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Myeloablative Fractionated Busulfan With Fludarabine in Older Patients: Long Term Disease-Specific Outcomes of a Prospective Phase II Clinical Trial

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Abstract

Compared to reduced-intensity conditioning regimen, myeloablative conditioning (MAC) for hematopoietic stem cell transplantation (HCT) reduces relapse but is avoided in older patients because of higher non-relapse mortality (NRM). To meet the need for a myeloablative regimen for older patients, we developed a novel fludarabine and busulfan MAC regimen. We fractionated the dose of busulfan and gave it for 6 days over a 2-week period and demonstrated the feasibility and safety of this approach. However, the disease-specific efficacy of this regimen is not known. The purpose of this study was to estimate the efficacy of fractionated busulfan regimen by estimating diseases specific survival outcomes. The conditioning regimen consisted of busulfan and fludarabine. On days −13 and −12 before HCT, patients received 80 mg/m^2 busulfan intravenously (IV) daily in an outpatient clinic. Additional chemotherapy was administered during inpatient treatment from day −6 through day −3, including fludarabine 40 mg/m^2 and busulfan IV once daily. The dosing of busulfan was determined from pharmacokinetic analyses to achieve for the course a target area under the curve of 20,000 ± 12% μmol/min, which is close to the average exposure of myeloablative dose of busulfan. One hundred fifty patients with high-risk

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hematological malignancies up to 75 years were enrolled in this prospective phase II study. The objective was to evaluate NRM, relapse, survival, the rates of graft-versus-host disease (GVHD), and long-term complications. The median age of the patient population was 61 years (interquartile range, 55–67). The most common diagnoses were acute myeloid leukemia (AML; N = 59 [39.3%]), myelodysplastic syndrome (MDS; n = 29 [19.3%]), and myelofibrosis (MF; N = 22 [14.7%]). Most had an unrelated donor (n = 93 [62%]) and received peripheral blood graft (n = 110 [73.3%]). Over half had an HCT-specific comorbidity index of ≥3 (n = 79 [52.7%]). The median follow-up among survivors was 43.4 months (interquartile range, 38.9–50.4). In patients with AML in complete remission, MDS, and myelofibrosis, 3-year overall survival was 66.7% (95% confidence interval [CI], 50.2–88.5%), 43.6% (95% CI, 28.6–66.4%), and 59.1% (95% CI, 41.7–83.7%) respectively. The cumulative incidence of NRM was 22% (15.3%−28.7%), extensive chronic GVHD was 27% (95% CI, 20–34%), bronchiolitis obliterans was 4.7% (95% CI, 1.3–8.1%), and secondary malignancy was 8.7% (95% CI, 4.1–13.2%) at 3 years. Lengthening the duration of busulfan (fractionation) permits safe delivery of myeloablative conditioning in older patients, leading to prolonged survival.

Keywords

Hematopoietic stem cell, transplantation; Myeloablative conditioning; Older patients; Fractionated Busulfan; AML; Long-term complications

Myeloablative conditioning (MAC) for allogeneic hematopoietic stem cell transplantation (HCT) reduces the risk of relapse and leads to superior survival despite higher non-relapse mortality (NRM) than with reduced-intensity conditioning (RIC) [1]. However, MAC is usually avoided in older patients and in those with high comorbidities because of poor tolerance and high risk of toxicities. A less toxic MAC regimen that can be tolerated by older and frail patients may improve the overall results of HCT. Therefore we developed a novel method of delivering myeloablative doses of busulfan over an extended period of time (fractionated course), rather than the traditional 4- to 6-day course [2,3], with dose monitored by pharmacokinetic (PK) guidance. The rationale of this approach was that simply lengthening the conditioning regimen over a 2-week period could allow us to deliver myeloablative doses of busulfan safely while still retaining anti-tumor efficacy [4]. This notion was adapted from previous studies showing encouraging results in patients with acute leukemia who were given a second course of chemotherapy 8 to 10 days after the first induction therapy in a timed-sequential manner [5−7]. A similar concept was noted to be promising when applied to the HCT setting, where patients were given a course of chemotherapy 4 to 14 days before the start of RIC [8,9], suggesting that sequential administration of chemotherapy agents may kill more leukemia cells without causing a major increase in toxicity. We adapted these principles to modify the method of delivering conditioning chemotherapy [4]. We previously also showed that PK-guided busulfan was superior to fixed-dose busulfan in terms of relapse, as well as NRM. The PK-guided systemic exposure of busulfan is represented by the area under the concentration versus time curve (AUC), which ranges from approximately 3600 to 6100 μmol/min daily (median, AUC ~5,000 μmol/min daily, or 20,000 μM-min total) when translated into a 4-day schedule [10]. After demonstrating that PK-guided busulfan leads to better outcomes than the fixed-

dose busulfan, we sought to determine the "optimal" (safe and effective) busulfan dose in older and frail patients. We started a randomized phase II trial that compared the safety of 2 myeloablative fractionated ("timed-sequential") busulfan with fludarabine (Bu-Flu) conditioning regimens: one with a lower dose of busulfan (AUC of 16,000 μmol/min [16K arm]) and one with a higher dose (AUC of 20,000 μmol/min [20K arm]). The average total intravenous (IV) busulfan dose given per patient was 9.7 mg/kg (range, 5.4–14.6) in the 16K arm and 12.5 mg/kg (range, 8.5–16.7) in the 20K arm. After 49 patients were treated on the 16K group and 48 patients on the 20K group, we stopped the randomization since the higher dose arm was as safe as the lower dose arm. The outcomes of those patients were previously reported, with the primary endpoint being day 100 NRM [4]. That study was not powered to analyze differences in the relapse or survival between the arms. Realizing that the higher dose arm was safe, and knowing that higher intensity conditioning is associated with reduced relapse, we continued enrollment of the trial as a single-arm study with increased accrual onto the 20K arm. Here, we report the long-term outcomes of 150 patients treated on the 20K arm, and disease-specific outcomes, with a median follow-up of over 3.5 years.

Reporting long-term data is crucial, as outcomes could be deceptively encouraging in studies with shorter follow-ups. This is highlighted by the fact that among patients who survive 2 years after HCT, the 10-year survival probability has a wide range from between 60% and 85% [11,12]. Moreover, even among those who survive HCT, long-term morbidity and late complications can be substantial and can be captured only with a longer follow-up. Herein, we report the long-term data of commonly reported HCT outcomes and disease-specific outcomes and describe the late complications experienced by these patients.

PATIENTS AND METHODS

Study design and participants

This study focuses on the analysis of patients who were enrolled in the higher-dose arm of the randomized phase II clinical trial completed at the University of Texas MD Anderson Cancer Center (MDACC) that compared 2 timed-sequential Bu-Flu conditioning regimens (16K versus 20K arms). The clinical trial (MDACC protocol 2011–0958; ClinicalTrials.gov identifier NCT01572662) was approved by the MDACC Institutional Review Board and was conducted in accordance with the Helsinki Declaration, and all participants provided written informed consent. The initial eligibility criteria included patients with any hematological malignancy up to 70 years of age, which was expanded to 75 years after safety was determined. Detailed inclusion and exclusion criteria were previously reported [4].

