OUTCOME AFTER AZACITIDINE TREATMENT IN PATIENTS WITH HIGH-RISK MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA IN THE CLINIC OF HEMATOLOGY AT ST. MARINA UNIVERSITY HOSPITAL, VARNA

Ilina Micheva¹,², Vladimir Gerov¹,², Stela Dimitrova¹,², Merlin Efraim¹,², Liana Gercheva¹,²

¹Department of Internal Diseases, Faculty of Medicine, Medical University of Varna
²Clinic of Hematology, St. Marina University Hospital, Varna

ABSTRACT

INTRODUCTION: Hypomethylating agents have become a standard therapy for high-risk myelodysplastic syndromes (MDS) and elderly patients with acute myeloid leukemia (AML).

AIM: The aim of the study was to assess the efficacy of azacitidine treatment in patients with MDS and AML followed for 18 months.

MATERIALS AND METHODS: Twenty-seven patients with MDS and AML treated in the Clinic of Hematology at St. Marina University Hospital, Varna were included in the study. Azacitidine was administered subcutaneously at a dose of 75 mg/m² for 7 days. Disease assessment was performed on the 3rd month, 6th month, and at progression.

RESULTS: Twenty-seven patients were analyzed. Their median age was 71.5 years. Nine had refractory anemia with excess of blasts II (RAEB II), 5 had chronic myelomonocytic leukemia II (CMML II), 1 was with unclassifiable MDS (MDS-U), and 12 with AML. The median number of administered cycles was 6 (1-19). Eleven patients completed 6 cycles of azacitidine. Partial response was achieved in 9 patients (33%) (7 MDS and 2 AML), stable disease in 8 (29%) (5 MDS and 3 AML). Progressive disease was observed in 10 patients (37%). The response correlated with the type of the disease (p=0.03), cytogenetic risk (p=0.01), and survival (p=0.000). At 18 months, 60% of MDS patients were alive compared to 41.7% in the AML group. The median time to death in the AML patient group was 2.5 months. The mean overall survival was 10.4 months (12.6 months for MDS patients and 5.4 months for AML patients).

CONCLUSION: The therapy with azacitidine is an option for elderly patients with high-risk MDS. In patients with AML a rapid progression is observed during the first two cycles with mortality rate of 58.3%. Scr Sci Med. 2018;50(1):31-35

Keywords: MDS, AML, hypomethylating agents, azacitidine
INTRODUCTION

DNA methylation is an important mechanism of epigenetic gene regulation. In human cells, DNA methylation occurs in cytosine residues that precede guanines (CpG) grouped in CpG-rich regions known as CpG islands. These islands are usually not methylated in normal cells. The methylation status of DNA is controlled by a family of DNA methyltransferases (DNMTs) (1). It is well known that complex changes in DNA methylation are characteristic feature of many cancers; tumor suppressor genes can be silenced by aberrant hypermethylation (2). Hypermethylation is found in patients with myeloid malignancies affecting hundreds of genes, involved in different signaling pathways. It has been shown that aberrant hypermethylation of genes is widespread in patients with myelodysplastic syndromes (MDS) and secondary acute myeloid leukemia (AML) (3). Hypermethylation increases with advanced disease and is a poor prognostic factor in MDS and AML. Patients with hypermethylation of at least one tumor suppressor gene have shorter survival (4).

This underlies the clinical efficacy of the hypomethylating agents for the treatment of patients with MDS and AML. Azacitidine is an analog of cytosine, where the carbon is replaced by nitrogen at the 5-position on the cytosine ring. DNMTs bind irreversibly to the cytosine analog but are unable to methylate it, which causes depletion of cellular DNMT levels. Azacitidine is integrated into both RNA and DNA, causing DNA hypomethylation and cytotoxicity with DNA damage and inhibition of protein synthesis (5).

Hypomethylating agents have become a standard therapy for high-risk MDS, chronic myelomonocytic leukemia II (CMML II) and elderly patients with AML who are not eligible for hematopoietic stem cell transplantation.

AIM

The aim of the study was to assess the efficacy of azacitidine treatment in higher risk patients with MDS and AML. The clinical workup included response assessment and survival.

MATERIALS AND METHODS

A group of 27 patients, 15 men and 12 women, with MDS and AML, treated in the Clinic of Hematology, St. Marina University Hospital, Varna were included in the study. Patients were eligible for azacitidine treatment if they were with high-risk MDS, determined by the revised international prognostic scoring system (IPSS-R) (6), CMML II and AML, aged 65 years or older, not eligible for intensive chemotherapy and hematopoietic stem cell transplantation. Azacitidine was administered subcutaneously in a standard dose of 75mg/m^2 per day for 7 days, every 28 days. Blood counts were done monthly. Disease assessment was performed on the 3rd and the 6th month after initiation of the treatment, or at progression. Response was evaluated according to the International Working Group (IWG) response criteria in myelodysplasia (7). Mean survival was estimated by the Kaplan-Meier method. For evaluation of linear relationships, a two-tailed Pearson Correlation test was used. Correlation was considered significant at the 0.05 level. Statistical analysis was performed using SPSS 19.

