Midostaurin in acute myeloid leukaemia with a *FLT3* mutation: Testing the waters

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and the Department of Medicine, University of Chicago, Chicago, USA.) Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. *N Engl J Med* 2017;**377:**454–64.

SUMMARY

Treatment for acute myeloid leukaemia (AML) has been standardized for the past many years with an anthracycline- and cytarabine-based regimen, followed by consolidation usually with high-dose cytarabine. Current data indicate overall complete response (CR) rate of 65% to 80% in patients with AML.[1] However, presence of a *FLT3* mutation in patients with AML of any age is a poor prognostic factor.[2] This multi-institutional, multinational, randomized, double-blind, placebo-controlled trial was done at 225 sites in 17 countries from May 2008 to March 2016. Only patients with *FLT3* mutations were enrolled. The patients were stratified based on a high FLT3 allelic fraction (≥0.7) or a low FLT3 allelic fraction (<0.7). A third subgroup of patients were those with mutations in the tyrosine kinase domain (TKD) (FLT3). The therapy constituted of standard induction therapy, i.e. the 3+7 regimen (daunorubicin 60 mg/m^2 i.v. days 1–3 and cytarabine 200 mg/m^2 days 1–7 i.v.) plus midostaurin (50 mg oral daily) or placebo. Patients who achieved a complete remission after one or two cycles of induction received consolidation (four cycles of cytarabine, 3 g/m^2 on days 1, 3 and 5; and midostaurin 50 mg oral daily or placebo), followed by 12 months of maintenance with midostaurin or placebo at the same dose. Midostaurin (or placebo) was not continued for patients who received stem cell transplantation (<50% of patients who received consolidation went on to receive maintenance). The primary end-point of the trial was overall survival (OS) and the secondary end-points included event-free survival (EFS). Addition of midostaurin to initial therapy led to a statistically significant improvement in OS and EFS. Patients receiving midostaurin had an OS of 74.7 months (95% CI 31.5 months, median not reached). The 4-year survival rate in the midostaurin arm was 51.4% and in the placebo group it was 44.2%. The CR rates at day 60 between patients receiving midostaurin (59%) and placebo (53%; p=0.15) were similar. Censoring of OS data at the time of transplant maintained the OS benefit achieved in patients in the midostaurin arm compared with those in the placebo arm. There was a significant improvement in OS in patients receiving midostaurin versus placebo (8 *v*. 3 months). Evaluation of toxicity revealed no significant adverse events in the midostaurin arm. The most common grade 3 adverse events in the placebo versus midostaurin arm were febrile neutropenia (82% *v*. 81%), infection (38% *v*. 40%), diarrhoea (16% *v*. 15%) and rash (13% *v*. 8%).

COMMENT

AML is a heterogeneous disease and its risk stratification is based on cytogenetics and molecular markers. This stratification of AML highlights the diverse disease biology of its subtypes, variations in response to chemotherapy and outcomes of treatment.[3] Cytarabine-based intensive chemotherapy remains the standard of care for patients with AML.[4,5] Although much progress has been made in understanding the biology of AML, there has been stagnation over the past many years with regard to the development of newer therapeutic options in this disease. With the identification of various molecular markers which herald a poor outcome, development of new drugs which target these markers has been an area of active research. One of these targets is *FLT3*, a tyrosine kinase, which plays a role in haematopoiesis. Mutations in this gene are believed to play a role in the development of AML. Two major classes of mutations of *FLT3* gene have been identified: point mutations in the TKD (*FLT3*) or the presence of internal tandem repeats (*FLT3*-internal tandem duplication [ITD]). Of the two classes, *FLT3*-ITD is more common, occurring in about 30% of patients with AML. It has been associated with a poor prognosis and shorter OS.[6] Midostaurin is a small molecule that inhibits multiple receptor tyrosine kinases including FLT3 wild type, FLT3 mutant kinases (ITD and TKD), KIT (wild type and D816 mutant), platelet-derived growth factor receptor α/β, vascular endothelial growth factor receptor-2 and members of serine/threonine kinase protein kinase C family. It has shown promising results in phase 1 and 2 trials in AML patients with FLT3 mutations.[7] Besides AML with *FLT3* mutation, midostaurin has also been effective in aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm or mast cell leukaemia.

Our single-centre data which included 2 prospective studies in both adult[8] and paediatric[9] cohorts suggest that in *FLT3*-ITD-negative patients, higher surface expression of *FLT3* significantly predicts poor EFS. In addition, in the study by Sharawat *et al*. in adult AML patients,[8] complete remission was achieved in 33 (64.6%) patients. In this study, at 57.3 months, the mean (SD) EFS was 26.9% (6.3%), disease-free survival (DFS) was 52.0% (9.2%) and OS was 34.5% (7.4%), while in children with AML,[9] all patients with *FLT3*-ITD achieved CR; however, those with FLT3-ITD mutation had inferior DFS (p=0.029).

This phase 3 trial was a well-designed trial and the patient characteristics in both groups were well balanced. The trial design underwent some amendments mid-study in view of the slow rate of events. Initially, it was planned to enrol 514 patients with 374 events; however, the trial was expanded to 714 patients in 2010, in view of the higher-than-expected number of patients who had undergone allogeneic haematopoietic stem cell transplantation (anticipated rate of transplantation, 15% and rate observed at the time of amendment, 25%). To factor in the effect of stem cell transplantation, the data were analysed after censoring the patients who underwent transplantation. Yet, the survival benefit was maintained. Majority of allogenic transplants were performed during the first remission. This strategy led to an overall transplantation rate of 57% in this trial and the trial therapy was discontinued at the time of transplantation. The effect and consequences of an early transplantation are still not known.

This study showed a significant survival difference in both groups. However, it is not powered for subgroup analyses. Furthermore, the trial was not designed to determine the independent effect of maintenance therapy.

The inclusion criteria were patients in the age group of 18–59 years who had AML and a *FLT3* mutation, but considering this will constitute only 25% of the newly diagnosed patients; it remains to be seen if chemotherapy and midostaurin might be beneficial for older adults or for those with wild-type *FLT3*. Midostaurin, which is a multitargeted kinase inhibitor, might also act on targets besides *FLT3* and this study did not consider the possible effects of midostaurin that might belie the spectrum of *FLT3* inhibition. Hence, this study can serve as a basis to investigate agents with more specific target profiles and what effect they will have on disease outcomes. Newer agents such as quizartinib,[10] gilteritinib[11] and crenolanib are also being developed to address the gap of targeted therapies in AML. The exposure to the *FLT3* inhibitor was relatively brief in this study and, since long-term benefits of midostaurin are still unknown, there might be some reluctance among practising oncologists and haematologists to incorporate it into standard practice.

With this study, the era of precision medicine has been extrapolated to haematological malignancies as well. It is high time that, rather than a uniform therapy plan, we tailor our therapy

according to individuals' predictive and prognostic factors. However, in our resource-limited setting, the question of cost of the drug and affordability of the patient is an aspect that cannot be ignored. Although this trial is a practice-changing study and has been incorporated as part of the NCCN 2017 guidelines[4] for AML and has been met with considerable anticipation and excitement among the physician community, how widespread will its use be in our setting is a question, only time will answer. Certainly, it is a desirable option to be used for patients with this mutation who are not candidates for transplantation.

Conflicts of interest. None declared

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