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Outcome of patients with high risk Myelodysplastic Syndrome (MDS) and advanced Chronic Myelomonocytic Leukemia (CMML) treated with decitabine after azacitidine failure

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ABSTRACT

Outcome of patients with high risk MDS and CMML who failed treatment with azacitidine remains poor with a median survival of 6 months, without established therapy available except allogeneic hematopoietic stem cell transplantation. The objective of our study was to evaluate efficacy of decitabine after azacitidine failure in a relatively large patient cohort based on conflicting results with 0–28% response rates (RR) in this setting in small patient series.

Thirty-six consecutive high risk MDS and CMML patients who received decitabine after azacitidine failure were retrospectively reviewed. Response was based on IWG 2006 criteria for MDS and CMML with WBC <13 G/l and also included for proliferative CMML the evolution of WBC, splenomegaly (SMG) and extramedullary disease (EMD). Patients received a median number of 3 (range 1–27) cycles of decitabine and 12 patients received at least 6 cycles.

Seven (19.4%) patients were responders including 3 marrow CR (mCR), 2 stable disease (SD) with HI-E, 1 SD with HI-N and HI-P and 1 SD with HI-N. In a CMML patient with SD, specific skin lesions resolved with decitabine. Responses were generally short lived (2–5 months) except 1 responder currently ongoing with +11 months follow up. Two non-responders had prolonged SD (without HI) of 21 and 27 months duration respectively. Median OS from onset of decitabine was 7.3 months, without significant difference between responders and non-responders.

Treatment with decitabine after azacitidine failure yielded modest ORR (19.4%) with short response duration and poor OS. Thus, use of decitabine in such patients who failed or progressed after azacitidine cannot be recommended, underscoring the need for novel strategies in this setting.

1. Introduction

Hypomethylating agents, including azacitidine and decitabine, are currently the mainstay for treatment of patients with IPSS intermediate 2 or high (higher risk) myelodysplastic syndromes, including CMML with WBC <13 G/l [1–3]. Treatment with azacitidine significantly improves overall response rates (ORR) and overall survival (OS) [3]. However, only about 50% of patients respond to azacitidine and the outcome of patients after azacitidine failure (primary failure or relapse) is poor with a median overall survival of 6 months from treatment failure [4]. No therapy including best supportive care, low dose chemotherapy, intensive AML-like chemotherapy and investigational agents have demonstrated a significant impact on survival in those patients except allogeneic bone marrow transplantation for the few eligible patients [4,5]. Thus, novel treatment strategies are urgently needed for patients failing treatment with azacitidine.

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Table 1
Studies of decitabine use after azacitidine failure [4,9–11].

Study	Borthakur et al.	Prébet et al.	Bhatnagar et al.	Duong et al.
No patients	14	16	22	25
ORR (IWG2006)/%	28	0	0	0
CR/%	21	0	0	0
mCR (HI)	7 (7)	0 (0)	0 (0)	0
PR	0	0	0	0
SD + HI	0	NA	0	0
OS (M, months)	6	11.8	ND	5.9

Decitabine, the other hypomethylating agent, is approved in the US and other countries (but not Europe) for the treatment of MDS and in Europe for the treatment of acute myeloblastic leukemia (AML) in the elderly [6].

Decitabine and azacitidine have somewhat different pharmacological properties suggesting potential non-cross resistance [7,8]: both drugs affect markers of azanucleoside incorporation into DNA including DNMT1 depletion and DNA hypomethylation with those markers being more sensitive to decitabine. Azacitidine affects the whole cell cycle while decitabine affects mainly G0/G1 to S transition. Decitabine modifies DNA-mediated mechanisms inducing DNA damage response besides epigenetic modulation while azacitidine is more potent in reducing cell viability and protein synthesis.

Conflicting results for decitabine salvage after azacitidine failure have been reported with 0–28% response rates (RR) in 3 small patient series with an overall survival up to 11.8 months in responding patients (Table 1) [4,9–11]. Based on these observations we retrospectively reviewed a larger cohort of 36 patients treated with decitabine after azacitidine failure.

