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Research paper

Outcomes of patients with myelodysplastic syndromes who achieve stable disease after treatment with hypomethylating agents

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ABSTRACT

Treatment with hypomethylating agents (HMAs) improves overall survival (OS) in patients who achieve a response of stable disease (SD) or better (complete remission [CR], partial remission [PR], or hematologic improvement [HI]). It is not well established if patients who achieve SD at 4–6 months of therapy should be offered different therapies to optimize their response or continue with the same regimen. Clinical data were obtained from the MDS Clinical Research Consortium database. SD was defined as no evidence of progression and without achievement of any other responses. Of 291 patients treated with AZA or DAC, 55% achieved their best response (BR) at 4–6 months. Among patients with SD at 4–6 months, 29 (20%) achieved a better response at a later treatment time point. Younger patients with lower bone marrow blast percentages, and intermediate risk per IPSS-R were more likely to achieve a better response (CR, PR, or HI) after SD at 4–6 months. Patients with SD who subsequently achieved CR had superior OS compared to patients who remained with SD (28.1 vs. 14.4 months, respectively, $p = .04$). In conclusion, patients treated with HMAs who achieves CR after a SD status had longer survival with continuous treatment after 6 months.

1. Introduction

Patients with higher-risk myelodysplastic syndromes (MDS) have a high likelihood of transforming to acute myeloid leukemia (AML) and an overall survival (OS) measured in months. The primary goal of therapy in these patients is to alter the natural course of the disease [1–3]. The DNA methyltransferase inhibitors azacitidine (AZA) and decitabine (DAC) are considered first-line therapies, with AZA having demonstrated an improvement in overall survival compared to conventional care regimens, at a median of 24.5 months vs. 15.0 months, respectively, in the AZA-001 study [4,5]. This impact on survival was observed in AZA-treated patients despite relatively low response rates (complete remission (CR) 17% and partial remission (PR) 12%) [6]. A subsequent analysis of the AZA-001 trial showed that treatment with AZA can prolong OS even in patients who did not achieve a CR or PR [7], raising the question of whether achieving a CR should be a therapeutic goal [8]. Furthermore, AZA-treated patients achieving a hematologic improvement (HI) or better had a 95% reduction in the risk of death compared to patients treated with conventional care (hazard ratio.05 [95% CI: .01–.43], $P = .006$) [9].

The decision of when to continue higher-risk MDS patients on AZA or DAC to maximize their chance of response, or of concluding that a response is unlikely to occur and switching to another agent,

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has been a challenge to address. In the AZA-001 trial, the median number of cycles to first response was three (range: 1–22); 81% of patients achieved a first response by six cycles, and 90% achieved a first response by nine cycles, suggesting that a median of 9 cycles of treatment is needed to realize the majority of responses [10]. In a subsequent analysis of the AZA-001 trial, 19% of patients who achieved stable disease (SD) as their best response to AZA at three months achieved a better response HI+ (CR, PR, or HI) at six months, while only 14% of patients with SD at six months achieved a better response by 9 months [9]. The outcome of patients who had SD on AZA therapy was similar to patients who received conventional care treatment while patients who achieved HI+ on AZA therapy had better outcome compared to those achieving HI+ on conventional care at any time point. Similarly, in a randomized, phase III trial of low dose decitabine versus best supportive care, 16 of 119 patients (13%) who received decitabine achieved CR, 7(6%) a PR, and 18 (15%) achieved HI [11]. Median time to best response was 3.8 months (range, 1.4–11.8 months) for all responders, with a median of 5.8 months to reach CR, 2.9 months for PR, and 3.8 months for HI [11]. It is thus not well established if patients who achieve SD by 6 months of therapy with HMAs should be offered different therapies to optimize their response, or continue with the same HMA regimen.

Here we compared the outcomes of patients who achieved SD to AZA or DAC as their best response (BR) to those achieving better responses. We also explored whether patients who achieve SD at 4–6 months of therapy and subsequently achieve a better response had improved outcomes compared to patients who achieve only SD as their best response at any time point during therapy.

