A dynamic year

2013 was a dynamic year for Cleveland Clinic’s Blood & Marrow Transplant (BMT) Program:

- The program performed 191 transplants, one of its highest annual volumes to date.
- Both the adult and pediatric components of the program achieved three-year Foundation for the Accreditation of Cellular Therapy (FACT) accreditation for all services and facilities inspected.
- It welcomed a new director, Navneet Majhail, MD, MS, an internationally known BMT expert (see sidebar, p. 56), as well as three other new BMT specialist physicians.
- The program introduced its first offerings in haploidentical transplantation (see sidebar, p. 59).

The program is one of the largest of its kind in Ohio and was one of the nation’s earliest BMT programs, with Cleveland Clinic’s first bone marrow transplant dating back to 1975. It has performed 3,996 blood and marrow transplants (or hematopoietic cell transplants [HCTs]) through 2013, and volumes have grown steadily in recent years (see graph on next page).

Full range of transplant types, donor cell sources

This experience has yielded extensive expertise in the full spectrum of transplant types — including autologous, allogeneic with myeloablative conditioning and allogeneic with reduced-intensity conditioning — and donor cell sources, including bone marrow, peripheral blood stem cells and umbilical cord blood. The pie chart on the next spread breaks down the BMT program’s 191 transplants in 2013 by procedure type.

In 2013, the program performed 54 autologous transplants for multiple myeloma/amyloidosis and 55 for non-Hodgkin lymphoma, which were the most common indications. Leading indications for allogeneic transplants were acute and chronic
myeloid leukemia, acute lymphoblastic leukemia and myelodysplastic syndromes. The program also takes on less common indications ranging from solid tumors and myeloproliferative disorders to aplastic anemia and a growing list of nonmalignant hematologic and immune diseases (see “Progressive pediatric program” below).

**Consistently solid outcomes**

Patient outcomes are detailed in the table below and remain comparable or superior to national benchmarks. In the publicly available 2013 *Report of Survival*

### 100-day patient survival for primary transplants, 2012-2013

<table>
<thead>
<tr>
<th>Transplant type and diagnosis</th>
<th>N</th>
<th>100-day survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin and Hodgkin lymphoma</td>
<td>126</td>
<td>97%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>86</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Allogeneic transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC, related donor: Acute and chronic leukemia and MDS</td>
<td>31</td>
<td>87%</td>
</tr>
<tr>
<td>RIC, related donor: Acute and chronic leukemia and MDS</td>
<td>20</td>
<td>95%</td>
</tr>
<tr>
<td>MAC, unrelated donor: Acute and chronic leukemia and MDS</td>
<td>29</td>
<td>97%</td>
</tr>
<tr>
<td>RIC, unrelated donor: Acute and chronic leukemia and MDS</td>
<td>19</td>
<td>95%</td>
</tr>
<tr>
<td>MAC, umbilical cord blood: Acute and chronic leukemia and MDS</td>
<td>12</td>
<td>83%</td>
</tr>
</tbody>
</table>

*MAC = myeloablative conditioning, RIC = reduced-intensity conditioning, MDS = myelodysplastic syndromes*
Statistics for Blood and Marrow Transplantation from the Center for International Blood and Marrow Transplant Research (CIBMTR), Cleveland Clinic’s one-year actual survival probability was 61.7 percent, which was within the program’s predicted survival probability range.

Other 2013 outcomes statistics for Cleveland Clinic’s BMT Program include:
• A median length of stay of 21 days for primary transplant patients
• Rankings above the national 90th percentile for the BMT inpatient unit in overall assessment scores for patient satisfaction on the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) in all four quarters of 2013

Full complement of clinical and support services

Cleveland Clinic’s BMT Program is well equipped and expertly staffed across all aspects and stages of the transplant process, from donor selection and patient preparation through post-transplant follow-up care. The 14 staff physicians across the program’s adult and pediatric components are supported by dedicated infectious disease specialists and by physician partners in various Cleveland Clinic in-house programs:
• An apheresis collection facility
• A progenitor cell processing facility
• Allogen Laboratories, Cleveland Clinic’s wholly owned histocompatibility and transplant immunology lab (see p. 77)

Collaboration with the apheresis unit recently enabled development of algorithms for peripheral progenitor blood cell mobilization that have reduced the number of leukophereses needed for total cell collection, reducing costs and patient inconvenience. Similarly, the program’s partnership with Allogen Laboratories allows a precision and granularity in matching donors (via methods such as maternally inherited compatibility antigens) that few other centers can match.

