FLT3 INHIBITORS FOR THE TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA: systematic review and meta-analysis

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BACKGROUND

Acute myeloid leukemia (AML), a heterogeneous hematologic malignancy, is the most common acute leukemia in adults. It is characterized by the clonal expansion of myeloid blasts in peripheral blood, bone marrow, and/or other tissues. In 2019, about 69,700 people were living with AML in the United States (USA). About 54% of cases are diagnosed after 65 years of age. The FLT3-ITD (*internal tandem duplication*) happens in 22-25% of the patients with AML and is associated with a poor prognosis. Some guidelines and health technology assessment (HTA) agencies have recently begun to recommend targeted therapy for the FLT3 mutation for R/R AML patients with an FLT3 mutation.

OBJECTIVE

To compare FLT3 inhibitors (FLT3i) with salvage therapy or other FLT3i for relapsed or refractory acute myeloid leukemia (AML) patients.

METHODS

This is a systematic review with direct meta-analyses. Structured searches were conducted on Medline (via PubMed), Lilacs/Ibecs (via BVS), and Embase. Additionally, a complementary search was conducted to guarantee sensitivity. Studies that compared a FLT3i with salvage therapy or other FLT3i for the treatment of AML in patients with FLT3 mutation were selected. The meta-analyses were conducted through the inverse variance method and the random-effects models were calculated by the DerSimonian and Laird method. Hazard ratios (HR) and relative risks (RR) were reported with their 95% confidence interval (95%CI), depending on the nature of the outcome. The methodological quality was assessed with the RoB 2 scale and the quality of evidence was estimated through the GRADE method. The protocol of this research is available in PROSPERO (CRD42022324118).

RESULTS

Three studies that compared FLT3i with salvage therapy were selected. The FLT3i were considered superior to salvage therapy in terms of overall survival (HR=0.67, 95%CI=0.57-0.79, valor-p<0.01, **Figure 1**), event-free survival (HR=0.74, 95%CI=0.56-0.99, p-value=0.04), hematopoietic stem-cell transplantation during treatment (RR=2.12, 95%CI=1.28-3.49, p-value<0.01), composite complete response (RR=2.17, 95%CI=1.74-2.73, p-value<0.01) and overall response rate (RR=2.43, 95%CI=1.97-3.00, p-value<0.01). There are safety issues, though. Serious adverse events were much more common with FLT3i than with salvage therapy (RR=1.76, 95%CI=1.09-2.83, **Figure 2**). The quality of evidence varied between very low and moderate, but the overall assessment suggests a recommendation strong in favor of the technology.

CONCLUSION

The FLT3i seem to be efficacious for the treatment of patients with acute myeloid leukemia. There is some preoccupation regarding the much higher risk of serious adverse events in this group. Nevertheless, the benefits seem to compensate the risks.

Figure 1. Direct meta-analysis of overall survival comparing the FLT3i with salvage therapy.

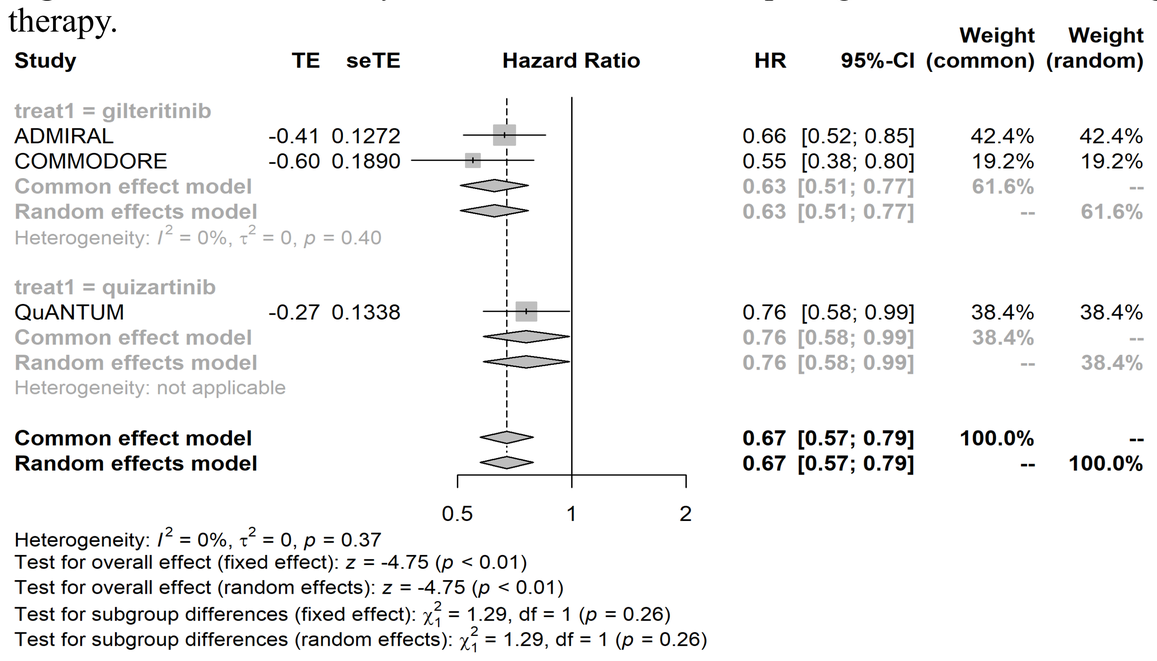
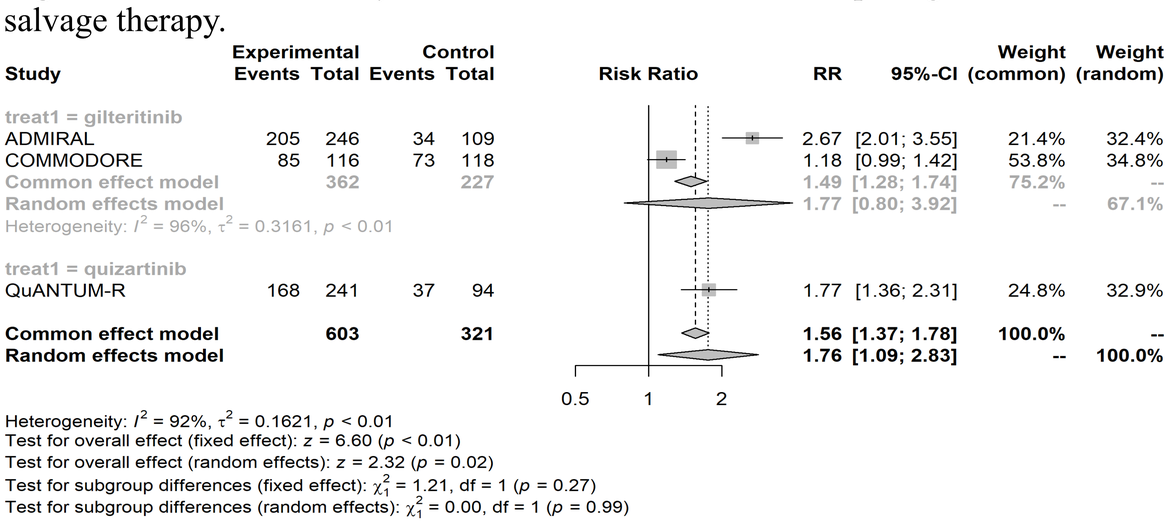


Figure 2. Direct meta-analysis of serious adverse events comparing the FLT3i with salvage therapy.



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