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Tandem Autologous versus Single Autologous Transplantation Followed by Allogeneic Hematopoietic Cell Transplantation for Patients with Multiple Myeloma: Results from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0102 Trial

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Abstract

Background—Autologous hematopoietic cell transplantation (HCT) improves survival in patients with multiple myeloma, but disease progression remains a challenge. Allogeneic HCT (alloHCT) has the potential to reduce disease progression through graft-versus-myeloma effects. The aim of the BMT CTN 0102 trial was to compare outcomes of autologous HCT (autoHCT)

followed by alloHCT with non-myeloablative conditioning (auto-allo) to tandem autoHCT (auto-auto) in patients with standard risk myeloma. Patients in the auto-auto arm were randomized to one year of thalidomide and dexamethasone (Thal-Dex) maintenance therapy or observation (Obs).

Methods—Patients with multiple myeloma within 10 months from initiation of induction therapy were classified as standard (SRD) or high risk (HRD) disease based on cytogenetics and beta-2-microglobulin levels. Assignment to auto-allo HCT was based on availability of an HLA-matched sibling donor. Primary endpoint was three-year progression-free survival (PFS) according to intent-to-treat analysis.

Results—710 patients were enrolled completed a minimum of 3-year follow up. Among 625 SRD patients, 189 and 436 were assigned to auto-allo and auto-auto, respectively. Seventeen percent (33/189) of SR patients in the auto-allo arm and 16% (70/436) in the auto-auto arm did not receive a second transplant. Thal-Dex was not completed in 77% (168/217) of assigned patients. PFS and overall survival (OS) did not differ between the Thal-Dex (49%, 80%) and Obs (41%, 81%) cohorts and these two arms were pooled for analysis. Three year PFS was 43% and 46% ($p=0.671$) and three-year OS was 77% and 80 % ($p=0.191$) with auto-allo and auto-auto, respectively. Corresponding progression/relapse rates were 46% and 50% ($p=0.402$); treatment-related mortality rates were 11% and 4% ($p<0.001$), respectively. Auto/allo patients with chronic graft-vs-host disease had a decreased risk of relapse. Most common grade 3 to 5 adverse events in auto-allo was hyponatremia (21/189) and in the auto-auto was peripheral neuropathy (52/436). Among 85 HRD patients (37 auto-allo), three PFS was 40% and 33% ($p=0.743$) and three-year OS was 59% and 67% ($p=0.460$) with auto-allo and auto-auto, respectively.

Conclusion—Thal-Dex maintenance was associated with poor compliance and did not improve PFS or OS. At three years there was no improvement in PFS or OS with auto-allo compared to auto-auto transplantation in patients with standard risk myeloma. Decisions to proceed with alloHCT after an autoHCT in patients with standard risk myeloma should take into consideration results of the current trial. Future investigation of alloHCT in myeloma should focus to minimize TRM and maximize graft-versus myeloma effects. This trial was registered in Clinicaltrials.gov (NCT00075829) and was funded by the National Heart, Lung and Blood Institute and National Cancer Institute.

Background

High-dose chemotherapy with autologous hematopoietic cell transplantation (autoHCT) improves survival in multiple myeloma (myeloma) patients younger than 65 years compared to conventional chemotherapy^{1, 2}. However, despite high remission rates and improved survival, there is continued risk of disease progression after a single or tandem autoHCT even in patients with “standard risk” myeloma. Investigational options to improve upon these results include tandem autoHCT, post transplant maintenance strategies and allogeneic HCT (alloHCT)^{3, 9}. Planned sequential autoHCT improves responses and survival outcomes compared to single autoHCT^{4, 6, 10}. Maintenance therapy with thalidomide and corticosteroids after autoHCT further prolongs progression-free (PFS) and overall survival (OS)^{4, 5}.

AlloHCT, which provides a tumor-free graft, is an attractive alternative treatment approach as it offers potential additional disease control through a graft-versus-myeloma effect (GVM). Early studies of alloHCT with myeloablative conditioning regimens demonstrated a higher frequency of molecular remissions and lower rates of relapse compared to autoHCT, but overall benefits were offset by high treatment-related mortality (TRM)^{11–14}. Nonmyeloablative conditioning regimens on the other hand, are designed more for immunosuppression than cytoreduction. Furthermore, when used after an autoHCT for

cytoreduction, AlloHCT with nomyeloablative conditioning adds a potential for GVM with lower TRM. . The multi-center phase II clinical trial of fifty four patients using this approach demonstrated complete responses (CR) of 57% and TRM of 15% that was far lower than historically alloHCT with myeloablative regimens⁷. Hence this approach appeared promising to explore in a phase III trial. Tandem autologous transplant (auto-auto) was chosen as the control arm based on data available at that time suggesting that this approach had the highest PFS of the various transplant strategies and potentially offered an OS benefit as well. Herein, we report the results of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0102 which compared outcomes of patients with myeloma receiving autoHCT followed by alloHCT (auto-allo) to auto-auto with or without maintenance therapy.

