AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA: IS IT STILL THE RIGHT CHOICE?

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ABSTRACT

Autologous stem cell transplantation (ASCT) is considered the standard of care for multiple myeloma patients aged <65 years with no relevant comorbidities. The addition of proteasome inhibitors and/or immunomodulatory drugs has significantly increased the percentage of patients achieving a complete remission after induction therapy, and these results are maintained after high-dose melphalan (Alkeran®), leading to a prolonged disease control. Studies are being carried out in order to evaluate whether short-term consolidation or long-term maintenance therapy can result in disease eradication at the molecular level, thus also increasing patient survival. The efficacy of these new drugs has raised the issue of deferring the transplant after achieving a second response upon relapse. Another controversial point is the optimal treatment strategy for high-risk patients, that do not benefit from ASCT, and for whom the efficacy of new drugs is still matter of debate.

Keywords: Autologous transplantation, myeloma.

STATE-OF-THE-ART

For many years the gold standard treatment for multiple myeloma (MM) was the combination of melphalan and prednisone (Deltasone®) (MP),[1] as different polychemotherapy regimens failed to demonstrate a superior efficacy.[2] MP was able to induce a response in >40% of treated patients; complete responses, however, were achieved in <5% of the cases, and overall patient survival did not exceeded 3 years. The first step towards the introduction of autologous stem cell transplantation (ASCT) in MM was the demonstration of a dose-response effect of melphalan in MM cells.[3] The potential to overcome resistance to melphalan by using higher doses of the drug was subsequently explored *in vivo*;[4] 27% of newly diagnosed patients reached a complete response (CR) upon treatment with high-dose melphalan (HDM), and this translated into a prolonged survival, even though treatment-related mortality was unacceptably high. In order to reduce the duration of profound cytopaenia related to the use of HDM, autologous stem cell rescue was then introduced in the clinical practice, initially for relapsed/refractory disease, and then for newly diagnosed MM.[5,6]

The formal demonstration that ASCT is superior to conventional chemotherapy in terms of response, duration of response, and overall survival (OS), came from two randomised trials, from the Intergroup Francophone du Myeloma (IFM)[7] and the Medical Research Council (MRC).[8] In order to ameliorate these results, the application of two subsequent ASCTs was then explored by IFM[9] and by the Bologna Follow-up Group;[10] both studies demonstrated an improvement in response rate (RR) and event-free survival (EFS); however, only the French study was able to show a survival advantage for patients receiving a double ASCT. Further analysis of the IFM trial[9] showed that a second ASCT could result in an increased OS only in patients failing to achieve at least a very good partial response (VGPR) after the first ASCT; these data were in agreement with a subanalysis of the Bologna trial[10] showing an improved EFS after a second ASCT in patients failing to achieve at least a near-CR after the first one. While the use of a

double ASCT is still matter of debate, from the late 90s onwards, a single ASCT has been referred as the standard of care (SoC) for newly diagnosed MM patients <65 years with no relevant comorbidities.

In addition to the clinical benefit offered by ASCT, in recent years the therapeutic results for MM have significantly improved due to the availability of drugs that are active both on neoplastic plasma cells and on bone marrow microenvironment, such as thalidomide (Thalidomid®), lenalidomide (Revlimid®), and bortezomib (Velcade®). Thalidomide was the first agent included in induction therapy for newly diagnosed MM patients eligible for ASCT; the drug was used in combination with high-dose dexamethasone, i.e. thalidomide-dexamethasone (TD), yielding interesting results as compared to conventional chemotherapy in a case-match retrospective analysis[11] or to high-dose dexamethasone in a prospective randomised trial.[12] In a further randomised trial (Total Therapy 2),[13] thalidomide was continuously applied in the various phases of the whole treatment programme until patient relapse; again, an advantage in terms of CR rate and EFS was observed in patients treated with thalidomide as compared to those not receiving the drug, but OS was similar in the two groups of patients. Subsequent trials were designed to evaluate the combination of TD with doxorubicin (Adriamycin®);[14] a significant improvement in RR was observed when compared to conventional chemotherapy (vincristine [Oncovin®]-doxorubicin-dexamethasone [Decadron®] [VAD]). Bortezomib was tested in combination to dexamethasone (VD) in a Phase II study;[15] a VGPR rate of >30% was achieved after induction and upgraded to >50% after ASCT. A further Phase II study was designed with the aim to compare VD to conventional VAD;[16] again the arm treated with the novel regimen showed a significantly higher RR (38% VGPR or better versus 15%) that was confirmed after ASCT. The combination of VD with cyclophosphamide (Cytoxan®) (VCD) was able to induce a VGPR or better in >60% of the patients,[17] similar results were reported using VD+ doxorubicin (PAD).[18] Lenalidomide was studied in a randomised trial in combination to high (RD) versus low (Rd) doses with dexamethasone.[19] After four courses patients were allowed to undergo ASCT or to proceed with the same therapy; even though RR was significantly higher in the RD group, survival was the same due to the higher toxicity experienced by the patients treated with high-dose dexamethasone.

