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Is There Still a Role for High-Dose Melphalan and Stem Cell Transplantation in the Treatment of Multiple Myeloma?

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Abstract Stem cell transplantation was demonstrated to have a survival value in the era prior to the introduction of novel agents for the treatment of multiple myeloma. It has become reasonable to begin to question the value of stem cell transplantation. In this review, we analyzed available data and ongoing trials to determine whether or not the evidence is sufficient to continue using stem cell transplantation as a primary modality for the treatment of the eligible patient with multiple myeloma.

Keywords: *high-dose melphalan, stem cell transplantation, multiple myeloma, bortezomib, lenalidomide; thalidomide*

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1. Introduction

Over the past 15 years, the use of the novel agents, thalidomide, lenalidomide, and bortezomib, have improved the overall response rate and depth of response in patients with multiple myeloma [1]. It is not unusual to find reports with partial response (PR) or better of 100% [2] and complete response (CR) rates of 60% [3]. There is data that demonstrates a continuous improvement in overall survival (OS) from 1999 through 2010 [4]. The ever-increasing response rate, depth of response, and OS has raised questions in the myeloma community as to whether stem cell transplantation remains necessary or, alternatively, should be considered as a salvage therapy at a later point in the overall disease process [5,6]. In other words, can or should multiple myeloma be managed only with novel drugs? A corollary question is, "Can myeloma be converted to a chronic disease without the economic and emotional disruptions associated with high-dose chemotherapy and autologous stem cell transplant?" which regularly requires patients to relocate to the transplant center for a period as long as two months.

When comparing OS between patients diagnosed during January 2001 through December 2005 vs. those diagnosed during January 2006 through December 2010, the median survival for the earlier group is 4.6 years and is now 6.1 years for the latter group [4]. There has also been an improvement in the one-year OS from 82% to 88%. Much of the survival advantage appears to be in the group of patients aged 65 years or older, where the six-year OS has improved from 31% to 56%. The OSbenefit in patients 65 years of age or younger, the transplant-eligible group, is less and is not significantly different. Both the IFM [7] and MRC [8] prospective randomized trials of autologous stem cell transplantcompared to non-transplant therapy were conducted before the introduction of thalidomide in 1999 [9]. Both of these trials showed an approximate 12-month prolongation of survival. These trials, published in 1996 and 2003, demonstrated that transplant was superior to the available agents at the time, which did not include immunomodulatory drugs or proteasome inhibitors. What data currently exists for the value of autologous stem cell transplant since novel agents were introduced?

2. Data on the Value of Transplant

There is one prospective randomized study that looked at early autologous transplant compared with transplant performed at relapse [10]. This trial, published in 1998, showed no survival benefit for early transplantation. However, there was an improved quality of life, primarily attributable to the fact that patients who were transplanted spent less time on chemotherapy. Currently, with the trend to use maintenance therapy following autologous stem cell transplant [11], it is unclear whether a quality of life benefit would be seen. It is also unclear whether the lack of a survival advantage comparing transplant early and late would still hold true in the era of novel agents.

Our group at the Mayo Clinic retrospectively looked at early vs. delayed autologous transplant after immunomodulatory agent-based induction therapy (primarily lenalidomide) in patients with newly diagnosed

multiple myeloma. This retrospective trial suffers from the selection bias that is inherent in determining which patients should go to early stem cell transplant and which patients should remain on a regimen which, in most patients, was lenalidomide and dexamethasone. However, with these caveats, no statistical difference was found between those patients on lenalidomide and dexamethasone that went to transplant after induction and those that went to transplant after progression on lenalidomide and dexamethasone [12].