Methods

Study Design

This is a phase III multicenter trial with biologic treatment arm assignment. The trial was conducted in 37 transplant centers of the BMT CTN¹⁹ (Appendix 1). Patients who met eligibility criteria were assigned to the auto-allo treatment arm if an HLA-matched sibling donor was identified. Treatment assignment occurred when donor availability status was confirmed; this could occur at any time from enrollment up to 30 days after the first autoHCT. No patient progressed or died prior to treatment assignment. Those without a suitable sibling donor were assigned to the auto-auto arm and randomized to receive one year of maintenance therapy with thalidomide plus dexamethasone (Thal-Dex) or observation (Obs). Block 1:1 randomization was done at time of treatment assignment to auto-auto. Details of the statistical design are described by Logan et al.²⁰. Patients were classified as having standard risk disease after enrollment if their serum β -2 microglobulin was < 4.0 mg/L and no deletion of chromosome 13 was detected by metaphase karyotyping. Karyotype reports were reviewed centrally. Cytogenetic analysis by fluorescence in situ hybridization was not an eligibility prerequisite and not performed routinely at participating centers. Comparison of auto-allo and auto-auto in standard risk patients was the primary objective of the study. Post-enrollment risk stratification was performed to minimize referral bias as described in Logan et al.²⁰. Combined analysis of patients with high and standard risk disease was not pre-specified in the planned analysis.

There were two primary hypotheses to be tested in patients with standard risk myeloma: 1) does maintenance therapy improve outcomes after auto-auto transplantation; and, 2) does an auto-allo approach prolong progression-free survival (PFS) compared to an auto-auto approach.

Patients

Between December 17, 2003 and March 30, 2007, 710 patients with myeloma were enrolled after completion of initial therapy. Median follow up of the study population is 40 months (inter-quartile range 38–43 months). Entry criteria included: age ≤ 70 years, no disease progression after start of initial therapy, serum bilirubin $< 2 \times$ upper limits of normal, liver transaminases $< 3 \times$ upper limits of normal, left ventricular ejection fraction $> 40\%$, creatinine clearance > 40 ml/min and Karnofsky performance score $> 70\%$. All patients received at least three cycles of any initial systemic anti-myeloma therapy and were within ten months of initiation of this therapy. The type of induction therapy was not specified in the protocol. Patients were required to have 4×10^6 autologous CD34+ cells/kg available for infusion. Enrollment at each participating center started after review and approval of the protocol and informed consent by the Internal Review Board at each participating center.

Treatment

The study schema is outlined in Figure 1. Enrolled patients received melphalan 200mg/m² (Mel200) followed by autologous peripheral blood stem cell (PBSC) infusion 48 hours later. The day of first autoHCT was designated as day 0. Filgrastim was started at day +5 and continued until neutrophil recovery.

Recovery from autografting was defined as hematopoietic recovery, no active infections, resolution of mucositis and gastrointestinal symptoms, and being off hyperalimentation and intravenous hydration. Once recovered, and at least 60 days after the first autoHCT, patients received a second HCT, according to treatment arm. Those assigned to auto-allo received 200 cGy of total body irradiation in a single fraction followed by allogeneic PBSC infusion. The target cell dose for allografts was 2.0×10^6 CD34+ cells/kg. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and mycophenolate mofetil (MMF). MMF was discontinued on day +28 after alloHCT. In patients without active GVHD, cyclosporine was tapered starting at day +84. Chimerism and engraftment analyses were performed as previously outlined⁹. Standard infection prophylaxis was administered and CMV reactivation was monitored and treated with ganciclovir per institutional guidelines.

Patients without an HLA-matched sibling donor received a second autoHCT with Mel200 conditioning. Stem cell infusion was the same as with the first autoHCT. For patients randomized to Thal-Dex, thalidomide (200 mg/day) and dexamethasone (40 mg/day for 4 consecutive days, once a month) orally was started at least 60 days after the second HCT, with a goal of one year of therapy.

Endpoints

The primary endpoint of the clinical trial was three-year PFS in patients with standard risk disease. PFS was defined as time to disease relapse or progression, initiation of non-protocol anti-myeloma therapy or death, measured from the time of first auto-HCT, with patients censored at time of last contact. Supporting data for disease status and non-protocol anti-myeloma therapy during the trial were centrally reviewed by an outcome adjudication committee blinded to treatment assignment.

Secondary endpoints were overall survival, incidence of disease relapse or progression, treatment-related mortality, disease response, and incidence of grade 3–5 adverse events (Common Terminology Criteria for Adverse Event v3). Tertiary endpoints included incidence of acute and chronic GVHD, donor-recipient chimerism, and quality of life.

