REVIEW

Minimal Residual Disease in Myeloma: Are We There Yet?

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Measurement of minimal residual disease is routine in diseases such as chronic myelogenous leukemia, precursor B cell acute lymphoblastic leukemia, and acute promyelocytic leukemia because it provides important prognostic information. However, the role of minimal residual disease testing has not been widely adopted in multiple myeloma (MM), with other parameters such as the International Staging System (ISS) and cytogenetic analysis primarily guiding therapy and determination of prognosis. Until recently, achieving a complete response (CR), as defined by the International Myeloma Working Group (IMWG) criteria, was rare in patients with MM. The use of novel agents with or without autologous peripheral blood stem cell transplantation (auto-PBSCT) has significantly increased CR rates, thus increasing overall survival (OS) rates. The majority of patients with MM have persistent levels of residual disease that are below the sensitivity of bone marrow (BM) morphology, protein electrophoresis with immunofixation, and light chain quantitation even after attaining CR and will eventually relapse. Measurement of minimal residual disease by more sensitive methods, and the use of these methods as a tool for predicting patient outcomes and guiding therapeutic decisions, has thus become more relevant. Methods available for monitoring minimal residual disease in MM include PCR and multiparameter flow cytometry (MFC), both of which have been shown to be valuable in other hematologic malignancies; however, neither has become a standard of care in MM. Here, we review current evidence for using minimal residual disease measurement for risk assessment in MM as well as incorporating pretreatment factors and posttreatment minimal residual disease monitoring as a prognostic tool for therapeutic decisions, and we outline challenges to developing uniform criteria for minimal residual disease monitoring.

Biol Blood Marrow Transplant 18: 1790-1799 (2012)

KEY WORDS: Minimal residual disease, Multiple myeloma, Flow cytometry, PCR

INTRODUCTION

Multiple myeloma (MM) is a very heterogeneous disease with protean manifestations, as well as an assortment of genetic and molecular alterations, making prognostic determination at diagnosis quite challenging. In 1975, Durie and Salmon [1] described an MM staging system using features such as tumor cell mass, the presence of end-organ damage, osteolytic bone lesions, and elevated serum Ig levels. More recently, the International Staging System (ISS) was developed that describes disease burden based on β2-microglobulin and serum albumin levels, with both having prognostic significance at diagnosis [2]. Cytogenetic abnormalities including 13q deletion and detection of t(4;14), t(14;16), and del17p by fluorescence in situ hybridization (FISH) have been shown to predict a less favorable survival, and the International Myeloma Working Group (IMWG) has proposed a new classification system based on molecular and cytogenetic criteria [3]. Gene expression profiling has also recently been used to determine high-risk populations but is not available for widespread use [4,5]. The use of these molecular and cytogenetic signatures to direct treatment, in the context of other staging parameters, variable disease manifestations, and expanding therapeutic options, is still being validated.

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Financial disclosure: See Acknowledgment on page 1797.

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Received March 20, 2012; accepted May 3, 2012

1083-8791/$36.00
doi:10.1016/j.bbmt.2012.05.009

The IMWG response criteria are based on (1) serum and urine M-protein by electrophoresis and immunofixation (IFX), (2) percentage of plasma cells on bone marrow (BM) biopsy, and (3) serum free light chains (sFLCs) [6]. The importance of achieving a complete response (CR), with an associated benefit in overall survival (OS), has been well-documented, although data also show that development of CR has the most significant benefit in only a small, high-risk group of patients as defined by gene expression profiling [7,8]. As CR rates have improved, more rigorous definitions of response have been developed, including stringent CR (sCR) by the IMWG that incorporates sFLCs along with immunohistochemistry and immunofluorescent techniques to establish plasma cell (PC) clonality [6]. It has been proposed that the sFLC ratio, which has been shown at diagnosis to be an independent prognostic factor and predict more aggressive disease, be incorporated into the ISS to help improve risk stratification as well [9-11]. The role of sFLC measurement as a minimal residual disease marker will be further discussed below.

