The Challenges of Analyzing and Reporting Outcomes in Hematopoietic Cell Transplantation

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It’s messy, complex, imprecise & often misinterpreted

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Outcomes Research: What is it?

“Collect and evaluate data that reflect real-world clinical practice and outcomes. Reports that allow comparison of practices to evidence-based performance standards”

Do we have evidence in HCT?

“The study of the effectiveness of health care using large data sources and other advanced technologies”

Small heterogeneous population

“Study the end results of particular health care practices and interventions including effects that people experience and care about, e.g. change in the ability to function”

Do we look beyond DFS?
Outcomes Research

- “Discover cost-effective approaches to improving the health of patients and populations, and to identify ways to put these improvements into practice”
  
  ASBMT Goal – advance the field

- “Outcomes research is epidemiology which uses analysis to separate the relationship between treatment and outcomes, adjusting for the roles of related patient characteristics”

Can we do this in HCT?
Clinical vs. Outcomes Research

- Efficacy
- Mechanisms of disease
- Experimental
- Biophysiological outcomes
- Disease-centered
- Inventing technology
- Drugs and Devices
- “Hard” sciences methods

- Effectiveness
- Impact of disease on patients
- Observational
- Patient-centered outcomes
- Symptom & function-centered
- Assessing technology
- Processes and delivery of care
- “Social” sciences methods
“The bloodwork came back kinda yucky.”
Quintiles of centers based on the predicted survival outcomes of patients at a center.

Centers may be different.
Regression Model for 1 year Survival
Significant Risk Factors

- Disease and stage
- Disease sensitivity (NHL and HL only)
- Co-existing disease
- Race of recipient
- Recipient Age
- Recipient CMV status
- Year of HCT
- Time from dx to tx (ALL and AML not in CR1/PIF only)
- Karnofsky/Lansky performance score
- Donor type/graft type and HLA
- Donor Age
- Donor/recipient sex match
- Conditioning regimen intensity
Regression Model for 1 year Survival

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What are the Difficulties?

- Heterogeneity
- Small sample sizes
- Timeliness of the data
- Data Collection
“O.K., let’s just have a look-see at this pre-mortem.”
Patients & their risk of complications are heterogeneous

- Age & gender
- Diagnosis
- Disease stage
- Performance status & comorbidities

Conditioning required for tumor control

- Donor & Graft source
Patients & their risks are heterogeneous

Age & gender

Diagnosis and prior therapies

**AML CR1 with intermediate risk cytogenetic/molecular phenotype**

*Is it the same after 7/3 \(\rightarrow\) CR; HIDAC consolidation as after 4 cycles of decitabine?*

*Both are CR1*
Patients & their risks are heterogeneous

Age & gender

Diagnosis and prior therapies

Is AML CR1 with intermediate risk cytogenetic/molecular phenotype the same after 7/3 \(\rightarrow\) CR; HIDAC consolidation as after 4 cycles of decitabine?

Both are CR1

Disease stage and thus risks of relapse

Is AML CR1 after 7/3 \(\rightarrow\) CR the same as AML CR1 following 4 complex and 1 investigational Rx to achieve CR? yet Both are CR1
Patients & their risk are heterogeneous

Age & gender
Diagnosis and prior therapies
Disease stage and thus risks of relapse
Performance status & comorbidities

CMV and prior infectious exposures

Conditioning intensity required for tumor control

Now we have 2 flavors: Heavy & Light

Donor & Graft source

Choices & options vary by family, by HLA and by center
Predictability of risks & survival

• Fair at best
  – Good risk patients can die
  – High risk patients can get cured
  – Multi-institutional, multivariate modeling can predict survival outcomes, but not for individuals or for patient groups at smaller centers.
Application of Risk Analyses

Risks for whom?

Patients;

Center survival outcomes;

and Payers

High risk patients need treatment too

High risk for medical, ethnic/racial, socioeconomic and regional factors.

Good care delivery requires tailoring needed therapy to each patient’s needs,

Yet centers and payers also assume liability for high risk patients
What are the Difficulties?

- Heterogeneity of patients
- Small sample sizes
- Timeliness of the data
- Data Collection
95% CONFIDENCE INTERVALS FOR SAMPLES DRAWN FROM A POPULATION RECEIVING A TREATMENT PRODUCING 50% SURVIVAL

These are all the same
95% CONFIDENCE INTERVALS FOR SAMPLES DRAWN FROM A POPULATION RECEIVING A TREATMENT PRODUCING 50% SURVIVAL

Most likely published
Most likely NOT published

95% CONFIDENCE INTERVALS FOR SAMPLES DRAWN FROM A POPULATION RECEIVING A TREATMENT PRODUCING 50% SURVIVAL
Most likely true

95% CONFIDENCE INTERVALS FOR SAMPLES DRAWN FROM A POPULATION RECEIVING A TREATMENT PRODUCING 50% SURVIVAL

[Graph showing 95% confidence intervals for samples drawn from a population receiving a treatment producing 50% survival. The graph illustrates the relationship between sample size and probability, with most likely true values indicated by stars.]
Adjusted Survival Rates for Transplant Centers with 11–20 Transplants
Adjusted Survival with 95% Confidence Interval

Transplant Center Code and Risk Score
Adjusted Survival

Likely different
Adjusted Survival Rates for Transplant Centers with 11–20 Transplants

Adjusted Survival with 95% Confidence Interval

Transplant Center Code and Risk Score

Adjusted Survival

Likely not

Likely different
What are the Difficulties?

