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Methodology Employed for Annual Report on Hematopoietic Cell Transplant Center-Specific Survival Rates

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CIBMTR® is a research collaboration between the National Marrow Donor Program® (NMDP)/ Be The Match® and the Medical College of Wisconsin

www.cibmtr.org

Milwaukee Campus
Medical College of Wisconsin
9200 W. Wisconsin Ave., Suite C5500
Milwaukee, WI 53226 USA
(414) 805-0700

Minneapolis Campus
National Marrow Donor Program/
Be The Match
3001 Broadway Street N.E., Suite 100
Minneapolis, MN 55413-1753 USA
(612) 884-8600

Introduction

The purpose of the annual report on transplant center-specific survival rates is to provide potential hematopoietic cell transplant (HCT) recipients, their families, and the general public with a comparison of survival rates among the centers in the C.W. Bill Young Cell Transplantation Program (CWBYCTP) network. Transplant centers may use these reports for quality improvement initiatives. Reporting center-specific survival rates is a requirement of the Stem Cell Therapeutic and Research Act of 2005 (re-authorized in 2010 and 2015), and prior to that, the 1990 Transplant Amendments Act. Because centers vary considerably in the risk level of cases treated, a statistical model was developed to adjust for several risk factors known or suspected to influence outcome. The outcome reported is one-year overall survival, for recipients of allogeneic HCT in the United States only. No attempts are made to incorporate other outcomes, such as relapse or disease-free survival.

The first center-specific risk-adjusted comparisons were published in 1994[1] and yearly since then. The current iteration of the report prepared by the Center for International Blood and Marrow Transplant Research (CIBMTR) includes recipients of both unrelated and related donor transplants facilitated by the CWBYCTP for a three-year time window. The methodology for this analysis has undergone various transformations over the years. The methodology in current use has been employed since 2005, thus allowing direct comparisons over the most recent eleven reports. This method adjusts for risk using a censored data logistic regression model[2,3,4] that allows inclusion of recipients with incomplete one-year follow-up. Note that although the method has remained the same, the types of patients studied changed with the inclusion of related-donor transplants in the 2010 report, which may affect comparisons over time. A risk-adjusted one-year survival rate is calculated for each center, based on results of the censored data logistic regression.

Results are accessible on the CWBYCTP website (http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/index.html), and a version of this report, as approved by HRSA, is distributed to HCT centers. This information is available online at www.bethematch.org/tcdirectory/search. Raw numbers of transplants and surviving recipients are published for each center, stratified by diagnosis and age. Each center included in the report performed at least one unrelated or related donor transplant over the three-year window of time for analysis.

Methods

Recipients and data

The current analysis includes first unrelated or related donor transplants performed in a three-year time interval, with follow-up through one year after the last recipient was transplanted. The rolling three-year window of transplants for inclusion was adopted with the 2011 report, replacing a rolling five-year window used previously. This change was based on the recommendation of the 2010 Center-Specific Outcomes Analysis Forum[5], in order to represent more current transplant center outcomes. A minimum of one-year follow-up is required for all

eligible cases. All U.S. transplant centers that performed at least one HCT in the time interval are considered for inclusion in the report, provided they had sufficient data with at least one year of follow-up available. Typically, about 180 U.S. transplant centers are included in the analysis, with about 23,000 first allogeneic transplants performed by domestic transplant centers in the CWBYCTP network during this time.

Demographics of the included cases are provided in tables for recipients of unrelated donor transplants and recipients of related donor transplants, broken down by donor type according to unrelated vs. Baseline and follow-up data used for the analysis are provided to the CIBMTR by the transplant centers at the time of transplant (baseline), and at 100 days, six months and annually post-transplant, using standardized forms. Race was self-reported by recipients or by the staff at the center.

Risk factors considered

Based on the recommendation of the 2010 Center-Specific Outcomes Analysis Forum, variables recognized as clinically important were forced into the model regardless of whether they were statistically significant. After careful discussion with clinical and statistical transplant experts, the following essential risk factors were included in the model:

- Diagnosis (and disease status / stage)
- Donor type: matched sibling donor vs. other related vs. unrelated donor
- Coexisting disease (HCT-specific comorbidity index (HCT-CI), Sorror [6])
- HLA matching*
- Recipient age
- Donor age (unrelated bone marrow or peripheral blood stem cells (PBSC) donors only)
- Recipient and donor gender
- Recipient cytomegalovirus (CMV) serology
- Recipient race (self-reported)
- Recipient Karnofsky / Lansky Performance Status score at transplant
- Prior autologous transplant
- Resistant disease in non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) only
- Time from diagnosis to transplant for acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) not in CR1 or PIF (used as surrogate for length of CR)
- Year of transplant

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* For PBSC and marrow transplants, high-resolution typing at HLA-A, -B, -C, and –DRB1 wasis used for the cases where it wasis available. For the remaining patients with PBSC and bone marrow graft sources, the best available matching information at HLA-A, -B, -C, and -DRB1 wasis used (Weisdorf et al. [12]).[8]). For single cord blood transplants, high-resolution typing at HLA-A, -B, -C, and –DRB1 wasis used for the cases where it was available. For the remaining patients with single cord blood graft source, low/intermediate-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1 only wereare considered. For multiple cord blood transplants, low/intermediate-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1 only wereare considered. The match grade of the worst-matched unit wasis analyzed.

