Long-term follow-up of CALGB (Alliance) 100001: Autologous followed by non-myeloablative allogeneic transplant for multiple myeloma

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Abstract

CALGB (Alliance) 100001 was a phase II study evaluating autologous stem cell transplant (ASCT) followed by non-myeloablative allogeneic stem cell transplant (alloSCT) in patients with multiple myeloma who had received no more than 18 months of prior therapy and had experienced no more than one prior progression event. Conditioning for ASCT was with high-dose melphalan (200 mg/m$^2$). The alloSCT reduced-intensity conditioning (RIC) regimen consisted of fludarabine (30 mg/m$^2$/day IV on days −7 through −3) and cyclophosphamide (1 g/m$^2$/day IV on days −4 through −3). The primary objective was to determine the six-month post-alloSCT treatment-related mortality (TRM) rate. Additional objectives included determining the proportion of patients who could complete this tandem ASCT-alloSCT approach in a cooperative group setting, overall response rates, rates of donor chimerism, rates of graft-versus-host (GVHD), disease-free survival (DFS) and overall survival (OS). Sixty patients were enrolled, of which 57 (95%) completed ASCT and 49 (82%) completed tandem ASCT-alloSCT. The TRM rate was 2% (1/49, 90% CI 0.10-9.3%). Moderate to severe (grade 2-3) acute GVHD was observed in 13 of 49 alloSCT patients (27%). One patient died due to GVHD within 9 months of alloSCT. Twenty-seven of the 49 patients (55%) who underwent alloSCT reported chronic GVHD as either limited (15/49; 31%) or extensive (12/49; 24%) in the first year post-alloSCT and prior to the start of non-protocol therapy for progressive disease. With a median follow-up for survival of 11 years, the median OS time is 6.6 years and the median time to disease progression is 3.6 years. Similar to other studies, this study confirmed that tandem ASCT/alloSCT is associated with durable disease control in a subset of patients. This study demonstrated the feasibility of performing tandem ASCT/alloSCT in a cooperative group setting and determined that a fludarabine/cyclophosphamide RIC regimen is associated with a very low TRM rate.

Keywords
multiple myeloma; autologous stem cell transplant; allogeneic stem cell transplant; reduced-intensity conditioning

Introduction

Multiple myeloma remains an incurable disease even with recent advances in the treatment that have included the introduction of immunomodulatory drugs (IMiDs), proteasome inhibitors (Pis), anti-CD38 monoclonal antibodies as well as emerging therapies such as chimeric antigen receptor (CAR) T-cell therapy. Autologous hematopoietic stem cell transplantation (ASCT) after induction therapy has become a standard component of upfront therapy for the transplant-eligible myeloma patient. Despite this approach, the vast majority of patients will relapse or develop progressive disease (PD) and require salvage therapy.
There has been significant interest over the past several decades in determining whether further consolidation with either a second ASCT ("tandem ASCT")\textsuperscript{2-6} or tandem ASCT-alloSCT\textsuperscript{7-16} results in improved long-term outcomes.

Prior reports have shown that myeloablative alloSCT resulted in high treatment-related mortality (TRM).\textsuperscript{17,18} However, reduced intensity conditioning (RIC) has led to lower TRM but may result in higher relapse rates when compared to myeloablative alloSCT.\textsuperscript{19} RIC regimens have been primarily fludarabine-based including fludarabine + total body irradiation (TBI), fludarabine + melphalan, and fludarabine + busulfan.\textsuperscript{19} Non-relapse mortality (NRM) rates for these regimens have ranged from 2-28%.\textsuperscript{20-23}

Cancer and Leukemia Group B (CALGB) designed this phase II tandem ASCT/alloSCT to determine if myeloablative ASCT followed by RIC alloSCT could generate long-term disease control similar to myeloablative alloSCT but without the high TRM. In addition, this study was designed to determine whether the tandem ASCT/alloSCT approach could be given to more than 70% of patients enrolled in a cooperative group setting. CALGB is now part of the Alliance for Clinical Trials in Oncology. In this study, we demonstrate that a tandem ASCT/alloSCT approach utilizing a RIC regimen of fludarabine and cyclophosphamide is feasible and associated with a low TRM. We report the long-term follow-up data from this study.

Materials and Methods:

Eligibility and enrollment

CALGB (Alliance) 100001 enrolled patients 18 to 64 years of age with histologically confirmed Durie-Salmon stage I-III active multiple myeloma requiring treatment and for whom an HLA-identical sibling donor by serologic typing (A, B, DR) meeting institutional standards for marrow or stem cell donation was identified. Additional eligibility criteria included: no more than 12 months of prior alkylating therapy, no more than 18 months of all prior therapy; no more than one prior progression after initial therapy, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-1, adequate liver function and renal function tests (total bilirubin and creatinine < 2 mg/dL; total AST and ALT < 3 x institutional upper limit of normal; creatinine clearance [by Cockcroft-Gault method] > 40 cc/min); adequate hematologic function (absolute neutrophil count [ANC] > 500/μL; platelet count [PLT] > 50,000/μL); diffusing capacity of the lung for carbon monoxide (DLCO) > 40% of predicted without symptomatic pulmonary disease; and left ventricular ejection fraction (by MUGA) ≥ 30%. Exclusion criteria included: chemotherapy, radiation, or surgery within 4 weeks of registration; uncontrolled diabetes mellitus, active serious infection; HIV infection/disease; pregnancy, or breast feeding. Supplemental Table 1 shows all of the eligibility criteria. Each participant signed an IRB-approved protocol-specific informed consent document in accordance with federal and institutional guidelines.

