A meta-analytic endpoint validation of surrogates used in clinical trials evaluating the efficacy of therapies in patients with chronic lymphocytic leukemia

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Background:

In clinical trials, it is crucial to derive treatment outcomes as early as possible. Therefore, there is a need for surrogate endpoints, which can be measured earlier than the true endpoint. While the number of oncology drugs approved by regulatory bodies based on surrogate endpoints is increasing, many surrogates have not demonstrated a correlation with clinically meaningful outcomes. To that effect, we evaluated surrogate endpoints used in randomized controlled trials (RCTs) that assess the efficacy of therapies in patients with chronic lymphocytic leukemia (CLL).

Aims:

This study aimed to evaluate the validity of objective response rate (ORR) as a surrogate endpoint for progression-free survival (PFS) and overall survival (OS), and PFS as a surrogate endpoint for OS in CLL.

Method:

A systematic literature review (SLR) of RCTs of various treatments in CLL published between January 2015 and January 2022 was conducted in line with NICE (2022) requirements and Cochrane methodology. RCTs reporting at least two endpoints of interest (ORR, PFS, OS) for CLL treatments were included in the SLR. Two independent reviewers extracted relevant data on comparative effectiveness measures reported in the trial publications, which were then used in a surrogate endpoint validation in alignment with health technology assessment (HTA) guidelines. The validation was carried out in two stages. First, the overall magnitude of the comparative effect of the surrogates was estimated using a bootstrapped Dersimmion-Laird random-effects model, then the association between the surrogate and final endpoint was assessed using correlation and regression analyses. Analyses were performed across all trials and separately across trials investigating either kinase inhibitor (Ki) or Bruton's tyrosine Ki (BTKi).

Results:

In total, 69 RCTs were identified. Of these, 28, 25, and 29 trials were available for the ORR versus PFS, ORR versus OS, and PFS versus OS comparisons, respectively. Respective numbers for Ki/BTKi trials within each comparison were 14/10, 13/10, and 13/11. Based on all trials, the overall magnitude of the comparative effect of the surrogate (95%-CI) were 0.18 (0.13-0.23) for the absolute difference in ORR, 0.52 (0.41-0.64) for the hazard ratio for PFS, and 0.80 (0-72-0.89) for the hazard ratio for OS.

Consistently significant treatment effects were also observed in the Ki and BTKi subgroups. Statistically significant correlations (r, 95%-CI) for ORR versus PFS were found across all therapies (r=0.67, 0.40-0.84), as well as in the Ki (r=0.68, 0.24-0.89) and BTKi (r=0.75, 0.22-0.94) subgroups (Figure 1). Based on the HTA guidelines, the correlation observed between ORR and PFS was categorized as moderate in the BTKi trials. The surrogate threshold effect (STE) was 0 for this comparison,fulfilling the requirement of being smaller than the 95% CI of the effect on the surrogate. No clear correlation between the comparative effect on ORR and OS was observed. A statistically significant association between the comparative effect on PFS and the comparative effect on OS based on all trials was shown (r=0.58, 0.27-0.78), but not in the Ki and BTKi subgroups. However, for Ki and BTKi subgroups, significant associations between comparative effects on PFS and OS were observed after weighting the regression by the number of patients in the trial.

Summary/Conclusion: We found robust evidence that ORR serves as a surrogate for PFS in CLL, especially when evaluating the treatment effect of BTKis. Some evidence of an association between PFS and OS were also found. Based on the trials assessed, no clear evidence of ORR as a surrogate for OS could be shown.

Figure 1: Scatterplot displaying the correlation between ORR and PFS