RESEARCH ARTICLE

Decitabine in the Treatment of Acute Myeloid Leukemia and Myelodysplastic Syndromes, Which Combined with Complex Karyotype Respectively

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Abstract

Background: We conducted a study exploring the clinical safety and efficacy of decitabine in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), combined with a complex karyotype. Materials and Methods: From April 2009 to September 2013, a total of 35 patients with AML/MDS combined with a complex karyotype diagnosed in the First Affiliated Hospital of Soochow University were included for retrospective analysis. All patients were treated with decitabine alone (20mg/m^2 daily for 5 days) or combination AAG chemotherapy (Acla 20mg qod*4d, Ara-C 10mg/m^2 q12h*7d, G-CSF 300μg qd, the dose of G-CSF adjusted to the amount in blood routinely). Results: In 35 patients, 15 exhibited a complete response (CR), and 6 a partial response (PR), the overall response rate (CR+PR) being 60% (21 of 35). Median disease-free survival was 18 months and overall survival was 14 months. In the 15 MDS patients with a complex karyotype, the CR rate was 53.3% (8 of 15); in 20 AML patients with complex karyotype, the overall response rate was 65% (13 of 20). The response rate of decitabine alone (22 cases) was 56.5% (13 of 22), while in the combination chemotherapy group (13 cases), the effective rate was 61.5% (8 of 13)(P>0.05). There are 15 patients with chromosome 7 aberration, after treatment with decitabine, 7 CR, 3 PR, overall response rate was 66.7% (10 of 15). Of 18 patients with 3 to 5 kinds of chromosomal abnormalities, 66.7% demonstrated a response; of 17 with more than 5 chromosomal abnormalities, 52.9% had a response. In the total of 35 patients, with one course (23 patients) and ≥two courses (12 patients), the overall response rate was 40.9% and 92.3% (P<0.05). Grade III to IV hematological toxicity was observed in 27 cases (75%). Grade III to IV infections were clinically documented in 7 (20%). Grades I to II non-hematological toxicity were infections (18 patients), haematuria (2 patients), and bleeding (3 patients). With follow-up until September 2013, 7 patients were surviving, 18 had died and 10 were lost to follow-up. In the 6 cases who underwent allogeneic hematopoietic stem cell transplantation (HSCT) all were still relapse-free survivors. Conclusions: Decitabine alone or combination with AAG can improve outcome of AML/MDS with a complex karyotype, there being no significant difference decitabine in inducing remission rates in patients with different karyotype. Increasing the number of courses can improve efficiency. This approach with fewer treatment side effects in patients with a better tolerance should be employed in order to create an improved subsequent chance for HSCT.

Keywords: Decitabine - complex karyotype - myelodysplastic syndrome - acute myeloid leukemia

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Introduction

Complex karyotype defined as more than or equal to 3 independent chromosomal abnormalities. The prognosis of acute myeloid leukemia (AML) patients can be grouped three categories (i.e. favorable, intermediate or unfavorable) according to the abnormal of cytogenetic and molecular genetics adopted by the standards of Southwest Oncology Group (SWOG) in 2000 (Slovak et al., 2000). Complex karyotype AML belongs to unfavorable category, this category of patients characterized by a low overall response rate and easy to relapse after clinical treatment (Yang et al., 2012;Wawrzyniak et al., 2013). Clonal abnormalities were detected in about 40%~70% myelodysplastic syndromes (MDS) patients (Solé et al., 2000). MDS was grouped low-risk, intermediate-risk and high-risk category based on cytogenetic aberrations determined by international prognostic scoring system (IPSS). The high-risk category includes patients with complex karyotypes whose imply an unfavorable outcome, a shorter median overall survival (OS), only 3 months, and propensity toward malignant transformation.

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Recent year, we apply decitabine induction chemotherapy alone or combination with other chemotherapeutic agents have been employed to treat AML/MDS patients with complex karyotype. Meanwhile, the clinical safety and efficacy were evaluated, the results of our study as follows.

