LETTER TO THE EDITOR

Reply to Comment on: The UK Experience of a Treatment Strategy for Pediatric Metastatic Medulloblastoma Comprising Intensive Induction Chemotherapy, Hyperfractionated Accelerated Radiotherapy, and Response-Directed High-Dose Myeloablative Chemotherapy or Maintenance Chemotherapy (Milan Strategy)

To the Editor: We thank Massimino and colleagues [1] for their comments on our paper.[2] Our study was a retrospective audit of survival, toxicity, and deliverability of this regimen in 14 UK centers. It was not our intention to criticize the Milan group's work.[3] However, it is essential to monitor outcomes when introducing new treatments, especially when these are of high intensity and in high-risk patients. Single-site studies may be influenced by local in-house practice not described in detail in publications. Case selection may also be an issue. Milan is a national referral center, but the UK patients were treated in their local specialist centers. Potentially, patients with more neurological damage who might not have been able to travel to a supraregional center may have been treated on this regimen in the UK.

The concerning toxicities seen in our retrospective audit highlight the importance of prospective audit and monitoring of any new treatments that are introduced. Given the rarity of the disease, this needs to take place at a national level, not at an institutional level. Large-scale phase III clinical trials are the gold standard to evaluate promising results from early phase trials. For example, in adult lymphoma, the Southwest Oncology Group (SWOG) trial showed that standard cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin®), prednisolone (CHOP) was actually better than three more complex regimens reported by single institutions to improve cure rates from 30% to 60%.[4]

In our series of metastatic medulloblastoma patients treated with the “Milan” regimen, we did not encounter any severe neurotoxicity unlike the series of patients treated for Supratentorial primitive neuroectodermal tumor (sPNETs) in the UK.[5,6] This important issue was included in the discussion of our findings and we described neurotoxicity as rare and not unexpected in our paper. This rarity is also noted in the papers referenced by the authors of the letter.[7–9]

The Milan group reference the conclusions of the international workshop[10] convened after clinically significant toxicity became so prominent that it could not be ignored. This workshop was convened after our paper was submitted and aimed at defining possible underlying reasons. However, UK audits of sPNET treated with the same therapy strategy described frequent, clinically devastating global neurotoxicity.[5,6] The combined use of high-dose chemotherapy with radiotherapy seems to have revealed this vulnerability.[6]

In conclusion, the introduction of intensified chemoradiotherapy in childhood brain tumors requires an active program of clinical trials. If these are not available, there needs to be an audit of outcomes of national interim guidance shared internationally to learn from the larger number of patients treated. This would highlight the importance of first careful guideline development, second the need for compliance with detailed clinical protocols, and finally prospectively monitored toxicity and outcomes. Adequate funding and resources for such an audit are essential when implementing any regimen across multiple centers at a national level.

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Conflict of interest: Nothing to declare.

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