Conditioning Regimen and Supportive Care

The conditioning regimen consisted of Bu-Flu, as described [4]. Briefly, the dosing of busulfan was determined from PK analyses conducted after the first (day −13) and third (day −6) busulfan dose to achieve a target AUC of 20,000 ± 12% μmol/min (20K arm). On days −13 and −12 before HCT, patients received 80 mg/m^2 busulfan intravenously (IV) daily in an outpatient clinic. Additional chemotherapy was administered during inpatient treatment from day −6 through day −3, including fludarabine 40 mg/m^2 and busulfan IV once daily

(Figure 1). On the basis of the PK analyses conducted after day −13 and day −6 busulfan doses, the last 2 busulfan doses (day −5 and day −4) were adjusted to achieve the desired total AUC of 20K. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus starting on day −2, aiming for a level of 8 to 11 ng/mL, and methotrexate 5 mg/m^2 IV given on days 1, 3, 6, and 11. Supportive care, including antimicrobials, growth factors, and others followed institutional standard [4].

Outcomes

Our primary objective was to evaluate NRM, relapse, progression-free survival (PFS), overall survival (OS), and GVHD-free relapse-free survival (GRFS) at 1 and 3 years after HCT. These outcomes were also analyzed within disease subsets−acute myeloid leukemia (AML) in complete remission (CR), AML not in CR, myelodysplastic syndrome (MDS), myelofibrosis, lymphoma, and multiple myeloma. Patients with chronic myeloid leukemia (CML, n = 7) or acute lymphoblastic leukemia (ALL, n = 3) were included in the analysis of overall outcomes, but not analyzed as separate groups due to the small number of patients with either condition. Secondary objectives were to assess the rates of acute GVHD (aGVHD) at day 100, chronic GVHD (cGVHD) at 1 and 3 years, and other long-term complications such as the incidence of secondary malignancies, avascular necrosis (AVN), diabetes mellitus, hypothyroidism, and cataracts.

Statistical Analysis

Kaplan-Meier analyses were used to estimate the distribution of OS, PFS, and GRFS after transplantation. Distributions were compared using log-rank tests. The cumulative incidence of NRM was assessed in a competing risks framework with relapse as the competing risk. Distributions were compared using Gray's test. The cumulative incidence of relapse with a competing risk of death without relapse was analyzed similarly. The cumulative incidence of aGVHD was assessed in a competing risks framework with competing risks of disease relapse and death without relapse. The cumulative incidence of cGVHD was assessed in a similar framework with the same competing risks. The cumulative incidence functions were compared using Gray's test. Statistical analyses were performed using R version 3.6.1 and used a significance level of 5%.

RESULTS

Patient Characteristics

Between June 2012 and December 2015, 150 patients were treated on the 20K arm. Of these, the first 48 were treated while the study was randomizing patients, and 102 were treated after randomization was terminated. The median age at HCT was 61 years (interquartile range [IQR], 55–67; range 24–75), and one third (n = 50 [33.3%]) were 65 years or older. Most were males (n = 91 [60.7%]), had an unrelated donor (n = 93 [62%]) and received a peripheral blood graft (n = 110 [73.3%]). The diagnoses included AML (n = 59 [39.3%]), MDS (n = 29 [19.3%]), myelofibrosis (n = 22 [14.7%]), myeloma (n = 17 [11.3%]), lymphoma (n = 13 [8.7%]), CML (n = 7), and ALL (n = 3). Overall, more than half of the patients had an HCT-Specific Comorbidity Index (HCT-CI) [13] ≥3 (n = 79 [52.7%]). Forty-seven (32%) had a high/very high disease risk index (DRI) [14],

and less than a quarter (n = 35 [23.3%]) were in CR at the time of HCT. Among the 59 patients with AML, 29 (49.2%) had intermediate risk, 24 (40.7%) had adverse risk, and 5 (8.5%) had favorable risk disease, per the European LeukemiaNet revised classification [15]. The median follow-up among survivors was 43.4 months (IQR, 38.9–50.4) [Table 1]. The median busulfan dose administered was 12.8 mg/kg (IQR, 10.8–14.4; range, 6.7–23.4).

Survival Data

Overall, 81 patients died, with relapse/progression of the underlying malignancy contributing to 45 (55.5%) of these deaths. Other causes included aGVHD (n = 13), cGVHD (n = 2), infections (6 bacterial, 1 *Pneumocystis jiroveci* pneumonia (PJP), 1 protozoal, and 3 undefined), interstitial or other pneumonia (n = 3), multi-organ failure (n = 4), 2 unknown causes, and 1 secondary malignancy. Fifty-seven (70.4%) deaths occurred within 1 year of HCT. Twelve (15%) deaths occurred in the second year, and the rest (n = 12) occurred after 2 years. Between 50% to 60% of the deaths each year were related to the relapse/progression of the underlying malignancy (Table 2; Figure 2).

NRM

Twelve deaths occurred within 100 days of HCT, 8 of which were due to non-relapse causes that included infection (n = 5; 3 bacterial, 1 protozoal, and 1 undefined), aGVHD (n = 2), or organ failure (n = 1). The estimated NRM rate was 5.3% (95% confidence interval [CI], 1.7%−8.9%) at day 100, 16.7% (95% CI, 10.7%−22.7%) at 1 year, and 22% (95% CI, 15.3%−28.7%) at 3 years (Table 3; Figure 3). Figure 4 depicts outcomes by disease subsets. As expected, the rates of NRM also differed significantly by HCT-CI. Among patients with HCT-CI scores of 0–2, NRM at 3 years was 14.1% (95% CI, 5.9%−22.3%) versus 29.1% (95% CI, 19%−39.2%) among those with HCT-CI scores ≥3 (Figure 5A). The 3-year NRM was 18.5% (95% CI, 8.9%−28%) in patients younger than 60 years versus 24.7% (95% CI, 15.4%−34%) in patients age ≥60 years.

Relapse

Eighty-six patients (57.3%) relapsed/progressed after HCT. The cumulative incidence of relapse was 31.3% (95% CI, 23.9%−38.8%) at 1 year and 40% (95% CI, 32.1%−47.9%) at 3 years (Table 3; Figure 3). The highest relapse rate was in patients with myeloma (58.8% at 1 year and 70.6% at 3 years). The relapse rate increased over time in all diseases, except for lymphoma and AML in measurable residual disease (MRD)−negative CR (Table 3; Figure 4). No patient with AML in MRD-negative CR experienced relapse in the first year after HCT. For AML, the rate of relapse was not different between patients not in CR compared to those in CR at 1 year (25.7% for those not in CR and 33.3% for those in CR) and at 3 years (37.1% for those not in CR and 41.7% for those in CR). Eleven of 24 AML patients in CR relapsed, of whom 10 were either MRD-positive (n = 6) or had unknown status (n = 4) at the time of HCT. Among MDS, 16/29 patients relapsed, mostly (n = 11) within the first year after HCT and with a 1-year relapse rate of 37.9% (95% CI, 19.8%−56%) and 51.7% (95% CI, 33%−70.5%) at 3 years. Ten of these 11 patients had a high/very high Revised International Prognostic Scoring System [16] score. The risk of relapse was similar in patients with a low/intermediate DRI and those with a high/very high DRI (Figure 5C).