There are currently three enrolling trials that are trying to address these questions of the value of early and late transplant as well as single and tandem transplant. In NCT01208766 (http://clinicaltrials.gov/), the European Myeloma Network, comprising Italian, German, and the Nordic Myeloma Study Groups with the Central European Myeloma Study Group, will compare bortezomib, melphalan, and prednisone followed by high-dose melphalan and autologous stem cell transplantand bortezomib, lenalidomide, dexamethasone as consolidation vs. no consolidation. There also will be a comparison of single vs. tandem high-dose melphalan with autologous stem cell transplantation. In other words, patients will either be on bortezomib, melphalan, and prednisone continuously compared with bortezomib, melphalan, and prednisone induction followed by high-dose melphalan and stem cell transplantation, representing the first randomization. The second randomization will be bortezomib, lenalidomide, and dexamethasone vs. no consolidation; and lenalidomide maintenance will be given in all patients. This trial has an accrual goal of 1500 patients with the primary statistical endpoint of progression-free survival (PFS). Patients over the age of 65 will not be eligible. PFS will be reported in two separate sets, those patients that were randomized to transplant or no transplant and then a second PFS in those patients randomized to consolidation or no consolidation. The secondary outcome measures will be OS, toxicity, and response. This study is estimated to complete its accrual goal of 1500 in October 2015.

The second trial is NCT01208662. This trial is a collaborative trial led by Dana Farber Cancer Institute and multiple centers within the United States. Patients over the age of 65 are not eligible. The primary outcome measure will bePFS between the two arms. All patients will receive one cycle of lenalidomide, bortezomib, and dexamethasone before randomization. Patients randomized to Arm A will complete three additional cycles of bortezomib, lenalidomide, and dexamethasone and then undergo stem cell collection and then receive five additional cycles of lenalidomide, bortezomib, and dexamethasone, followed by lenalidomide maintenance treatment. Patients in Arm B will also have stem cells collected after the third cycle and then will go immediately to autologous stem cell transplantation, followed by two cycles of lenalidomide, bortezomib, and dexamethasone consolidation, followed by lenalidomide maintenance treatment until disease progression. In Arm A, the collected stem cells are available for salvage transplant. In the non-transplant arm, they will receive a total of eight cycles of bortezomib, lenalidomide, and dexamethasone. In the transplant arm, they will receive five cycles of this triplet combination as well as a stem cell transplant sandwiched in between. The total accrual goal is 660 patients.

In Trial CTN0702, 750 patients are scheduled to be enrolled with an estimated primary completion date of May 2016 and a primaryendpoint of PFS at three years. In this trial, patients may be enrolled up to age 70. There is a randomization to three treatment arms that will be performed at the completion of unspecified induction therapy and prior to stem cell collection. In Arm 1, patients will undergo a single autologous stem cell transplant followed by 36 months of lenalidomide maintenance. In Arm 2, patients will undergo an autologous stem cell transplant followed by four cycles of consolidation with bortezomib, lenalidomide, and dexamethasone, followed by lenalidomide maintenance for 36 months. In the final arm, patients will undergo tandem autologous stem cell transplant followed by 36 months of lenalidomide maintenance. Although this trial will not answer the question as to whether or not stem cell transplant is required, it will address the value of tandem stem cell transplant and whether or not back-end consolidation with a triplet combination adds value to maintenance therapy alone. Until these three trials have been reported, it will be impossible to definitively answer what the role of stem cell transplantation will ultimately be. However, inferences can be made based on currently available information as discussed next.

3. Can Multiple Myeloma be Cured?

The most aggressive intervention for multiple myeloma is total therapy based on the rationale that patients should receive prolonged exposure to all agents known to be active in the treatment of multiple myeloma in the hope that multiple clones can be eradicated and that there will not be enough time for evolution of resistant clones [13]. In the University of Arkansas Research Center Total Therapy 1, 231 patients were enrolled. And with a median follow-up of 17 years, 23 of the patients remained progression free at 14 years, representing 10% functionally cured on no therapy [14]. In a review of 344 patients transplanted between 1989 and 1998, with a median follow-up of 12.75 years, there was an OS plateau at 11 years, and no late relapses occurred beyond 11 years. This trial from the Spanish Myeloma Study Group suggests a potential for cure, although only in 35% of patients achieving a CR and 11% of patients in a $\geq$PR [15].

