Hematopoietic Cellular Therapy Program
Annual Quality Report for FACT
Report Date: December 27, 2017

Response to the following FACT standards:

B4.7.5 The Clinical Program should achieve one-year survival outcome within or above the expected range when compared to national or international outcome data.

B4.7.5.1 If expected one-year survival outcome is not met, the Clinical Program shall submit a corrective action plan.

OBJECTIVES

1. Meet 1-year expected survivorship outcome for first allogeneic recipients as established by the annual Transplant Center-Specific Report (TCS report).
2. Identify areas for improvement resulting from examining and reviewing past and current clinical practices.
3. Establish a process for reviewing all patient deaths after transplant to determine primary and contributing cause of death.

BACKGROUND: OUTCOMES

A. First Allogeneic Transplant Outcomes per CIBMTR Report Years

The first allogeneic transplant outcome is a measure used by the Center for International Blood and Marrow Transplant Research (CIBMTR) to report center-specific one-year survival rate of allogeneic stem cell recipients in the US. The yearly report is based on the following factors:

1. Cumulative annual survival rate for all first allogeneic recipients transplanted for 3-year cohorts.
2. These reports are based on combined outcomes for pediatric and adult recipients.
3. Transplant centers are compared based on statistically-adjusted risk factors.

A center's designation depends if its performance falls within the confidence interval as in:-1 if underperforming; 0 if performing within expectation, and; +1 if performing above expectation. 's performance for the past 4 years as published in the publicly reported CIBMTR Survival Report is as follows:

Table 1: First allogeneic survival at for CIBMTR report years 2013 to 2016

Date report was published	December 2013	December 2014	December 2015	December 2016
Inclusive dates (all first allo events)	Jan 1, 2009 to Dec 31, 2011	Jan 1, 2010 to Dec 31, 2012	Jan 1, 2011 to Dec 31, 2013	Jan 1, 2012 to Dec 31, 2014
First Allo 1-year survival outcome (%)	57.3*	58.5*	62.8	59.6*
TCS report designation	-1	-1	0	-1

*underperformed compared to other centers

B. First Allogeneic Transplant 1-year Survival Outcomes per Year

Historically at , we were reporting combined outcomes for pediatric and adult recipients. Beginning in December 2016, we have separated our CIBMTR reporting process to account for the differences in risk factors and overall outcomes in the adult and pediatric populations. Our survival outcomes are being reported as for adult transplants and for pediatric transplant events. As such, we have reviewed separate adult and pediatric outcomes from previous years as summarized below.

Table 2: First allo 1-year survival for adult recipients

Transplant year	2012	2013	2014	2015	2016
Adult outcomes (%)	56.6	72.55	54.24	66.67	75.00

Table 3: First allo 1-year survival for pediatric recipients

Transplant year	2012	2013	2014	2015	2016
Pediatric outcomes (%)	62.5	55.56	53.85	76.92	91.67

C. First Allogeneic Transplant Outcomes per CIBMTR 3-Year Reporting (Current Year)

The most current TCS Annual Report published on December 11, 2017 places both the adult and pediatric clinical outcomes at "0" or performing within expectations.

Table 4: First allogeneic survival at

Center	Inclusive dates (all first allo events)	First allo 1-year survival outcome (%)	TCS report designation
(Adult)	Jan 1, 2013 to Dec 31, 2015	63.2	0
(Pediatrics)	Jan 1, 2013 to Dec 31, 2015	62.9	0

MORTALITY REVIEW

A. Overall Causes of Death

Beginning July of 2014, all patients who passed away are presented at the weekly program conference regardless of the number of days post-transplant. The information from this process helps us ascribe cause of death to possible gaps in our practice and identify opportunities for improvement.

Table 9: Pediatrics First Allo Cause of Death Before 1 Year

Deaths (n)	2013 (N=9)		2014 (N=13)		2015 (N=13)		2016 (N=12)	
	n	%	n	%	n	%	n	%
GVHD	1	11.11	0	0	1	7.69	0	0
ARDS	0	0.00	0	0	0	0	0	0
Infection	1	11.11	2	15.38	2	15.38	1	8.33
Organ Failure	0	0.00	2	15.38	0	0	0	0
Relapse	1	11.11	0	0	0	0	0	0
PTLD	1	11.11	2	15.38	0	0	0	0

Table 10: Adult First Allo Cause of Death Before 1 Year

Deaths (n)	2013 (N=51)		2014 (N=59)		2015 (N=51)		2016 (N=40)	
	n	%	n	%	n	%	n	%
Relapse	4	7.84	12	20.34	9	17.65	4	10
GVHD	5	9.8	4	6.78	2	3.92	0	0
Infection	2	3.92	5	8.47	4	7.84	0	0
Organ Failure	4	7.84	2	3.39	2	3.92	6	15
Other	0	0	4	6.78	0	0	0	0

B. Causes of Low 1-Year Survival Rate

Our data show that 2014 was a challenging year for both our pediatric and adult patients with low 1-year survival rates. Among adult patient deaths in 2014, 22% occurred within D100 of transplant while 24% happened between D100 to D365. The two main categories of cause of death are attributed to transplant-related (infection, GVHD) and relapsed disease. The same can be said about cause of pediatric deaths in 2014: transplant-related causes up to D100; and relapsed disease after D100.