In addition, the following variables were believed to be of uncertain clinical relevance, and so they were included in the model only if statistically significant ($p<0.05$).

- T-cell lineage in ALL, Philadelphia chromosome in ALL
- Recipient ethnicity (self-reported)
- NHL subtype[†]
- Donor parity
- Donor race
- Donor ethnicity
- Donor CMV serology

New variables considered for the 2018 report

Additional variables for risk adjustment, particularly for disease risk, were proposed for inclusion on data collection forms at the Center-Specific Outcomes Analysis Forum in 2012. These variables were collected beginning in October 2013 and were available for testing for the 2018 report. The additional variables tested in this year's report include:

- History of mechanical ventilation
- History of invasive fungal infection
- AML transformed from Myelodysplastic (MDS) / myeloproliferative (MPN) diseases
- Therapy related AML or MDS
- AML ELN risk group (Dohner et al. [7])
- Number of induction cycles to achieve latest CR before HCT for AML and ALL patients in CR
- ALL cytogenetic risk group (Moorman et al. [8])
- ALL molecular marker - BCR/ABL at any time between diagnosis and HCT
- MDS with predisposing conditions
- MDS IPSS-R prognostic risk category/score at HCT (Greenberg et al. [9])
- Del 17p in CLL
- Multiple myeloma cytogenetics risk group (Palumbo et al. [10])
- Multiple myeloma International Staging System (ISS) stage at diagnosis
- Plasma cell disorder disease status at HCT
- Plasma cell leukemia

[†] **NHL subtypes: Indolent B-cell lymphoma** includes the following sub-types: Lymphoplasmacytic; splenic marginal zone B-cell; extranodal marginal B-cell of mucosal-associated lymphoid tissue; nodal marginal zone B-cell; grades I, II and III follicle center cell; follicle center cell, grade unknown; Waldenstrom's macroglobulinemia. **Aggressive B-cell lymphoma** includes the following sub-types: Diffuse large B-cell including primary mediastinal B-cell lymphoma, Burkitt, and high grade Burkitt-like B-cell. **Mantle cell lymphoma** includes the following sub-type: Mantle cell lymphoma. **Nodal T-cell lymphoma** includes the following sub-types: Anaplastic large-cell T/null-cell, primary cutaneous type; peripheral T-cell NOS; angioimmunoblastic T-cell; anaplastic large cell T/null-cell, primary systemic type. **Extranodal T-cell lymphoma** includes the following sub-types: Extranodal NK/T-cell nasal type; enteropathy-type T-cell; hepatosplenic gamma-delta T-cell; subcutaneous panniculitis-like T-cell; mycosis fungoides; sezary syndrome; large T-cell granular lymphocytic leukemia; aggressive NK-cell leukemia; adult T-cell lymphoma/leukemia. **Other B-cell lymphoma. Other T-cell/NK-cell lymphoma.**

- Socioeconomic status (median household income) based on zip code of residence of recipient

Statistical Analysis

Rationale for a fixed effects censored data logistic regression model

One of the CIBMTR's goals for the transplant center-specific outcomes analysis is to calculate a fair and accurate predicted survival rate given a center's recipient case mix. To do this, a fixed effects censored regression model is used. The fixed-effect logistic regression model provides information about how the recipients actually treated in a particular center would have fared had they been transplanted at a "generic" transplant center within the CWBYCTP. This model assumes *no center effect*. In other words, it assumes that recipients are dying at the same uniform rate across all CWBYCTP transplant centers, after adjusting for covariates. The model also adequately accounts for recipients with incomplete follow-up at one year.

Every effort is made to update follow-up information on each recipient. Some recipients are indeed lost to follow-up, and their final survival status at one year is unknown. To address this problem, the analysis only includes centers that demonstrated 90% completeness of follow-up, meaning that the one-year status was known for at least 90% of their transplanted recipients. However, there are still some recipients for whom survival status at one year is incomplete, although many recipients had follow-up done just prior to one year. If these recipients are excluded from the center-specific analysis, it may bias the survival estimates. A censored data version of logistic regression based on pseudo-values proposed by Andersen et al.,[2] Klein and Andersen,[3] and Klein et al.[4] addresses this issue. This method is a generalization of logistic regression that simplifies to logistic regression (on the one-year survival probabilities) when there is no censoring present. This regression technique is used to estimate the fixed effects and predict the recipients' survival probabilities based on their patient characteristics alone. These predicted survival probabilities are then used to construct confidence limits for a center's survival probability according to the characteristics of the patients transplanted at that center. The actual survival observed at that center can be compared to these intervals to assess the performance of the center. This method is described in more detail below.