The rate of relapse at 3 years was 40% (95% CI, 27.9%−52.1%) in patients younger than 60 years versus 38.8% (95% CI, 28.4%−49.3%) in patients age ≥60 years.

OS, PFS, and GRFS

Sixty-nine patients (46%) were alive by the end of the study. The estimated OS rate was 62% (95% CI, 54.7%−70.3%) at 1 year, and 49.1% (95% CI, 41.7%−57.8%) at 3 years (Table 3; Figure 3). The best 3-year OS was among patients with AML in MRD-negative CR (72.7%; 95% CI, 50.6%−100%), lymphoma (69.2%; 95% CI, 48.2%−99.5%), followed by myelofibrosis (59.1%; 95% CI, 41.7%−83.7%). The OS decreased between 1 and 3 years in almost all diseases (except lymphoma), with a substantial decline noted in AML patients in CR (79.2% at 1 year to 66.7% at 3 years), AML not in CR (45.7% to 31.4%), MDS (72.4% to 43.6%) and myeloma (52.9% to 40.3%) (Figure 40. The OS differed significantly by HCT-CI score, in which 3-year OS was 57.2% (95% CI, 46.7%−70.1%) in patients with an HCT-CI score 0–2 versus 41.7% (95% CI, 32.2%−54.2%) with an HCT-CI score ≥3 (Figure 5B). There was no difference in OS by DRI (Figure 5D). The OS at 3 years was 56.7% (95% CI, 45.8–70.2%) in patients younger than 60 years versus 43.5% (95% CI, 34.1%−55.4%) in patients age ≥60 years.

Fifty-one patients (34%) were alive without relapse or progression at the end of the study. The PFS rate was 52% (95% CI, 44.6%−60.6%) at 1 year, and 38% (95% CI, 30.9% −46.6%) at 3 years. Detailed PFS by diseases is shown in Table 3. The estimated GRFS was 36% (95% CI, 29.1%−44.6%) at 1 year, and 22.6% (95% CI, 16.8%−30.4%) at 3 years.

GVHD and late effects

Overall, 78 patients developed grade II-IV aGVHD, of which 28 had grade III-IV aGVHD. The cumulative incidence of grade II-IV and III-IV aGVHD at day 100 was 38% (95% CI, 30.2%−45.8%) and 11.3% (95% CI, 6.2%−6.4%), respectively (Table 4).

Sixty-four patients developed cGVHD, of which 12 were de novo. The cumulative incidence of overall cGVHD was 23% (95% CI, 17%−30%) at 1 year and 29% (95% CI, 21%−36%) at 3 years. Limited-stage cGVHD occurred in 13 patients that started at a median of 469 days (range 271–1379; IQR, 329–1012). Most patients had extensive stage cGVHD (n = 51) that developed at a median of 309 days (range 85–1358; IQR, 222.5–410.5). The cumulative incidence of extensive cGVHD was 21% (95% CI, 15%−28%) at 1 year and 27% (95% CI, 20%−34%) at 3 years (Table 4, Figure 6). Nine patients developed bronchiolitis obliterans syndrome (BOS) at a median of 706 days (range, 86–1412; IQR, 519–968), three of whom died (2 because of BOS and 1 because of relapse of the underlying malignancy). The cumulative incidence of BOS was 1.3% (95% CI, 0%−3.2%) at 1 year, and 4.7% (95% CI, 1.3%−8.1%) at 3 years (Figure 6).

Fifteen patients developed a secondary malignancy, at a median of 622 days (range 71–1105; IRQ, 256.5–807.5). Cumulative incidence of secondary malignancies was 4.0% (95% CI, 0.8%−7.2%) at 1 year and 8.7% (95% CI, 4.1%−13.2%) at 3 years (Figure 6). The most common malignancy involved skin (7 squamous cell carcinoma, 3 basal cell carcinoma, and 1 invasive lentigo maligna type melanoma). All these patients were treated with local excision or Mohs surgery. Other malignancies included metastatic gastrointestinal

stromal tumor (n = 1) that was fatal, pancreatic cancer (n = 1), bladder cancer (n = 1), and plasmacytoma (n = 1). The patient with pancreatic cancer received chemotherapy with 5-fluorouracil, which was discontinued because of relapsed leukemia. The patient with plasmacytoma did not receive treatment because of severe steroid-refractory GVHD, which was the terminal event. The patient with bladder cancer was treated and remains in remission. Of the 15 patients with a secondary malignancy, 8 had cGVHD (4 squamous cell carcinoma, 2 basal cell carcinoma, 1 gastrointestinal stromal tumor), 6 had a history of aGVHD but no cGVHD, and 1 (bladder cancer) had no history of GVHD. Hypothyroidism developed in 7 patients after HCT and 3 patients experienced AVN, all of whom had a history of either acute (n = 1), or both acute and extensive chronic GVHD (n = 2) requiring systemic steroids. Other long-term complications such as cataract (n = 1) and diabetes (n = 2) were infrequent.

DISCUSSION

In this extended follow-up of a prospective phase II clinical trial, we report the long-term outcomes of our higher-dose myeloablative Bu-Flu conditioning regimen in 150 patients with a median follow-up of 43.4 months. The larger sample size and longer follow-up allowed us to validate our findings and highlight some of the late complications of HCT. This population had a median age of 61 years, of whom more than 75% were not in CR, about a third had a high/very high DRI, and 52.7% had an HCT-CI of ≥3. Traditionally, many of these patients are precluded from getting MAC for HCT [1,17−19], and some are denied HCT [20] because of the high risk of NRM.

The safety of this regimen is reflected by a low NRM rate, which was 5.3% at day 100 and 16.7% at 1 year. The NRM rate was <10% at 1 year and <15% at 3 years in AML patients in CR and those with MDS. Patients with myeloma and lymphoma also had low NRM despite being heavily pretreated, as is usually the case for patients undergoing allogeneic HCT for these diseases, with 12 of 17 myeloma patients having received a prior autologous or allogeneic HCT. As expected, patients with HCT-CI scores of 0–2 had lower NRM (about 14% at 3 years, versus an expected rate of 21% at 2 years [13]) than those with HCT-CI ≥3 (about 29% at 3 years, versus an expected rate of 41% at 2 years [13]).

The regimen was also effective. Among AML patients, the risk of relapse was comparable between those not in CR and those who were in CR at the time of HCT, suggesting that the regimen was fairly effective in controlling some of the high-risk diseases. This was corroborated by the finding of similar risk of relapse among patients with high/very high DRI and those with low/intermediate DRI. The relatively high rate of relapse among AML patients in CR reflected their MRD status at the time of HCT, which is consistent with our previous findings [21]. Myelofibrosis patients had acceptably low risk of relapse and favorable survival as compared to the outcomes reported by other MAC regimens in younger patients [22−24] and RIC regimens [25−29] in older patients.

The long-term follow-up period in our study offers other important insights. First, most of the relapses, NRM, and deaths occurred within the first year of HCT. Yet, between 1 and 3 years, we noticed a modest absolute reduction in OS and absolute increase in relapse rate,

but a minimal increase in NRM. Moreover, although the OS was about 49% at 3 years, less than a quarter of patients attained that without relapse or any preceding major GVHD event.

