The Value of Outcomes Databases: Collaboration for Clinical Research in Blood and Marrow Transplantation

Mary M Horowitz, MD, MS
Chief Scientific Director, CIBMTR
Chief of Hematology and Oncology, Medical College of Wisconsin, Milwaukee
January 2017
A Little History…….

Bortin, Transplantation, 1970
In the Beginning......

First Advisory Committee of the International Bone Marrow Transplant Registry

Don Thomas
George Mathe
George Santos

Mort Bortin
JJ Bergan, JL Fahey, Bob Levey, GN Rogentine

Dirk van Bekkum
Bob Good
Fritz Bach
OUTCOMES REGISTRIES – A Part of the HCT Community Since the “Beginning” and Continuing to Grow

IBMTR – 1970; EBMT - 1974
National: US, Japan, Germany, France, etc – 1980s-90s
International: Asian-Pacific BMT Group; Eastern Mediterranean BMT Group; Eurocord – 1990s-2000s; LABMT - now

IBMTR Established
NMDP Established
NMDP & IBMTR join to form CIBMTR
First 200 Patients Reported to IBMTR
1968-73, 11 Countries, 35 Centers
82 with Malignancy; 108 with SCID/Marrow Failure
IBMTR – 1985

1970 - 1985
- 200 centers
- 1,000 transplants
- 35 publications

Mortimer M. Bortin, MD
Scientific Director

Al Rimm, PhD
Statistician

D’Etta Waldoch
Sharon Nell
Diane Knudsen
Data Management

Karen Gurgul
Admin. Assistant
Key Contributions

Transplants Can Be Done Safely and Can Cure

- Bortin MM, Buckner CD. Major complications of marrow harvesting for transplantation. Experimental Hematology. 1983

Disease Specific Outcomes

- Bortin MM, Rimm AA. **Severe combined immunodeficiency disease:** characterization of the disease and results of transplantation. Transplantation Proceedings. 1977
- Bortin MM, Rimm AA. Allogeneic bone marrow transplantation for of 144 patients with **severe aplastic anemia**. JAMA. 1981
Key Contributions

Risk Factors
- Bortin MM, Rimm AA. Factors influencing success and failure of human marrow transplantation: a review from the International Bone Marrow Transplant Registry. Experimental Hematology Today. 1979
- Bortin MM, Kay HEM, Gale RP, Rimm AA. Factors associated with interstitial pneumonitis after bone-marrow transplantation for acute leukaemia. Lancet. 1982

HLA Associations
- Rimm AA, Bortin MM. HLA antigens and SCID. Lancet. 1977
- D'Amaro JD, van Rood JJ, Rimm AA, Bortin MM. HLA associations in Italian and non-Italian Caucasoid aplastic anaemia patients. Tissue Antigens. 1983
- D'Amaro JD, van Rood JJ, Bach FH, Rimm AA, Bortin MM. HLA C associations with acute leukaemia. Lancet. 1984
Distribution of Allotransplant Volumes Among 162 US Centers Reporting Data to CIBMTR in 2012

Individual transplant centers treat relatively few patients and these patients are heterogeneous in many factors that affect outcomes.
95% Confidence Intervals for Samples Drawn from a Population Receiving a Treatment Producing 50% Survival

Sample Size, N

Probability, %

70% Publish

40% Don’t publish
CIBMTR 440,000 Cases Registered, up to ~10,000 variables per person (most with repeated observations, some extending over >30 years), >1000 publications

- Allogeneic
- Autologous
- Cumulative Total

Health Services Research
QOL, Long-term Follow-up
Immunobiology/genetics*
Multicenter Clinical Trials
Technology Assessment
Prognostic factors
Descriptive

1st NIH Funding for IBMTR
NMDP Established
Managing adverse event and IND reporting for unrelated PB and CB HCT

*NMDP Repository - Specimens for 40,000 donor-recipient pairs.
The Value of Outcome Registries: Understanding Trends in Use, Practice and Outcomes
The Value of Outcome Registries: Identifying patients most likely to benefit from BMT

Probability of Overall Survival after HCT for AML not in Remission by CIBMTR Risk Score

- Risk score = 0, N = 148, 42% (39-50)
- Risk score = 1, N = 326, 27% (23-33%)
- Risk score = 2, N = 342, 15% (11-19%)
- Risk score = 3, N = 321, 6% (3-9%)

Duval, JCO, 2010
The Value of Outcome Registries: Clinical Evidence of Biologic Effects (e.g. graft versus tumor effects)

RELAPSE AFTER 2,254 HLA-IDENTICAL SIB TRANSPLANTS FOR EARLY LEUKEMIA

Years

Relapse rates for different groups:
- Twins (N=70)
- T Depletion (N=401)
- No GVHD (N=433)
- CGVHD Only (N=127)
- AGVHD Only (N=738)
- AGVHD + CGVHD (N=485)

Horowitz, Blood, 1990
Outcomes after Transplantation of Cord Blood or Bone Marrow from Unrelated Donors in Adults with Leukemia

Mary J. Laughlin, M.D., Mary Eapen, M.B., B.S., Pablo Rubinstein, M.D., John E. Wagner, M.D., Mei-Jei Zhang, Ph.D., Richard E. Champlin, M.D., Cladd Stevens, M.D., Juliet N. Barker, M.D., Robert P. Gale, M.D., Ph.D., Hillard M. Lazarus, M.D., David I. Marks, M.D., Ph.D., Jon J. van Rood, M.D., Andromachi Scaradavou, M.D., and Mary M. Horowitz, M.D.

Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia

Vanderson Rocha, M.D., Ph.D., Myriam Labopin, M.D., Guillermo Sanz, M.D., William Arcese, M.D., Rainer Schwerdtfeger, M.D., Alberto Bosi, M.D., Niels Jacobsen, M.D., Tapani Ruutu, M.D., Marcos de Lima, M.D., Jürgen Finke, M.D., Francesco Frassoni, M.D., and Eliane Gluckman, M.D., for the Acute Leukemia Working Party of European Blood and Marrow Transplant Group and the Eurocord–Netcord Registry*

Number of transplants

- Adults
- Children

Year:
- 1992
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011

Graph showing the number of transplants for adults and children from 1992 to 2011.
The Value of Outcome Registries: Understanding the Influence of HLA


[Graphs showing survival over months after transplant for different disease stages and HLA matches.]
Survival After Unrelated Donor Transplantation
Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS

Odds of 1-year survival increased by 8% per year (95% CI, 7-9%) on average between 1990 and 2011
Side Comment

• The importance of HLA and other donor characteristics will need re-evaluated in the setting of post-transplant cyclophosphamide for GVHD prophylaxis
The Value of Outcomes Registries: Understanding Long-term Outcomes

Cumulative Incidence of Solid Tumors

Cumulative Incidence of Solid Tumors
- Upper Confidence Limit
- Lower Confidence Limit

Years

0% 5% 10% 15% 20% 25%

Rizzo JD, Curtis RE et al CIBMTR 2008
The Value of Outcomes Registries: Center-Specific Outcomes

Adjusted Survival Rates for Transplant Centers with 11–20 Transplants

Adjusted Survival with 95% Confidence Interval
The Value of Outcomes Registries: Understanding Macro-Economic Influences on Survival Globally

Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia (Giebel at al, Blood 2010)
Why Should A Registry Be Considered When BMT Is Just Developing in a Country or a Region or When Resources Are Limited?
Because to Develop a Therapy Effectively, We Need DATA

- **Assessment** – identify the most important problems and most promising solutions
- **Analysis** - determine efficacy – overall and for specific subgroups/regions; monitor long-term outcomes
- **Advancing best practices** - Optimize treatment strategies/improve outcome in the real world with real resource constraints
- **Allocation** of resources – research and clinical care
Data Are Needed:

• At the center level
  – Quality improvement
  – Understanding costs and resource needs (and making the case for them to hospital and local authorities)
  – Scientific study

• At the national level
  – Understanding access, costs and resource needs (and making the case for them)
  – To advance best practices
Data Are Needed:

• At the regional level
  – Facilitate research **relevant to regional issues**
  – The process of sharing data also creates opportunities for **professional, educational and scientific collaboration** in a community that faces similar challenges and affords the potential for sharing expertise and resources

• Create and pursue a **scientific agenda** that is **relevant to the region**
  – Attract resources for clinical trials
Data Are Needed:

• At the global level
  – To understand differences and commonalities in access, practice and outcomes
  – To communicate with regulatory and funding bodies about needs
  – To advance the science and practice of HCT: the region has the some unique opportunities to make important contributions
Why Is It Important?

• Because building a culture of evaluating and understanding outcomes is critical for
  – effective quality management systems to improve patient care
  – building an effective clinical research infrastructure to improve patient care

• When numbers of transplants in individual centers and countries are small, sharing data allows examination of important issues with greater power
How Might Existing Registries Help?

Making Use of Existing Resources May Make Data Sharing More Feasible Logistically and Financially
CIBMTR Resources

- Existing electronic data collection system
- Existing database structure
- Existing quality control systems
- Existing training resources for data management staff
- Reimbursement for comprehensive data forms
- Available statistical expertise
eDBtC: Enhanced Data Back to Centers

- Make selections
- Clear selections
- Minimized icons
- Cycle and drill buttons
- Printing and exporting
- Navigate between tabs

*A video tutorial is also available*
Tab: Survival

You are viewing data for Center: CCN – Center’s name
Total N Patients: 1,408 (based on filter selections)
Total N Transplants: 1,601 (based on filter selections)

Survival Probability of Selected Cases

* First HCT in the selected years and with survival status reported to the CIBMTR
Data Download

- Validated data
- Data dictionary
- Differentiate between TED or CRF data
- Future: Expand scope of data
Data Retrieval for Statistical Analyses

• Quarterly retrieval of validated data into SAS analysis files
  – These are the files used by CIBMTR statisticians for all CIBMTR studies
  – Shared with BMT CTN for patients on BMT CTN trials
  – Subset could be shared with other groups
  – Easily converted into EXCEL and other formats
Summary

• Outcomes Registries can
  – Allow assessment and improvement of HCT
  – Facilitate scientific collaboration; attract research funds
  – Change practice

• Regional Outcomes Registries can foster pursuit of a scientific agenda that is relevant to regional issues

• Collaboration with existing international registries can allow development of a regional registry in a cost-effective manner
Questions

1. What are the potential benefits of expanding the EMBMT registry?
2. What are the challenges in expanding the registry?
3. What can existing international registries do to support the EMBMT?