Definition of disease response utilized the International Uniform Response Criteria for myeloma assessment with the addition of a category of near complete response (nCR), defined as evidence of disease by immunofixation electrophoresis without morphologic evidence of bone marrow involvement by myeloma^{21–23}. Disease assessments were performed prior to first autoHCT, at time of second transplantation, and after second transplantation at eight weeks, six months, and every six months up to three years.

Statistical Analysis

Target enrollment was 150 patients with standard risk myeloma assigned to the auto-allo arm. It was estimated that the probability of having an available HLA-matched sibling donor was between 20% and 30%, so that 350 to 600 standard-risk patients would be enrolled on the auto-auto arm if the target auto-allo enrollment were met. This sample size would provide at least 80% power to detect a difference of 15% between auto-allo and auto-auto in the three-year probability of PFS, assuming a baseline probability of 45% PFS in the latter population.

Primary analysis was performed using the intent-to-treat principle, i.e., patients were classified according to their original assigned treatment, even if they did not receive all prescribed interventions. All outcomes were measured from the time of first autoHCT.

Analysis of the primary endpoint was planned to be performed in two steps. First, three-year PFS was compared between Thal-Dex and Obs using the pointwise difference in Kaplan-Meier estimates at three years. If no statistically significant difference was found, the two auto-auto groups were to be pooled and three-year PFS after auto-auto compared with auto-allo. Otherwise the superior arm of Thal-Dex and Obs would be compared with auto-allo. Survival distributions were estimated using the Kaplan-Meier method, while TRM, relapse/progression, acute and chronic GVHD were estimated using cumulative incidence. Groups were compared using pointwise differences in survival at three years or using Gray's test in cumulative incidence. To address concerns of covariate imbalance in a biologic assignment trial, we conducted a protocol-specified secondary analysis of PFS using a Cox proportional hazards model²⁴. This model was to include some or all of the following prospectively-defined variables, if their distribution differed ($p < 0.1$) between the auto-auto and auto-allo at baseline: $\beta 2$ microglobulin, Karnofsky Performance Status and age.

Monitoring for accrual and toxicity according to sequential probability ratio stopping guidelines was performed by the NHLBI-appointed Data and Safety Monitoring Board. First, the proportion of patients assigned to the auto-allo arm at each center was monitored as described in Logan et al.²⁰. Second, TRM was monitored, with the null hypotheses that the rate of six-month TRM was less than 5% after autoHCT and less than 20% after an alloHCT, and that the rate of nine-month TRM was less than 20% in subjects aged 65 years or older. Third, specific toxicities were monitored separately in each treatment arm, including deep vein thrombosis, sensory neuropathy, and cyclosporine-associated renal and hepatic toxicity. No boundaries for safety end points were triggered during the trial.

Unplanned post hoc analysis was performed to assess the impact of GVHD on relapse or progression in patients receiving allo-HCT. Development of chronic GVHD was analyzed as a time dependent covariate in a Cox regression model of disease relapse or progression.

Data were analyzed using statistical software SAS (v9.2, SAS Institute, Cary, NC) and R (v2.10.0).

Findings

Standard Risk Disease

Patients—Demographic information for all patients is depicted in Table 1. Imbalances between the auto-auto and auto-allo arms were found in age and race; patients in the auto-allo group were younger and more often Caucasian. Median times from first to second transplantation were 105 days (61–262 days) for auto-allo and 98 days (58–193 days) for auto-auto ($p=0.004$). A disease status prior to first autoHCT of very good partial response (VGPR) or better was observed in 41% (78/189) and 42% (185/436) of patients assigned to auto-allo and auto-auto, respectively ($p=0.678$). Compliance with second transplantation was 83% (156/189) and 84% (366/436) for auto-allo and auto-auto, respectively (Figure 1). Reasons for not undergoing second transplantation are shown in Table 2.

Maintenance Therapy—Fifty-nine patients (27%) randomized to Thal-Dex refused to start maintenance and 168 patients (77%) did not complete Thal-Dex. The cumulative incidence of premature maintenance discontinuation was 84%. Probabilities of three-year PFS and OS after first autoHCT of patients randomized to Thal-Dex maintenance were 49% (95% confidence interval [CI], 43–57%) and 80% (95% CI, 75–86%), respectively,

compared with 43% (95% CI, 37–50%, $p=0.080$) and 81% (95% CI, 75–86%, $p=0.817$) in the Obs group. Thal-Dex and Obs groups were combined into a single auto-allo arm for comparison with auto-allo. Among patients who tolerated Thal-Dex ($N=116$) the median time of maintenance therapy was 256 days (range 3 to 466 days).

