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Efficacy of FMS-like Tyrosine Kinase 3 (FLT3) inhibitors in patients with acute myeloid leukemia

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INTRODUCTION

- The FMS-like tyrosine kinase 3 (FLT3) gene is mutated in 30% of all patients with acute myeloid leukemia (AML).
- Mutation in the internal tandem duplication (FLT3-ITD) domain is most encountered, often indicating high leukemic burden, higher relapse rates, and poor prognosis in patients.
- Recent clinical studies with the next-generation FLT3Is have shown greater potency and less off-target effects, suggesting the potential benefit of incorporating FLT3I in combination regimens for treatment of AML.

AIM

- We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to explore the overall efficacy of FLT3I in patients with AML.

METHOD

- We conducted a systematic search of Medline, Embase, ClinicalTrials.Gov databases, and meeting abstracts through October 31, 2019, to find out all the RCTs comparing a FLT3 inhibitor-based regimen with other agents in the treatment of patients with AML.
- Pooled estimates of hazard ratios (HR) with respective 95% confidence intervals (CI) for overall survival (OS) and event-free survival (EFS) were calculated using the generic inverse variance method.
- We used the random effects model. Heterogeneity of effect size was quantified using I2 statistic and Cochran's Q.
- All statistical analyses were performed with Review Manager (RevMan Version 5·3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

- A total of five RCTs (two phase II and three phase III) randomizing 1919 patients (1088 in the FLT3I arms and 831 in control arms) were included in the final analysis.
- Randomization ratio was 2 to 1 in QuANTUM-R and ADMIRAL trials, and 1 to 1 in other studies.
- Sorafenib was used as FLT3I in two studies; midostaurin, quizartinib, and gilteritinib were used in one study each. FLT3I was used in newly diagnosed AML patients in three studies.
- Recently published QuANTUM-R and ADMIRAL trials tried FLT3I as salvage therapy for patients with relapsed/refractory AML.
- All participants were FLT3 mutated in RATIFY, QuANTUM-R, and ADMIRAL trials.
- Median age of patients ranged from 47·9 to 68 years. Including data from all studies, pooled HR for OS was not statistically significant for FLT3I compared to control [0·81, 95% CI: 0·65–1·02, P = 0·07].
- In patients with newly diagnosed AML (n = 1181), pooled HR for OS showed trend towards statistical significance [0·85, 95% CI: 0·72–1·00, P = 0·05] on analysis of three studies.
- A significant pooled OS benefit was observed for FLT3I in the setting of salvage therapy for patients with relapsed/ refractory AML (n = 738) [pooled HR 0·69, 95% CI: 0·57–0·83, P < 0·0001].
- Pooled HR for EFS did not reach statistical significance overall (four studies), and in patients with newly diagnosed AML [0·87, 95% CI: 0·68 - 1·11, P = 0·26, and 0·86, 95% CI: 0·61–1·22, P = 0·40, respectively].
- No to substantial heterogeneity was noted among studies, depending on type of analysis.

Table 1. Characteristics of Studies Included in Final Analysis

Study Name	Author, Year	Study phase	Line of Therapy	Stage of Disease/ Treatment	FLT3 status	Regimen Used		FLT3I Dose	Median Age of Patients (years)	Median Duration of follow up (months)	Total Number of Patients	
						FLT3I arm	Control arm				FLT3I arm	Control arm
SORAML	Rollig 2015	2	1	Induction, consolidation, and maintenance	Wild type and mutated	Sorafenib + Standard chemo	Placebo + Standard chemo	400 mg BID	50	36	134	133
NA	Serve 2013	2	1	Induction, consolidation, and maintenance	Wild type and mutated	Sorafenib + Standard chemo	Placebo + Standard chemo	400 mg BID	68	29.3	102	95
RATIFY	Stone 2017	3	1	Induction, consolidation, and maintenance	Mutated	Midostaurin+Standard chemo	Placebo + Standard chemo	50 mg BID	47.9	59	360	357
QuANTUM-R	Cortes 2019	3	> 1	Salvage therapy for Relapsed/ Refractory Disease	Mutated	Quizartinib	Investigator' choice chemo	60 mg daily	55 & 57.5*	23.5	245	122
ADMIRAL	Perl 2019	3	> 1	Salvage therapy for Relapsed/ Refractory Disease	Mutated	Gilteritinib	Salvage chemo	120 mg daily	62	NR	247	124

[NA- Not Applicable, FLT3I- FMS-like Tyrosine Kinase 3 Inhibitor, BID- Twice daily, mg- Milligram, NR- Not Reported, * - Reported separately for both arms.]

