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Deconstructing the Kaplan-Meier curve: Quantification of treatment effect using the treatment effect process.

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1 Introduction

One important question arising in clinical trials is the survival experience of two or more treatment groups. The usual way to estimate this is with Kaplan-Meier curves. We can deduce quite a bit from these figures alone. When the curves are distinct, an advantage in survival probability for one treatment over the other will be immediately apparent. For distinct curves, the magnitude of this advantage will again be apparent. Though more nuanced, the figures also provide information on the hazard rates, for each group and, numerically and visually, an assessment of the differences between these rates. However, the hazard rates themselves cannot be read directly from the Kaplan-Meier curves, and it takes an experienced and skillful eye to detect how the relationship between these rates may change with time.

There is one particular situation, that of proportional hazards, in which the ratio of rates does not change with time. When the ratio of rates is constant with time, so is the ratio of the logarithms of the survival curves. This simplifies things greatly, but it is not easy to detect from the Kaplan-Meier curves on their own how reasonable of an assumption a proportional hazards one might be. When looking at a Kaplan-Meier plot, many of us would not find it easy to judge the quality of such an approximation.

Our arguments here are emphasized by focusing on a recently published phase III trial [1]. By appealing to a particular statistical tool, the treatment effect process, we can glean valuable information via the deconstruction of the Kaplan-Meier curves presented by the authors. This brings any time-dependent effects into sharp focus. Our approach is

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Competing Interest

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of an entirely empirical nature, i.e., based on the observations by themselves and with no modeling or further assumptions involved. As for the Kaplan-Meier curves, there are always some working mathematical assumptions, but these are minimal and detailed in Chauvel and O'Quigley [2]. The treatment effect process is thoroughly detailed in Chauvel and O'Quigley [3] and O'Quigley [4], and we give a summary description here. This process results from a change in the time scale, and we describe that first. Then, in Section 4 we see how the process allows us to gain greater insight into the short-term and long-term impact of treatment over time.

2 Transformation of the time-scale

The time-dependent nature of treatment effects - are they constant (proportional hazards), are they delayed or do they decrease with time, for example - are immediately visualized via the treatment effect process [2–5]. The underlying idea is based on a non-linear transformation of the time scale. For the treatment effect process, we assign the same constant value to the gaps between observed events rather than measure time in weeks or months. In this way, the time until the 12th event is taken to be 4 times that of the time to the 3rd event, 3 times that of the time to the 4th event and 12 times that of the time to the first event. The last event is assigned the time point value of 1.0 giving us a graph between 0.0 and 1.0. The Supplemental Section S1 provides further details on the transformation. A key consideration is that any identified time points of interest on this new time scale can be easily back-transformed to the original time scale.

3 Treatment effect process

For a graphical representation of treatment effects, the previous section describes the horizontal time scale. The vertical increments are random - a particular kind of random walk - where the expected size and sign of the increment, i.e., change from the current position, is proportional to the logarithm of the time-dependent relative risk together with the sample size. The graphical representation (see Figure 1 B) describes, quite accurately, the time-dependent structure of the treatment effects. This effect is tied naturally to a lesser or greater extent to the natural variation of the treatment variable. While very subtle effects may still escape us, hidden behind the statistical noise, we will usually be able to discern the main effects: treatment effects remaining constant, treatment effects diminishing with time, or a delayed effect. Supplemental Figure S1 illustrates these different effects. At the arrival point ($t = 1$) of the process, the distance traveled by the process, i.e., the vertical distance from the horizontal axis, is equivalent to the log-rank statistic [2].

4 Dabrafenib and Trametinib in Stage III Melanoma

A phase III randomized trial examined the benefit of 12 months of dabrafenib and trametinib, taken twice daily and daily, respectively, compared to placebo in patients with stage III melanoma with BRAF mutations [6]. For relapse-free survival (RFS), the investigators found a significant treatment benefit with an estimated hazard ratio of 0.47 (95% CI: 0.39–0.58). A follow-up study reported the five-year survival results, with an updated RFS hazard ratio of 0.51 (95% CI, 0.42–0.61) [1].

