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Brief Communication

Azacitidine Combined with Cytarabine in Older Patients with Newly Diagnosed AML

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SUMMARY

Azacitidine (AZA) combined with cytarabine was used for newly diagnosed older patients with acute myeloid leukemia (AML). Since 2017, 28 newly diagnosed older AML patients (> 65 years old) had received AZA combined with low dose cytarabine (LDAC) in our hospital. 9 patients (32%) achieved a CR, 7 (25%) achieved a CRi, and 10 (36%) achieved a PR for an ORR (CR+CRi+PR) rate of 93%. The median PFS and OS were 9.3 months (95% CI 7.55–11.05 months) and 12.6 months (95% CI 8.6–16.6 months), respectively. The 1-year PFS and 1-year OS were 31% and 50%, respectively. Post hoc univariate analysis showed that median OS was longer for patients with secondary AML (16.8 months) and WBC count < 30×10^9/L at onset (16.7 months). AZA plus LDAC could obtain a better effect for the older AML patients ineligible for IC, and would be more suitable for older AML patients in China.

1. Introduction

Acute myeloid leukemia (AML) is a malignant clonal hematopoietic stem cell disease. For patients under 60 years old, the cure rate is 35–40% after high intensity chemotherapy (IC), while for the older patients, it was generally not exceeding 15% for the physiological failure of bone marrow (BM) resulting in stem cells reducing and the recover time prolonging after chemotherapy. The National Comprehensive Cancer Network (NCCN) guidelines recommended IC for AML patients with age ≥ 60 years and more favorable prognostic features, but many older AML patients did not meet above criteria because of host- and disease-related adverse prognostic risk factors, included history of myelodysplastic syndrome (MDS), unfavorable karyotypes, comorbidities and etc.

Both NCCN and the European Society of Hematology recommended hypomethylating agents for older newly diagnosed AML patients ineligible for IC, as they can increase the 3-year survival rate to 24% and the cure rate to 15%. Azacitidine (AZA), as one of the hypomethylating agents, had been shown to prolong median overall survival (OS) in several clinical trials.[1] Cytarabine (Ara-C), a kind of cycle-dependent cytotoxic drug, could be strengthened by hypomethylating agents. In china, AZA combined with CAG regimen [aclacinomycin (Acla) 20 mg qod × 4 d, Ara-C 10 mg/m^2 q12h × 14 d, Granulocyte Colony-Stimulating Factor (G-CSF) 300 ug/d, the dose of G-CSF adjusted by the amount of blood routine] was common used in the treatment of older AML patients. However, the BM suppression was serious, which resulted in chemotherapy intermission delaying and the patients' survival decreasing. Since 2017, AZA combined with low dose cytarabine (LDAC) had been used in the treatment of newly diagnosed older AML patients in our hospital. This retrospective study mainly analyzed the efficacy of AZA+LDAC on older AML patients.

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2. Patients and methods

Since Jan 2017, there were 28 older patients (> 65 years old) newly diagnosed AML in our hospital. They received AZA (75 mg/m^2, d1-7) combined with Ara-C (10 mg/m^2, Q12h, d1-14) for a maximum of eight cycles chemotherapy. If white blood cell (WBC) count more than 30×10^9/L at onset of the disease, Ara-C (25 mg/d) should be used before chemotherapy until WBC less than 30×10^9/L. BM should be performed before every circle to evaluate the efficacy of treatment. All patients had been followed up 24 months. Overall response rate (ORR), complete response (CR) rate, progression-free survival (PFS), and OS were analyzed by statistics. The subgroup analysis of OS was calculated in terms of age, sex, ECOG, BM blasts at the onset, WBC at the onset, and AML subtype. PFS, and OS were estimated using Kaplan-Meier method. Mean was described as median (95% confidence interval) between group. For post hoc analysis, log-rank test was used for comparing OS between subgroups. $P < 0.05$ was statistical significance.

3. Results

3.1. Patient characteristics

From Jan 2017 to Jun 2018, 28 older patients (> 65 years old) were diagnosed AML in our hospital: 11 (39.3%) with de novo, 17 (60.7%) with secondary to MDS (Table 1). Median age was 75.8 years (range, 66–90 years) with male predominance (54%). All patients complicated with other chronic diseases, among which 9 with diabetes, 17 with hypertension, 7 with coronary heart disease, 2 with cirrhosis, 1 with bronchitis and 1 with tuberculosis. On presentation,

Table 1
Patients characteristics (N = 28).

