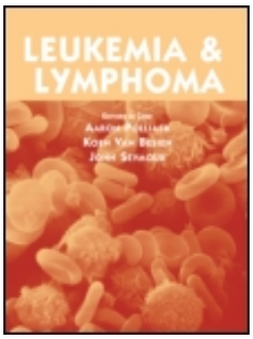

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Andrew Wirth (2011) Primary central nervous system lymphoma: the challenge continues, Leukemia & Lymphoma, 52:11, 2037-2038, DOI: 10.3109/10428194.2011.603451

To link to this article: https://doi.org/10.3109/10428194.2011.603451

Leukemia & Lymphoma, November 2011; 52(11): 2037–2038

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2011.603451

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COMMENTARY

Primary central nervous system lymphoma: the challenge continues

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Clinicians managing primary central nervous system lymphoma (PCNSL) face challenges in two distinct areas. The first is the disease itself. PCNSL is an aggressive malignancy for which current therapies have limited long-term success, and for which treatment intensification can often lead to unacceptable toxicity. The second challenge is the knowledge base informing the management of this condition, which rests largely on phase II trials and retrospective studies, with a paucity of prospective randomized trial data. Thus, key questions regarding optimal management remain unresolved.

What can be gleaned from the currently available data? We know that important clinical prognostic factors include patient age and performance status, with lactate dehydrogenase (LDH), raised cerebrospinal fluid protein level and involvement of deep brain structures also significant in a large analysis [1,2]. With respect to treatment, it is widely accepted that high-dose methotrexate-based chemotherapy is the cornerstone of management. Beyond that, adding a second drug – in particular cytarabine – appears to be advantageous [3–5]. Although a number of multiagent chemotherapy regimens are currently in use for PCNSL, simpler regimens may also be effective [6]. The superiority of more complex (and usually more toxic) regimens has not been demonstrated in a rigorous manner.

Radiation therapy as a sole modality is now established to be less effective than combined modality therapy for PCNSL, although it is possible that patient selection based on age and performance status contributes to the inferior outcome observed after radiation alone [3,7]. Following treatment with effective chemotherapy, consolidative radiation therapy reduces the risk of relapse, but has not been proven to enhance survival, and is associated with an increased rate of debilitating neurotoxicity [3,8]. Because of these confounding effects, the role of consolidative radiotherapy following chemotherapy has been a matter of ongoing debate, particularly in the treatment of older patients who are at increased risk of radiation-related toxicity [9]. This issue was addressed in a recently published, prospective randomized trial [10]. The study demonstrated a statistically significant improvement in progression-free survival when radiation was administered after a complete or partial response to chemotherapy, but there was no statistically significant survival advantage. Concerns over study methodology have led to uncertainty regarding the interpretation of these results [9,11,12]. One approach that may provide a path forward in this disease is the selective use of response-adapted radiotherapy, with low-dose radiotherapy used after a complete response to chemotherapy. Although results reported for the efficacy and toxicity of reduced dose radiation have varied, a recent prospective study suggests that this strategy may allow the maintenance of tumor control but with a potential reduction in long-term neurotoxicity [13–15].

Another response to concerns over late radiation-related neurotoxicity is to defer initial radiotherapy, and explore a range of novel approaches including the incorporation of new drugs and biological agents, high-dose chemotherapy supported by autologous stem-cell reinfusion and alternative methods of drug delivery such as blood–brain barrier disruption and intraventricular administration [16]. Many of these approaches have shown promising results in small phase II studies or single center experience, but none has yet been compared with standard therapy in a randomized trial.

In this issue of ***Leukemia and Lymphoma,*** Motomura *et al*. report a retrospective review of a treatment program predicated on the use of a non-methotrexate-based regimen (dexamethasone, etoposide, ifosfamide and carboplatin) plus radiotherapy [17]. This was a somewhat unusual cohort in that the majority of cases were described as having unifocal disease, completely resected by the initial diagnostic biopsy. The results of the study are broadly comparable with those reported with a range of methotrexate-based regimens plus radiotherapy, but as with retrospective studies generally, do not allow for definitive statements about the relative efficacy of this treatment program. Importantly, despite the omission of methotrexate, this regimen was not without neurotoxicity, which may not be unexpected when using 45 Gy of radiation after CNS penetrating chemotherapy.

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

In the future, advances in the management of PCNSL may come from three directions. The first is a greater understanding of the specific cellular mechanisms of treatment failure – why does PCNSL have a much poorer outcome than comparably staged diffuse large B-cell lymphoma originating in other sites? Investigation into the origin of the malignant cell and into tumor environment is starting to provide insights into this question [18–20]. The second is clinical, and involves the more widespread use of uniform staging, response and toxicity criteria in single center/phase II trials that might contribute to overviews such as that performed by the International Extranodal Lymphoma Study Group (IELSG) [21]. Ideally this process should underpin the conduct of well-designed and appropriately powered prospective randomized trials – a challenging task in this rare disease. Finally it is critical that optimal care as currently understood be delivered effectively in the community [22].

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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