

Immunophenotyping of Acute Leukemias: Insight into Prognosis since the Outset

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Introduction

An accurate estimation of prognosis is a basic principle of modern treatment of acute leukemia (AL). A proper and early definition of the probability of outcome allows the modulation of treatment strategy, including chemotherapy and/or allogeneic hematopoietic stem cell transplantation (HSCT) [1,2].

Among prognostic factors, karyotype and molecular genetics are the most relevant; indeed, they represent the framework of main risk stratification systems of AML [3] and ALL [4]. In fact, they allow to define patients' subgroups featured by high likelihood to achieve complete remission (CR) and long survival and at the opposite a category with scarce response to chemotherapy and dismal prognosis. However, in the absence of genetic determinants, these stratifications merge patients with heterogeneous diseases, where their clinical utility has major concerns.

Immunophenotyping has mainly a diagnostic role in AL field. At any rate, there are some specific subsets where flow cytometry assumes a significant prognostic weight, independently on cytogenetics, upon which clinicians can apply a proportional treatment strategy. Beyond single antigenic aberrancies, the prediction of outcome by the phenotypic profile relies on its correlation with peculiar biological and genetic features. The aim of this paper is to review briefly the circumstances where immunophenotyping can aid substantially the prognostic stratification of patients affected by AL.

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia has two main characteristics: life-threatening coagulopathy and sensitivity to a differentiating treatment consisting of all-trans retinoic acid [5]. Both of them prompt the urgency of a correct suspect and consequent diagnosis. In this light and given the rapidity of results, the interpretation of the phenotypic profile of blasts can be crucial. Leukemic promyelocytes typically have the phenotype of their normal counterpart (*i.e.*, high side scatter signal with intense expression of CD33 and CD64, heterogeneous expression of CD13, negativity for HLA-DR) but with dim/negative CD15. Cross-lineage expression of CD56 can occur, with debatable prognostic meaning [6]. A population of basophils with extremely high side scatter signal can also be revealed. In this context, rather than a prognostic meaning *per se*, immunophenotype can predict a specific underlying genotype leading to an early therapeutic intervention.

Mixed Phenotype AL (MPAL)

The concomitance of expression of antigens belonging to different lineages has demonstrated to correlate with dismal prognosis. Consistently, WHO classification considers these cases as a separate entity and establishes

precise criteria for their diagnosis. Highly lineage-specific antigens are required for T-(cytoplasmic CD3) and myeloid- (Myeloperoxidase and/or evident monocytic differentiation) lineage attribution [7]. For B-lineage, one or three B-lineage markers have to be expressed depending upon intense or weak expression for CD19. MPAL are often associated with unfavorable karyotype, MLL/11q23 rearrangements or BCR/ABL gene fusion. Patients affected by MPAL are characterized by unfavorable prognosis and should be considered for allogeneic HSCT once in CR [8].

T-Lineage ALL

In adults, ALL of T-lineage is featured by poor outcome and rare known genetic abnormalities. Within this disease, cortical T ALL (EGIL T-III) is defined by the expression of CD1a. In a large multicentre prospective trial by UKALL and ECOG, a lower relapse risk and a longer overall survival were observed for this category of patients [9]. This immunological feature is often used for prognostic stratification of T-ALL. At the opposite, a specific immature T phenotype (so-called "early T"), featured by absence of CD1a and CD8, weak CD5, and expression of one or more myeloid or stem cell-related antigens, has been associated with low response rate to chemotherapy and dismal prognosis [10].

Neoplasm of Precursors of Plasmacytoid Dendritic Cells

Neoplasm of precursors of plasmacytoid dendritic cells is a novel subset in WHO classification of myeloid neoplasms, with heterogeneous clinical presentation and variable extra-hematological infiltration. The normal counterpart of this tumor resides in the plasmacytoid dendritic cell lineage and as such its diagnosis depends on revealing a dendritic cell-related phenotype [11,12]. The typical phenotypic profile consists of positivity for CD4, CD56, CD123 together with intense expression of HLA-DR and negativity for main lineage antigens. In this setting, the phenotype provides an important clinical information since this disease has a dismal outcome with chemotherapy consolidation and allogeneic HSCT seems to provide better chances of cure [13]. The proper induction therapy is still under debate due to rarity of the disease and the lack of prospective data; so far, the available studies suggest that an ALL-like treatment might be the most suitable bridge to allogeneic transplant consolidation [13].

AML: The Role of Multi-Lineage Dysplasia

Several papers have addressed the role of multi-lineage dysplasia (MLD) in AML leading to conflicting results, possibly because of technical and biological reasons [14,15]. Technical reasons deal with morphological assessment of residual hematopoiesis at AML diagnosis, operator-dependant and even more complicated in this context because residual non-blast cells are very few. Biologically, the MLD-related unfavorable prognosis would rely on clonal involvement at stem cell level or on pre-

existing clonal hemopoiesis, but it might merely result from pathologic differentiation/maturation of AML. Being an emergent method to study dysplasia, we exploited immunophenotype to estimate MLD in AML. We focused our analysis on NPM1-mutated (NPM1+) AML, where this issue has relevant implications since this category correlates with a relatively good prognosis (especially when FLT3-wt) [16,17]. Our study provided evidence that MLD, as assessed by immunophenotype, has no impact on clinical characteristics and outcome in NPM1+ AML. By investigating NPM1 status on separated cell compartments, we have established a correlation between MLD and belonging to AML clone [18]. Our findings support MLD to be part of the spectrum of NPM1+ AML, without any relevant influence on outcome, suggesting that the prognostic stratification of this subset should not be based upon MLD.

Early Assessment of Response

Most clinical and biological prognostic factors are surrogate for disease's chemo sensitivity but they lead to a risk stratification that groups patients with wide differences in terms of outcome. The BM response to chemotherapy allows refining the pre-treatment risk stratification as it expresses the actual disease chemo sensitivity resulting from leukemic cells killing. The value of minimal residual disease in acute leukemia is well established [19-21] and it is not the primary subject of this article. In early BM evaluation of response, most frequently in childhood ALL, sometimes a sizable expansion of B cell precursors (otherwise defined hematogones) can occur, which is potentially misinterpreted as resistance to chemotherapy by morphological analysis. In this view, immunophenotyping can effectively distinguish a normal, regenerative antigenic pattern from a pathological neoplastic phenotypic profile [22].

Concluding Remarks

In spite of expanding genetic knowledge of AL, some subgroups still have unclear prognostic definition. In this context, immunophenotyping can effectively predict outcome, highlighting poor or favorable risk categories in otherwise "grey" zones and thus driving the application of treatment strategies upon individual probability of being cured.

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