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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The efficacy and toxicity of the CHG priming regimen (low-dose cytarabine, homoharringtonine, and G-CSF) in higher risk MDS patients relapsed or refractory to decitabine

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Abstract

Purpose Myelodysplastic syndromes (MDSs) refractory or relapsed after hypomethylating agents (HMAs) remain a therapeutic challenge. The CHG regimen has been demonstrated to be effective in initially treating higher risk MDS. The current study evaluated the efficacy and toxicity of the CHG regimen in patients who were resistant to decitabine.

Methods Patients with higher risk MDS relapsed or refractory to decitabine were enrolled in this study. Each patient received the CHG regimen (cytarabine (25 mg/day, days 1–14) and homoharringtonine (1 mg/day, days 1–14) intravenously with G-CSF (300 μg/day) subcutaneously from day 0 until neutrophil count recovery to 2.0×10^9 cells/L). Next gene sequencing with a 31-gene panel was carried out in patients.

Results Thirty-three patients were enrolled, including 12 relapsed and 21 refractory cases. The overall response rate (ORR) was 39.4% (13 of 33), with 9 (27.3%) achieving complete remission (CR), 2 having marrow CR (mCR), and 2 achieving partial remission (PR). The CR rate was higher in patients harboring fewer gene mutations (0–1) (55.6%) than in those with more gene mutations (> 1) (12.5%) ($p = 0.021$). The median overall survival (OS) of the 33 patients was 7.0 months. Patients who achieved a response had significantly longer survival times than were found in those without a response (21.0 M vs. 4.0 M, $p < 0.0001$). The regimen was endurable for most of the patients.

Conclusions The CHG priming regimen provided a safe and effective salvage regimen for higher risk MDS patients who were resistant to decitabine. Further studies involving larger samples will be needed. Clinical trial No. ChiCTR-ONC-11001501.

Keywords Myelodysplastic syndromes · Decitabine · Cytarabine · Homoharringtonine · Granulocyte colony-stimulating factor (G-CSF)

Introduction

Myelodysplastic syndrome (MDS) includes a heterogeneous group of clonal hematopoietic stem cell disorders characterized by peripheral cytopenia and hypercellular bone marrow (BM) with higher risk of evolution to acute myeloid leukemia (AML) (Tefferi and Vardiman 2009; Bejar and Steensma 2014). Higher risk MDS patients [intermit-2 or high-risk defined by the international prognosis scoring system (IPSS) (Greenberg et al. 1997) as well as part of intermediate (> 3.5), high risk, and very high risk according to the IPSS-R (Greenberg et al. 2012)] are generally progressive in nature. Hypomethylating agents (HMAs), including azacitidine and decitabine, are considered standard therapy for higher risk MDS (Fenaux et al. 2009; Kantarjianet al 2006) who are not suitable for hematopoietic stem cell transplant (HSCT). Despite their ability to induce complete remission and prolonged survival even in elderly patients, HMAs are not curative without HSCT) (Craddock et al. 2013; Santini 2012). However, there is a subgroup of MDS patients who are primarily refractory to HMA, and most of response patients will relapse even during HMA therapy if they do not receiving HSCT. Survival of refractory/relapsed

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patients is extremely short for high-risk patients. Because there are limited therapeutic options in this setting (Santini 2019), this represents a challenging cohort of patients and constitutes an important area of clinical research.

Low-dose chemotherapy was first proposed for the treatment of AML in 1995, which consists of low-dose cytarabine and aclarubicin combined with granulocyte colony-stimulating factor (G-CSF) priming and is referred to as CAG (Yamada et al. 1995). The CAG priming regimen has been demonstrated to be efficacious in the treatment of elderly AML as well as higher risk MDS, and has been widely used in China and Japan for the past 2 decades (Saito et al. 2000). However, the cardiac toxicity associated with aclarubicin limits to a certain extent the application of the CAG regimen, especially in elderly patients. A new chemotherapy regimen with less cardiac toxicity was developed that consists of low-dose homoharringtonine (HHT) and cytarabine as well as G-CSF priming and is abbreviated as CHG.