Details of fixed effects censored data logistic regression and confidence limits

Modeling for the center-specific survival analysis can be broken down into four steps, as outlined below.

I. Definition of pseudo-values

To compute the pseudo-value for recipient *i*, first compute the pooled sample Kaplan-Meier estimate of survival at one year based on the entire sample, $\hat{S}_p(1)$. Next compute the Kaplan-Meier estimate of survival at one year based on the entire dataset with observation *i* removed $\hat{S}_p^{(i)}(1)$. The *i*th pseudo-value is defined by $\hat{\theta}_i = n\hat{S}_p(1) - (n-1)\hat{S}_p^{(i)}(1)$.

If there is no censoring, then the *i*th pseudo-value is simply the indicator that the *i*th recipient was alive at one year. These pseudo-values will then be used in a regression model using a logit link, similar to a standard logistic regression model, as described in the next

section. The parameters of the regression model can be estimated using generalized estimating equations (GEE), which are implemented in PROC GENMOD in SAS.

II. Model building

Let ($Z_{i1},...,Z_{ip}$) denote the set of covariates in the final model for recipient i . First fit a fixed effects censored data logistic regression model with no center effect,

$$\varphi_i = \ln\frac{\theta_i}{1-\theta_i} = \beta_0 + \sum_{l=1}^{p}\beta_l Z_{il} \ .$$

III. Predicted and observed survival

From the fitted logistic regression model, each recipient has an estimated survival rate

$$\hat{p}_i = \frac{\exp(\hat{\varphi}_i)}{1+\exp(\hat{\varphi}_i)}$$

based on his or her risk characteristics. The predicted survival rate at center *j* based on recipient characteristics $E(S_j)$ is the average of the estimated survival rates for all recipients at center *j*,

$$E(S_j) = \left(\sum_{i\in C_j}\hat{p}_i\right) * \frac{1}{n_j} .$$

The observed one-year survival rate at center *j* can be computed using the Kaplan-Meier estimate of survival using the recipients at center *j*. This simplifies to the sample proportion of recipients alive when there is no censoring prior to one year present.

IV. Confidence Limits

Confidence limits are generated using a bootstrapping methodology. However, the bootstrap technique was modified slightly from previous years' reports to improve the coverage probabilities of the intervals, as described in Logan et al.[6] Previously, binary outcomes were generated for each individual to simulate the confidence limits; however, a more accurate prediction interval that controls the type I error rate can be obtained by re-sampling the residuals from the general linear model instead. Define the scaled Pearson residual for patient *i* by

$$r_i = \frac{\hat{\theta}_i - \hat{p}_i}{\sqrt{\hat{p}_i(1-\hat{p}_i)}} ,$$

then the bootstrap re-sampling algorithm to generate a prediction interval for center *j* is as follows. For *b*=1 to 10,000:

1. Generate r_i^{*b} for patient *i* by sampling with replacement from the set of residuals $\{r_i, i=1,...,n\}$
2. Compute the bootstrap predicted value for patient *i* as $Y_i^{*b} = \hat{p}_i + r_i^{*b}\sqrt{\hat{p}_i(1-\hat{p}_i)}$
3. Compute the predicted center outcome for center *j* as

$$S_j^{*b} = \frac{1}{n_j} \sum_{i \in C_j} Y_i^{*b} .$$

Then the 95% predicted confidence bounds for survival at center *j* are obtained by taking the 2.5th and 97.5th percentile of S_j^{*b} across the 10,000 bootstrap samples.

This confidence interval refers to the survival rate that might be observed at that center if there were no center effect and those recipients had been transplanted at any center in the network. The observed survival rate can be compared with this confidence interval to see if there is evidence of the center over-performing or under-performing the overall network.

Occasionally, data are not available for significant characteristics for subjects as reported by the centers. If there were sufficient numbers of such subjects, they were included in the multivariate modeling as a distinct category of the covariate. However, when the number of subjects with data not available for a variable is too small (generally less than 20 subjects) to fit the model as its own category, those subjects were imputed to the relevant highest frequency category within the variable for categorical variables, and to the median value for ordinal or numeric variables (e.g. HCT-CI).

Results

Patient demographics

Demographics of the patient population are provided in the report, displayed by donor type according to unrelated vs. related donor.