Study Treatment Course

Peripheral blood stem cell (PBSC) mobilization for ASCT consisted of cyclophosphamide (4 g/m\textsuperscript{2}) on day 1 and G-CSF (10 μg/kg/day) starting on day 5 until PBSC collection was
completed. PBSC collection began when the white blood cell count was > 5000/μL. PBSC collection was continued until >2 x 10^6 CD34+ cells/kg body weight were obtained. Levofloxacin (or equivalent) and fluconazole were started on day +5 and continued until ANC >500/μL.

Autologous stem cell transplant: ASCT was to begin 2-4 weeks after PBSC collection ended. Melphalan (200 mg/m2 IV) was administered day −2, two days prior to infusion of thawed cryopreserved PBSC (day 0). G-CSF was given starting on day +5 post-ASCT and continued until count recovery (ANC ≥1500/μL for two days or ANC ≥5000/μL for one day). Levofloxacin (or equivalent) and fluconazole were started on day +2 and continued until ANC >500/μL.

Allogeneic stem cell transplant: Patients were eligible to undergo alloSCT within 2 to 4 months of ASCT if they had recovered from any infection or stomatitis, their serum creatinine was <2 mg/dL, bilirubin <2 mg/dL and 1.0 x 10^7 CD3+ cells/kg body weight was collected from their HLA-identical sibling donor. The conditioning regimen consisted of fludarabine, 30 mg/m^2/day x 5 days IV on days −7 through −3 and cyclophosphamide 1 g/m^2/day x 2 days IV on days −4 through −3. Allogeneic G-CSF-mobilized peripheral blood donor cells were infused on day 0. Graft-versus Host Disease (GVHD) prophylaxis consisted of tacrolimus given from day −1 to day +90 then tapered off by day +150 if no significant GVHD. The whole blood tacrolimus target level was 5-10 ng/mL. Tacrolimus was tapered more quickly (day +60 to day +90) if the donor CD3 T cell chimerism was <50% at day +60 or if disease was non-responsive. Methotrexate was given at 5 mg/m^2/day IV on days +1, +3, and +6. G-CSF was started on day +7 and was continued until the ANC was >1000/μL for three consecutive days. Supportive medications included trimethoprim/sulfamethoxazole (twice daily two days per week starting on day −3 through day +100), acyclovir (200-400 mg TID day −3 through day +100) and fluconazole (or other standard of care anti-fungal agent, day +1 through day +100).

Patients with PD and no evidence of GVHD prior to day +60 were tapered off tacrolimus as tolerated. In the case of no evidence of active GVHD, donor lymphocyte infusions (DLI) were allowed 30 days after complete cessation of GVHD prophylaxis treatment. The protocol specified that the first DLI should be 1 x 10^7 CD3+ cells/kg while the second and third infusions should be 5 x 10^7 CD3+ cells/kg.

**Tests and Procedures while on protocol treatment**

Patients were assessed serially during the study for toxicity (using CTCAE v. 2.0) and disease response (European Blood and Marrow Transplant (EBMT) response criteria\textsuperscript{24}). As dictated by the protocol, patients underwent history and physical exams, with assessment of performance status, laboratory assessments including liver function tests, renal function tests and complete blood counts, drug level monitoring, serum and urine protein studies and quantitative immunoglobulin studies within 14 days of study registration, prior to ASCT, post-ASCT, prior to alloSCT, post-alloSCT at 3, 6, 9, 12, 24, and 36 months, and pre- and 90 days post-DLI. Chimerism analysis on peripheral blood samples was performed on donor and recipient prior to registration as well as on the recipient on days +30, +60, +90, +120, +180. During the 30-day post-alloSCT period, physical examinations and toxicity
assessments were performed weekly and blood tests (complete blood counts, renal function and liver function tests) were obtained twice weekly. GVHD assessments were carried out at the post-alloSCT evaluations (3, 6, 9, 12, 24, and 36 months). Grading scales for acute and chronic GVHD are shown in Supplemental Tables 2.1-2.3.

**Statistical considerations**

The primary objective of this clinical trial was to determine whether ASCT followed by non-myeloablative alloSCT had a 6-month post-alloSCT mortality rate (TRM) of no more than 20%. A one-stage phase II clinical trial design with a one-sided significance level of 0.10 and power of 0.90 was chosen to assess whether the 6 month post-alloSCT TRM was more than 40% against the alternative that it was less than 20%. An interim analysis was planned after the first 18 patients had been followed until death or a minimum of 6 months post-alloSCT. The study was designed such that if 7 or more of these 18 patients had died due to treatment, the trial would then cease all enrollment. Otherwise, an additional 32 patients were to be enrolled. A 90% confidence interval for the TRM rate was calculated using the Duffy-Santner method to account for the sequential nature of the testing. An additional primary objective was to determine whether ASCT followed by alloSCT could be given to more than 70% of patients enrolled in a cooperative group trial. Secondary endpoints included tumor response, progression free survival (PFS) and overall survival (OS). Tumor response was assessed by the treating institution using EBMT response criteria over the course of the study and then retrospectively by two of the authors (SAH and PLM) utilizing the International Myeloma Working Group (IMWG) response criteria. An estimate of the cumulative incidence function for disease progression was obtained where the event of interest was disease progression (by EBMT criteria) and the competing event was the initiation of non-protocol treatment. OS was defined as the time from registration to death due to any cause and estimated using the Kaplan-Meier method. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. All analyses were based on the study database frozen on June 6, 2018. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

**Results**

Sixty patients were enrolled between March 2002 to March 2008. The study was closed out a number of local IRBs during the merger of CALGB and North Central Cancer Treatment Group (2011-2014) and then the remaining sites were officially closed in June 2018. Therefore, no further queries could be made prior to completion of the analyses presented here. As shown in the CONSORT diagram (Figure 1), eligibility could not be confirmed for two patients and one patient withdrew consent prior to initiating protocol treatment. The remaining 57 patients proceeded to ASCT, and of these, 49 (86%) completed the planned tandem ASCT-alloSCT.

