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LETTER TO THE EDITOR

Combination of decitabine, idarubicin, cytarabine, and G-CSF (DIAG) regimen for the treatment of high-risk myelodysplastic syndrome and acute myeloid leukemia

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Dear Editor,

Sixty to eighty percent of patients with newly diagnosed acute myeloid leukemia (AML) can achieve complete remission (CR) after intensive chemotherapy**.** However, current therapy remains unsatisfactory for high-risk AML patients, including the elderly, relapsed, refractory, and secondary AML [1]. Myelodysplastic syndrome (MDS) comprises a very different group of myeloid malignancies with very distinct natural histories. Interventions have been evolved significantly over the last decade in high-risk disease. However, the median survival of these patients was only 0.5 years [2]. Generally, the effect of intensive chemotherapy on these patients is insufficient because of drug resistance, poor performance status (PS), dysfunction of multiple organs, and high treatment-related toxicities, leading to high early death (ED) rate. Novel agents and regimens have been developing for this group of patients with AML and high-risk MDS [3–6].

The combination of new drugs and low-toxicity chemotherapy drugs can reduce early mortality and improve long-term survival of elderly AML patients [4]. This study aims to evaluate the efficacy and safety of DIAG (decitabine, idarubicin, cytarabine, and G-CSF) regimen in the treatment of patients with high-risk MDS and AML. From August 2015 to December 2018, 10 patients with high-risk MDS and AML enrolled in the study at our department. Patients were newly diagnosed with high-risk MDS and de novo or secondary AML according to the World Health Organization (WHO) criteria. The median age was 61 years (range, 42–80 years, see Table 1). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 with a normal creatinine level and total bilirubin of ≤ 2 mg/dL. This study was performed in accordance with the Declaration of Helsinki and all patients gave written informed consent for retrospective data collection and analysis, which was approved by our local ethics committee. This individualized treatment regimen was discussed with every patient prior to the initiation of treatment and all patients agreed to it. All patients were treated with 15 mg/m^2 decitabine intravenously for 5 consecutive days (days 1–5) and 300 μg/day G-CSF (days 6–19) combined with 10 mg/m^2 cytarabine q12h for 14 days (days 6–19) and 10 mg/day idarubicin for 1 day (day 6) (DIAG). The G-CSF priming would be suspended if white blood count (WBC) was $> 20 \times 10^9$/L. Hydroxyurea was permitted as rescue medication to control WBC $< 5.0 \times 10^9$/L and was suspended at least 24 h before the decitabine treatment.

The treatment responses of the enrolled patients to DIAG regimen were shown in Table 1. All 10 patients were evaluated for response assessment following the DIAG induction therapy and had an overall response rate (CR plus PR) of 80% after the first to three cycles. Among them, 6 (60%) achieved CR and 2 (20%) had PR, while 2 (20%) had HI. The CR was observed in secondary AML arose from JAK2-mutated essential thrombocythemia (ET) and high-risk MDS and 1 patient with de novo AML. However, 1 patient with CALR-mutated ET transformed to AML and 3 patients with de novo AML had not achieved CR. For patients with a normal karyotype, 62.5% of them achieved CR. One of 2 patients with complex karyotypes achieved CR.

Most frequently observed adverse events are summarized in Table 2. In particular, grades 3 and 4 hematologic toxicities included thrombocytopenia and neutropenia were more commonly noted. Moreover, febrile neutropenia occurred in all enrolled patients. Other uncommon toxicities including 1 patient of grade 2 liver dysfunction were observed. None of the enrolled patients had developed renal dysfunction, heart

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Table 1 Summary of MDS and AML patients clinical characteristics

Case	Sex	Age years	Diagnosis	BM blasts (%)	Mutant genes	Antecedent hematologic disease	Chromosomal karyotype	Previous therapy	Treatment	Outcome
1	M	66	ALAL	39	JAK2V617F	ET	46, XY[20]	No	1 cycle of DIAG	CR
2	M	60	M5	57	JAK2V617F	ET	47,XY,+ 1,der(1;7)(q10;p10), +8,add(14)(q32)[20]	No	2 cycles of DIAG	CR
3	M	56	M2	68	CALR and ASXL1	ET	45,XY,-5,del(7)(q32), del(12)(p13)[20]	1 cycle of IA	2 cycles of DIAG	PR
4	F	48	M2	48.5	Not detected	No	46, XX[20]	1 cycle of IA	3 cycles of DIAG	CR
5	M	80	M2	31	Not detected	MDS	46, XY[20]	Supportive therapy	2 cycles of DIAG	CR
6	M	64	MDS	17	Not detected	No	46, XY[20]	No	1 cycle of DIAG	CR
7	F	50	MDS	12	Not detected	No	46, XX[8]	No	5 cycles of DIAG	CR
8	M	62	M5	40	Not detected	No	46, XY[5]	No	2 cycles of DIAG	PR
9	M	42	M5	54	FLT3/ITD and WT1	No	46, XY[20]	2 cycles of IA	1 cycle of DIAG	HI
10	M	64	M2	43	Not detected	No	46, XY[20]	1 cycle of IA	1 cycle of DIAG	HI

BM, bone marrow; *M*, male; *F*, female; *ALAL*, acute leukemia of ambiguous lineage; *ET*, essential thrombocythemia; *MDS*, myelodysplastic syndrome; *IA*, idarubicin and cytarabine; *DIAG*, decitabine, idarubicin, cytarabine, and G-CSF; *CR*, complete remission; *PR*, partial remission; *HI*, hematologic improvement

damage, and skin rashes during the exposure to DIAG regimen. It was suggested that the incidence of non-hematological adverse events was low. In conclusion, the DIAG regimen was well tolerated.

