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Effectiveness and safety of different azacitidine dosage regimens in patients with myelodysplastic syndromes or acute myeloid leukemia☆

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ABSTRACT

We investigated the effectiveness and tolerability of azacitidine in patients with World Health Organization-defined myelodysplastic syndromes, or acute myeloid leukemia with 20–30% bone marrow blasts. Patients were treated with azacitidine, with one of three dosage regimens: for 5 days (AZA 5); 7 days including a 2-day break (AZA 5-2-2); or 7 days (AZA 7); all 28-day cycles. Overall response rates were 39.4%, 67.9%, and 51.3%, respectively, and median overall survival (OS) durations were 13.2, 19.1, and 14.9 months. Neutropenia was the most common grade 3–4 adverse event. These results suggest better effectiveness–tolerability profiles for 7-day schedules.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis leading to gradually worsening cytopenias, and a high risk of progression to acute myeloid leukemia (AML). Prognosis varies widely – patients with International Prognostic Scoring System (IPSS)-defined Low- or Intermediate (Int)-1-risk MDS have a median survival of 5.7 and 3.5 years, respectively. In contrast, patients with IPSS-defined Int-2- or High-risk MDS have a shorter median survival (1.2 and 0.4 years, respectively) and a higher risk of progression to AML [1].

Azacitidine (Vidaza®; Celgene Corporation, Summit, NJ, USA) significantly reduces red blood cell (RBC)-transfusion dependence, decreases risk of transformation to AML, improves quality of life, and increases overall survival (OS) compared with supportive care

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in patients with MDS across all French–American–British (FAB) subtypes [2,3]. In a large phase III trial, azacitidine resulted in significantly increased hematologic response rates in higher-risk MDS patients. It also significantly extended OS and time to AML progression in higher-risk MDS patients, and in elderly patients with World Health Organization (WHO)-defined AML with 20–30% bone marrow blasts, when compared with conventional care regimens (best supportive care, low-dose cytarabine, or intensive chemotherapy) [4–6].

Azacitidine is approved in the USA for the treatment of all 5 FAB subtypes of MDS [7], and is also approved in Europe for treating adult patients ineligible for hematopoietic stem cell transplantation who have IPSS-defined Int-2- or High-risk MDS, chronic myelomonocytic leukemia with 10–29% bone marrow blasts without myeloproliferative disorders, or AML with 20–30% bone marrow blasts and multilineage dysplasia according to the WHO criteria [8]. The approved starting dose of azacitidine is 75 mg/m^2/day administered subcutaneously (USA and Europe) or intravenously (USA only), on days 1–7 of each 28-day cycle for at least 4–6 cycles (USA) or 6 cycles (Europe), until disease progression or unacceptable adverse events (AEs) ensue [7,8]. However, AVIDA, a prospective, longitudinal, multicenter patient registry in the USA, found that the majority of patients receiving azacitidine in a community-based setting do not receive the approved schedule of 7 consecutive treatment days [9].

Before receiving marketing authorization in May 2009, azacitidine was available in Spain through clinical trials or compassionate use. This retrospective, multicenter study analyzed a Spanish compassionate use registry to investigate the effectiveness and tolerability of various azacitidine dosing schedules used in daily clinical practice in patients with MDS or WHO-defined AML with 20–30% bone marrow blasts.

2. Patients and methods

This retrospective analysis of clinical data from a multicenter Spanish compassionate use registry included patients who initiated azacitidine treatment between February 6, 2006, and May 5, 2009. The protocol was approved by an independent ethics committee in April 2009.

2.1. Patients and treatment

Patients aged ≥18 years with either a confirmed diagnosis of WHO-defined MDS, or a confirmed diagnosis of de novo (primary) or secondary AML according to WHO criteria with 20–30% bone marrow blasts were included [10]. All patients were required to have received ≥1 cycle of azacitidine at a starting dose of 75 mg/m^2/day under compassionate use conditions, with a documented dosage regimen as follows (all 28-day cycles): days 1–5 (AZA 5); days 1–5, weekend (2 days) without treatment, followed by 2 days of treatment (AZA 5-2-2); or days 1–7 (AZA 7). Azacitidine dosing schedule and administration route (subcutaneous or intravenous) were chosen at the physician's discretion based on the patient's Eastern Cooperative Oncology Group (ECOG) performance status score and the feasibility of weekend drug administration.

2.2. Outcome measures

The primary endpoint was clinical response. Hematologic response (defined as complete response [CR], partial response [PR], marrow CR [mCR], or hematologic improvement [HI]), stable disease (SD), and progressive disease (PD) were assessed according to the International Working Group 2003 and 2006 criteria for AML and MDS, respectively [11,12]. Overall response rate (ORR) was defined as CR + PR + mCR + HI. Secondary endpoints included OS according to dosing schedule, cytogenetic risk groups at baseline, best response achieved, and clinical response at four and six cycles of azacitidine treatment, as well as safety of azacitidine treatment. OS was defined as time from azacitidine initiation to death from any cause, and the median duration of follow-up was 1.4 years. Cytogenetics were classified according to IPSS criteria [1]. AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

2.3. Statistical methods

Baseline characteristics between azacitidine dosing groups were compared using chi-square, Fisher's exact, or LR chi-square tests for qualitative variables where appropriate; and analysis of variance, Mann–Whitney–Wilcoxon, or Kruskal–Wallis tests for quantitative variables as appropriate. Comparison of response to azacitidine across dosing groups was tested for homogeneity of distributions using chi-square test.

A multivariate logistic regression identified potential risk factors for best overall response. Variables included: bone marrow blast percentage; platelet count; time since diagnosis; sex; age; ECOG performance status score; IPSS risk; azacitidine administration route and dosing schedule; cytogenetics; WHO classification; disease status; and transfusion dependence. Continuous variables were: age; time since diagnosis; platelet count; and bone marrow blast percentage. The categorical variables were: sex; disease status; WHO classification; IPSS risk; cytogenetics; ECOG performance status score; transfusion dependence; azacitidine administration route; and dosing schedule.

OS was described with median survival values, 95% confidence intervals (CIs), as well as using the Kaplan–Meier method. To compare OS between the dosing groups, a Cox proportional hazards regression model was used. In a separate multivariate Cox model, sex, age, disease status, time since diagnosis, WHO classification, IPSS risk, cytogenetics, ECOG performance status score, and azacitidine administration route and dosing schedule were included as prognostic factors for OS. To simplify the multivariate model, a backward selection method was applied, using $p \geq 0.05$ as a criterion for variable exclusion.

The relationship between response to azacitidine and OS was analyzed using a Cox proportional hazards model. To prospectively explore this relationship, responses to azacitidine treatment at cycles 4 and 6 were used as dependent variables to explain and predict the OS of those patients alive and not censored after 4 or 6 months of treatment, respectively.

Statistical analyses were performed by the statistics department of the Autonomous University of Barcelona, Spain, using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, USA). The nominal significance level was 5% ($p < 0.05$) for all statistical tests performed. No corrections for multiplicity of statistical tests were applied due to the exploratory nature of the study. Data were included up to a cutoff date of June 30, 2010.

3. Results

3.1. Patient demographics

Of 240 patients treated with azacitidine-based regimens in the Spanish compassionate use registry, 200 met the inclusion criteria: 66 (33.0%) received AZA 5; 56 (28.0%) received AZA 5-2-2; and 78 (39.0%) received AZA 7. Baseline characteristics were similar across the 3 dosing groups (Table 1). The majority of patients (67.0%) were male and 83.0% had primary MDS. The median age was 69 years (range 28–86 years). There were fewer patients without excess blasts in the AZA 5 and

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