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EFFICACY OF MIDOSTAURINE IN ACUTE MYELOID LEUKEMIA WITH FLT-3 MUTATION

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RESUME
Detection of FLT3-ITD mutation in patients with acute myeloid leukemia (AML) is associated with a poor prognosis and is an indication to transplantation of allogeneic hematopoietic stem cells in the first remission. Midostaurin is the first FLT3 inhibitor approved ny for the treatment of patients with AML with FLT3 mutation.

Keywords: acute myeloid leukemia, mutation, midostaurin

INTRODUCTION

Fms-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase that is normally expressed by hematopoietic stem cells and plays an important role in growth and differentiation bone cells [10]. Mutations in the FLT3 gene are among the most common in acute myeloid leukemia (AML) and are found in about 30% of adult patients with newly diagnosed AML. These mutations lead to independent activation of the FLT3 receptor and cell proliferation [1,2,3]. The most common FLT3 mutations are known as internal tandem duplications (ITD) and account for approximately 75% of all FLT3 mutations in AML [10,11]. Point mutations in the tyrosine kinase domain (TKD) are the second most common type of mutation in the FLT3 gene and account for approximately 25% of all FLT3 mutations in AML [4,5,6,7,8,9,11]. Midostaurin is the first FLT3 inhibitor approved for the treatment of AML patients with FLT3 mutation [12,13]. Improved survival with a satisfactory toxicity profile has been shown in several large studies of midostaurin in combination with chemotherapy [13]. However, the addition of midostaurin to program chemotherapy does not exclude the need for transplantation of allogeneic hematopoietic stem cells if indicated [12]. The ease of oral administration and the relatively safe toxicity profile contributed to the rapid introduction of this drug into
clinical practice.

The Purpose of this Work

Is to study the effectiveness of midostaurin in acute myeloid leukemia.

MATERIALS AND METHODS

The study included 46 patients with identified AML. The diagnosis of AML was made in the presence of 20% blast cells and more in peripheral blood and bone marrow. The standard cytogenetic study of the bone marrow served as diagnostic methods. All patients underwent a molecular biological study to detect mutations in the FLT3 gene.

RESULTS

The median age of patients was 38 years (range 18–68 years). The median blood leukocyte level was $26{,}6\times10^9$/l (range $1{,}5–118{,}5\times10^9$/l). FLT3-TKD mutation was detected in 8 (17,3%) patients. In the distribution of patients included in the study, according to the ELN-2017 classification, 1 (2,1%) patient with

t (8; 21) was assigned to a favorable molecular genetic prognostic group, 4 (8,6%) - to the intermediate and 2 (4,2%) - to unfavorable. Cytogenetic study by standard karyotyping was performed in 46 (100%) patients.

The Effectiveness of Induction Therapy

All patients with the FLT3-TKD mutation achieved remission. The median duration of remission was 11 months. (range 3–24 months). No lethal outcomes were registered in remission. In 10 (21,7%) patients, after 2 courses of induction, a primary resistant course of AML was noted. Subsequently, 4 of them were treated with another FLT3 inhibitor, gilteritinib, and the remaining 4 were symptomatic. On the background of chemotherapy, early mortality was 14%. 3 patients died as a result of sepsis development: 2 - from necrotic enteropathy. Recovery of peripheral blood parameters after combined (midostaurin + chemotherapy) therapy was as follows: a median level of neutrophils over $0,8 \times 10^9$/l was noted on average on day 28 (range 12–40 days), platelets over $100,0 \times 10^9$/l - on the 25th day (range 10–32 days). Relapses developed in 6 (13,0%) patients. The median duration of remission was 7,5 months (range 3,5–13 months). The recurrence rate was higher in women ($n = 4$; $p = 0.01$). At relapse, 2 patients were prescribed gilteritinib. The 2-year overall survival and event-free survival in all patients was 55 (95% confidence interval and 45% (95% CI 27-63%), respectively. Median overall survival was not achieved, median event-free survival was 15,3 months. 2 -year disease-free survival in patients who achieved remission was 62% (95% CI 45-86%).

CONCLUSION

The present study demonstrates the safety and importance of including midostaurin in the treatment of FLT3-mutated AML. The appointment of midostaurin in maintenance therapy, both after alloHSCT and without it, can lead to a significant improvement in overall and disease-free survival.

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