The impact of venetoclax based regimens in the preemptive of measurable residual disease in acute myeloid leukemia

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To The Editor:

The role of measurable residual disease (MRD) in prognosis and treatment in acute myeloid leukemia (AML) is evolving. Studies have demonstrated the correlation between MRD and risks of relapse in adult AML: persistently positive MRD after induction is associated with a high risk of relapse,[1,2] and these patients should consider allogeneic transplantation (allo-Hematopoietic Stem Cell Transplantation (HSCT)) and clinical trial, even in favorable-risk groups. However, because of the financial issue or lack of suitable transplant donors, many of the patients could not receive allo-HSCT, so how to prolong the relapse-free survival of these patients remains a challenge. Platzbecker et al treated MRD-positive patients with azacytidine (AZA), and found pre-emptive therapy with AZA can prevent or substantially delay hematological relapse in MRD-positive patients with MDS (myelodysplastic syndrome) or AML who are at a high risk of relapse.[3,4] What's more, the application of venetoclax has markedly altered the treatment landscape in AML and provided new opportunities, and preclinical studies have indicated that venetoclax could enhance the activity of anti-leukemic drugs such as HMA (hypomethylating agents),[5,6] cytarabine, and idarubicin.[7] Moreover, venetoclax with AZA has superior efficacy compared to AZA alone in the treatment of elderly unfit AML patients.[8] Moreover, MRD negative rate after the induction therapy of venetoclax with HMA is much higher (54%–81%)[9,10] than traditional chemotherapies. Hence, we consider that venetoclax-based regimens could be an efficacious pre-emptive option in patients with persistent MRD positive after induction and consolidation therapy, which may hold promise in prolonging the relapse-free time and overall survival of these patients. In this study, we treated 10 MRD positive patients who could not receive allo-HSCT, with venetoclax-based regimens, and we found that venetoclax-based regimens were effective as pre-emptive therapy for patients with persistent MRD positive as we hypothesized.

All the 10 AML patients were diagnosed and treated at the Leukemia Center in Institute of Hematology and Blood Diseases Hospital from March 2020 to March 2021. They were all diagnosed by the "MICM mode", which included morphology, immunology, cytogenetics, and molecular biology. The detailed clinical characteristics are listed in Table 1. All patients received induction therapy and consolidation therapy. Detailed regimens are listed in Table S1, http://links.lww.com/BS/A37. After the routine therapy, patients with the MRD value ≥0.1% detected by flow cytometry (FCM) or PCR (including AML1-ETO, CBFB-MYH11, IDH2, NPM1 transcripts) were defined as MRD positive. There were 6 male and 4 female patients, with a median age of 55 years old (range, 23–68 years old). The median WBC count was 6.89×10^9/L (range, $1.04–43.4 \times 10^9$/L). The median therapy cycles of the 10 cases received before the pre-emptive therapy was 7 (range: 4–14). All the patients were followed-up, with a median follow-up time of 13.2 months (range: 4.8–18.3) (Table 1). Five patients were FCM-detected MRD positive (median: 0.43%, range: 0.16%–1.21%), and another five were molecular MRD positive detected by PCR (median: 3.55%, range: 0.2%–19.6%).

The specific pre-emptive regimens were as follows: patients were continuously treated with venetoclax (100 mg d1, 200 mg d2, 400 mg d3–28, daily, po) in tandem with AZA (75 mg/m^2, daily d1–7; 7 patients) or with combined chemotherapy (AZA + aclacinomycin + cytarabine: 3 patients) (Table S1, http://links.lww.com/BS/A37). Once the pre-emptive therapy was effective in MRD positive patients, the same regimens were maintained until disease progression. Patients who had elevated MRD levels in the pre-emptive therapy course received another kind of combined chemotherapy or new target drugs treatment. When co-administrated with strong CYP3A4 inhibitors (such as posaconazole, voriconazole in the treatment or prevention of fungal infections), the venetoclax dose was reduced to 100 mg.

Five out of ten (50%) patients achieved negative MRD after one or two venetoclax-based pre-emptive therapy (FCM MRD positive: 2 cases; molecular MRD positive: 3 cases), the median MRD negative survival of the five patients was 7.3 months (range: 5.67–13.8 months). Two FCM MRD positive patients (2/

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Table 1

The clinical characteristics of the 10 cases.

Total (N)	Gender		Age	WBC count	ELN risk stratification			Regimen		Median OS (months, from pre-emptive therapy)
	Male	Female			LR	IR	HR	Ven + AZA	Ven + chemotherapy	
10	6	4	55 (23–68)	13.87 (1.04–43.4)	6	0	4	6	4	13.2 (4.8–18.3)

AZA = azacytidine, ELN = European Leukemia Net, IR = intermediate risk, HR = high risk, LR = low risk, OS = overall survival, Ven = venetoclax, WBC = white blood cell.

