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Allogeneic Hematopoietic Cell Transplant for Adult Chronic Myelomonocytic Leukemia

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for patients with chronic myelomonocytic leukemia (CMML), however, few data exist regarding prognostic factors and transplant outcomes. We performed this retrospective study to identify prognostic factors for post-transplant outcomes. The CMML-specific prognostic scoring system (CPSS) has been validated in subjects receiving non-transplant therapy and was included in our study. From 2001–2012, there were 209 adult subjects who received HCT for CMML reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The median age at transplant was 57 years (range 23–74). Median follow up was 51 months (range, 3–122). On multivariate analyses, CPSS scores, Karnofsky performance status (KPS), and graft source were significant predictors of survival (p=0.004, p=0.01, p=0.01, respectively). Higher CPSS scores were not associated with disease-free survival, relapse, or transplant-related mortality. In a restricted analysis of subjects with relapse following HCT, those with intermediate-2/high risk had a nearly two-fold increased risk of death after relapse compared to those with low/intermediate-1 CPSS scores. Respective 1, 3 and 5-year survival rates for low/intermediate-1 risk subjects were 61% (95% confidence interval [CI], 52%–72%), 48% (95% CI, 37%–59%), and 44% (95% CI, 33%–55%), and for intermediate-2/high risk subjects were 38% (95% CI, 28%–49%), 32% (95% CI, 21% – 42%), and 19% (95% CI,8%–29%). We conclude that higher CPSS score at time of transplant, lower KPS, and a bone marrow (BM) graft are associated with inferior survival after HCT. Further investigation of CMML disease-related biology may provide insights into other risk factors predictive of post-transplant outcomes.

Keywords

Chronic Myelomonocytic Leukemia; Allogeneic Hematopoietic Cell Transplant; Transplant Outcomes

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with both myelodysplastic and myeloproliferative properties. In the original French-American-British (FAB) classification, it was included under myelodysplastic syndromes (MDS) with 2 subtypes based upon white blood cell count, an MDS variant (CMML-MD) and a myeloproliferative variant (CMML-MP). However, these concomitant properties made it difficult to classify, prompting a new category of myeloproliferative/myelodysplastic disorders (MPD/MDS) that was formed in the World Health Organization (WHO) classification of myeloid disorders in 2001.[1,2] The diagnosis of CMML is characterized by a

peripheral blood monocytosis, absence of Philadelphia chromosome, absence of rearrangements of PDGFRA or PDGFRB, presence of <20% blasts in the blood and bone marrow, and evidence of dysplasia in at least one precursor cell lineage (although if myelodyspasia is absent, the diagnosis of CCML can still be made if there is a clonal abnormality or persistent monocytosis and all other causes have been excluded). CMML is further divided into two subcategories with prognostic significance: CMML-1 (presence of <5% blasts in the peripheral blood and <10% blasts in the bone marrow) and CMML-2 (presence of 5–19% blasts in the peripheral blood and 10–19% in the bone marrow). The diagnosis of CMML-2 can also be made if Auer rods are present, irrespective of blast count.[3,4]

CMML has a heterogeneous clinical course, with much variability in survival and rates of transformation to acute myeloid leukemia. Expected survival ranges from months to several years.[5–7] Rates of transformation to acute myeloid leukemia (AML) range from 4% to 44%.[5–7] In a study reported from MD Anderson Cancer Center (MDACC) of 213 patients, the median survival was 12 months with 19% progressing to AML after a median of 7 months (range, 1 to 96 months).[5] Given this wide variability, studies have focused on identifying important risk factors for prognosis and outcomes. A CMML-specific prognostic scoring system (CPSS) assessed at the time of diagnosis has been validated in the non-transplant setting.[8] The CPSS incorporates CMML FAB type, CMML WHO type, CMML-specific cytogenetics, and RBC transfusion dependence.

Unfortunately, effective treatment options for CMML are limited. There are no specific therapies for CMML and the optimal treatment is not yet defined. Several studies in patients with MDS receiving azacitidine and decitabine have included CMML patients, however, the number of CMML patients included is small and results are difficult to interpret for this population.[9,10] Allogeneic hematopoietic cell transplant (HCT) remains the only potentially curative treatment and outcomes following transplant are sparse.[11–18] Some of these reports suggest that the percentage of blasts present in the peripheral blood, cytogenetic abnormalities, and transplant type may have prognostic importance following transplant. However, the studies are limited by small numbers of patients from single institutions and no definitive conclusions have been made.

Our retrospective study assessed the outcomes of 209 consecutive adult subjects who underwent HCT for CMML reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) registry from 2001 through 2012. The purpose of our study was to identify prognostic risk factors for post-transplant outcomes.

Patients and Methods

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic allogeneic and autologous HCT to a centralized Statistical Center. Observational studies conducted by CIBMTR are performed in compliance with all applicable federal

regulations pertaining to the protection of human research participants. Protected health information issued in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere.[19]

Subject Eligibility

Between 2001 and 2012, 209 adult patients (18 years of age or older) who underwent first HCT from HLA-identical sibling or adult unrelated-donor for CMML were identified for this analysis. Patients receiving cord blood transplants (N=20), ex-vivo T cell depletion (N=6), CD34-selection (N=6), or post-transplant cyclophosphamide (N=1) as part of their graft-versus-host disease (GvHD) prophylaxis were excluded. Subjects missing 100-day follow-up data were also excluded.