Improving CR rates, with associated increases in OS and event-free survival (EFS), have made the measurement and monitoring of minimal residual disease in MM with more sensitive techniques a relevant pursuit. Microscopic BM examination, radiographic imaging, molecular, and flow cytometric techniques have all been used for this purpose. Two very sensitive techniques that have been studied with increasing frequency during the past few years are PCR and multiparameter flow cytometry (MFC). However, for a variety of reasons including the heterogeneity of the disease and the technical complexity of some of the techniques, minimal residual disease monitoring with highly sensitive techniques has not become routine clinical practice. Here, we review the use of these approaches and outline the challenges to developing uniform and available methods for minimal residual disease measurement in MM.

Techniques for Assessing Minimal Residual Disease in MM

Protein and imaging studies

Measurement of serum and urine paraprotein levels with IFX, sFLC and urine free light chains, and morphologic examination of the BM are all widely available methods used to measure disease burden in MM. One definition of CR is defined by the IMWG as <5% PCs in the BM with negative serum and urine IFX, and the clinical significance of achieving CR has been well-described [6,7]. Data from the Total Therapy trials have demonstrated the importance of CR on long-term outcomes [12]. These treatment regimens, though, are rigorous and may not be amenable for use outside of large referral centers. A report from the Korean Multiple Myeloma Working Party demonstrated that achieving a CR/near CR (nCR) before autologous peripheral blood stem cell transplantation (auto-PBSCT) significantly increased 2-year OS from 70.9% to 86.6% compared with patients achieving a partial response, providing data that achieving CR has prognostic significance even before high-dose therapy (HDT) and auto-PBSCT [13].

As BM biopsies are expensive, time-consuming, and pose some risk to patients, it has been argued that BM examination is not necessary in patients with negative serum and urine electrophoresis and IFX due to the low likelihood of increased PCs under these circumstances [14]. However, the independent value of BM examination has been examined in 2 studies. Data from Chee et al. [15] showed in 92 patients that 14% with negative IFX and 10% of patients with a normal sFLC ratio had ≥5% BM PCs in the marrow, with clonality demonstrated in 85% of patients with residual PCs [15]. In patients who are IFX-negative, they found significantly improved OS from time of IFX-negativity in patients with <5% total PCs compared with those with ≥5% (6.2 versus 2.3 years; $P = .01$). More recently, Fernández de Larrea et al. [16] showed in 35 patients after auto-PBSCT that the total number of PCs present in patients in CR after auto-PBSCT correlates with progression-free survival (PFS) but not OS [16]. There was a nonsignificant difference in median OS in patients with ≤1.5% PCs versus >5% PCs (median OS not reached versus 9.7 years; $P = .195$). These results demonstrate that microscopic assessment of the BM can have prognostic significance regardless of the status of protein studies, although the sensitivity of morphology alone is crude and limited by the number of cells evaluated as well as sampling variability.

Imaging by fluorodeoxyglucose-positron emission tomography (PET) has also been shown to have prognostic significance, with a significant improvement in PFS and OS in patients with 100% standardized uptake value reduction compared with <100% standardized uptake value reduction after treatment with thalidomide-dexamethasone and auto-PBSCT in 1 study [17]. This held true even among patients otherwise achieving a CR. Moreover, they demonstrated a significant improvement in post-relapse OS if the fluorodeoxyglucose-PET was negative versus positive at 36 months. Although PET imaging is widely available, not all patients with MM will have PET-avid lesions, and heterogeneity of visual criteria and poor interobserver reproducibility can be a problem with interpretation of data from these imaging studies.

As CR rates have improved, more sensitive techniques to measure the depth of response have been investigated. The sFLC ratio has been shown to have prognostic significance at the time of diagnosis [9]. Using this ratio to monitor disease status during