Reasons for not proceeding to alloSCT on study included patient refusal (n=4), non-protocol therapy (n=2; one patient received pomalidomide and dexamethasone and one chose to undergo alloSCT at a non-affiliated institution), unresolved toxicity from ASCT (n=1) and
death due to heart attack or pulmonary embolism (n=1). The demographic and disease characteristics are shown in Table 1. Cytogenetic and/or FISH results from diagnostic bone marrow biopsies were available for only a small number of patients (Supplemental Table 3). Of those with reported abnormalities, the majority included complex karyotypes, with one patient noted to have del(17p) on cytogenetics and FISH. More patients had cytogenetic and/or FISH results from their on-study (post-induction) bone marrow biopsies, however the majority had normal results (Supplemental Table 4). No high-risk abnormalities were reported in the on-study bone marrow biopsies.

**Engraftment and Toxicity:**

All 57 patients had peripheral blood count recovery after ASCT. The median time to neutrophil engraftment following ASCT (defined as >0.5 cells x 10^9/L) was 11 days (n: 46, range: 7-20 days) and the median time to platelet recovery (defined as >20 x 10^9/L) was 11.5 days (n: 42, range: 7-32 days). Two patients did not have toxicity evaluations performed post-ASCT. The most common severe (grade 3-5) adverse events reported post-ASCT among the remaining 55 patients included: ANC decrease (n=52, 94.5%), platelet decrease (47, 85.5%), febrile neutropenia (17, 30.9%), and serum phosphate decrease (12, 21.81%). Table 2 presents all grade ≥2 toxicities reported post ASCT.

Among the 49 patients who underwent alloSCT, the median time between ASCT and alloSCT was 3.2 months (range 2.2-10.0 months). The median number of CD34+ cells infused was 5.1 x 10^6/kg (n: 49, range: 1.8-18.9 x 10^6/kg) and the median number of CD3+ cells infused was 21.7 x 10^6/kg (n: 38, range: 0.6-62.1 x10^6/kg). All patients engrafted. The median time to neutrophil engraftment following alloSCT was 11 days (n: 45, range: 7-16 days) and the median time to platelet recovery was 11 days (n: 15, range: 9-15 days).

Table 2 presents all grade ≥2 toxicities post alloSCT. The (grade 3-5) adverse events reported post-alloSCT included: ANC decrease (39, 79.6%), platelet decrease (21, 42.9%), and leukocyte decrease (6, 12.2%). In total, 21 patients (43%) were reported to have acute GVHD (organ stage ≥1), with overall grades of 1 (n=8, 16%), 2 (n=6, 12%) or 3 (n=7, 14%) (using the grading systems shown in Supplemental Tables 2.1 and 2.2). There were no grade 4 cases reported. Supplemental Table 5 shows the organ stage and overall grade of acute GVHD by patient. There were 27 patients (57%) reported to have chronic GVHD, as either limited (n=15) or extensive (n=12) in the first year post-alloSCT (but prior to the start of non-protocol therapy, if applicable). One patient died due to GVHD within 9 months post-alloSCT. One patient was reported to have limited GVHD in the first year post-alloSCT after starting non-protocol therapy.

T cell, B cell, myeloid and unfractionated chimerism testing in peripheral blood was performed at 30, 60, and 90 days post-alloSCT and from bone marrow at 90 days post-alloSCT (Table 3). The median donor chimerism was 90% or greater in all cell fractions at all three time points in peripheral blood and in bone marrow. During the first 90 days post-transplant, the goal of 90% was not reached for CD3 for 7 patients (n=41; 17%); CD14/15 for 11 patients (n=41; 27%); and for whole blood/bone marrow for 12 patients (n=41; 29%).

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Eight patients received at least one DLI prior to the initiation of non-protocol therapy. The reasons DLI was administered included: stable disease (63%), PD (25%) or not stated (13%).

Seven patients were reported to have second primary malignancies (SPMs), including two hematological malignancies, one astrocytoma and four skin cancers (one basal cell carcinoma, two squamous cell carcinomas, and one melanoma in situ). The hematological SPMs included a B-cell acute lymphoblastic leukemia and a B-cell lymphoproliferative disorder. The latter was classified as a post-transplant lymphoproliferative disorder, however the pathology report indicated that this was chronic lymphocytic leukemia that was of donor origin. Details regarding the patient and SPM characteristics are shown in Supplemental Table 6.

**Disease response:**

The disease responses post-ASCT, day 100 post-alloSCT and best overall (as reported by the treating clinician using EBMT criteria) are shown in Table 4. Rates of partial response (PR) or better were achieved by 61% (35/57) of patients in the post-ASCT period and 65% of patients (32/49) in the post-alloSCT period. Approximately 40% (18/49) of patients were reported to have achieved a complete response (CR) as the best response post-alloSCT. Supplemental Table 7 shows the centrally reviewed responses using IMWG criteria.

