Population-Average Effect Estimates of Quizartinib and Midostaurin in Newly Diagnosed Patients with FLT3-Internal-Tandem-Duplication-Positive Acute Myeloid Leukaemia Using Multi-Level Network Meta-Regression

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INTRODUCTION

- Acute myeloid leukaemia (AML) is the most common form of leukaemia in adults[1]. FLT3-ITD mutations are common in AML and associated with a poor prognosis and higher relapse rates[2].
- Treatments for AML include induction chemotherapy to achieve complete remission, followed by consolidation therapy[3]. The FLT3 inhibitor midostaurin is approved for treating newly diagnosed FLT3-mutated AML[4] based on results from the RATIFY study, which enrolled patients aged 18-59 having either ITD or TKD mutations.
- Quizartinib, a highly potent and selective second generation type II FLT3 inhibitor, was assessed in newly diagnosed FLT3-ITD (+) AML patients aged 18-75 in the phase 3 trial QuANTUM-First[5,6]. Following results from the QuANTUM-First trial, quizartinib received approval for treating newly diagnosed FLT3-ITD (+) AML[7-10].
- There is no direct head-to-head randomized controlled trial comparing quizartinib and midostaurin for the treatment of newly diagnosed FLT3-ITD (+) AML patients. Evidence synthesis is complicated by differences in the trial populations assessing quizartinib and midostaurin, necessitating population-adjusted indirect comparisons.
- Matching-adjusted indirect comparisons (MAIC) are frequently used to estimate treatment effects in an aggregate data (target) population by matching individual patient data to summary statistics from the aggregate data available. However, when population-average conditional effect estimates of both interventions in both populations are needed, multi-level network meta-regression (ML-NMR) can be used, as it allows for the estimation of treatment effects in any target population.

AIMS AND OBJECTIVES

- To obtain population-average conditional effect estimates of quizartinib and midostaurin in newly diagnosed FLT3-ITD (+) AML using ML-NMR, which allows for the estimation of treatment effects in the QuANTUM-First population.
- To present results of a case study comparing outcomes stemming from a ML-NMR.

METHODS

- A feasibility assessment was conducted to evaluate whether it would be both feasible and logical to conduct a population-adjusted ITC.
  - RATIFY trial population included patients ages 18-59 with either TKD or ITD mutations while QuANTUM-First trial consisted of FLT3-ITD (+) patients ages 18-75 only.
  - Stratification factors between the trials differed as the RATIFY population was stratified by FLT3 mutation subtype (ITD or TKD) and the QuANTUM-First stratification occurred by age, region and white blood cell count, which were not stratified for in RATIFY.
  - Median follow-up time was longer in the RATIFY trial.
- An indirect treatment comparison in the form of an ML-NMR was conducted using published evidence on RATIFY's limited FLT3-ITD (+) subpopulation[11] comparing midostaurin and placebo, and individual patient data (IPD) from QuANTUM-First.
- The assessed ML-NMR outcomes included complete remission (CR) as a binary outcome, cumulative incidence of relapse (CIR), and overall survival (OS) as continuous outcomes. Treatment effect modifiers (TEMs) and prognostic variables (PVs) were identified based on the literature and input from clinical experts.
- An ML-NMR was conducted integrating QuANTUM-First IPD and RATIFY FLT3-ITD aggregated data within a single probabilistic model, extending the standard network meta-analysis framework by incorporating covariate information from both trials for more accurate population adjustments. As the approach can generate adjusted estimates for any target population of interest, outcomes were generated for the QuANTUM-First trial population, and the RATIFY trial population. Fixed and random effects models were fitted.
  - CR models were compared using the Deviance Information Criterion, while CIR and OS models were evaluated with the Pareto-smoothed importance sampling leave-one-out cross-validation information criterion. For survival outcomes, proportional hazard Weibull and m-spline models were fitted.
- The R packages multinma and loo were used.

