering from long-term debilitating morbidity due to intrathecal treatment, then intrathecal MTX is not only an inappropriate prophylactic practice but also a medical mistake.

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References

Response

Intrathecal methotrexate and central nervous system events

We thank Brugieres et al for their comments and the additional information coming from their study in children with anaplastic large cell lymphoma.1 The authors raise important questions, which we would like to answer as follows:

Twenty of 58 patients with central nervous system (CNS) events (34.5%) in our study had achieved complete response or complete response, unconfirmed, and subsequently relapsed in the CNS; only 12 patients (20.6%) experienced isolated CNS relapses. These occurred in 9 of 47 (19.1%) patients who had not and in 3 of 11 (27.3%) patients who had received intrathecal methotrexate (MTX; P = .681). Thus, the percentage of patients with isolated CNS relapse was really small (0.99% of all study patients), with no significant differences between patients receiving or not receiving intrathecal MTX. All other patients either had progressed during or shortly after first-line therapy or had died from therapy or unknown causes.

In patients with isolated CNS relapse, no difference was observed between those treated with chemotherapy and rituximab (R) and those treated with chemotherapy alone. Seven of 36 (19.4%)
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