A further improvement in the results obtained with novel drugs ± steroids ± chemotherapy was achieved by combining two novel drugs with dexamethasone. The combination bortezomib-thalidomide and dexamethasone (VTD) was randomly compared to TD as induction therapy prior to ASCT (Table 1), yielding a significant advantage in terms of response, both CR and VGPR.[20] These data were confirmed by a recent study of the Pethema group.[21] A bortezomib + thalidomide-containing regimen was also used in the Total Therapy 3 trial,[22] in the context of a polychemotherapy programme involving induction, ASCT, consolidation, and maintenance; as compared to Total Therapy 2, in which only TD was used,[13] a significant prolongation of EFS was observed. A randomised study conducted by the IFM in newly diagnosed MM patients[23] demonstrated that the triple combination VTD, with reduced dose bortezomib and thalidomide, was superior to VD in terms of response, both after induction and after ASCT. So far, these results indicate that induction therapy in preparation to ASCT should include bortezomib + dexamethasone + an immunomodulating agent, either thalidomide or lenalidomide, that is presently being explored in Phase II trials.[24]

DEBATED ISSUES

Is Complete Remission a Goal to be Pursued?

When MP was the only available therapeutic strategy for MM, the attainment of CR was no matter of concern as only a minority of patients could achieve a minimal residual disease status. The introduction of more aggressive therapeutic programmes including ASCT prompted a better evaluation of minimal residual disease, also including cytofluorimetric analysis[25] and molecular techniques.[26] At present, the International Myeloma Working Group (IMWG)[27] has provided the definition of 'stringent CR' including negative serum/urine immunofixation together with a normal serum free-light chain ratio and absence of clonal plasma cells in the bone marrow. Several groups have analysed the relationship between CR and patient outcome, and have pointed out that CR is a strong predictor of survival,[28] especially when extended over several years;[29] for this reason it is now generally recognised that every effort should be made in order to achieve maximal disease eradication through the various phases of the treatment programme.[30]

Table 1: Results obtained with novel drug combinations used as induction therapy prior to ASCT.

		Induction	Post ASCT		
Author (reference)	Regimen	≥VGPR (%)	≥VGPR (%)	PFS	OS
Harousseau[16]	VD	38	54	36 months	81% at 3 years
Reeder[17]	VCD	61	74	NR	NR
Sonneveld[18]	PAD	42	61	35 months	NR
Cavo[20]	VTD	62	82	68% at 3 years	86% at 3 years
Rosinol[21]	VTD	60	46 (CR)	56.2 months	74% at 4 years
Richardson[24]	RVD	61	NR	75% at 18 months	97% at 18 months
Rajkumar[48]	Rd	40	NR	63% at 2 years	92% at 3 years

ASCT: autologous stem cell transplantation; VGPR: very good partial response; PFS: progression free survival; OS: overall survival; VD: bortezomib + dexamethasone; VCD: bortezomib + cyclophosphamide + dexamethasone; PAD: bortezomib + dexamethasone + doxorubicin; VTD: bortezomib + thalidomide + dexamethasone; RVD: lenalidomide + bortezomib + dexamethasone; Rd: lenalidomide + dexamethasone (low dose); CR: complete response; NR: no response.

Can Consolidation or Maintenance Therapy Improve Patient Outcome?

The administration of some kinds of treatment upon completion of major therapy in order to improve/maintain its efficacy represents the SoC in several lymphoproliferative neoplasms, such as acute lymphoblastic leukaemia, low-grade lymphoma, or mantle cell lymphoma, and for this reason it has been considered an attractive option also for MM.

