Role of Flow Cytometry in the Diagnosis and Prognosis of Plasma Cell Myeloma

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KEYWORDS

• Flow cytometry • Myeloma • Plasma cells • MGUS • Minimal residual disease

ABSTRACT

This article provides an overview of the role of flow cytometry in the diagnosis and follow-up of plasma cell myeloma. A brief introduction to the general immunophenotypic features of normal and myeloma plasma cells is provided, followed by a discussion of technical issues as they relate to the application of flow cytometry in this entity. The prognostic and therapeutic utility of flow cytometric immunophenotyping in myeloma is also analyzed, with an emphasis on the growing role of minimal residual analysis as potential biomarker for evaluating treatment efficacy and for tailoring risk-adapted treatment, in prospective clinical trials.

Key Features

- During the past decade, a growing body of evidence has supported the role for flow cytometry (FC) in plasma cell myeloma (PCM), both at diagnosis and follow-up.
- Routine FC in myeloma requires careful consideration of several technical aspects related to plasma cell (PC) analysis.
- There are potential applications for FC in the differential diagnosis, prognosis, and treatment of PCM.
- Minimal residual disease (MRD) analysis by FC is a powerful predictor of outcome in myeloma in the clinical trial setting.

Abbreviations

AL	Amyloid light chain
BMPC	Bone marrow plasma cell
CR	Complete response
CRAB	Hypercalcemia, renal insufficiency, anemia, bone lesions
FC	Flow cytometry
FS	Forward scatter
IMWG	International Myeloma Working Group
LPL	Lymphoplasmacytic lymphoma
MGUS	Monoclonal gammopathy of undetermined clinical significance
MM	Multiple myeloma
MRD	Minimal residual disease
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PC	Plasma cell
PCM	Plasma cell myeloma
PFS	Progression-free survival
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes
sFLCs	Serum free light chains
SMM	Smoldering multiple myeloma
SS	Side scatter
VGPR	Very good partial response
WHO	World Health Organization

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OVERVIEW

PCM or multiple myeloma (MM) is a common hematologic malignancy (10%–15% of hematopoietic neoplasms) and is defined by a triad of clinicopathologic criteria, including

1. The presence of a serum or urine monoclonal protein
2. The presence of a clonal PC population in the bone marrow (or plasmacytoma)
3. Disease-related end-organ or tissue impairment, usually summarized under the CRAB acronym:
   a. Hypercalcemia
   b. Renal insufficiency
   c. Anemia
   d. Bone lesions

and also including hyperviscosity, amyloidosis, or recurrent infections.

The current diagnostic criteria, as listed in the 2008 World Health Organization (WHO) classification of hematolymphoid neoplasms[1] and initially defined by the International Myeloma Working Group (IMWG) in 2003,[2] apply to symptomatic PCM (ie, requiring therapy) and have been used for the past decade in clinical practice and research trials.[3] The spectrum of PC neoplasms encompasses other entities, however, such as monoclonal gammopathy of undetermined clinical significance (MGUS); asymptomatic or smoldering MM (SMM); PC leukemia; solitary plasmacytoma; polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome; and systemic amyloid light chain amyloidosis.[1] From a clinical standpoint, it is postulated that PCM is almost always preceded by MGUS, which is present in 3% to 4% of the general population ages greater than 50 years[4,5] and has a rate of progression to PCM of approximately 1% per year.[6,7]

SMM is, by definition, an asymptomatic condition that constitutes an intermediate clinical phase between MGUS and PCM and has a higher risk of progression to myeloma (10% per year, during the first 5 years) compared with MGUS.[8]

Table 1 summarizes and compares the diagnostic criteria for PCM, SMM, and MGUS, as recently updated by the IMWG.[9,10] The rationale for updating these definitions is based on observations from several studies that a subset of patients with SMM showed a much higher progression risk to PCM, even in the absence of traditional CRAB features.[11–15] The introduction of these new myeloma-defining biomarkers (such as bone marrow plasma cells [BMPCs] ≥60%, involved:uninvolved serum free light chains [sFLCs] ratio ≥100, and MRI findings with more than 1 focal lesion) removes the need for documenting end-organ damage as an obligatory requirement for the definition of a neoplastic condition (PCM) and allows the identification of a cohort of SMM patients that may benefit from treatment initiation prior to the occurrence of irreversible end-organ damage. It is the recommendation of the IMWG that these criteria should be implemented in routine

Table 1
Revised International Myeloma Working Group diagnostic criteria for plasma cell myeloma, smoldering myeloma, and monoclonal gammopathy of undetermined clinical significance

Entity	Diagnostic Criteria	Progression Rate to Plasma Cell Myeloma
PCM	• Clonal bone marrow PCs ≥10% or biopsy-proved plasmacytoma • One or more myeloma-defining events: ◦ CRAB ◦ Clonal bone marrow PCs ≥60% ◦ Serum-free light chain ratio ≥100 ◦ >1 Focal lesion on MRI scan	N/A
MGUS (non-IgM)	Serum monoclonal protein <30 g/L Clonal bone marrow PCs <10% Absence of myeloma-defining events or amyloidosis	1% Per year
SMM	Serum monoclonal protein >30 g/L or Urine monoclonal protein ≥500 mg/24 h Clonal bone marrow PCs 10%–60% Absence of myeloma-defining events or amyloidosis	10% Per year (first 5 y)

Adapted from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e541; and Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood 2015;125:3070.