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Has introduction of azacytidine in everyday clinical practice improved survival in late-stage Myelodysplastic syndrome? A single center experience

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ABSTRACT

Data derived from clinical trials consistently show a prolongation of overall survival of late-stage MDS patients with the introduction of azacytidine. Nevertheless, the applicability of the above results to real-world clinical settings may be questionable due to the strict design, the controlled medical environment, and the limited patient sample of explanatory studies. We retrospectively compared the outcome of two well-balanced groups of late-stage MDS patients. The first consisted of 46 patients treated with azacytidine (AZA cohort) and the second of 41 patients treated with other agents (non-AZA cohort). Patients in the AZA cohort displayed superior survival compared to the non-AZA ones. However, subgroup analysis revealed that azacytidine conferred a significant survival advantage only in patients with AML–MDS and those who attained a CR at any time after treatment initiation, while all other patients displayed comparable outcome with the non-AZA cohort. Larger series are needed to determine which patients benefit most from azacytidine therapy.

1. Introduction

The introduction of azacytidine has radically transformed the therapeutic approach of patients with late-stage Myelodysplastic syndrome (MDS) patients and has led to a significant prolongation of overall survival, as repeatedly demonstrated in clinical trials [1]. However, the so-called "real-life" experience often differs significantly from the results of randomized trials for several reasons. Well-controlled, explanatory trials measure the efficacy of a given intervention in limited populations by using strict selection criteria and operating in a controlled-and somehow artificial medical environment. As a result, the applicability and generalization of the results from such trials in an extended patient population and the everyday clinical setting is questionable [2].

In particular, the actual effectiveness of azacytidine in real life settings is a debatable issue. In the landmark AZA-001 trial the median OS of azacytidine treated patients reached 24 months [3]. By contrast, most real-world data published by institutional series and national registries show a median overall survival ranging from less than a year to up to 19 months depending on the cohort characteristics [4–6]. In keeping with these data, extended follow up in 282 patients of the GFM compassionate program, the largest series so far, revealed a median OS of only 13.5 months [7]. Though these results cannot be directly compared with prospective data, they underscore the grave prognosis of individuals with late-stage MDS in everyday practice even after the introduction of azacytidine.

Apart from the above, only about half of the patients achieve a response, while azacytidine evokes considerable toxicity, predominantly in old and frail individuals, leading to a discontinuation rate of 5% even in clinical trials [3]. Although not being officially stipulated in the recommendations of most drug regulatory agencies, it is becoming increasingly evident that comorbidities may seriously compromise the outcome of patients treated with azacitidine and should rather be placed first in the treatment algorithm to determine patient eligibility for azacytidine [8–11]. Thus, it remains obscure which patients benefit most from azacytidine rendering the latter a typical paradigm of the need for distinction between the efficacy of an intervention in clinical trials and the effectiveness in the real-world daily practice.

We retrospectively compared the outcome of two well-balanced cohorts of late-stage MDS patients managed in our institution in a non clinical trial setting. The first cohort consisted of patients

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treated with azacytidine and the second of patients treated with other therapies.

2. Methods

2.1. Patients

Eighty-seven MDS patients managed in our institution from November 2000 to May 2013 were included in the study after Institutional Review Board approval. All patients had late-stage MDS as defined based on either International Prognostic Scoring System (IPSS) or WHO Classification-Based Prognostic Scoring System (WPSS), an ECOG performance status of 0–2 and were managed in a non-clinical trial setting.

2.2. Treatment

In the first cohort azacytidine was initiated at 75 mg/m^2 SC for 7 days on 28-day cycles. Dose reductions of 25%–50% and/or treatment delays were considered for severe myelotoxicity or myelosuppression-related complications. Granulocyte colony-stimulating factors were used at the discretion of the treating doctor, whereas no erythropoiesis stimulating agents were administered to any patient. Response to therapy and toxicity were evaluated using the International Working Group (IWG) Response Criteria for MDS [12] and Common Terminology Criteria for Adverse Events (CTCAE 3.0), respectively. Six patients of the above group also received intensive chemotherapy after azacytidine failure. The induction consisted of the classic "7 + 3" cytarabine plus idarubicin regimen in 4/6 and high dose cytarabine plus mitoxantrone (MAC) in 2/6 patients. Three out of four individuals in the "7 + 3" regimen were further treated with the idarubicin-FLAG scheme and two of them proceeded to allogeneic hematopoietic stem cell transplantation. Seven patients of the second cohort were treated with intensive chemotherapy, 11 with low-dose chemotherapy consisted of oral melphalan ($n = 4$), 6-mercaptopurine ($n = 2$), hydroxyurea ($n = 4$) and etoposide ($n = 1$), whereas the remaining 23 patients received best supportive care only.

2.3. Statistical methods

Significance of differences was assessed by Mann–Whitney *U*-test or χ^2 tests as appropriate and survival with Kaplan–Meier analysis and log-rank test. Overall survival (OS) was defined as the time from diagnosis of late MDS to death from any cause and event-free survival (EFS) as the time from diagnosis to disease progression, relapse or death. Surviving patients were censored at last follow up.