Materials and Methods

Patient characteristics

From 2009 to 2013, 35 adult patients (26 males, 9 females) of AML/MDS combined with complex karyotype from our hospital were included for study, the diagnosis was base on bone marrow aspirate and MICM (Morphology, Immunology, Cytogenetics, Molecular). the median age was 43.3 years (range 3~72 years).

Diagnosis criteria

MDS is based on Vienna criteria (2006) and the World Health Organization (WHO, 2008) classification criteria, the diagnosis of AML according to the WHO diagnosis and classification criteria. 15 patients with MDS, among them 9 intermediate-risk-2 and 6 high-risk (1 RCUD, 5 RCMD, 4 RAEB-I, 5 RAEB-II); 20 patients with AML (8 MDS transformated, 9 relapsed or refractory AML, 2 BP-CML, 1 MPD-AML). The characteristics of 35 AML/MDS patients with complex karyotype are shown in Table 1.

Treatment

Decitabine is produced by company of Pharmachemie B.V. (Netherlands) and provided by Xi An Janssen company (China). All subjects were treated with decitabine alone (22 patients) compared to combination with AAG chemotherapy (13 patients). 22 patients were treated with decitabine alone 20mg/m^2 daily for 5 days, 13 other patients were treated with decitabine (20 mg/m^2/day for 5days) combination AAG (ACR 20mg,qod*4d, Ara-C 10mg/m^2, qd*7d, G-CSF 300μg daily, the dose of G-CSF adjust to the amount of blood routine). There are 9 patients received hematopoietic stem cell transplantation after treated by decitabine. Among them, 5 patients received the allogeneic hematopoietic stem cell transplantation (allo-HSCT) from HLA completely matched compatriot, 2 patients received unrelated hematopoietic stem cell transplantation (HLA completely matched) and 2 patients received the haploid-HSCT.

Adverse events of decitabine

Toxicity was graded according to WHO criteria. Liver and kidney function attached to routine blood were detected regularly during the period of chemotherapy. We take measures to therapy complications caused by bone marrow inhibition after the treatment of decitabine, such as component blood infusion, granulocyte-colony stimulating factors (G-CSF) and thromboietin (TPO). If the infection occurs, antibiotics must be used immediately.

Statistical analysis

SAS 9.2 software package was used to perform χ^2 test Fisher's exact probability and survival analysis. Patient characteristics were compared using the Wilcoxon rank-sum test for continuous data such as age and leukocyte count, and the chi-square test or Fisher's exact test was used for categorical data such as the degree of karyotypic abnormality. The duration of overall survival (OS) was calculated from the beginning of induction chemotherapy to the date of the last follow-up or death from any cause. Disease-free survival (DFS) was calculated from date of CR to relapse, death in remission or the last visit. Probabilities of OS and DFS rates were estimated according to the Kaplan and Meier method and compared by the log-rank test

Criteria of response

Responses were assessed using International Working Group criteria (Cheson et al., 2003; Cheson et al., 2006). A complete remission (CR) required normalization of peripheral blood counts with neutrophils≥1.0×10^9/L and platelets≥100×10^9/L and bone marrow with ≤5% blasts. A partial remission (PR) required all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5%~25% in the bone marrow aspirate. A no response (NR) required not to achieve at least PR, but no evidence of progression for>8 wks. cytogenetic complete response defined as disappearance of the chromosomal abnormality without appearance of new clones.

Results

Response to remission induction chemotherapy

A total of 15 of 35 (42.85%) patients achieved CR, 6 PR, overall response rate (CR+PR) was 60% (21 of 35). variables (sex, leukocyte count, blast count, duration of agranulocytosis) had no correlation with the results of remission induction (Table 2). The median number of courses was 3 cycles, the average courses was 1.9. Analysis of 15 MDS patients with complex karyotype received the treatment of decitabine, 8 patients achieved CR, 7 NR, the CR rate was 53.3%(8 of 15); 20 AML patients with complex karyotype treated with decitabine were also analysed. 7 CR, 6 PR, 7 NR, overall response rate was 65% (13 of 20) (Table 3).

