Flow Cytometric Assessment of Chronic Myeloid Neoplasms

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KEYWORDS

• Flow cytometry • Myelodysplastic syndrome • Myeloid neoplasm • Diagnosis

KEY POINTS

- Flow cytometry immunophenotyping of the cells from the bone marrow can be used to help with diagnosis, prognosis, and therapy of chronic myeloid neoplasms.
- The number of abnormalities detected by flow cytometry correlates with disease severity and cytogenetic complexity.
- Scoring systems have been developed to quantify aberrancies for diagnostic and prognostic purposes.
- Flow cytometry remains only an adjunct diagnostic modality, which has to be correlated with clinical, morphologic, and genetic findings.

INTRODUCTION

Chronic myeloid neoplasms, including myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), and MDS/MPN, are clonal disorders of hematopoietic stem cells. They manifest as aberrancies of number, morphology and/or function in one or multiple lineages of hematopoietic elements. The World Health Organization classification of myeloid neoplasms is based on a mixture of clinical, morphologic, and genetic criteria.[1–3] The role of flow cytometry immunophenotyping (FCIP) in the diagnosis, classification, prognosis, and management of chronic myeloid neoplasms remains controversial, mainly owing to the lack of established standardized criteria. Nevertheless, an increasing number of mostly academic health care centers incorporate FCIP in the routine workup of patients with myeloid malignancies. This review is primarily centered on FCIP in MDS because that is the focus of the vast majority of studies so

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far. Because the number and extent of phenotypic changes are correlated with the degree of dysplasia, the changes are less prevalent, and not as applicable in MPN.

HISTORY AND RATIONALE FOR MYELOID FLOW CYTOMETRY IMMUNOPHENOTYPING

The history of FCIP in the diagnosis of chronic myeloid neoplasms can be roughly divided in 3 phases. In the first phase, from the mid 1980s to the mid 1990s, a scarcity of antibodies for hematopoietic cells resulted in rare published observations, most of which focused on apoptotic features, ploidy assessment, and proliferative index of cells in MDS.[4–10] From the mid 1990s to the mid 2000s, there was an increasing number of reported changes in myelopoiesis that could be detected by FCIP. Most of these studies were qualitative and correlative in nature, identifying FCIP aberrancies that correspond with the diagnosis of MDS.[11–17] Finally, since about the mid 2000s, there has been a stronger advocacy within the flow cytometry community for a quantitative approach and standardization among different laboratories.[18–21] The newly published studies have become more rigorous in determining the predictive value of FCIP changes in MDS, with longer clinical follow-up, and potential therapeutic impact.[22,23]

The basis of FCIP in the diagnosis of myeloid neoplasms is the ability to distinguish normal from abnormal myeloid cells. If we think of genetic and epigenetic changes as a root cause of abnormal hematopoiesis (or any other carcinogenesis), and the defect in number and function of cells as a final result of this process, then both morphology and immunophenotype fall somewhere in between. Unlike with FCIP, we have had tens or even hundreds of years of experience in using morphologic findings for diagnostic and therapeutic guidance. Knowledge in medicine is built on previous knowledge, and therein lies the challenge with incorporating any new approach: if a previous study to evaluate treatment for a myeloid malignancy used morphologic criteria to define a disease, then we cannot be sure that the results would have been the same had we defined it in a different way (ie, immunophenotypically). This leads to an ever-increasing number of correlative retrospective studies, but no truly prospective, therapy-guiding endeavors.

IMMUNOPHENOTYPING OF BLASTS (IMMATURE MYELOID PRECURSORS)

Blasts are a particularly appealing target for FCIP evaluation of myelopoiesis. First, because chronic myeloid neoplasms are clinical disorders of hematopoietic stem cells, blasts are likely to be affected in all cases, regardless of the number of lineages with morphologic dysplasia. Second, blast phenotype may be more stable than that of mature granulocytic cells. Third, FCIP can help with blast enumeration, which is an essential component of MDS and MDS/MPN stratification. Finally, morphologic assessment of blasts is limited mostly to enumeration (particularly at low blast percentages) because there are no definitive morphologic criteria for “abnormal blasts.” In contrast, FCIP can identify phenotypically aberrant blasts. Because “blasts” are defined morphologically, the flow cytometry community started using the term “immature myeloid precursors” to avoid confusion with morphologic findings. However, it is uncertain whether this distinction is clear to hematologists in a routine clinical practice.

To date, for the purpose of diagnosis, subclassification, and prognostication, the gold standard for blast enumeration remains a morphologic assessment of the bone marrow aspirate. Blast definition by FCIP varies from study to study. The most commonly used definition is $CD34^{+}CD45^{dim}$, which tends to slightly underestimate the percentage of blasts. The best correlation with morphologic counts was obtained