Response

**MRP4 gene polymorphisms and treatment response in adult ALL**

We thank Brüggemann and colleagues for their interest in our paper that recently reported an association between *MRP4* gene polymorphisms (regulatory T-1393C and A934C leading to Lys304Asn substitution) and outcome in childhood acute lymphoblastic leukemia (ALL) patients treated on Dana-Farber Cancer Institute (DFCI) protocols. Given the preliminary character of this study, replication in an additional cohort of sufficient size was suggested. Brüggemann et al analyzed same polymorphisms in adult ALL patients who underwent treatment with German Multicenter ALL (GMALL) protocols. The cohort was enough powered to detect genotype-associated differences, but nevertheless failed to do so, further confirming little concordance that exist between pharmacogenetics findings in childhood and adult ALL. The authors suggest that the difference in methotrexate (MTX) dose between protocols account for observed discrepancy. While we agree with such a possibility, we would like to emphasize several other reasons possibly contributing to this finding. ALL in childhood and adulthood are distinct diseases as based on the observed difference in etiology, incidence rate, disease characteristics and survival. Disease-free survival in childhood ALL is as high as 80%, whereas it barely reaches 40% in adults. ALL blasts are more resistant than...
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.3

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 study1 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.

Central nervous system prophylaxis in mantle cell lymphoma

In their thorough review of mantle cell lymphoma (MCL),1 Ghielem and Zuca 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,2 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,
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