There is an important scientific rationale for the introduction of autologous stem cell transplant. It has been demonstrated that clonal evolution occurs in patients with multiple myeloma and that patients present with as many as five different clones detectable by FISH assay [16]. The proportion of the various clones changes by selection based on drug exposure as the disease evolves from standard-risk multiple myeloma into terminal plasma cell leukemia. Eight different FISH assays can be used to indicate the relative proportion of multiple competing clones as defined by array CGH [17].

Multiple clones can also be demonstrated using whole genome sequencing. Genomic sequence variants can be found that wax and wane with time. These multiple independent but related clones rise and fall in dominance, acquiring single nucleotide variations and truncating mutations. Multiple groups have illustrated the evolutional clonal architecture in multiple myeloma at diagnosis and

relapse. This development of subclones with unique branching mutations is non-linear and occurs simultaneously across time [18]. At diagnosis, there is coexistence of dominant and minor subclones that have evolved from a common ancestral tumor-initiating cell. At relapse, multiple evolutionary patterns can be followed with clones identical to the diagnostic sample. This occurs without genomic alterations, or alternatively can have linearly derived mutations, or third can evolve from an ancestral minor clone with newly acquired genomic mutations or structural rearrangements [19]. With gene expression profiling, multiple clones can also be detected using single cell genetic analysis. Newly diagnosed multiple myeloma can be demonstrated to be composed of two to six different clones. The clonal diversity combined with varying selective pressures, usually produced by chemotherapy exposure, is the foundation for tumor progression and treatment resistance [20,21]. How can this clonal evolution to be prevented?

Theoretically, the use of sequential single agentsor doublets in myeloma can permit the emergence of aggressive drug-refractory populations [22]. If this theory is correct, the use of a late stem cell transplant could be much less likely to provide benefit because at the time salvage therapy is introduced, new resistant clones can emerge, which could eliminate any value of stem cell transplantation. This can manifest as shorter PFS with delayed stem cell transplantation [23]. It has been demonstrated that disease refractory to novel agents will not be sensitive to high-dose chemotherapy [24]. After novel agent induction, the remaining clones should be exposed to the unique tumoricidal properties of high-dose melphalan to allow elimination of emergent treatment-resistant clones [25].

Researchers who ask whether stem cell transplant is necessary in the era of novel agents are asking an either/or question. However, a more appropriate framing of this question is to allow our patients to avail themselves of the best therapies that utilize both novel agent induction as well as the value of stem cell transplantation. This has been demonstrated by studies that have shown a doubling of CR rate and sequential deepening of response from induction to transplant to consolidation and to maintenance and can neutralize the genetic features that have historically been considered adverse, such as -17p and t(4;14). Both novel agents and high-dose melphalan have radically different mechanisms of action and are complimentary in their ability to incrementally increase the rates of deep response. In the first trial that demonstrated the value of bortezomib, thalidomide, and dexamethasone induction, 236 patients enrolled [26]. After induction therapy, the CR rate was 18% but after the first stem cell transplant, increased to 37%; after the second stem cell transplant, to 42%; after consolidation, to 48%; and finally, the overall CR rate was 58%. This reflects the overall value of combining all available technologies to deepen the response where cure becomes theoretically possible. In the joint HOVON-65/GMMG-HD4, 413 patients were randomized to induction with bortezomib, doxorubicin, and dexamethasone. After induction, the≥nCR rate was 11%, but after high-dose melphalan, increased to 31%, and the overall response rate at the completion of the trial, rose to 49% [27], an example of the importance of combining all available options to optimize outcomes.