For this illustrative example, a digitized data set of Dummer et al. [1] relapse-free survival results was created [7, 8]. Figure 1 (A) shows the Kaplan-Meier estimated RFS curves. These curves visually demonstrate an RFS benefit to receiving dabrafenib and trametinib. These curves, along with the estimated hazard ratio, are where many analyses end. However, there is another layer to the story, which is unraveled by examining the treatment effect process, shown in Figure 1 (B). The process shows the benefit of the treatment by the initial strong linear trend. However, the benefit does not persist over time as there is a shift in the treatment effect process around 0.45 on the transformed time scale, where the process flattens, indicating an absence of an effect. Connecting the beginning and end of the process at 0 and 1, respectively, the red dashed in Figure 1 (B) would be the approximate linear trend of the process if proportional hazards held. From this representation of the treatment effect process, the proportional hazards is not a reasonable assumption for these data, a point potentially missed by examining only the Kaplan-Meier curves. The point of 0.45 on the transformed time scale corresponds to 9.5 months, slightly before when the daily combination therapy ended at 12 months. To further investigate what we observe in Figure 1 (B), we can estimate RFS conditional on surviving to 9.5 months. As shown in Supplemental Figure S2 (A), the estimated RFS curves indicate no treatment benefit among patients who are relapse-free at 9.5 months. The treatment effect process, re-estimated starting at 9.5 months, further demonstrates the lack of treatment benefit.

5 Discussion

The treatment effect process throws light on the study of Dummer et al. [1] that was not apparent when examining the Kaplan-Meier curves alone. While the curves show the superior estimated survival for patients treated with dabrafenib and trametinib over five years, the duration of the treatment effect is contained in the relatively brief period of 9.5 months following randomization. This short benefit is made clear by the conditional Kaplan-Meier curves (Figure S2 B). This observation could play a central role in determining the proposed therapy's short-term and long-term effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data Availability

The Kaplan-Meier curve of Dummer et al. [1] was digitized using publicly available software [7, 8].

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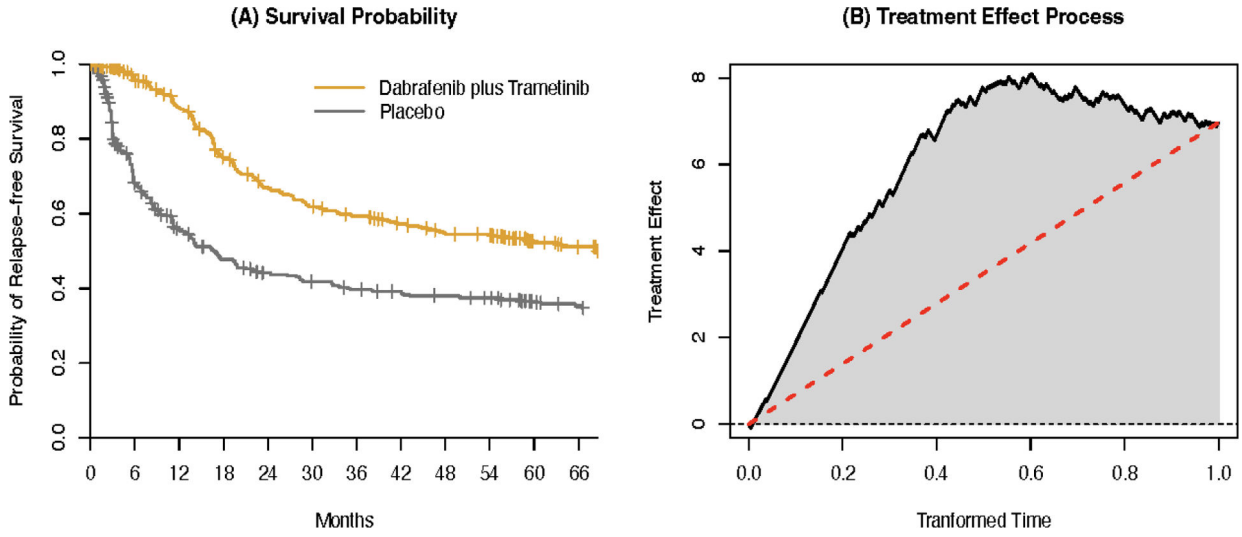

Figure 1:

(A) Estimated relapse-free survival for patients treated with dabrafenib and trametinib compared to placebo in [1]. (B) The corresponding treatment effect process (black line). The dashed red line is the approximate linear trend of the process if proportional hazards held. This shows a severe violation of the proportional hazards assumption. This violation is not immediately apparent from the Kaplan-Meier curves alone.