The CHG regimen (low-dose cytarabine and homoharringtonine in combination with granulocyte colony-stimulating factor (G-CSF)) was reported to be effective and safe in our previous study in initial treatment higher risk MDS patients (Wu et al. 2009, 2011). The overall response rate was 71.9% after one course of the CHG regimen in initially treated patients, with 46.9% achieving complete remission (CR). This overall survival rate was comparable to that of decitabine therapy in initially treated patients (median 15.3 months in the CHG group and 18.2 months in the decitabine group) (Wu et al. 2016). The CHG regimen has also been reported to be effective and safe in other centers in China (Xie et al. 2016). Based on the responses to the CHG regimen observed in patients with higher risk MDS, CHG has been recommended as a selectable regimen for higher risk MDS in China and has been included in the Chinese guidelines for MDS treatment.

Based on the differences in the mechanisms of HMA and the CHG priming regimen, it has been proposed that the CHG regimen may be an effective regimen for patients who are relapsed or refractory to decitabine. Here, we analyzed the clinical efficacy and toxicities of the priming CHG regimen as a salvage therapy for higher risk MDS patients who are relapsed or refractory to decitabine therapy.

Patients and methods

Patients

Between December 2011 and December 2016, patients met the following criteria were enrolled in this study: (1) age 16–80 years; (2) had been diagnosed as refractory anemia with excess blasts (RAEB) [including RAEB-1 and RAEB-2 based on the 2008 WHO classification (Brunning et al. 2008)] or RAEB in transformation (RAEB-t) according to the FAB classification (Bennett et al. 1976); (3) had failed to respond to decitabine (disease progressed after two cycles of decitabine or no response observed after four cycles of decitabine therapy) or relapsed after achieving a response to decitabine [including CR, marrow CR, partial remission (PR), or hematological improvement (HI)]; (4) a performance status of 0–3 according to the Eastern Cooperative Oncology Group (ECOG); (5) had no evidence of severe concurrent pulmonary, cardiac, and neurologic diseases; (6) adequate hepatic (serum bilirubin level $< 2 \times$ upper normal limit) and renal (serum creatinine $< 2 \times$ upper normal limit) function tests. The exclusion criteria included other progressive malignant diseases.

Peripheral blood counts, BM smear analyses, BM section analyses, chromosome analyses, serum lactate dehydrogenase (LDH) levels, and serum ferritin levels were available from all patients before CHG therapy. Next gene sequencing with a 31-gene panel containing the genes commonly mutated in MDS as reported in our previous study (Xu et al. 2015) was carried out in some patients with BM DNA sample available. The Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital approved the study and informed written consent in accordance with the Declaration of Helsinki from all patients was obtained from all patients participated in the study.

CHG protocol

The CHG priming regimen consisted of low-dose cytarabine (25 mg/day) and homoharringtonine (1 mg/day) intravenously continuous infusion in combination with G-CSF (300 μg/day) by subcutaneous injection from day 0 until the peripheral neutrophil count recovered to 2.0×10^9 cells/L. G-CSF was given intermittently when the peripheral white blood cell (WBC) count increased above 20×10^9 cells/L. BM aspirates and biopsy were obtained to assess the treatment response 2–3 weeks after the CHG regimen was completed.

Evaluation of efficacy

Baseline and efficacy evaluations were undergone for each patient. The baseline evaluation as mentioned above included blood cell count, urine, and biochemical analyses [including serum lactate dehydrogenase (LDH) levels, and serum ferritin levels], BM smear analyses, BM section analysis, chromosome analysis, and targeted sequencing of a 31-gene panel containing the genes commonly mutated in MDS as reported in our previous study (Xu et al. 2015). These evaluations were performed 7–14 days prior to the start of the CHG regimen. The efficacy evaluation, which

Table 1 General data of 33 MDS patients treated with CHG who were relapsed/refractory to decitabine