Group of decitabine alone compare with combined AAG

The CR+PR of decitabine alone (22 cases) was 59.0%, to the combination group (13 cases), the CR+PR rate was 61.5% (Table 3). The difference was not statistically

Table 1. Patients Characteristics

Characteristic	No.of MDS (n=15)	No.of AML (n=21)
Sex		
Male, no.subjects (%)	13(86.9%)	13(61.9%)
Female, no.subjects (%)	2(13.3%)	8(38.1%)
Median age, y (range)	44.1(31~72)	43.6(3~69)
Diagnosis, MICM (no.subjects)	MDS-RCUD(1)	M0(2)
	MDS-RCMD(5)	M2(5)
	MDS-RAEB-I(4)	M4(3)
	MDS-RAEB-II(5)	M5(4)
		M6(2)
		unknown(5)

significant (P>0.05).

Efficacy of the patients with chromosome 7 aberration

There are 15 patients with chromosome 7 aberration. After treatment with decitabine, 7 CR, 3 PR, overall response rate was 66.7% (Table 3).

The degree of karyotypic abnormality and response

18 patients with 3 to 5 unrelated chromosomal abnormality, 8 patients had a CR, 4 patient had a PR, 6 patient had a NR, 66.7% patients had a response; 17 with more than 5 unrelated chromosomal abnormality, 7 patients had a CR, 2 patients had a PR, 8 patients had a NR, and 52.9% had a response (Table 3). The difference was not statistically significant (P>0.05).

The relationship between course of treatment and efficacy

A total of 35 patients, one course of therapy was received by 22 patients, two was received by 3 patients, three was received by 5 patients, four was received by 3 patients, five was received by 1 patient and 1 patients received six courses of therapy. the average courses was 2.6 (range 1~6 courses). 22 of 35 patients those received one courses of decitabine which resulted in a CR in 22.7% (5 of 22 patients), a PR in 18.1% (4 of 22), a NR in 54.5% (12 of 22), and overall response rate was 40.9% (9 of 22). At least two courses of treatment was received by 13 patients, and the results achieved a CR in 76.9% (10 of 13), a PR in 15.3% (2 of 13), a NR in 33.3% (1 of 13), the overall response rate was 92.3% (Table 3). The difference was statistically significant (P<0.05).

Cytogenetic response

In total, 15 patients had a CR after the treatment of decetabine, the chromosome achieved to normal in 7 patients, The complexity of karyotype was reduced in 2 patients. Cytogenetics in 3 cases were no remission, 3 cases did not review the chromosome after the treatment. the rates of cytogenetic remission was 58.3% (7 of 12 patients). In 35 patients, 26 patients review the chromosome after the treatment of decetabine, the chromosome achieved to normal in 12 patients, among them, 7 patients had a hematological CR, 3 patient PR, 2 patients had NR, overall response rate was 83.3% (10 of 12 patients).

Toxicity

Side effects were evaluated in all 35 patients. Common adverse events were fever and infection results from bone marrow suppression. Grade III to IV hematological toxicity was observed in 27 cases (75%). Grade III to IV infections were clinically documented in 8 patients (22.2%), Grade I to II non-hematological toxicity contain infections (18 of 36, 50%), haematuria (2 of 36, 5.55%), bleeding (3 of 36, 8.33%). These patients were treated with G-CSF, antibiotics, infusion of red blood cells and fresh platelets and so on. 35 patients were successfully discharged from bone marrow suppression.

Survival

35 patients treated with decetabine who underwent follow-up at the end of the study, 7 patients were survival, 19 deaths, 9 were lost to follow-up. Among the 7 surviving patients, 1 patient was diagnosed MDS-RCMD, although he needed red blood cell transfusion once a week, the

Table 3. Treatment Response

Group	CR	PR	NR	CR and PR	*P*-value
Therapeutic Efficacy					
Complex karyotype (n=35)	15	6	14	0.6	
Chemotherapy					
decitabine alone (n=22)	11	2	9	0.59	
combination (n=13)	4	4	5	0.615	>0.05
Chromosome 7 aberration					
with (n=15)	7	3	5	0.667	
without (n=20)	8	3	9	0.55	>0.05
The degree of karyotypic abnormality					
3~5 unrelated abn (n=18)	8	4	6	0.667	
≥5 unrelated abn (n=17)	7	2	8	0.529	>0.05
Course of treatment					
1 course (n=22)	5	4	12	0.409	
≥2 courses (n=13)	10	2	1	0.923	<0.05

