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Chapter

Introductory Chapter: Update on Multiple Myeloma

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1. Introduction

Multiple myeloma (MM) is a heterogeneous and an incurable disease that is characterized by periods of remission alternating with relapses or progressions that ultimately lead to refractory disease [1, 2]. High-risk (HR) MM is defined by the presence of specific cytogenetic and molecular abnormalities [3, 4]. Double-hit myeloma refers to the presence of ≥2 HR features, while triple-hit MM refers to the presence of ≥3 HR abnormalities [3, 4].

Over the last two decades, the utilization of various novel therapies such as proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies (MoAbs) in the treatment of patients with MM has improved the depth and duration of disease response and has eventually translated into improved overall survival (OS) [5, 6]. The therapeutic modalities of MM include alkylating agents such as melphalan; corticosteroids including dexamethasone; anthracyclines such as liposomal doxorubicin; IMiDs such as lenalidomide, and pomalidomide; PIs including bortezomib, and carfilzomib; MoAbs such as daratumumab; histone deacetylase inhibitors such as panobinostat; exportin-1 inhibitors such as selinexor; BCL2 inhibitors such as venetoclax; chimeric antigen receptor (CAR) T-cells; and bispecific T-cell engaging (BiTE) therapy [1, 4].

For standard risk (SR) and transplant-eligible patients with MM, induction therapy with a PI, an IMiD, and dexamethasone followed by autologous hematopoietic stem cell transplantation (HSCT) represent the standard care [7, 8]. In SR patients, three-four cycles of the triplet regimen bortezomib, lenalidomide, and dexamethasone (VRd) are recommended while in HR patients daratumumab is added to VRd [3, 9–13]. Patients who are not candidates for transplant are treated with 8–12 cycles of VRd, followed by lenalidomide maintenance. Alternative regimens include daratumumab, lenalidomide, dexamethasone (DRd) or daratumumab, bortezomib, melphalan, and prednisolone (D-VMP) [3, 14–16].

Autologous HSCT is still considered the standard of care in the treatment of patients with MM who are eligible for transplantation [5, 17–20]. The standard conditioning regimen for patients with MM undergoing autologous HSCT is high-dose (HD) melphalan but in patients with renal dysfunction or failure, reductions in melphalan doses according to creatinine clearance are required [4, 5, 17–19]. Cryopreservation of the harvested stem cells is routinely employed prior to autologous HSCT [17, 20, 21]. However, autologous HSCT using non-cryopreserved stem cells has been shown to be safe and cost-effective and leads to short-term and long-term results that are at least equivalent to autologous HSCT using cryopreserved stem cells [17, 21–23]. Patients with MM are ideal candidates for outpatient autologous HSCT due to the ease of administration of HD melphalan, the relatively low

extra-hematological toxicity, and the brief period of neutropenia [24, 25]. Outpatient HSCT has certain inclusion criteria and exclusion criteria as well as several advantages that include: significant reduction in costs; saving hospital beds; lower rate of infections; and lower morbidity and treatment-related mortality [24, 26–28].

In patients with MM, maintenance therapy after autologous HSCT has been shown to deepen and prolong responses and increase OS and progression-free survival (PFS) [29]. Lenalidomide maintenance given after autologous HSCT till disease progression is the standard of care in patients with SR MM while bortezomib maintenance therapy after autologous HSCT is preferable in MM patients having: HR cytogenetics, renal insufficiency, inability to tolerate lenalidomide, and previous history of another cancer [30–32]. Continuous therapy has been shown to significantly improve OS and PFS [33, 34]. Continuous therapy till disease progression has become a key strategy in the treatment of patients with MM as it has been shown to improve duration of remission and it represents the standard approach for patients with MM both at diagnosis and at relapse [35, 36].

Unfortunately, nearly all MM patients ultimately relapse, even those who experience a complete response (CR) to initial therapy [19]. Management of the relapsed disease remains a critical aspect of MM care and an important area of ongoing research [19]. New treatment strategies and therapeutic modalities are needed to treat MM in relapse, particularly in case of triple-refractory disease [1]. Treatment of relapsed MM should depend on: the number of relapses encountered; the previous anti-myeloma treatment; the presence of de novo or acquired drug resistance; aggressiveness of disease relapse particularly in case of extramedullary disease, plasma cell leukemia, or clonal evolution [3, 37].

Minimal residual disease (MRD) is an important factor that can independently predict the prognosis of MM during treatment as undetectable MRD has been shown to improve PFS and OS regardless: disease status, prior transplant, or cytogenetic risk [38]. Flow cytometry has become a valuable tool to monitor MRD and evaluate the depth of CR. However, next-generation flow cytometry is more sensitive than the standard flow cytometry in detecting MRD in patients with MM [39]. Finally, the development of novel targeting therapies with different mechanisms of action is needed to achieve deep and durable responses in an attempt to cure MM while identification of tumor intrinsic and extrinsic resistance mechanisms may direct the design of combinations of novel drugs that prevent or overcome drug resistance so as to improve patient survival [40, 41].

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