Progression-Free and Overall Survival—Probabilities of three-year PFS were 43% (95% CI, 36–51%) and 46% (95% CI, 42–51%, $p=0.671$) after auto-allo and auto-auto, respectively (Figure 2A). Among the three pre-specified baseline variables, only age differed significantly between the arms and was included in a multivariate Cox regression analysis. The hazard ratio (HR) of treatment failure (death or relapse/progression), adjusted for age, for patients assigned to auto-allo versus auto-auto was 1.17 (95% CI, 0.94–1.46, $p=0.17$).

Probabilities of one, two and three-year OS were 91% (95% CI, 87–95%), 85% (95% CI, 80–91%) and 77% (95% CI, 72–84%) after auto-allo; and 95% (95% CI, 93–97%), 93% (95% CI, 86–92%) and 80% (95% CI, 77–84%, $p=0.191$) after auto-auto, respectively (Figure 2B).

Disease Progression/Relapse and Treatment-Related Mortality—Cumulative incidences of disease relapse or progression at three years were 46% (95% CI, 39–54%) and 50% (95% CI, 46–55%, $p=0.402$) after auto-allo and auto-auto, respectively (Figure 2C). Corresponding incidences of three-year TRM were 11% (95% CI, 7–16%) and 4% (95% CI, 2–5%, $p<0.001$) (Figure 2D).

Disease Response—Overall CR rates were 50% and 40% for the auto-allo and auto-auto groups, respectively ($p=0.03$) (Table 3). Rates of VGPR or better disease responses were 62% with auto-allo and 65% with auto-auto ($p=0.482$). Among patients not in CR prior to second transplantation ($n=415$), 48% and 35% of auto-allo and auto-auto patients upgraded their disease status to CR, respectively ($p=0.009$).

Overall Toxicities—Grade 3 to 5 toxicities were reported in 46% (87/189, grade 3, 41%; grade 4, 15%; grade 5, 6%) and 42% (185/436, grade 3, 36%; grade 4, 9%; grade 5, 5%) of auto-allo and auto-auto patients, respectively. Specific grade 3–5 toxicities at 1 and 3 years after the second transplant are shown in table 4. Grade 3 to 5 toxicities among patients in the auto-auto arm were similar except for grade 3 and 4 neuropathy of 18% (39/217) and 11% (24/219) reported in patients assigned to Thal-Dex and Obs, respectively.

Auto-Allo Chimerism Analyses—Ten patients (6.4%, 10/156) had graft failure after alloHCT. Two patients failed to engraft and eight had secondary graft failure. Six secondary failures occurred prior to day 100 and two by day 365. The median percentages of overall donor chimerism were 91%, 97%, 98%, 100%, and 100% at days 28, 56, 84, 180, and 365 after allo-HCT, respectively.

Auto-Allo Graft-versus-host Disease—Cumulative incidences of grades II–IV and III–IV acute GVHD at 100 days were 26% (95% CI, 19–33%) and 9% (95% CI, 4–14%), respectively. Cumulative incidences of chronic GVHD at one and two years were 47% (95% CI, 39–56%) and 54% (95% CI, 46–63%), respectively. The relative risk of disease relapse or progression was 0.44 (95% CI, 0.24–0.81, $p=0.008$) for patients with versus those without chronic GVHD. Among auto-allo recipients alive at six months post allo-HCT, those who developed chronic GVHD ($n=29$) in the first six months had a cumulative incidence of disease relapse or progression of 17% at three years post allo-HCT compared to 39% for patients who did not develop chronic GVHD by six months ($n=99$; $p=0.012$).

Causes of Death—Sixty (32%, 60/189) auto-allo patients and 108 (25%, 108/436) auto-auto patients died. The leading cause of death was myeloma, accounting for 37% (22/60) of auto-allo deaths and 72% (78/108) of auto-auto deaths. Other causes in the auto-allo group were organ failure (20%), infection (17%), GVHD (13%), idiopathic pneumonia syndrome (5%), acute respiratory distress syndrome (3%), graft failure (2%), and other causes (3%). In the auto-auto group, other causes were organ failure (14%), infection (2%), other causes (8%), and unknown causes (4%).

High Risk Disease

Table 1 depicts demographics of patients with HR disease. Patients in the auto-allo group were younger. PR was the most frequent disease status at study entry in both treatment arms. Probabilities of three-year PFS were 40% (95% CI, 27–60%) and 33% (95% CI, 22–50%, $p=0.743$); and corresponding probabilities of OS were 59% (95% CI, 45–78%) and 67% (95% CI, 54–82%, $p=0.460$) after auto-allo and auto-auto, respectively (Figure 3A,3B). Cumulative incidences of disease relapse or progression at three years were 38% (95% CI, 22–54%) and 57% (95% CI, 42–71%, $p=0.079$) after auto-allo and auto-auto, respectively. Corresponding incidences of three-year TRM were 22% (95% CI, 8–35%) and 11% (95% CI, 2–19%, $p=0.311$).