Study Endpoints

Primary endpoints were treatment-related mortality (TRM), relapse/progression, disease-free survival (DFS) and survival. TRM was defined as death from any cause in the first 28 days post transplantation, irrespective of relapse status, or death beyond day +28 without any evidence of disease recurrence; relapse was considered a competing event. Relapse/progression was defined as reported by the transplantation centers. DFS is defined as time to relapse or death from any cause. Survival is defined as time to death from any cause. Subjects were censored at time of last follow-up. Secondary endpoints included hematopoietic recovery, acute and chronic graftversus- host disease (GvHD). Hematopoietic recovery was defined as time to absolute neutrophil count $\geq 0.5 \times 10^9$ /L for ≥3 consecutive days and time to platelets $\geq 20 \times 10^9$ /L without transfusions for 7 days, using the first of 3 consecutive results obtained on different days. Acute and chronic GvHD were diagnosed and graded using consensus criteria.[20,21] For hematopoietic recovery and GvHD, death without the event was considered a competing event. The transplantation conditioning regimen intensity was determined according to the CIBMTR Reduced-Intensity Conditioning (RIC) Regimen Workshop.[22] CPSS scores were calculated at the time of transplant and were based on information from CIBMTR registry. The CPSS scoring system incorporates CMML FAB type, CMML WHO type, CMML-specific cytogenetics, and RBC transfusion dependence.[8] Within the CPSS scoring system, there are 4 risk groups: low (score = 0), intermediate-1 (score =1), intermediate-2 (score = 2–3, and high (score = 4–5). each variable is assigned the same weight. A score is calculated by adding together the points according to risk factors. WHO subtype CMML-1 and CMML-2 are assigned 0 and 1 points, respectively. FAB subtype CMML-MD and CMML-MP are assigned 0 and 1 points, respectively. CMML-specific cytogenetic risk classification is as follows: low, normal and isolated -Y (0 points); intermediate, other abnormalities (1 point); high (2 points), trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7. Of note, the CPSS scoring system also include red blood cell transfusion defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months. The CIBMTR registry includes information about transfusion dependency, but does not specify the frequency of transfusion.

Statistical Analysis

Descriptive tables of donor- and collection-related variables were prepared. Probabilities of DFS and survival at 1, 3, and 5 years were calculated using the Kaplan-Meier estimator, with lost follow-up treated as a censoring event. Incidence rates for other outcomes were generated using the cumulative incidence estimates to adjust for competing risks (death without the event of interest). Point-wise p-values were calculated to evaluate the differences at specified time points.

Multi-variate analyses for survival, TRM, relapse, and GVHD were performed using the Cox proportional hazard model adjusting for the effects of covariates. Logistic regression was utilized to analyze neutrophil engraftment at 28 days and platelet recovery at 100 days. Covariates considered for prognostic value included: patient-related variables (patient age, gender, and Karnofsky score), disease-related variables (time from diagnosis to transplant, CPSS prior to transplant, treatment prior to transplant), and transplant-related variables (graft source, donor type, donor age, antithymocyte globulin (ATG)/alemtuzumab use, GvHD prophylaxis, donor/recipient sex match, donor/recipient CMV status, year of transplantation). Adjusted analyses of the outcomes were performed where additional covariates and interactions were determined by stepwise selection. We attempted to identify a profile for high vs. low risk prognosis for survival and relapse. Due to the small sample size available, the entire cohort was used for training to select the model and five-fold cross-validation was used to assess out-ofsample performance. We also performed multi-variate analysis for OS restricted to patients who relapsed following HCT. Adjusted cumulative incidence curves were produced for TRM and relapse of the high vs. low risk groups. SAS 9.3 (SAS Inc.) was used for all analyses.

Results

Transplantation Subjects

Subject- and disease-related characteristics are presented in Table 1. Between 2001 and 2012, 209 consecutive adult patients from 94 institutions underwent HCT for CMML. The median ages at transplant for patients with low/intermediate-1 and intermediate-2/high were 59 years and 55 years, respectively. The majority of patients were male (71% in patients with low/intermediate-1 and 66% in intermediate-2/high). Most patients had Karnofsky Performance Scores (KPS) of 90–100%. CPSS scores at the time of transplant (HCT specific CPSS scores) were available for 80% of subjects. Cytogenetic data were available for 86% of subjects. Median time from diagnosis to transplant was 8 months. Approximately one-third of subjects were transplanted from an HLA-identical sibling. The remaining two-thirds were transplanted from unrelated donors; a majority of these subjects (70%) were from well-matched unrelated donors. Peripheral blood (PB) was used as the graft source in 84% of subjects. Myeloablative conditioning regimens were given to 51% of subjects. Almost all patients received non-total body irradiation (TBI) based therapies (only 5 patients received TBI). GVHD prophylaxis mostly consisted of tacrolimus-based regimens (61%). The median follow up of surviving patients was 51 months.