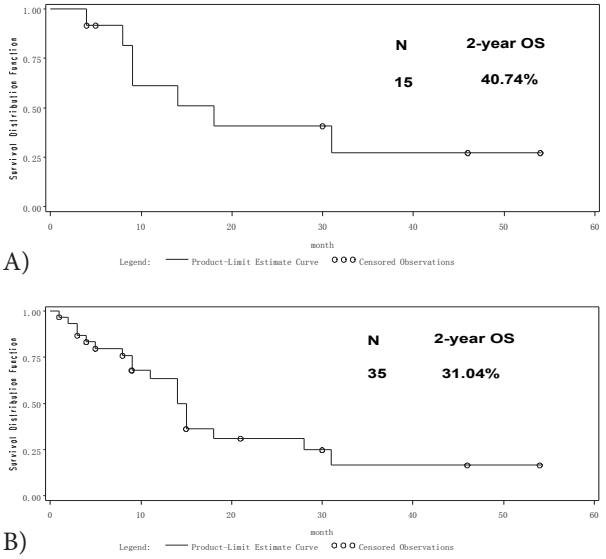

Figure 1. Overall Survival (a) in 35 AML/MDS Patients Treated with Decitabine and Disease-free Survival (b) in 15 Patients who Achieved Complete Remission

Table 2. Effect of Clinical Characteristics on Response in Remission Induction Therapy

Disease status	Complete remission	No response	*P*-value
Number of patients	15	20	
Median age (years)	42.5(27~64)	43.9 (3~72)	0.5371
Leukocyte count (×10E9/L)	7.74(1.09~46.19)	15.30 (0.6~172.2)	0.6851
Blast in bone marrow (%)	30.1(4.5~77.5)	38 (1~75)	0.302
Duration of agranulocytosis (d)	11(0~31)	22 (0~66)	0.0684

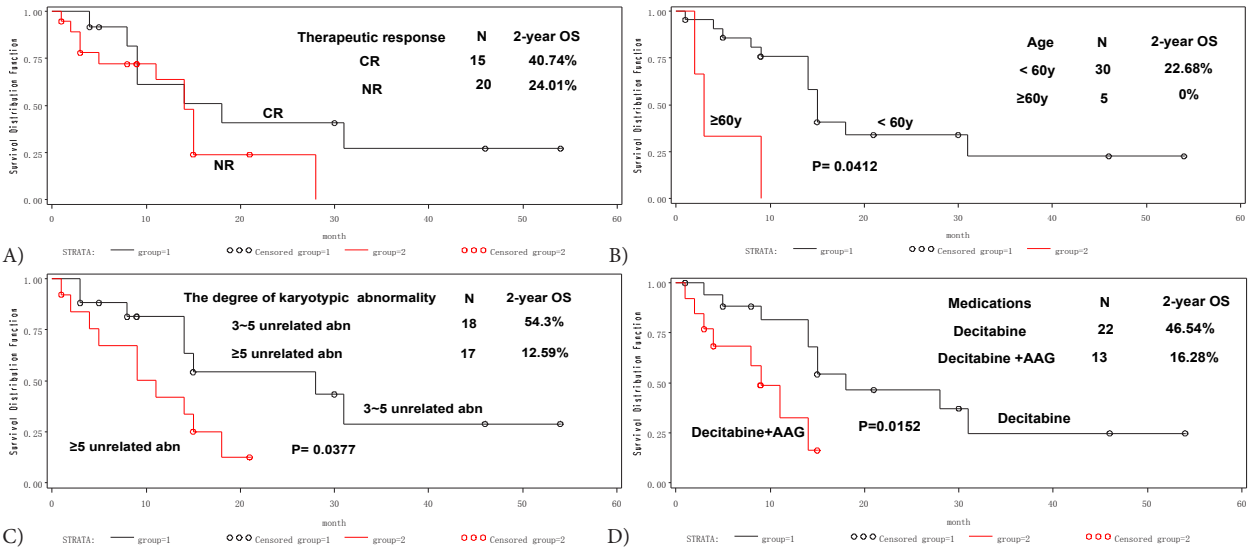

Figure 2. Overall Survival in AML/MDS Patients According to Response to Induction Therapy (a), Age (b), the Degree of Karyotypic Abnormality (c) and Medications(d)

