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Informative Censoring in CDK4/6 Inhibitor Adjuvant Therapy for Early Breast Cancer: A Sensitivity Analysis of Invasive Disease-Free Survival in the monarchE Trial

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INTRODUCTION

The estimation of survival curves and hazard functions relies on the assumption of non-informative censoring—that is, the censoring time for an individual provides no further information about that person's likelihood of survival at a future time, had the individual continued the study [1]. This assumption is inherently untestable [2] and, if violated, may introduce bias in the estimation of treatment effects, such as the hazard ratio (HR). This issue is particularly relevant in oncology trials evaluating disease recurrence or progression, where follow-up may be affected by treatment-related toxicity. Patients with early toxicity or clinical deterioration may be more likely to discontinue treatment and withdraw from follow-up, introducing potentially informative censoring.

This topic has gained attention in the interpretation of the monarchE trial—a large phase III study evaluating adjuvant CDK4/6 inhibitor in early breast cancer patients with hormone receptor-positive, HER2-negative, high-risk of recurrence —where the magnitude of benefit in invasive disease-free survival (IDFS) (HR = 0.68; 95% CI: 0.60-0.77) was not paralleled by an overall survival (OS) advantage (HR = 0.90; 95% CI: 0.75-1.09). Informative censoring due to toxicity-related dropouts has been suggested as a possible explanation for this discordance, potentially resulting in an overestimation of the IDFS benefit [3,4].

A previous reanalysis of the monarchE data applied a sensitivity analysis by balancing reverse Kaplan–Meier curves over the entire 72-month follow-up period, treating all excess censored patients in the experimental arm as if they had experienced the event [3]. This approach yielded an attenuated IDFS HR of 0.82 (95%CI: 0.72-0.94), casting doubt on the magnitude of the reported benefit. However, this strategy implicitly assumes that all censoring is informative, including late censoring events that are more plausibly administrative that may overcorrect the estimate.

AIM

We reanalysed the monarchE trial data by describing and comparing censoring patterns between treatment arms, then estimating the potential bias on the IDFS HR through clinically motivated sensitivity analyses.

METHODS

In the absence of individual patient data, pseudo-individual data were reconstructed from published Kaplan–Meier curves using Guyot's algorithm [6].

To describe censoring patterns and compare arms, reverse Kaplan–Meier curves were used [7], which invert the roles of events and censoring and estimate the probability of remaining under observation over time, assuming no events occur.

Two sensitivity analyses were conducted using clinically motivated time intervals: i) the first sensitivity analysis (24 months) considered 0–24 months interval, corresponding to treatment duration, during which toxicity could cause drop-

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outs; ii) the second sensitivity analysis (48 months) considered 0–48 months interval, representing the minimum time before administrative censoring could occur. Before 48 months, all censoring must be attributed to loss to follow-up.

For each analysis, the difference in censored patients between treatment arms—defined as the 'excess' censoring—was calculated. Assuming that this excess censoring could be attributed to treatment-related toxicity, an equal number of censored patients matching this excess were then randomly selected from the experimental arm and reclassified as having experienced the event at their censoring time. A new HR was subsequently estimated.

RESULTS

In the first 24 months, there were 27 excess censored patients in the experimental group (214 vs. 187), with 186 and 268 events in the experimental and control arms, respectively. Over 48 months, the difference in censoring decreased to 23 (351 vs. 328), with 362 and 523 events, respectively.

Reverse Kaplan–Meier analysis showed a marked increase in censoring rates from 48 months onwards, consistent with the expected start of administrative censoring. The censoring rates were similar between arms during the entire study period.

When reclassifying the excess censored patients in the 24-month window in the experimental arm as events, the IDFS HR changed from 0.68 (95% CI: 0.60–0.77) to 0.72 (95% CI: 0.64–0.82). Similar results were obtained in the 48-month analysis, with an HR of 0.72 (95% CI: 0.63–0.81).

To observe a less relevant effect (defined as an IDFS HR higher then 0.80), it was necessary to reclassify 80 censored patients in the experimental arm as events within the first 24 months—the duration of treatment, whose toxicity is suspected to cause the bias. This is a very large number, especially considering that just 186 events were actually observed in the same time interval.

CONCLUSIONS

Informative censoring is a potentially important source of bias in oncology trials. Reverse Kaplan–Meier curves help visualize temporal patterns in censoring, and sensitivity analyses based on clinically justified time windows provide realistic estimates of the possible bias. In the monarchE trial, the observed IDFS benefit appears robust even under conservative scenarios. Therefore, the discrepancy between IDFS and OS does not seem to be attributable to informative censoring and may be better explained by prolonged post-recurrence survival, as the discontinuation of CDK4/6 inhibitors at the time of progression limits their impact beyond recurrence. Extended survival after recurrence can make it inherently difficult to detect an OS benefit, even when a true delay in recurrence—as reflected by improved IDFS—is present [8]. Even where OS remains unchanged between treatment arms, improvements in IDFS can still provide meaningful value, extending the time patients remain free from chronic disease and its psychological, social, and financial burdens.

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