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Research paper

Effect of granulocyte colony-stimulating factor priming combined with low-dose cytarabine and homoharringtonine in higher risk myelodysplastic syndrome patients

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ABSTRACT

As sensitization of leukemia cells with granulocyte colony-stimulating factor (G-CSF) can enhance the cytotoxicity of chemotherapy in myeloid malignancies, a pilot study was conducted in order to evaluate the effect of G-CSF priming combined with low-dose chemotherapy in patients with higher risk myelodysplastic syndrome (MDS). The regimen, G-HA, consisted of cytarabine (Ara-C) 7.5 mg/m^2/12 h by subcutaneous injection, days 1–14, homoharringtonine (HHT) 1.5 mg/m^2/day by intravenous continuous infusion, days 1–14, and G-CSF 150 mg/m^2/day by subcutaneous injection, days 0–14. 56 patients were enrolled, 34 patients (61%, 95% confidence interval: 51.44–70.56%) achieved complete remission (CR). Median duration of neutropenia was 7 days (ranging from 2 to 16 days). Grade 1–2 nonhematologic toxicities were documented, including nausea and vomiting (5%), liver function abnormality (5%), and heart function abnormality (2%). No central nervous system toxicity was found. Mortality within the first 4 weeks was 4%. The G-HA regimen is effective in remission induction for higher risk MDS patients and well tolerated due to the acceptable toxicity in maintenance therapy in the patients who cannot undergo Hematopoietic cell transplantation (HCT).

1. Introduction

MDS is a heterogeneous clonal hematopoietic stem cell disorder characterized by morphologic dysplasia, ineffective hematopoiesis, and bone marrow failure. It is a disease primarily of the elderly although younger patients are also at risk, with 30% of all cases progressing to acute myeloid leukemia (AML) [1]. According to the widely used International Prognostic Scoring System (IPSS), the higher risk groups, including IPSS intermediate-2 and high, have median survival times of 1.2 years and 0.4 years, respectively. 5-year survival rates of these two groups were 7% and 0%, respectively [2].

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative treatment option for patients with MDS. However, most MDS patients were 60–70 years old, a population which may have risk of increased morbidities during transplantation treatment and a relative malfunction of body or important organisms due to aging. Therefore, such patients are poor candidates for hematopoietic stem cell transplantation. As another treatment choice, intensity induction chemotherapy also has an increasing risk of treatment-related mortality and morbidity, and usually is reserved for younger patients and those with good performance status.

Despite recent advances in the treatment of MDS and the availability of three agents approved by the US Food and Drug Administration (FDA), including azacitidine, decitabine and lenalidomide, few patients with intermediate −2 or high risk groups would achieve remission and their overall survival rate remains poor. Given the highly complex pathogenesis of MDS and the aggressive clinical phenotype in patients with advanced disease, multi-agent combination therapy may be more effective than single agents in this population.

G-CSF may increase the fraction of leukemic blasts in the S-phase, thereby enhancing the cytotoxicity of S-phase-active chemotherapeutic agents such as cytarabine, a conception of G-CSF priming was raised by Yamada and most widely used as GAA(G-CSF, Ara-C, AcR) [3]. But the cardiac toxicity of caclarubicin has limited its application in the treatment of most elderly MDS patients.

Homoharringtonine (HHT) is an ester of the alkaloid cephalotaxine isolated from the Cephalotaxus species, an evergreen tree ubiquitous to China. HHT can induce apoptosis in myeloid leukemia

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Table 1
Base-baseline characteristics and remission induction results.

Characteristics	CR	X^2	P value
Age (median and range)		0.774	0.379
<60 years	18/27(67)[a]		
≥60years	16/29(55)		
FAB classification		0.186	0.666
RAEB	19/30(63)		
RAEB-T	15/26(58)		
IPSS		1.194	0.275
Intermediate-2	22/33(67)		
High-risk	12/23(52)		
Karyotype		0.580	0.748
Good prognosis	9/14(64)		
Intermediate prognosis	13/20(65)		
Poor prognosis	12/22(55)		

[a] Values in parentheses indicate percentages.

cells and has been used successfully in treatment of acute and chronic myeloid leukemia for more than 40 years in China. Moreover, the combination regimen of HHT and Ara-C has synergistic effect both in vivo an in vitro [4,5].