RESULTS

Between June 2016 and December 2017, 27 patients were treated with azacitidine. According to the WHO classification 9 patients were with refractory anemia with excess of blasts II (RAEB II), 5 with CMML II, 1 with MDS unclassifiable (MDS-U) and 12 with AML. Median age was 71.5 years (range 44-80) and 70.3% of the patients were over 65 years. According to IPSS-R 2 MDS patients were scored as very high risk, 1 as high, and 5 as intermediate (Fig. 1a). Four of the AML patients were high and 8 - intermediate risk (Fig. 1b). According to cytogenetics 16 patients were with normal karyotype, 6 with complex, and 5 patients were with other cytogenetic abnormalities [46, XY, del (7) (n=2), 46, XY, add(16q) (n=1), 47, XY, +19 (n=1)], 47, XY, +C (n=1)]. In 23 patients the treatment with azacitidine was first-line chemotherapy. In 3 patients with AML, azacitidine was initiated after failure of 7+3 or low doses Ara-C, 1 patient with CMML II was previously treated with hydroxyurea.

Azacitidine was given for a median of six cycles (1-19). The median azacitidine cycle length was 28 days. Seventeen patients completed three cycles of treatment, 11 patients - six cycles. Disease assessment was performed on the 3rd and the 6th month after ini-
The best response is presented on Fig. 2. Partial response (PR) was achieved in 9 patients (33%) (7 with MDS and 2 with AML). Eight patients (29%) had stable disease (SD) (5 with MDS and 3 with AML). Ten patients (37%) had progressive disease (PD). The response correlated with the type of the disease (MDS or AML) \( (p=0.03) \), cytogenetic risk \( (p=0.01) \) and survival \( (p=0.000) \). AML transformation was observed in 3 patients with MDS (MDS-U, CMML II, and RAEB II) with time of transformation 3, 6, and 15 months, respectively. Hematological improvement (HI) of hemoglobin was achieved in 5 patients and HI of platelets – in 9 patients (Fig. 3).

All patients with HI became transfusion-independent. The age had no influence on response and survival. At 18 months, on the basis of Kaplan-Meier estimates, 60% of all MDS patients were alive compared with 41.7% in the AML group. All patients
died as a result of PD with a median time to death 2.5 months. Mean Kaplan-Meier overall survival was 10.4 months: 12.6 months for MDS patients and 5.4 months for AML patients (Fig. 4).

DISCUSSION

Myelodysplastic syndromes comprise a heterogeneous group of hematopoietic stem cell disorders that differ by clinical phenotype and risk stratification (8). Patients with high-risk MDS have inferior survival and a high-risk for progression to AML. The median overall survival in very high and high-risk MDS patients is 0.8 and 1.6 years, respectively (6). The therapeutic options in these risk groups are limited; no treatment strategies other than allogeneic stem-cell transplantation offer the potential to change the natural history of the disease (9). The first study of a Cancer and Leukemia Group B, comparing treatment with azacitidine with best supportive care in high-risk MDS patients suggested improved overall survival with azacitidine (10). These results were confirmed by a large, prospective, randomized, phase III, clinical trial in which the median overall survival was 24.5 months for the azacitidine group versus 15.0 months for the conventional care group (11).

AML is an aggressive malignancy with poor prognosis. Older patients with AML over 65 years of age, who are at greatest risk of developing AML, have particularly poor survival rates (12). Treatment options are limited because of a variety of adverse prognostic risk factors, such as history of MDS, unfavorable karyotypes, poor performance status, and comorbidities. As a result, many older patients receive only palliative care. There is no universally accepted standard approach to treating AML in older patients.

It was recently shown that azacitidine increases median overall survival by 3.8 months compared to current commonly used AML treatments (13).

In our study, after 18 months of follow-up, 60% of high-risk MDS patients were alive and continued their treatment. 46.6% of MDS patients have achieved PR and 26.6% remained in SD. Three patients died because of transformation into AML. Median survival is 12.6 months. In the AML patient group, 58.3% died within a median time of 2.5 months. However, 5 out of the 12 patients with AML continued their treatment at the end of the 18-month follow-up - 2 with PR and 3 with SD. All patients with MDS and AML who achieved PR or SD showed improvement or stabilization of blood counts with reduction of the number of infectious complications and transfusions during azacitidine treatment. Patients with MDS achieved better response compared to AML and showed better survival rates.

CONCLUSION

The therapy with azacitidine is an option for elderly patients with high-risk MDS. Patients with AML show rapid progression during the first two cycles of azacitidine with high mortality. This is the first study reporting results form azacitidine treat-
ment in Bulgaria. A larger cohort of patients and longer follow-up is required for further conclusions.

REFERENCES


