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ORIGINAL ARTICLE

Efficacy and safety of combined decitabine and ruxolitinib in the treatment of chronic myelomonocytic leukemia*

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Abstract

Objective The aim of the study was to evaluate the clinical efficacy of decitabine (DEC) combined with ruxolitinib (RUX) in the treatment of chronic myelomonocytic leukemia (CMML).

Methods The clinical characteristics of 12 patients with CMML were analyzed retrospectively and subsequent target sequencing was performed to investigate the efficacy of the combined treatment with DEC and RUX and the molecular signatures therein.

Results Among the 12 cases, clinical improvement was observed in all patients (100%), spleen reduction was observed in six patients (67%), and hematologic improvement was observed in four patients (33%). In the CMML-1 group, the overall response was 50% (3/6), one case achieved complete response, one achieved bone marrow remission, and one achieved hematological improvement. In the CMML-2 group, the overall response was 17% (1/6), one case achieved complete response, four showed disease progression (PD), and one exhibited no response. As expected, ASXL1 mutation was predictive for the outcome of CMML (hazard ratio of 2.97, 95% confidence interval of 1.21–7.06; $P = 0.02$).

Conclusion The use of DEC combined with RUX in the treatment of CMML effectively improved the clinical response and quality of life, especially for CMML-1 patients. Ongoing clinical trials will further evaluate the safety and efficacy of this novel therapeutic approach.

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Key words: decitabine (DEC); ruxolitinib (RUX); chronic myelomonocytic leukemia (CMML)

Chronic myelomonocytic leukemia (CMML) is a clonal disease of bone marrow hematopoietic stem cells. Its incidence rate is approximately 1 to 2 in 100 000, and it occurs more commonly among the elderly, with amedian age of onset of 65–75 years. The survival period is 20 to 40 months, and 15% to 30% of patients experience progression into acute leukemia. However, CMML is not treated satisfactorily. We retrospectively analyzed the clinical features and efficacy of decitabine (DEC) combined with ruxolitinib (RUX) in six patients with CMML-1 and six patients with CMML-2.

Patients and methods

Patients

This observational study began in 2016 and is currently ongoing. Ethical approval for the study was obtained from Ruijin Hospital affiliated to Shanghai JiaoTong University School of Medicine, China. The inclusion criteria of all patients included diagnosis of CMML according to the guidelines of the American Society of Hematology, with a duration of less than one month. Table 1 summarizes the patients' main characteristics at baseline. There were 8 males and 4 females, with a median age of 63 (38–72) years. The median percentage of primitive monocytes in the bone marrow smear and number of white blood cells in the peripheral blood among all patients were 11% (3%–

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Table 1 Baseline patient demographics (*n*)

	CMML-1 (*n* = 6)	CMML-2 (*n* = 6)	All (*n* = 12)
Median age (years)	61 (38–68)	63 (60–72)	63 (38–72)
Male	5	3	8
Female	1	3	4
ECOG			
0–1	1 (16.7%)	0 (0.0%)	1 (8.0%)
2–3	5 (83.3%)	6 (100.0%)	11 (92.0%)
Gene mutation			
TET2	4 (66.7%)	3 (50.0%)	7 (58.0%)
ASXL1	4 (66.7%)	1 (16.7%)	5 (42.0%)
SRSF2	2 (33.3%)	3 (50.0%)	5 (42.0%)
NRAS	1 (16.7%)	2 (33.3%)	3 (25.0%)
DNMT3A	0 (0.0%)	1 (16.7%)	1 (8.0%)
JAK2	0 (0.0%)	2 (33.3%)	2 (16.7%)
TP53	0 (0.0%)	1 (16.7%)	1 (8.0%)
RUNX1	1 (17.7%)	1 (16.7%)	2 (16.7%)
Blasts	9% (3%–9%)	13% (12%–17%)	
Karyotype			
Normal	4 (66.7%)	4 (66.7%)	8 (67.0%)
Complex	2 (33.3%)	1 (16.7%)	3 (35.0%)

17%) and 17 (6–27) × 10^9 cells/L, respectively. The level of hemoglobinand the number of platelets decreased, with a median of 45 (36–97) g/L and 40 (10–234) × 10^9 cells/L, respectively. Abdominal B ultrasound showed that nine patients had different degrees of splenomegaly, the largest with a spleen thickness of 96 mm and a long diameter of 228 mm.

Gene sequencing

After initial diagnosis and treatment, bone marrow was extracted from the patients and sent to Shanghai Aositai Biotechnology (China) for DNA sequencing. Detection of 22 myelodys plastic syndrome (MDS)/myeloproliferative neoplasm (MPN) genome sets including SF3B1, SRSF2, U2AF1, DNMT3A, Iso-lemon IDH1, IDH2, TET2, TP53, RUNX1, NRAS, EZH2, JAK2, CBL, ETV6, and ASXL1 was performed. We found four patients with CBL gene mutations, three with SRSF2 gene mutations, three with TET2 gene mutations, two with ASXL1 gene mutations, one with RUNX1 gene mutation, one with SETBP1 gene mutation, one with NRAS gene mutation, and one with JAK2 gene mutation.

