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Cladribine an Alternative for Midostaurine in FLT3 Positive Acute Myeloid Leukemia

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Letter to Editor

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Letter to the Editor

Midostaurin is registered for the indication newly diagnosed acute myeloid leukemia that is FLT3 mutation positive in combination with standard cytarabine and daunorubicine induction and cytarabine consolidation. The registration is based on a study of 717 patients that examined the addition of midostaurin 50 mg orally twice daily or placebo to standard induction on days 8 to 21 of a cycle for a maximum of two induction cycles [1]. In case of complete remission patients received four cycles of 28 days cytarabine consolidation with midostaurin 50 mg twice daily on days 8 to 21. Patients who remained in complete remission after consolidation therapy entered a maintenance phase in which patients received midostaurin 50 mg twice daily or placebo for twelve 28 days cycles. The complete remission rate was 58.9% versus 53.5% respectively. Median disease free survival was 26.7 m versus 15.5 months respectively. The 4-years overall survival was 51.4% and 44.3% respectively. The median overall survival was 74.4 months versus 25.6 months respectively. This difference was explained by the inflection rates of the Kaplan Meyer curves. The hazard ratio for death 0.78 (95% CI 0.63-0.96) reflected the magnitude of the benefit.

Zhang, et al. [2] reported the addition of sorafenib to standard chemotherapy. Details do not exist as the publication is in Chinese. The study included 55 patients with a FLT3 mutation. The complete response rate in the chemotherapy plus sorafenib group was 86.4% and in the chemotherapy plus placebo group 35.5%. The one year progression free survival was 75.9% versus 42.4% respectively and the one year overall survival 78.3% vs 50% respectively.

A study in elderly with sorafenib in combination with intensive chemotherapy did not result in significant improvement in event free and overall survival in the FLT3 mutation positive subgroup [3]. The patients had received standard induction chemotherapy plus sorafenib 400 mg twice daily or placebo from three days post induction to three days prior to next induction chemotherapy course. Patients with complete remission had received two cycles consolidation cytarabine and the same sorafenib or placebo regimen. Patients in complete remission received maintenance with sorafenib or placebo. This regimen is more or less comparable with that in the study with midostaurin, but did not yield positive results.

Libura, et al. [4] reported a retrospective study of 227 patients in which 55 patients were identified that were FLT3-ITD positive. In the original study standard induction chemotherapy for maximal two cycles with daunorubicine and cytabine and cladribine 5 mg/m^2 days 1-5 (DAC) versus placebo (DA) were compared [5,6]. Consolidation treatment had consisted of two courses of cytarabine day 1 to 3, mitoxantrone days 3 to 5 and high dose cytarabine twice daily days 1,3 and 5, in the DAC arm accompanied by cladribine 5 mg/kg i.v. on days 1,3 and 5. Maintenance treatment was given for up to two years and consisted of daunorubicine i.v. day 1 and cytarabines twice daily days 1 to 5, alternated with 6 thioguanine days

1 to 5 and cytarabine twice daily days 1 to 5. Patients in the DAC arm received cytarabine 5 mg/m^2 i.v. days 1 to 3 [5,6]. In the analysis for FLT3-ITD acute myeloid leukemia 22 patients with FLT-ITD positive acute myeloid leukemia had received DAC and 33 patients DA [4]. The complete remission rate was 86% and 61% respectively. The four years probability of overall survival was 37% and 14% respectively with most prominent overall survival improvement after censoring at the time of allogeneic hematopoietic stem cell transplantation. The four years probability of survival in poor risk patients was 60% and 18% respectively.

Although midostaurin is approved in among others the USA and Europe the costs of administration may not be affordable in several countries. In such instance addition of cladribine may offer a cost efficient alternative in FLT3 positive acute myeloid leukemia.

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