Interpretation

In this trial of autoHCT followed by alloHCT using a non-myeloablative conditioning regimen in patients with SRD, we demonstrate no benefit of this approach in three-year PFS or OS compared to auto-auto. There was indirect evidence of a graft-vs.-myeloma effect with a 60% reduction in the risk of relapse in patients diagnosed with chronic GVHD. TRM was significantly higher in the auto-allo group (11% vs. 4%), despite use of a non-myeloablative conditioning regimen. This was largely due to GVHD and infections. There was no statistically significant difference in the risks of progression or relapse between the two groups. Although VGPR and better responses were similar in both arms, a larger proportion of patients in the auto-allo group upgraded their response to a CR. Differences in toxicities and causes of death are inherent to the transplant approach. AlloHCT recipients experienced more complications related to organ dysfunction and immune deregulation as a result of the use of chronic immunosuppression and the development or treatment of GVHD. AutoHCT recipients experienced more neuropathy related to thalidomide use. Additional analysis comparing quality of life assessments between treatment arms is planned for a subsequent publication of this study.

We observed no benefit to maintenance therapy in this trial, but since compliance with Thal-Dex was poor, definitive conclusions about the role of Thal-Dex maintenance cannot be drawn. Earlier trials demonstrated benefit of thalidomide maintenance on survival outcomes^{4, 25, 26}, but compliance with maintenance was also a challenge in those trials. In fact, the IFM 99-02 trial in which most patients were not exposed to thalidomide at induction, 39% of patients discontinued thalidomide due to toxicity. The median time of thalidomide maintenance in the IFM99-02 was 15 months, similar to BMT CTN 0102⁴. Hence, presumable prior thalidomide related neuropathy could in part be a reason for a higher rate of noncompliance in the BMT CTN 0102.

This was a biologic assignment rather than a randomized trial and several measures were used to minimize selection bias²⁰ including: separation of the cohort by disease risk; planned multivariate analysis adjusting for pre-specified demographic characteristics; and, active monitoring of auto-allo enrollment at each center. Despite limitations of biologic assignment trials, both groups were comparable, and adjusted and unadjusted comparisons of the primary endpoint yielded similar results. It is noteworthy that separation according to

disease risk after enrollment indeed resulted in a more balanced ratio of donor vs. no donor cohorts in the SRD compared to HRD.

Three similar biologic assignment trials have compared auto-allo with auto-auto HCT approaches in myeloma^{15, 16}. Bruno et al. demonstrated superior event-free survival (EFS) and OS in 58 and 46 recipients of auto-allo and auto-auto, respectively^{15, 17}. Biologic assignment in this trial was performed in patients with siblings. However, of note, there was a fairly high drop out rate with ultimately only 46 of 82 patients in the auto-auto arm completing two transplants. Superiority of the auto-allo arm in this trial could be attributed to small number of patients at risk beyond 2 years. In addition, the second transplant conditioning regimen consisted of varying doses of melphalan down to as low as 100mg/m². This may in part be the reason for the low CR rate of 26% in the auto-auto arm. In the Spanish Group trial (PETHEMA), biologic assignment occurred after the first transplant in patients not in CR or nCR (n=110) and 25 patients received an alloHCT¹⁶. Median EFS and OS were similar in the allo-auto and auto-auto arms. Bjorkstrand et al¹⁸ showed longer PFS and OS with auto-allo approach using a combination of fludarabine and TBI 200cGy in patients followed beyond three years. Outcomes in autoHCT arm appear inferior to the BMT CTN 0102 trial at 48 months, possibly due to a combination of single and tandem autoHCT as the control arm, and inclusion of patients with high risk disease as defined in the BMT CTN 0102 trial. Additionally, in the “as treated” analysis among 91 recipients of auto-allo, overall survival was similar to the autoHCT arm.

Differences in EFS observed in the Italian Group trial occurred after 30 months. CR rates were higher in the auto-allo arm in both the Italian Group¹⁵ and BMT CTN trial; and thus longer follow-up of patients treated on BMT CTN 0102 is important in order to assess whether the observed differences in CR rates will translate into better long-term survival, as shown in other myeloma trials^{1, 3, 18}.

The French Group (IFM) ran two parallel phase II trials in patients with high-risk myeloma, defined by deletion of chromosome 13 or β -2 microglobulin > 3 mg/L. IFM99-03 analyzed patients with available HLA-match sibling donors who received an alloHCT with reduced intensity conditioning (n=65) after an autoHCT. Outcomes of these patients were compared to patients enrolled in IFM99-04 (n=219), an auto-auto trial. Similar to BMT CTN 0102, EFS and OS were not significantly different for patients receiving auto-allo and auto-auto in the IFM trials²⁷. The transplant related mortality of 10.9% was also similar to BMT CTN0102, however, the relapse or progression rate was strikingly high at 56.5% in the auto allo group. Despite the definition of HRD in the BMT CTN 0102 not including most recent cytogenetic markers of poor prognosis, patients with HRD experienced worse outcomes than patients with SRD. Although limited by small number of patients, the comparison in HRD group demonstrated similar survival outcomes.