If myeloma is to be cured, patients need to achieve astringent CR, defined as a CR with a normal free light chain ratio and the absence of clonal plasma cells in the bone marrow by flow or immunohistochemistry. Measurements of minimal residual disease, either by amplification of tumor DNA or detecting aberrant immunophenotypes of plasma cells by flow has been introduced. For prolonged PFS, minimal residual disease (MRD) negativity must be achieved and in patients who achieve a traditional CR without achieving MRD negativity, relapse is inevitable [28]. In a small trial where 20 patients achieved astringent CR plus an immunophenotypic response (MRD negativity) compared with 11 patients who achieved astringent CR but did not have immunophenotypic response (MRD positivity), the PFSwas 40% at 40 months in the former group compared with 92% in the latter group. Survival was also significantly improved [29].

In patients who undergo stem cell transplantation, the development of MRD negativity is the most powerful factor predicting prolonged PFS. The five-year PFS in patients who had MRD assessment at day-100 post-transplant was 22% for those patients who were MRD-positive but was 60% for those who were MRD-negative. In a sequential analysis, stem cell transplantation converted 48 patients in a trial of 157 patients from MRD positivity to MRD negativity [30].

4. What is the Data on Utilization of Stem Cell Transplant Currently?

Stem cell transplantation is becoming a much safer therapy as patient selection criteria have been refined, and the technique has developed widespread applicability at community centers. A review of data from the CIBMTR for three time periods (1995-1999, 2000-2004, and 2005-2010) were reported. The numbers of myeloma patients in the three cohorts were 2226; 6408; and 11,644, respectively. The hazard ratio for death using the 1995-1999 cohort as the baseline hazard of 1 showed a reduction in hazard to 0.77 from 2000-2004, and 0.68 from 2005-2010 [31]. Reviewing Mayo Clinic data for patients transplanted in first remission, the day-100 all-cause mortality was reported to be one-half of 1%, reflecting the relative safety of the technique [32].

A review of transplant utilization that assessed the rate of auto stem cell transplant, up to age 74 based on the number of new incident cases, shows increasing utilization in the United States. In the era 1994-1995, there were 18,422 new incident cases <age 75. The rate of auto stem cell transplant was 5.1%. With each successive two-year period, the rate increased through 2004-2005, where among 22,123 new incident cases, the rate of auto stem cell transplant was 25.1%, reflecting the increasing comfort of applying high-dose therapy in an eligible population [33].

A publication that reviewed utilization of autologous hematopoietic stem cell transplantation in initial therapy of multiple myeloma demonstrates an important impact of socio-geo-demographic factors. In 1998, among 9000 new patients, the number transplanted were estimated at

approximately 400, representing approximately 5% of patients. In 2010, when the number of patients was 12,000, the percent transplanted was 12%. Factors that reduced the likelihood of stem cell transplantation included age, race, education, income, and insurance [34].

5. Other Available Data on the Value of Stem Cell Transplant

Total therapy-3 administered at the University of Arkansas Medical Center includes the incorporation of novel agents as part of induction, consolidation, and maintenance. Among 303 patients, only 56 have shown relapse or progression with a five-year estimate of relapse of only 18.7%. With a median follow-up of 8.7 years, the PFS and OS are 50% and 62%, respectively [35]. Comparison of total therapy-3 to total therapy-2 with thalidomide showed a significantly improved PFS and OS for total therapy-3 using tandem transplant and novel agents. In a published subset analysis of the ECOG E1A03 trial a landmark analysis after four cycles of lenalidomide and low-dose dexamethasone in patients that were <age 65 years was performed. This analysis subdivided those patients that elected a stem cell transplant vs. those that continued lenalidomide and weekly dexamethasone. The OS at three years was 94% in the early transplant group vs. 78% in those electing to continue lenalidomide and dexamethasone [36]. However, in another study, when looking at patients who had induction with bortezomib, lenalidomide, and dexamethasone followed by autologous stem cell transplant and no further therapy, compared to bortezomib, lenalidomide, and dexamethasone continuously until progression, analysis showed no significant difference in survival. However, at the time of publication, there were only 4 progressions among 28 untransplanted patients and 2 progressions in the transplanted population, making these estimates highly subject to change with longer follow-up [37].