The review of causes of death helped guide us establish clinical practice improvements to closely monitor each post-allo patient. Additionally, starting in July 2014, we instituted a weekly review of all post-allogeneic patients who are 1 year or less removed from their transplant. At a minimum, the following issues are addressed at this meeting: GVHD, medication compliance, chimerism, active infection if any, overall physical state, and psychosocial issues if any. As a response to relapsed disease, post-transplant maintenance therapy is also discussed for each patient on a weekly basis.

The lack of a standardized approach across the program to discuss issues for post-allo patients, follow-up visit requirements and cause of death review prior to 2014 makes it difficult to attribute our low 1-year survival rate to only one or few reasons. We believe that having a consistent follow-up schedule for all patients after transplant will provide us with better understanding of patients' progress throughout the days after transplant.

CORRECTIVE AND IMPROVEMENT ACTIONS

We performed a thorough review of our data, outcomes and clinical practices. We recognize a challenging year in 2014 as evidenced by our outcomes for both pediatric and adult allogeneic transplants performed that year. Beginning in mid-2014 and as a response to previous years' CIBMTR report outcomes, we formed a dedicated team within the HCT Program to examine data reported and to perform root-cause analyses for identified challenges in our clinical program. We did a retrospective review of possible risk-disease correlation for all deaths occurring within 1 year of transplant. A series of focused meetings and discussions with program leadership resulted in several clinical practice changes to deliver a more defined transplant management process.

A. Mandatory Patient Discussion for Transplant Eligibility

Prior to 2014, the decision to proceed with transplantation relied mainly at the discretion of the primary oncologist. As a result of our program practice review, we established a system where all upcoming transplant patients are discussed at appropriate disease program conferences (for example, all AML patients discussed at the weekly leukemia program conference). Physicians at each program conference provide recommendations on the course of treatment, including transplant. The decision to proceed or not to transplant is then brought forward by the primary transplant physician to the weekly transplant program conference as a "new transplant candidate". This conference is multidisciplinary and is attended by transplant physicians and personnel. Furthermore, at least 2 weeks prior to admission, upcoming patients are presented again for work-up results, to address bridging issues such as new infection if any, disease status, transition of care, and other patient/caregiver needs.

B. High Risk Consensus Review

We have established high risk parameters for all upcoming transplant patients and beginning in July 2014, our program instituted a high risk consensus discussion which became mandatory for all transplant candidates deemed high risk based on these criteria. This consensus approval process is to ensure that transplant physicians carefully weigh the risks and benefits of transplant as well as address ways that we can optimize patient's status through subspecialty consults, physical therapy, mobilizing family support, etc. before proceeding with transplantation. Performance score and comorbid conditions (Sorror, 2013) are carefully reviewed throughout the work-up process leading to the start of preparative regimen. We believe this has led to improvement in our outcomes as seen in our 1 year survival for years 2015-2017 (see tables 2 and 3). Unfortunately, this process was implemented in the latter half of 2014 during which more than half of our patients have already proceeded with transplantation, and so improvements are not reflected in those results.

Table 5: High risk criteria

Allogeneic	Autologous
• HCT-CI score ≥ 3 • Creatinine ≥ 1.5 • KPS < 80% • Disease not in response • Leukemia not in remission • MDS with marrow blasts > 10% • Lymphoma with less than a PR • Living more than 1 hour drive away	• KPS <70% • Lymphoma less than a PR • HCT-CI score ≥ 5

C. Transplant Optimization Program Clinic

Transplant Optimization Program (TOP) is a nationally-renowned program dedicated to developing the best possible treatment plan for transplant patients 50+ years of age. It is a multidisciplinary team led by our program's clinical director ( ) who works with a core group and other physician specialty consultants. TOP's core group includes the following experts:

- Geriatric oncologist
- Infectious disease physician
- Physical therapist
- Registered dietician
- Oncology-transplant pharmacist
- Social worker
- Transplant-specialty advanced practice nurse (APN)
- Transplant research coordinator

Table 6: TOP Clinic

Allogeneic	Autologous
• All patients 60 and over • Patients who are deemed high risk due to specific organ function issues for patients 50 and over	• All patients 70 and over • Patients who are deemed high risk due to specific organ function issues for patients 60 and over

As a testament to the TOP clinic's dedication to the vulnerable older adult population who are undergoing transplant, we have seen a positive correlation between our optimization activities and outcomes for patients 60 years old and over.