RESULTS

- Based on the literature and clinical experts' input, the identified TEMs/PVs were sex, NPM1 mutation status, age, and platelet count. Baseline characteristics of the QuANTUM-First and RATIFY trial populations employed in the ML-NMR are presented in **Table 1**.
  - QuANTUM-First patients included in the ML-NMR had higher age and lower platelet counts as well as a lower proportion of NPM1-positive mutation status compared to RATIFY patients. The proportion of male patients was comparable across the two populations.

Table 1. Baseline characteristics of the QuANTUM-First and RATIFY trial populations employed in the ML-NMR

Baseline characteristics	QuANTUM-First FLT3-ITD	RATIFY FLT3-ITD
Age, mean	54.0	47.1
Sex, male (%)	45	45
Platelet count, x10^9/L, mean	30.0	44.6
NPM1 mutation status, positive (%)	52	57

Complete remission

- The fixed effects model was selected for the ML-NMR of CR. Estimates from the ML-NMR compared to results reported from the QuANTUM-First and RATIFY trials are presented in **Table 2**.
- In the QuANTUM-First population, results from the ML-NMR showed a comparable OR for quizartinib as in the QuANTUM-First trial. The OR estimated for midostaurin was numerically higher than for quizartinib, but statistically insignificant.
- In the RATIFY population, the ML-NMR estimated similar ORs for quizartinib.

Table 2. Outcomes of ML-NMR for CR, CIR, and OS, compared to trial estimates

Comparison	Method	CR OR (95% CrI)	CIR HR (95% CrI)	OS HR (95% CrI)
Outcomes in the QuANTUM-First Population				
Midostaurin vs placebo	ML-NMR	1.51 (0.91-2.48)	1.01 (0.62-1.65)	0.77 (0.56-1.05)
Quizartinib vs placebo	ML-NMR	0.97 (0.68-1.39)	0.49 (0.31-0.79)	0.78 (0.61-1.01)
Quizartinib vs placebo	Trial data	1.00 (0.71-1.40)	0.57 (0.38-0.86)	0.78 (0.62-0.98)
Outcomes in the RATIFY Population				
Quizartinib vs placebo	ML-NMR	1.15 (0.72-1.84)	0.37 (0.18-0.73)	0.71 (0.51-1.00)
Midostaurin vs placebo	ML-NMR	1.82 (1.14-2.99)	0.75 (0.46-1.15)	0.70 (0.52-0.95)
Midostaurin vs placebo	Trial data	1.25 (0.79-1.99)	0.80 (0.56-1.15)	0.79 (0.59-1.06)

Abbreviations: CIR – Cumulative incidence of response; CR – Complete remission; CrI – Credible interval; HR – Hazard ratio; ML-NMR – Multi-level network meta-regression; OR – Odds ratio; OS – Overall survival.

Cumulative incidence of relapse

- CIR results from the trials and the ML-NMR are presented in **Table 2**. For the ML-NMR, the fixed effects m-spline baseline hazard model demonstrated the best fit.
- In the QuANTUM-First population, the ML-NMR estimated quizartinib to be statistically favorable vs. placebo with an HR of 0.49, aligning with the trial data (HR=0.57). No difference was seen between midostaurin and placebo.
- In the RATIFY population, no statistical difference was seen between midostaurin and placebo. In line with the trial data, ML-NMR showed quizartinib to be statistically favorable vs. placebo (HR=0.37).
- Estimated CIR curves (**Figure 1**) showed an acceptable visual fit of the ML-NMR model with the observed data. However, low patient numbers resulted in wide CrI.

Overall survival

- OS results from the trials and ML-NMR are presented in **Table 2**. For the ML-NMR, the fixed effects m-spline baseline hazard model demonstrated the best fit.
- In the QuANTUM-First population, the ML-NMR estimated borderline statistically significant favorable OS HRs for midostaurin and quizartinib. Point estimates from the ML-NMR and trial data closely aligned for quizartinib.
- Similar to the QuANTUM-First population, the ML-NMR showed comparable estimates for quizartinib and midostaurin in the RATIFY population to the trial data.
- Estimated OS curves (**Figure 2**) showed a good visual fit of the ML-NMR model with the observed data.

