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Immunotherapy for multiple myeloma: Current status and future directions

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ABSTRACT

Multiple myeloma (MM) is a plasma cell neoplasm which constitutes about 10% of all hematologic malignancies and has been in the limelight of fast-track development of novel drugs that have contributed to the transformation of a rapidly lethal disease into a chronic illness with significant improvement in quality of life. Nonetheless, MM remains an incurable disease in many patients. Immunotherapy has been one of the approaches that had the highest hope for curing this disease. More than two decades of research and clinical trials in immunotherapy for MM have however resulted in very little impact on patient survival. The various immunotherapy approaches that have been attempted over the last two decades but were fraught with failure have already been extensively summarized in many published reviews.

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Stem cell transplant
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Nevertheless, in view of better understanding of the immune checkpoints, the innate immune system, and improved biotechnology, there is renewed hope. In this review, we will briefly discuss the unsuccessful approaches and emphasize the lessons learned, highlight the challenges that lie ahead, and discuss the more promising approaches, that already exist or being developed such as use of allogeneic stem cell transplants (allo-SCT) as a form of cellular immunotherapy, new monoclonal antibodies, chimeric antigen receptor (CAR) T-cell adoptive therapy, and NK cell therapy.

1. Introduction

Multiple myeloma (MM) is a plasma cell neoplastic disease that often runs an aggressive and incurable course. It accounts for about 10% of hematologic malignancies and carries an annual incidence of up to 5.6 per 100,000 persons in the western hemisphere (Smith et al., 2011; Palumbo and Anderson, 2011). The hallmark feature of MM is monoclonal expansion of plasma cells in the bone marrow with accompanying excessive production of monoclonal immunoglobulins that produce an "M spike" on serum protein electrophoresis (Raab et al., 2009). Indeed, MM has been described as an evolving spectrum with isolated monoclonal antibody overproduction, an essentially benign condition referred to as monoclonal gammopathy of undetermined significance (MGUS), at one end and symptomatic, extramedullary MM at the other (Kuehl and Bergsagel, 2002). In between lies what is often referred to as asymptomatic (or smoldering) myeloma which is characterized by clonal expansion of plasma cells in the bone marrow in addition to excessive monoclonal antibody production but without the classic syndrome of symptomatic myeloma that is often described by the acronym CRAB (elevated calcium, renal insufficiency, anemia, bone disease).

Recent advances in the understanding of MM's pathophysiology and the arrival of novel therapeutic agents have revolutionized the management of this disease and dramatically improved survival in the last 2 decades. Indeed, median survival increased from about 2 years in the 1980s up to 5 years in 50% of patients treated today (and even up to 10 years or longer in about 20%) (Engelhardt et al., 2010). Nevertheless, MM still remains an incurable disease and the quest for more efficient myeloma therapy and induction of meaningful and durable responses persists.

A better understanding of the immune evasion by myeloma cells and the role of interactions between tumor cells and other elements in the bone marrow microenvironment inspired many ongoing studies targeting immunologic pathways implicated in myeloma growth and survival (Noonan and Borrello, 2011). Immunotherapy bears significant promise in myeloma treatment and in this review, we will examine various immunotherapeutic approaches currently being employed or evaluated in the management of MM.

2. Stem cell transplantation as immunotherapy: allogeneic stem cell transplantation

2.1. Background

Allogeneic stem cell transplantation (allo-SCT) is a form of cellular immunotherapy insofar as that it employs the donor's immune system to exert anti-myeloma activity. Allo-SCT has been shown to produce durable responses in MM patients who received grafts from HLA-matched sibling donors (Gahrton et al., 1991). It is, however, notorious for higher treatment-related toxicity, especially with myeloablative conditioning regimens which have been supplanted by reduced-intensity conditioning (RIC) regimens (Garfall et al., 2013). Despite the development of the latter, allo-SCT is still not routinely employed due to lack of survival advantage over standard ASCT (Lokhorst et al., 2010). Nevertheless, the attractive potential of achieving long-term disease control and cure through the graft-*versus*-myeloma (GVM) effect of allo-SCT has led to evaluation of the latter in several studies over the past decade (Bjorkstrand et al., 2011; Bruno et al., 2007; Garban et al., 2006; Krishnan et al., 2011; Rosinol et al., 2008). Essentially, these studies compared tandem ASCTs with ASCT followed by RIC allo-SCT and have mostly yielded mixed results with no consistent OS benefit. It is worth noting, however, that a subset of MM patients do benefit from allo-SCT, namely those who develop chronic graft-*versus*-host disease (GVHD) with GVM effect (Krishnan et al., 2011). Again, such benefit is often overshadowed by treatment-related morbidity and mortality. This GVM benefit and the potential complications are best illustrated in our case report published in 2005 (Khan and Moreb, 2005). The patient discussed in that report had primary refractory myeloma and is fortunately still alive and in remission more than 13 years later.

2.2. DLI

One particular aspect of allo-SCT that capitalizes on the GVM effect of donor cells is the administration of donor lymphocyte infusions (DLIs) to control disease relapse after transplantation (Lokhorst et al., 2004; Salama et al., 2000). DLIs are fraught with the development of significant GVHD. One study noted the occurrence of acute and chronic GVHD in 57% and 47% of patients receiving DLI, respectively (Lokhorst et al., 2004). The development of GVHD was also noted to correlate with clinical response which further supports the role of GVM effect in controlling disease activity. Significant occurrence of GVHD following DLIs may partly be attributed to relatively high lymphocyte doses and may be mitigated through use of gradual CD3+ cell dose escalation (Peggs et al., 2003).

2.3. Use of novel agents with allo-SCT

Novel agents which include immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), have transformed disease management in myeloma patients following allo-SCT, particularly in the setting of relapse. Thalidomide (Thal) is one IMiD that has been shown to produce objective responses in patients with disease progression after allo-SCT but its use has been fraught with toxicity in addition to development of GVHD (Mohty et al., 2005). It has been largely supplanted by Len, a better tolerated agent. The latter has been shown, both alone and in combination with dexamethasone (Dex), to be effective in relapsed MM following allo-SCT, with ORR up to 87.5% (Minnema et al., 2009). In that same study, both lenalidomide (Len) monotherapy and a shorter interval between allo-SCT or DLI and administration of Len correlated with higher GVHD occurrence. Another study evaluated the 3 novel drugs (bortezomib, Len, and Thal) as posttransplant therapies in MM patients not achieving complete response (CR) following allo-SCT (Kroger et al., 2009). The use of posttransplant DLI upgraded 27% of patients to CR and this was further increased to 59% by the additional use of novel agents.