Hematopoietic Recovery

On univariate analysis, rates of neutrophil recovery at days 28 and 100 were comparable between subjects with low/intermediate-1 and those with intermediate-2/high HCT specific CPSS scores (94% [95% CI, 86%–98%] and 89% [95% CI, 79% to 95%] at day 28, respectively, p=0.40; 99% [95% CI, 87% to 100%] and 96% [95% CI, 80% to 99%] at day 100, respectively, p=0.51). Platelet recovery at day 28 was comparable between groups. However, more subjects in the low/intermediate-1 group achieved platelet recovery at day 100 compared to the intermediate-2/high risk group (94% [95% CI, 86% to 98%] compared to 80% [95% CI, 69% to 87%] (p=0.007). There were no primary graft failures. (Table 2)

Neutrophil engraftment and platelet recovery between subjects receiving PB and BM graft were also compared. Neutrophil engraftment at day 28 was lower for subjects in the BM group; however by day 100, groups were similar: BM group 78% (95% CI, 59%–89%) and PB group 94% (95% CI, 89%–97%) at day 28, BM group 94%(95% CI, 69%–99%) and PB group 98%(93%–99%) at day 100. Platelet recovery at day 28 was again lower for subjects in the BM group; however by 100, groups were again similar: BM group 44% (95% CI, 26%–60%) and PB group 70% (95% CI, 62%–76%) at day 28, BM group 73%(95% CI, 51%–86%) and PB group 88%(95% CI, 82%–92%) at day 100.

Acute and Chronic GvHD

On univariate analysis, the cumulative incidence of grades ≥2 to 4 acute GvHD at day 100 were comparable between those with low/intermediate-1 and intermediate-2/high risk disease groups (34% [95% CI, 24% to 44%] and 38% [95% CI, 27% to 49%], respectively). On multivariate analysis, only donor type was associated with acute GvHD (p=0.002). The cumulative incidence of chronic GVHD at 1, 3, and 5 years were also comparable between groups (50% [95% CI, 38% to 60%] and 41% [95% CI 30% to 52%] at 1 year; 51% [95% CI, 40% to 61%] and 41% [95% CI, 30% to 52%] at 3 years; 51% [95% CI 40% to 61%] and 41% [95% CI, 30% to 52%], respectively). (Table 2) On multivariate analysis, only donor type was associated with acute GvHD (p=0.002). (Table 3)

Treatment Related Mortality

On univariate analysis, there was no significant difference in TRM at 1, 3, or 5 years between low/intermediate-1 (15% [95% CI, 9% to 24%], 20% [95% CI, 12% to 29%] and 22% [95% CI, 13% to 32%]) and intermediate-2/high risk groups (19% [95% CI, 11% to 29%], 21% [95% CI, 12% to 31%], and 26% [16% to 37%], respectively). (Table 2) On multivariate analysis, higher HCT specific CPSS scores and KPS scores were not associated with TRM (p=0.08 and p=0.03, respectively). (Table 3)

Relapse

On univariate analysis, relapse rates at 1, 3, and 5 years between low/intermediate-1 and intermediate-2/high groups were comparable (46% [95% CI, 35% to 56%], 50% [95% CI, 39% to 61%], 52% [95% CI, 40% to 63%], respectively, and 54% [95%CI, 41% to 64%], 56% [95% CI, 44% to 67%], and 60% [95% CI, 47 % to 70%], respectively). On multivariate analysis, HCT specific CPSS scores were not associated with relapse (p=0.112). (Table 3)

Survival Outcomes

On univariate analysis, DFS rates were comparable: for low/intermediate-1 risk groups, at 1, 3, and 5 years were 38% (95% CI, 28% to 49%), 30% (95% CI, 20% to 40%), and 26% (95% CI, 17% to 37%), respectively, and for intermediate-2/high risk groups were 28% (95% CI, 18% to 38%), 23% (95% CI, 14% to 33%), and 14% (95% CI, 6% to 24%), respectively. On multivariate analysis, CPSS scores did not impact DFS (p=0.21), however higher KPS scores were associated with improved DFS (p=0.02). (Table 3)

On univariate analysis, low/intermediate-1 risk groups had higher rates of OS at 1, 3, and 5 years: corresponding rates for low/intermediate-1 risk groups were 61% (95% CI, 51% to 71%), 48% (95% CI, 37% to 59%), and 44% (95% CI, 33% to 56%) respectively and for intermediate-2/high risk groups were 38% (95% CI 27% to 49%), 31% (95% CI, 21% to 42%), and 18% (95% CI, 8% to 30%) respectively. (Table 2) On multivariate analysis, HCT specific CPSS scores, KPS and graft source were significant predictors of survival (p=0.005, p=0.01, and p=0.02, respectively). Patients receiving PB had more favorable outcome. (Table 3) Adjusted OS and DFS starting at time of transplant, based on HCT specific scores, are shown in Figures 1 and 2.

To investigate why higher HCT specific CPSS scores were associated with higher mortality but not DFS, we performed multivariate analysis restricted to patients with relapse following HCT. Those with intermediate-2/high risk had nearly two-fold increased risk of death after relapse compared to those with low/intermediate-1 HCT specific CPSS scores.

On multivariate analysis, survival of patients who received pre-HCT treatment with hypomethylating agents (HMA), chemotherapy, or both was not different compared to those who received no prior therapy (p=0.96).