No	Sex	Age	Diagnosis	IPSS score	IPSS-R	Blasts in BM (%)	Karyotype	Gene mutations	LDH (U/L)	Ferritin (ng/ml)	Blood counts			Response
											WBC (10^9/l)	Hgb (g/l)	Plt (10^9/l)	
1	M	60	RAEB-1	2.0	7	5.0	46,XY,der(7) t(1;7)(q21;q21) [17]/46,XY[8]	RUNX1/EZH2	230	69	3.0	82	30	mCR
2	M	53	RAEB-1	1.0	4	5.0	46,XY[20]	No	596	1053	2.8	82	216	CR
3	F	58	RAEB-1	1.0	3.5	5.0	46,XX[25]	ND	151	654	3.9	125	50	NR
4	M	79	RAEB-1	1.5	7	6.5	46,XY,der(2), der(17),inc[5]	DNMT3A/TET2/ITIH3	248	1329	0.9	56	41	NR
5	F	83	RAEB-1	1.0	5.5	6.5	46,XX[15]	ND	182	1025	1.8	66	20	NR
6	M	67	RAEB-1	1.0	5	6.5	46,XY[14]	ND	341	424	2.2	98	34	NR
7	M	67	RAEB-1	1.0	5.5	6.8	46,XY[16]	DNMT3A/FZR1/PTPRD	298	1479	3.5	75	32	PR
8	M	57	RAEB-1	1.5	6.5	7.3	46,XY,+1,der(1;7) (q10,p10)[12]	No	168	969	6.7	55	17	NR
9	M	60	RAEB-1	1.0	4	7.6	46,XY[20]	ND	182	ND	1.6	149	33	NR
10	M	62	RAEB-1	1.0	4	8.0	46,XY[20]	U2AF1	210	347	2.8	131	11	NR
11	F	59	RAEB-1	1.0	4.5	8.5	46,XX[25]	ASXL1	227	462	2.57	78	142	CR
12	M	60	RAEB-1	1.5	7	8.5	46,xy,t(3;5)(q21;q31) [4]/46,xy[16]	ND	212	433	1.2	60	30	NR
13	M	54	RAEB-1	1.0	4	8.6	46,XY[20]	IDH2/STAG2/UPF3A	378	953	3.5	96	337	mCR
14	M	65	RARB-1	1.0	5.5	9.6	46,XY[20]	DNMT3A/GATA2/ SF3B1	96	1017	1.9	48	46	NR
15	M	70	RAEB-2	2.0	4	10.0	46,XY[20]	ND	175	841	1.8	94	384	CR
16	F	46	RAEB-2	2.0	6	11.8	46,XX[20]	DNMT3A	248	960	10	70	91	CR
17	F	63	RAEB-2	3.0	6.5	13.2	48,X,-X,der(7)t(7;11)(q13q11),+3mar,inc[2]/46,xx[8]	DNMT3A/ITIH3	165	785	2.2	144	55	CR
18	M	52	RAEB-2	3.0	9.5	13.5	44,XY,5q-,8q+, der(11), t(11;13) [12]	EZH2	287	ND	4.2	70	20	NR
19	F	70	RAEB-2	2.0	7	13.5	46,XX[20]	IDH1	152	1195	0.6	65	39	CR
20	M	79	RAEB-2	3.0	9.5	15.0	46,XY,t(5;12)(p14;p13) del(5)(q13),del(7) (q21),+8,-17,-21,+mar[25]	TP53	187	1480	1.5	74	13	NR
21	F	78	RAEB-2	2.0	6.5	15.5	46,XX[20]	ND	242	ND	1.5	67	24	CR
22	M	68	RAEB-2	2.5	7.5	15.5	47,XY,+11[13]	No	235	5981	1.2	74	31	CR
23	F	64	RAEB-2	3.0	8.5	16.0	45, XX, -7[22]/46,XX[3]	RUNX1	352	1253	8.3	76	7	NR
24	M	62	RAEB-2	2.0	5	17.4	46,XY[12]	ND	129	2108	2.5	109	43	NR
25	F	70	RAEB-2	2.0	6.5	18.0	46,XX,del(20) (q12)[25]	U2AF1/KIF20B	172	1022	1.3	77	15	NR
26	M	79	RAEB-2	2.0	5	19.5	46,XY[20]	ASXL1/TET2/STAG2	156	736	2	92	200	CR

Table 1 (continued)

