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Guideline

Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation

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A B S T R A C T

Therapeutic strategies for multiple myeloma (MM) have changed dramatically over the past decade. Thus, the role of hematopoietic stem cell transplantation (HCT) must be considered in the context of this evolution. In this evidence-based review, we have critically analyzed the data from the most recent clinical trials to better understand how to incorporate HCT and when HCT is indicated. We have provided our recommendations based on strength of evidence with the knowledge that ongoing clinical trials make this a dynamic field. Within this document, we discuss the decision to proceed with autologous HCT, factors to consider before proceeding to HCT, the role of tandem autologous HCT, post-HCT maintenance therapy, and the role of allogeneic HCT for patients with MM.

INTRODUCTION

The landscape of multiple myeloma (MM) has changed dramatically over the last several years, with numerous new therapies and improved patient outcomes [1]. Since the last publication of American Society for Blood and Marrow Transplantation (ASBMT) guidelines for MM (2003) the

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Table 1
Levels of Evidence [4]

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2−	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Nonanalytic studies, eg, case reports or case series.
4	Expert opinion.

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paradigm for therapy (induction and after transplantation) has evolved significantly. As the utilization of autologous hematopoietic stem cell transplantation (auto-HCT) for MM has increased, the demographics of this therapy have shifted to provide improved outcomes for patients over 40 and 60 years old [2]. These exciting changes require a critical review of the role of hematopoietic stem cell transplantation (HCT) for this disease.

Data published between June 1, 2002 and December 31, 2014 were reviewed. We searched the PubMed database using the terms *multiple myeloma* and *transplant* as well as topics relevant to each particular discussion section. Only finalized peer-reviewed publications were included for review. Studies were graded according to the criteria set forth by the Steering Committee for Evidence-Based Reviews from ASBMT [3], adapted from the original recommendations of the Scottish Intercollegiate Guidelines Network Grading Review Group [4]. Levels of evidence were assessed and a grade was assigned to each recommendation following the criteria in Tables 1 and 2.

AUTO-HCT VERSUS CONVENTIONAL CHEMOTHERAPY

A significant survival advantage of high-dose chemotherapy (HDC) and auto-HCT over conventional chemotherapy was reported in the pivotal Intergroupe Francophone du Myelome (IFM) trial in 1996 [5]. Thereafter, several additional trials have been published to support these findings, the details of which are outlined in Table 3. Of the 6 trials presented, 4 have shown a benefit in progression-free survival (PFS) and 3 have shown a benefit in overall survival (OS) for auto-HCT. Of note, only 1 of these studies was published after 2010. A meta-analysis from 2007 also found an improvement for PFS in the auto-HCT arm but no benefit in OS [12]. Although the most recently published prospective trial by Palumbo et al. employed 2 cycles of melphalan 200 mg/m^2, patients received a more relevant lenalidomide-based induction [11]. In addition, an analysis of toxicity done by Fermand et al. [8] also favored the auto-HCT arm.

Based on these data, in conjunction with the previously reported results from the IFM study, we recommend HDC and auto-HCT as consolidative therapy for patients with MM (grade A recommendation). Prospective studies are in progress to further clarify if this recommendation will be upheld in the era of novel agents for induction therapy.

Table 2
Grades of Recommendation [4]

A	At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

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TIMING OF AUTO-HCT: EARLY VERSUS LATE

A systematic literature search did not identify any prospective, randomized trials comparing early versus delayed auto-HCT in MM since the publication of 2003 guidelines. Although the randomized study by Fermand et al. [8] showed a significant event-free survival (EFS) benefit and longer time without symptoms, treatment, or treatment toxicity with early transplantation in MM patients receiving conventional inductions, no such prospective data are available for MM patients receiving modern (immunomodulatory drug (IMiD)- or proteasome inhibitor-based) induction regimens.

Two retrospective studies have examined this issue more recently. Kumar et al. and Dunavin et al. retrospectively evaluated the role of early (within 12 months of diagnosis) versus delayed auto-HCT in MM patients (n = 290) who received IMiD-based inductions [13] or any novel induction [14]. The time to progression and OS from time of diagnosis were similar between the 2 groups in both studies.

These retrospective studies suggest feasibility of delayed auto-HCT in the modern era, but they are not a substitute for randomized data. The reason for employing early versus delayed transplantation in individual patients in these studies is not clear. Hence, which subset of MM patients is likely to benefit the most from delayed auto-HCT remains unknown. More importantly, no patient-reported outcome or quality of life data comparing early versus late auto-HCT in the modern era are available. Similarly, reliable cost effectiveness data comparing early transplantation against continuation of often expensive novel agent inductions are not available. Finally, in carefully selected MM patients receiving lenalidomide-based inductions with intent for a delayed auto-HCT, the importance of early stem cell collection and cryopreservation cannot be overemphasized [15-17]. Further recommendations on stem cell mobilization are discussed in the recently published ASBMT guidelines [18,19].

Therefore, based on available prospective data, we continue to recommend early (up-front) auto-HCT. However, given the recent and rapid changes in induction therapy, it is also reasonable to consider enrollment on a clinical trial that addresses the question of transplantation timing. The multicenter DFCI 10-106 (NCT01208662) trial is ongoing to address this exact question in the era of novel combination therapy.