A prospective randomized trial of melphalan, prednisone, and lenalidomide with tandem stem cell transplantation using MEL200 followed by maintenance with lenalidomide or no maintenance has been published in abstract form. There were 402 patients enrolled. Lenalidomide and weekly dexamethasone was given for four cycles, and then the first randomization was between six additional cycles of melphalan, prednisone, and lenalidomide; and in the other arm, tandem stem cell transplant was performed. The second randomization was all patients in either arm receiving either lenalidomide 10 mg maintenance vs. no maintenance. With a median follow-up of 48 months, the median PFS in the melphalan, prednisone, and lenalidomide group was 24.2 months and was 38.6 months in the tandem transplant group ($p<0.0001$). The OS at five years was 71% in the transplant group, 62% in the MPR group, which did not as yet achieve statistical significance. Lenalidomide maintenance significantly reduced the risk of progression and of death [38]. When this trial was updated in full manuscript form, stem cell transplant was found to provide a significant benefit in relapse-free and OS. The hazard ratio for progression or death with high-dose melphalan was only 0.44, and the hazard ratio for death alone with high-dose melphalan was 0.55 ($p=0.02$). Interestingly, lenalidomide produced a reduction in risk for progression when used as maintenance but did not produce statistically significant survival benefit as maintenance therapy [39]. In summary, tandem transplant produced superior survival to lenalidomide-based novel agent therapy. Complete response rates did not differ between the two groups and the survival benefit persisted even though many patients in the melphalan, prednisone, and lenalidomide arm received stem cell transplant at relapse. This suggests that late stem cell transplant salvage was insufficient to rescue patients and suggests late clonal evolution of resistant populations abrogated any potential value of salvage stem cell transplant. One criticism of this trial is the lack of exposure to bortezomib during consolidation or maintenance.

Another trial looked at stem cell transplant vs. cyclophosphamide, lenalidomide, and dexamethasone with maintenance. In this trial, lenalidomide and weekly dexamethasone was given for four months and then patients were randomized to either cyclophosphamide, lenalidomide, and dexamethasone for six cycles or MEL200 as a single transplant. The second randomization was lenalidomide and prednisone (50 mg QOD) maintenance or lenalidomide alone. Progression-free survival at three years was 60% vs. 38%, favoring stem cell transplant ($p=0.003$). Lenalidomide and prednisone produced superior PFS compared to lenalidomide in the stem cell transplant arm but not in the cyclophosphamide, lenalidomide, and dexamethasone arm. High-dose melphalan with stem cell transplant significantly improved progression-free survival compared to cyclophosphamide, lenalidomide, and dexamethasone. Adding prednisone to lenalidomide reduces the risk of progression without a significant increase in toxicity [40].

A subset analysis of the 827 adult patients with multiple myeloma in the HOVON-65/GMMG-HD4 trial analyzed a subset randomized to bortezomib, doxorubicin, and dexamethasone induction followed by stem cell collection [27]. All patients who were in the Dutch section of the trial received a single autologous stem cell transplant (n=210). In the German patients, all patients received a tandem stem cell transplant (n=142). Bortezomib maintenance was given to 229 patients in the cohort. A multivariate analysis of risk factors for PFS and OS demonstrated that the hazard ratio for OS in the tandem transplant group was 0.75 compared to 1.0 for the single arm transplant group with a p-value of 0.03. This does not answer the question of transplant vs. no transplant; but if a tandem transplant independently improves OS compared to a single transplant, it would suggest that high-dose therapy plays an important role in prolonging the survival of patients with multiple myeloma. In the single-transplant arm receiving bortezomib, doxorubicin, and dexamethasone induction, the five-year OS was 55% with a relapse-free survival of 32 months. However, in the tandem transplant arm, the five-year OS was 70% with a relapse-free survival of 36 months [27].

