Higher Infection Rate After 7- Compared With 5-Day Cycle of Azacitidine in Patients With Higher-Risk Myelodysplastic Syndrome

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Abstract

Azacitidine (AZA) dose reduction is a common practice in cytopenic patients. We herein report on a correlation between AZA dose and infection complications in high-risk myelodysplastic syndrome and leukemia patients. Infectious events were more frequent after doses of 75 mg/m^2 for 7 days than 75 mg/m^2 for 5 days, regardless of the patient's age. Reduction of AZA dose should therefore be considered in patients with high infection risk.

Introduction: Azacitidine (AZA) dose reduction is a common practice in cytopenic patients. However, a correlation between AZA dose and infection complications has never been studied. **Patients and Methods:** Higher-risk patients with myelodysplastic syndrome or acute myeloid leukemia treated with AZA in 18 Israeli hospitals between the years 2008 and 2011 were included in a former national survey. To reveal the effect of AZA dosage on infection risk we limited our analysis to the infection rate after the first AZA dose alone. We excluded subsequent cycles of AZA from the analysis, because infectious events during these cycles might be related to other cofactors such as disease response to AZA therapy. **Results:** After the first AZA cycle, infectious events were more frequent after doses of 75 mg/m^2 for 7 days than 75 mg/m^2 for 5 days (36/106 [34%] and 10/67 [14.9%], respectively; $P = .008$), regardless of the patient's age. Of the 46 recorded infectious events, the causative pathogen was identified as bacterial in 25 (54.3%) and as viral or fungal in 2 (4.3%) and 2 (4.3%) cases, respectively. No pathogen was identified in 17 (37%) cases. Infections were significantly more prevalent among patients who presented with platelet counts < 20,000 (43.6% vs. 23.6%; $P = .012$) and poor risk cytogenetics (40.7% vs. 19.8%; $P = .008$). **Conclusion:** Reduction of AZA dose might decrease infection rate and therefore should be considered in patients with high infection risk.

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Introduction

Patients who suffer from higher risk myelodysplastic syndrome (MDS) were found to benefit from azacitidine (AZA) therapy. Given at a dose of 75 mg/m^2 for 7 days every 4 weeks, AZA was shown to improve patients' blood counts, delay leukemic transformation, and prolong overall survival.[1] The most common life-threatening adverse events after administration of hypomethylation agents (AZA or decitabine), are infections that are more prevalent after the initial 2 cycles of therapy.[1-4] Based on a retrospective study, patients who presenting with low platelet counts, poor cytogenetics, and neutropenia were previously identified as prone to infections during AZA therapy.[4] When the infection risk was reevaluated before each AZA cycle, a platelet count < 20,000 cells/μL and poor cytogenetics remained the only significant predicting factors. Although in that analysis, infection risk was not found to correlate with an AZA dose, it was suggested that current clinical practice to reduce the AZA dose in subsequent cycles after an infectious event could mask such correlation. To unveil the potential dose-dependent effect of AZA, we analyzed data of the previously reported series of 184 patients with MDS, with a focus on the 4-week period after the first AZA cycle only. The incidence of infections of any cause after 7- or 5-day AZA cycles was compared.

Patients and Methods

The former survey was designed to include all higher-risk MDS or acute myeloid leukemia (AML) patients treated with AZA in 18 Israeli hospitals between the years 2008 and 2011. The study was approved by institutional review boards of participating medical centers. All adult patients diagnosed with higher-risk MDS or AML who received AZA were included in the analysis. Excluded were those who were found to have an International Prognosis Scoring System (IPSS) score of < 1.5. Data on 216 of 223 (97%) patients who received AZA in Israel during the study period were collected including multiple clinical, demographic, and laboratory data, on the first day of the first AZA cycle. Parameters selected for assessment in univariate analysis were: age, sex, serum creatinine level, cytogenetics, percentage of blasts in the bone marrow (BM) aspirate, transfusion dependence, and neutrophil, platelet, and hemoglobin levels measured on the first day of therapy. Doses of AZA were grouped into 3 categories: a standard dose of ≥ 75 mg/m^2 for 7 days with a total dose of 525 mg/m^2 (75*7), a lower dose of 75 mg/m^2 for 5 days with a total dose of 375 mg/m^2 (75*5) and a total dose of < 350 mg/m^2 for a cycle (low). The analysis was limited to comparison of infectious outcome between 75*7 and 75*5 doses; thus, patients who received lower doses of AZA at the first cycle were excluded.

