Case Report
Treatment of acute myeloid leukemia converted from myelodysplastic syndrome with ATC regimen in a patient with chromosome 8 abnormality

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Abstract: This study evaluated the efficacy of ATC regimen in the treatment of acute myeloid leukemia (AML) transforming from myelodysplastic syndrome (MDS) in a patient with chromosome 8 abnormality. ATC regimen was administered for 3 months in each course for a total of 14 courses, and thalidomide was administered at 100 mg qd for maintenance therapy. Bone marrow cell morphology showed CR; flow cytometry was done to detect CD13+, CD33+, and MPO+ cells and indicated MRD at 10^{-4}; karyotyping and FISH showed cytogenetic remission was achieved after 1 course treatment with ATC regimen, and chromosome 8 abnormality was absent; recurrence was not observed with the prolongation of treatment. Lymphocyte subtyping showed the function of T cells and NK cells was improved, peripheral blood granulocytes and red blood cells rapidly returned to normal, followed by recovery of platelets with the prolongation of treatment with ATC regimen. Clinical observation indicated the patient was tolerant to this therapy and there were no adverse effects. The recurrence free survival time was as long as 47 months. In conclusion, ATC regimen is effective in the therapy of MDS or leukemia of patients with chromosome 8 abnormality, which may be ascribed to the clearance of malignant cloning of abnormal chromosome 8 and improvement of cellular immunity. Patients are tolerant to this regimen and have little adverse effects. Thus, it is preferred for patients who are not willing to receive intense chemotherapy and have no chance of cell transplantation.

Keywords: ATC regimen, therapy, myelodysplastic syndrome, leukemia transformation, chromosome 8 abnormality

Introduction

Myelodysplastic syndrome (MDS) is a group of myeloid neoplasms and characterized by reduction in erythrocyte lineage, leukocyte lineage or full blood cell count with anemia, hemorrhage and infection of different extents. The pathogenesis of MDS involves multiple levels including epigenetics, cytogenetics, immunology and bone marrow microenvironment. In recent years, the therapies for MDS become diverse and individualized. However, these therapies have a poor efficacy for moderate to high risk MDS, which has a high risk for transformation into acute myeloid leukemia (AML). Combined chemotherapy is an effective therapy currently accepted for the treatment of moderate to high risk MDS. However, patients are usually intolerant to this therapy, the remission rate is low, and recurrence rate is high, which bring difficul-ties to the therapy and causes a poor prognosis. In our department, we used ATC regimen (arsenite [ATO], thalidomide [THd] and vitamin C [VitC]) in the treatment of AML transforming from MDS in a patient, achieving favorable efficacy. Herein, we reported our experience and reviewed the literatures.

Case reports

A female patient aged 51 years developed fatigue of unknown cause in March 2007 and repeated routine blood test showed reduction in leukocytes (2.5-3.3×10⁹/L). She did not pay attention to it. In March 2011, the fatigue deteriorated, with concomitant night sweats and weight loss, and routine blood test showed white blood cell (WBC) count was 2.3×10⁹/L, neutrophil (ANC) count was 0.90×10⁹/L, hemoglobin (HB) was 93 g/L and platelet (PLT) count
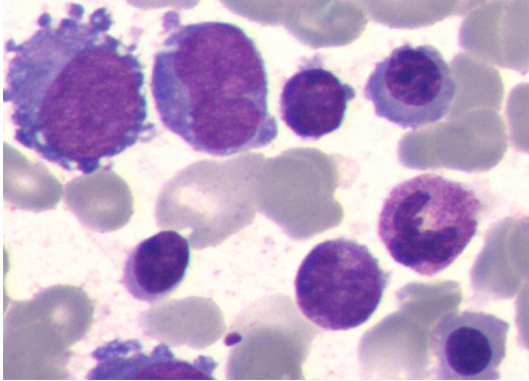
Figure 1. Auer body was not observed, erythrocyte lineage was hyperplasic, some immature monocytes became megaloblastic, multinucleated or petal like in their nuclei, the number and morphology of megakaryocytes were largely normal and platelets were diffuse and observable.