Discussion

Allogeneic HCT remains the only potentially curative treatment for patients with CMML. Few data exist regarding transplant outcomes and there are no randomized clinical trials comparing transplant to non-transplant approaches. Most studies are limited by their retrospective nature and small sample size. (Table 4) While our study is also retrospective, it represents a large series with a long median follow up. The median age of our patients was 57 years, older than in other reported studies.[11–18, 22] The median follow up in our study is 51 months, longer than in most other reported studies.[11–13, 15–18, 23–27] Subjects underwent either myeloablative or RIC preparative regimen. The majority of patients received PB as their graft source. Our study is unique in that we not only describe transplant outcomes, but we also validated a predictive model for survival and relapse. Patient stratification according to HCT specific CPSS scores was prognostic for transplant outcomes.

Given the heterogeneity of clinical outcomes for patients with CMML, it is important to better define and stratify risk for patients with CMML. The International Prognostic Scoring System (IPSS) is widely used for myelodysplastic syndrome. However, for CMML patients, analysis and validation were restricted to patients with WBC < 12×10^9/L, excluding patients with myeloproliferative characteristics and not applicable for all patients with

CMML.[28] There are several prognostic scoring systems developed for CMML, however, they each have limitations and have not been validated in the setting of transplant.[5,6,29–31] (Table 5) The CPSS incorporates CMML FAB type, CMML WHO type, CMML-specific cytogenetics, and RBC transfusion dependence. The CPSS calculated at diagnosis is a simple scoring system that was developed in the large patient sample size and was externally validated, in the non-transplant setting.[8] The CPSS score at diagnosis has been shown to be predictive of survival and risk of progression to AML. Our study sought to validate the CPSS, calculated at the time of transplant, in the setting of HCT. In multivariate analysis, higher HCT specific CPSS scores were associated with inferior survival. It was not, however, associated with DFS, relapse, or TRM. In order to further investigate why higher HCT specific CPSS scores were associated with higher mortality, but not with DFS, we performed an analysis restricted to subjects who relapsed after transplant. This revealed that subjects with intermediate-2/high risk HCT specific CPSS scores had a nearly two-fold increased risk of death after relapse compared to those with low/intermediate-1 HCT specific CPSS scores. Intermediate-2/high risk patients do have higher disease burden and poorer risk cytogenetic abnormalities. Higher HCT specific CPSS scores are predictive of poorer treatment response and more aggressive biology. Interestingly, regardless of HCT specific CPSS scores, the main cause of death was primary disease. (Table 6) Post-transplant donor lymphocyte infusion and/or 2nd HSCT were similar between groups. Other post-transplant strategies, such as azacitidine maintenance in patients with myelodysplastic syndromes or acute myeloid leukemia, may be beneficial for these patients and warrants further investigation.[32]

We observed favorable survival with PB graft compared to BM. The majority of subjects received PB grafts. While the incidence of acute or chronic GVHD was comparable between those who received PB or bone marrow grafts, subjects who received PB grafts had improved survival compared with those who received bone marrow. This is contrary to what has been reported in other studies.[33–36] It is also interesting to note that no deaths in the bone marrow graft group were due to graft failure. It is unclear why those patients with BM had poorer survival; however our study is limited in that only a small number of subjects received bone marrow grafts (16%).

We also evaluated the effect of prior therapy on transplant. Few published studies have included information on use of HMA and transplant outcomes. Over the last decade, hypomethylating agents have become a cornerstone of therapy for MDS and CMML.[37–42] We cannot determine whether pre-transplant HMA therapy or chemotherapy affected transplant eligibility. However, our data shows that pre-transplant treatment with HMA therapy or chemotherapy had no impact on transplant outcomes. This is contrary to a recent publication from Kongtim *et al* that reports lower relapse and improved progression-free survival for patients treated with hypomethylating agents prior to alloHCT.[18]

Our registry-based study is limited to the data contained in the CIBMTR database. Transplantations were performed at many different institutions, with varying conditioning regiments and GvHD prophylaxis. We recognize that the original CPSS score was calculated at time of diagnosis. We use the same variables that are part of the original CPSS, now calculated at the time of transplant, to attempt to validate this scoring system in the HCT

setting. Another limitation of our study is that data regarding CPSS was missing for many of our subjects (20%). Another limitation is regarding missing details of transfusion dependence; as part of criteria for the CPSS, transfusion dependence is defined as requiring at least 1 red blood cell transfusion every 8 weeks over a period of 4 months.[8] While patients may meet this minimal criteria, we do not have data on how many transfusions and how frequently these transfusions were required for our subjects. We also do not have data on whether subjects had splenomegaly prior to HCT, which has been suggested to also have prognostic significance.[25]

We conclude that allogeneic HCT remains an important treatment that is curative for some patients with CMML. Higher HCT specific CPSS scores, lower KPS, and bone marrow graft source are associated with inferior outcomes following allogeneic HCT. Future investigation to further elucidate the biology of CMML may help identify other risk factors that better predict which patients benefit most from transplant.

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Highlights

- Hematopoietic cell transplant is an important and potentially curative treatment option for patients with chronic myelomonocytic leukemia.
- Higher CPSS scores, lower performance status, and bone marrow graft are associated with inferior survival post-BMT.
- Treatment with hypomethylating agents or chemotherapy prior to transplant did not impact transplant outcomes.