No	Sex	Age	Diagnosis	IPSS score	IPSS-R	Blasts in BM (%)	Karyotype	Gene mutations	LDH (U/L)	Ferritin (ng/ml)	Blood counts			Response
											WBC (10^9/l)	Hgb (g/l)	Plt (10^9/l)	
27	F	63	RAEB-t	3.0	7	20.5	46,XX,der(16)t(1;16)(q21;q21), del(20)(q12)[20]	SRSF2/WT1	298	ND	8.3	67	95	NR
28	M	78	RAEB-t	2.5	5.5	21.0	46,*xy*,del(20)(q11.2) [20]	RUNX1/DNMT3A/SRSF2/WT1	260	16,544	1.2	48	102	NR
29	M	58	RAEB-t	2.5	5.5	24.5	46,XY[16]	IDH2	264	ND	2	81	65	NR
30	M	49	RAEB-t	3.0	8	26.0	46, XY, t(2;11)(p23;q24.3) [20]	RUNX1/SETBP	178	2886	1.0	45	40	NR
31	M	56	RAEB-t	2.5	5.5	27.0	46,XY[20]	ND	ND	ND	2.3	99	90	NR
32	M	71	RAEB-t	3.5	8.5	28.5	48,XY,der(3),-5, + 13, + mar2[6]/46,XY [1]	No	193	ND	3.1	82	50	NR
33	M	57	RAEB-t	2.5	5.5	29.0	46,XY[20]	BCOR/ITIH3	ND	29	2	88	150	PR

BM bone marrow, *WBC* white blood cells, *Hgb* hemoglobin, *Plt* platelet count, *LDH* lactate dehydrogenase, *ND* not detected, *CR* complete remission, *PR* partial remission, *NR* not response

was performed after the completion of one cycle of CHG therapy, consisted of a blood cell count, BM smear analyses, BM section analysis, and chromosome analysis. The treatment response was determined according to the IWG 2006 criteria for MDS (Cheson et al. 2006). The overall response rate (ORR) included CR, marrow CR (mCR), PR, and HI [including HI-neutrophil (HI-N), HI-erythrocyte (HI-E) and HI-platelet (HI-P)].

Evaluation of toxicity

The Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (Trotti et al. 2003) was used to evaluate the drug-induced toxicity in each patient. The evaluation consisted of a complete physical examination, blood cell counts (obtained every 3 days), evaluations of biochemical parameters (every week), and urine analysis (every week). Other appropriate laboratory tests were performed when needed. With respect to the hematologic toxicity evaluation, the majority of the patients had experienced leukocytopenia or thrombocytopenia before treatment. If a patient experienced leukocytopenia or thrombocytopenia higher than the National Cancer Institute (NCI) grade II during treatment, this event was recorded. All other adverse drug effects were recorded.

Statistical analysis

All of the included patients were considered in the statistical analysis. SPSS 19.0 software (SPSS Inc.; Chicago, IL, USA) was used for analyzing the data. The Kaplan–Meier method was used to estimate the survival of patients. The log-rank test was used to compare Kaplan–Meier survival estimates between different groups. The Pearson χ^2 or Fisher's exact was applied to compare the enumeration data between the groups. A two-tailed test was used in all the calculations. The limit of significance for all analyses was defined as $p < 0.05$.

Results

Patient characteristics

A total of 33 higher risk MDS patients, including 12 relapsed and 21 refractory to decitabine, were enrolled in this study. The detailed data for the 33 patients who received the CHG regimen are listed in Table 1. Twenty-five cases underwent next-generation target sequencing for 31 genes commonly mutated in MDS.