was 157×10^9/L. Bone marrow aspiration and examination showed bone marrow hyperplasia, the ratio of granulocytes to nucleated red blood cells was 0.633:1, granulocytes at different stages were observable, the primitive cells accounted for 10%, Auer body was not observed, erythrocyte lineage was hyperplasic, some immature monocytes became megaloblastic, multinucleated or petal like in their nuclei, the number and morphology of megakaryocytes were largely normal and platelets were diffuse and observable (**Figure 1**). Iron staining showed the proportion of iron positive was 32%, and extracellular iron was ++. Chromosome analysis showed 47, XX, +8 [1]/46, xx [2] (**Figure 2**). She was diagnosed with MDS (RAEB-2), IPSS score was 1.5, suggesting moderate risk [2, 3], and IPSS-R score was 5.5, suggesting high risk. The patient refused intensified therapy, and only oral Leucogen tablets and other drugs for hematopoietic and supportive therapy, but the blood condition remained unchanged. In November 2011, she was admitted to our hospital, and treated with decitabine (DAC) and low dose CAG (DAC: 15 mg/m^2, iv, qd, d1-5; aclacinomycin: 10 mg, iv, qd, d3-6; cytosine arabinoside: 15 mg, im, bid, d3-9; granulocyte colony stimulating factor: 300 μg, ih, qd, d0-12). After 2-course treatment, the blood condition remained unchanged, and re-examination of bone marrow showed the primitive naive cells accounted for 20%, had moderate cytoplasm and irregular karyotype, and 38% of them were positive for POX. Immunophenotyping showed naive cells accounted for 21%, were

positive for CD13, CD33 and MPO, but negative for other markers, suggesting the myeloid cells. Chromosome examination showed 47, XX, +8 [4]. Gene mutation detection showed no mutations in C-Kit e8 e17, NPM1, FLT3 TKD and ITD. She was diagnosed with AML transforming from MDS (moderate risk). Since February 12, 2012, HA regimen was used for induction treatment (homoharringtonine: 3 mg, qd, d1-7; cytosine arabinoside: 75 mg, bid, d1-7). After a course of treatment, the blood condition remained unchanged, and re-examination of bone marrow showed primitive naive cells accounted for 9%.

Treatment with ATC regimen and outcome

The patient was intolerant to HA treatment and refused to receive treatment with above and similar regiment. On March 27, 2012, ATC was employed for the treatment: arsenite (10 mg, qd, d1-7), thalidomide (100 mg, qd) and vitamin C (3.0, iv, qd, d1-7). After a course of therapy, the blood condition was improved, and neutrophil count increased significantly. Routine blood test showed WBC was 4.3×10^9/L, N, 2.6×10^9/L, HB, 76 g/L and PLT, 9×10^9/L. Ultrasonography showed the length of the spleen reduced from 124 mm to 115 mm. Bone marrow cytological examination showed remission (primitive naive cells: 1%). Chromosome examination showed 46, XX, [5]. Consolidation therapy was further performed with ATC regimen for 3 month in a course for a total of 4 courses. The bone marrow and blood conditions continued to recover. Since March 2013, following ATC regimen was used for consolidation therapy: arsenite (10 mg, qd, d1-14), thalidomide (100 mg, qd) and vitamin C (3.0, iv, qd, d1-14). Treatment was done for 3 months in a course for a total of 10 courses. Routine blood test, detection of live function, kidney function, blood glucose, electrolytes, coagulation function, electrocardiography, lymphocyte subtyping, bone marrow cytological examination, immunophenotyping, karyotyping (or FISH) and abdominal ultrasound examination were performed for monitoring of disease condition. The blood condition continued to recover and returned to nearly normal, the function of lymphocytes was improved, bone marrow condition recovered, FISH showed negative, and chromosome examination showed normal (**Table 1**). After the last arsenite therapy in June
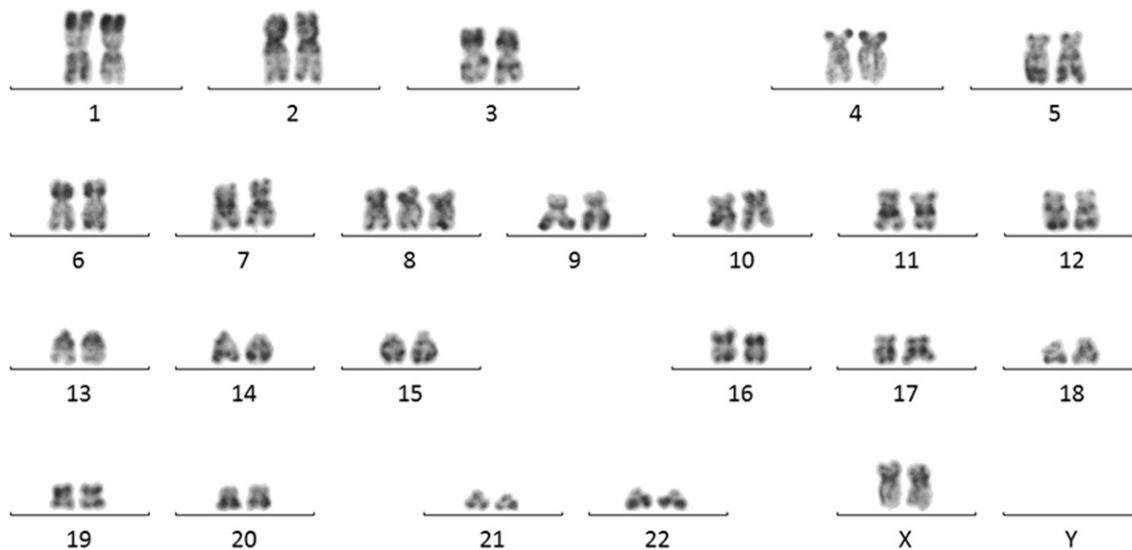
Figure 2. Chromosome analysis showed 47, XX, +8/46, xx.