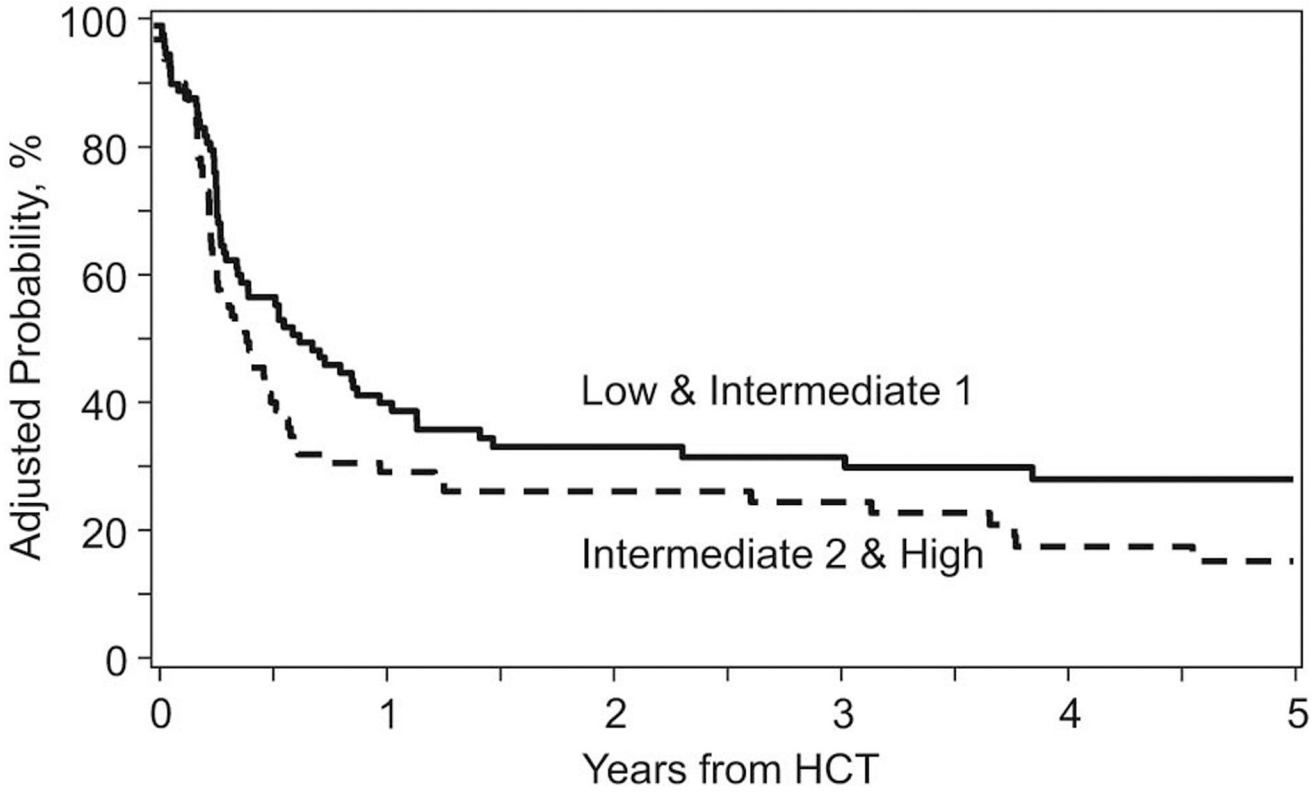

Figure 1.
Adjusted disease free survival and overall survival, starting at the time of transplant, by HCT Specific CPSS