The cumulative incidence of extensive cGVHD in our study was 21% at 1 year, which occurred at a median of 309 days. The slightly longer time to development of chronic GVHD, as compared to other studies, may be related to our practice of tacrolimus taper versus other factors, such as the differences in underlying patient populations. Our standard is to keep the recipients of unrelated or mismatched donors on therapeutic tacrolimus through day 180 after HCT and then taper off gradually in the absence of acute GVHD, and the recipients of matched related donors are kept on therapeutic tacrolimus for the first 100 days after HCT. Although cGVHD-related mortality was low, that does not reflect its associated morbidity and other complications such as AVN and secondary malignancies [30]. In our study, 3 of 94 patients who survived 1 year developed AVN, which compares favorably to the reported incidence of 5% to 10% in the literature [31,32]. Likewise, the risk of secondary malignancies in our study is similar to the expected rate of under 5% after MAC-HCT [31,33], which occurs more frequently with radiation-based [34], compared to chemotherapy-based regimens [30]. Other complications, such as diabetes mellitus and hypothyroidism are more commonly reported in younger patients [31], who are also at higher risk of cataracts; especially in those receiving total-body irradiation [31]. Our study's inclusion of an older population and radiation-free conditioning explains the relatively low risk of these long-term complications.

Our study lacks data on other important survivorship outcomes, including that of skeletal complications other than AVN (such as osteoporosis), quality of life, health-care utilization, and psychosocial functioning. Also, the number of patients within individual disease subsets is rather limited, especially patients with CML and ALL, which restricts our ability to make meaningful conclusions about individual diseases. Moreover, with small numbers, it is challenging to perform subgroup risk-factor analysis to control for potential confounders that may explain the reported differences in outcomes, and to examine outcomes within individual disease groups (eg, stratifying AML by European Leukemia Network classification). Therefore the results should be interpreted with caution. Nonetheless, our study benefits from its prospective nature and inclusion of a cohort where all patients were treated uniformly and monitored closely on a clinical trial. Moreover, the data presented here are mature and deliver a snapshot of the trajectory of events over time up to 5 years after HCT and treated with a novel fractionated Bu-Flu MAC regimen, which was previously shown to be superior to the standard nonfractionated Bu-Flu MAC [35], although prospective comparative trials would be needed to make firm conclusions about its superiority to the standard non-fractionated Bu-Flu MAC, or to other regimens [36,37].

Acknowledging the high-risk study population, the long-term outcomes of our regimen are encouraging. To reduce the incidence and severity of GVHD and its related long-term complications, our ongoing studies are assessing the impact of using novel GVHD prophylaxis regimens, such as post-HCT cyclophosphamide, with the fractionated Bu-Flu regimen. This may further reduce NRM, because GVHD is the leading contributor to NRM occurring between day 100 and 1 year [38]. Other modifications of this fractionated Bu-Flu regimen to further enhance its efficacy, such as with the addition of other

chemotherapy agents, and further extending the conditioning regimen over 3 weeks period, are ongoing as well (clinicaltrial.gov: NCT02250937, NCT03247088), with an eventual plan to perform randomized trials comparing this regimen to the others. Overall, the fractionated myeloablative Bu-Flu conditioning regimen is well tolerated and leads to an acceptable risk of NRM, relapse, and long-term survival in older patients, those with high-risk disease, and high comorbidities.

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Conflict of interest statement:

R.S.M. received research funding from CSLBehring, Kadmon, and Incyte. K.R. received researching funding from Affimed Therapeutics and Pharmacyclics; served on advisory boards for Adicet Bio, ViroGen and GemoAb; holds a patent on the generation of BKV CTLs for the treatment of HC or PML and a patent on the generation of CAR NK cells; has license and research agreements with Takeda to develop CB-CAR NK cells for the treatment of B-cell malignancies and other cancers.

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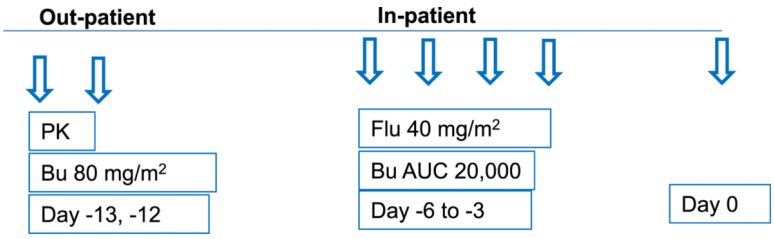


Figure 1.
Treatment regimen and study schema.

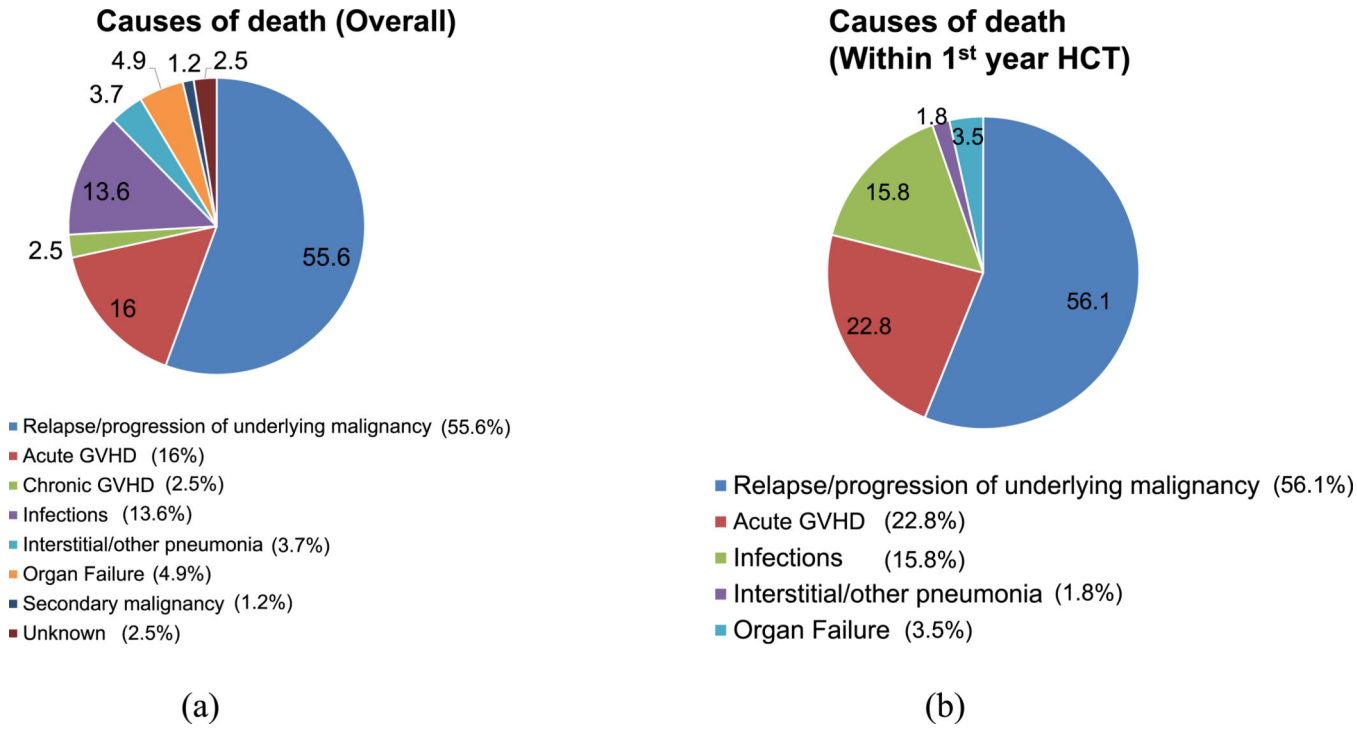


Figure 2.
Causes of death overall (A), and within first year of HCT (B).