Response to CHG treatment

After one cycle of CHG therapy, 9 of the 33 patients (27.3%) achieved complete remission (CR), 2 (6.1%) achieved marrow CR (mCR), and 2 (6.1%) achieved partial remission (PR), resulting in an ORR of 39.4% (see Fig. 1a). Twenty-five cases underwent next-generation target sequencing of a 31-gene panel. The results showed that the CR rate was significantly higher in patients harboring fewer gene mutations (0–1) (55.6%) than in those harboring more gene mutations (more than one) (12.5%) ($p=0.021$) (see Table 2). Most CR patients harbored mutations in genes related to epigenetic regulation. Among the seven of nine patients who achieved CR (excepting 2 cases without detection), two cases harbored ASXL1 mutations, two had DNMT3A mutations, one had an IDH1 mutation, and another two had no gene mutation (see Fig. 1b). A higher CR rate was achieved in patients with a marrow blast percentage of 10–20% (58.3%) than in those with a blast < 10% (14.3%) or 20–30% (0) ($p=0.008$) (see Table 2). Neither the CR nor the ORR was different between the relapsed and refractory cases ($p=0.429$ and 0.278, respectively). Karyotype analysis was available in 33 patients, including 19 with a normal karyotype and 14 with an abnormal karyotype. The treatment response was not significantly different among the different karyotype groups ($p=0.214$), although there was a trend toward a higher CR rate in the normal karyotype group. Neither serum LDH nor ferritin levels affected the CR or ORR (see Tables 2, 3).

Overall survival

Median overall survival (OS) was calculated from the beginning of CHG therapy to death or the end of follow-up. Among the 33 patients evaluated, the median OS was 7.0 months (1–48 months) (Fig. 2a). There was no significant difference in OS between relapsed and refractory cases (8.5 M vs. 6.0 M, respectively, $p=0.602$) (see Fig. 2f). Patients who achieved a response had significantly longer survival times than were found in those without a response (21.0 M vs. 4.0 M, $p<0.0001$) (Fig. 2b). The median OS rates of the patients with < 10%, 10–20%, and > 20% blasts in the bone marrow were 11, 10, and 3.5 months, respectively ($p=0.040$) (Fig. 2c). High lactate dehydrogenase (LDH) levels in serum was an adverse factor for OS (12.0 M in the normal LDH group vs. 4.5 M in the high LDH group, $p=0.040$) (Fig. 2d). There was no significant difference in OS among patients with good, intermediate, or poor karyotypes (8, 5 and 3 months, respectively ($p=0.164$) (Fig. 2e). Patients with fewer mutated genes showed a trend toward longer survival times, although this trend was no significant (10.0 M in the 0–1 mutation gene group vs. 5.5 M in the more than one mutated gene group, $p=0.131$) (Fig. 2g). Ferritin levels did not significantly affect OS in the enrolled patients (Fig. 2h).

Toxicities

Among the 33 patients who received the CHG regimen, two patients died within 1 month after the initial therapy. One patient died of pulmonary hemorrhage due to heavy thrombocytopenia. Another patient died of intracranial hemorrhage. Both of these patients had a significantly low platelet count of less than 10×10^9 cells/L before CHG therapy. Marrow suppression is the major toxicity of this regimen. A total of 11 (33.3%) patients had absolute neutrophil counts (ANC) lower than 0.5×10^9 cells/L, and 10 (30.3%) patients had platelet counts lower than 20×10^9 cells/L during the induction therapy. The median time for the recovery of ANC ($>0.5\times10^9$ cells/L) was 10 days (4–22 days), while that of platelet recovery ($>50\times10^9$ cells/L) was 16 days (5–26 days). Four cases (12.1%) suffered from pneumonia, and five

