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Safety and efficacy of 5-azacytidine treatment in myelodysplastic syndrome patients with moderate and mild renal impairment

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ABSTRACT

Myelodysplastic syndrome (MDS) patients with renal impairment (RI) were not assessed in the approval trials of 5-azacytidine, thus the optimal use of 5-azacytidine in such patients is currently undefined. We retrospectively analyzed 42 IPSS intermediate-2 and high-risk patients with moderate, mild or no RI undergoing 5-azacytidine therapy in a non-trial setting. We demonstrate that patients in all three groups achieved comparable responses and had similar overall and event-free survival. Likewise, both treatment toxicity and dose adjustments were not significantly influenced by renal function status. A transient but reversible decline in glomerular filtration rate was observed in patients either with or without RI, without affecting the therapeutic schedule. Our results provide the first evidence that 5-azacytidine is effective and well-tolerated in patients with mild and moderate RI and, if confirmed by prospective randomized studies, advocate that such patients can be managed in an analogous fashion to patients with normal renal function.

1. Introduction

The introduction of 5-azacytidine in myelodysplastic syndromes (MDS) has led to a significant prolongation of overall survival along with a substantial reduction in treatment toxicity, thus allowing the use of 5-azacytidine in frail and/or elderly patients who comprise the majority of MDS population [1–4]. The main dose-limiting toxicity is myelotoxicity; yet, as the primary route of elimination of 5-azacytidine and its metabolites is renal excretion [5], renal abnormalities were observed in early animal studies [6]. Moreover, high doses of the drug or combination with conventional chemotherapeutic agents may induce renal tubular dysfunction with electrolyte abnormalities [7], whereas even fatal cases of renal failure have been reported in patients treated with intravenous 5-azacytidine in combination with other chemotherapeutic agents [8]. The mechanism of 5-azacytidine-mediated nephrotoxicity is not clear but may involve induction of reactive oxygen species (ROS) in renal tubule cells [9], potentially via epigenetic activation of the p66shc adaptor protein [10].

Chronic kidney disease (CKD), has a remarkably high prevalence in general population which increases as age advances [11]. A decline in estimated glomerular filtration rate (eGFR) is one of the most predictable changes associated with age, as it declines approximately 1 mL/min for every year over 40 years of age [12]. Patients with MDS are typically elderly and may thus have compromised eGFR despite the apparently normal or borderline creatinine levels. Nevertheless, patients with decreased renal function were not assessed in the approval trials of 5-azacytidine. As a result, the optimal management of MDS patients with renal impairment (RI) undergoing 5-azacytidine therapy is currently not established. The current prescribing information of 5-azacytidine acknowledges that no formal studies have been conducted in patients with decreased renal function and advises close monitoring for toxicity in such patients. To our knowledge, only one single-center, retrospective study addressed the feasibility of 5-azacytidine treatment in 13 patients with moderate and severe RI [13], whereas a single case of successful 5-azacytidine treatment in an adolescent MDS patient with severe RI has also been reported [14]. In the former study the authors suggested that 5-azacytidine achieves satisfactory clinical responses, although at the expense of a higher incidence of toxicity [13]. In addition, a phase I study in 5 cancer patients with various malignancies and severe renal failure defined as an eGFR < 30 mL/min/1.73 m^2, reports comparable 5-azacytidine pharmacokinetics and toxicity with patients with normal renal function. However, all studies included a very small number of

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Table 1
Characteristics of the study cohort ($n = 42$).

Parameter	Normal renal function ($n = 14$)	Mild renal impairment ($n = 16$)	Moderate renal impairment ($n = 12$)	p-value
Median GFR (mL/min/1.73 m^2)	93.5 (87–140)	66.5 (57–76)	40.5 (33–48)	<0.001
Sex (Male/Female)	10/4	13/3	8/4	0.66
Age (median)	70.3 (52–79)	68.8 (59–79)	77 (65–81)	0.006
Karyotype risk (Good/Intermediate/Poor)	7/5/2	5/2/9	4/6/2	0.052
IPSS risk group (Int-2/High)	9/4	7/7	7/3	0.49
WPSS risk group (High/Very high)	7/7	7/7	7/3	0.6
ANC($\times 10^9$/L)	0.7 (0.08–13.3)	1.99 (0.05–15.5)	3.75 (0.74–6,3)	0.115
Hemoglobin (g/dl)	8.35 (6.1–10.1)	9.1 (6.8–11.5)	9.35 (6.2–12.8)	0.32
Platelets ($\times 10^9$/L)	139.5 (11–311)	64 (12–150)	51.5 (15–160)	0.178
Heavily transfused (Yes/No)	9/5	9/7	9/3	0.59
Median number of cycles (range)	5.5 (1–30)	6 (1–31)	4 (1–26)	0.48
Median follow up time from treatment initiation (months-range)	10.1 (4.9–42)	10.41 (1.2–42.2)	8 (1–27.2)	0.33

patients, whereas no comparative analysis of the efficacy and safety of 5-azacytidine administration between patients with or without renal impairment (RI) has been performed yet. In the present work, we retrospectively analyzed 42 IPSS intermediate-2 and high-risk MDS patients with normal renal function, mild and moderate RI treated with 5-azacytidine in a non-trial clinical setting.

