Best Practice & Research Clinical Haematology
Vol. 20, No. 4, pp. 747–759, 2007
doi:10.1016/j.beha.2007.09.006
available online at http://www.sciencedirect.com

11

Role of autologous stem-cell transplantation in multiple myeloma

Michel Attal MD
Professor of Hematology and Head of Hematology Department
Centre Hospitalier de Purpan, Place du Dr Baylac, 31059 Toulouse, France

Jean-Luc Harousseau* MD
Professor of Hematology and Head of Hematology Department
Centre Hospitalier Universitaire Hôtel-Dieu, Place Alexis Ricordeau, 44093 Nantes Cedex 01, France

Multiple myeloma (MM) is one of the diseases in which the impact of dose intensity has been demonstrated. Consequently, in 2005 MM was the first disease for which autologous stem-cell transplantation (ASCT) was indicated in Europe and the US. However, ASCT is not curative, and most patients relapse in a median of 3 years. The introduction of novel agents such as thalidomide, bortezomib (Velcade®) or lenalidomide (Revlimid®) was logical to try to improve the high-dose strategy, and promising results have been reported. This article will focus on the current results of ASCT and will discuss the main research area to try to improve this strategy.

Key words: multiple myeloma; high-dose therapy; autologous stem-cell transplantation; double transplantation; novel agents; thalidomide; bortezomib; lenalidomide; induction; maintenance.

High-dose therapy (HDT) with autologous stem-cell transplantation (ASCT) was introduced in the treatment of multiple myeloma (MM) 20 years ago,[1,2] and its role is still controversial. The use of peripheral-blood stem cells instead of bone marrow has markedly improved feasibility, and in newly diagnosed patients transplant-related mortality is 1–2% in fit patients younger that 65 years and with a normal renal function. In this group of patients, randomized studies have shown the superiority of ASCT compared with conventional chemotherapy. Therefore, until now, ASCT is considered the standard of care in this population of patients. However, it is currently challenged by the introduction of novel agents such as thalidomide, bortezomib and lenalidomide. When they are used in combination with dexamethasone or with chemotherapy, these agents appear to yield results that are comparable to those achieved with ASCT. The

* Corresponding author. Tel.: +33 2 40 08 32 71; Fax: +33 2 40 08 32 50.
E-mail address: jean-luc.harousseau@univ-nantes.fr (J.-L. Harousseau).

question is now to determine whether novel agents should replace ASCT as first-line treatment or whether they should be used in combination with ASCT.

RANDOMIZED STUDIES COMPARING CONVENTIONAL CHEMOTHERAPY AND ASCT

The Intergroupe Francophone du Myélome (IFM) was the first to conduct a randomized trial showing the superiority of HDT with ASCT compared to conventional chemotherapy in 200 patients <65 years of age. In this IFM 90 trial, HDT significantly improved the response rate, event-free survival (EFS), and overall survival (OS).[3] Similar results were published 7 years later by the British Medical Research Council (MRC).[4] As a consequence of these two studies, ASCT has been proposed worldwide as part of frontline therapy, although two randomized studies have demonstrated a longer EFS and time without symptoms, treatment and treatment toxicity in the ASCT arm, but no benefit in OS.[5,6]

Another important finding from the IFM 90 trial was the strong relationship between quality of response and OS. Patients achieving complete remission (CR), or at least very good partial remission (VGPR), had a longer OS than patients with only partial remission (PR).[3] This led to two important changes in the management of patients with MM: (1) CR (or at least VGPR) achievement is now considered an objective of any treatment, and (2) response criteria have been redefined to introduce CR and VGPR, responses that were rarely obtained previously with conventional chemotherapy.[7,8]

However, two more recent studies have raised concerns due to the lack of significant survival benefit from ASCT compared to conventional chemotherapy.[9,10] In the first study, from Spain, only patients whose disease responded to initial chemotherapy were randomized to undergo ASCT or further chemotherapy.[9] Although the CR rate was higher in the ASCT arm (30% versus 11%), no difference was seen in EFS and OS. Compared with other studies, where randomization occurred at diagnosis, the design of this trial introduced a selection bias, and only 75% of the patients entering the study were randomized. This fact is important since ASCT is a useful salvage treatment for patients with primary refractory MM.[11,12] In the US Intergroup study, there was also a possible selection bias.[10] Since randomization occurred after induction chemotherapy, only 516/813 registered patients were randomized, and only 424 actually underwent the assigned therapy. No differences in response rate, EFS or OS were seen between the two arms. However, while results achieved with ASCT were quite comparable to those achieved in the IFM 90 trial, results of chemotherapy were much better (Table 1). Of special interest is the CR rate achieved with conventional chemotherapy, which was much higher than that in the French trial and identical to that achieved with ASCT.

The following conclusions can be drawn from these randomized studies:

Table 1. Comparison of the IFM 90 trial with the US Intergroup S9321 trial.

	CR rate		7-year EFS		7-year OS	
	CC	ASCT	CC	ASCT	CC	ASCT
IFM 90[3]	5%	22%	8%	16%	27%	43%
S9321[10]	17%	17%	16%	17%	42%	37%

IFM, Intergroupe Francophone du Myélome; CR, complete response; EFS, event-free survival; OS, overall survival; CC, conventional chemotherapy; ASCT, autologous stem-cell transplantation.