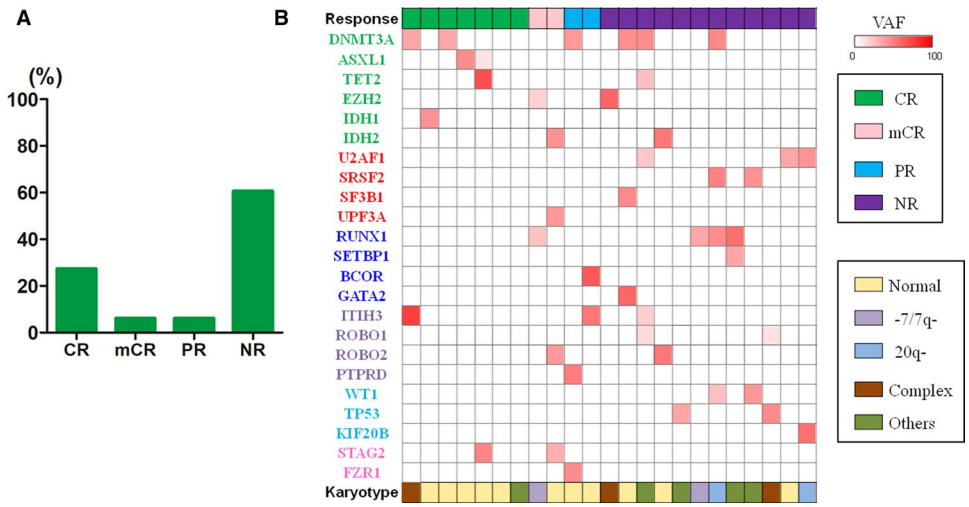

Fig. 1 Treatment response of CHG in decitabine-relapsed/-refractory patients and relationships between gene mutations/chromosomal abnormalities and responses. **a** The treatment response of all enrolled patients. Next-generation targeted 31-gene-panel sequencing results were available for 23 CHG-treated decitabine-relapsed/-refractory patients. The variant allele frequencies (VAF) of the mutated genes are indicated by a color gradient. The responses and karyotypes of the patients are shown in the indicated colors (**b**)

Table 2 Factors affect treatment response to CHG regimen

Disease status	No. of patients	CR, *n* (%)	*P* value	OR, *n* (%)	*P* value
Decitabine relapse or refractory			0.429		0.278
Refractory	21	7 (33.3)		10 (47.6)	
Relapse	12	2 (16.7)		3 (25.0)	
Blast (%) in BM			0.008		0.203
< 10%	14	2 (14.3)		5 (35.7)	
10–20%	12	7 (58.3)		7 (58.3)	
> 20%	7	0 (0)		1 (14.3)	
Karyotype			0.241		0.158
Normal	19	7 (36.8)		10 (52.6)	
Abnormal	14	2 (14.3)		3 (21.4)	
Somatic gene mutation number			0.021		0.434
0 or 1	9	5 (55.6)		5 (55.6)	
≥ 2	16	2 (12.5)		6 (37.5)	
Serum LDH			0.704		0.879
Normal	18	6 (33.3)		7 (38.9)	
High	12	3 (25.0)		5 (41.7)	
Ferritin, *n* (%)			0.218		0.462
< 1000 ng/ml	11	5 (45.5)		6 (54.5)	
≥ 1000 ng/ml	15	3 (20.0)		6 (40.0)	

Good = normal, -Y alone, del (5q) alone or del (20q) alone; Poor = complex (≥ 3 abnormalities), chromosome 7 anomalies; intermediate = other abnormalities

BM bone marrow, *CR* complete remission, *OR* overall remission, *LDH* lactate dehydrogenase

patients (15.2%) experienced neutropenic fever without the presence of microorganisms or sites of infection. Nonhematological toxicities were comparatively light. Grade 1–2 nausea/vomiting occurred in four patients (12.1%), and toxicity in the heart, liver, and kidney was not observed.

Discussion

Although HMA (including decitabine or azacitidine) is effective for the treatment of higher risk MDS (Fenaux et al. 2009; Kantarjianet al 2006), there is still a significant proportion of patients with MDS who are refractory to or relapsed after HMA. Until now, there were limited therapeutic options for these patients, who are also not transplant candidates. This population represents a challenging cohort of patients and constitutes an important area of clinical research. According to the NCCN guidelines, for higher risk MDS patients who are not transplant candidates, clinical trials or supportive care will be recommended if he or she fails to respond to HMA. The CHG regimen has been reported to be effective and safe in initially treated higher risk MDS patients in our and other centers' previous studies performed in China (Wu et al. 2009, 2011; Xie et al. 2016). To further investigate the effect and toxicity of the CHG regimen in decitabine-refractory or relapsed higher risk MDS patients, in the current study, a total of 33 cases were enrolled. Notably, among the 12 decitabine-relapsed and 21 decitabine-refractory cases, nine (27.3%) achieved CR with an ORR of 39.4% (13 of 33). Although this study involved a small number of patients, these results indicate that there may be no cross resistance between the CHG regimen and decitabine, and this may be due to the different mechanisms involved in the two regimens. The therapeutic property of low-dose decitabine has been generally attributed to its ability to facilitate promoter demethylation and reactivate