2015, thalidomide was administered (100 mg, qd) for maintenance therapy. She was followed up until now, and recurrence was not observed with the recurrence free survival time of 47 months.

Discussion

Chromosomal abnormality reflects the malignant cloning in MDS. In China and Southeast Asia, the most common chromosomal abnormality is chromosome 8 abnormality. In the IPSS R scoring system, chromosom 8 abnormality is an independent predictor and suggests a karyotype with moderate prognosis. However, in the subgroup analysis of MDS, studies [6, 7] indicate the prognosis in RAEB group is poorer than in non-RAEB group. On the basis of medical history, this patient was definitely diagnosed with MDS of RAEB with chromosome 8 abnormality, which had high risk and its prognosis was moderate or poorer.

According to the guideline of WHO for the diagnosis and treatment based on risk stratification, combined chemotherapy and demethylation therapy are preferred for the treatment of high risk MDS, besides the allogeneic stem cell transplantation (SCT). This patient did not want to receive hematopoietic stem cell transplantation, and standard AML regimen for induction has a low rate of complete remission and short time of remission and patients are usually intolerant to this regimen. Conditioning with CAG

regimen may achieve the complete remission rate of 40-60% in MDS in China. Low dose DAC has the demethylated activity and may induce the expression of tumor suppressor genes (such as P53, P15 and P16) in MDS patients, leading to the normalization of cell differentiation and suppression of tumor cell growth [8]. Although demethylation drug DAC alone is effective on MDS and may alter the progression of MDS [9], its overall effectiveness rate is limited (30%). Taken together, DAC plus low dose CAG were used for combined therapy.

However, 2 courses of "DAC plus low dose CAG" failed to alter the progression of MDS, and chromosome abnormality remained. Moreover, it transformed into leukemia. For young patients with AML, allogeneic hematopoietic stem cell transplantation after chemotherapy is recommended. In the present report, the patient and her relatives refused to receive intense chemotherapy and did not want to receive stem cell transplantation. Thus, the mild HAG regimen (see above) was used for induction. After a course of treatment, bone marrow examination showed the chromosome abnormality remained, but the proportion of primitive naive cells reduced to 9% (**Table 1**), suggesting partial effectiveness. However, the patient was intolerant to this treatment and developed fatigue, nausea and vomiting during chemotherapy. Thus, she refused to receive a second chemotherapy with this regimen. In the following treat-