Statistical Analysis

Data were analyzed using SPSS (IBM, Chicago, IL) for Windows version 18. Normal distributions of the quantitative variables were evaluated with the Kolmogorov-Smirnov tests. Continuous parameters were presented using means and standard deviations (SDs), and categorical parameters were presented using frequencies and percentages. The *t* test and Mann-Whitney *U* tests were used to assess differences between the groups. Fisher exact test or Pearson χ^2 was used to determine the relationship between several parameters and infection incidence. Pearson correlation was used to estimate linear correlation between quantitative variables (hemoglobin, neutrophil, creatinine, White blood cells, platelets). The logistic regression model was applied for prediction of the relation of infection rate and several independent parameters.

Results

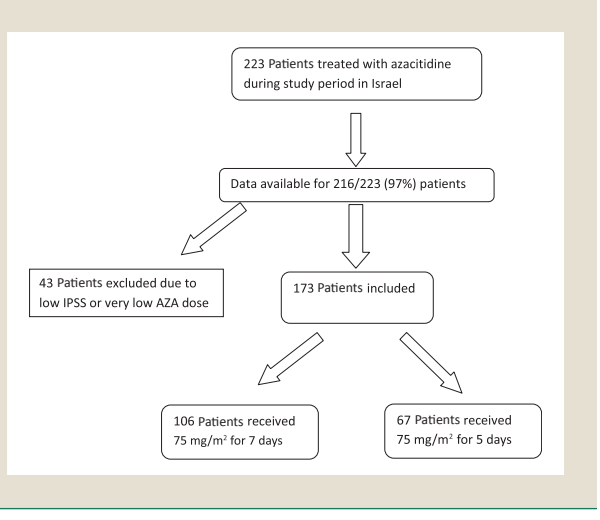
Patient Characteristics

Review of medical charts showed that 43 patients had an IPSS score of < 1.5 or received AZA doses < 75*5. We herein report the analysis of data on 173 patients, 106 of whom received the 75*7 dose and 67 who received the 75*5 dose (Figure 1). The groups were comparable in terms of pretreatment characteristics (Table 1). Patient age, sex, hemoglobin level, platelet, and neutrophil counts, transfusion dependence, cytogenetics, and percentage of blasts in the BM were similar in both groups. Infection was defined as any event diagnosed as such by the treating physician. The study included patients with microbiologically documented infection along with cases of neutropenic fever that required antibiotic therapy. A full 75*7 AZA dose was prescribed to 80 of 134 (60%) patients who presented with platelet counts > 20,000 cells/μL, and to 26 of 39 (67%) patients who presented with platelet counts < 20,000 cells/μL.

Infectious Events and Outcome

All patients underwent extensive microbiology investigation as per their institution guidelines to identify the infectious pathogen responsible for the reported event. Of 173 patients, infectious events were reported in 46 (26.6%) during the 4 weeks that followed the first AZA dose. Of these events, the pathogen was identified as bacterial in 25 (54.3%) and as viral or fungal in an additional 2 (4.3%) and 2 (4.3%) cases, respectively. No pathogen was identified in 17 (37%) cases (Table 2). Infections were significantly more prevalent among patients who received a standard dose of AZA versus the reduced dose (34% vs. 14.9%; $P = .008$) and in patients who presented with platelet counts < 20,000

Figure 1 Patient Selection for the Study



Abbreviations: AZA = Azacitidine; IPSS = International Prognosis Scoring System.