Table 7: First allo 1-year survival for adults 60 and older

Transplant year	2010	2011	2012	2013	2014	2015
60+ adult outcomes (%)	15.38	35.29	58.82	43.75	47.06	65.00

D. Standardization of Care

It is well understood that standardization of practice leads to better outcomes. We have applied standardization in many areas as is practical, and continue the ongoing improvement work of standardizing both clinical and administrative practices. Below are our significant standardization initiatives.

1. Standardized chemotherapy regimen. Prior to 2015, the preparative chemotherapy regimen and dose for our patients relied mainly at the discretion of their respective attending physicians. We have standardized our chemo preparative regimens and dose guided by our core team of transplant physicians and pharmacists.

2. Standardized post-transplant follow-up. Prior to the required follow-up visits, patients were seen at the clinic on irregular intervals or referred back to their local physicians. In 2014, we started a standardized follow-up frequency for all transplant patients after being discharged from the inpatient unit. This allows us to evaluate patients closely and monitor their progress to 1 year. Through standardization of follow-up clinic visits, patients come to clinic for thorough assessment and medication management starting at 3 times per week for the first few weeks, with reducing frequency over time. This allowed transplant providers to closely monitor patients for complications brought about by transplant, progress of disease and other issues.
3. Standardized benchmark disease evaluation after transplant. We have established benchmark days for disease re-evaluation to monitor disease progression after transplant. The minimum days for disease re-evaluation are at D+30, D+100, D+180 and 1 year. This allows our physicians to watch out for disease relapse or graft failure and establish course of treatment in a timely manner.
4. Standardized review of all post-allogeneic patients. As indicated in our review of causes of death, relapsed disease figures as the leading cause of death in 2014 for both adult and pediatric patients (20 and 11 percent, respectively) along with organ failure and infection. Standardized re-evaluation days including chimerism and consistent clinic visits allowed us to closely monitor disease progression and refer patients to appropriate maintenance and further treatment. All patients who are 1 year or less removed from their allogeneic transplant are discussed weekly at the transplant conference meeting attended by transplant physicians, APPs, nurses, pharmacists and social workers. We also enlisted the help and expertise of an infectious disease physician who consults with our patients at the meeting. In addition to follow-up clinic visit with their providers, the following issues are addressed weekly: presence/treatment of GVHD, medication compliance, chimerism, active infection if any, overall physical status, psychosocial issues and maintenance therapy.
5. Standardized communication with referring doctors. Our transplant physicians communicate regularly with patients' primary oncologists and primary care physicians. This ensures continuity of care and provides patients' doctors with appropriate recommendations for caring for post-transplant patients.
6. Standardized social support requirements. We recognize that pre- and post-transplant care relies partly on patients' socio-economic position. We have social workers who are well-versed with the unique needs of transplant patients and their families who perform psych-social assessment and assist patients with available resources. We now require patients to have a 24/7 caregiver and to live locally up to 12 weeks post-transplant. The presence of a 24/7 caregiver ensures that patients are safe in the home through the transplant phase and the subsequent neutropenic phase. Living locally (1 hour away for allo, 2 hours for auto) also allows for patients to reduce travel time to frequent clinic visits, and to be within a few miles of clinic or ER in case of emergency.

E. Expansion of Clinical Services

Our patients are now seen more frequently at the clinic and all our clinicians have been required to be specifically trained in transplantation and heme-onc. We recognize that to accommodate these changes and provide a safe and highly-specialized transplant service, we have expanded our team and welcomed additional positions since 2014. Our physicians, providers and clinicians in the program are trained in caring for patients who are undergoing cell therapy and transplantation.

Table 8: Additional clinical personnel since July 2014

Adult Transplant	Pediatric Transplant
• 2 adult transplant physicians • 10 advanced practice providers (total:12) • 3 transplant RN coordinators (total:6) • 5 apheresis RNs (total: 7)*	• 2 pediatric transplant physicians • 1 advanced practice provider (total:3)

*Apheresis RNs perform both adult and pediatric cell collections

We have established patient-staff ratio to allow for expansion depending on census. In addition, we have expanded our program support staff to better manage day-to-day challenges to meet the high standards we place on ourselves in caring for our patients. In addition to the positions listed above, in the past 3 years we have also added 2 full-time data manager positions, both of whom have been especially helpful as we have seen inaccurate

data in the past through our internal data audits. Our support staff expanded to include a dedicated transplant social worker, cell lab quality lead, and clinical research assistants, among others.

