Individual-patient data meta-analysis (IPD MA) in the presence of competing risks

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When is survival analysis (time-to-event data) needed?

- Not all events of interest actually occurred
- Events occur at different times
- Variable length of follow-up for those who are not known to experience an event.
Censoring makes survival analysis different: a key analytical problem in survival analysis

• We have some information about individual survival time
  – typically, it is at least as long as the period the person has been followed

• but we don’t know the survival time exactly
  – an observation is *censored* (typically *right censored*)
    • i.e. We do not observe all events (deaths) but we know that it is beyond some limit
Censoring - when/why?

• a person does not experience the event before the study ends
• a person is lost to follow-up during the study period
• a person withdraws from the study because of death (if death is not event of interest) or some other reason (e.g. adverse drug reaction)

Kleinbaum DG, 1996
Censoring must be “non-informative”

- Censoring is typically assumed to be “non-informative” i.e. the probability of observing the subsequent event of interest is not affected by any characteristics of the study patients.
  - i.e. we assume that if patients could be followed beyond the point in time when they are censored, they would have the same rate of outcome as those not censored at that time
  - random, independent of outcomes

Kleinbaum DG, 1996; Clark et al. 2003
Kaplan-Meier estimates and its complement (1-KM)
Allogeneic peripheral blood stem cell transplant vs. bone marrow transplant in the management of hematological malignancies: an individual patient data meta-analysis of 9 randomized trials and 1,111 patients

Stem Cell Trialists Collaborative Group

J Clin Oncol 2005;23:5074-5087
Allogeneic stem cell transplant: only curative treatment for many patients with hematological malignancies

• Which stem cell source?
  – Peripheral blood?
  – Bone marrow?
Key statistical principles of IPD meta-analysis

• Patients in one trial are not directly compared with those in another trial
  – the original randomization in each trial is preserved
• Each trial is analysed separately
• Early Breast Cancer Trialists‘ Collaborative Group methods were followed
  – Summary statistics are calculated for each trial
    • log-rank test for each trial
• These summary statistics are added together in the meta-analysis
  – The individual log-rank statistics from each trial were then combined to give an overall estimate of the effect of PBSCT vs. BMT on the outcomes of interest.
    • the overall log-rank statistics was used to calculate the significance levels (p value)
    • For plotting survival curves the log-rank statistics were calculated for each trial at various time points of follow-up and converted into the probability estimates based on the estimated failure rate of patients in PBSCT vs. BMT arm

• Second method employed general fixed (inverse-variance weighted model) using Kaplan Meier statistics at various time points
IPD allo-SCT meta-analysis: main results

• PBSCT led to decreased relapse in hematological malignancies.
• It may also improve overall and disease-free survival in patients with unfavorable prognostic features.
• However, it was also associated with very high risk of extensive chronic GVHD.
• This trade-off between benefits and harms should be taken into account in the choice of a stem cell source.
Chronic Graft-Versus Host Disease

A multi-system chronic alloimmune and autoimmune disorder that occurs later after allogeneic hematopoietic stem cell transplantation, featured by immunosuppression, immune dysregulation, decreased organ function and impaired survival.

Courtesy of Dr. Pavletic

NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I. Diagnosis and Staging Working Group Report
Dry eyes

Oral lesions

Nail dystrophy

Skin sclerosis

Deep sclerosis

Infections

Endocrine

Metabolism

Nutrition

Pain

Quality of life

Disability

Bronchiolitis obliterans

Loss of bile ducts

Fasciitis

Skin ulcers

In cGVHD

Spectrum of manifestations

Courtesy of Dr. Pavletic
IPD MA: PBSCT vs. BMT
cGHVHD (ext): no competing risks

GF: general-fixed effect model
Inverse-variance weighted model using Kaplan-Meier statistics

Person-years model: as described by Early Breast Cancer Trialists’ Collaborative Group (Oxford method)
Competing risks

• “An event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event”

• Therefore, if event of interest is not random, but is dependent on another outcome, this (these) competing risk(s) should be taken into account in the analysis of survival data.

Gooley et al, 1999
Competing risks for cGVHD

• Death *without* cGHVD
• Relapse *without* cGVHD
  – It is a competing risk because patients are given immunosuppressive therapy (IST) to prevent cGHVD. Once the patients develop relapse, IST is withdrawn. Therefore, relapse fundamentally alters the probability of occurrence of cGVHD.
Objective: to develop methods for performing a meta-analysis in the presence of competing risks

- no methods described in the literature how to perform a meta-analysis in the presence of competing risks
Meta-analysis: taking competing risks into account

- Each trial was analyzed separately
  - The effect of competing risk in each trial was assessed using method of Gaynor et al.
  - **Cumulative incidence** - the probability of failure (cGVHD) in the presence of competing risk was determined for each trial
    - *J Am Stat Assoc* 1993, **88**(422):400-409
- Data were pooled between trials using an inverse-variance weighted model
- Test statistics (Ho:S1=S2;Ha:S1≠S2)
  - Based on the difference in the sums of the probability of the cause-specific failure (cumulative incidence) at the different time points weighted by the variance
- The analyses implemented in STATA
IPD MA: PBSCT vs. BMT
cGVHD (ext): competing risks vs. no competing risk comparison

No competing risk

In the presence of competing risks
IPD MA: PBSCT vs. BMT
Event of interest cGHVHD (ext): competing risks (death w/o cGVHD; death & relapse w/o cGVHD)

“if one is interested in comparing actual probabilities between two groups then CI estimates should be used…”
“…if one is interested in evaluating the effect of treatment on the hazard of failure from the cause of interest, the use of CI estimates and tests related to them may be misleading if the treatment also affects the hazard of the competing risk. In such situations, the logrank test is appropriate for inference since it is a function solely of the hazard of failure from the cause of interest and failures from the competing risk therefore can be censored”… …”one must be careful to understand the relationship of treatment to various causes of failure…”

(Gooley et al. Stat Med 1999)
Conclusions

• IPD MA of time-to-event data may produce dramatic differences in the results depending on whether competing risks are taken into account

• Interpretation of evidence should be done in the context of hypotheses
  • Theory-laden (Popper)

• The users of such evidence should be aware of this.
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