Types of transplants performed (adult and pediatric), 2013

- Autologous, 124 (55%)
- RIC related, 10 (5%)
- MAC related, 16 (8%)
- MAC unrelated, 12 (6%)
- MAC cord, 7 (4%)
- RIC cord, 3 (2%)
- RIC unrelated, 19 (10%)

$100\text{-day survival rates of}\ 97\text{-}99\% \text{ for autologous transplants in 2012-2013}$
This team helped ensure the program’s three-year FACT accreditation award in 2013 for all services and facilities inspected, including:

- Adult and pediatric allogeneic and autologous hematopoietic progenitor cell transplantation
- Marrow and peripheral blood cellular therapy product collection
- Cellular therapy product processing with minimal manipulation

The program’s physicians are also supported by a cadre of transplant nurses, physician assistants, social workers who provide in-hospital and post-discharge psychosocial support, and transplant coordinators who ensure continuity of care across all treatment settings, including exceptional collaboration with community physicians before and after transplant. The program’s support services include a music therapy program (directed by a board-certified music therapist) that received approximately 100 referrals in 2013.

NEW PROGRAM DIRECTOR HAS DEEP ROOTS IN BMT RESEARCH

The new director of Cleveland Clinic’s BMT Program, Navneet Majhail, MD, MS, was recruited from the National Marrow Donor Program (NMDP), where he was Medical Director of Health Services Research, and the University of Minnesota, Minneapolis, where he was an adjunct associate professor of medicine. He also has served as Assistant Scientific Director with the Center for International Blood and Marrow Transplant Research (CIBMTR).

These roles with the NMDP and the CIBMTR have given Dr. Majhail deep experience in coordinating collaborative efforts among national and international BMT experts, which he will bring to bear for Cleveland Clinic.

“We have a strong program with a well-established research infrastructure,” says Dr. Majhail. “My aim is to build on that, mainly by broadening our portfolio of clinical trials and clinical research protocols. We will emphasize making care even more patient-centered. Cleveland Clinic is already on the forefront in that regard, and we are proud of our team-based, multidisciplinary approach to providing high-quality, cutting-edge patient care.”
**Ambitious research portfolio**

The program also has a robust and diverse clinical research component, demonstrated by its participation in 15 active clinical trials in 2013. These include the following important national collaborative studies:

**Blood and Marrow Transplant Clinical Trials Network (BMT CTN).** As a member of the Case Consortium, Cleveland Clinic serves as a core clinical trial site in this NIH-funded national cooperative group. Two clinical studies — the BMT CTN 0901 and 1101 trials — were open through the BMT program in 2013.

**Chronic Graft-vs.-Host Disease Consortium.** The program is an active member of this NIH-funded multicenter consortium that is investigating biology and novel therapies for the prevention and treatment of chronic graft-vs.-host disease.

**Center for International Blood and Marrow Transplant Research.** Cleveland Clinic participates in two studies through this national NIH-funded initiative:
- A multicenter trial of hematopoietic cell donor safety and quality of life
- A study of killer-cell immunoglobulin-like receptor (KIR) genotyping for unrelated donor selection prior to HCT for acute myeloid leukemia

**Pediatric Blood and Marrow Transplant Consortium.** The program’s pediatric component is part of a national phase 2 study of a conditioning regimen of treosulfan, fludarabine and low-dose total body irradiation for children with acute myeloid leukemia and myelodysplastic syndromes.

**Children’s Oncology Group (COG).** The program’s pediatric component is also an active member of this NIH-funded pediatric oncology group collaborative that is investigating novel therapies and supportive treatments in HCT.

**A collaboration with the Fred Hutchinson Cancer Research Center** on a national study of the use of low-dose total body irradiation and fludarabine with or without alemtuzumab for HCT in children with primary immunodeficiencies and other non-malignant inherited disorders.

The program also directed a number of active investigator-initiated clinical trials in 2013, including:
- A study of personalized monitoring of IV busulfan dosing for patients with lymphoma undergoing autologous stem cell transplantation
- An assessment of low-dose lenalidomide after nonmyeloablative allogeneic stem cell transplantation with bortezomib as prophylaxis against graft-vs.-host disease in high-risk multiple myeloma (see patient profile at right)
- A study of hematopoietic stem cell supermobilization in patients with lymphoma
- Several research projects focusing on psychosocial issues in transplant recipients

The program is likewise an active member of the CIBMTR’s international transplant outcomes registry, and many program staff physicians serve as principal investigators on registry studies.
Progressive pediatric program

Cleveland Clinic has performed blood and marrow transplants in children since the mid-1970s, but its pediatric HCT offerings were invigorated with their formalization into a Pediatric Blood & Marrow Transplant Program in 2011 following the arrival of pediatric HCT specialist Rabi Hanna, MD, who serves as the program’s director.