Acute myeloid leukemia (AML) has been characterized as a heterogeneous disease, and the majority of AML patients exhibit a poor prognosis even after intensive therapy. Myelodysplastic syndromes (MDS) are stem cell diseases, which are characterized as cytopenias, dysplasia in one or more cell lines, ineffective hematopoiesis, and an increased risk of progression to secondary acute myeloid leukemia (AML) [3]. The median overall survival of high-risk MDS is less than 6 months. The combination of novel drugs and chemotherapy has been developed to reduce the early mortality and improve the benefit-risk ratio to achieve long-term survival in AML and high-risk MDS patients [4–6].

Table 2 Side effect of treatment with decitabine combined with IAG regimen

Toxic effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	0	0	0	0	10
Thrombocytopenia	0	0	0	0	10
Anemia	0	1	6	0	3
Nausea and vomiting	0	0	0	0	0
Liver dysfunction	0	0	1	0	0
Renal dysfunction	0	0	0	0	0
Heart damage	0	0	0	0	0
Blood in the urine	0	0	0	0	0
Skin rashes	0	0	0	0	0
Fever	0	6	4	0	0

Decitabine, a DNA hypomethylating agent shows therapeutic efficacy against leukemic cells [7]. Recently, it was incorporated into the treatment for myelodysplastic syndromes (MDS) and was recommended for the treatment of AML [5, 6]. In clinical practice, decitabine treatment decreases methylation and induces a better clinical response. Although the mechanism of the clinical activity of decitabine has not been completely defined, the clinical and biologic properties of decitabine are promising. Recently, a prospective phase II, the open-label study suggested that D-CAG regimen was well tolerated and showed a promising clinic efficacy in elderly patients with AML [8].

Due to the scarcity of aclarubicin in our department, we used idarubicin instead of aclarubicin to compose an IAG regimen. In our study, we evaluated the effects of the DIAG regimen in a small group of high-risk MDS and AML patients. The result showed that DIAG regimen was well tolerated and effective with ORR of 80% in high-risk MDS and AML patients, including secondary AML and AML resistant to IA regimen.

We reported two patients with JAK2V617F mutation positive-essential thrombocythemia (ET) being treated with hydroxyurea, whose disease evolved into acute leukemia. Post-MPN AML has a dismal prognosis with a median survival of less than 6 months and long-term remissions can only be achieved through allogeneic hematopoietic stem cell transplantation [9]. However, whether the JAK2V617F mutation is involved in the conversion of ET to acute leukemia remains unclear [10]. The two patients had shown a complete response, with repeated bone marrow JAK2V617F analyses demonstrating an unchanged mutation after treatment with DIAG regimen chemotherapy. Interestingly, case 1 had also

transformation to JAK2 V617F-mutated ET for almost 12 months longer without further treatment. This phenomenon has not been described before. Case 2 also received two cycles of DIAG chemotherapy and achieved complete remission, with repeated bone marrow JAK2V617F analysis demonstrating an unchanged mutation. These results suggest that JAK2V617F mutation may not be involved in the development of ET transformation to acute leukemia.

In PMF, the presence of ASXL1 mutations in the type 2 CALR mutation-positive patients is frequently is associated with a poor survival rate [11]. However, the role of ASXL1 mutation in CALR mutation-positive ET patients has not been elucidated. A recent study [12] showed that CALR mutation occurred in 50 patients in among all the 190 counterparts, and 8 CALR-mutated patients with ET had ASXL1 mutation. Among these 8 patients with ET, 2 patients evolved to post-ET MF but no one progressed to AML. In our studies, the patient with AML transformed from ET with the coexistence of CALR and ASXL1 mutation did not achieve disease remission with 28.5% bone marrow blasts and a repeated bone marrow CALR gene analysis demonstrated a mutant allele burden of 49.39%, suggesting that CALR mutation may participate in the leukemic transformation of ET. To our knowledge, this is the first case suggests that coexistence of CALR and ASXL1 mutation may involve in the leukemic transformation of ET and the AML clone may derive from CALR-mutated ET clone.

The adverse events of decitabine and IAG regimen mainly include myelosuppression, infection, nausea, vomiting, liver, and kidney dysfunction. In this group of patients, all patients had grade 4 bone marrow suppression. Some of them even had a fever and infection later. After active anti-infection treatment, blood transfusion, administration of G-CSF and interleukin-11, and supportive care, the risk of myelosuppression was removed and the infection was effectively controlled. Bone marrow hematopoietic function was then restored. Moreover, there were no other serious adverse events caused by DIAG regimen observed, such as myocardial infarction, gastrointestinal bleeding, and mental changes.

In summary, our study suggests that DIAG regimen may be an alternative choice in the treatment of high-risk MDS and secondary AML patients but further observation is required.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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