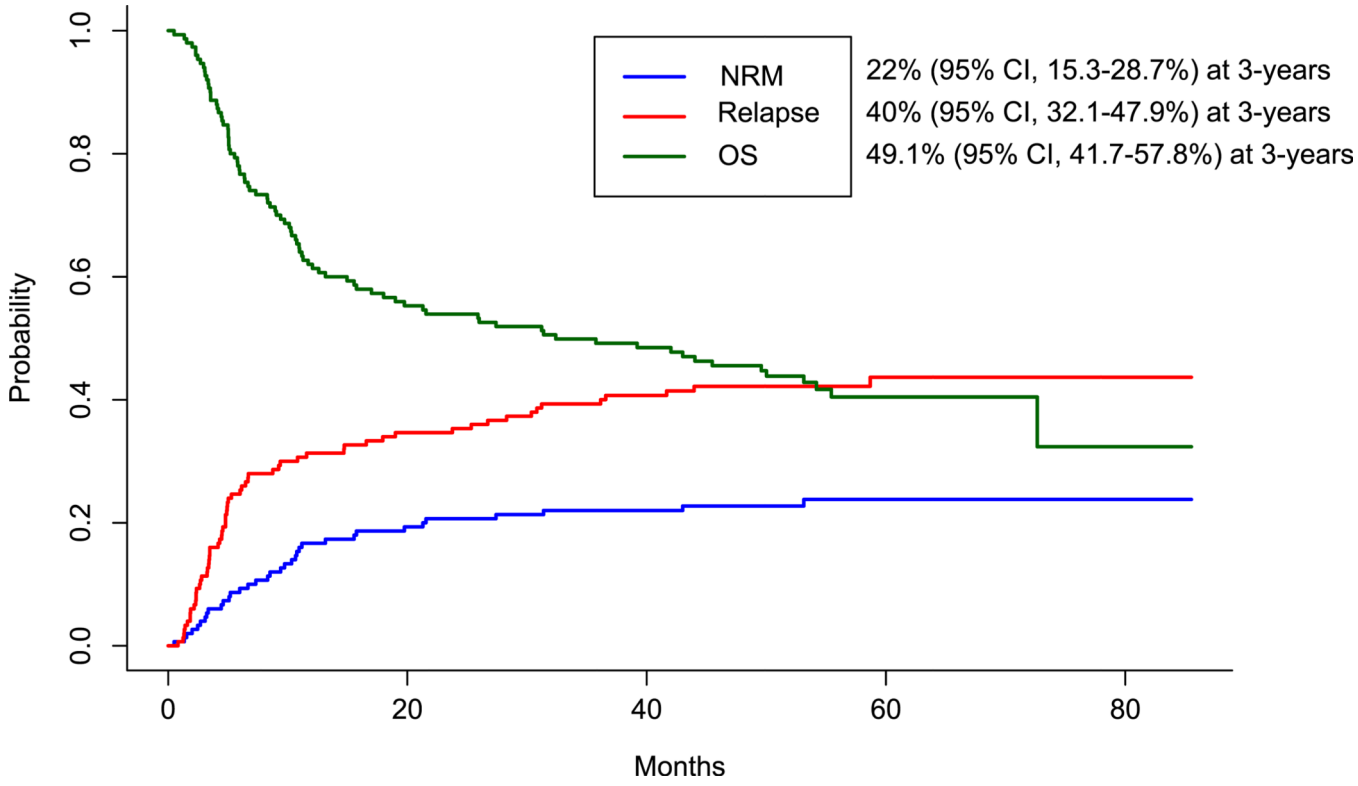
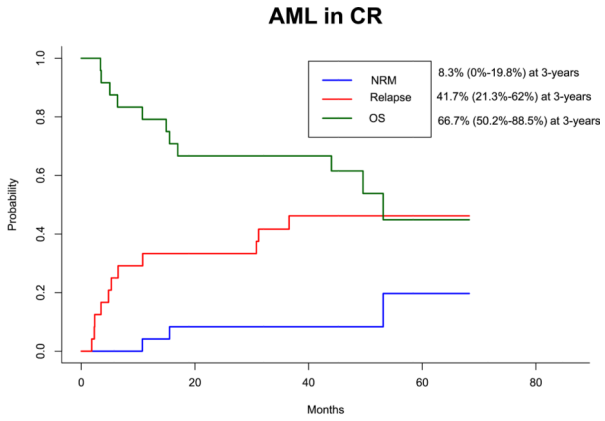
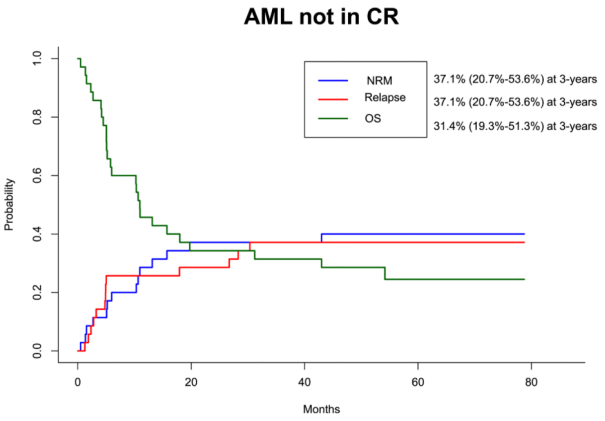


Figure 3.
Overall outcomes of the patient population. Overall nonrelapse mortality (NRM, blue), relapse (red), and overall survival (OS, green) rates among the whole patient cohort.



(a)



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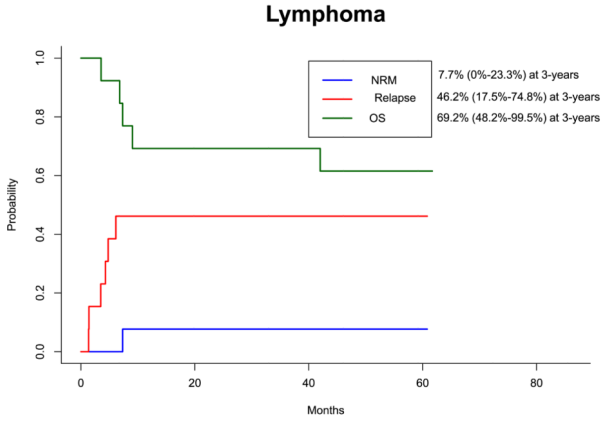


(c)