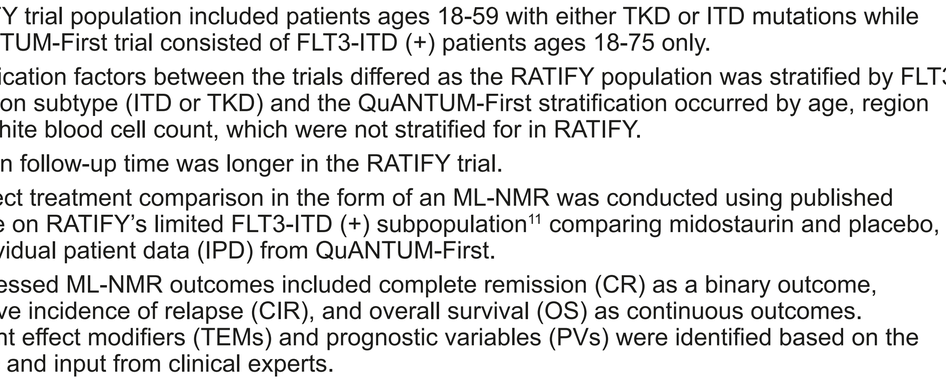

Figure 1. CIR ML-NMR - estimated CIR curves on each treatment in each study population, mspline baseline hazards survival model

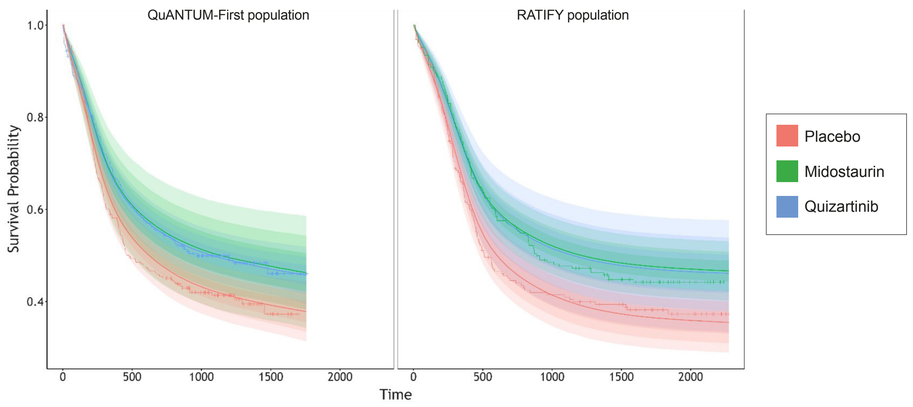

Figure 2. OS ML-NMR - estimated survival curves on each treatment in each study population, mspline baseline hazard survival model

Discussion and conclusion

- The ML-NMR approach allowed for the estimation of treatment effects in two target populations, which was not possible with a previously employed MAIC and highlights a major advantage of ML-NMR over STC and MAIC, as discussed by Phillippo et al. (2020).[12] Hence, the methodology can be used in larger treatment networks, which makes it a more appealing option in a range of scenarios.
- Based on ML-NMR outcomes for CIR quizartinib had a lower HR compared to placebo than midostaurin vs placebo, which suggests a higher efficacy in reducing the incidence of relapse. For OS, both quizartinib and midostaurin exhibit similar HRs when compared to placebo, indicating comparable efficacy in terms of survival. It is worth noting that, due to limited overlap between the populations of the RATIFY and QuANTUM-First trials, reported confidence intervals are quite wide.
- In conclusion, the results of this analysis suggest that quizartinib offered better outcomes in reducing CIR than midostaurin, which is clinically meaningful for FLT3-ITD (+) AML patients given the higher relapse rates associated with this mutation.
- The results of this analysis largely agreed with a previously conducted MAIC[13] and did not present a shiftshift in the conclusion that quizartinib has a better efficacy in reducing the incidence of remission compared to midostaurin.
- As the ML-NMR method is relatively new, it is recommended that the MAIC estimates are used as the baseline efficacy estimates for economic evaluations, with the ML-NMR results as a secondary estimate due to their complexity and the novelty of the method.

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