Risk factors included in final multivariate model

The results of the multivariate model are presented in a set of tables where each variable and its associated odds ratio are described, along with 95% confidence limits.

Factors included in the final model are:

- Factors considered in prior years analyses:
    - Recipient age
    - Recipient race‡
    - Karnofsky / Lansky score at transplant
    - Prior autologous transplant‡
    - Recipient CMV status
    - Coexisting disease (Sorror HCT-CI)
    - Disease and disease status/stage
    - Time from diagnosis to transplant for AML and ALL in CR2 (used as surrogate for length of CR)
    - T-cell lineage in ALL patients

‡ Maintained in the model but not statistically significant

    - Philadelphia chromosome in ALL patients
    - CLL and other chronic leukemia stage
    - Sensitivity to chemotherapy in NHL and HL
    - NHL subtype
    - Year of transplant
    - HLA matching by donor and graft type
    - Donor/Recipient sex match (bone marrow or PBSC only)‡
    - Donor age (unrelated bone marrow or PBSC donors only)
- New factors introduced in this year's analysis
    - History of mechanical ventilation
    - History of invasive fungal infection
    - AML transformed from MDS/MPN
    - AML ELN risk group
    - ALL cytogenetic risk group
    - MDS with predisposing condition‡
    - MDS IPSS-R risk score at HCT
    - Plasma cell disorder disease status
    - Recipient median household income based on zip code
- With the addition of new variables, there were some changes from the 2017 model: Donor/recipient sex match was no longer significant but was forced in due to being recognized as clinically important, as described in the Methods section.
- ALL T-cell lineage is significant.
- Many new variables were significant as described above.

The Beta_0 intercept term for the model is made available in the formal report.

Center-specific results

Final center-specific results are presented, along with centers' historical performance in tables, and on the public website. Numbers of transplanted recipients at each center, actual (observed) survival at one year, predicted survival at one year, 95% confidence intervals for predicted survival, and performance status are displayed for each center. Centers whose actual survival is outside the 95% confidence limits for predicted survival have a "–1" in the performance status column if performing below the confidence limit, and a "1" in the performance status column if performing above the confidence limit. Centers with a "0" in the performance status column are performing as predicted. Most centers performed as predicted with respect to overall performance in previous years. Since the censored data logistic regression model assumes no center effect, centers with smaller numbers of transplants (e.g. N = 1 or 2) will *not* have their predicted survival proportion regress toward the network average. Rather, the confidence limits around the predicted survival at that center will simply be much wider than those of larger centers.

Results are also displayed for centers via a visual box-plot graphic. Centers are arranged by center number, while reading from left to right across these figures. The actual survival at each center is superimposed with each box plot (using the symbol '•') to give the reader an

instantaneous picture of how close the center is to under- or over-performing. A dashed line is included to denote the overall network survival average, using the Kaplan-Meier estimate of one-year survival from the entire cohort of patients who underwent first allogeneic HCT in the time interval included in the analysis.

Patients can find information about all U.S. transplant centers performing allogeneic transplants in the online U.S. Transplant Center Directory on http://bethematch.org. Listings are organized by state and can be found at bethematch.org/tcdirectory/search. Along with center outcomes, each listing includes a description of that center's program, contact information, the number of transplants performed over a specified time period and survival statistics by patient's age, disease type and stage for both related and unrelated donor transplants. A link to the Transplant Center Directory can also be found on the Health Resources and Services Administration (HRSA) http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/index.html website.

Because the outcome of interest is one-year survival, at least one year of follow-up time is required to be included in the analysis. Data are refreshed once a year. After the report on transplant center-specific survival rates is approved by HRSA, the Transplant Center Directory is repopulated with the new data.

Summary

A censored data logistic regression model is fitted to survival data for first unrelated and related donor hematopoietic cell transplants at U.S. centers. The model is adjusted for recipient age, recipient race, Karnofsky/Lansky score, prior autologous transplant, recipient CMV status, history of mechanical ventilation, history of invasive fungal infection, Sorror HCT-CI, disease/stage, interval from diagnosis to transplant in ALL and AML in CR2, AML transformed from MDS or MPN, AML ELN risk group, T-cell lineage and Philadelphia positive-status in ALL, ALL cytogenetic risk group, CLL and other chronic leukemia disease status, MDS predisposing condition, MDS IPSS-R risk score at HCT, NHL subtype, sensitivity to chemotherapy in NHL and HL, Plasma cell disorder disease status, year of transplant, donor type/graft type/HLA matching, BM or PBSC donor/recipient sex match, BM or PBSC donor age at transplant, and recipient median household income.. The report on transplant center-specific survival rates helps to identify centers that may have performed above or below confidence limits compared to the overall network of transplant centers during this specified time period.

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