Table 1. CNS involvement in MCL

Study	Patients with CNS involvement/ total no. of patients	Median time to CNS disease, mo	No. of patients with blastoid morphology	No. of patients with involvement at diagnosis	First-line treatment with CNS-penetrating agents	Prophylaxis with intrathecal chemotherapy
Oinonen et al[6]	4/94 (5%)	51	1	0	Some (unknown)	Unknown
Valdez et al[5]	25/108 (23%)	15.5	2	1	Unknown	0
Ferrer et al[3]	11/82 (13%)	25	5	1	20%	0
Gill et al[4]	4/62 (6.5%)	12	2	1	16%	10%

patients may achieve more prolonged survival. It is controversial whether CNS prophylaxis for NHL can prevent CNS disease.[7] In most MCL cohorts only a minority of patients received prophylaxis. Gill et al describe 10 patients who received prophylaxis with CNS-penetrating agents or intrathecal injections; none had developed CNS disease, compared with 4 of 52 not receiving such treatment.[4] In contrast, Ferrer et al found no prophylactic advantage in patients receiving systemic high-dose MTX.[3]

It is the policy at our institution to provide CNS prophylaxis to those MCL patients with high-risk features, according to the NCCN guidelines for DLBCL. We use the addition of 2 high-dose MTX (> 3 gr/m^2) courses if not included in the original chemotherapy protocol and 4 injections of intrathecal MTX. Given that the rate of CNS involvement at relapse may exceed one-quarter of patients, and more in those with blastoid variants, and the prospect of obtaining prolonged remissions with curative treatment attempts, we believe that CNS prophylaxis is warranted until further recommendations are prospectively investigated in clinical trials.

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References

1. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood.* 2009;114:1469-1476.
2. Cheung CW, Burton C, Smith P, Linch DC, Hoskin PJ, Ardeshna KM. Central nervous system chemoprophylaxis in non-Hodgkin lymphoma: current practice in the UK. *Br J Haematol.* 2005;131:193-200.
3. Ferrer A, Bosch F, Villamor N, et al. Central nervous system involvement in mantle cell lymphoma. *Ann Oncol.* 2008;19:135-141.
4. Gill S, Herbert KE, Prince HM, et al. Mantle cell lymphoma with central nervous system involvement: frequency and clinical features. *Br J Haematol.* 2009;147:83-88.
5. Valdez R, Kroft SH, Ross CW, et al. Cerebrospinal fluid involvement in mantle cell lymphoma. *Mod Pathol.* 2002;15:1073-1079.
6. Oinonen R, Franssila K, Elonen E. Central nervous system involvement in patients with mantle cell lymphoma. *Ann Hematol.* 1999;78:145-149.
7. Hill QA, Owen RG. CNS prophylaxis in lymphoma: who to target and what therapy to use. *Blood Rev.* 2006;20:319-332.

Response

CNS prophylaxis in MCL

We thank Dr Gatt and Dr Grisaro for raising the issue of central nervous system (CNS) prophylaxis in mantle cell lymphoma (MCL), which we admit having addressed only indirectly in our review.[1] We agree with most of the content of their letter, in particular the fact that the true incidence of CNS involvement in MCL is unknown, that most CNS involvements are part of a systemic relapse and therefore the role of primary prophylaxis is probably limited, and, finally, that it is controversial whether prophylaxis can really prevent CNS relapse.

Basically, as there are no data allowing clear recommendations to be made, each center is left to make up its own policy. The available data would support the concept that initial treatments including CNS-penetrating agents at high-dose (with or without intrathecal therapy) may provide sufficient prophylaxis, at least in the younger patients[2] and in our center the treatment of patients younger than 65 years of age is Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternated with high doses of methotrexate and cytarabine (Hyper-CVAD/HD-MTX-AraC); therefore, we are left with the question of what to do with elderly patients and with those who are unfit for aggressive treatment. For these patients, based on the uncertainities mentioned above, we think that the cost-benefit ratio of routine CNS prophylaxis is unfavorable, and therefore we do not propose it. Because of the same uncertainities, on the other hand, it may not be wrong to offer CNS prophylaxis (as suggested by Gatt and Grisaro) to the patients supposed to be at higher risk.

It should be noted, however, that the definition of patients at risk for CNS relapse is still controversial even in the most common setting of diffuse large B-cell lymphoma (DLBCL),[3] and that, perhaps with the exception of raised lactate dehydrogenase, the prognostic indicators for MCL[2] may not necessarily be the same described in DLBCL.