**Progression and Overall Survival:**

At the time of the data lock, patients had been followed until death or a minimum of 3.3 years (median: 11 years; maximum: 14 years). Disease progression was documented in 37 patients. Five of the progressions had occurred in patients who had received non-protocol treatments. The median time to disease progression was 3.6 years (Figure 2). For those patients who received salvage therapy at time of relapse post-alloSCT, the majority received lenalidomide-, bortezomib-, or thalidomide-based therapies (Supplemental Table 8). Thirty patients have died. The reported causes of death were progressive myeloma (n=16, 53%), sepsis/infection (n=5, 17%), cardiopulmonary failure (n=4, 13%), gastrointestinal GVHD (n=1, 3%), grade 4 glioma (n=1, 3%) and unknown causes (n=3, 10%). The median OS time is 6.6 years (Figure 3). The six-month TRM rate was 2% (n=1, 90% CI 0.10-9.3%). This patient progressed at day 100 post-alloSCT, began bortezomib salvage therapy, was not reported to have GVHD and died two months later due to sepsis. Of the other four patients who died of sepsis/infection, one did so 13 months after alloSCT (para-influenza) and had no history of GVHD, one did so 14.9 months after alloSCT (sepsis) and had a history of grade 2 acute GVHD (diarrhea) and extensive chronic GVHD, one did so 1.5 years after alloSCT (sepsis) and had a history of grade 3 acute GVHD and limited chronic GVDH, and one did so 9.9 years after alloSCT and had a history of extensive chronic GVHD.

**Discussion**

We have presented the long-term follow up of 49 myeloma patients who received high dose melphalan and ASCT followed by RIC-alloSCT with fludarabine/cyclophosphamide conditioning. This phase II study was designed to determine the feasibility of this approach
in the cooperative group setting and it was successful in demonstrating that this approach could be applied to more than 70% of enrolled patients. Importantly, this study was initiated before the widespread incorporation of novel agents into induction, consolidation and maintenance of the transplant-eligible myeloma patient. Overall, this study demonstrated a very low 6-month TRM of 2% (90% CI 0.10-9.3%), well below the estimated 20% rate. At the time this study was designed, there was not a standard-of-care TRM endpoint for a post-nonmyeloablative alloSCT.

The use of alloSCT for myeloma therapy has been controversial and there have been no consistent findings in this population. Earlier studies used full intensity transplant that resulted in high levels of toxicity.\(^{17,18}\) Subsequently, RIC regimens such as low-dose TBI or fludarabine-based regimens have been utilized with lower reported TRM.\(^ {19}\) In this phase II study, we confirm that RIC-alloSCT with fludarabine/cyclophosphamide is safe with minimal TRM and minimal long-term toxicity. Two general strategies have been employed with RIC alloSCT in myeloma. One is to utilize a high dose ASCT for disease control followed by a RIC alloSCT.\(^ {7-20}\) The second is to increase the intensity of the RIC alloSCT but use a single alloSCT instead of a tandem approach.\(^ {21,29}\) The major limitation of alloSCT in patients with myeloma has been high relapse rates, and even with using higher intensity regimens (with or without ASCT), relapse remains problematic.

The CR rate in this study was low, as the majority of patients achieved PR. It appears as though the graft-versus-myeloma effect from alloSCT was limited, especially in comparison to the graft-vs-leukemia effect that is seen with leukemias such as chronic myeloid leukemia.\(^ {30}\) The majority of patients received vincristine/doxorubicin/dexamethasone- or thalidomide-based regimens prior to ASCT and there were patients who entered the study with M-spike >1 g/dL (25%) or bone marrow aspirate plasma cell counts >10% (40%). Thus, the increased disease burden at the time of study entry may have contributed to the low CR rates. The current standard of care therapy for transplant eligible patients includes lenalidomide plus PI-based induction regimens and the majority of patients enter ASCT after achieving at least a very good partial response.\(^ {6,31}\) Thus, it is presumed that the CR rate of tandem ASCT/alloSCT would be higher following a more effective induction regimen. Analysis of the EBMT NMAM2000 study revealed that achievement of CR prior to the second transplant was predictive of PFS and OS.\(^ {32}\) In addition, achievement of CR after tandem ASCT/alloSCT (HR 0.53, p=0.027), but not after tandem ASCT (HR 0.81, p=0.390), was associated with a prolonged PFS.\(^ {32}\) There was not a statistically significant association between achievement of CR after second transplant and OS.\(^ {32}\) Despite the inferior induction regimens and disease burdens prior to transplant in the present study, it is notable that there were patients who achieved a CR post-ASCT/alloSCT and have not relapsed, suggesting that there may be a population of patients for whom this approach could yield prolonged survival. Whether outcomes could be further improved by the incorporation of maintenance therapy post-ASCT/alloSCT remains to be determined. The use of lenalidomide maintenance post-alloSCT has been complicated by induction of GVHD.\(^ {33,34}\) The BMT CTN 1302 study (NCT02440464), which involved randomization to ixazomib vs placebo maintenance therapy following alloSCT, closed prior to completing accrual, and results have not yet been presented.
A summary of the prospective studies that have evaluated tandem ASCT/alloSCT is provided in Table 5. The conditioning regimens for the alloSCT vary across studies. Multiple studies have compared tandem ASCT to tandem ASCT/alloSCT. Armeson et al., conducted a meta-analysis of six of those studies.\(^{35}\) In these studies, patients were assigned to treatment arm based on availability of an HLA-matched donor (n=1192 for tandem ASCT, n= 630 tandem ASCT/alloSCT). No difference in OS or PFS was observed and there was three-fold increase in TRM with the tandem ASCT/alloSCT (RR 3.3, 95% CI 2.2-4.8). Kharfan-Dabaja et al., also conducted a meta-analysis including five studies.\(^{36}\) Although higher rates of CR were noted in the ASCT/alloSCT group (RR 1.65, 95% CI 1.25-2.19, p=0.0005), there were no differences in event-free survival or OS and non-relapse mortality was higher in the ASCT/alloSCT group (RR 3.55, 95% CI 2.17-5.80, p<0.00001).\(^{36}\)