Characteristics	Values
Age ≥ 75 y, n (%)	15 (53.6)
Median age (range), y	75.8 (66–90)
Male, n (%)	15 (53.6)
ECOG status, n (%)	
0 to 1	25 (89.3)
2	3 (10.7)
Comorbidities, n (%)	
Diabetes	9 (32.1)
Hypertension	17 (60.7)
Coronary heart disease	7 (25)
Cirrhosis	2 (7.1)
Bronchitis	1 (3.6)
Tuberculosis	1 (3.6)
AML type, n (%)	
De novo	11 (39.3)
Secondary from MDS	17 (60.7)
AML FAB classification, n (%)	
M2	12 (42.9)
M4	2 (7.1)
M5	11 (39.3)
Unknown	3 (10.7)
Cytogenetic risk group, n (%)	
Intermediate	18 (64)
Normal karyotype	8 (29)
+8	6 (21)
del (20q)	3 (10)
-13	1 (4)
High	8 (29)
Complex karyotypes	6 (21)
-7	1 (4)
-17	1 (4)
Median BM blasts (range), %	58.63 (25–94.1)
Median WBC count (range), $\times 10^9$/L	29.45 (0.54–158.84)

FAB, French-American-British.

median WBC count and BM blasts were 29.45 × 10^9/L (range, 0.54–158.84 × 10^9/L) and 58.63% (range, 25–94.1%), respectively. 26 patients (93%) had cytogenetic analysis performed at baseline: 8 (29%) had high-risk and 18(64%) had intermediate-risk cytogenetic abnormalities.

3.2. Efficacy, response rates and survival

Twenty-eight patients received a median of 5.9 cycles (range, 1–8 cycles), 9 patients (32%) achieved a CR, 7 (25%) achieved a CRi, and 10 (36%) achieved a PR for an ORR (CR+CRi+PR) rate of 93%. Median time to CR/CRi/PR was 2.046 months (range, 0.8–4.4 months), with 2 patients requiring more than 4 cycles of therapy to respond. With a follow-up of 24 months, 2 patients (7.1%) died of infection (n = 1) and upper gastrointestinal hemorrhage (n = 1) in first cycle, 24 patients (85.7%) exhibited progression of disease (PD), and 2 patients (7.1%) were persistent in CRi. Among the 24 relapsed patients, 21/24 patients received low dose chemotherapy or best supportive care (BSC) after relapse, and 3/24 patients did not received any therapy.

Survival analysis showed that median PFS and OS were 9.3 months (95% CI 7.55–11.05 months) and 12.6 months (95% CI 8.6–16.6 months), respectively. The 1-year PFS and 1-year OS were 31% and 50%, respectively (Figure 1). Post hoc univariate analysis showed that median OS was longer for patients with secondary than de novo AML (16.8 months [95% CI, 8.73–24.87 months] vs. 11.8 months [95% CI, 7.42–16.18 months], p = 0.035); the patients with WBC count < 30 × 10^9/L at onset survived longer than these with WBC ≥ 30 × 10^9/L (16.7 months [95% CI, 13.37–20.03 months] vs. 9.2 months [95% CI, 7.81–10.59 months], p < 0.001) (Figure 1). In this study, median OS did not show significant difference in age (p = 0.176), sex (p = 0.648), ECOG (p = 0.057), BM blasts at onset (p = 0.75), and cytogenetic risk (p = 0.393). The hematologic adverse effects (AE) occurring in all patients were neutropenia, anemia, and thrombocytopenia, with less than grade 3 AE in about 80% patients who were recovered safely with the support therapy, included living in laminar air-flow wards, G-CSF treatment and blood transfusion. The severe hematologic AE occurring in about 20% patients were infection caused by febrile neutropenia, and less than 10% patients were thrombocytopenia. In addition, the nonhematologic AEs were all less than grade 3 with nausea (89.2%), fatigue (93%), constipation (82%), and decreased appetite (93%).

4. Discussion

AZA had been recommended by Food and Drug Administration and European Union for the treatment of older AML patients. A phase 3 clinical trial (AZA-AML-001)[1] in older patients with newly diagnosed AML compared AZA with conventional care regimen (CCR, included LDAC, standard induction chemotherapy or BSC)[1] showed that AZA had significantly improved the median OS (10.4 months) and 1-year survival (46.5%) than that of CCR (6.5 months, 34.2%). And the survival of patients with TP53 mutations were prolonged than before.[2] The quality of lives in patients received AZA were improved significantly.