Table 1. Parameters before therapy

Time point	Routine blood test				Lymphocyte subsets (%)						Primitive cells in BM (%)	Chromosome examination	Spleen length (mm)
	WBC 10⁹/l	ANC 10⁹/l	Hb g/l	BPC 10⁹/l	T	CD3CD4	CD3CD8	CD4/CD8	B	NK			
Before first D+CAG	1.8	0.48	84	154	88.41	56.03	30.29	1.85	4.45	5.15	10	+8	124
Before second D+CAG	6.1	2.8	79	246	83.38	29.08	49.69	0.59	9.67	1.95	3	+8	131
Before HA	1.6	0.3	71	51	91.54	50.84	37.68	1.35	3.59	2.24	20	+8	126
Before first ATC	1.2	0.3	63	25	88.08	36.18	48.06	0.75	5.17	2.18	9	+8	121
Before second ATC	3.2	1.8	89	14	90.06	42.98	43.23	0.99	3.73	3.10	1	Normal	115
Before third ATC	3.8	2.7	110	37	83.53	43.71	39.07	1.12	10.06	5.38	1	Normal	133
Before forth ATC	4.2	2.3	111	27	80.71	46.79	33.19	1.47	15.64	3.84	0	Normal	Untested
Before fifth ATC	5.0	2.8	120	36	79.96	34.91	42.99	0.81	12.96	5.77	1	Normal	128
Before sixth ATC	4.4	2.8	109	34	51.90	33.09	18.56	1.78	8.21	36.53	0.5	Normal	111
Before seventh ATC	5.6	3.0	94	46	65.10	39.10	26.54	1.47	9.20	21.51	0	F-	Untested
Before eighth ATC	5.7	2.9	118	59	69.80	29.90	39.84	0.75	10.80	15.30	0	F-	106
Before ninth ATC	5.8	2.9	107	66	71.05	32.14	37.84	0.85	11.00	11.37	0	F-	115
Before tenth ATC	5.9	3.1	115	79	74.04	34.57	38.42	0.90	12.15	7.68	0	F-	Untested
Before eleventh ATC	6.4	3.9	114	83	75.36	35.84	36.91	0.97	14.24	5.89	0	F-	126
Before twelfth ATC	5.6	2.79	123	65	75.03	36.09	37.01	0.98	14.01	7.40	0	F-	110
Before thirteenth ATC	5.5	2.8	128	110	73.01	37.69	34.90	1.07	14.89	8.76	0	F-	Untested
Before fourteenth ATC	5.0	2.6	127	108	73.86	37.26	35.02	1.05	13.74	9.50	0	F-	107

Notes: ANC (neutrophils): before first D+CAG (February 2012); before first ATC (March 2013); Before fourteenth ATC (June 2015); F- (FISH showed negative for chromosome 8 abnormality); normal (Karyotyping after staining with MC method showed normal); normal ranges of lymphocyte subsets: T cells (50-84%), CD3+CD4+ cells (27-51%); CD3+CD8+ cells (15-44%), CD4/CD8 (1-2.5), NK cells (7-40%); B cells (5-18%).

ments, arsenite containing regimen was used for consolidation therapy.

Studies have shown that arsenite can be used alone or in combination with other drugs for the therapy of blood cancers and other solid cancers [1, 4, 10]. For MDS, arsenite may induce cell apoptosis and differentiation via several pathways [11, 12]: it may interact with EVI1 gene at specific sites (EVI1 is expressed in most MDS patients [13]); it promotes the apoptosis of mononuclear cells and MTUZ-1 cells in the bone marrow and reduces bcl2/bax ratio in MDS patients; it inhibits the autocrine and paracrine of vascular endothelial growth factor, induces the apoptosis of vascular endothelium and exerts anti-angiogenic effect, contributing anti-tumor activity. Numerous studies have confirmed the therapeutic effect of arsenite on MDS. A multicentered phase II clinical trial conducted by UK, USA and Belgium further confirmed the therapeutic effectiveness of arsenite in MDS of different subtypes [14]. Schiller et al [10] summarized the results from a multicentered phase II clinical trails about arsenic trioxide. In this study, treatment was done with arsenic trioxide (0.25 mg/kg/d) for 5 days weekly for 4 weeks in a course. At least 2 courses of treatment were required. Their results showed the blood condition was signifi-

cantly improved (39% for low risk and moderate risk-1; 9% for moderate risk-2 and high risk). In a Chinese study, arsenite dominant regimen was used in the treatment of high risk MDS in old patients (n=21), the overall effectiveness rate was as high as 61.9%, and patients had a favorable tolerance.