In conclusion, with three years of follow-up, we observed no improvement in PFS or OS in patients with standard-risk myeloma assigned to auto-allo HCT vs. auto-auto HCT. Disease relapse remains a major problem in both groups suggesting that additional pre and post transplant therapies to reduce the risk of relapse are warranted^{28–30}. The results of the BMT CTN 0102 trial is the largest trial to address the role of alloHCT in standard risk myeloma and lack of superiority compared to an auto-auto approach should be part of the treatment decision discussions with patients. Nonetheless, this trial offers glimpses of the anti-tumor activity of the alloHCT approach as seen in the reduced risk of relapse in patients with chronic graft GVHD. Further improvements in alloHCT to reduce TRM and/or augment GVM will prompt future investigation.

Research in Context

The main objective of this trial was to assess the role of an auto-allo as part of upfront treatment of myeloma in patients with standard risk disease. The investigational auto allo arm was demonstrated to be feasible and demonstrated initial promising results (Maloney et al, Blood 2003). The most appropriate comparative treatment arm was the auto-auto based on the data from the French Group (IFM) which demonstrated an improvement in progression free survival with tandem transplants using melphalan 200mg/m² as a conditioning regimen compared to a single auto transplant. (Attal et al, NEJM 2003). During the same period, data on the use of thalidomide was maturing, which suggested a role of maintenance of this drug. Early observation from investigators from the IFM group demonstrated that it was feasible to administer thalidomide post transplant and that it was well tolerated in the maintenance setting (Attal et al, Blood 2006). Additionally, during clinical trial development, data from the Center for International Blood and Marrow Transplant Research (CIBMTR) was used to assess the number of transplants performed in the most active US centers to target participation and analyze the expected outcomes of patients who would fulfill the anticipated trial eligibility criteria.

Other trials addressing the role of auto-allo were recently reported. The Italian group randomized all patients with available sibling donors but there was a significant drop out of patients from enrollment to time of starting intervention. This trial demonstrated an event free and overall survival benefit of the auto-allo approach, although the overall number of patients who received both interventions was small (Bruno B. et al NEJM 2005). The Spanish group also published their results of auto-allo approach compared to auto-auto and despite improvement in time to progression, no survival benefit was identified in with the auto-allo approach. Again the number of patients was small, , in the Spanish trial only 25 patients were assigned to the auto-allo arm (Rosignol et al, Blood 2008). Most recently the European Blood and Marrow Transplant group (EBMT) trial updated their long term results, which with a median follow up of 61 months demonstrated a superiority of the auto-allo approach over single or tandem auto. (Bjorkstrand B et al, JCO 2011). This study analyzed patients irrespective of disease risk and differences in survival outcomes did not emerge till beyond 24 months. Although, the overall survival benefit in the auto-allo arm was minimized in the as treated analysis there was a highly significant benefit in risk reduction over time in the auto allo arm. Thus this question remains controversial. However, the current BMT CTN trial is the largest to date to address this question, and it shows that an auto-allo approach is not different from an auto-auto one among patients with standard risk myeloma. The BMT CTN 0102 trial is the definitive trial which demonstrates that the auto-allo approach is not different than the auto-auto approach for patients with standard risk myeloma. Clinicians should discuss BMT CTN 0102 results with patients and the decision to proceed with allogeneic transplant in patients with standard risk disease should be carefully considered. Additional implications of these results include development of studies with focus to explore GVM and reduction of TRM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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*The role of the sponsors in the study design.

NHLBI statisticians are members of the protocol team and assisted in the development of the study design.

*The role of the sponsors in the collection, analysis, or interpretation of the data.

NHLBI and NCI had access to data presented to the Data and Safety Monitoring Board.

*The role of the sponsors in the writing of the report.

NHLBI revised and offered in input to this manuscript.

*Those who had access to the raw data (by author initials).

MCP, BL, and JW

The corresponding author had full access to all of the data and the final responsibility to submit for publication.