This retrospective study was performed in 28 older AML patients by AZA combination with LDAC. Thirty-two percent patients achieved a CR, 25% patients achieved a CRi, and 36% patients achieved a PR for an ORR (CR+CRi+PR) rate of 93%. Most of the patients obtained respond at the early stage of treatment, with 2 patients required more than 4 cycles of therapy to respond. Although ORR was significantly improved, the efficacy of most patients could not be sustained, with a median PFS of 9.3 months and a 1-year PFS

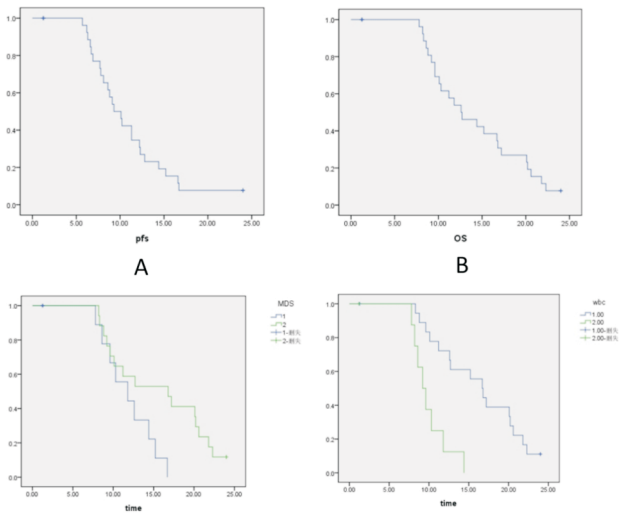

Figure 1. Outcomes of patients treated with azacitidine plus low dose cytarabine. (A) PFS for the whole population. (B) OS for the whole population. (C) OS stratified by AML subtype (de novo = 1, secondary to MDS = 2). (D) OS stratified by WBC status (< 30 × 10^9/L = 1, ≥ 30 × 10^9/L = 2). PFS, progression-free survival; OS, overall survival; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; WBC, white blood cell.

of 31%. The median OS in this study was 12.6 months with a 1-year OS rate of 50%, both might be a little higher than OS in AZA-AML-001 clinical trial,[1] which suggested that AZA combined with LDAC might have longer OS than that of AZA alone. In addition, post hoc univariate analysis showed that median OS was longer for patients with secondary AML (16.8 months) and WBC count < 30×10^9/L at onset (16.7 months) (Figure 1). Guillermo[3] performed pracinostat combined with AZA for older AML patients, which showed patients secondary to MDS had longer median OS than that of de novo patients. Latagliata found WBC count more than 50×10^9/L was an adverse prognostic factor for OS, which was proved by our study that the OS was significantly shortened when WBC count $\geq 30 \times 10^9$/L in older AML patients. Most patients could tolerate the common adverse effects, incuded leukocytopenia, anemia, and thrombocytopenia.

In the current era of new drugs, AZA combined with new drugs had achieved better efficacy. A highly selective small-molecule Bcl-2 inhibitor, Venetoclax, could eliminate AML stem cells by interfering with energy metabolism. AZA could downregulate an anti-apoptotic protein, McL-1, which is associated with resistance to Venetoclax, so the better efficacy would obtain when these two drugs combined. DiNardo[4] showed that the newly diagnosed older AML patients received Venetoclax plus AZA treatment, 67% patients achieved CR+CRi, the median duration of CR+CRi was 11.3 months, the median OS was 17.5 months. As a result, 2019 NCCN guidelines recommended AZA combined with Venetoclax used in the treatment of newly diagnosed older AML with adverse genotype or without IDH or FLT3 mutations, and this combination also showed a certain efficacy to refractory/relapse AML. AML patients with FLT3-ITD mutations received FLT3 inhibitors-Sorafenib combined with AZA, the ORR was 78%, the median duration of respond was 14.5 months, OS was 8.3 months,[5] then AZA combined with Sorafenib was recommended to use in the treatment of newly diagnosed older AML with FLT3-ITD mutation and ineligible for IC by 2019 NCCN guidelines. Pracinostat, a pan-HDAC inhibitor, combined with AZA performed in the treatment of newly diagnosed older AML, ORR was 83%, the median OS was 19.1 months, and the median PFS was 12.6 months with a 1-year OS rate of 62%.[3] Although AZA combined with new drugs had achieved better efficacy, in China, most of the new drugs are still in the stage of clinical trials. Even if they are approving for clinical use later, most patients will not be able to use them and benefit from them because of their high price.

5. Conclusions

For older AML patients ineligible for IC, AZA plus LDAC would be more suitable than AZA alone in China, especially for patients with a history of MDS or WBC count at onset less than 30×10^9/L. Prospective clinical trials will be needed in the future for further confirmation.

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