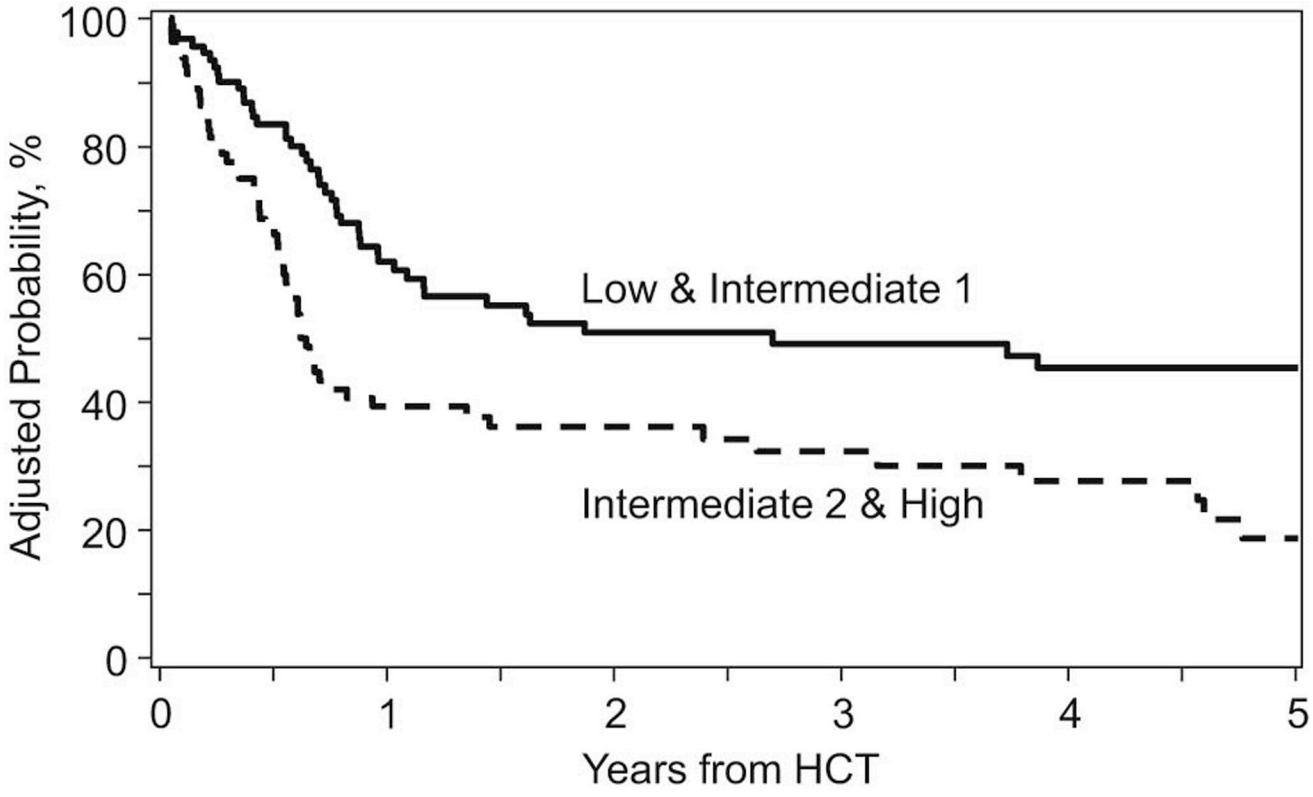

Figure 2.
Adjusted disease free survival and overall survival, starting at the time of transplant, by HCT Specific CPSS

Table 1

Characteristics of patients received allogeneic HCT for CMML between 2001 and 2012

Variable	N (%)
Number of patients	209
Number of centers	94
Patient-related	
Age, median	57 (23–74)
Gender	
Male	146 (70)
Female	63 (30)
Karnofsky score	
90–100%	127 (61)
< 90%	74 (35)
Missing	8 (4)
Disease-related	
Time from diagnosis to transplant, months	8 (2–170)
HMA and chemotherapy prior to transplant	
HMA	74 (35)
Chemo	19 (9)
HMA & chemo	6 (3)
No HMA or chemo	106 (51)
Missing	4 (2)
CMML-1 vs. CMML-2	
CMML-1	140 (67)
CMML-2	52 (25)
Missing	17 (8)
Blast in marrow prior to transplant	
≤ 5%	136 (65)
> 5%	56 (27)
Missing	17 (8)
HCT Specific CPSS	
Low	38 (18)
Intermediate-1	52 (25)
Intermediate-2	63 (30)
High	16 (8)
Missing	40 (19)
Platelet count prior to transplant	
≥ 100×10^9/L	88 (42)
< 100×10^9/L	121 (58)
ANC prior to transplant	
≥ 1500 /uL	143 (68)
< 1500 /uL	54 (26)

Variable	N (%)
Missing	12 (6)
Transplant-related	
Graft type	
Bone marrow	33 (16)
Peripheral blood	176 (84)
Type of donor	
HLA-identical sibling	73 (35)
Well-matched unrelated	95 (45)
Partially-matched unrelated	32 (15)
Mis-matched unrelated	4 (2)
Unrelated (matching indeterminable)	5 (2)
Donor age, median	
HLA-identical sibling	54 (27–74)
URD	34 (19–61)
D-R sex match	
M-M	96 (46)
M-F	40 (19)
F-M	50 (24)
F-F	22 (11)
Missing	1 (<1)
D-R CMV status	
+/+	47 (22)
+/−	24 (11)
−/+	63 (30)
−/−	65 (31)
Missing	10 (5)
Year of transplant	
2001–2003	39 (19)
2004–2006	51 (24)
2007–2009	53 (25)
2010–2012	66 (32)
Conditioning regimen combination	
Myeloablative	105 (50)
RIC/NMA	99 (48)
Missing	5 (2)
Serotherapy used	
ATG alone	58 (28)
CAMPATH alone	8 (4)
No ATG or CAMPATH	132 (63)
Missing	11 (5)
GVHD prophylaxis	
CSA based	78 (37)

Variable	N (%)
TAC based	127 (61)
MTX alone	2 (<1)
Missing	2 (<1)
Median follow-up of survivors (range), months	51 (3–122)

Table 2

Univariate analysis for patients who received allogeneic HCT for CMML between 2001 and 2012

	Study population (N = 209)	
Outcomes	**N Eval**	**Prob (95% CI)**
Neutrophil engraftment	206	
28-day		92 (88–95)%
100-day		97 (95–99)%
Platelet recovery	207	
28-day		66 (59–72)%
100-day		86 (81–90)%
Acute GVHD	209	
100-day		36 (30–43)%
Chronic GVHD	209	
1-year		45 (38–52)%
3-year		47 (40–54)%
5-year		47 (40–54)%
Relapse	200	
1-year		46 (39–53)%
3-year		50 (43–57)%
5-year		52 (45–59)%
Treatment related mortality	200	
1-year		19 (14–25)%
3-year		23 (18–30)%
5-year		28 (21–35)%
Disease free survival	200	
1-year		35 (28–42)%
3-year		27 (21–33)%
5-year		20 (14–27)%
Overall survival	209	
1-year		50 (43–57)%
3-year		38 (31–45)%
5-year		30 (23–37)%

Table 3

Multi-variate analysis for adult CMML subjects who received allogeneic HCT between 2001 and 2012[1]