2. Patients and methods

2.1. Patients

Baseline characteristics, overall response rate (ORR) and outcome of high risk MDS and CMML patients who received decitabine after azacitidine failure from June 2007 to April 2013 in three French hematology centers were analyzed. Decitabine was administered as 20 mg/m^2/day for 5 consecutive days every 28 days, as previously reported [12,13]. Response was based on IWG 2006 criteria for MDS and CMML with WBC <13 G/l and also included for CMML with WBC ≥13 G/l, evolution of WBC, splenomegaly (SMG) and extramedullary disease (EMD) [14,15]. Patients receiving at least one cycle of decitabine were considered evaluable for response. Informed consent of patients for the use of clinical data had been obtained, in accordance with the modified declaration of Helsinki. All cases were classified according to French American British (FAB) group and World Health Organization (WHO) criteria. All patients were followed up until decitabine failure or death or April 2014, closing date of the study.

2.2. Statistical analysis

Baseline characteristics and response rates were compared by non-parametric tests: Fisher's exact test for qualitative variables and Kruskal–Wallis test for quantitative variables. Censored endpoints were estimated by the non-parametric Kaplan–Meier method and compared by the log-rank test. Survival was measured from the onset of therapy with decitabine. Type I error was fixed at the 5% level. All tests were two-tailed. Statistical analysis was performed with the StataSE 10.1 (StataCorp, College Station, TX, USA) software.

3. Results

3.1. Patient characteristics

Thirty-six patients with higher risk MDS (IPSS intermediate 2 or high) or advanced CMML having no response (n = 19), progressive disease (n = 2) or patients relapsing after an initial response (n = 15) following azacitidine treatment were studied. Median age at decitabine onset was 70.5 years (53–84) including 21 males and 15 females (Table 2).

3.2. Treatment with azacitidine

Time to onset of treatment with azacitidine was 5.7 months (0.1–120) from diagnosis with 2 patients having Refractory Cytopenia with Multilineage Dysplasia (RCMD), 5 Refractory Anemia with Excess of Blasts 1 (RAEB 1), 17 RAEB 2, 6 Acute Myeloid Leukemia post MDS (AML, including 4 RAEB in transformation according to FAB), 4 Chronic Myelomonocytic Leukemia 1 (CMML 1) and 2 CMML 2. Median BM blast count was 13% (2–72). Karyotype was normal in 15 (41.7%) patients, 9 (25%) patients had unfavorable cytogenetics including 7 complex karyotypes and 2 monosomy 7, 5 (13.9%) patients had trisomy 8, 3 (8.3%) del 20q, 3 (8.3%) other anomalies and 1 (2.8%) cytogenetic failure. Twenty-eight patients had either IPSS ≥intermediate 2 or CMML 2 and 8 patients for whom IPSS could not be calculated as WBC was >13 G/l (2 patients) or due to missing data and/or AML progression (5 patients). Accordingly, IPSS-R was intermediate for 15 patients, high for 4 patients, very high for 9 patients and could not be determined for 8 patients. Median number of cycles with azacitidine was 8 (3–41) while 8 patients received less than 6 cycles (2–5) including 1 patient who received allo HSCT and 1 patient who had progessive disease. For 6 patients treatment by azacitidine was stopped for inefficacy before achieving 6 cycles. For patients receiving at least 6 cycles, 12 were considered to have failed treatment by azacitidine, 1 patient progressed and 15 patients relapsed after achieving either complete remission (CR; n = 9), partial remission (PR; n = 1), marrow CR (mCR; n = 1), mCR with hematologic improvement (mCR + HI; n = 2) or stable disease with HI (SD + HI; n = 2). A total of 3 responding patients received allo HSCT (2CR and 1 SD + HI). Except the 3 allografted patients,

Table 2
Characteristics of patients at onset of decitabine.

	N = 36	Median	Range
Age (y)	–	70.5	53–84
Sex (M/F)	21/15	–	–
WBC (G/l)	–	4.25	0.2–57
ANC (G/l)	–	1.55	0–25.7
Hb (g/dl)	–	9.1	6.6–11.5
Platelets (G/l)	–	40.1	4–651
BM blasts (%)	–	23	7–82
WHO (FAB)			
AML (RAEBt)	22 (11)		
RAEB 1	1		
RAEB 2	8		
CMML 1	4		
CMML 2	1		
IPSS			
Intermediate 2	10		
High	10		
NA	16		
IPSS R			
Intermediate	3		
High	11		
Very high	6		
NA	16		