There have also been several reports utilizing registry data to compare outcomes of patients who underwent tandem transplants. In an analysis of the CIBMTR database, the median OS from time of diagnosis was 86.3 months in the patients who received tandem ASCT/alloSCT compared to 75 months in the tandem ASCT group.\(^{37}\) A higher rate of early relapse (defined as within six months of the second transplant) were noted in the ASCT/alloSCT group (46%) compared to the tandem ASCT group (26%).\(^{37}\) The TRM at 1 year was 6% (ASCT/alloSCT) vs 1% (tandem ASCT). A review of the Japanese registry reported a 6-year OS rate of 54.4% in patients undergoing tandem ASCT/alloSCT and 58.5% for tandem ASCT (p=0.47).\(^{38}\) A review of the EBMT database reported a 5-year OS rate of 59% for tandem ASCT/alloSCT compared to 42% for upfront RIC alloSCT without prior ASCT (p=0.001).\(^{39}\)

The current standard of care for those patients deemed candidates for high-dose therapy includes a single ASCT followed by lenalidomide maintenance. While inclusion of lenalidomide maintenance results in significant PFS and OS benefit, the magnitude of the benefit is largest for those patients with standard risk disease.\(^{40,42}\) Therefore, the question as to whether consolidation with a second ASCT or with alloSCT improves outcomes for patients with high-risk cytogenetics continues to be of significant interest. Two recent phase 3 randomized studies have reported disparate findings with respect to the benefit of incorporating a second ASCT into consolidation. The BMT CTN 0702 study randomized patients to one of three arms: single ASCT, double ASCT, or single ASCT followed by lenalidomide/bortezomib/dexamethasone consolidation, with all arms receiving lenalidomide maintenance.\(^{6}\) Statistically significant differences in PFS or OS were not detected between the three groups. Patients with high-risk disease had inferior PFS and OS relative to standard risk disease but there were no differences in outcomes for the high-risk disease patients across the three treatment groups. In contrast, an analysis of patients who underwent single vs tandem ASCT in the EMN 02 study has reported a superior 3-year PFS rate for high-risk patients receiving tandem transplant (65% vs 41%, p=0.05).\(^{43}\) In this study, patients did not receive an IMiD with induction.

It has been hypothesized that the inclusion of alloSCT as consolidation may overcome the adverse prognosis associated with high-risk cytogenetics.\(^{44,45}\) The BMT CTN 0102 study reported that the 3-yr PFS rates did not differ between treatment groups (tandem ASCT vs ASCT/alloSCT) in patients with high-risk cytogenetics (p=0.743).\(^{12}\) The DSMM V trial, which only included patients with del(13q), reported that the CR rate was higher in the
ASCT/alloSCT group than in the tandem ASCT group (58.6% vs 30.9%, p=0.001). While the median PFS was superior in the ASCT/alloSCT group compared to the tandem ASCT group (34.5 vs 21.8 months, p=0.003), there was no difference in median OS (70.2 vs 71.8 months, p=0.856). The IFM99-03 and IFM99-04 studies also focused on patients with del(13q) and compared ASCT/alloSCT (IFM99-03) to tandem ASCT (+/- anti-IL6 antibody, IFM99-04). No significant differences were observed between the two approaches with respect to either event-free survival or OS. As del(13q) is no longer considered a high-risk cytogenetic feature in the era of PI therapy, these studies provide limited insight into the role of tandem ASCT/alloSCT for high-risk disease. Interpretation of the present study with respect to impact of cytogenetic risk on outcome is limited because the majority of enrolled patients did not have diagnostic cytogenetic data available. In addition, our patient population was within 18 months of initiation of therapy, reflecting a less heavily treated population and possibly including fewer high risk patients. Other studies evaluating alloSCT (not in the context of tandem ASCT/alloSCT) have reported disparate outcomes, with several noting no differences in outcomes based on cytogenetic risk while others reporting inferior outcomes associated with certain high-risk cytogenetics. Thus, the lack of consistent data demonstrating a beneficial effect of alloSCT on survival of patients with high-risk disease, coupled with the potential morbidity (i.e., GVHD) and issues with universal access to matched donor stem cells, has limited the routine use of this therapeutic modality in myeloma.

In conclusion, this cooperative group study demonstrates the safety and feasibility of upfront ASCT followed by non-myeloablative alloSCT for patients with myeloma. The observed 6-month TRM rate associated with the use of a fludarabine/cyclophosphamide RIC regimen was low and no unusual toxicities were observed. While the results from this study, similar to other myeloma alloSCT studies, suggest that inclusion of alloSCT may result in long-term survival in a subset of patients, it is not possible to identify which subset is most likely to benefit. These results do support the hypothesis that it is possible to manipulate the immune system to induce long-lasting myeloma disease control, and argue for the inclusion of comprehensive immune profiling studies in clinical trials in order to gain an understanding of the optimal immunophenotype. The advent of new immunotherapeutic therapies, including CAR T-cell therapy, appear poised to change the therapeutic landscape for myeloma. In particular, whether CAR T-cell therapy could replace ASCT and/or alloSCT, or could be used in combination with ASCT and/or alloSCT is of considerable interest and remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- CALGB (Alliance) 100001 evaluated tandem autologous/allogeneic transplant for myeloma
- A fludarabine/cyclophosphamide conditioning regimen was associated with a very low treatment-related mortality rate
- Long-term follow-up demonstrates a subset of patients who derived benefit from this approach
Figure 1.
CONSORT flow diagram of patient disposition at the current data cut-off.
Figure 2.
Cumulative incidence of progression.
Figure 3.
Kaplan-Meier estimates of overall survival.
### Table 1.