Administration and criteria for response

Treatment was determined based on the patient's condition and willingness. DEC at 20 mg/(m^2·d), on days 1–3 and RUX at 5–20 mg, qd (adjusted according to the number of platelets), on days 1–28, were administered every 4–6 weeks during one course of treatment (Table 2). Bone marrow evaluation (including cytogenetic and molecular studies) was performed at the end of each course of treatment. Therapy continued until disease progression was observed, unacceptable toxicity has developed, concurrent illness prevented further treatment, or the patient requested withdrawal from the study. Prevention of infection, blood transfusion of components, and other supportive treatment during the period of myelosuppression were acceptable. The criteria for response to treatments according to the literature [1] were as follows: complete remission (CR), bone marrow remission (mCR), hematologic improvement (HI), no response (NR), and disease progression (PD).

Follow-up

The follow-up period began on the date of treatment after the diagnosis of the disease, and the follow-up deadline was July 1, 2019. Follow-up was conducted by telephone contact.

Table 2 The efficacy of DEC and RUX in the treatment of CMML

Patient	Starting dose of Rux	Maintenance dose of Rux	Duration of Rux (months)	Number of cycles of therapies	Sequence of treatment	Duration of follow-up (months)
1	5 mg bid	5 mg bid	9	3	DEC + RUX	15
2	5 mg bid	5 mg bid	4	1	DEC + RUX	22
3	5 mg qd	5 mg qd	5	1	DEC + RUX	9
4	5 mg qd	5 mg qd	1	4	DEC + RUX	13
5	5 mg bid	5 mg bid	19	3	DEC + RUX	19
6	5 mg bid	5 mg bid	1	1	RUX + DEC	1
7	5 mg bid	10 mg bid	13	2	RUX + DEC	17
8	5 mg bid	10 mg bid	7	5	RUX + DEC	23
9	5 mg bid	5 mg bid	1	3	DEC + RUX	9
10	5 mg bid	5 mg bid	4	3	DEC + RUX	13
11	5 mg qd	5 mg qd	3	4	DEC + RUX	15
12	5 mg bid	5 mg bid	8	6	DEC + RUX	28

Note: bid, twice a day; qd, once a day

Results

Efficacy of treatment

Some objective responses (clinical improvement, spleen reduction, and hematologic improvement) were evaluated. Before treatment, constitutional symptoms (fatigue, fever, chills, night sweats, and loss of muscle mass) were present in CMML patients. After treatment, there were some improvements in terms of fatigue, loss of muscle mass, and weight loss in all patients. The spleen sizes of six patients (67%) were reduced to various extents compared to those before treatment. For example, palpable splenomegaly decreased to 9 cm in case 1, 8 cm in case 9, and 4 cm in case 11. At the time of diagnosis, red blood cell (RBC) transfusion was required every two weeks for case 1, 2, 8, and 12. After two cycles of treatment, RBC transfusion was required on a monthly basis.

The efficacy of treatment was also evaluated. The overall response rate of all patients to the combination of DEC and RUX was 33%. In the CMML-1 group, the overall response was 50% (3/6), one case achieved CR, one achieved mCR, one achieved HI, two had NR, and one showed PD. In the CMML-2 group, the overall response was 17% (1/6), one case achieved CR, one had NR, and four showed PD. The efficacy and outcome of the 12 patients after treatment are shown in Table 3.

Safety of treatment

All patients completed the therapeutic schedule for more than one cycle. DEC and RUX were well tolerated, although some patients experienced mild gastrointestinal reactions such as nausea, vomiting, and diarrhea. Myocardial suppression occurred in 10 patients after chemotherapy. Among them, myelosuppression was the most severe and the longest period of myelosuppression was observed in case 1, 7, and 10. The computed tomography chest scans of case 1, 2, 3, 7, and 10 showed pulmonary infection. These patients were treated with active anti-infection (anti-bacterial and anti-fungal) agents, and all of them showed improvements after treatment.

Molecular genetic abnormalities

Three patients showed complex karyotype abnormalities, two being in the CMML-1 group (45, XY, -7,-5q karyotype, with ASXL-1 and TET2 gene mutations; 48, XY, +8, +10 karyotype, with ASXL-1 and RUNX1 gene mutations) and one in the CMML-2 group (47, XY, +8 karyotypes, with JAK2, TET2, and SRSF2 gene mutations).

According to the results of 22 MDS/CMML-related gene mutations, positive mutations were detected in all patients. Further analysis of the effect of gene mutations on the response rate revealed that two patients with TET2 mutations showed HI and mCR, two with NRAS mutations showed HI and CR, three with ASXL1 mutations showed PD, two with ASXL1 mutations showed NR, two with JAK2 and TET2 mutations obtained PD, one with TP53 mutation in the CMML-2 group showed PD, and one with RUNX1 mutation showed PD. The ASXL1 mutation was common among CMML patients, and it is predictive for the outcome of CMML (hazard ratio of 2.97, 95% confidence interval of 1.21–7.06; $P = 0.02$).

