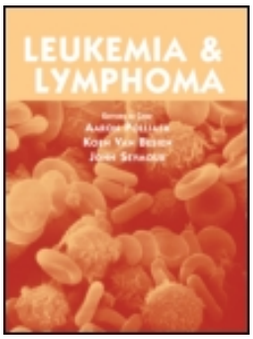

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COMMENTARY

Refining the predictors of risk for central nervous system involvement in patients with mantle cell lymphoma

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A critical clinical question facing clinicians caring for patients with non-Hodgkin lymphoma is whether that individual patient's risk of central nervous system (CNS) involvement by their disease justifies the morbidity, inconvenience and cost of CNS-directed prophylaxis. Aggressive and highly proliferative subtypes such as Burkitt or lymphoblastic lymphoma carry the highest risk (up to 30%) [1], and prophylaxis is considered mandatory. On the other hand, in indolent forms such as follicular lymphoma, CNS involvement is highly unusual ($<1\%$) [2] and prophylaxis is very rarely, if ever, justified. The reported risk of CNS relapse in unselected series of patients with diffuse large B-cell lymphoma (DLBCL) is 4–7% [2–4], but various indices [1,5] have been developed to stratify risk allowing the identification, with moderate sensitivity and specificity, of those patients in whom CNS prophylaxis is warranted.

Overall, mantle cell lymphoma (MCL) is associated with an intermediate risk of CNS involvement, with 4–26% of cases reported to develop CNS involvement at some time after initial diagnosis [6–9]. It should be noted that in the largest series reported so far from the European Mantle Cell Lymphoma Network (EMCLN) representing 1396 patients, the crude incidence was 4% [10], which is likely to be close to the true frequency. If we accept this estimate, the frequency of CNS involvement in MCL is perhaps comparable to unselected series of DLBCL [11]. CNS involvement at initial diagnosis of MCL is rarer, with an estimated incidence of 0–2% [6–9].

With this low overall incidence of CNS relapse, treating all patients with CNS-directed prophylaxis is not warranted. Several studies have recently shed some light on the risk factors for CNS involvement in MCL, with their aim to identify robust predictive markers for patients at high risk for CNS involvement to allow clinical trial design to test prophylactic strategies and facilitate the development of risk-adapted therapy. Previously, blastoid histology at diagnosis and transformation at relapse [6–10,12], elevated serum level of lactate dehydrogenase (LDH) [6,10] and systemic disease relapse [6–9,12] have been described as risk factors for the development of CNS involvement in MCL. Other potential risk factors suggested by univariate analysis include high "mantle cell lymphoma international prognostic index" (MIPI) (score ≥ 6) [13], the presence of B-symptoms and Eastern Cooperative Oncology Group performance status of ≥ 2 [10]. It is clear that many of these are features associated with highly proliferative disease, and indeed blastoid histology stands out as the only consistently identified risk factor on multivariate analyses.

In this issue of ***Leukemia and Lymphoma***, Conconi *et al*. report a retrospective analysis of 11 patients experiencing CNS relapse from a pooled database of 124 patients with MCL treated at two European centers over a 30-year period [14]. They found that 11/124 (7.8%) of their cohort developed CNS relapse, though like most published series, only a minority of patients had received prior rituximab (35%) or CNS-penetrating doses of methotrexate or cytarabine and/or intrathecal chemotherapy (15%) during their primary treatment. The true incidence of CNS relapse in the current era of primary therapy using intensive chemoimmunotherapy protocols (such as Hyper-CVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone] [15] and alternating cycles of CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] and DHAP [dexamethasone, cytarabine, cisplatin] with rituximab [16]) may potentially be lower due to the incorporation of CNS-penetrating doses of cytarabine and/or methotrexate, although this remains to be proven. It should be noted that, in both this and the EMCLN cohort, neither high-dose cytarabine/methotrexate nor intrathecal chemotherapy was completely effective in eliminating CNS relapse [10]. Indeed, disappointingly, Conconi *et al*. also found that no specific primary treatment (autologous stem cell transplant, intravenous high-dose antimetabolite or intrathecal chemotherapy) appeared to statistically significantly reduce the risk of CNS relapse, although the small numbers of patients so treated, and the uncertainty regarding the

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criteria for selection of those patients to receive these modalities, mean that such analyses are not definitive. None of the cohort had CNS involvement at initial diagnosis, and, in keeping with reported series, the median time to CNS involvement was 14 months and the outcome from time of development of CNS relapse was dismal, with median survival around 6 months [6–10]. Blastoid histology stood out again as the sole predictor on multivariate analysis of CNS risk.

An important future area for study is the optimal agents, doses and schedules to prevent clinically manifest CNS disease.

So, given these findings, how should we manage patients with newly diagnosed MCL? Our unit policy is to perform cerebrospinal fluid (CSF) sampling, including flow cytometry [17–19], and cerebral imaging in those patients considered to be at "high risk" of CNS involvement, as defined by the presence of blastoid histology (either at initial presentation or at relapse), and consideration for such assessment in those with non-blastic, but highly proliferative disease, as defined by the presence of two or more of raised LDH, B symptoms or MIPI score ≥ 6. CSF sampling is delayed in patients with leukemic phase disease until the clearance of the peripheral blood, to avoid contamination of diagnostic specimens or introduction of disease into this space. We administer 12 mg of intrathecal methotrexate as CNS prophylaxis immediately following CSF sampling in patients at "high risk" of CNS disease, and once per cycle of chemotherapy irrespective of the primary treatment protocol, but recognize that the efficacy of intrathecal prophylaxis is unproven, and may make a smaller contribution in those patients treated with regimens containing CNS-penetrating doses of antimetabolites (cytarabine [ara-C] and methotrexate [MTX]). Based on both their established greater efficacy against systemic disease, and the potential for a contribution to the control of subclinical CNS disease, regimens incorporating high-dose ara-C and/or MTX are preferred in those patients able to tolerate such treatment intensity [15,16,20,21]. In patients with systemic relapse of MCL, if attainment of a durable complete remission is the therapeutic aim, we would consider administration of CNS prophylaxis with intrathecal chemotherapy, as outcomes with patients using novel approaches such as the Bruton's tyrosine kinase (BTK) inhibitor iburitinib [22] and anti-apoptotic agents such as ABT-199 [23] are demonstrating impressive overall response rates in relapsed/refractory MCL and have the potential to achieve high quality durable remissions, although their penetration into, and anti-tumor efficacy within, the CNS compartment are unknown.

The Conconi article is an important initial step toward the development of a robust clinical and biological predictive index of CNS risk, as has been developed for DLBCL [1], which will ultimately allow the sensitive and specific identification of patients at risk, allowing targeted study to determine the optimal prophylactic strategy. The achievement of these aims will contribute to the ultimate goal of developing curative treatment for this disease [21].

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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