Table 3 Adverse events of CHG therapy

Adverse events	CHG-treated patients (*n* = 33)
Neutropenia, grade 3–4, *n* (%)	15 (45.5)
Thrombocytopenia, grade 3–4, *n* (%)	16 (48.5)
Infection, *n* (%)	9 (27.3)
Hemorrhage, *n* (%)	2 (0.6)
Hepatic, *n*	0
Renal, *n*	0
Cardiac, *n*	0
Nausea/vomiting, grade 1–2, *n* (%)	4 (12.1)
Median duration of neutropenia, days	10 (4–22)
Median duration of thrombocytopenia, days	16 (5–26)

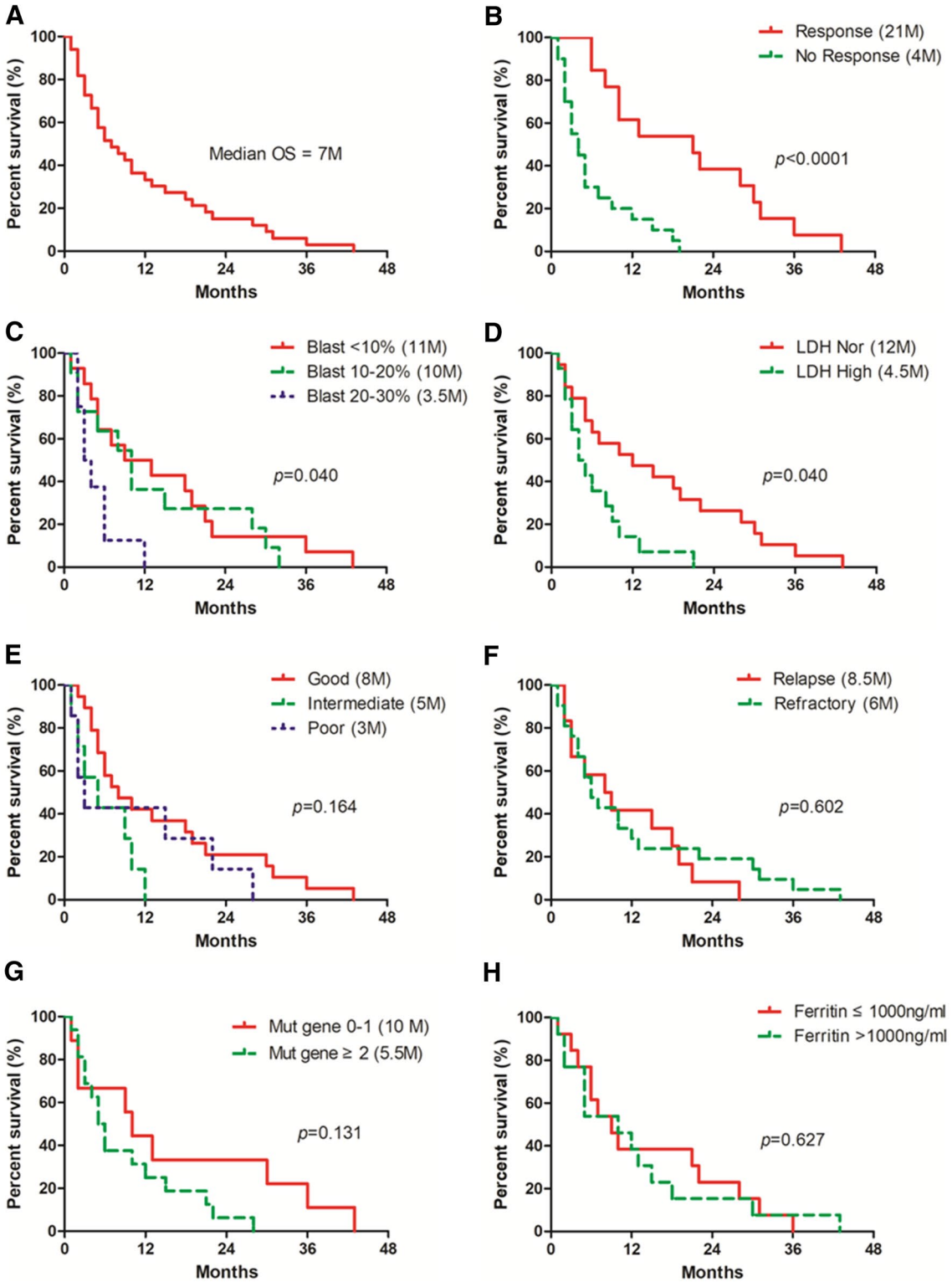

Fig. 2 Overall survival (OS) analysis of the enrolled patients. The OS of all enrolled patients (**a**). Patients with a response had significantly longer survival times than were found in those without a response (**b**). OS among patients with different blast percentages in the BM (**c**). Patients with high serum LDH levels had shorter survival times than were found in those with normal LDH levels (**d**). OS was not significantly different among patients with different karyotypes (**e**), those who were relapsed or refractory (**f**), those with different mutated gene numbers (**g**), and those with different ferritin levels (**h**)

silenced tumor suppressor genes (Issa and Kantarjian 2009), a mechanism that is different from that of the CHG regimen (Feldman et al. 1992; Jie et al. 2007; Zhou et al. 1990). Based on these differences in mechanisms, CHG provides a therapeutic option for patients with decitabine resistance. Furthermore, CHG was relatively safe and well tolerated in decitabine-refractory/relapsed patients.

Target gene-panel sequencing showed that the CR rate was higher in patients with fewer gene mutations (0–1) (55.6%) than in those harboring more gene mutations (more than one) (12.5%) ($p=0.021$) in HMA-relapsed/-refractory patients treated with the CHG regimen. Compared to those with abnormal karyotypes, patient with normal karyotypes showed a trend toward a higher CR rate, although this relationship was not significant. (36.8% vs. 14.3%, $p=0.241$, Table 2, Fig. 1b). These results indicate that the CHG regimen may be effective in patients with a relatively stable cytogenetic status. However, randomized-controlled studies with large samples will be needed to confirm our preliminary findings. As shown in previous studies (Li et al. 2013), decitabine resulted in a higher CR rate in patients