result of bone marrow aspirate showed not progress many times. 6 cases underwent HSCT in appropriate condition and they still relapse-free survival now. Survival analysis show: The median duration of DFS was 18 months (range 4~54 months) and the median OS was 14 months (range 1~54months). Two-year OS and DFS rates were 31.04% and 40.74%, respectively. (Figure 1). There were significant correlations of two-year OS with age, the degree of karyotypic abnormality and medications, but not with response to induction therapy, presenting leukocyte count and sex. (Figure 2).

Discussion

The aberrant DNA methylation play an important role during the malignant occurrence and transformation. Decitabine (5-Aza-2'-deoxycytidine) is a hypomethylating agent which inhibit the DNA methyltransferase. Decitabine has been approved by the USA Food and Drug Administration (FDA) for the treatment of the MDS in 2006. And it also yielded promising results in patients with other haematological disease such as AML and chronic myeloid leukemia (CML).

AML/MDS with complex karyotypes were categorized into unfavorable groups. This group of patients characterized by a lower CR rate, a highr rate of relapse and a significantly short overall survival (OS). U.S. Cancer and Leukemia Group B (CALGB) 8461 studied the cytogenetics of 1213 adults AML patients achieved CR, the results showed a significantly worse outcome for patients with complex karyotypes, because the CR rate, cumulative relapse frequencies for 5 years (CIR) and overall survival at 5 years rate (OS) was 32%, 92% and 5% respectively, which was lower in intermediate groups(67%, 67% and 24%, respectively) and favorable groups(88%, 54%, 55%, respectively) (Byrd et al., 2002). Patients with MDS defined as unfavorable groups or association with chromosome 5 and 7 aberrations (without 5q-) treated with decitabine, the rate of response and survival was better than traditional chemotherapy arms eventually (Ravandi et al., 2009). Many studies have shown that decitabine triphosphate can incorporate into replicating DNA and irreversible deplete the DNA methyltransferase through covalent bonding. The methylation-associated silent tumor suppressor genes were reactivated by demethylation (Shin et al., 2013). So far, decitabine was used for intermediate-risk and high-risk MDS patients those risk factors were base on the International Prognostic Scoring System (IPSS), refractory or relapsed MDS, AML transformated from MDS and elderly leukemia (Joeckel et al., 2012).

35 AML/MDS patients with complex karyotypes were enrolled our study, the result showed overall response rate was 60%. 13 of 20 AML patients achieved remission (CR and PR) (65%), 8 of 15 MDS patients achieved remission (53.3%), which have a higher efficacy compare with those reported before (Kantarjian et al., 2007). The possible reasons result in a higher CR rate as follows: (1). lower dose schedules of decitabine (20mg/m^2 for 5days) or combination with AAG have higher efficacy in patients. The U.S. D-0007 Study Group found that the arm of 20mg/m^2 on days 1-5 is the best choice (Kantarjian et al., 2007), that is to say, the dose of decitabine was 20 mg/m^2 per day for 5 consecutive days, as a 1 h continuous infusion. (2). We studied patients with complex karyotype who diagnosed with high-risk category of AML/MDS; several clinical trials have confirmed that decitabine showed high overall response rate in patients with MDS grouped intermediate-risk and high-risk category (range 30% to 73%) (Steensma et al., 2009; Kantarjian et al., 2007; Lübbert et al., 2011), which consistent with our results. (3). A total of 15 of the 35 patients were treated with decitabine more than two course of treatment (range 2 to 6 courses). Previous study showed that with the number of course increased, a higher overall response rate was acquired (Kantarjian et al., 2007). Our study showed significantly higher overall response rate for patients receiving more than two courses compare with one course (92.3% versus 40.9%), and the results showed statistically significant, $P<0.05$.