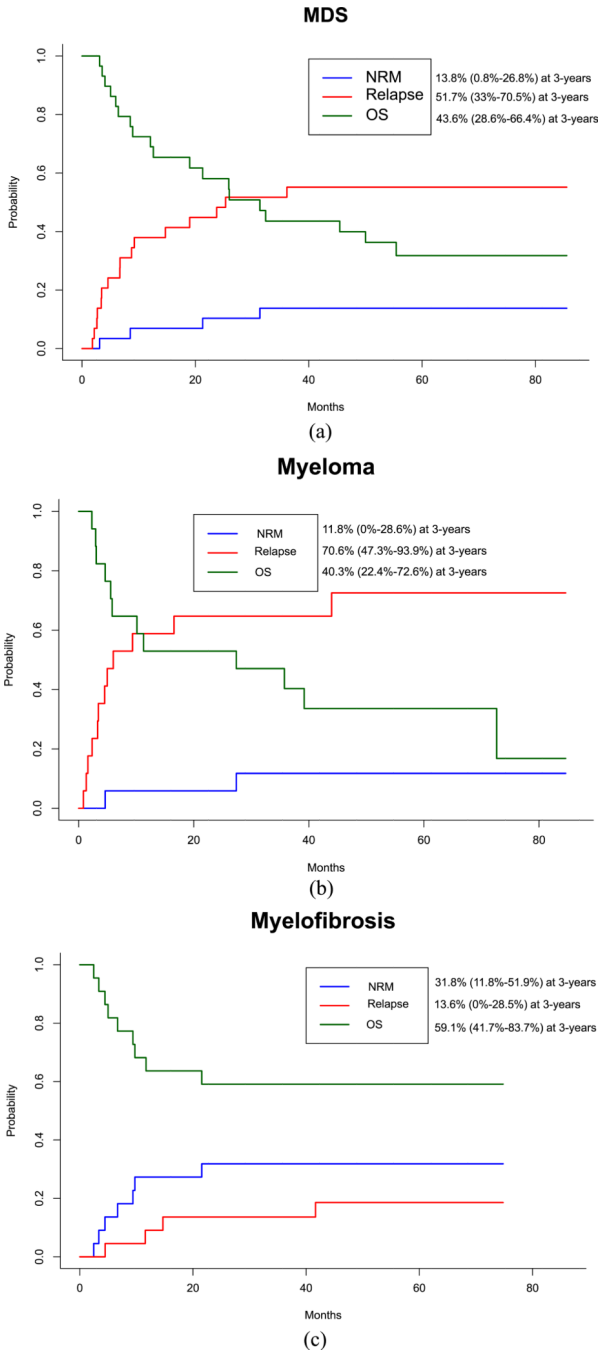
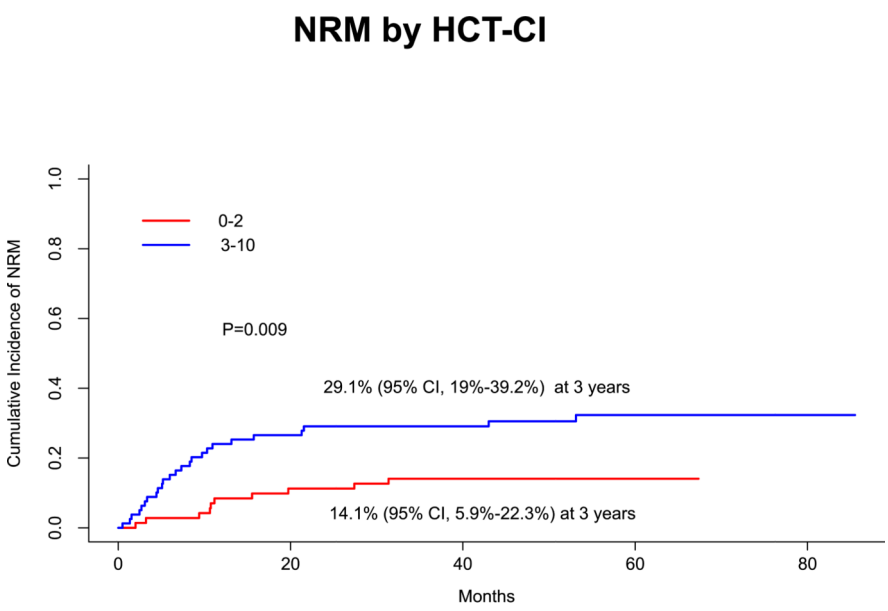
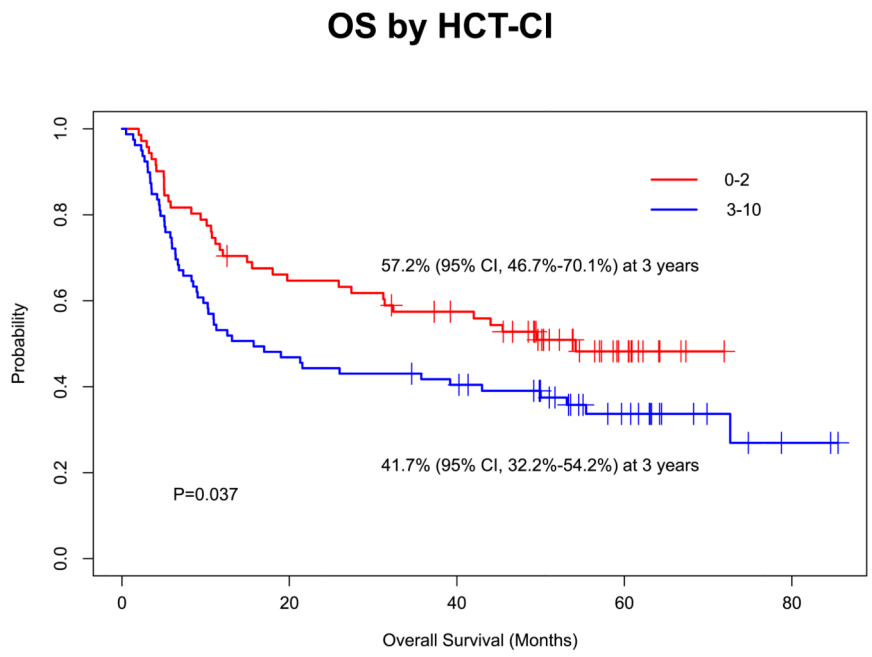


Figure 4.

Outcomes by disease subset. Nonrelapse mortality (NRM, blue), relapse (red), and overall survival (OS, green) rates among patients with AML in CR (A), AML not in CR (B), lymphoma (C), myelodysplastic syndrome (MDS, D), myeloma (E), and myelofibrosis (F).