The myeloma MRC-X Trial was a phase 3 trial of 174 patients, randomizing relapsed patients to either a second course of high-dose therapy (n=89), or 85 randomized to conventional chemotherapy, allpatients had a prior autologous stem cell transplant shortly after diagnosis. Seventy-three percent of those transplanted had the

procedure performed >24 months following their first stem cell transplant. The median time to progression in the transplant arm was 19 months compared to those who received conventional chemotherapy at 11 months. No OS benefit was seen, but 20% of patients who received conventional therapy subsequently crossed over to receive a stem cell transplant, potentially obscuring any survival benefit [41].

6. Conclusion

Although a sufficient number of randomized controlled studies have not been published to definitively answer the question, the preponderance of the evidence suggests that stem cell transplant, for the time being, remains the standard of care for patients that can safely undergo high-dose therapy. Clinical trials that are currently under way to better address this question may change this conclusion; but pending their completion, there is no data to suggest that novel agents, in the absence of high-dose therapy, consistently produce outcomes that are as good as those seen by combining novel agents and autologous stem cell transplant.

References

[1] Offidani M, Leoni P, Corvatta L, Polloni C, Gentili S, Liberati AM, Pulini S, Gozzetti A, Ballanti S, Nozzoli C, Palumbo A. "Outcome and toxicity in the modern era of new drugs for multiple myeloma: a reappraisal for comparison with future investigational trials," *Clin Lymphoma Myeloma Leuk*, 10 (5), 353-60, 2010.

[2] Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, Al-Zoubi A, Anderson T, Nordgren B, Detweiler-Short K, Stockerl-Goldstein K, Ahmed A, et al. "A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma," *Blood*, 120 (9), 1801-9, 2012.

[3] Anderson K. "Multiple myeloma: advances reported in 2013 are useful in the clinic," *J Natl Compr Canc Netw*, 12 (5 Suppl), 808-11, 2014.

[4] Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, Lust J, McCurdy A, et al. "Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients," *Leukemia*, 28 (5), 1122-8, 2014.

[5] Atanackovic D, Schilling G. "Second autologous transplant as salvage therapy in multiple myeloma," *Br J Haematol*, 163 (5), 565-72, 2013.

[6] Gertz MA, Lacy MQ. "Salvage autologous stem cell transplant is an effective regimen for relapsed multiple myeloma," *Leuk Lymphoma*, 54 (10), 2096-7, 2013.

[7] Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, Casassus P, Maisonneuve H, Facon T, Ifrah N, Payen C, Bataille R. "A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome," *N Engl J Med*, 335 (2), 91-7, 1996.

[8] Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT, Selby PJ. "High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma," *N Engl J Med*, 348 (19), 1875-83, 2003.

[9] Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, Munshi N, Anaissie E, Wilson C, Dhodapkar M, Zeddis J, Barlogie B. "Antitumor activity of thalidomide in refractory multiple myeloma," *N Engl J Med*, 341 (21), 1565-71, 1999.

[10] Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, Macro M, Pertuiset E, Dreyfus F, Mariette X, Boccacio C, Brouet JC. "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*, 92 (9), 3131-6, 1998.

[11] McCarthy PL, Palumbo A. "Maintenance therapy for multiple myeloma," *Hematol Oncol Clin North Am*, 28 (5), 839-59, 2014.

[12] Kumar SK, Lacy MQ, Dispenzieri A, Buadi FK, Hayman SR, Dingli D, Gay F, Sinha S, Leung N, Hogan W, Rajkumar SV, Gertz MA. "Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma," *Cancer*, 118 (6), 1585-92, 2012.

[13] Barlogie B, Anaissie E, van Rhee F, Pineda-Roman M, Zangari M, Shaughnessy J, Epstein J, Crowley J. "The Arkansas approach to therapy of patients with multiple myeloma," *Best Pract Res Clin Haematol*, 20 (4), 761-81, 2007.