**Patient characteristics**

| Characteristic                                      | N=57                        |
|-----------------------------------------------------|-----------------------------|
| Median age (range)                                  | 50 years (33-64 years)      |
| Race                                                |                             |
| White                                               | 42 (73.7%)                  |
| Black or Afro-American                              | 11 (19.3%)                  |
| Not provided                                        | 4 (7.0%)                    |
| ECOG performance status                             |                             |
| 0                                                    | 34 (59.6%)                  |
| 1                                                    | 22 (38.6%)                  |
| 2                                                    | 1 (1.8%)                    |
| Disease Stage (Durie-Salmon)                        |                             |
| I                                                    | 6 (10.5%)                   |
| II                                                   | 11 (19.3%)                  |
| III                                                  | 32 (56.1%)                  |
| Not provided                                         | 8 (14.0%)                   |
| Number of prior chemotherapy regimens               |                             |
| None                                                 | 2 (3.5%)                    |
| One                                                  | 34 (59.6%)                  |
| Two                                                  | 16 (28.1%)                  |
| Three                                                | 4 (7.0%)                    |
| Four                                                 | 1 (1.8%)                    |
| Most common prior chemotherapy regimens             |                             |
| Thalidomide alone or in combination                 | 28 (49.1%)                  |
| Vincristine/Adriamycin/Dexamethasone                 | 20 (35.1%)                  |
| Other                                                | 9 (15.8%)                   |
| Median time from end of chemotherapy to ASCT         |                             |
| (n, range)                                          | 75 days (50; 51-236 days)   |
| Bone Marrow Plasma Cells at registration             |                             |
| <10%                                                 | 30 (52.6%)                  |
| ≥10%                                                 | 23 (40.4%)                  |
| Not provided                                         | 4 (7.0%)                    |
| Plasmacytoma present                                | 7 (12.3%)                   |
| Lytic bone lesions                                  |                             |
| 0                                                    | 12 (21.1%)                  |
| 1-2                                                  | 7 (12.3%)                   |
| 3 or more                                            | 34 (59.6%)                  |
| Not provided                                         | 4 (7.0%)                    |
| CMV serology                                         |                             |
| Positive                                             | 19 (33.3%)                  |
| Negative                                             | 36 (63.2%)                  |
| median age (range) | N=57 |
|-------------------|------|
| Not provided      | 50 years |
|                   | (33-64 years) |
|                   | 2 (3.5%) |
### Table 2.

All grade 2-4 toxicities reported during the post-ASCT and the post-alloSCT periods (regardless of attribution)