1. Survival					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	88	1			0.0045
Intermediate 2 & High	79	1.927	1.299–2.858	0.0011	
Missing	42	1.571	0.976–2.529	0.0627	
KPS					
90–100%	127	1			0.0119
<90%	74	1.717	1.200–2.457	0.0031	
Missing	8	1.444	0.625–3.336	0.39	
Graft type					
BM	33	1			0.0196
PB	176	0.584	0.371–0.917	0.0196	
Contrast					
Intermediate 2 & High vs. Missing		1.2263	0.774–1.942	0.3845	
<90% vs. Missing		1.1893	0.508–2.784	0.6896	
2. DFS					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	85	1			0.2065
Intermediate 2 & High	76	1.38	0.965–1.972	0.0772	
Missing	39	1.137	0.729–1.773	0.5722	
KPS					
90–100%	119	1			0.0183
<90%	74	1.607	1.156–2.234	0.0047	
Missing	7	1.297	0.562–2.997	0.5423	
Contrast					
Intermediate 2 & High vs. Missing		1.2138	0.781–1.886	0.3885	
<90% vs. Missing		1.2387	0.530–2.894	0.621	
3. TRM					Overall

	N	RR	95% CI	p-value	p-value
HCT Specific CPSS					0.0884
Low & Intermediate 1	85	1			
Intermediate 2 & High	76	1.485	0.762–2.895	0.2455	
Missing	39	2.183	1.089–4.375	0.0277	
KPS					0.0301
90–100%	119	1			
<90%	74	2.15	1.219–3.790	0.0081	
Missing	7	1.348	0.315–5.768	0.6869	
Contrast					
Intermediate 2 & High vs. Missing		0.6803	0.344–1.343	0.2668	
<90% vs. Missing		1.5943	0.369–6.887	0.5321	

4. Relapse					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	85	1			0.118
Intermediate 2 & High	76	1.321	0.869–2.009	0.1929	
Missing	39	0.719	0.393–1.316	0.2851	
Contrast					
Intermediate 2 & High vs. Missing		1.8369	1.001–3.372	0.0498	

5. Acute GVHD					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	88	1			0.592
Intermediate 2 & High	79	1.266	0.779–2.057	0.3418	
Missing	42	1.014	0.544–1.890	0.9656	
Donor					0.0017
HLA identical sibling	73	1			
Well-matched URD	95	1.063	0.633–1.785	0.8165	
Partially-matched URD or MM URD	36	2.836	1.560–5.156	0.0006	
Missing (URD)	5	2.304	0.694–7.651	0.1727	
Contrast					
Intermediate 2 & High vs. Missing		1.2483	0.677–2.304	0.478	
Well-matched URD vs. Partially-matched or MM URD		0.3749	0.211–0.665	0.0008	

Well-matched URD vs. Missing (URD)		0.4614	0.140–1.516	0.2024	
Partially-matched or MM URD vs. Missing (URD)		1.2308	0.361–4.198	0.7401	
6. Chronic GVHD					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	88	1			0.9131
Intermediate 2 & High	79	1.087	0.681–1.734	0.7263	
Missing	42	1.107	0.623–1.967	0.7289	
Contrast					
Intermediate 2 & High vs. Missing		0.9819	0.535–1.802	0.953	
7. OS after relapse[2]					Overall
HCT Specific CPSS	N	RR	95% CI	p-value	p-value
Low & Intermediate 1	46	1			0.0262
Intermediate 2 & High	44	1.993	1.199–3.311	0.0078	
Missing	14	1.737	0.836–3.608	0.1389	

[1]The majority of the patients achieved neutrophil engraftment by day 28 and platelet recovery by day 100 (Table 2), therefore multi-variate analysis was not performed for them.

List of abbreviations: disease free survival (DFS), overall survival (OS), transplant related mortality (TRM), non-relapse mortality (NRM), bone marrow (BM), myeloablative (MAC), second primary malignancy (SPM), lactate dehydrogenase (LDH), red blood cell (RBC), peripheral blood (PB)

[2]Overall survival was compared with relapse instead of using the left-truncated model, so analysis was performed starting at the time of relapse and non-relapse patients were excluded in this model.