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APPENDIX

A-1 – List of participating transplant centers

Baylor College of Medicine/The Methodist Hospital
Blood & Marrow Transplant Program at North side Hospital
City of Hope National Medical Center
City of Hope Samaritan
Dana Farber Cancer Institute/Brigham & Women's Hospital
Duke University Medical Center - Adult BMT
Emory University
Fox Chase - Temple University - BMT Program
Fred Hutchinson Cancer Research Center
Hackensack University Medical Center
Indiana BMT at Beech Grove
Jewish Hospital BMT Program
Loyola University Medical Center
Medical College of Wisconsin
Memorial Sloan-Kettering Cancer Center
Oregon Health & Science University
Rocky Mountain BMT Program
Scripps Clinic/Green Hospital
Stanford Hospital and Clinics
Texas Transplant Institute
Tufts Medical Center
University of California San Diego Medical Center
University Hospitals of Cleveland/University Hospitals Case Medical Center
University of Alabama at Birmingham
University of Florida College of Medicine (Shands)
University of Kansas Hospital
University of Michigan Medical Center
University of Minnesota
University of Nebraska Medical Center
University of Oklahoma Medical Center
University of Pennsylvania Abramson Cancer Center

University of Texas/MD Anderson Cancer Research Center
University of Wisconsin Hospital & Clinics
University of Utah Medical School
Vanderbilt University Medical Center/VA Tennessee Valley Healthcare System
Virginia Commonwealth University MCV Hospitals
Wichita CCOP

Figure 1.

Study schema outlying the number of patients at each step of the trial.

*Primary analysis of the clinical trial focused on patients meeting protocol criteria of standard risk multiple myeloma. Biologic assignment occurred when HLA-typing results were available after enrollment. Randomization to Thal/Dex or Observation occurred once patients were assigned to auto-auto group. Abbreviations: Mel200, melphalan 200mg/m²; TBI; total body irradiation; Thal/Dex, thalidomide and dexamethasone.

Figure 2A

Figure 2B

Figure 2C

Figure 2D

Figure 2.

Figure 2A: Progression-free survival of standard risk auto-auto and auto-allo groups

Figure 2B: Overall survival of standard risk auto-auto and auto-allo groups.

Figure 2C: Cumulative incidence of disease progression or relapse for standard risk auto-auto and auto-allo groups.

Figure 2D: Cumulative incidence of transplant-related mortality for standard risk auto-auto and auto-allo groups.

Figure 3A

Figure 3B

Figure 3.

Figure 3A: Progression-free survival of high risk auto-auto and auto-allo groups

Figure 3B: Overall survival of high risk auto-auto and auto-allo groups.

Table 1
Demographic characteristics of patients with multiple myeloma with standard risk disease enrolled in the BMT CTN 0102.

	Standard Risk			High Risk		
	Auto-Auto N (%) (n=436)	Auto-Allo N (%) (n=189)	P-value ¹	Auto-Auto N (%) (n=48)	Auto-Allo N (%) (n=37)	P-value ¹
Male	260 (63)	111 (59)	0.833	27 (56)	21 (57)	0.963
Median Age	55 (22–70)	53 (29–68)	0.006	57 (32–70)	51 (32–66)	0.012
Race			0.032			0.458
African American	77 (18)	18 (10)		8 (17)	3 (8)	
Caucasian	335 (77)	161 (85)		38 (79)	33 (89)	
Other	24 (5)	10 (5)		2 (4)	1 (3)	
Performance Score 90	334 (77)	148 (78)	0.642	27 (56)	26 (70)	0.186
β-2 Microglobulin, median	2.0	2.0	0.949	4.4	3.7	0.035
Durie-Salmon			0.739			0.702
Stage I-II	142 (33)	59 (31)		10 (21)	9 (24)	
Stage III	294 (67)	130 (69)		38 (79)	28 (76)	
Interval from diagnosis to transplantation, median in months (range)	7 (3–55)	7 (4–35)	0.925	7 (5–22)	7 (3–38)	0.683
Disease Status ^{2,3}			0.678			0.028
CR	41 (10)	24 (13)		1 (2)	3 (8)	
Near CR	65 (15)	22 (12)		1 (2)	2 (5)	
Very Good PR	79 (19)	32 (17)		1 (2)	7 (19)	
PR	158 (37)	76 (40)		21 (44)	14 (38)	
MR	31 (7)	17 (9)		10 (21)	3 (8)	
SD	21 (5)	6 (3)		6 (13)	4 (11)	
Not Evaluable ⁴	30 (7)	12 (6)		8 (17)	4 (11)	
Interval from first to second transplantation, median in days (range)	98 (58–193)	105 (61–262)	0.004	101 (63–155)	111 (61–155)	0.397

¹ P-values of treatment arm characteristics shown after biologic assignment.

²Disease status at time of first autologous transplantation represents the result from initial multiple myeloma therapy received prior to trial enrollment.

³Details of induction regimens were not collected.

⁴Not evaluable are cases without available comprehensive disease assessment at time immediately prior to initial multiple myeloma therapy. Abbreviations: auto-allo, autologous followed by allogeneic hematopoietic cell transplantation; auto-auto, double autologous hematopoietic cell transplantation; CR, complete response; MR, minimal response; PR, partial response; SD, stable disease.

Table 2

Reasons for not proceeding to second transplantation or maintenance therapy among patients with standard risk disease enrolled in the BMT CTN 0102 trial.