[14] Barlogie B, Tricot GJ, van Rhee F, Angtuaco E, Walker R, Epstein J, Shaughnessy JD, Jagannath S, Bolejack V, Gurley J, Hoering A, Vesole D, et al. "Long-term outcome results of the first tandem autotransplant trial for multiple myeloma," *Br J Haematol*, 135 (2), 158-64, 2006.

[15] Martinez-Lopez J, Blade J, Mateos MV, Grande C, Alegre A, Garcia-Larana J, Sureda A, de la Rubia J, Conde E, Martinez R, de Arriba F, Viguria MC, et al. "Long-term prognostic significance of response in multiple myeloma after stem cell transplantation," *Blood*, 118 (3), 529-34, 2011.

[16] Keats JJ, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E, Van Wier S, Blackburn PR, Baker AS, Dispenzieri A, Kumar S, Rajkumar SV, et al. "Clonal competition with alternating dominance in multiple myeloma," *Blood*, 120 (5), 1067-76, 2012.

[17] Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S, Middha S, Asmann Y, Schmidt J, Braggio E, Keats JJ, Fonseca R, et al. "Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides," *Blood*, 120 (5), 1060-6, 2012.

[18] Bahlis NJ. "Darwinian evolution and tiding clones in multiple myeloma," *Blood*, 120 (5), 927-8, 2012.

[19] Melchor L, Brioli A, Wardell CP, Murison A, Potter NE, Kaiser MF, Fryer RA, Johnson DC, Begum DB, Hulkki Wilson S, Vijayaraghavan G, Titley I, et al. "Single-cell genetic analysis reveals the composition of initiating clones and phylogenetic patterns of branching and parallel evolution in myeloma," *Leukemia*, 28 (8), 1705-15, 2014.

[20] Hajek R, Okubote SA, Svachova H. "Myeloma stem cell concepts, heterogeneity and plasticity of multiple myeloma," *Br J Haematol*, 163 (5), 551-64, 2013.

[21] Hosen N. "Multiple myeloma-initiating cells," *Int J Hematol*, 97 (3), 306-12, 2013.

[22] Gourzones-Dmitriev C, Kassambara A, Sahota S, Reme T, Moreaux J, Bourquard P, Hose D, Pasero P, Constantinou A, Klein B. "DNA repair pathways in human multiple myeloma: role in oncogenesis and potential targets for treatment," *Cell Cycle*, 12 (17), 2760-73, 2013.

[23] Dunavin NC, Wei L, Elder P, Phillips GS, Benson DM, Jr., Hofmeister CC, Penza S, Greenfield C, Rose KS, Rieser G, Merritt L, Ketcham J, et al. "Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma," *Leuk Lymphoma*, 54 (8), 1658-64, 2013.

[24] Gertz MA, Kumar S, Lacy MQ, Dispenzieri A, Dingli D, Hayman SR, Buadi FK, Hogan WJ. "Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction," *Blood*, 115 (12), 2348-53; quiz 560, 2010.

[25] Barlogie B, Mitchell A, van Rhee F, Epstein J, Morgan GJ, Crowley J. "Curing myeloma at last: defining criteria and providing the evidence," *Blood*,2014.

[26] Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, et al. "Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study," *Lancet*, 376 (9758), 2075-85, 2010.

[27] Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, 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*, 30 (24), 2946-55, 2012.

[28] Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, Buadi F, Dingli D, Russell SJ, Hayman SR, Witzig TE, Lust JA, Leung N, Lin Y, et al. "Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma," *J Clin Oncol*, 31 (36), 4529-35, 2013.

[29] Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E, Alonso L, Oriol A, Teruel AI, de Paz R, Larana JG, Bengoechea E, et al. "Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma," *J Clin Oncol*, 29 (12), 1627-33, 2011.

