Editorial

Censoring Analysis of the INvestigating VorasiDenib In GliOma (INDIGO) Phase III Randomized Controlled Trial

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EDITORIAL

Censoring Analysis of the INvestigating VorasiDenib In GliOma (INDIGO) Phase III Randomized Controlled Trial

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The recently published INvestigating VorasiDenib In GliOma (INDIGO) phase III randomized controlled trial[1] examined the effect of an isocitrate dehydrogenase (IDH) inhibitor (vorasidenib) at an oral daily dose of 40 mg on patients with residual or recurrent IDH-mutant grade 2 oligodendroglioma or astrocytoma having previously undergone only operative resection. These patients were randomized to vorasidenib or placebo, with the primary trial endpoint being progression-free survival (PFS). The INDIGO trial concluded that vorasidenib significantly improved PFS, potentially providing a new management option for this patient population. As with any trial, bias has the potential to confound results; theoretically, phase III randomized controlled trials are the least susceptible to bias. A key assumption for trials to be free of bias is that any censoring that occurs during the trial is similar between the control arm and the treatment arm and is noninformative.[2] Bias occurs when the assumption that participants who drop out of a trial are similar (regarding trial endpoints) to those remaining in the trial is not met.

Informative censoring is described as a bias that occurs when participants are lost to follow-up due to reasons related to the study.[2] In a randomized controlled trial, this may occur due to various reasons and could affect the data analysis in research trials. For example, participants may be lost to follow-up due to reasons related to the study, such as progressive cancer in the control arm. Another example is that participants in the treatment arm may stop taking the study drug due to reasons such as toxicity caused by the study drug. This may cause different attrition rates, with the sickest participants leaving the study, thereby introducing a bias and favoring the treatment arm over the control arm. Therefore, unequal attrition rates between the treatment and control arm can introduce bias in the PFS analysis. However, it is possible for informative censoring to still occur even when there are equal attrition rates between both arms.[2]

We compared the imaging-based progression-free survival (time from randomization to the first documented progressive disease or death from any cause) and time to next intervention (time from randomization to the initiation of the first subsequent anticancer therapy or death from any cause) between the treatment and the control group in the INDIGO study at time intervals prior to the unblinding of the trial which occurred at median 14 months follow-up.[1] The aim was to determine whether informative censoring bias existed between the two arms.

We examined the rate of censoring at 6, 10, and 14 months using the Kaplan-Meier PFS plot (reported in Figure 2A of the INDIGO trial), based on rough visual estimates of event rates at these time intervals. At 6 and 10 months, there is equal censoring in both arms; which may be informative or noninformative.[1,2] However, at 14 months, the number of patients in the treatment arm (n = 168) minus the patients having the event (roughly 25% with a progression event per the Kaplan-Meier curve; n = 42) is 126, which is 74 more than the 52 patients reported at this interval, meaning that these 74 patients were censored. In the control arm, the number of patients censored was number of patients (n = 163)—progression events (roughly 65%; n = 106)—number of patients reported (n = 29) which yields 28 patients censored; the rate of censoring is 74/168 (44%) in the treatment arm and 28/163 (17%) in the control arm, a statistically significant difference by χ^2 testing (GraphPad Software Inc.). This is depicted in Table 1.

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