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Chapter 1

Introductory Chapter: Multiple Myeloma in the Era of Novel Therapeutics

Khalid Ahmed Al-Anazi

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http://dx.doi.org/10.5772/intechopen.82174

1. Introduction

Multiple myeloma (MM), the second most common hematologic malignancy (HM), is a malignant B-cell neoplasm that is characterized by clonal expansion of plasma cells in the bone marrow (BM) with subsequent production of monoclonal immunoglobulins [1–8]. The disease has several complications including anemia; renal dysfunction or failure; bone involvement including osteopenia, lytic lesions, and pathological fractures; hypercalcemia; immunodeficiency; and various infectious complications [1, 4, 5, 7–12]. The incidence of MM has increased since the year 1990 with the largest increase in resource-poor countries [13]. MM is a heterogeneous disease even in its etiology, and there are several risk factors for the disease that include old age; obesity; ionizing radiation; exposure to solvents and pesticides; agricultural occupations; autoimmune disorders such as pernicious anemia and ankylosing spondylitis; monoclonal gammopathy of undetermined significance; and familial predisposition [14–18]. One hallmark of MM is the presence of heterogeneous chromosomal aberrations and numerous genetic mutations that not only can help in risk stratifying the disease but also can affect management and prognosis to a large extent [7, 8, 19]. Recently, MM is stratified according to stage of the disease, plasma cell labeling index, cytogenetics, and gene expression profiling [20–22].

Over the past two decades, the outcomes of patients with MM have improved substantially even in patients with relapsed or refractory (RR) disease [1–4, 23–28]. The remarkable improvement in the outcome of MM is due to the following reasons: (1) the evolution of advanced technology that facilitated understanding biology of the disease and helped in the diagnosis, risk stratification, and follow-up of patients; (2) the introduction of several novel therapies, monoclonal antibodies, and immunotherapies; (3) the widespread utilization of high-dose (HD) chemotherapy followed by autologous stem cell transplantation (HSCT); (4) the recent improvements in supportive care and antimicrobial therapies; and (5) the evolution of new

therapeutic strategies such as consolidation and maintenance treatments as well as total or continuous therapy [1–5, 24–29]. Currently, the following novel therapies are available for patients with MM: (1) immunomodulatory agents such as thalidomide, lenalidomide, and pomalidomide; (2) proteasome inhibitors such as bortezomib, carfilzomib, and ixazomib; (3) monoclonal antibodies such as daratumumab and elotuzumab; and (4) histone deacetylase inhibitors such as panobinostat and vorinostat [1–5, 26–29]. Other novel therapeutic options that are available for patients with RR-MM include chimeric antigen receptor T cells as well as other cellular and immunotherapies such as the use of specific antigen-presenting cells to overcome immune incompetence and engineered T cells as well as natural killer cell products [30–32].

Several studies and meta-analyses have shown that the most beneficial induction therapies in terms of overall response rate, overall survival (OS), and progression-free survival (PFS) in transplant-eligible patients with newly diagnosed MM are (1) bortezomib, lenalidomide, and dexamethasone (VRD), (2) bortezomib, cyclophosphamide, and dexamethasone, and (3) bortezomib, thalidomide, and dexamethasone [1, 33–35]. However, the standard induction therapy in patients with newly diagnosed MM is the VRD triplet regimen [4, 8]. Also, autologous HSCT is the standard of care for transplant eligible patients either upfront or at relapse [4, 8, 27]. Therefore, HD chemotherapy followed by autologous HSCT, which is an integral part in the treatment of the disease, is considered the standard of care for patients with MM who are eligible for HSCT [36–39]. With the recent advances in supportive care, autologous HSCT has been extended to include older patients with MM and those with comorbid medical conditions such as renal failure (RF) [37, 38]. Nevertheless, autologous HSCT and novel therapies are complementary to each other in the management of patients with MM [37, 40].