- Heterogeneity of patients
- Small sample sizes
- Timeliness of the data
- Data Collection
“Give it to me nuanced, Doc.”
SURVIVAL AFTER HEMATOPOIETIC STEM CELL TRANSPLANTS, 1996-2001

Are these the same or different outcomes? Is followup sufficient to know?

Probability, %

Years

0 1 2 3 4 5

0 100

Probability, %

0 20 40 60 80 100

HLA-identical sib (N = 14,473)

Unrelated (N = 5,358)

Autotransplant (N = 23,857)
Timeliness of Results from a Center

- Because of small sample sizes, need to combine data from multiple years

- One year’s bad experience can negatively affect assessments for several subsequent years (even if problems have been fixed)
NMDP predicted one-year survival rate for unrelated patients from this center 01/01/02 through 12/31/06 was 57.5%, with 95% statistical confidence that the predicted survival was between 42.3% and 72.8%.

NMDP national one-year estimated actual survival was 54.0% in the 8,847 patient transplanted in the U.S.

1 Year Survival Following Unrelated Donor Product Transplantation in an "Underperforming" Transplant Center

Was something important fixed; or is this bad, followed by good luck
What are the Difficulties?

- Heterogeneity of patients
- Small sample sizes
- Timeliness of the data
- Data Collection
"We're not that well organized, but we know where everybody is."
DATA COLLECTION

• Can only adjust for items that can be measured or reported with:
  consistency and accuracy
  systematic collection all data, all centers

• Requires substantial effort, expensive
• Some data elements frequently unmeasured or poorly measured
  socioeconomic status
  income, coverage status
  chronic health conditions
Limitations

- Heterogeneity of patients
- Data Collection – parsimony
  - Analyze only what is collected
- Small sample sizes
- Timeliness of the data/report
- Recognize-- but not discourage/punish investigational approaches in cohorts
Limitations

▪ Unintended consequences
  Not intended to compare centers

▪ Translating results into improvement

▪ How to trend survival upwards without limiting patient access to care
...and of course

Show me the $$

Costs and Cost-effectiveness in BMT
Why is BMT so expensive? & why are the costs so hard to measure?

• Long & complex therapy
  Extended period of risk (3+ years);
  Long followup—often remote from Center

• High risk procedure; Somewhat unpredictable risks of dangerous *and expensive* complications

• Complications nearly always need in-hospital management and often ICU
Survival can be costly

- Intensified management can rescue patients from serious complications
  - Graft rejection
  - Infections (prophylaxis, screening & therapy)
  - Transfusion support
  - Respiratory failure (from treatable cause)
  - GVHD [acute & chronic]
  - Relapse (added therapy and/or DLI)
Application of Cost analyses

- Costs as measures of efficiency
- Costs as measures of team and coordinated care
- Costs for whom
- Costs as surrogate for quality
Application of Cost analyses

• Costs for whom?
  Patient and Payers
  – Care delivery requires tailoring needed therapy to each patient’s needs
  – High risk patients need treatment too
    • High risk for medical, ethnic/racial, socioeconomic and regional factors.
Application of Cost analyses

• Costs as surrogate for quality
• Better survival at reasonable costs
  – Value proposition for payers

  – Discourages high risk patients who have expectedly lower survival or more complications

  – Survival for them at what price
What about “Value”?

• No systematic cost data available
• Increasingly of interest to payers, patients, policy makers
• Costs among most rapidly growing
  • 2009 – BMT has highest percentage growth in costs of any hospital procedure (AHRQ HCUP)
  • 2011: Approximately 20,000 Transplants per year in U.S.
     – ~$5-10 Billion in estimated billed charges
     Nearly $500,000 billed first 180 days after alloHCT (Friedman, Optum)
Treatment and Cost Effectiveness

Initial Health Status → Outcome Health Status

Treatment: Skill
How well was it done?

Treatment: Process
What was done?
Initial Health Status \rightarrow \text{Outcome Health Status}

Treatment: Skill
How well was it done?

Treatment: Process
What was done?

Effect of the treatment will depend on the baseline characteristics; and how skill modifies the effect of the process
Caution about valid inferences about treatment effects

Initial Health Status → Outcome Health Status

Treatment: What was done and how well

Correlate of Treatment

Unmeasured factor associated with both treatment and outcome leading to --- attribution bias ---

Claiming credit for success & Taking no blame for failure
Threats to valid inference

Unmeasured risk factor associated with both initial health status and treatment leading to selection bias
- cherry picking patients ---
Pitfalls in Cost Effectiveness Analysis

- Changing perspectives can eliminate some costs, yet generate others
  - Patient (out-of-pocket, work loss)
  - Provider (ignore post-Hosp costs)
  - Payor (include only fixed DRG cost)
  - Society (covers everything including increasing complexity and real improvements)

- Sensitivity Analysis
Tips for Outcomes Research

- Don’t develop your own measures
  - But understand the problems with the ones you use
- Generate and critique a conceptual model
- Create clinician-methodologist partnership
- Get statistical help
- Understand the tentative nature of your conclusions
Just Don’t Give Up