Based on the evidence mentioned above, we administered G-CSF to AML patients with either refractory or relapse in 2003, in combination with low-dose Ara-C and HHT treatment and reported a response rate of 64% [6]. This study prompted us to conduct a trial of the combination therapy in MDS group of higher risk which is reported in the current study. In this study, we reported the toxicity and response to the combined regimen in 56 patients with high-risk MDS at our institution. Our results confirm the high response rate and acceptable toxicity of this regimen in high-risk subgroup of MDS patients.

2. Patients and methods

2.1. Patients

Between December 2005 and March 2013, 56 patients diagnosed with higher risk MDS were admitted to our hospital and enrolled in the clinical trial. 38 were male and 18 were female, with a median age of 57 years ranging from 19 to 75 years. All the patients fulfilled the following criteria: the diagnosis of higher risk MDS was established according to the FAB classification system [7] and IPSS. 30 were with MDS-RAEB, 26 were with MDS-RAEB-t; 33 were in the intermediate-2 risk group and 23 were in the high-risk group. Karyotypic findings were classified according to Greenberg et al. for patients with MDS [8]. Peripheral blood count, bone marrow aspirate and biopsy, cytogenetic analysis performed before therapy; informed consent form signed. The study was conducted in accordance with the principles of the Declaration of Helsinki. Main patient characteristics are shown in Table 1.

2.2. Combination therapy

The regimen consisted of cytarabine (7.5 mg/m^2/12 h, subcutaneously, on days 1–14), homoharringtonine (1.5 mg/m^2/day, intravenously, on days 1–14), and G-CSF administered 1 day before chemotherapy (150ug/m^2/day, subcutaneously, on days 0–14). The administration of G-CSF was postponed or interrupted in the event of leukocytosis (leukocytes $\geq 30 \times 10^9$/l) until the white blood cell count fell $<20 \times 10^9$/l. Complete blood count and bone marrow aspirate were performed to assess the response two weeks after each treatment cycles. If the bone marrow showed residual disease, the patient was given a second treatment cycle. For those who showed no response after two courses, other therapies were chosen. For those achieved CR, an intensification or consolidation therapy was given according to their age and performance status. Antibiotic or supportive treatment was given according regular guideline. All patients underwent assessments of full clinical examination before, during and after the therapy. ECG was required before and after each cycle, as the same as liver and kidney function test. All the indexes monitoring was more frequent if necessary. Blood counts were obtained weekly during the therapy. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) version 2010.

Table 2
Non-hematological toxicity.

	WHO grade	
	Grade 2 or lower (%)	Grade 3 or higher (%)
Nausea/vomiting	5	2
Skin	2	–
Mucositis	2	–
Diarrhoea	–	–
Renal	1	–
Liver	5	–
Pulmonary	2	2
Cardiac	2	–
Neurological	–	–

2.3. Response criteria

Responses were assessed according to the 2006 international working group (IWG) criteria [9]. The primary endpoint was complete response (CR) which was defined as <5% myeloblasts with and peripheral blood evaluation showing hemoglobin >11 g/l, neutrophils 1500/mm^3 or more without growth factors and platelets 100,000/mm^3 or more without growth factors. The secondary endpoint was the overall survival. Failure of the treatment was defined as death during treatment or disease progression characterized by worsening of cytopenias, increased percentage of bone marrow blasts or progression to a more advanced MDS subtype. Early death was death which happened within 4 weeks of starting treatment (Table 2).

2.4. Statistical analysis

Numerical data were described using means or medians and percentiles as appropriate. Comparisons of numerical values across groups were made using analysis of variance. Analysis was performed using SPSS 12.0. All tests were two-sided and P values less than 0.05 were considered statistically. OS was defined as the time from randomization until death from any cause. Surviving patients were censored at last follow-up. An OS curve at 2 years was generated using Kaplan–Meier methods.

3. Results

3.1. Patients and cytogenetic characteristic

Of the 56 patients with confirmed diagnosis of higher risk MDS, 50 had primary MDS and 6 had secondary MDS, and 54 were newly diagnosed, 2 had received other therapy. Baseline karyotype was available for all patients. 14 patents (25%) had good, 20 (36%) had intermediate and 22 (40%) had poor-risk cytogenetics according to IPSS criteria. Eastern cooperative oncology group performance status was estimated at 0, 1, 2 and 3 in 21 (38%), 17 (30%) patients, 15 (27%) and 3 (5%) patients, respectively.

3.2. Response and outcome

After the first induction course, 30 patients (54%) achieved CR (95% CI, 44.23–63.77%). 26 out of 56 patients did not achieve