Consolidation therapy is defined as a short course of treatment administered after ASCT, which is aimed at further reducing tumour load. A study from the Nordic group[31] has evaluated the efficacy of a short course of Bortezomib, and an increased percentage of CRs was observed. Two different studies analysed the effects of a short course of VTD administered as consolidation after ASCT, and both trials showed that a molecular response can be achieved in up to 60% of the patients.[32-34] Maintenance therapy is defined as long-term treatment aiming at preventing disease recurrence or progression. Alpha interferon has been widely tested after ASCT, and despite two reports showing an improved survival, side-effects greatly overcome the possible advantage, so that this approach has been definitely abandoned.[35] A limited efficacy was also reported with long-term use of steroids.[36] Thalidomide has been studied in six trials,[13,14,37-40] and in three, the drug was also used in induction phase. Although all the trials showed an advantage in terms of EFS or progression free survival (PFS), an OS advantage for patients treated with thalidomide was observed only in two trials. A major concern regarding the use of this drug as maintenance therapy is the high percentage of patients dropping out due to long-term side-effects, specifically peripheral neuropathy.[36-39] Furthermore, the likelihood of selecting MM clones resistant to thalidomide and responsible for short post-relapse survival should probably be taken into consideration[13,14,40] as well as the limited efficacy of the drugs in case of poor-risk cytogenetics.[39] Due to its favourable toxicity profile, and specifically to the lack of long-term neurological toxicity, lenalidomide has been tested as maintenance therapy in two randomised studies,[41-42] both of which showed a significant advance in time to progression, while OS was significantly improved only in one study.[42] Side-effects were mainly hematological, and a higher percentage of second primary malignancies were observed in lenalidomide-treated patients;[41,42] however, these data need further observation as it is clear that survival benefit outgrows the risk of death from second malignancies.[43] A recent report analysed the role of bortezomib maintenance after ASCT;[18] patients showed a significant advantage in terms of PFS and OS, even though the potential of neurological toxicity should be taken into consideration. Despite these interesting results, however, data are not mature enough to recommend a specific strategy, and the issue of consolidation and/or maintenance treatment remains still debated.

Should ASCT be Performed Upfront or After First Relapse?

Early studies on ASCT in MM were performed in patients with relapsed/refractory disease but, due to the poor results that were obtained,[44] the procedure is now preferentially employed in newly diagnosed patients.[45] Furthermore, a time-dependent application of ASCT seems to be crucial in determining an optimal response.[46] A randomised study from the French group,[47] however, demonstrated a comparable outcome in terms of survival in patients undergoing early versus deferred ASCT (64.4 versus 64 months OS). These data were obtained when only chemotherapeutic agents were available; it is now evident that new drugs, when applied during induction, are able to determine a deeper response than that obtained with conventional chemotherapy combinations. Several groups have thus designed studies aimed at evaluating efficacy of long-term treatment with new drugs as compared to ASCT,[48,49] resorting to transplant only upon relapse. Results that have been published so far failed to show a difference in patient survival even though early ASCT is related to a shorter duration of treatment and drug exposure. A recent retrospective study has shown that, in patients treated with thalidomide or lenalidomide followed by early stem cell mobilisation,[50] comparable results were achieved after early versus late ASCT. Data from further studies are awaited.

Is ASCT Feasible in Elderly Patients?

Patients aged >65 years are not considered good candidates to ASCT as their survival is significantly shorter than that observed in younger patients (50% versus 68%, respectively, at 5 years[51]). Several reports, however, have identified a 'grey zone' represented by patients aged 65-70, who are in good clinical condition, and who could potentially take advantage from this procedure. In particular, a randomised study conducted in these patients has demonstrated that intermediate dosage of melphalan (100 mg/m^2) with PBSC support results in a significantly prolonged EFS and OS as compared to MP.[52] On the other hand, a later study conducted in older patients (65-75 years) failed to show the advantage of intermediate melphalan dose as compared to MP, and both regimens were inferior to the combination MP + thalidomide.[53] At present, however, MP does not represent the SoC for elderly MM patients, and no data can unequivocally establish whether an ASCT program including new drugs can be useful in older patients as it happens in younger ones. Only one Phase II study has been reported which aimed to evaluate the toxicity and the efficacy of bortezomib and lenalidomide included in pre-transplant induction and post-transplant consolidation and maintenance in patients aged 65-75 years.[54] The percentage of patients obtaining a CR increased progressively through the various phases of the treatment programme (13% after induction, 43% after transplant, and 73% during consolidation/maintenance) and hematological and non-hematological toxicities were acceptable. These data indicate that an ASCT programme including new drugs can be safely performed in selected elderly patients, thus representing a possible therapeutic option.[55]

Is ASCT the Best Treatment for High-Risk Patients?

