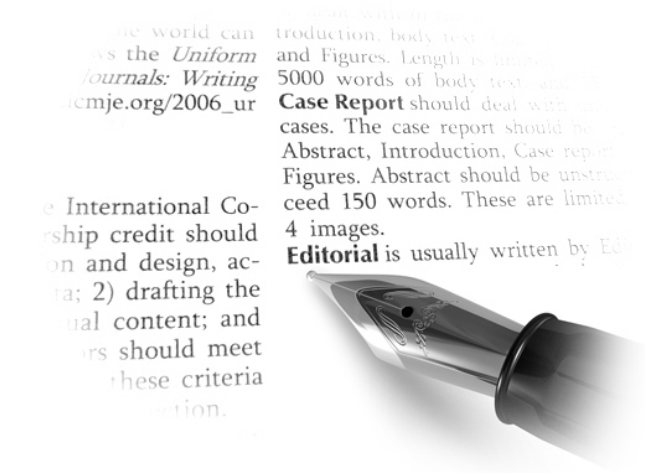

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Editorial

Mixed-phenotype acute leukemia (MPAL) and beyond

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Mixed-phenotype acute leukemia (MPAL) is a rare but difficult to treat hematologic malignancy with immunophenotypic co-expression of at least two cell lineages, or with only rare cases involving all three lineages, e.g. myeloid with B- or T-lymphoid or all three of myeloid, B- and T-lymphoid altogether. The WHO has classified MPAL as biphenotypic and bilineal leukemias as a heterogeneous category of 'acute leukemias of ambiguous lineage', but excluding the more cases with recurrent genetic abnormalities. Instead, the European Group for the Immunological Classification of Leukemia (EGIL) simply defines the MPAL by the scoring criteria for diagnosis. Therefore, there are some issues to be considered when we diagnose and treat patients with MPAL by using either the WHO or EGIL guidelines. By the EGIL criteria, biphenotypic acute leukemia is diagnosed when a score more than 2 points is noted for each lineage of myeloid or lymphoid. According to the literature, it is more common in adults and many reports showed poor-prognostic cytogenetics including a complex karyotype, t(9;22), and 11q23 [1]. However, this unusual but particular situation of 'MPAL' in a category of 'acute leukemias of ambiguous lineage' in 2008/2016 WHO classification is still not well known the pathobiology and appropriate treatment in clinic.

Previously, it was named differently as 'biphenotype acute leukemia (BAL)' as a rare disease entity that comprises less than 3% of all acute leukemias and the optimal therapeutic approach for BAL has been unknown yet. As we may know the difference by morphologic, cytochemical and immunophenotypic characteristics of both myeloid and B/T-lymphoid lineages, even the scoring system for markers by the EGIL is partly useful in some ways of making an appropriate therapeutic decision. Sometimes many cases of AML at diagnosis show one or more lymphoid marker(s) as a manifestation of aberrant lineage expression together. Moreover, recent data showed that leukemia stem cells (LSCs) with lymphoid characteristics can propagate MPAL, which was resulting from several other studies showing that the *MLL-ENL* fusion gene or t(8;21) *RUNX1/RUNX1T1* positive AML could induce lineage reassignment of T cell progenitors to generate AML [2-4]. These findings suggest that in some cases of MPAL the AML/ALL-LSCs can be initiated by malignant transformed hematopoietic stem cells, possibly during hematopoiesis of common myeloid precursors as well as common lymphoid precursors or their downstream myeloid/lymphoid progenitors. What can we do for this group of patients with vague characteristics? It is very unclear whether patients with MPAL should be treated with regimens against AML or ALL or both [5-8]. Or which strategy is more appropriate to target sequentially as to pursue lymphoid followed by myeloid or vice versa? Or are there any specific predictors as to let us know the arms face this peculiar phenotype acute leukemia?

In the present issue of *Blood Research*, Pomerantz *et al.* [9] suggested that a significantly worse disease-free survival and overall survival (OS) noted when comparing MPAL patients to other acute leukemias and better OS in patients treated with ALL-type chemotherapy compared

to AML-type regimens. Most of all, authors nicely demonstrated that because they found with regard to a better OS in group 4, which was comprised of patients diagnosed with MPAL using the EGIL classification but not by the 2008/2016 WHO criteria, when compared to other acute leukemia patients, the 2008/2016 WHO classification is underpowered to diagnose all MPAL cases, potentially resulting in the suboptimal treatment of some individuals with MPAL. Of note, their message is clear to recognize that underdiagnosed with non-MPAL when the 2008/2016 WHO criteria are still used, either the impact of using AML-type regimens on outcome with ineffective therapeutic decision-making or misdiagnosis of non-MPAL would be very worrisome in real clinic. Also, some coincident reports have revealed that MPAL patients have a better outcome when an ALL-type regimen is used, as they revealed in the study.

However, some limitations in the study, and particularly some critical issues that underlie in many aspects for MPAL are still present. Firstly, the conclusion that patients who were diagnosed by EGIL criteria are more predictive to foresee the outcome with ALL-type chemotherapy is based on relatively small sample size (just 21 cases of MPAL in total in Mexico) compared to other previous reports [1, 6], and may not be perfect enough to be supported by this retrospective study results. Secondly, the incidence of MPAL with t(9;22) and high-risk groups of patients may be inaccurately low compared to the recent reports showing more complex or poor-risk patients in MPAL [8]. Although they argued with their results of inferior AML-type treated arm, some data showed that even AML-type regimen could impact on more positive results when it comes to the intensive chemotherapeutic regimens against MPAL. Furthermore, the patients in the subgroup who were treated with AML-type regimen were likely older and their lower numbers compared to patients in MPAL but treated with ALL-type chemotherapy, and as comparably shown in ALL. Lastly, through the Figures demonstrated for all patients' survival rates in the study, the long-term survival results of Mexican AML patients are much superior than those of ALL and MPAL patients. In addition, the worst survival rates of MPAL in their shown figures are not quite understandable. Therefore, it might cause inevitably the inferior results of AML-type treatment in MPAL, but in contrast the ALL-type treated cases were relatively not.

As all we know well but with very much limited clues in this disease category, the concept of effective and appropriate approaches to MPAL patients should be reconsidered more accurately under the background of well-studied evidences with more large clinical trials or accumulated data. It is still unsure whether we diagnose it confirmatively with feasible therapeutic options. Undoubtedly, it is still ongoing challenges that we easily define the MPAL as ALL-type treatment is most appropriate or WHO criteria is weak or so compared to EGIL and so on. We should admit that it is an unresolved area for MPAL, especially for more elderly patients who are in danger of underpowered diagnostic and therapeutic approaches in real clinic. If we look at the novel clue-finding tools such as next generation sequencing method and digital PCR in our field, the new useful knowledge instead of old conceptual posture with the dynamic changes of leukemic clones or subclones during treatment and after diagnosis of MPAL would be far appropriate in understanding the hidden impacts of genetic/epigenetic defects in the molecular era. We may be dead wrong in recognition of MPAL so far, when it comes to the old concepts as compared to in real genetic aspects of mixed-phenotype or mixed-lineage and beyond. In the near future, we should redefine AML/ALL patients with bilineage clonal hematopoiesis as a novel and distinct high-risk group of patients that can be identified early at diagnosis through multi-modality diagnostic studies on hand [10], and as to focus on more specifically accurate target therapies with or without transplantation.

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