Multiple Myeloma – Pathophysiology and Epidemiology

Multiple myeloma (MM) is a plasma cell malignancy in which abnormal, clonal plasma cells proliferate and accumulate within the bone marrow. These abnormal cells, referred to as myeloma cells, disrupt normal bone marrow function and invade the surrounding bone. Myeloma cells produce and secrete significant quantities of monoclonal protein (M-protein) into the blood and/or urine.1 This increases M-protein and calcium levels, and leads to renal dysfunction, anemia and bone disease. Bone pain is the most common symptom of MM.2

- MM is the second most common hematologic malignancy and accounts for approximately 17% of all hematologic cancers.3
- Every year, an estimated 159,985 new cases of MM are diagnosed globally and 106,105 deaths can be attributed to the disease.4
- MM predominantly affects elderly people; it is most frequently diagnosed in those aged between 65–74 years. MM is more common in males and African Americans compared to females and Caucasians, respectively.5
- The incidence of MM increased by 126% between 1990 and 2016, with the highest rates in Western Europe, North America and Oceania.6
- Overall, the 5-year survival among adults with MM is 50.7%.3

Complete Response Categories in MM7-10

Improvements in therapeutic agents and regimens have driven the evolution of the International Myeloma Working Group (IMWG) response criteria to include deeper measures of response. The definition of a complete response (CR) was first introduced in 1998 and refined in 2006 to include stringent CR.7,8 Definitions for molecular and immunophenotypic CR (not shown) were introduced in 2011.3 In 2016, the IMWG was updated to include measurements of minimal residual disease (MRD).10

| CR* | Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates |
| sCR* | CR plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≤ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells) |
| MRD-negative‡ | Absence of aberrant clonal plasma cells on bone marrow aspirate, ruled out by an assay† with a minimum sensitivity of 1 in 10^5 nucleated cells or higher (i.e. 10^4 sensitivity) |
| Imaging-positive MRD-negative‡ | MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue |
| Sustained MRD-negative‡ | MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined above, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years) |

Minimal Residual Disease – Why Assess It?

The treatment of MM has improved significantly over the last decade, resulting in many patients exhibiting a CR to front-line therapy.9,10 Unfortunately, the disease course of MM is characterized by a pattern of recurrent remissions and relapses.1 After an initial CR, many patients inevitably relapse; therefore, MM remains an incurable disease.4,11

Relapses in MM may be attributed to the persistence of minimal residual disease (MRD) below the limits of detection by morphological examination.10,12 MRD refers to the persistence of small numbers of myeloma cells that remain in the body after therapy and contribute to relapse and disease progression.10,11 In recent years, increasingly sensitive assays to detect MRD have been developed.13

In a retrospective analysis of 3 clinical trials, 40% of patients with MM relapsed within 4 years of achieving a CR14

Hypothetical Correlation Between Depth of Response and Risk of Relapse

Future applications and clinical potential

Relapses in MM may potentially indicate the presence of residual disease. Recently, technological advances in molecular testing, particularly in NGF and NGS, and imaging techniques, such as PET/CT, have enabled the detection of myeloma cells with greater sensitivity and may potentially guide treatment decisions. Ongoing studies will continue to define MRD’s value and its role in improving long-term outcomes for patients with MM.

Numerous studies have demonstrated the prognostic importance of MRD; however, the standardization of MRD testing, as well as the role of MRD status in driving treatment decisions, is ongoing. Large clinical trials that incorporate response-based treatment strategies based on MRD status will be informative and have the potential to define the depth of response required for sustained benefit. Future standardized MRD testing techniques may therefore become part of the standard of care for patients with MM.

References


MRD: minimal residual disease; MFC: Multiparametric flow cytometry; ASO: Allele-specific oligonucleotide; Q-PCR: quantitative polymerase chain reaction; NGS: Next-generation sequencing; PET: positron emission tomography; CT: computed tomography; VDJ: variable diversity joining