(a)



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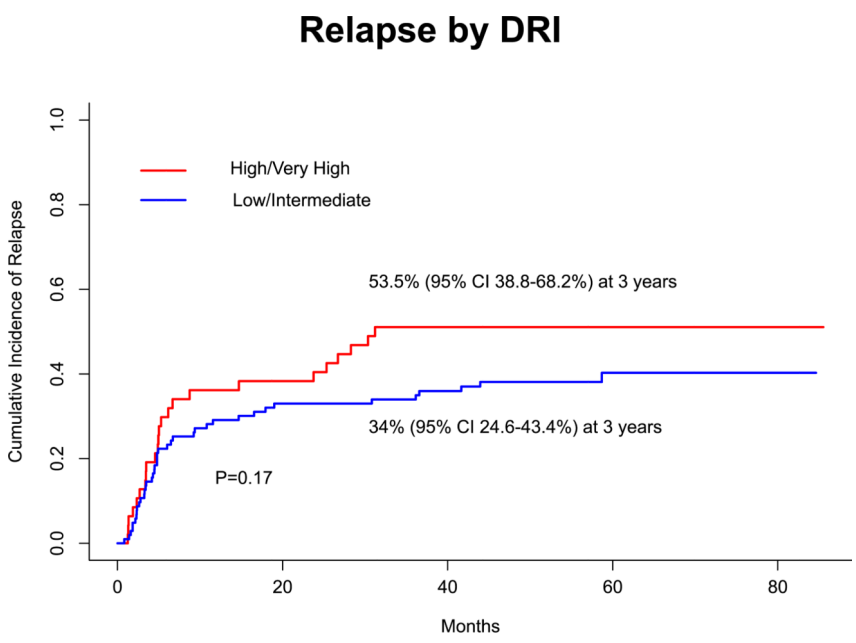

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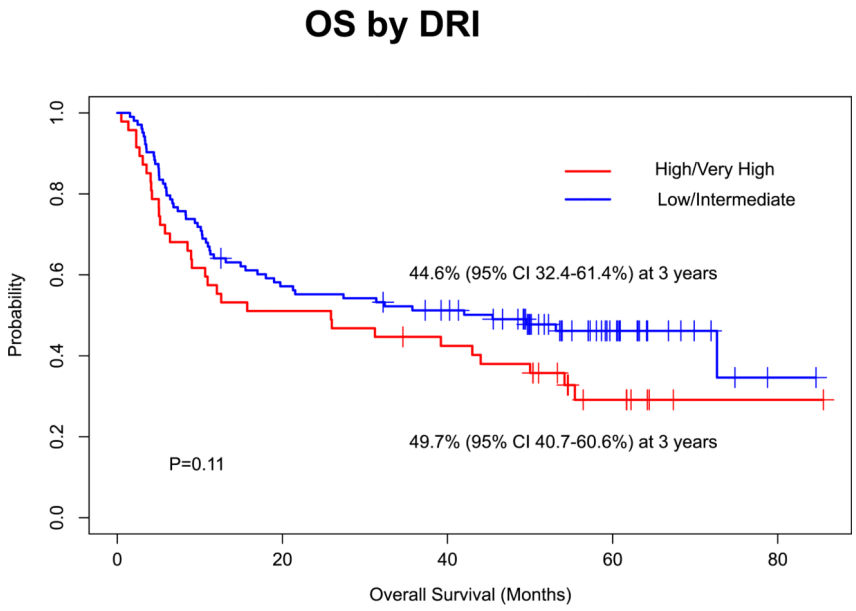

(d)

Figure 5.

Outcomes by HCT-CI and DRI. Outcomes stratified by HCT-specific comorbidity index (HCT-CI) scores of 0–1 (red) and 3–10 (blue). (A) Nonrelapse mortality (NRM) and (B) overall survival (OS). Outcomes stratified by disease risk index (DRI) of high/very high (red) and low/intermediate (blue). Incidence of relapse (C) and OS (D).

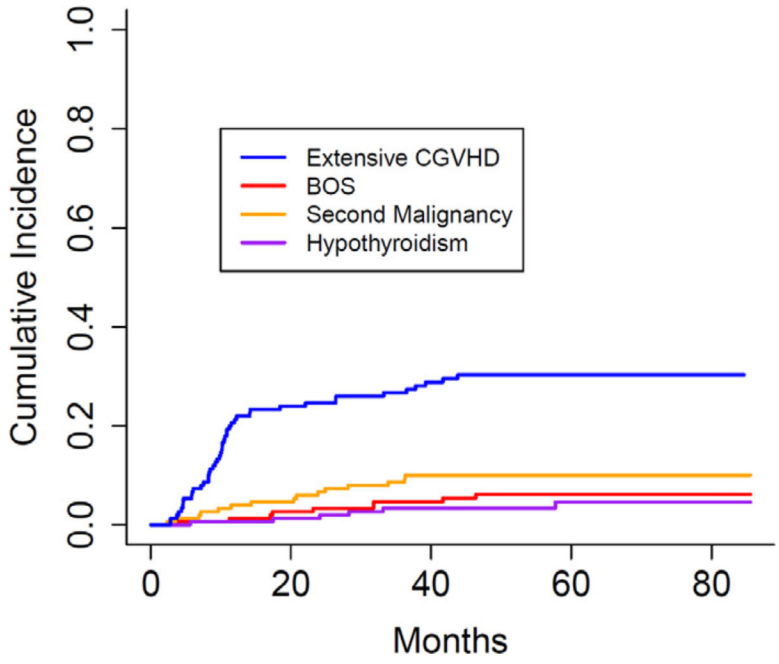

Figure 6.
Cumulative incidence of extensive chronic graft versus host disease (cGVHD), bronchiolitis obliterans syndrome (BOS), secondary malignancies, and hypothyroidism.

Table 1

Baseline Patient Characteristics

Characteristic	No. (%)
No. of patients	150
Age at HCT in years, median (interquartile range) [range]	61 (55-67) [24-75]
Age group	
>65 years	50 (33.3)
Sex	
Male	91 (60.7)
Female	59 (39.3)
Race	
White	131 (87.3)
Other	19 (12.7)
Diagnosis	
Acute myeloid leukemia *	59 (39.3)
Myelodysplastic syndrome	29 (19.3)
Myelofibrosis	22 (14.7)
Multiple myeloma	17 (11.3)
Lymphoma †	13 (8.7)
Chronic myeloid leukemia	7 (4.7)
Acute lymphoblastic leukemia	3 (2)
Prior HCT	
Multiple myeloma ‡	12 (8)
Myelodysplastic syndrome §	4 (2.7)
Disease status/ response prior to HCT	
Acute myeloid leukemia ‖	59
CR	24 (40.7)
CR (MRD positive [n = 8])	11/24 (45.8)
CR (MRD negative [n = 11])	8/24 (33.3)
MRD status unknown (n = 5)	5/24 (20.8)
Relapsed	9 (15.3)
PIF	26 (44.1)
Myelodysplastic syndrome	29
CR	3 (10.3)
PIF	21 (72.4)
Untreated	3 (10.3)
Relapsed	2 (6.9)
Myelofibrosis	22
Untreated	2 (9.1)

Characteristic	No. (%)
Multiple myeloma	17
nCR	2 (11.8)
VGPR	3 (17.6)
PR	8 (47.1)
SD	3 (17.6)
PD	1 (5.9)
Lymphoma	13
CR 1	3 (23.1)
CR ≥2	3 (23.1)
PIF	7 (53.8)
Chronic myeloid leukemia	7
Complete cytogenetic response	3 (42.9)
Minor cytogenetic response	1 (14.2)
No response	3 (42.9)
Donor	
HLA-matched unrelated	93 (62)
HLA-matched sibling	57 (38)
Graft source	
PBPC	110 (73.3)
BM	40 (26.7)
Refined DRI	
Low	6 (4.1)
Intermediate	94 (64)
High	45 (30.6)
Very high	2 (1.4)
HCT-CI	
0-2	71 (47.3)
≥ 3	79 (52.7)
Follow-up among surviving patients, in months; median (interquartile range)	43.4 (38.9-50.4)

BM indicates bone marrow; CR, complete remission; DRI, Disease Risk Index; HCT, hematopoietic cell transplantation; HCT-CI, Hematopoietic Cell Transplantation-Specific Comorbidity Index; HLA, human leukocyte antigen; MRD, measurable residual disease; nCR, near complete remission; PBPC, peripheral blood progenitor cells; PD, progressive disease, PIF, Primary induction failure; PR, partial remission; SD, stable disease; VGPR, very good partial remission.