3. Results

3.1. Study cohorts

Patients' characteristics are presented analytically in Table 1. Two groups were defined based on whether patients were treated or not with azacytidine. The first cohort included forty-six consecutive patients treated with azacytidine (hereafter named AZA cohort). Median follow up and number of completed cycles were 38.5 months and 6 (1–33), respectively, whereas 57% (26/46) of the patients had received ≥6 cycles. Time from diagnosis to first line treatment with azacytidine ranged from 0 to 15.6 months (median 0 months). The second group was comprised by 58 subjects who did not receive azacytidine, because either it was not available at that time in our institution, or a different approach was chosen *at the discretion* of the treating *physician* (non-AZA cohort). From this initial cohort we excluded 17 patients from further analysis because of incomplete medical records. Median follow up was 32.5 months. As shown in Table 1, the two cohorts were well balanced for all characteristics and prognostic parameters.

3.2. Response rates

The overall response rate in the AZA cohort was 58.7%. Twenty-six percent (12/46) of the patients achieved a complete response (CR), 15.2% (7/46) hematologic improvement (all platelet responses, HI-P), 17.4% (8/46) had stable disease (SD), and 41.3% (19/46) failed treatment. Eleven out of 12 patients in the AZA arm obtained a CR after the end of the 4th cycle, whereas the remaining patient reached a CR at the end of the 9th cycle. Also, all 7 patients achieved a HI-P prior to the start of the 4th cycle. None of these 7 patients improved further the HI-P response during the treatment course. No correlations were found between the type of response and IPSS ($p = 0.6$), WPSS ($p = 0.6$), IPSS-R ($p = 0.8$), cytogenetics ($p = 0.4$), sex ($p = 0.3$), WHO subtype ($p = 0.4$), transfusion requirements (more or less than 4 units per month, $p = 0.6$), bone marrow blasts (more or less than 15%, $p = 0.4$) and peripheral blood blasts (presence or absence, $p = 0.9$). Eighteen patients were treated with conventional care regimens in the non-AZA arm. The ORR was 22% and only patients who underwent intensive chemotherapy ($n = 7$) reached CR ($n = 1$) and PR ($n = 3$), while the remaining patients failed treatment.

Table 1
Patients' characteristics. Median values and ranges are shown. N/A: not available/not applicable; AML–MDS: AML with myelodysplasia related changes and less than 30% blasts; MDS/MPD: all patients had CMML-II.

	Non-AZA ($n = 41$)	AZA ($n = 46$)	*p*-value
Age	72.3 (45–84.7)	73.5 (33–83)	0.9
>65	33 (80%)	34 (74%)	
<65	8 (20%)	12 (26%)	
Sex			0.6
Male	28 (68%)	33 (70%)	
Female	13 (32%)	13 (30%)	
WHO classification			0.11
RCMD	1 (2%)	1 (2%)	
RAEB-I	9 (22%)	3 (6.5%)	
RAEB-II	17 (41)	16 (35%)	
MDS/MPD	4 (10%)	12 (26%)	
AML–MDS	10 (24%)	14 (30.5%)	
Baseline blood counts			
Hemoglobin (g/dL)	8.8 (4.1–11.3)	9 (6.1–12.1)	0.47
ANC ($\times 10^9$/L)	0.91 (0.14–14.5)	1.89 (0.07–31)	0.1
Platelets ($\times 10^9$/L)	75 (3–485)	70 (11–311)	0.18
IPSS			0.07
Intermediate-1	3 (7%)	0 (0%)	
Intermediate-2	14 (34%)	18 (39%)	
High	11 (27%)	22 (41%)	
NA	13 (32%)	6 (20%)	
WPSS			0.72
High	14 (34%)	12 (26%)	
Very high	8 (20%)	10 (22%)	
NA	19 (46%)	24 (52%)	
IPSS-R			0.06
Intermediate	6 (15%)	2 (4%)	
High	7 (17%)	18 (39%)	
Very high	15 (37%)	20 (44%)	
NA	13 (31%)	6 (13%)	
IPSS-R cytogenetic risk			0.51
Good	12 (29%)	18 (39%)	
Intermediate	6 (15%)	11 (24%)	
Poor	4 (10%)	9 (20%)	
Very poor	6 (15%)	4 (8.5%)	
N/A	13 (31%)	4 (8.5%)	
Treatment			
Azacytidine	0	46	
Intensive chemo	7	6	
Low intensity	11	0	
Allo-BMT	0	2	
Hospitalization			
Times	4 (0–37)	7 (0–16)	0.2
Total days	25.5 (0–213)	17 (0–43)	0.07
Toxicity (grade 3/4)			
Infections	22 (54%)	13 (28%)	0.028
Bleeding	10 (24%)	9 (20%)	0.79
Thrombocytopenia	32 (82%)	25 (58%)	0.03

3.3. Outcomes and adverse events

Compared to the non-AZA ones, patients in the AZA cohort showed significantly longer median OS (7.84 vs 11.84 months, respectively, $p = 0.014$) and median EFS (5.4 vs 9 months, respectively, $p = 0.021$, Fig. 1a). One and 2 year survival was 46% and 23%, respectively in the AZA patients and 35% and 7% in the non-AZA cohort. No patient in the non-AZA group reached a 3 year OS, while