Original Study

Patterns of Infection in Patients With Myelodysplastic Syndromes and Acute Myeloid Leukemia Receiving Azacitidine as Salvage Therapy. Implications for Primary Antifungal Prophylaxis

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Abstract

Patients treated with azacitidine who previously received intensive chemotherapy are at a highest risk for fungal infection (invasive aspergillosis; $P = .015$).

Incidence, etiology, and outcome of infectious episodes in patients with myeloid neoplasms receiving azacitidine are uncertain, with no prospective data available in this group of patients. The aim of the current study was to analyze the incidence and factors related to the probability of infection in a cohort of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) treated with azacitidine who did not receive any type of antimicrobial prophylaxis. Significantly, the group of patients who received prior intensive chemotherapy had more infectious episodes ($P = 10^{-4}$), and particularly, invasive aspergillosis ($P = .015$), than patients who received frontline azacitidine. Primary antifungal prophylaxis might be recommended in MDS and AML patients receiving azacitidine as salvage therapy after intensive regimens.

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Introduction

Infection is a recurrent cause of morbidity and mortality in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) undergoing intensive chemotherapy (IC) (idarubicin combined with cytarabine).[1] Most of these patients routinely receive antimicrobial prophylaxis (AIP) with fluorquinolones or antifungal agents according to the current guidelines for the prevention of infection in neutropenic patients with cancer.[2-7] Hypomethylating agents (HMAs) are considered the standard of care in higher-risk MDS (intermediate-2 and high risk according to International Prognostic Scoring System (IPSS)) and AML patients with low blast counts for whom allogeneic stem cell transplant (AlloSCT) is not suitable.[8] In addition, there is an increasing use of HMAs in patients with relapsed or refractory disease after IC who are not candidates for reinduction therapy and patients for whom these agents are intended as an alternative approach to classic induction regimens prior to AlloSCT.[9-11]

However, the role of AIP in patients treated with azacitidine (AZA) or decitabine has not been widely analyzed.[12] Lee et al. reported an incidence of 11.5% febrile episodes requiring hospitalization per AZA course (15/131 courses of treatment) in a cohort of MDS patients treated with decitabine.[13] Antimicrobial prophylaxis

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was administered in 72.5% of decitabine courses. In this study, the incidence of febrile episodes was higher in patients who did not receive prophylaxis (22.2% vs. 7.4%; $P = .017$) and in patients with platelet or neutrophil count after each course of therapy $< 50 \times 10^9$/L or $< 0.5 \times 10^9$ cells/L, respectively. Recently, a multicenter retrospective study conducted in Israel including 184 higher-risk MDS and AML patients reported a high incidence of documented bacterial infections (59% among cases with microbiological analysis available), with a significant proportion of these cases with febrile episode requiring hospitalization (74.5%). In this study, only 10% of the patients received prophylaxis.[14] Again, peripheral cytopenias, particularly platelet count $< 20 \times 10^9$/L and adverse karyotype, significantly influenced the risk of infection in multivariate analysis. Interestingly, both studies included patients who received AZA or decitabine as frontline therapy either for MDS or AML. In summary, the incidence and etiology of infections in MDS and AML receiving AZA is not well characterized, and the role of antimicrobial prophylaxis is not clearly defined.

The aim of this study was to evaluate the incidence and pattern of febrile episodes (FE) attributable to both clinically and microbiological documented infections occurred in a cohort of MDS and AML patients treated with AZA who did not receive antimicrobial prophylaxis. The secondary objectives were to analyze factors related to an increased probability for infection and to identify a subset of these patients who could possibly benefit from prophylaxis.

Design and Methods

Patients

This is a retrospective study including consecutive patients with MDS and AML treated with AZA at our institution. Only patients receiving at least 2 courses of AZA were included in the study. Sixty-four patients with MDS and AML were analyzed for a total of 523 AZA courses administered. All patients were diagnosed according to World Health Organization (WHO) Classification[15] at Hospital Universitario Virgen del Rocío (Seville, Spain) between 2009 and 2012. Median age was 68 years (range: 29-83 y). Forty-three patients had MDS and 21 patients had AML. The demographic, clinical, and biological characteristics of patients at the time of diagnosis are shown in Table 1. All higher-risk MDS (defined as bone marrow blasts > 10% or IPSS categories intermediate-2 or high risk) and AML patients received AZA at a recommended dose

Table 1 Patient Characteristics

	Global Series (n = 64)	Prior IC (n = 18; 28.1%)	Frontline AZA (n = 46; 71.9%)	*P* Value[d]
Age, years, median (range)	68 (29-83)	66 (29-78)	68 (35-83)	.33
Number of AZA courses, n (median)	6 (1-50)	6 (2-16)	9 (2-50)	.08
WHO, n (%)	RARS: 2 (3.2) RCMD: 9 (14) CMML: 3 (4.7) RAEB-1: 3 (4.7) RAEB-2: 26 (40.6) AML: 21 (32.8)	MDS: 4 (22.2)[a] AML: 14 (77.8)	MDS: 39 (84.8)[b] AML: 7 (15.2)	<.001 <.001
IPSS, n (%)[c]				ns
Low Risk	3 (7)	0	3 (8.6)	
Int-1	10 (23.2)	1 (33.3)	8 (22.8)	
Int-2	11 (25.6)	1 (33.3)	10 (28.6)	
High Risk	19 (44.2)	1 (33.3)	14 (40)	
Karyotype (MDS), n (%)				ns
Good	21 (48.2)	1 (25)	20 (51.2)	
Intermediate	5 (11.3)	1 (25)	4 (10.3)	
Poor	12 (27.4)	1 (25)	11 (28.2)	
NA/IM	5 (11.3)	1 (25)	4 (10.3)	
Karyotype (AML) n (%)				
Favorable	0 (0)	0	0	
Intermediate	10 (47.6)	5 (35.7)	5 (71.4)	.08
Adverse	6 (28.5)	6 (42.8)	0	.05
NA/IM	5 (23.9)	3 (22.5)	2 (28.6)	.9
ANC ($<0.5 \times 10^9$ cells/L), n (%)	29/64 (45.4)	8/18 (35)	21/46 (45.7)	.9
Time dx-AZA, mo (range)	2 (0.5-68)	7 (1-55)	1 (0.5-68)	.02

Abbreviations: AML = acute myeloid leukemia; ANC = absolute neutrophil count; AZA = azacitidine; CMML = chronic myelomonocytic leukemia; Dx = diagnosis; IC = intensive chemotherapy; IPSS = International Prognostic Scoring System; MDS = Myelodysplastic syndrome; NA/IM = not available/insufficient metaphases; ns = nonsignificant; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; WHO = World Health Organization Classification.

[a]All MDSs were RAEB-2.

[b]RAEB-1 and RAEB-2: 25 (64% of MDS patients), Lower-risk MDS: 14 (36% of MDS patients).

[c]Intermediate-2/High Risk: 69.8% in the group of previous IC vs. 68.6% in the frontline AZA group; $P = .63$.

[d]*P* values denote differences between group that received previous IC vs. AZA frontline for the corresponding parameter (Mid-P exact test).

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