ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Mixed-Phenotype Acute Leukemia: Disease Features and Outcome

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H&O Can you provide some background on mixed-phenotype acute leukemia (MPAL)?

EM MPAL is a very rare form of acute leukemia; the precise incidence among acute leukemias is difficult to establish. According to approximate figures from the centers involved in our European Group for the Immunological Classification of Leukemias (EGIL), approximately 0.5–1% of acute leukemia cases are MPAL, including pediatric and adult cases. It is very likely that MPAL derives from the neoplastic transformation of an early stem cell precursor with the ability to undergo myeloid and lymphoid differentiation, although further studies are needed. MPAL essentially comprises 2 main subgroups according to the lineage of differentiation of the leukemic cells, whether myeloid and B-lymphoid or myeloid and T-lymphoid. Trilineage differentiation, or cases involving the 2 main lymphoid lineages, are very rare.

The World Health Organization (WHO) categorizes MPAL into 2 distinct cytogenetic subgroups: MPAL with *BCR-ABL* rearrangement and MPAL with *MLL* rearrangement. However, in the EGIL experience, these subgroups account for only 20–25% of cases. Thus, the great majority of patients have other chromosomal abnormalities; a normal karyotype is rare. The presence of *BCR-ABL* rearrangement has a prognostic impact in MPAL—and thus there is a rationale for considering patients with this abnormality to be a distinct subgroup. In contrast, prognosis in patients with the *MLL* rearrangement is not significantly worse than that of patients with other abnormalities or even a normal karyotype.

H&O What role does the current WHO classification play in determining lineage in MPAL?

EM The WHO criteria have done a good job in defining and refining the definition of MPAL. Prior to the 2008 WHO criteria, the diagnosis of MPAL was made according to the guidelines from our EGIL group, which left out a number of cases. The WHO criteria have ensured that lineage commitment is demonstrated by the expression of strictly lineage-specific antigens, regardless of whether other lineage-associated antigens are expressed. This approach was possible for the myeloid and T-lymphoid commitment because there are very specific markers for these lineages. More difficulties were encountered in the attempt to demonstrate with certainty the B-lymphoid commitment because it was necessary to rely on the expression of a constellation of B-cell–associated antigens rather than a specific marker. The WHO simplified the diagnosis of MPAL, as the criteria decreased the number of monoclonal antibodies required. We acknowledge that the WHO criteria may miss some cases, such as patients with lymphoid plus megakaryoblastic or erythroid differentiation, and therefore these criteria are less sensitive than previous guidelines. However, these patients are a minority, and by applying the WHO criteria, there is a

gain on specificity. Further, the WHO criteria excluded patients with recurrent chromosomal abnormalities or dysplasia–related changes from the umbrella diagnosis of MPAL. It is important to emphasize that most of the patients included in our recent study of the WHO criteria would have been diagnosed as MPAL with the EGIL criteria, and very few would have been excluded. As classifications are dynamic and change with the emergence of new data, it would not be surprising if the present WHO criteria for the definition of MPAL become more refined in the future.

H&O What were some highlights from your recent work on MPAL and the WHO classification?

EM Our work is the only study examining a large series of patients reported with a diagnosis of MPAL according to the WHO criteria. It describes the heterogeneity of this leukemia and its likely unfavorable outcome. All previous data are not useful for interpretation, as these reports include a small number of cases with a miscellaneous diagnosis, admixing true MPAL with cases of acute lymphoblastic or myeloblastic leukemias with aberrant antigen expression. It has become apparent from our data that MPAL is more frequent in adults and is heterogeneous in its disease features, presenting like an acute lymphoblastic leukemia or an acute myeloid leukemia. Particularly, our findings on cytogenetics and molecular genetics point out that there is no recurrent genetic abnormality in MPAL. Indeed, a complex karyotype involving a variety of chromosomes was the most commonly found abnormality, even more frequent than the *BCR-ABL* rearrangement. Whether these abnormalities are secondary and represent clonal evolution remains uncertain.

H&O What is the prognosis for patients with MPAL?

EM At present, it is difficult to be categorical on the prognosis in MPAL. The reported data are scanty and misleading. Our study was retrospective and included patients from different centers. However, considering that the therapeutic schedules used were very similar in terms of drugs and their delivery, it would appear that the prognosis for the overall group of MPAL is unfavorable, with an overall median survival of 18 months. Aside from this, one must consider the factors that may influence survival in patients with MPAL. In a multivariate analysis, our data showed that the 3 predictors for a poor outcome were age, the presence of *BCR-ABL* rearrangement, and AML-induction type therapy.

H&O What are the treatment options for MPAL?

EM Management of MPAL is a dilemma for many clinicians. Whether it should be treated using acute myeloid leukemia protocols, acute lymphoblastic leukemia protocols, or allogeneic stem cell transplant is difficult to discern, and data are lacking. It will be very difficult to perform prospective studies in such a rare type of leukemia.

Although our work is retrospective, we believe that we are in a position to recommend the appropriate management of these patients. Our data show that ALL-directed therapy is more effective than AML-targeted therapy and that the poorest outcomes are seen in adults and patients with the *BCR-ABL* rearrangement. Patients with this cytogenetic abnormality should be offered allogeneic stem cell transplant in first remission, as it is recommended in other non-MPAL acute leukemia patients who have that abnormality. This therapeutic scenario should also be considered in patients, particularly adults, who achieve a complete remission but remain minimal residual disease–positive. Treatment options for other cases should be left open to clinicians, who should take patient preferences into account. A prime scenario is that children who achieve a complete remission and do not have the *BCR-ABL* rearrangement may very well be cured with standard treatment for ALL.

H&O Where are future efforts needed?

EM Considering that MPAL is a very rare leukemia, efforts need to be made on a worldwide, collaborative scale in order to better establish the natural history and behavior of this disease, as well as to discover the putative deregulated genes responsible for triggering the disease. We have good specific markers for the T-lymphoid and myeloid commitment. A truly specific B-cell marker to be used by flow cytometry will be desirable to unequivocally demonstrate the commitment of the blasts to the B-lymphoid lineage. Ideally, uniform protocols for diagnosis and, particularly, for treatment of these patients, should be devised and followed in different countries. Analysis of global gene expression profiling in well-characterized MPAL cases is needed in order to shed light on the pathogenesis of this leukemia and allow for the discovery of deregulated genes, which could be potential therapeutic targets.

Suggested Reading

Matutes E, Pickl WF, Van't Veer M, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. *Blood.* 2011;117:3163-3171.