Table 4

Allogeneic hematopoietic transplant studies in patients with CMML

	Patients	Median age	Conditioning	Cell source	DFS/PFS %	OS %	TRM/NRM %	Relapse %	Median follow up, months	Factors predictive of OS
Zang et al (2000)[10]	21	47	MAC: 21 RIC: 0	BM: 21 PB: 0	25 (3 yrs)	39 (3 yrs)	34	23	Unknown	Patients transplanted early (< 12 months from diagnosis) had better survival.
Kroger et al (2002)[11]	50	44	MAC: 50 RIC:0	BM: 40 PB: 9	18 (5 yrs)	21 (5 yrs)	52	49	40 (range, 11 to 110)	No correlation
Mittal et al (2004)[12]	8	51	MAC: 4 RIC: 4	BM: 4 PB: 4	37 (2 yrs)	47 (2 yrs)	13	63	17.5	Number too small
Kerbauy et al (2005)[13]	43	48	MAC: 41 RIC: 2	BM: 23 PB: 20	41 (4 years)	41 (4 years)	34	23 (4 years)	69 (range, 7 to 171)	MDAPS not correlative. Higher comorbidity scores associated with worse OS
Elliot et al (2006)[14]	17	50	MAC:16 RIC: 1	BM: 8 PB: 7	18 (3 yrs)	18 (3 yrs)	41	41	34.5	No correlation
Laport et al (2008)[15]	7	59	MAC: 0 RIC: 7	Unknown, likely PB	43 (3 yrs)	43 (3 yrs)	32 (3 years)	57	47 (range, 6 to 89)	Number too small
Krishnamurthy et al (2010)[14]	18	54	MAC:1 RIC 17	BM: 18 PB: 36		31% (3 yrs)	22	44	40 (range, 1 to 59)	None
Eissa et al (2011)[23]	85	51	MAC: 58 RIC: 27	BM: 32 PB: 53	40 (10 yrs)	42 (5 years)	35 (10 years)	27 (10 yrs)	62 (range, 6 to 229)	MDAPS not correlative. Mortality negatively correlated with pre-HCT hematocrit and increased high-risk cytogenetics, higher HCT comorbidity index, and increased age
Lim et al (2013)[24]	7	43	MAC: 3 RIC: 7	BM: 2 PB: 7	51 (5 years)	42% (5 years)	14	29 (5 years)	47.5 (range, 4.6 to 98.8)	Number too small
Park et al (2013)[25]	73	53	MAC: 30 RIC: 43	BM: 27 PB: 46	29 (3 years)	42 (2 years) 32 (3 years)	36 (3 years)	29 (3 years)	23 (range, 1–145)	Palpable SPM, transplant performed prior to 2004 correlated with poorer OS

	Patients	Median age	Conditioning	Cell source	DFS/ PFS %	OS %	TRM/NRM %	Relapse %	Median follow up, months	Factors predictive of OS
Bajel et al (2014)[26]	57	56	MAC:28 RIC: 29	BM: 3 PB: 54	40 (6 years)	27 (6 years)	39 (6 years)	35 (6 years)	15.3 (range, 0.6 to 154)	In multivariate analysis, age < 50yo, non-sibling donor, and lymphocyte count > 2.9×10^9/L were associated with worse OS and PFS. Bone marrow blasts pre-transplant were associated with higher risk of relapse.
Sanchez et al (2014)[27]	28	60	MAC: 16 (T-cell depleted) RIC: 12	BM: 2 PB: 23 Cord: 3	74 (3 years)	71 (3 years)	7 (1 year)	13 (1 year)	39.6 (range, 3 to 35)	
Symeonidis et al (2015)[17]	513	53	MAC: 249 (52%) RIC: 226 (48%)	BM: 119 (23%) PB: 394 (77%)	27% (4 years)	33% (4 years)	31% (1 year) 41% (4 years)	32 (4 years)		Patients transplanted in CR had lower probability for non-relapse death and longer survival.
Kongtim et al (2016)[18]	83	57	MAC: 64 (77%)	BM: 35 (42%) PB: 48 (58%)	34% (3 years)	CMML-1/2: 36% (3 years) CMML/AML: 32% (3 years)	25% (day 100) 31% (1 year)	33% (3 years)	48	Use of HMA therapy was associated with lower relapse at 3 years (22% compared to 35%, p=0.03) and higher PFS at 3 years (43% compared to 27%, p=0.04)

List of abbreviations: myeloablative (MAC), reduced intensity conditioning (RIC), bone marrow (BM), peripheral blood (PB), disease free survival (DFS), progression free survival (PFS), overall survival (OS), transplant related mortality (TRM), nonrelapsed mortality (NRM), MDAPS (MD Anderson Prognostic Score)

Table 5

Prognostic scoring systems in CMML patients

	Patients	External Validation	Variables included in final scoring system	
MD Anderson prognostic score[5]	213	No	**1**	Hemoglobin < 12g/dL
			2	Circulating immature myeloid cells
			3	Absolute lymphocyte count > 2.5×10^9/l
			4	Bone marrow blasts ≥ 10%
Dusseldorf score[6,29]	288	No	**1**	Bone marrow blasts ≥ 5%
			2	LDH > 200 u/l
			3	Hemoglobin ≤ 9g/dL
			4	Platelets ≤ 100×10^9/l
Spanish cytogenetic risk stratification system[30]	414	No	**1**	Low risk: normal karyotype or loss of Y chromosome as single anomaly
			2	High risk: presence of trisomy 8 or abnormalities of chromosome 7, or complex karyotype
			3	Intermediate risk: all other abnormalities
CMML-specific prognostic scoring system[8]	578	Yes	**1**	CMML FAB type
			2	CMML WHO type
			3	CMML-specific cytogenetics *
			4	RBC transfusion dependence
Mayo prognostic model[31]	226	Yes	**1**	Absolute monocyte count > 10×10^9/l
			2	Presence of circulating blasts
			3	Hemoglobin < 10g/dL
			4	Platelet count < 100×10^9/l

* CMML-specific cytogenetic risk classification: low, normal and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7

Table 6

Causes of death, according to HCT Specific CPSS

Cause of death	Low / Intermediate-1	Intermediate-2 / High
Primary disease	21 (46)	23 (41)
Graft failure	0	2 (4)
GVHD	5 (11)	13 (23)
Infection	3 (7)	7 (13)
IPn/ARDS	3 (7)	0
Organ failure	4 (9)	8 (14)
Secondary malignancy	3 (7)	0
Other cause	3 (7)	2 (4)
Unknown	3 (7)	1 (2)
Missing	1 (2)	0