Thalidomide is an immunosuppressant containing glutamate derivative and able to regulate the immune function. It can inhibit the production of pro-inflammatory cytokines including Tumor necrosis factor-α (TNF-α), promote T cell activation and inhibit angiogenesis [5, 15-19]. Studies have showed it is able to inhibit the formation of new blood vessels [20-22] and suppress the malignant cloning. Xu et al [23] found thalidomide could effectively induce the generation of Th2 cells, inhibit the TNF-α production and suppress VEGF synthesis, which inhibit the apoptosis of bone marrow hematopoietic stem cells, exerting therapeutic effect on MDS. Strupp et al treated 34 MDS patients with thalidomide, achieving the overall effectiveness rate of 56%. Zorat et al used thalidomide in the treatment of 30 MDS patients, the erythrocyte lineage was improved after 12-week treatment in 33% of patients, 6 patients did not require blood transfusion, and 4 had remission for more than 1 year. Zhou et

al [12] treated 20 MDS patients with thalidomide, the overall clinical effectiveness rate was 75%, and the survival time was significantly prolonged in patients responding to this treatment. During the therapy, severe adverse effects, except for mild bone marrow suppression, were not observed. The therapeutic efficacy was similar to previously reported. In this patient, the function of lymphocytes was abnormal at disease onset (**Table 1**), T cell ratio was inverted, and NK cells reduced, which support the use of thalidomide.

Taken together, arsenite or thalidomide alone is effective on MDS and has little adverse effects, but their overall effectiveness rate is limited, and thus increasing clinicians attempt to apply arsenite combined with thalidomide. Ruan et al [24] used both arsenite and thalidomide in the treatment of MDS. They found both had complementary actions, the bone marrow microenvironment was significantly improved, the normal cells proliferate continuously, and the abnormal cloning of cells was inhibited. Raza et al [25] reported arsenite combined with thalidomide could synergistically improve the bone marrow microenvironment, promote the growth of normal cells, inhibit the abnormal cloning and achieve a better efficacy in patients positive for inv(3)(q21q26.2) or with high EVI1 expression. Chang et al [26] also found that combined use of arsenite and thalidomide was able to significantly increase the effectiveness rate as compared to control group, accompanied by reduction in the incidence of adverse effects.

VitC is a water-soluble vitamin and may increase the sensitivity of cells to arsenite and elevate the anti-tumor activity of arsenite. VitC combined with arsenite has been used in the therapy of promyelocytic leukemia and multiple myeloma and they were found to exert synergistic effect, but little is known about its effect on MDS. VitC may also protect vitamin A, E and B against oxygenation, exerting cytoprotective, detoxicating and hepatotective activities, which also reduces the adverse effects of arsenite.

Once MDS transforms into leukemia, it will be non-responsive to most treatments. To date, no study has been conducted to use arsenite, thalidomide and VitC (ATC) in the treatment of leukemia transforming from MDS. In this report, we used ATC regimen to treat AML trans-

forming from MDS in a patient with simple chromosome 8 abnormality. In the treatment, chromosomal abnormality disappeared, granulocytes and platelets increased significantly, and blood condition improved continuously, suggesting a favorable efficacy. This patient was followed up for more than 4 years without recurrence. Moreover, she was tolerant to this treatment, and there were no evident adverse effects. Although chromosome 8 abnormality is a common chromosomal abnormalities in MDS, simple chromosome 8 abnormality is not a determinant of primary MDS [27], and it is also present in acute myeloid leukemia, chronic myelogenous leukemia and aplastic anemia. In this patient, chromosome 8 abnormality was detectable since the disease onset, but abnormalities of other genes and karyotypes were not detectable. This indicates that the disease is caused by the malignant cloning of abnormal chromosome 8, and not related to the chemotherapy and demethylation treatment. After treatment with ATC regimen, chromosome 8 abnormality disappeared, and complete remission was observed. Thus, we speculate that this regimen is effective for leukemia transforming from MDS in patients with simple chromosome 8 abnormality and thus can be used in patients who have no chance of stem cell transplantation and do not want to receive intense chemotherapy.

Whether ATC regimen is able to improve the prognosis of RAEB patients with simple chromosome 8 abnormality is required to be proven in clinical studies with large sample size. ATC regimen may abolish the malignant cloning of abnormal chromosome 8 and improve the cellular immunity to exert therapeutic effect. Examinations of lymphocyte subsets, primitive cells in bone marrow and chromosomes (**Table 1**) showed the immune function is improved, proportions of NK cells increases, proportion of T cells becomes normal, blood condition is also improved continuously, and leukemia remits continuously. These suggest that this regimen may improve the T cell function, especially the NK cell function, to supervise and clear malignant clones and recover the normal haemopoiesis. However, the specific mechanisms are needed to be further studied.

Disclosure of conflict of interest

None.

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