	Auto-Auto	Auto-Allo
Total assigned	436	189
Total not receiving 2 nd transplantation	70 *	33
Reasons for no 2nd transplantation		
Adverse Event (grade 3–5)	4 (6%)	1 (3%)
Death	4 (6%)	1 (3%)
Progression/Relapse	10 (14%)	6 (18%)
Insurance Coverage denied	2 (3%)	0
Inadequate physical recovery from first transplant	2 (3%)	2 (6%)
Patient refused/withdrew consent	43 (61%)	19 (58%)
Other reasons ^I	4 (6%)	4 (12%)
Reason Unknown	1 (<1%)	0

* One patients assigned to auto-auto group did not receive the first transplant due to disease progression

^I Auto-auto: Nocardia infection, physician decision (n=3). Auto-Allo: Donor failed to mobilized sufficient cell dose according to protocol, cardiac amyloidosis diagnosed after the first transplant, psychosocial issues, donor deemed not medically eligible to donate.

Table 3

Best disease responses in patient with standard risk disease by treatment arm.

		Complete Responses						Very Good Partial Responses and Better*			
Time	Population	N	Auto/Auto N (%)	N	Auto/Allo N (%)	P-values	N	Auto/Auto N (%)	N	Auto/Allo N (%)	P-values
1 st HCT	All Patients (N=625) ¹	436	175 (40%)	189	94 (50%)	0.026	436	285 (65%)	189	118 (62%)	0.482
	Patients not in CR (N=560) ²	395	142 (36%)	165	74 (45%)	0.049	395	252 (64%)	165	98 (59%)	0.327
2 nd HCT	All Patients (N=522) ³	366	164 (45%)	156	90 (58%)	0.007	366	272 (74%)	156	113 (72%)	0.655
	Patients not in CR (N=415) ⁴	295	102 (35%)	120	58 (48%)	0.009	295	210 (71%)	120	81 (68%)	0.457

¹ Include all patients with standard risk disease enrolled in the trial.

² Subset of patients with less than complete response (CR) at study entry.

³ Subset of patients who received a second transplant.

⁴ Subset of patients who received a second transplant and who were not in complete remission immediately prior to the second transplant.

* Very good partial response (VGPR) includes VGPR near complete response and complete responses.

Table 4Specific Grade 3–5 toxicities by treatment arm after second transplant¹.

	1 year		3 years	
	Auto-Auto (%)	Auto-Allo (%)	Auto-Auto (%)	Auto-Allo (%)
Abnormal Liver Enzymes	11 (2.5)	9 (4.8)	25 (5.7)	17 (9.0)
Ataxia	1 (0.2)	3 (1.6)	1 (0.2)	3 (1.6)
Capillary Leak Syndrome ²	0 (0)	4 (2.1)	0 (0)	4 (2.1)
Cardiac Arrhythmias	7 (1.6)	2 (1.1)	7 (1.6)	2 (1.1)
Deep Vein Thrombosis	14 (3.2)	7 (3.7)	14 (3.2)	7 (3.7)
Dyspnea	25 (5.7)	17 (9.0)	56 (12.8)	35 (18.5)
Hemorrhage	1 (0.2)	1 (0.5)	1 (0.2)	1 (0.5)
Hemorrhagic Cystitis	2 (0.5)	3 (1.6)	7 (1.6)	4 (2.1)
Hyperbilirubenemia ²	9 (2.1)	20 (10.6)	14 (3.2)	21 (11.1)
Hyperglycemia ²	20 (4.6)	20 (10.6)	20 (4.6)	20 (10.6)
Hypertension ²	10 (2.3)	17 (9.0)	10 (2.3)	17 (9.0)
Hypotension	12 (2.8)	8 (4.2)	12 (2.8)	8 (4.2)
Hypoxia	19 (4.4)	12 (6.4)	41 (9.4)	23 (12.2)
Left Ventricular Dysfunction	2 (0.5)	3 (1.6)	2 (0.5)	3 (1.6)
Mucositis ²	32 (7.3)	4 (2.1)	32 (7.3)	4 (2.1)
Peripheral Motor Neuropathy	10 (2.3)	6 (3.2)	23 (5.3)	17 (9.0)
Peripheral Sensory Neuropathy ²	33 (7.6)	4 (2.1)	52 (11.9)	11 (5.8)
Seizures	1 (0.2)	0 (0)	1 (0.2)	0 (0)
Somnolence	6 (1.4)	7 (3.7)	6 (1.4)	7 (3.7)
Thrombotic Microangiopathy	1 (0.2)	2 (1.1)	1 (0.2)	2 (1.1)

¹Toxicities observed from day 0 of second transplant to 1 year and 3 years.²Indicates significant difference between the two treatment arms (p<0.05).