[30] Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, Sureda A, Montejano L, Gutierrez NC, Garcia de Coca A, de Las Heras N, Mateos MV, et al. "Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation," *Blood*, 112 (10), 4017-23, 2008.

[31] Costa LJ, Zhang MJ, Zhong X, Dispenzieri A, Lonial S, Krishnan A, Freytes C, Vesole D, Gale RP, Anderson K, Wirk B, Savani BN, et al. "Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma," *Biol Blood Marrow Transplant*, 19 (11), 1615-24, 2013.

[32] Gertz MA, Ansell SM, Dingli D, Dispenzieri A, Buadi FK, Elliott MA, Gastineau DA, Hayman SR, Hogan WJ, Inwards DJ, Johnston PB, Kumar S, et al. "Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative," *Mayo Clin Proc*, 83 (10), 1131-8, 2008.

[33] McCarthy PL, Jr., Hahn T, Hassebroek A, Bredeson C, Gajewski J, Hale G, Isola L, Lazarus HM, Lee SJ, Lemaistre CF, Loberiza F, Maziarz RT, et al. "Trends in use of and survival after autologous hematopoietic cell transplantation in North America, 1995-2005: significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age," *Biol Blood Marrow Transplant*, 19 (7), 1116-23, 2013.

[34] Al-Hamadani M, Hashmi SK, Go RS. "Use of autologous hematopoietic cell transplantation as initial therapy in multiple myeloma and the impact of socio-geo-demographic factors in the era of novel agents," *Am J Hematol*, 89 (8), 825-30, 2014.

[35] Usmani SZ, Crowley J, Hoering A, Mitchell A, Waheed S, Nair B, AlSayed Y, Vanrhee F, Barlogie B. "Improvement in long-term outcomes with successive Total Therapy trials for multiple myeloma: are patients now being cured?," *Leukemia*, 27 (1), 226-32, 2013.

[36] diCapua Siegel DS, Jacobus S, Rajkumar SV, Abonour R, Callander NS, Katz MS, Fonseca R, Vesole DH. "Outcome with Lenalidomide Plus Dexamethasone Followed by Early Autologous Stem Cell Transplantation In the ECOG E4A03 Randomized Clinical Trial (Abstract 38)," *Blood (ASH Annual Meeting Abstracts)*, 116 38, 2010.

[37] Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, Avigan DE, Xie W, Ghobrial IM, Schlossman RL, Mazumder A, Munshi NC, et al. "Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma," *Blood*, 116 (5), 679-86, 2010.

[38] Gay F, Cavallo F, Caravita T, Cavalli M, Nagler A, Montefusco V, Pogliani EM, Buttignol S, Zamagni E, Palladino C, Marcatti M, Musto P, et al. "Maintenance Therapy With Lenalidomide Significantly Improved Survival Of Yong Newly Diagnosed Multiple Myeloma Patients (Abstract 2089)," *Blood* 122 2089, 2013.

[39] Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, Pezzatti S, Caravita T, Cerrato C, Ribakovsky E, Genuardi M, Cafro A, et al. "Autologous transplantation and maintenance therapy in multiple myeloma," *N Engl J Med*, 371 (10), 895-905, 2014.

[40] Palumbo A, Gay F, Spencer A, Di Raimondo F, Zdenek A, Larocca A, Falcone AP, Catalano L, Finsinger P, Vlastimil S, Aschero S, Offidani M, et al. "A Phase III Study Of ASCT Vs Cyclophosphamide-Lenalidomide-Dexamethasone and Lenalidomide-Prednisone Maintenance Vs Lenalidomide Alone In Newly Diagnosed Myeloma Patients (Abstract 763)," *Blood*, 122 763, 2013.

[41] Cook G, Williams C, Brown JM, Cairns DA, Cavenagh J, Snowden JA, Ashcroft AJ, Fletcher M, Parrish C, Yong K, Cavet J, Hunter H, et al. "High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial," *Lancet Oncol*, 15 (8), 874-85, 2014.