Jahns-Streubel et al indicated that leukaemic blasts

with complex aberrant karyotypes have a low proliferative activity (as a result of low production of growth stimulatory cytokines), that is associated with a poor response to induction therapy (Jahns-Streubel et al.,1997). Chemotherapy priming with granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage CSF (GM-CSF) which is capable of stimulating leukemia blast cells to become more sensitive to cell-cycle-specific drugs was tested in some clinical trials. In a multicenter randomized trial, Löwenberg et al treated AML with cytarabine plus idarubicin (cycle 1) and cytarabine plus amsacrin (cycle 2) with granulocyte colony-stimulating factor (G-CSF) (321 patients) or without G-CSF (319 patients)(Löwenberg et al., 2003). After induction chemotherapy, the rates of response were not significantly different in the two groups. But for the patients of standard-risk, the overall survival (OS) and disease-free survival (EFS) in the G-CSF group were significantly superior to the group without G-CSF. However, G-CSF did not improve the outcome in the subgroup with an unfavorable prognosis. The reports about the decitabine combination with AAG were little. We had summarized the effect of the decitabine combination with AAG regime treating the patients with AML/MDS. The overall response was 72.7%, which was no-significantly difference with the response of decitabine signally. In the clinical trial of ChiCTR-TNC-11001566 registered by the First Affiliated Hospital Nanjing Medical University, All patients with high-risk myelodysplastic syndromes were treated with low-dose cytarabine and aclarubicin in combination with decitabine (D-CAG), the overall response rate was 80.1%, which was higher than the effect of decitabine signally according to the report of document (Kantarjian et al., 2007). But the response of complex karyotypes AML was 57.1%, which was not superior to the effect of decitabin alone. In our study, the response of decitabine alone and decitabine combination with AAG was separately 59.0% and 61.5%, the difference was not statistically significant (P>0.05). On the contrary, the overall survival of decitabine was superior to combination with AAG (overall survival 46.54% *vs* 16.28%, P<0.05), but the size of sample is too small to sure the relationship between them, we need increase the number of cases to conformed the explanation.

There was also a higher remissions in patients treated with decitabine who had chromosome 7 abnormalities. chromosome 7 abnormalities characterized by a poor outcome which grouped the unfavorable risk category determined by IPSS, WPSS and MD Anderson cancer center (MDACC) prognostic system, and lack of chromosome 5 or 7 abnormalities were associated with longer OS(Jabbour et al., 2013). In our study, 15 patients with chromosome 7 abnormalities, 10 patients achieved CR and PR (66.7%), the rate of CR and PR was similar in patients without chromosome 7 abnormalities (55.0%, P>0.05), These results suggest that decitabine may improve the prognosis of AML/MDS patients with 7 chromosome abnormalities.

The malignant degree of leukemia is associated with the number of chromosomal abnormalities. Multiple chromosomal abnormalities usually indicate a poor prognosis and the treatment also difficulty. We confirmed that decitabine induced remission rate in AML/MDS with complex karyotype was similar to with extremely complex karyotype. There are 18 patients with more than 3 to 5 chromosomal abnormalities and 17 patients with more than 5 abnormalities were enrolled our study. The remission rate of the former group (66.7%, 12 of 18 patients) was higher than the later group (52.9%, 9 of 17 patients). However, no significant difference between the two groups (P>0.05).

Based on observations, we found that the most important adverse event was bone marrow suppression results from decitabine-treated patients. and the main complication was pneumonia. In our study, the incidence of pulmonary infection was 44.4% (16 of 36 patient), which higher than those in ADOPT clinical trial (Steensma et al., 2009). 35 patients were successfully security from the term of bone marrow suppression, so the safety of decitabine was worth affirmed. However, traditional therapy is associated with frequent grade III/IV hematologic toxicity, requiring dose delays and/or dose reductions(DD/DR), this new treatment may be safely accomplished once the patient has achieved CR without impacting outcome(Ghanem.,2013).

The results described above suggest that decitabine can improve outcome of the patients with chromosomal complex abnormalities. In order to create a chance for HSCT later on, untreated or relapsed AML/MDS patients with complex karyotype should be advised to receive the treatment of decitabine alone or combination with other agents.

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