Trifluridine/tipiracil in metastatic gastric cancer

Kohei Shitara and colleagues[1] assessed the efficacy and safety of trifluridine/tipiracil for heavily pretreated metastatic gastric cancer. The endpoints were overall survival and progression-free survival. Median overall survival was 5·7 months for the trifluridine/tipiracil group and 3·6 months for the placebo group. The authors did not report a formal comparison of these medians. The hazard ratio (HR) was 0·69 (95% CI 0·56–0·85; p=0·00058). Median progression-free survival was 2·0 months for trifluridine/tipiracil and 1·8 months for placebo (difference 0·15 months). This clinically insignificant difference contradicts the highly significant HR (0·57, 95% CI 0·47–0·70; p<0·0001). This finding is not surprising, since median failure-time is a local summary of progression-free survival, which does not capture short-term or long-term aspects of the survival profile. Furthermore, valid HR analysis requires the proportional hazards assumption—ie, that the ratio of two hazard curves is constant over time. The authors explicitly stated that the proportional hazards assumption was not verified. On the basis of the profiles of the Kaplan-Meier curves in figures 2 and 4, the proportional hazards assumption was probably not met.[1] Consequently, it is unclear how to interpret the HRs for overall survival and progression-free survival. Moreover, even if the proportional hazards assumption is valid, there is no hazard curve from the placebo group to serve as a reference to clinically interpret the HRs of 0·69 or 0·57. The issues with using HRs or medians to quantify treatment effects have been discussed extensively.[2–5]

An alternative approach is based on restricted mean survival time (RMST): the area under the Kaplan-Meier curve across a specific follow-up period. Unlike the median, RMST takes all survival information into account. Using reconstructed data from the overall survival curves in figure 2,[1] the 24-month RMSTs were 7·48 months for trifluridine/tipiracil and 5·76 months for placebo. That is, it is expected that patients treated with trifluridine/tipiracil and scheduled for 24 months of follow-up will survive for 7·48 months. The difference in RMSTs was 1·72 months (95% CI 0·52–2·92; p=0·005) in favour of trifluridine/tipiracil, with an efficacy gain of 30% (ie, [1·72/5·76]×100). On the basis of figure 4,[1] the 12-month RMSTs for progression-free survival were 3·44 months for trifluridine/tipiracil and 2·21 months for placebo (difference 1·23 months, 95% CI 0·81–1·65; p<0·0001). The efficacy gain was 56% (ie, [1·23/2·21]×100). These timescale summary measures are more clinically interpretable than HRs.[5] Clinicians and patients might appreciate using RMSTs for weighing the added benefit of trifluridine/tipiracil against potential risks. In the study by Shitara and colleagues, grade 3 or worse adverse events occurred in 267 (80%) patients from the trifluridine/tipiracil group, but only in 97 (58%) patients from the placebo group.

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1 Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018; **19:** 1437–48.

2 Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J Clin Oncol* 2014; **32:** 2380–85.

3 Pak K, Uno H, Kim DH, et al. Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. *JAMA Oncol* 2017; **3:** 1692–96.

4 Uno H, Wittes J, Fu H, et al. Alternatives to hazard ratios for comparing the efficacy or safety of therapies in noninferiority studies. *Ann Intern Med* 2015; **163:** 127–34.

5 McCaw ZR, Orkaby AR, Wei LJ, Kim DH, Rich MW. Applying evidence-based medicine to shared decision making: value of restricted mean survival time. *Am J Med* 2018; published online Aug 1. DOI:10.1016/j.amjmed.2018.07.026.