The Relationship Between Surrogate Endpoints and Overall Survival in Myelofibrosis Clinical Trials: Results from a Targeted Literature Review

#5670

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INTRODUCTION

- Primary myelofibrosis (MF) is a rare bone marrow cancer characterized by altered bone marrow function and fibrosis, leading to anaemia, spleen enlargement, abnormal blood cell production and a range of associated complications with a significant symptom burden.[1]
- Overall survival (OS) is the gold standard trial endpoint for HTA, but a median survival of approximately 4-5 years for primary MF[2] makes timely evaluation of new treatments challenging.
- There is a need to identify surrogate endpoints for OS to reduce the resources required to conduct clinical trials and expedite patient access to effective therapies through earlier reporting of clinically significant results.
- We conducted a targeted literature review (TLR) to explore the potential of intermediate clinical outcomes as surrogate endpoints for OS – including spleen volume reduction (SVR), total symptom score (TSS), which are the gold standard assessments in clinical trials.

METHODS

- A targeted literature review was conducted using a multi-pronged strategy: a targeted EMBASE search for surrogate and prognostic endpoints, AI-assisted literature search, Google Scholar review, and evaluation of relevant clinical guidelines and NICE HTAs.
- A separate targeted EMBASE search was conducted to identify relevant meta- and network meta-analyses.
- Publications were screened for evidence on the association between post-treatment changes in intermediate clinical outcomes and OS.

STUDY IDENTIFICATION

- 11 publications (9 unique studies) were identified from EMBASE, with an additional 4 relevant studies found through AI-assisted searches, giving 13 studies in total.[3-17]
- 2 meta-analyses were also identified.[18,19]
- The findings on the various potential surrogate endpoints are described below.

RESULTS: POTENTIAL SURROGATE ENDPOINTS

SPLEEN VOLUME REDUCTION (SVR)[3,10,11,13,14,15,17]

- Patients on JAK-inhibitors (JAKi) who reached a specified SVR% cut-off (ranging from 10%-50%) had a lower risk of death (HR 0.45, 95% CI: 0.30-0.69, p < 0.001) across 8 studies versus those not reaching the the cut-off. Higher cut-offs were associated with improved survival.[14]
- COMFORT-1&2 trials: 10% reduction in SVR significantly associated with 9% reduction in risk of death (HR=0.91 per 10% reduction, p=0.02) in ruxolitinib arm.[13]
- SIMPLIFY-1 trial: SVR ≥35% was associated with improved OS in patients randomised to ruxolitinib (HR = 0.450, p = 0.0078), with a trend towards improvement in the momelotinib arm.[11,15]
- PERSIST-2 trial: Association between SVR and OS in patients treated with pacritinib but not in the 'best available therapy' arm.[3,17]
- SVR is a component of the RR6 (Response to Ruxolitinib After 6 Months) predictive model.[10]

ANAEMIA RESPONSE[5]

- Analysis of the SIMPLIFY-1 & -2 trials of momelotinib suggested anaemia response* was associated with a survival benefit at 12 years (HR 0.5 (95% CI: 0.3 to 0.9, p=0.02))

*defined by modified revised International Working Group for MF Research and Treatment (IWG-MRT) criteria (transfusion independence for ≥12 weeks for transfusion-dependent patients and an increase in hemoglobin ≥2 g/dl lasting ≥12 weeks in transfusion-independent patients with hemoglobin below lower limit of normal.

BONE MARROW FIBROSIS (BMF)[12]

- Analysis of SIMPLIFY-1 found that changes in bone marrow fibrosis during treatment with momelotinib or ruxolitinib did not correlate with efficacy outcomes.
  - The authors questioned the use of BMF assessment as a surrogate marker for clinical benefit with JAK inhibitors.

TRANSFUSION INDEPENDENCE (TI)[4,6,7,8,10,11,15,16]

- Transfusion independence (TI) or TI-R (TI and no haemoglobin <8 g/DL) at 12 or 24 weeks was associated with prolonged OS in several studies:
  - MOMENTUM study of momelotinib[4,16]
  - SIMPLIFY 1&2 study of momelotinib[7,8,11,15]
  - Medicare retrospective cohort[6]
  - RUXOREL-MF study of ruxitinib[10]
- Association seen in patients treated with JAKi, danazol, and in combined populations (active treatment and control).

TOTAL SYMPTOM SCORE (TSS)[11,15]

- Myelofibrosis Symptom Assessment Form Total Symptom Score version 4.0 (MFSAF TSS v4.0) – assesses 7 symptoms on 1-10 scale
- Used in the SIMPLIFY-1 and -2 trials of momelotinib, but TSS response (≥ 50% reduction at 24 weeks) not significantly associated with OS in either the control or treatment arms.

NETWORK META-ANALYSES (NMA)[18,19]

- Two NMAs were identified in patients treated with JAKi:
  - Chen (2024) included 9 studies and examined SVR, TSS and OS[18]
  - Sureau (2021) included 7 studies and examined SVR and TSS[19]
- The trials included in these NMAs could be analysed in a multivariate analysis to quantify the strength of association between intermediate endpoints and survival outcomes.

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CONCLUSIONS

- **SVR, anaemia and transfusion status were promising surrogate endpoints identified by this review, with evidence of association with OS in patients with MF.**
- **BMF is challenging as there is high variability in the results and assessment, and patient-reported symptom scores can be highly subjective.**
- **Other potential surrogate outcomes, such as variant allele frequencies (VAFs) of JAK2 and other driver mutations, are emerging and merit future research.**
- **Further validation using systematic literature review and multivariate meta-analysis is recommended to quantify the strength of the relationship of candidate surrogate endpoints with OS.**

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