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References

1. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood.* 2009;114:1469-1476.
2. Gill S, Herbert KE, Prince HM, et al. Mantle cell lymphoma with central nervous system involvement: frequency and clinical features. *Br J Haematol.* 2009;147:83-88.
3. Ferreri AJ, Assanelli A, Crocchiolo R, Ciceri F. Central nervous system dissemination in immunocompetent patients with aggressive lymphomas: incidence, risk factors and therapeutic options. *Hematol Oncol.* 2009;27:61-70.

To the editor:

Vascular complications after splenectomy for hematologic disorders

In a recent issue of *Blood*, Crary and Buchanan published the most perceptive and comprehensive review to date of thrombotic vascular complications arising with functional or surgical asplenia in patients with hematologic, and especially hemolytic, disorders.[1] Their overview of the literature presents a great deal of food for thought regarding the apparent role of splenic function in protecting against thromboembolic disease, including venous thrombosis, pulmonary thromboembolism, and even arteriosclerosis and pulmonary hypertension. As the authors describe, these risks are reported even in subjects without hematologic disease who undergo splenectomy, but chronic hemolytic disease may compound this risk. I would like to point out 2 important additional pathophysiologic links.

The authors discuss the paradox that the incidence of arteriosclerotic events is lower in hereditary spherocytosis patients with intact spleens compared with their hematologically unaffected first degree relatives, and this low risk of arteriosclerosis is shared with patients with sickle cell disease. Crary and Buchanan propose a protective effect of hemolysis, mediated possibly by the lower serum cholesterol level seen in several forms of anemia.[2] Importantly, clearance of hemoglobin-haptoglobin or heme-hemopexin complexes by CD163- and CD91-expressing reticuloendothelial macrophages triggers induction of hemeoxygenase-1 (HO-1), an enzyme that performs the first committed step in heme catabolism.[3] Besides producing carbon monoxide, a molecule with putative antiapoptotic, anti-inflammatory, and antiproliferative properties, HO-1 itself has similar protective functions, as do its metabolic products, biliverdin and bilirubin. I would suggest that part of the paradoxical protective benefit of hemolytic anemia against coronary arteriosclerosis in patients in part involves this induction of HO-1 and production of carbon monoxide, biliverdin, and bilirubin. Supporting this idea, HO-1 gene transfer experiments in mice protect against the development of arteriosclerosis.[4]

In patients with chronic hemolysis, I agree with Crary and Buchanan that loss of splenic function shifts the predominant site of hemolysis from extravascular to intravascular. More specifically, Westerman and colleagues have observed that plasma hemoglobin and microparticle levels are higher in splenectomized thalassemia patients than those with intact splenic function.[5] Although in a nonrandomized study such as this, splenectomy might simply be a marker of patients who underwent splenectomy due to more severe disease, the findings are fully consistent with a delay in hemolysis, but with a proposed shift of site of hemolysis to intravascular, causing plasma hemoglobin levels to rise. The significance of this shift lies in the pathologic effect of plasma hemoglobin, which is documented to scavenge nitric oxide. This decreased nitric oxide bioavailability promotes a generalized vasculopathy phenotype of vasoconstriction, smooth muscle proliferation, and activation of adhesiveness of platelets and endothelial cells, with particular affinity to the pulmonary vasculature.[6] Furthermore, microparticles are believed to be prothrombotic.[7]

I would like to commend Drs Crary and Buchanan for their valuable contribution to the literature on vascular disease and splenic function. *Blood* readers should also be aware of the emerging biology of heme-induced HO-1 vasculoprotection and of splenectomy-associated shifts of hemolysis promoting a state of relative nitric oxide deficiency. It is likely that these proposed mechanisms are only part of a multifactorial pathobiology linking asplenia and vasculopathy.

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References

1. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood.* 2009;114:2861-2868.
2. Westerman MP. Hypocholesterolaemia and anaemia. *Br J Haematol.* 1975;31:87-94.
3. Ryter SW, Choi AM. Heme oxygenase-1/carbon monoxide: from metabolism to molecular therapy. *Am J Respir Cell Mol Biol.* 2009;41:251-260.
4. Juan SH, Lee TS, Tseng KW, et al. Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice. *Circulation.* 2001;104:1519-1525.
5. Westerman M, Pizzey A, Hirschman J, et al. Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy. *Br J Haematol.* 2008;142:126-135.
6. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA.* 2005;293:1653-1662.
7. Davizon P, López JA. Microparticles and thrombotic disease. *Curr Opin Hematol.* 2009;16:334-341.

To the editor:

Restoration of the human stem cell niche after stem cell transplantation

Recently, Dominici et al very elegantly demonstrated restoration of the osteoblastic hematopoietic stem cell (HSC) niche after lethal marrow radioablation in mice.[1] Based on their data, the authors propose a model in which radiation induced an increase in stromal cell–derived factor 1α (SDF-1α), causing the attraction of CXCR4-positive megakaryocytes that survived radiation. A concomitant