[*] Thirteen (22%) patients had secondary AML with a preceding history of myelodysplastic syndrome or myeloproliferative disorder.

[†] 6 Mycosis fungoides, 3, Peripheral T-cell Lymphoma, 1 Diffuse large B cell lymphoma, 1 Mantle cell lymphoma and 2 other, unclassifiable.

[‡] Two patients had two prior autologous HCT and one patient had 1 prior autologous and 1 prior allogeneic HCT.

[§] Three patients had 1 prior autologous HCT and one patient had 2 prior autologous HCT.

[‖] European LeukemiaNet revised classification: adverse risk (n = 24 [40.7%]), intermediate risk (n = 29 [49.2%]), favorable risk (n = 5 [8.5%]), and 1 missing.

Table 2

Causes of Death

	Within first year of HCT	1-2 years after HCT	2-3 years after HCT	Beyond 3 years HCT	Total
Relapse/progression of underlying malignancy	32[*]	6[†]	4[‡]	3[§]	45
NRM events	25	6	3	2	36
Total	57	12	7	5	81
Causes of NRM					
Acute GVHD	13	0	0	0	13
Chronic GVHD	0	1	0	1	2
Infections	9	1	1	0	11
Bacterial	5	1	0	0	6
PJP	1	0	0	0	1
Protozoal	1	0	0	0	1
Unspecified	2	0	1	0	3
Interstitial/other pneumonia	1	1	1	0	3
Organ failure	2	1	1	0	4
Secondary malignancy	0	0	0	1	1
Unknown	0	2	0	0	2

GVHD indicates graft-versus-host disease; HCT, hematopoietic stem cell transplantation; PJP, *Pneumocystis jiroveci* pneumonia

[*]13 AML, 6 MDS, 7 myeloma, 3 lymphoma, 2 myelofibrosis, 1 ALL.

[†]3 AML, 3 MDS.

[‡]2 MDS, 1 AML, 1 myeloma.

[§]1 MDS, 1 AML and 1 myeloma.

Table 3

Outcomes

Outcome	NRM	Relapse	PFS	OS
Overall				
1 year	16.7% (10.7%-22.7%)	31.3% (23.9%-38.8%)	52% (44.6%-60.6%)	62% (54.7%-70.3%)
3-year	22% (15.3%-28.7%)	40% (32.1%-47.9%)	38% (30.9%-46.6%)	49.1% (41.7%-57.8%)
Age ≤60 years				
1 year	15.4% (6.5%-24.3%)	27.7% (16.7%-38.7%)	56.9% (46.1%-70.3%)	66.2% (55.6%-78.7%)
3-year	18.5% (8.9%-28%)	40% (27.9%-52.1%)	41.5% (31.1%-55.4%)	56.7% (45.8%-70.2%)
Age ≥60 years				
1 year	17.6% (9.5%-25.8%)	34.1% (24%-44.3%)	48.2% (38.7%-60.1%)	58.8% (49.2%-70.3%)
3-year	24.7% (15.4%-34%)	38.8% (28.4%-49.3%)	36.5% (27.5%-48.3%)	43.5% (34.1%-55.4%)
AML in CR				
1 year	4.2% (0%-12.4%)	33.3% (14%-52.7%)	62.5% (45.8%-85.2%)	79.2% (64.5%-97.2%)
3-year	8.3% (0%-19.8%)	41.7% (21.3%-62%)	50% (33.5%-74.6%)	66.7% (50.2%-88.5%)
AML in CR, MRD negative				
1 year	0% (0%- 0%)	18.2% (0%-42.2%)	81.8% (61.9%-100%)	81.8% (61.9%-100%)
3-year	9.1% (0%- 27.1%)	18.2% (0%-42.2%)	72.7% (50.6%-100%)	72.7% (50.6%-100%)
AML in CR, MRD positive				
1 year	12.5% (0%- 38.8%)	62.5% (24%-100%)	25% (7.5%- 83%)	62.5% (36.5%-100%)
3-year	12.5% (0%- 38.8%)	62.5% (24%- 100%)	25% (7.5%- 83%)	50% (25%-100%)
AML not in CR				
1 year	28.6% (13.3%-43.9%)	25.7% (11%-40.5%)	45.7% (31.9%-65.6%)	45.7% (31.9%-65.6%)
3-year	37.1% (20.7%-53.6%)	37.1% (20.7%-53.6%)	25.7% (14.6%-45.2%)	31.4% (19.3%-51.3%)
MDS				
1 year	6.9% (0%-16.3%)	37.9% (19.8%-56%)	55.2% (39.7%-76.6%)	72.4% (57.8%-90.7%)
3-year	13.8% (0.8%-26.8%)	51.7% (33%-70.5%)	34.5% (20.9%-56.9%)	43.6% (28.6%-66.4%)
Myelofibrosis				
1 year	27.3% (8.1%-46.4%)	9.1% (0%-21.5%)	63.6% (46.4%-87.3%)	63.6% (46.4%-87.3%)
3-year	31.8% (11.8%-51.9%)	13.6% (0%-28.5%)	54.5% (37.2%-79.9%)	59.1% (41.7%-83.7%)

Outcome	NRM	Relapse	PFS	OS
Overall				
Lymphoma				
1 year	7.7% (0%-23.3%)	46.2% (17.5%-74.8%)	46.2% (25.7%-83%)	69.2% (48.2%-99.5%)
3-year	7.7% (0%-23.3%)	46.2% (17.5%-74.8%)	46.2% (25.7%-83%)	69.2% (48.2%-99.5%)
Multiple myeloma				
1 year	5.9% (0%-17.7%)	58.8% (34.1%-83.5%)	35.3% (18.5%-67.2%)	52.9% (33.8%-82.9%)
3-year	11.8% (0%-28.6%)	70.6% (47.3%-93.9%)	17.6% (6.3%-49.3%)	40.3% (22.4%-72.6%)

AML indicates acute myeloid leukemia; CR, complete remission; MDS, myelodysplastic syndrome; MRD, minimal (measurable) residual disease; NRM, non-relapse mortality; OS, overall survival; PFS, progression free survival.

Table 4

GVHD and GRFS

Acute GVHD, day 100	
Grade II-IV	38% (30.2%-45.8%)
Grade III-IV	11.3% (6.2%-16.4%)
Chronic GVHD	
Overall, 1 year	23% (16%-29%)
Overall, 3 years	29% (21%-36%)
Extensive, 1 year	21% (14%-27%)
Extensive, 3 years	27% (20%-34%)
GRFS	
1 year	36% (29.1%-44.6%)
3 years	22.6% (16.8%-30.4%)

GVHD indicates graft-versus-host disease; GRFS, GVHD-free relapse-free survival.