Multiple Myeloma

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80.1 Definition, Epidemiology, and Diagnosis

Multiple myeloma (MM) consists of a malignant proliferation of BM plasmatic cells (BMPCs), which produce a monoclonal protein that can be found in serum and/or urine, resulting in skeletal involvement, hypercalcemia, anemia, renal function impairment, and/or soft-tissue plasmacytomas. The cause is unknown.

The annual incidence is four per 100,000. It represents 1% of all malignant diseases and about 15% of all hematological malignancies. The median age at diagnosis is between 65 and 70 years. Only 15% and 2% are younger than 50 and 30 years, respectively.

The diagnosis of symptomatic MM requires the presence of clonal BMPCs, usually >10%, or plasmacytoma, the presence of serum and/or urine M-protein (except in the uncommon nonsecretory) and related organ or tissue impairment (end-organ damage, including bone lesions). In the absence of organ damage, the presence of >60% BMPCs, a serum-free light-chain (FLC) ratio >100 or the presence of more than one focal lesion at the MRI defines symptomatic MM requiring therapy.

80.2 Risk Stratification

The International Staging System (ISS), based on the serum beta2-microglobulin and albumin levels discriminates three prognostics subgroups:

- Stage I (beta2-m <3.5 mg/L and albumin >3.3 g/dL),
- Stage III (beta2-m >5.5 mg/L) and
- Stage II (all remaining cases).

FISH can identify the following poor cytogenetic findings: t(4;14), t(14;16), and/or del 17p which account for about 25% of patients with MM, the remaining 75% having a so-called standard risk. High LDH, the presence of hematogenous extramedullary disease, and the coexistence of plasma cell leukemia are also poor prognostic indicators. A revised ISS incorporating cytogenetics and LDH have been developed as follows:

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- R-ISS I: ISS I, standard-risk cytogenetics and normal LDH,
- R-ISS III: ISS III, plus high-risk cytogenetics or high LDH and
- R-ISS II: all remaining cases.

An ultra-high-risk group, accounting for 5–7% of patients eligible for auto-HSCT and who received bortezomib-based regimens, with a median OS of less than 2 years, has been recognized (ISS III and high-risk cytogenetics or high LDH).

80.3 First-Line Treatment (Induction Prior to Auto-HSCT)

Conventional chemotherapy (VAD, VBMCP/VBAD, CY/DEX) or the doublets thalidomide (THAL)/DEX or bortezomib (BOR)/DEX results in 10% CR pre-auto-HSCT, 25–35% CR post-auto-HSCT and in 5–10% in continued CR beyond 10 years from HSCT.

The triplets combining BOR/DEX with an immunomodulatory drug (IMiD), thalidomide (VTD), or lenalidomide (VRD) result in a pre-auto-HSCT CR of 20–35%, and a post-auto-HSCT CR of 45–55%. However, there is not enough follow-up to determine the proportion of patients in continued CR >10 years beyond auto-HSCT.

The results of BOR-based triplets PAD and VCD (including Adriamycin or CY), widely used in Europe, are inferior to the reported with the combination of proteasome inhibitors plus IMiDs. Although most groups administer four induction cycles, the dose intensity and the induction exposure with an increased depth of response overtime and with higher CR rates pre- and post-auto-HSCT with six cycles have been observed with both VTD and VRD. The potential benefit of adding a MoAb, particularly daratumumab, to VTD or VRD is being investigated.

80.4 Criteria of Response and Progression

Complete remission (CR): negative serum and urine immunofixation, less than 5% BMPCs and no soft-tissue plasmacytomas.

Stringent CR: as above plus normal free light-chain ratio and absence of clonal plasma cells.

Very good partial response (VGPR): 90% or more decrease in the serum M-protein and urine M-protein <100 mg/24 h.

Partial response (PR): 50% or more decrease in the serum M-protein, 90% or more decrease in urine M-protein or to <200 mg/24 h plus 50% or more decrease in soft-tissue plasmacytomas.

Progressive disease (PD) requires one or more of the following: increase in 25% or more from nadir in serum M-protein (absolute increase of at least 0.5 g/dL), urine M-protein (absolute increase of at least 200 mg/24 h), BMPC (absolute increase of at least 10%), soft-tissue plasmacytomas, and development of new bone lesions, soft-tissue plasmacytomas, or hypercalcemia.

80.5 High-Dose Therapy (HDT), Consolidation, and Maintenance

Auto-HSCT remains the standard of care for young and fit MM patients. MEL 200 mg/m^2 (MEL-200) is the standard high-dose regimen, and the source of PBS. The addition of BOR peri-transplant, as well as other attempts, is of no benefit. MEL-140 plus IV BU vs. MEL-200 is being investigated. The increase in the CR with HDT is 15–20%.

Recent trials have shown that early transplant is superior to delayed (at relapse) auto-HSCT, even in the era of novel agents.

It seems that patients with high-risk cytogenetics are the most likely to benefit from tandem auto-HSCT.

The TRM with auto-HSCT is very low (1–2%), the best reported median PFS is 50–56 months and the expected median OS of 8–10 years. The proportion of patients operationally cured (i.e., in continued CR beyond 10 years) with the current regimens is still unknown.

