COMPARISON OF TIME-DEPENDENT TREATMENTS: AN APPLICATION IN STEM CELL TRANSPLANTATION

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Introduction

Treatments for potentially life-threatening chronic diseases often present a trade-off between safety and efficacy. In many situations a first treatment is followed after some time by an intensifying intervention, or more simply the wait-and-see approach is abandoned starting a treatment characterized by increased mortality in the short term. The comparison of long-term outcomes between the different strategies is difficult when not based on the intended protocol, the core problem being the time-dependency of the treatment. Standard approaches like using time-dependent covariates in Cox regression or estimating transition probabilities by the Aalen–Johansen estimator in a non-parametric multi-state model may not sufficiently tackle the complexity of the problem. In this study we focus on the relevance of multiple time-scales. The motivating examples belong to research in stem cell transplant, specifically related to the analysis of the impact of a second ("tandem") transplant, usually given between 2 and 9 months from the first in absence of disease progression, where the use of allogeneic (donor) cells is associated to a peak of mortality during the first 3-6 months, as compared to autologous (patient's) cells and to single auto transplant.

Objectives

The main case study was conducted within the European society for Blood and Marrow Transplantation. The aim was to assess the differences of outcomes (overall and progression-free survival, OS and PFS) in multiple myeloma patients comparing Single Auto, Tandem Auto and Tandem Auto-Allo. The analysis was based on 24,936 disease histories reported in the international transplant registry of the EBMT society. Our goal was to provide accessible (familiar) measures for comparison, specifically hazard ratios (HR) and estimated probabilities for the three groups.

Methods

The histories were represented as multi-state models with 4 states (start at first auto transplant, stop at OS and PFS failure, two transient states at administration of second auto or allo) and 5 transitions. The main time-scale was time since first transplant. We preliminarily investigated post-second transplant hazards for non-proportionality and trend along a second time-scale, time since second transplant, by nonparametric smoothed estimates [1]. In a first approach based on Cox regression, this information was incorporated together with substantive knowledge leading to modelling the time-varying effects of tandem auto and allo (included as time-dependent covariates) as piecewise-constant on 4 intervals along the second time-scale. This first model allows to obtain standard forest plots of HRs for visualizing differences (with p-values). As a second approach we fitted a parametric Poisson regression model with baseline hazard given by the product of three components, each depending on one of the three time-scales (dependence on time since tandem auto and on time since allo applicable only for the post-second transplant hazard in the pertinent groups) [2]. We used restricted cubic splines with 6 knots to model the baseline hazards [3]. This second model allows to visualize the trend in time of hazards and HRs (with 95%CI). In both models we adjusted for the most relevant clinical characteristics measured at fist auto.

Both Cox and Poisson approaches can be a basis to estimate transition probabilities for the non-Markovian multi-state model by simulation although this is a rather cumbersome application. For the quantification of differences in terms of OS and PFS probabilities we alternatively computed dynamic prediction curves using the landmarking approach [4]. The supermodel on stacked landmark datasets was formulated with effects

of tandem transplants piecewise-constant along the same intervals as in the former Cox regression. We focused on the conditional 8-yrs OS and 3-yrs PFS.

Results

We report results for PFS. The core characteristic of time-dependence of second transplant effect along the time since its administration was evident in the nonparametric smoothed estimated hazard (Figure 1, panel a), and highly significant ($p<0.001$) by Likelihood Ratio test within the Poisson model. The output of the latter is shown in Figure 1, panels b) and c). We obtained consistent HRs using the Cox model. The PFS hazard advantage for patients who received allogeneic transplantation was quantified after 2 years from its administration by HR=0.5, 95%CI 0.42-0.59. The conditional 3-yrs PFS probability showed an improvement after about 1yr, which is modest with Single and Tandem Auto and more marked with Auto-Allo. At the end of the prediction period this had an advantage by +19% vs Tandem Auto and +25% vs Single Auto.

Conclusions

Our study is representative of many real-life medical research comparing time-dependent treatments with non-ignorable time-varying effects that require the consideration of multiple time-scales. For modelling hazards the approach using Cox regression with piecewise constant HRs has the advantages of simplicity of implementation and ease of interpretation, and limitations in the rigidity of the structure and in the choice of the time cut-points. Using more flexible functions for the time-varying effect is possible but at the cost of losing the advantages just described. The approach using Poisson regression can be seen as a convenient extension [5], it allows a more flexible structure for all relevant time-scales and provides accessible graphical output for hazards and HRs. Alternatively flexible parametric survival models can be used, with overlapping results [6,7]. The other methodological challenge in these studies is evaluating how hazard ratios varying in time translate in terms of survival probabilities. Dynamic prediction curves can be difficult for medical audience, however the landmarking approach can be proposed using the concepts of the familiar landmark analysis.

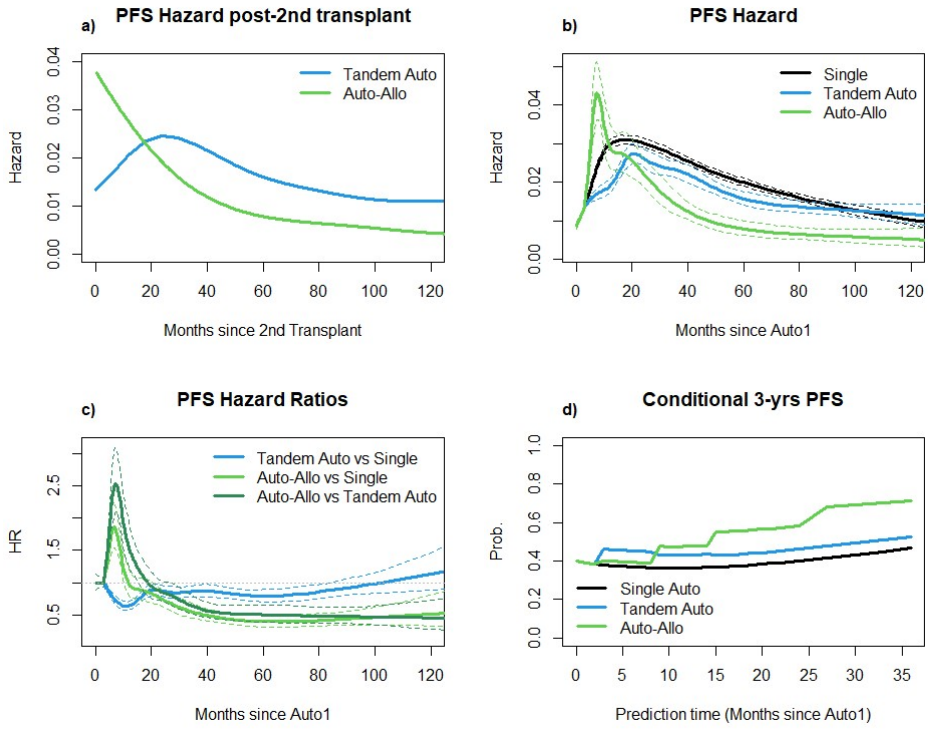

Figure 1. From top-left, clock-wise: a) Non-parametric estimate of PFS hazard functions after second transplant. b) and c) Output of the Poisson model with 2 time scales, respectively and HRs (dashed lines correspond to the limits of 95%CI). d) Dynamic prediction curves. Conditional 3-yrs PFS (for a specific pattern of covariates and timing of tandem transplant equal to 3 months after first auto).

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