F. Outpatient Adult Transplant Clinic

We opened an adult outpatient transplant clinic in 2014 to expand our transplant-specialty services to cover patients at different phases of their treatment. The outpatient transplant facility is managed by providers and nurses who are trained and oriented in the care of transplant patients, and all transplant cases are overseen by a transplant physician. The services provided here has been instrumental in managing symptoms and complications in a timely manner, thus reducing trips to the ED and inpatient admission. The outpatient clinic facility provides 3 key services to transplant patients which are:

1. The option to receive outpatient preparative chemo, stem cell infusion, daily labs and overall patient monitoring during the transplant phase.
2. Coordination of treatment when transitioning from inpatient to home and follow-up care.
3. The availability to receive assessment and urgent care for post-transplant complications after a patient is discharged home.

G. Formalizing Donor Selection

In the later part of 2014, we formalized our unrelated allogeneic and cord blood selection process by forming the donor selection team that meets once a week to discuss donors. The team is led by our donor coordinator(s), and core members include transplant physicians, transplant RN manager and the Transplant Immunology Laboratory director or designee. Our program clinical director ( ) provides oversight of the donor selection process. All donor related issues are discussed and prepared by the team including: CMV status, ABO-Rh compatibility, degree of HLA-match or mismatch, cell dose, and donor coordination. This process provided an opportunity to address possible issues and mitigate post-transplant complications for recipients such as GVHD. Additionally, having a dedicated team of experts who meets consistently to discuss and select a most appropriate donor reduced delay in the transplant process.

H. Data Management and CIBMTR Reporting

Although disease status and comorbidities are highly predictive of outcomes (Sorror, 2015), prior to 2014, the decision to proceed with transplantation relied mainly at the discretion of the attending physician. As a response, all upcoming transplant candidates are now discussed at the weekly conference. An internal audit was conducted for all patients who underwent their first allogeneic transplant in the years 2009-2012 focusing on:

1. patient performance status
2. disease status at the time of transplant
3. comorbidities using the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI).

We found error rates ranging from 20-50% for these 3 fields for our combined adult and pediatric data. These factors are used as adjustment variables by CIBMTR in the calculation of our predicted survival. We reviewed our data submission against patient charts and worked with CIBMTR to re-submit our corrected data. After an internal audit and data correction in 2014, our program placed increased focus on data quality and management to reflect accurate patient status prospectively starting in June 2014. The specific actions included re-training of current staff and reviewing training materials for our 2 new-hired data manager positions. Additionally, we perform a weekly audit of the above data for upcoming transplant patients. The data management piece has been a key factor that helped us assess our practices.

I. Patient Education

We recognize that patient and caregiver education are integral in improving patient care and outcomes. We have placed a premium on making sure that we have a well-informed clientele. In addition to consultation and consent visits with patient's transplant physician, we launched 2 teaching projects this year.

1. APP-led patient and family conference. This education session is a supplement to consult and consent visits in the clinic with transplant physician and nurses. Transplant advanced practice providers (APP) make sure that patients and at least one family member or caregiver is present to reinforce the

information they learned from other clinicians. This family conference is held while patient is in the active phase of transplant which begins during the preparative regimen. It focuses on clinical management of the disease and complications of transplant, as well as making sure there is smooth transition from acute transplant phase to the process of discharge to home.

2. RN-led patient and family class. This is a classroom –style teaching method led by RNs to teach patients and their family or caregiver the ongoing transplant process, what to expect afterwards, when to safely resume activities, and the importance of complying to the care plan. The separate courses for the allogeneic and autologous classes were developed in collaboration among nurses in the program who brought different approaches to patient teaching.

CONCLUSION

Our efforts to improve survival outcomes began with closely examining our practices and instituting focused clinical improvement initiatives have resulted in better survival outcomes starting from year 2015. As we integrate more protocols and new standard of care treatments (such as immune effector cell therapy) to our transplant program, we will continue to explore all avenues to maintain patient safety and better quality of life, ultimately leading to improved overall survival rates. We are projecting to meet our TCS report predicted outcomes in the next 2 years, and possibly claim a "performing above expectations" designation in the years following.

Improvement in survival came from the combined efforts of transplant physicians and staff who reviewed and modified our practices. The key changes include: expanding transplant services; training staff specifically for transplantation; patient teaching and standardization of practice and processes.

Chart 1: First Allo 1 Year Survival Rate