Pediatric transplant volumes have grown steadily since then (see graph, p. 54), with eight HCT procedures performed in pediatric patients in 2013. Across the 19 primary pediatric transplants performed from 2011 through 2013, 100-day survival was 90 percent.

The pediatric program performs the full range of HCT procedures (autologous, allogeneic with myeloablative conditioning, allogeneic with reduced-intensity conditioning) and has led Cleveland Clinic’s efforts in haploidentical transplantation (see sidebar, opposite page), with participation in several multicenter trials of the procedure in children.

The program added a second pediatric HCT specialist physician in 2013 and expanded its team of dedicated specialized midlevel providers, who provide family-centered care on a 24/7 basis. Facilities include a dedicated pediatric inpatient unit and a pediatric outpatient infusion suite.

Inventive approaches to nonmalignant pediatric conditions

The pediatric program uses HCT protocols to treat a wide range of childhood cancers — leukemias and lymphomas, brain and spinal cord tumors, myelodysplastic and myeloproliferative diseases, and solid organ cancers — and has distinguished itself through the innovative application of HCT to a growing list of nonmalignant conditions including:

• Primary immunodeficiency disorders
• Bone marrow failure syndromes and hematologic disorders, such as sickle cell disease and thalassemia
• Inherited metabolic disorders, such as Hurler syndrome and various leukodystrophies
• Histiocytic disorders
• Other rare disorders, such as osteopetrosis

Young patients benefit from access to emerging therapies and research protocols through the program’s status as a designated Children’s Oncology Group transplant center and a Pediatric Blood and Marrow Transplant Consortium member as well as through its participation in national trial networks such as the BMT CTN (see “Ambitious research portfolio” above).

Zavier Nagel: Proof of BMT’s Potential in Nonmalignant Diseases

Zavier Nagel (right) was born with congenital amegakaryocytic thrombocytopenia (CAMT), a rare hematologic disease that prevented his bone marrow from making platelets. After a couple of misdiagnoses and unsuccessful treatment attempts, Zavier’s parents brought him to Cleveland Clinic Children’s, where Rabi Hanna, MD, identified Zavier’s CAMT and placed him on a regimen of weekly platelet transfusions.

The transfusions gave Zavier energy but put him at high risk of internal bleeding, so Dr. Hanna suggested a bone marrow transplant. Zavier’s older brother, Jeradt (left), was a match, and an initial transplant of healthy bone marrow from Jeradt to Zavier in October 2011 gave the younger brother an initial boost, but it didn’t last.

In July 2012, Dr. Hanna extracted 20 million stem cells from Jeradt through apheresis and gave them to Zavier. After one more platelet transfusion, Zavier’s platelet count rose and remained high.

Now 6 years old, Zavier is healthy and energetic. Dr. Hanna considers him cured. The Nagels say their boys, who were always close, now share a special bond.
Ideally, patients in need of HCT can be matched with a sibling who has the same human leukocyte antigen (HLA) tissue type, as such transplants have the greatest chance for success. Yet only about one-third of candidates for allogeneic HCT have HLA-matched siblings.

Improvements in HLA typing have enabled the use of HLA-matched unrelated donors, but the chances of identifying such a match vary significantly by the recipient’s racial and ethnic background, with nearly one-third of minority patients unable to find a suitable unrelated donor.

Until recently, patients without an HLA-matched sibling or unrelated donor were limited to cells derived from umbilical cord blood or from an HLA-mismatched unrelated donor — and both these options carry a high risk of transplant-related mortality.

Enter haploidentical transplant

Cleveland Clinic is among a limited number of institutions that have begun offering patients another option: HLA-haploidentical HCT. Also known as a “half-matched” transplant, the procedure involves a donor who shares identity with the recipient for one HLA haplotype and is variably mismatched for HLA genes on the unshared haplotype.

Because every individual inherits one HLA haplotype from each parent and passes one haplotype to each child, any patient with a living biological parent or child has a potential HLA-haploidentical donor for HCT (see illustration).

The major advantage of haploidentical HCT is that it significantly broadens the donor pool and gives nearly all patients the chance to benefit from a transplant, including those with life-threatening nonmalignant disorders.

FUTURE OF TRANSPLANTATION: EXPANDING OPTIONS THROUGH HAPLOIDENTICAL TRANSPLANTATION

Haploidentical activity at Cleveland Clinic

In 2013, Cleveland Clinic’s BMT Program developed its own protocol using a myeloablative conditioning regimen to reduce relapse risk and improve survival in children and adults undergoing haploidentical HCT. The program also began offering haploidentical transplantation through its participation in multicenter clinical trials of the procedure.

The program continues to develop new haploidentical HCT protocols to individualize treatment choices based on patients’ particular disease, health status and comorbidities.