In recent years, many attempts have been made in order to identify patients at high-risk of relapse and poor survival, and several parameters have been taken into consideration. The simplest and cheapest one is the International Staging System prognostic model,[56] designed by the IMWG, based on beta-2 microglobulin and albumin level; a significantly different survival (62 months, 44 months, and 29 months) was shown in Stage 1, 2, or 3 patients, respectively. The major pitfall of this risk stratification is that it does not take into account cytogenetic alterations that are now considered the main parameter affecting patient prognosis. No agreement exists on which - among fluorescence *in situ* hybridisation, comparative genomic hybridisation, and gene expression profile - is the best method to use in order to detect chromosomal abnormalities. However, patients showing t(4;14), t(14;16) deletion 17p[57] or 1q abnormalities[57,58] carry a worse prognosis and should be treated differently from patients with no chromosomal abnormality.[59] Very few data, however, are presently available concerning the efficacy of different therapeutic regimens in poor-risk patients. A bortezomib-containing induction therapy seems to improve the outcome of patients carrying t(4;14).[20,21] This is not the case for thalidomide,[60] especially in maintenance trials,[36] while conflicting results were reported regarding lenalidomide-dexamethasone induction.[61] On the other hand, patients with 17q deletion seem not to benefit from bortezomib followed by ASCT.[62] Dose-dense regimens, upfront myeloablative ASCT,

or novel agents are presently proposed for high-risk patients in the context of clinical trials, which are aiming at finding a proper therapeutic approach.

CONCLUSION

In the last few years the outcome of MM patients has significantly improved with the introduction of novel drugs in the clinical practice. The inclusion of thalidomide, lenalidomide, or bortezomib in various combinations in the different phases of an ASCT programme increases the percentage of patients achieving a CR, thus, potentially leading to patient cure. Data are not mature enough, so far, to establish whether a combination of new drugs, administered for a prolonged period of time, could render ASCT unnecessary. At present, in many US Institutions, both physicians and patients are in favour of a delayed ASCT policy in order to avoid complications related to the period of myelosuppression related to the procedure. It cannot be taken for granted, however, that patient quality of life may be worse in the case of a short time myelosuppression as in ASCT, rather than in the case of a prolonged therapy with any of the new drugs that are presently available and whose side-effects are well known. At present, at least in Europe, ASCT is still considered the SoC for young patients with newly diagnosed MM, and the issue is how the results can be further improved. A number of new drugs are presently being tested in MM, at various disease phases. Among them is carfilzomib (Kyprolis®), an irreversible proteasome inhibitor that, after having proven effective in relapsed/refractory disease, has been tested in combination with lenalidomide in newly diagnosed MM patients[63] inducing up to 40% stringently defined CR. Pomalidomide (Pomalyst®), a thalidomide derivative, has demonstrated to be effective even in lenalidomide or bortazomib-refractory patients.[64] These drugs will probably be included into induction therapy prior to ASCT in order to further improve disease eradication.

REFERENCES

1. Bergsagel DE et al. Evaluation of new chemotherapeutic agents in the treatment of multiple myeloma. IV. L-Phenylalanine mustard (NSC-8806). Cancer Chemother Rep. 1962;21:87-99.

2. Gregory WM et al. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. J Clin Oncol. 1992;10(2):334-42.

3. Ben-Efraim S et al. Increase in the effectiveness of melphalan therapy with progression of MOPC-315 plasmacytoma tumor growth. Cancer Immunol Immunother. 1983;15(2):101-7.

4. Selby PJ et al. Multiple myeloma treated with high dose intravenous melphalan. Br J Haematol. 1987;66(1):55-62.

5. Barlogie B et al. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67(5):1298-301.

6. Alexanian R et al. Early myeloablative therapy for multiple myeloma. Blood. 1994;84(12):4278-82.

7. Attal M et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med. 1996;335(2):91-7.

8. Child JA et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-83.

9. Attal M et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495-502.

10. Cavo M et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007;25(17):2434-41.

11. Cavo M et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005;106(1):35-9.

12. Rajkumar SV et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24(3):431-6.

13. Barlogie B et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354(10):1021-30.

14. Lokhorst HM et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010;115(6):1113-20.

15. Harousseau JL et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica. 2006;91(11):1498-505.

16. Harousseau JL et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28(30):4621-9.

17. Reeder CB et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009;23(7):1337-41.

18. Sonneveld P et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30(24):2946-55.

19. Rajkumar SV et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11(1):29-37.

20. Cavo M et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus

dexamethasone as induction before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376(9758):2075-85.