| Condition                                | Post ASCT (n=55) | Post Allo (n=49) |
|-----------------------------------------|------------------|------------------|
|                                        | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 |
| Acidosis                                | 0       | 0       | 0       | 0       | 0       | 1 (2%)  |
| Adult respiratory distress syndrome     | 0       | 0       | 1 (2%)  | 0       | 0       | 0       |
| Alanine aminotransferase increased      | 2 (4%)  | 2 (4%)  | 0       | 4 (8%)  | 4 (8%)  | 1 (2%)  |
| Alkaline phosphatase increased          | 0       | 0       | 0       | 2 (4%)  | 0       | 0       |
| Alopecia                                | 11 (20%)| 0       | 0       | 3 (6%)  | 0       | 0       |
| Adult respiratory distress syndrome     | 0       | 0       | 0       | 2 (4%)  | 0       | 0       |
| Anemia                                  | 15 (27%)| 9 (16%) | 1 (2%)  | 14 (29%)| 4 (8%)  | 0       |
| Anorexia                                 | 10 (18%)| 2 (4%)  | 3 (5%)  | 3 (6%)  | 0       | 0       |
| Anxiety                                 | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Arthralgia                               | 1 (2%)  | 0       | 0       | 0       | 1 (2%)  | 0       |
| Aspartate aminotransferase increased    | 1 (2%)  | 1 (2%)  | 0       | 4 (8%)  | 4 (8%)  | 0       |
| Back pain                               | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Blood bilirubin increased               | 2 (4%)  | 0       | 0       | 3 (6%)  | 0       | 0       |
| Blood disorder                          | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Blood glucose increased                 | 9 (16%) | 3 (5%)  | 0       | 3 (6%)  | 3 (6%)  | 0       |
| Bone pain                               | 8 (15%) | 1 (2%)  | 0       | 6 (12%) | 2 (4%)  | 0       |
| Cardiac disorder                        | 2 (4%)  | 1 (2%)  | 0       | 2 (4%)  | 0       | 0       |
| Cardiac troponin I increased            | 0       | 0       | 0       | 0       | 0       | 1 (2%)  |
| CD4 lymphocytes decreased               | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Chest pain                              | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Coagulopathy                            | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Conduction disorder                     | 0       | 0       | 1 (2%)  | 0       | 0       | 0       |
| Constipation                            | 5 (9%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Cough                                   | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Creatinine increased                    | 1 (2%)  | 0       | 0       | 3 (6%)  | 2 (4%)  | 0       |
| Dehydration                             | 1 (2%)  | 0       | 0       | 1 (2%)  | 2 (4%)  | 0       |
| Depressed level of consciousness        | 1 (2%)  | 1 (2%)  | 0       | 1 (2%)  | 0       | 0       |
| Depression                              | 1 (2%)  | 0       | 0       | 1 (2%)  | 3 (6%)  | 0       |
| Diarrhea                                | 8 (15%) | 5 (9%)  | 0       | 3 (6%)  | 2 (4%)  | 0       |
| Dizziness                               | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Dry eye syndrome                        | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Dysgeusia                               | 2 (4%)  | 0       | 0       | 0       | 0       | 0       |
| Dyspepsia                               | 3 (5%)  | 0       | 0       | 0       | 0       | 0       |
| Dysphagia                               | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Dyspnea                                 | 4 (7%)  | 0       | 1 (2%)  | 0       | 1 (2%)  | 1 (2%)  |
| Condition                                      | Post ASCT (n=55) | Post Allo (n=49) |
|------------------------------------------------|------------------|------------------|
|                                                | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 |
| Epistaxis                                      | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Esophagitis                                    | 0       | 4 (7%)  | 0       | 0       | 0       | 0       |
| Extra-pyramidal disorder                      | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Eye disorder                                   | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Fatigue                                        | 8 (15%) | 0       | 0       | 3 (6%)  | 0       | 0       |
| Fever                                          | 2 (4%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Flatulence                                     | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Gamma-glutamyltransferase increased           | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Gastritis                                      | 2 (4%)  | 0       | 0       | 0       | 0       | 0       |
| Gastrointestinal disorder                     | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Headache                                       | 5 (9%)  | 0       | 0       | 2 (4%)  | 0       | 0       |
| Hiccups                                        | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Hemorrhage w/grade 3+thrombocytopenia         | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Hot flashes                                    | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       | 0       |
| Hypersensitivity                               | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Hypertension                                   | 3 (5%)  | 1 (2%)  | 0       | 1 (2%)  | 3 (6%)  | 0       |
| Hypophosphatemia                               | 3 (5%)  | 10 (18%)| 2 (4%)  | 0       | 0       | 0       |
| Hypotension                                    | 6 (11%) | 3 (5%)  | 0       | 1 (2%)  | 0       | 0       |
| Hypothyroidism                                 | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Hypoxia                                        | 0       | 2 (4%)  | 0       | 0       | 0       | 0       |
| Ill-defined disorder                           | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Infection with grade 3 or 4 neutropenia       | 1 (2%)  | 14 (25%)| 0       | 1 (2%)  | 4 (8%)  | 0       |
| Infection with unknown ANC                    | 2 (4%)  | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       |
| Infection without neutropenia                 | 5 (9%)  | 3 (5%)  | 0       | 2 (4%)  | 1 (2%)  | 0       |
| Insomnia                                       | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Intracranial hemorrhage                        | 0       | 0       | 1 (2%)  | 0       | 0       | 0       |
| Large intestinal mucositis (funct/sympt)       | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Left ventricular failure                       | 0       | 0       | 0       | 0       | 0       | 1 (2%)  |
| Leukocyte count decreased                      | 0       | 2 (4%)  | 3 (5%)  | 0       | 1 (2%)  | 5 (10%) |
| Lipase increased                               | 0       | 0       | 0       | 0       | 1 (2%)  | 0       |
| Lymphocyte count decreased                     | 0       | 3 (5%)  | 2 (4%)  | 0       | 5 (10%) | 0       |
| Mucositis oral (clin exam)                     | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Mucositis oral (funct/sympt)                   | 20 (36%)| 7 (13%) | 1 (2%)  | 5 (10%) | 0       | 0       |
| Muscle weakness                                | 1 (2%)  | 0       | 0       | 0       | 0       | 0       |
| Musculoskeletal disorder                       | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Myalgia                                        | 1 (2%)  | 0       | 0       | 0       | 1 (2%)  | 0       |
| Myocardial ischemia                            | 0       | 0       | 0       | 0       | 0       | 1 (2%)  |
|                          | Post ASCT       | Post Allo       |                  |
|--------------------------|----------------|----------------|-----------------|
|                          | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 |
| Nausea                   | 25 (46%) | 3 (5%)  | 0       | 6 (12%) | 3 (6%)  | 0       |
| Neuralgia                | 2 (4%)   | 0       | 0       | 1 (2%)  | 0       | 0       |
| Neutrophil count decreased| 0       | 6 (11%) | 46 (84%)| 4 (8%)  | 9 (18%) | 30 (61%)|
| Pain                     | 8 (15%)  | 0       | 0       | 3 (6%)  | 0       | 0       |
| Pelvic pain              | 1 (2%)   | 0       | 0       | 0       | 0       | 0       |
| Peripheral sensory neuropathy | 3 (5%)  | 0       | 0       | 2 (4%)  | 0       | 0       |
| Platelet count decreased | 3 (5%)   | 20 (36%)| 27 (49%)| 8 (16%) | 11 (22%)| 10 (20%)|
| Pleuritic pain           | 0       | 1 (2%)  | 0       | 1 (2%)  | 0       | 0       |
| Pneumonitis              | 1 (2%)   | 1 (2%)  | 0       | 0       | 0       | 0       |
| Pruritus                 | 2 (4%)   | 0       | 0       | 1 (2%)  | 0       | 0       |
| Psychosis                | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Rash desquamating        | 5 (9%)   | 0       | 0       | 2 (4%)  | 0       | 0       |
| Renal Failure            | 0       | 0       | 0       | 0       | 1 (2%)  | 0       |
| Respiratory disorder     | 1 (2%)   | 0       | 0       | 1 (2%)  | 0       | 0       |
| Serum albumin decreased  | 13 (24%) | 0       | 0       | 4 (8%)  | 0       | 0       |
| Serum calcium decreased  | 11 (20%) | 3 (5%)  | 1 (2%)  | 2 (4%)  | 0       | 0       |
| Serum magnesium decreased| 0       | 0       | 0       | 3 (6%)  | 0       | 0       |
| Serum magnesium increased| 0       | 1 (2%)  | 0       | 0       | 1 (2%)  | 0       |
| Serum potassium decreased| 0       | 6 (11%) | 0       | 0       | 0       | 0       |
| Serum potassium increased| 0       | 2 (4%)  | 0       | 0       | 0       | 0       |
| Serum phosphate decreased| 0       | 0       | 0       | 3 (6%)  | 2 (4%)  | 0       |
| Serum sodium decreased   | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Skin bradycardia         | 0       | 1 (2%)  | 0       | 1 (2%)  | 0       | 0       |
| Skin disorder            | 0       | 1 (2%)  | 0       | 0       | 0       | 0       |
| Syncope                  | 0       | 2 (4%)  | 0       | 0       | 0       | 0       |
| Thrombosis               | 0       | 1 (2%)  | 1 (2%)  | 0       | 0       | 0       |
| Upper respiratory infection(gr 3/4 ANC) | 1 (2%) | 0 | 0 | 0 | 0 | 0 |
| Upper respiratory infection(gr 0/1/2 ANC) | 1 (2%) | 0 | 0 | 0 | 0 | 0 |
| Urinary retention        | 1 (2%)   | 0       | 0       | 0       | 0       | 0       |
| Urogenital disorder      | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Urticaria                | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
| Vision blurred           | 1 (2%)   | 0       | 0       | 0       | 0       | 0       |
| Vomiting                 | 22 (40%) | 2 (4%)  | 0       | 6 (12%) | 1 (2%)  | 0       |
| Wound Infection          | 0       | 0       | 0       | 1 (2%)  | 0       | 0       |
Table 3.

