TREATMENT-FREE REMISSION SURVIVAL ANALYSIS IN CHRONIC MYELOID LEUKEMIA: COMPARISONS BETWEEN CLASSICAL AND MACHINE LEARNING TECHNIQUES

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Introduction

Over the past 15 years, various research studies have examined the outcomes of patients with Chronic Myeloid Leukemia (CML) who achieved a sustained deep molecular response (DMR) and discontinued tyrosine kinase inhibitors (TKIs). These studies have demonstrated the safety of discontinuing TKI treatment in accordance with current recommendations.

Objectives

Our aim is to perform a survival analysis for treatment-free remission (TFR) duration assessment, while also examining differences between patients who discontinued a first-generation or second-generation TKI.

Methods

We have designed a retrospective and prospective observational study focusing on patients in Italy with CML who have discontinued TKIs. Patients with a minimum of 1 year of follow-up will be included in the analysis. We will evaluate the influence of the last administered TKI (either a first or second-generation inhibitor) prior to discontinuation on the loss of DMR. Several potential confounding and prognostic factors will be considered, including age, gender, Sokal score, ELTS risk, transcript type, duration of TKI therapy, time to DMR achievement, DMR duration, line of therapy at discontinuation, depth of molecular response, and reasons for discontinuation. We will employ causal machine learning techniques such as targeted minimum loss-based estimation (TMLE) and causal survival forests, based on multiple causal decision trees. The results will be compared to the inverse probability of treatment weighting (IPTW) method in order to estimate the adjusted hazard ratio for DMR loss and the different TKI groups [1,2]. Additionally, a simulation study will be conducted to compare the performance of the estimators in terms of bias, coverage probability, type I and type II errors. Finally, we will discuss the advantages and disadvantages of the various approaches.

Results

Of the 467 patients enrolled so far, 54.0% were males, and, in particular, 54.5% of pts who discontinued a first-generation TKI (I gen) and 53.2% of pts who discontinued a second-generation TKI (II gen) ($p = 0.27$). Median age at discontinuation was 59.0 (IQR: 48.0-71.0) for the whole sample, 60.0 (49.0-69.3) for I gen, 58.0 (46.0-71.0) for II gen ($p = 0.65$). No differences between the two groups were found for Sokal Score, ELTS, and type of transcript. I gen group had a longer duration of the last TKI treatment before discontinuation than II gen ($p < 0.01$), of time to DMR ($p < 0.01$), and of DMR duration ($p < 0.01$). Median time of TFR duration was 20.8 (IQR: 6.3-52.2) months for the overall sample, 21.9 (6.1-54.3) for I gen group, and 20.8 (6.6-45.7) for II gen ($p = 0.62$). Regarding classical survival analysis, when performing the log-rank test, no differences were noted between the two groups (Figure 1). From preliminary Cox univariate regression models, higher age at discontinuation showed to increase the hazard ratio (HR) of treatment restart (HR on a difference of 23 years: 0.61; 95%CI: 0.46-0.81; $p < 0.001$), contrary to duration therapy before discontinuation (HR on a difference of 6 years: 0.67; 95%CI: 0.51-0.88; $p = 0.004$). Generation of the last TKI did not modify the risk of losing TFR ($p = 0.252$). Further analyses with causal machine learning techniques will be conducted.

Conclusions

Based on our population, we have not observed a significant impact of the type of TKI used at discontinuation on the loss of DMR. Estimators that effectively separate baseline covariates from treatment effects can mitigate potential bias resulting from post hoc selection of covariates. Machine learning approaches demonstrate robustness in modeling miss-specification.

Bibliography

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Figure 1. Survival Kaplan-Meier curves for TFR loss in the I (blue curve) and II (red curve) generation TKI groups. Log-rank test p-value is provided.