21. Rosiñol L et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120(8):1589-96.

22. Pineda-Roman M et al. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. Br J Haematol. 2008;140(6):625-34.

23. Moreau P et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011;118(22):5752-8.

24. Richardson PG et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679-86.

25. Martinelli G et al. Molecular remission after allogeneic or autologous transplantation of hematopoietic stem cells for multiple myeloma. J Clin Oncol. 2000;18(11):2273-81.

26. Paiva B et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood. 2008;112(10):4017-23.

27. Durie BG et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.

28. Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. J Clin Oncol. 2010;28(15):2612-24.

29. Barlogie B et al. Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. Cancer. 2008;113(2):355-9.

30. Cavo M et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood. 2011;117(23):6063-73.

31. Mellqvist UH et al. Improved response rate with bortezomib consolidation after high dose melphalan: first results of a Nordic Myeloma Study Group randomized phase III trial. Blood (ASH Annual Meeting Abstracts). 2009;114:Abstract 530.

32. Ladetto M et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol. 2010;28(12):2077-84.

33. Cavo M et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012;120(1):9-19.

34. Terragna C et al. Molecular remission after bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as consolidation therapy following double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. Blood (ASH Annual Meeting Abstracts). 2010;116:Abstract 861.

35. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. Ann Oncol. 2000;11(11):1427-36.

36. Berenson JR et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. Blood. 2002;99(9):3163-8.

37. Attal M et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108(10):3289-94.

38. Spencer A et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009;27(11):1788-93.

39. Stewart AK et al. A randomized phase III trial of thalidomide and prednisone as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): the NCIC CTG MY.10 trial. Blood (ASH Annual Meeting Abstracts). 2010;116:Abstract 39.

40. Morgan GJ et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7-15.

41. Attal M et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-91.

42. McCarthy PL et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-81.

43. Palumbo A et al. The clinical safety of lenalidomide in multiple myeloma and myelodysplastic syndromes. Expert Opin Drug Saf. 2012;11(1):107-20.

44. Vesole DH et al. High-dose melphalan with autotransplantation for refractory multiple myeloma: results of a Southwest Oncology Group phase II trial. J Clin Oncol. 1999;17(7):2173-9.

45. Barosi G et al. Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). Haematologica. 2004;89(6):717-41.

46. Barlogie B et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood. 1999;93(1): 55-65.

47. Fermand JP et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92(9):3131-6.

48. Rajkumar SV et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11(1):29-37.

49. Palumbo A, Rajkumar SV. Multiple myeloma: chemotherapy or transplantation in the era of new drugs. Eur J Haematol. 2010;84(5):379-90.

50. Kumar SK et al. Early versus delayed autologous transplantation after immunomodulatory agent-based induction therapy in patients with newly diagnosed multiple myeloma. Cancer. 2012;118(6):1585-92.

51. Barlogie B et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354(10):1021-30.

52. Palumbo A et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood. 2004;104(10):3052-7.

53. Facon T et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370(9594):1209-18.

54. Palumbo A et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. J Clin Oncol. 2010;28(5):800-7.

55. Ozaki S, Shimizu K. Autologous stem cell transplantation in elderly patients with multiple myeloma: past, present, and future. BioMed Research International. 2014;2014:394792.

56. Greipp PR et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.

57. Avet-Loiseau H et al. Long-term analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t(4;14), del (17p), 1q gains] play a major role in defining long-term survival. J Clin Oncol. 2012;30(16):1949-52.

58. Sawyer JR et al. Evidence for a novel mechanism for gene amplification in multiple myeloma: 1q12 pericentromeric heterochromatin mediates breakage-fusion-bridge cycles of a 1q12 approximately 23 amplicon. Br J Haematol. 2009;147(4):484-94.

59. Stewart AK et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. Leukemia. 2007;21(3):529-34.

60. Zamagni E et al. Prognostic impact of cytogenetic abnormalities on outcomes of newly diagnosed multiple myeloma patients treated with thalidomide-dexamethasone incorporated into double autologous stem cell transplantation: an analysis of 593 patients. Blood (ASH Annual Meeting Abstracts). 2010;116:Abstract 3562.

61. Kapoor P et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. Blood. 2009;114(3): 518-21.

62. Avet-Loiseau H et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). J Clin Oncol. 2010;28(30):4630-4.

63. Jakubowiak AJ et al. A phase ½ study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012;120(9):1801-9.

64. Lacy MQ et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. 2011;118(11):2970-5.