Chimerism data

| Day  | +30   | +60   | +90   | +90   |
|------|-------|-------|-------|-------|
| Source | PB    | PB    | PB    | BM    |
|       | median (range) number | median (range) number | median (range) number | median (range) number |
| CD3 (T cells) | 95% (51-99%) n=39 | 95% (54-100%) n=39 | 97% (50-99%) n=37 | 95.5% (51-100%) n=36 |
| CD14/15 (myeloid cells) | 90% (26-100%) n=38 | 94% (38-100%) n=39 | 98% (45-100%) n=37 | 97% (55-100%) n=36 |
| CD19 (B cells) | 92.5% (42-98%) n=36 | 94% (23-100%) n=37 | 97% (29-100%) n=36 | 97% (51-100%) n=35 |
| Unfractionated | 89% (42-99%) n=40 | 92% (46-100%) n=39 | 97% (54-100%) n=37 | 94.5% (58-100%) n=36 |

Abbreviations: BM, bone marrow; PB, peripheral blood
Table 4.

Investigator-reported responses

| Responses                  | Post-ASCT (n=57) | Day +100 post-alloSCT (n=49) | Best response after alloSCT* (n=49) |
|----------------------------|------------------|-----------------------------|-----------------------------------|
| Complete Response (N) (%)  | 8 (14%)          | 9 (18%)                     | 18 (37%)                          |
| Partial Response (N) (%)   | 27 (47%)         | 23 (47%)                    | 18 (37%)                          |
| Minimal Response (N) (%)   | 3 (5%)           | 2 (4%)                      | 4 (8%)                            |
| Stable Disease (N) (%)     | 14 (25%)         | 10 (20%)                    | 6 (12%)                           |
| Progressive Disease (N) (%)| 1 (2%)           | 3 (6%)                      | 3 (6%)                            |
| Missing (N) (%)            | 5 (9%)           | 2 (4%)                      | 0                                 |

* prior to initiation of non-protocol therapy
### Table 5.
Summary of prospective upfront tandem ASCT/alloSCT studies

| Study            | n       | Induction | AlloSCT | OS      | TRM      | Other                     |
|------------------|---------|-----------|---------|---------|----------|---------------------------|
| IFM99-03<sup>7, 9</sup> | 65 (46 completed) | VAD       | Bu/Flu/AT G | Median: 35 mos | 10.9% | Del(13q) (FISH) and β2MG >3 |
| PETHEMA/GEM -2000<sup>10</sup> | 25 | VBMCP/VBAD | FluMel   | 5 yrs: 62% | 16% | Not in nCR/CR post-ASCT |
| DSMM V<sup>46</sup> | 126 | Anthracycline/dex.-based followed by one cycle of ifosfamide/etoposide | FluMel | Median: 70.2 mos | 12.7% at 2 yrs | Del(13q) (FISH) |
| BMT-CTN 0102<sup>12</sup> | 226 (185 completed) | Not specified | TBI 200 cGy | 3 yrs: 77% | 11% at 3 yrs |
| HOVON-50/54<sup>15</sup> | 122 | VAD or TAD | TBI 2 Gy | 6 yrs: 55% | 16% at 6 yrs (NRM) |
| Bruno et al.<sup>8, 13</sup> | 80 (58 completed) | VAD | TBI 200 cGy | Median NR after median f/u of 7 years | 10% |
| EBMT-NMAM2000<sup>14, 16</sup> | 108 | Not specified | TBI 2 Gy + Flu | 5 yrs: 65% 8 yrs: 49% | 12% at 3 yrs (NRM) |
| Kroger et al.<sup>18</sup> | 73 | Ida/Dex, VAD, or BD | Flu/Mel/AT G | 5 yrs: 54% | 23% at 1 yr |
| CALGB 100001 | 57 (49 completed) | Not specified | Flu/Cy | Median: 6.6 yrs | 2% at 6 month s |

Abbreviations: β2MG, β2-microglobulin; BD, bortezomib/dexamethasone; Bu, busulfan; CR, complete response; Cy, cyclophosphamide; Dex, dexamethasone; Flu, fludarabine; Ida, idarubicin; nCR, near complete response; NRM, non-relapse mortality; TAD, thalidomide/doxorubicin/dexamethasone; TBI, total body irradiation; VAD, vincristine/doxorubicin/dexamethasone; VBAD, vincristine/carmustine/dexamethasone; VBMCP, vincristine/carmustine/melphalan/cyclophosphamide/prednisone.