Discussion

CMML is a rare and often aggressive myeloid malignancy characterized by features of both MDS

Table 3 Clinical outcomes of CMML patients treated with DEC and RUX

Case	Constitutional symptom (pre-Tx)	Improvement in symptoms (post-Tx)	Spleen size (cm)		Peripheral blasts (%)		Response
			Pre-Tx*	Post-Tx**	Pre-Tx*	Post-Tx**	
1	F, NS, WL, LM	All	23	14	4	5	HI
2	F, LM, F/C	All	15	14	9	13	NR
3	F, WL, P	Weight gain	19	15	7	37	PD
4	F, NS, WL, F/C	Weight gain	N	N	15	17	PD
5	F, NS, P, F/C	All	23	21	3	1	CR
6	F, NS, WL, LM, F/C	Weight gain	14	13	15	24	PD
7	F, NS, LM, F/C	All	23	21	7	18	NR
8	F, P, F/C	No fever	18	10	17	30	PD
9	F, WL, F/C	Weight gain, No fever	12	11	14	42	PD
10	F, NS, WL	All	13	9	13	16	NR
11	F, NS, P	All	N	N	4	1	mCR
12	F, NS, F/C	All	N	N	15	3	CR

Note: Tx, treatment; F, fatigue; NS, night sweats; WL, weight loss; LM, loss of muscle mass; P, pruritus; F/C, fever and chills. * Pre-Tx: spleen size and peripheral blood blast percentage values were collected prior to initiation of either ruxolitinib or DNMT inhibitors. ** Post-Tx: spleen size and peripheral blood blast percentage values were collected when patients were on stable doses of both treatments

and MPNs. Therefore, therapeutic options for CMML are largely developed from those dealing with MDS and MPNs. CMML has shown poor prognosis, and effective treatment options are limited but include hydroxyurea, low-dose chemotherapy, supportive care, and hematopoietic stem cell transplantation. Because of comorbidities, poor tolerance to chemotherapy, and the lack of indication of transplantation, most elderly patients choose supportive treatment. Recently, a number of novel approaches using unapproved therapies (lenalidomide, ruxolitinib, sotatercept, and tipifarnib) have demonstrated some efficacy in CMML [2].

Hypomethylatingagents (HMAs) are usually the standard first-line therapy used to reverse the DNA methylation process and induce tumor cell differentiation or apoptosis. Many recent studies have attempted to identify CMML patients that can most likely benefit from HMAs [3–5]. RUX is a Janus kinase (JAK)1/2 inhibitor for the treatment of myeloproliferative diseases that can inhibit tumor proliferation and thus achieve a significant spleen-reducing effect. Notably, responses were seen even in the absence of detectable JAK2 mutations. Recently, RUX has shown good efficacy in CMML-1 patients with high white blood cell count, and this drug can still effectively improve clinical symptoms and reduce the proportion of bone marrow blast cells after the failure of HMA treatment [6–7]. The 12 CMML patients reported in this study revealed that a combination of DEC and RUX may be a safe and effective treatment scheme in CMML patients.

In this study, the complementary effects of DEC and RUX resulted in symptomatic relief and hematological improvement, potentially addressing relevant contributors to disease pathogenesis. In particular, 67% of the patients exhibited spleen reduction to varying degrees, 33% showed a decrease in the frequency of RBC transfusion, and some clinical improvement (fatigue, loss of muscle mass, and weight loss) was present in all patients. In addition, the combination of DEC and RUX in the treatment of CMML-1 achieved an effective response rate of 50%. Based on the results of this study, we confirmed the combination of DEC and RUX was safe and tolerable. Although patients treated with 20 mg of RUX attained the greatest blast count and spleen size reduction, patients treated with 5 mg of RUX were able to continue therapy for a longer duration. Collectively, this regimen may serve as a basis to which other novel/targeted therapeutic agents may be added to further improve efficacy against CMML.

Many studies have focused on somatic mutations as drivers of pathogenesis in CMML patients, with the TET2 gene showing higher mutation frequency, followed by SRSF2, ASXL1, and RAS. Based on the results of the single-cell follow-up test, the priming-driven mutation of CMML occurred in TET2 and ASXL1 [8–9]. Patnaik and colleagues identified TET2-mutant patients without the ASXL1 mutation to have improved overall survival in comparison toco-mutant patients, who had the shortest survival [10]. In this study, we further evaluated the impact of the ASXL1 mutation on the outcome of CMML. Indeed, three patients with ASXL1 mutations showed PD and two showed NR. It was suggested that the ASXL1 mutation is predictive for inferior outcome in CMML. Future studies will evaluate the functional consequence on protein function based on the type of ASXL1 mutation.

In summary, the preliminary results of this study showed that DEC combined with RUX effectively ameliorated the clinical symptoms and improved the quality of life of CMML patients. Because of the small number of participants and short follow-up period in this study, the safety and efficacy of DEC and RUX require further evaluation in large-scale clinical trials.

Ethics approval and consent to participate

Patient data were used after obtaining approval from the Ethics Committee of Ruijin Hospital affiliated to Shanghai JiaoTong University School of Medicine, China.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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