Comparing Two Treatments of Bone Marrow Transplant in the Context of Competing Risks Failure Time

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Introduction

Bone Marrow transplantation

- First successful use in 1968
- Widely used in patients with leukemia
- Two important sources of stem cells:
  - bone marrow (BM)
  - peripheral blood (PB)
- Complication:
  - graft-versus-host disease (GVHD)
Introduction

Objectives:

- To define and document competing risks for patients with GVHD
- To compare two treatments using nonparametric approaches that consider or ignore competing risks
- To compare two treatments using models that account for competing risks or ignore competing risks
Introduction

Graft-versus-host disease

- graft-versus-host disease
- GVHD

- acute GVHD
- chronic GVHD
  - cGVHD
    - limited cGVHD
    - extensive cGVHD
Introduction

Competing risk(s)

- Definition: an event either precludes the occurrence of another event or fundamentally alters the probability of occurrence of the other event.

- Competing risks of cGVHD: death due to other causes, relapse

- Competing risks of extensive cGVHD: death due to other causes, relapse, limited cGVHD
Materials and Methods

Data
- Multi-center randomized phase III clinical trials
- 228 patients with AML, CML and MDS
- Patient-donor pairs were stratified by disease type and study centre
- Two treatment groups: BM and PB
- Outcome measure:
  - time to cGVHD
  - time to extensive cGVHD
Materials and Methods

Methods ignoring competing risk(s)
- 1-KM
  - Log-rank test
- Cox proportional hazards model

Methods accounting for competing risk(s)
- Cumulative incidence
  - Gray’s K-sample test
- Fine & Gray’s competing risks regression model
Kaplan Meier estimator

\[ \hat{S}(t_i) = \prod_{i,t_i < t} \left( \frac{n_i - d_i}{n_i} \right) \]

- \( t_i \) is the distinct ordered observed times
- \( n_i \) is the number of patients who at risk beyond \( t_i \)
- \( d_i \) is the number of event of interest at \( t_i \)
- *Product-limit estimator of the survivor function*
Cox’s proportional hazards model

\[ \ln h_i(t) = \ln h_0(t) + Z^T(t) \beta \]

- \( h_0(t) \) is the unspecified baseline hazard
- \( Z(t) \) functions of covariates \( z \) and \( t \)
Cumulative incidence estimator

\[ CI(t) = \sum_{t_i < t} \frac{d_i}{n_i} DFS(t_i) \]

- \( t_i \) is the distinct ordered observed times
- \( n_i \) is the number of patients who are at risk beyond \( t_i \)
- \( d_i \) is the number of event of interest at \( t_i \)
- \( DFS(\cdot) \) is the Kaplan-Meier estimate of the probability of being free of all events at time \( t_i \)
Fine & Gray’s competing risks regression model

\[ g\{F_1(t;Z)\} = h_0(t) + Z'(t)\beta \]

- \( g \) is the log (-log) transformation
- \( Z(t) \) functions of covariates \( z \) and \( t \)
Results – time to cGVHD

1-KM

- There was no significant difference between the two treatment groups ($p = 0.18$)

Cumulative incidence

- The difference between the two treatments was statistically significant ($p = 0.03$)
Results – time to cGVHD

Cox model
- Stratified by study centre and disease type
- No significant difference between the two treatments, HR = 1.16 (PB vs. BM), 95% CI 0.83 - 1.62, \( p = 0.37 \)

Fine & Gray’s competing risks regression model
- Stratified by study centre
- Treatment was significant \( (p = 0.039) \)
- Disease type was significant \( (p = 0.011) \)
Results – time to cGVHD

![Graph showing cumulative incidence of cGVHD over survival time (in days)]
Results – time to extensive cGVHD

1-KM

- There was no significant difference between the two treatment groups ($p = 0.15$)

Cumulative incidence

- The difference between the two treatments was not significant ($p = 0.18$)
Results – time to extensive cGVHD

Cox model
- Stratified by study centre and disease type
- No significant difference between the two treatments, HR = 1.386 (PB vs. BM), 95% CI 0.91 – 2.10, $p = 0.12$

Fine & Gray’s competing risks regression model
- Stratified by study centre
- Treatment was not significant ($p = 0.22$)
Results – extensive cGVHD

![Graph showing cumulative incidence of extensive cGVHD over survival time (in days).]
Conclusions

- Cumulative incidence is the unbiased estimator in the presence of competing risk(s).

- Using PB stem cells over bone marrow leads to higher cumulative incidence of cGVHD.

- But this trend does not extend to the cumulative incidence of extensive cGVHD.


Pepe M.S., Mori M. Kaplan-Meier, marginal or condition probability curves in summarizing competing risks failure time data? Statistics in Medicine, Vol.12, 737 –751, 1993.