those from children to several drugs used in ALL treatment, suggesting that different mechanism can contribute to or modulate constitutive and acquired resistance. Adding to this is the versatile nature of MRP4, reflected in affinity for a variety of substrates that can, upon exposure, differentially regulate MRP4 expression.[4]

There are several differences in treatment modalities between childhood ALL DFCI protocol and GMALL adult ALL trial regarding drug type and dose, and schedule of administration.[5,6] Beside noted difference in MTX dose, high-dose MTX in GMALL trial is given at several instances during consolidation phase compared with earlier single administration during remission induction in DFCI protocol.

The association of *MRP4* polymorphisms seen in childhood ALL seems to be more apparent in the standard risk group, as reflected in our article's data supplement.[1] Brüggemann et al report the analysis of standard risk patients only. However, the risk classes between 2 protocols are not comparable. Beside already mentioned age difference, the GMALL protocol does not encounter CNS disease at presentation among risk classification criteria, whereas the standard risk groups also includes the subset of T-cell leukemia.[5,6]

One possible explanation for association found in our study[1] is that higher frequency of toxicity in A934 carriers would lead to more frequent drug withdrawal or dose reduction, which might cause higher frequency of relapse. However, this reduction probably would not be sufficient to explain reduction in event-free survival, and other mechanisms contribute as well. For instance, MRP4 participates also in efflux of folate; down-regulation of MRPs might result in decreased folate efflux, thereby leading to expansion of the intracellular folate pool and antifolate resistance.[7] This further illustrates the complexity of MRP effects and regulation.

In conclusion, we believe that the report of Brüggemann et al is important, as it highlights the applicability of pharmacogenetic findings in childhood ALL to adults, yet further studies analyzing more comparable childhood ALL populations are needed to establish the role of *MRP4* polymorphisms.

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To the editor:

Central nervous system prophylaxis in mantle cell lymphoma

In their thorough review of mantle cell lymphoma (MCL),[1] Ghielmini and Zucca describe that central nervous system (CNS) disease involvement, albeit rare at presentation, has an incidence of 4% to 22% in relapsed patients. Nevertheless, they do not state their recommendations regarding prophylaxis to MCL patients. The National Comprehensive Cancer Network (www.nccn.org) guidelines for diffuse large B-cell (DLBCL) lymphoma recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate (MTX) and/or cytarabine for patients with aggressive lymphomas who have paranasal sinus, testicular, epidural, bone marrow, 2 extranodal site involvement, or HIV lymphomas. The guidelines for MCL patients further suggest lumbar puncture at diagnosis for patients with blastic variants or with neurologic symptoms, but do not state any recommendations for prophylactic treatment at either diagnosis or relapse. Because there are no definite guidelines, and most patients are not treated with CNS-penetrating agents such as high dose MTX/cytarabine regimens,[1] it is left to the physician's discretion whether to administer CNS prophylaxis or not. For instance, in the United Kingdom, one-third of hematologists administer prophylaxis to MCL patients and only in specific circumstances.[2] Among the many reports of MCL in the literature, 4 concentrated their efforts on direct assessment of CNS involvement in MCL,[3-6] and all are retrospective (Table 1); therefore, the true incidence is unknown.

Interestingly, although most patients with CNS involvement develop symptoms at or after first relapse, not only the blastoid variant MCL had this propensity while having a higher risk. It might be argued that since most patients will succumb to their disease, which is rarely curable, and because CNS disease is only one part of a systemic relapse,[3] there is limited application for primary prophylaxis. Nevertheless, in all reports, CNS disease was associated with worse overall survival. In addition, with the advent of newer agents and curative treatment attempts,

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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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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