2. Methods

2.1. Patients

Patient data from the MDS Clinical Research Consortium institutions (Moffitt Cancer Centre $n = 259$, Cleveland Clinic $n = 221$, MD Anderson Cancer Centre $n = 192$, Cornell University $n = 100$, Dana-Farber Cancer Institute $n = 45$, and Johns Hopkins $n = 29$) were included. Patients were diagnosed with MDS (according to 2008 WHO criteria and confirmed at each participating institution) and had higher-risk disease by the International Prognostic Scoring System (IPSS) or the revised IPSS (IPSS-R) [12]. All patients were treated with either AZA or DAC for 5–7 days of 28-day cycles. All data collected from each institution were stored and secured in an IRB approved database at Cleveland Clinic.

2.2. Responses and outcome

Response definitions, including CR, PR, HI, SD, and progressive disease (PD) were defined per International Working Group (IWG) 2006 criteria [8]. Responses were characterized as initial response (IR) and BR. IRs were defined as responses after 4–6 cycles of treatment with either AZA or DAC. BR was defined as the best response achieved by a patient at any time point after or including IR. For example, if a patient achieved SD after 4–6 cycles of treatment and then achieved an HI thereafter, that patient's IR would be SD and BR would be HI.

2.3. Statistical analysis

Overall survival (OS) was calculated from time of initiation of treatment to time of death or last follow up. Leukaemia-free survival was calculated from the time of treatment initiation to time of AML transformation. Differences among variables were evaluated by the Chi Square and Mann–Whitney *U* test for categorical and continuous variables among patient groups, respectively. Time-to-event analyses were performed by the Kaplan–Meier method, and survival curves were compared using the 2-tailed log rank test. A two-sided *P* value $\leq .05$ was considered to be statistically significant.

Table 1
Patient characteristics.

Parameter	No. (%)/[range]
Total	291
Median age, years	70 [35–99]
Gender	
Male	193 (66)
Female	98 (34)
Race	
White	259 (89)
African American	13 (4)
Hispanic	6 (2)
Others	13 (4)
Clinical characteristics	
Median white blood cell count $\times 10^9$/L	4.80 [0.58–68]
Median hemoglobin, g/dl	9.3 [3.7–14.3]
Median absolute neutrophil count $\times 10^9$/L	1.05 [0.01–24.8]
Median platelet $\times 10^3$/mL	73 [4–659]
Median bone marrow blast%	9 [0–21]
Cytogenetics by IPSS-R	
Very good	0 (0)
Good	85 (29)
Inter	45 (15)
Poor	60 (21)
Very poor	95 (33)
Not documented	6 (2)
IPSS-R risk category	
Intermediate	58 (20)
High	107 (37)
Very high	126 (43)
Not applicable	6 (2)
IPSS risk category	
Intermediate-1	65 (22)
Intermediate-2	173 (59)
High	47 (16)
Not applicable	6 (2)
WHO classifications	
RCUD	5 (2)
RCMD	30 (10)
RARS	3 (1)
RAEB-1	90 (31)
RAEB-2	135 (46)
MDS associated with isolated del (5q)	2 (1)
MDS-U	5 (2)
MDS/MPN	13 (5)
Missing	10 (4)

Abbreviations: IPSS-R, International Prognostic Scoring System-Revised; IPSS, International Prognostic Scoring System; WHO, World Health Organization; RCUD, refractory cytopenia with unilineage dysplasia; RCMD, refractory cytopenia with multilineage dysplasia; RARS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess blasts.

3. Results

3.1. Patient characteristics

Of 846 patients with MDS treated with AZA or DAC, we identified 291 higher-risk patients who had response data documented at each time point (initial and best response) and met our inclusion criteria. Patient characteristics are summarized in Table 1. The median age was 70 years (range, 35–99), 248 patients (85%) received treatment with AZA and 43 (15%) with DAC. IPSS risk categories included 65 patients (22%) who were intermediate-1, 173 (59%) intermediate-2, 47 (16%) high, and 6 (2%) not assessable (missing values). Per IPSS-R, 58 patients (20%) were intermediate