Studies have shown that post-HSCT consolidation and maintenance treatments can further improve the outcome of patients with MM [8, 27, 41]. In particular, the use of either proteasome inhibitors such as bortezomib or immunomodulatory drugs such as lenalidomide in the maintenance therapy is associated with increased OS and PFS [42–46]. However, for transplant-eligible patients, stratified maintenance therapy based on risk features and depth of response is recommended [47]. Monitoring disease response at various stages of treatment is essential, and studies have shown that monitoring of minimal residual disease (MRD) is associated with longer PFS and OS [48, 49]. Patients with high-risk (HR) cytogenetics require not only specific induction therapies but also autologous HSCT as well as consolidation and maintenance therapies [50, 51]. For such patients, deeper responses should be obtained as several studies and meta-analyses have shown that MRD negativity is a strong predictor of clinical outcome and is associated with long-term survival [49, 52, 53].

The numerous treatment modalities that are available for patients with MM have shown their efficacy, but they have their own adverse effects that include BM suppression and infectious complications that may be life-threatening [9, 10, 54].

Also, there is very limited access to effective care in many countries particularly in sub-Saharan Africa. Additionally, the available novel therapies are rather expensive, and the economic burden of the disease is huge [13, 14, 55–57].

Progression of MM is related to the underlying BM microenvironment and to the genetic heterogeneity of the disease [7, 19]. Studies have shown that the main causes of death in patients with MM are infections, comorbid medical conditions such as RF, having RR disease, and the presence

of HR features such as adverse cytogenetics or advanced stage of the disease at presentation [54, 58, 59]. The second-line treatment for patients with RR-MM is rather heterogeneous [60]. Different novel therapeutic agents that are usually given in various combinations are currently available for the treatment of patients with RR disease [61, 62]. However, in the setting of RR disease, treatment options become more complex, but the aim should be to provide the patient with specific drug combination so as to gain clinical benefit while minimizing drug toxicity [63]. Additionally, studies have shown clinical benefit for continued therapy. However, improved outcome is paralleled by certain barriers such as drug toxicity and evolution of drug resistance [64, 65].

Current treatment standards for patients with RR-MM include (1) salvage therapy using a combination of novel agents, (2) salvage autologous HSCT, (3) allogeneic HSCT in highly selected patients with RR-MM, and (4) post-HSCT consolidation and maintenance therapies [39, 66–68]. The available novel drug combinations that have been shown to be effective in RR disease include (1) daratumumab, lenalidomide, and dexamethasone, (2) daratumumab, bortezomib, and dexamethasone, (3) carfilzomib-based combinations with panobinostat or elotuzumab, and (4) pomalidomide-based combinations with carfilzomib or dexamethasone [24, 66, 69–72]. However, the choice of therapeutic regimen should take disease-related factors and patient-related factors into consideration [62, 63, 73].

Life expectancy in patients with MM has recently increased due to the availability of large numbers of novel agent with different mechanisms of action against the disease [3, 24, 27, 74]. For example, in the year 2015, five new novel agents were approved for the treatment of RR-MM [24]. Unfortunately, despite the progress achieved in the diagnostics and therapeutics including the plethora of new novel agents and despite the remarkable improvements in supportive care and stem cell therapies, the disease remains mostly incurable as patients usually experience disease relapse after enjoying a certain period of disease control [1, 3–5, 24, 28, 74, 75].

Hopefully, the following will optimize antimyeloma management in the near future: (1) better understanding of the biology of the disease, (2) characterization of genetic and molecular basis of the disease, (3) incorporation of risk stratification in the management of newly diagnosed MM patients, (4) availability of several novel agents as well as monoclonal antibodies and effective management of their adverse effects, (5) availability of safer autologous HSCT, (6) improvement of supportive care and management of comorbid medical conditions, and (7) designing new novel therapies to restore autologous antimyeloma immunity and to target protein degradation as well as aberrant biology [4, 65, 76–78]. Finally, it is essential to reduce the costs of the novel therapies so that patients with low income can afford them and make benefit from utilizing them particularly in the setting of RR-MM [13, 79–81].

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