2. Methods

2.1. Patients

Forty-two IPSS intermediate-2/high-risk MDS patients with a median age of 73.7 (range 55–81) years were included in the study after Institutional Review Board approval. Patients were classified according to the revised WHO classification as having RAEB-II ($n = 18$), AML/MDS with less than 30% blasts ($n = 6$), CMML-II ($n = 8$), MDS/MPN ($n = 4$), RAEB-I ($n = 3$) and RCMD ($n = 3$). All patients had normal hepatic function with bilirubin levels of 1.5 mg/dL or less and an ECOG performance status of 0–2. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) or the Cockroft-Gault for lean body weight formulas, the latter used for patients weighing >25% beyond the ideal body weight [15]. Heavily transfused patients were defined as those requiring ≥4 RBC units/8 weeks.

2.2. Treatment

In all patients 5-azacytidine was started at 75 mg/m2 SC for 7 days on 28-day cycles. Response to therapy and toxicity were evaluated using the International Working Group (IWG) Response Criteria for MDS [16] and Common Terminology Criteria for Adverse Events (CTCAE 3.0), respectively. 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.

2.3. Statistical methods

Significance of differences was assessed by one-way analysis of variance (ANOVA) or χ^2 tests as appropriate. Overall survival (OS) was defined as the time from first 5-azacytidine administration to death from any cause and event-free survival (EFS) as the time from first 5-azacytidine administration to leukemic transformation or death from any cause. Surviving patients were censored at last follow up. Survival analysis was performed using the Kaplan–Meier method and survival curves were compared by the log-rank test. Multivariate survival analysis was based on Cox's proportional hazards model with simultaneous entry of all covariates of interest.

3. Results

3.1. Patient demographics

Patients' characteristics are listed analytically in Table 1. Three groups were defined based on eGFR levels and presence or absence of kidney damage. Patients with no RI (eGFR >90 mL/min/1.73 m^2) and absence of kidney damage (CKD stage 0, $n = 14$), mild RI (eGFR 60–89 mL/min/1.73 m^2, CKD stage 2, $n = 16$) and moderate RI (eGFR 30–59 mL/min/1.73 m^2, CKD stage 3, $n = 12$). No differences regarding gender, MDS subtype, IPSS and WPSS risk groups, transfusion needs, follow up time and number of completed cycles were noticed among the three groups. By contrast, patients with moderate RI were significantly older than the ones with either no or mild RI ($p = 0.006$), whereas the mild RI group displayed marginally higher rate of poor cytogenetics ($p = 0.052$).

3.2. Response and outcomes

The median follow up time from the onset of 5-azacytidine for all patients was 31.4 (range 1–42.2) months and the median number of completed cycles was 5.5 (1–29). As depicted in Fig. 1a, no differences in overall response rates (ORR) were observed among patients with moderate RI (50%), mild RI (31%) and no RI (35%, $p = 0.59$). Notably, the CR rate was remarkably higher in the no RI group (35%) compared to mild RI (19%) and moderate RI (17%), but without reaching statistical significance ($p = 0.27$). Likewise, patients with moderate RI experienced more frequently hematological improvement of platelets (33%, HI-P) compared to the non-RI (0%) and mild RI (12%) groups, but, again, the differences were not significant ($p = 0.052$). The median overall and event-free survival for all patients was 10.4 and 7.8 months, respectively. The median OS was similar among the no RI (10.4 months), mild RI (13.5 months) and moderate RI (9.5 months) groups ($p = 0.46$ by log-rank test, Fig. 1b). No differences were also noticed in median EFS ($p = 0.56$, Fig. 1b) between patients with no, mild and moderate RI (7.9 vs. 6.7 vs. 6.4 months, respectively). In univariate analysis, age, gender, transfusion needs and karyotype were not associated with OS, while only karyotype was associated with EFS ($p = 0.03$) (data not shown). Multivariate analysis was subsequently performed. Karyotype (favorable vs. others) was simultaneously evaluated with age and eGFR as continuous covariates. Surprisingly, decreasing eGFR was the only independent predictor of inferior OS (hazard ratio 0.975, 95% confidence intervals 0.953–0.998, $p = 0.03$, supplementary Table 1), despite the absence of any difference among the 3 groups, but also when patients were grouped in those with (median OS 9.6 and median EFS 6.6 months) or without RI ($p = 0.52$ and $p = 0.59$, respectively, supplementary Fig. 1). Neither eGFR nor age or karyotype had any statistically significant independent prognostic effect on EFS.

3.3. Toxicity and adverse events

All three groups experienced comparable rates of adverse events (Table 2). Grade 3/4 myelosuppression was a frequent event and was equally common across all groups (neutropenia 50–62.5%, thrombocytopenia 50–75%). Also, although not statistically significant, higher rates of serious infections and grade 3/4 hemorrhagic events were observed in patients with moderate RI (58% and 58%, for infections and bleeding respectively) and mild RI (56%