Although the results of post transplant consolidation are controversial, it seems to be a promising approach and usually recommended by experts. Post-auto-HSCT maintenance with lenalinomide (LENA) has been recently approved. The optimal maintenance duration based on sequential MRD studies, as well as

whether or not the association of other drugs such as glucocorticoids, proteasome inhibitors or MoAb can be of benefit, is currently investigated.

80.6 Treatment at Relapse After Auto-HSCT

There is a consensus that a rescue or salvage auto-HSCT could be tried when the response duration to the first transplant in longer than 18–24 months. Such rescue transplant should only be performed in patients with sensitive disease, so prior salvage chemotherapy is needed. The components of the initial therapy, depth and the duration of response as well as the toxicity are crucial in selecting the rescue regimen. Among a number of possible combinations at relapse, the more effective combinations are IMiD-containing (carfilzomib, LENA, and DEX [KRd] or daratumumab, LENA, and DEX [DRd]) and non-IMiD-containing (carfilzomib and DEX [Kd] or daratumumab, BOR and DEX [DVd]). If the rescue auto-HSCT is performed, post transplant maintenance should be considered. In the event that the transplant is not done, the above treatments are in general until progression.

80.7 Allogenic HSCT in MM

The role of allografting for the treatment of MM remains controversial. The first clinical reports employing MAC regimens proved to be curative for small patient subsets but were associated with an unacceptable high TRM. In the late 1990s, the introduction of minimal intensive conditioning regimens (primarily based on low-dose TBI), which relies on the graft-versus-myeloma (GvM) effect for tumor eradication, drastically reduced TRM, but at the expense of higher disease relapse.

Combining cytoreductive high-dose MEL with an autograft and a subsequent minimal intensity conditioning with an allograft, aimed at inducing GvM, was better tolerated up to the age of 65–70 years old. Before the era of new drugs, seven prospective trials were designed to compare clinical outcomes of auto-HSCT versus tandem autologous-minimal intensity and allo-HSCT in newly diagnosed MM patients. Results were discordant regarding response, OS, and PFS. This may have partly been due to differences in conditioning regimens, GVHD prophylaxis, patient inclusion criteria, and randomization strategies. Thus, comparisons between trials are difficult. However, allografting has steadily been used in Europe in recent years. Sobh et al. recently described use and outcomes of allo-HSCT for MM in Europe between January 1990 and December 2012. A study population of 7333 patients (median age at transplant, 51 years) was divided into 3 groups: allo-HSCT upfront (n = 1924), tandem auto-allo-HSCT (n = 2004), and allo-HSCT as a second-line treatment or beyond (n = 3405). After 2004, 5-year survival probabilities from transplant were 42%, 54%, and 32%, for the three groups, respectively. Unfortunately, only a very minority of MM patients were enrolled in prospective control trials. Remarkable heterogeneity in using allo-HSCT was observed among the different European countries.

80.8 Allogenic HSCT and New Agents

The role of the combination of "new drugs" with GvM has not yet been explored in well-designed prospective studies. In only a Phase II study feasibility of BOR within a RIC and as maintenance post-allografting was evaluated. Conditioning consisted of FLU/MEL/BOR while maintenance treatment of cycles of IV BOR. Sixteen high-risk patients relapsed after an auto-HSCT was prospectively enrolled. Nine/16 (56%) and 5/16 (31%) achieved CR and partial remission. In this heavily pretreated high-risk population, 3-year cumulative incidence of NRM, relapse and OS were 25%, 54%, and 41%, respectively. The latter trial showed the feasibility and efficacy of an intensified conditioning with a "new drug" in poor prognosis patients. Moreover, the concept of maintenance treatment after an allograft was also introduced. A synergy between new drugs and GvM in the relapse setting has recently been described

clearly suggesting that allo-HSCT and new drugs are not mutually exclusive.

Whether long-term persistence of MRD negativity may coincide with disease eradication remains a matter of debate though persistent molecular remission of several years may cautiously suggest cure. PCR-based MRD detection represents a powerful predictor of clinical outcomes.

80.9 Indications of allo-HSCT in MM

The role of allo-HSCT in the era of new drugs remains highly controversial, and there are no clear guidelines, despite the relatively high numbers of allo-HSCT yearly performed in Europe. Well-designed prospective trials combining "graft-vs.-myeloma" and new drugs are needed, especially in young high-risk/ultra-high-risk patients whose treatment remains an unmet clinical need.

Key Points

- Auto-HSCT is the preferred treatment approach (standard of care) in young and fit myeloma patients.
- Prior to auto-HCT, patients should receive a BOR-based triplet induction regimen aiming to achieve a deep response.
- High-dose MEL 200 mg/m^2 is the standard conditioning for auto-HSCT in myeloma.
- Patients should receive some form of post auto-HSCT therapy (consolidation and/or maintenance therapy).
- Double auto-HSCT can be considered for high risk myeloma (e.g., patients with a del17p cytogenetic abnormality).
- The role of allo-HSCT is highly controversial in myeloma and should be performed as part of a clinical trial whenever possible.

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