Figure 1. Pooled Hazard Ratio for Overall Survival (All Studies)- FLT3 Inhibitor vs. Control

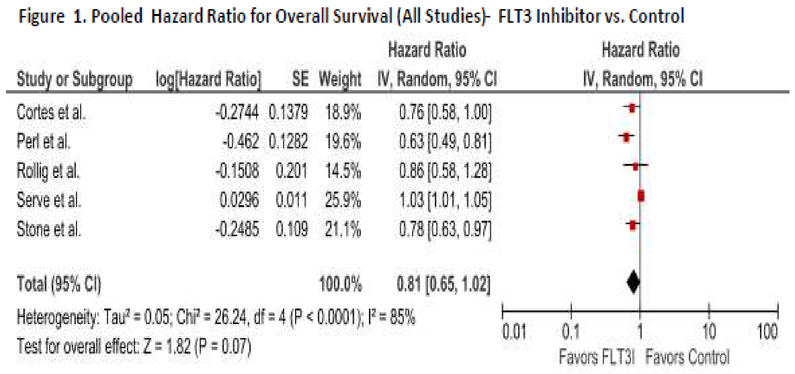


Figure 2. Pooled Hazard Ratio for Overall Survival in Newly Diagnosed AML- FLT3 Inhibitor vs. Control

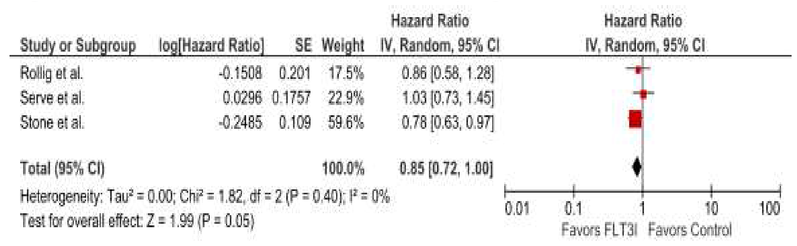


Figure 3. Pooled Hazard Ratio for Overall Survival as Salvage Therapy- FLT3 Inhibitor vs. Control

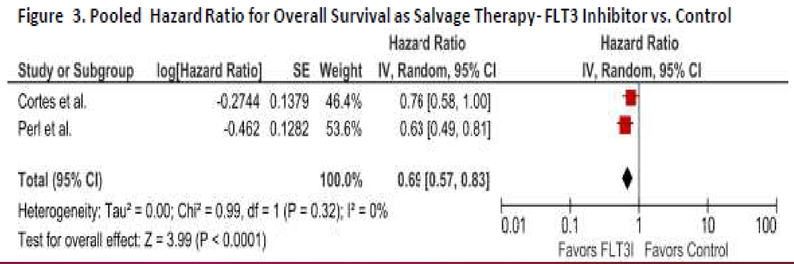
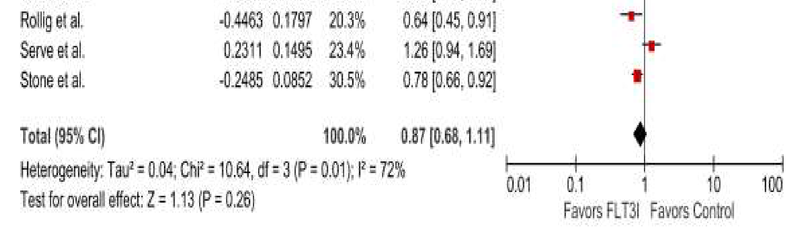


Figure 4. Pooled Hazard Ratio for Event Free Survival (Four Studies)- FLT3 Inhibitor vs. Control



CONCLUSIONS

- FLT3Is demonstrated a significant improvement in OS in patients with relapsed/ refractory AML and a trend towards improvement in OS in newly diagnosed AML patients.
- However, pooled EFS across therapy settings were not found to be statistically significant.
- Future randomized studies exploring further novel agents, especially the next generation FLT3Is should help formulate optimal combination regimens to improve the outcomes in this high-risk subset of AML patients.

REFERENCES

1. Cortes JE, Khaled S, Martinelli G, Perl AE, Ganguly S, Russell N et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):984-97. doi:10.1016/s1470-2045(19)30150-0.
2. Röllig C, Serve H, Hüttmann A, Noppeney R, Müller-Tidow C, Krug U et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2015;16(16):1691-9. doi:10.1016/s1470-2045(15)00362-9.
3. Serve H, Krug U, Wagner R, Sauerland MC, Heinecke A, Brunnberg U et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. J Clin Oncol. 2013;31(25):3110-8. doi:10.1200/jco.2012.46.4990.
4. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. New England Journal of Medicine. 2017;377(5):454-64. doi:10.1056/NEJMoa1614359.
5. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N Engl J Med. 2019;381(18):1728-40. doi:10.1056/NEJMoa1902688.

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