with poor karyotypes, indicating that decitabine might be more effective on MDS cells harboring relatively unstable cytogenetic changes, although the mechanism remains unknown. Therefore, in patients with relatively stable genomes (i.e., those with normal karyotypes or fewer gene mutations), the CHG regimen is more likely to be effective after resistance to decitabine. For patients with genomic instability (i.e., poorer karyotypes or more mutations), the CHG regimen is not a good choice. This latter population may need to select other targeted agents.

Although the median survival time of all enrolled patients was only 7 months, the median survival time of the responding patients was 21 months, which was significantly longer than that of the nonresponding cases, suggesting that the acquisition of therapeutic response is still a necessary prerequisite for prolonging survival. However, CR patients still had recurrence problems, with a median relapse time of 8 months. Further clinical studies are needed to find effective treatments for patients with CHG recurrence. Although a higher serum LDH level was not related to the response of the CHG regimen, it was demonstrated to be a poor prognostic factor for OS. This result is consistent with a previous report showing that the serum LDH levels can be used as a predictor of prognosis in MDS patients (Germing et al. 2005) and our previous report of the effects of the CHG regimen in elderly MDS patients (Wu et al. 2011).

In summary, CHG is an effective and relatively safe treatment for patients with decitabine relapse or refractory high-risk MDS. Follow-up with an enlarged sample and randomized-controlled studies are needed to confirm our preliminary findings.

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Compliance with ethical standards

Conflict of interest Lingyun Wu has received research grants from National Science Foundation of China and declares that she has no conflict of interest. Cai Xiu, Xiao Li, Feng Xu, Qi He, Zheng Zhang, Dong Wu, Luxi Song, Jiying Su, Liyu Zhou, Youshan Zhao, Ying Tao, and Chunkang Chang 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 written consent was obtained from all individual participants included in the study.

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