5, 40%) who were responsive to the pre-emptive therapy relapsed at the seventh and tenth month, respectively. The other three patients responsive to the pre-emptive therapy remained MRD negative until the follow-up time. Besides the five patients, another one patient (Patient 4, Table S1, http://links.lww.com/BS/A37) had a decreased MRD level after 3 cycles of venetoclax plus AZA therapy in 6 months (from 1.21% to 0.21%, by FCM), but relapsed at the seventh month (this patient was still analyzed in unresponsive group), and five patients (including the patient just mentioned) who had no response to the pre-emptive therapy all relapsed. The relapse-free survival time of the 5 patients who were responsive to the preemptive therapy was longer than patients who were unresponsive to the therapy. The median time from the start of the pre-emptive therapy to relapse of responsive patients versus unresponsive patients was: not reached (range: 5.67–13.8 months) versus 4.8 months (range: 1.3–9.2 months)

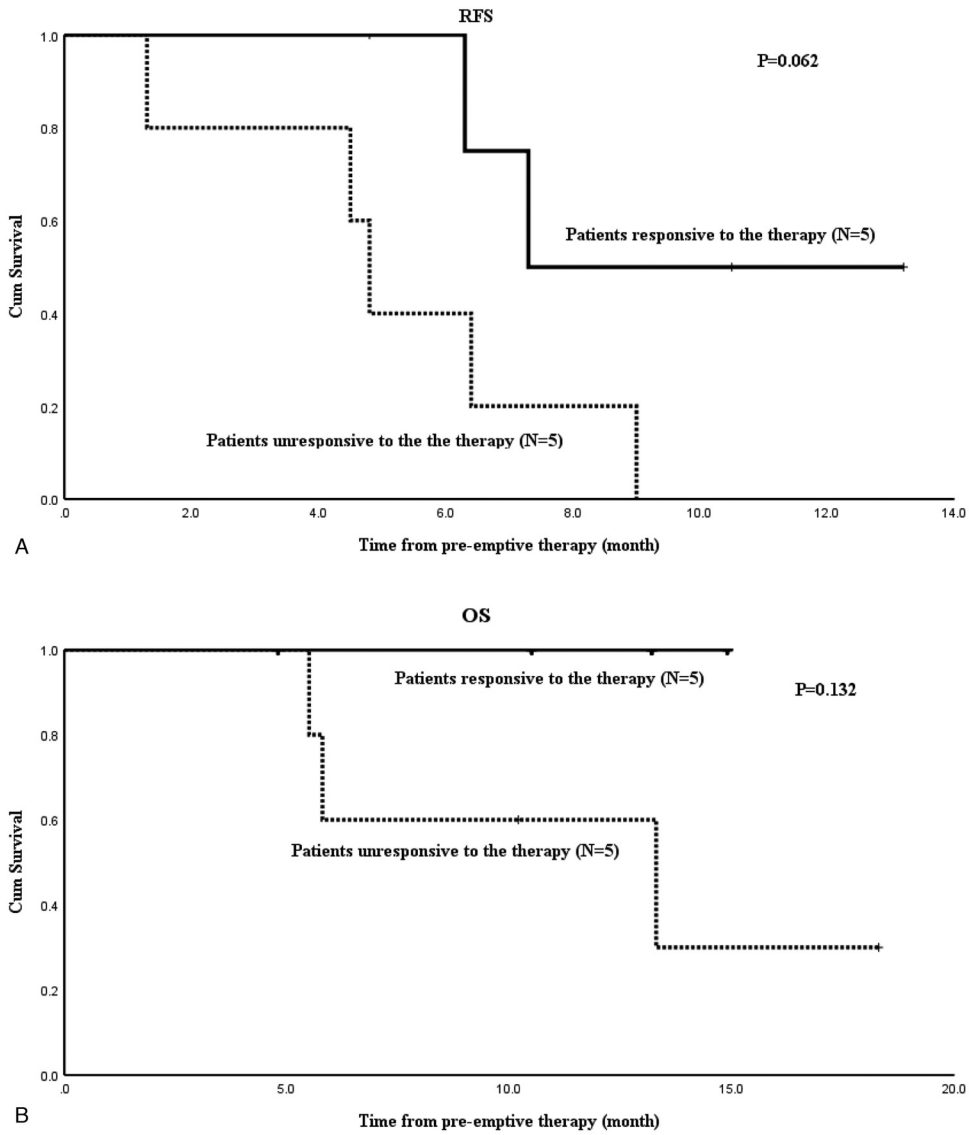

Figure 1. (A) The 1-year RFS of the patients who were responsive to the pre-emptive therapy versus the patients who were unresponsive to the pre-emptive therapy. (B) The 1-year OS of the patients who were responsive to the pre-emptive therapy versus the patients who were unresponsive to the pre-emptive therapy. OS, overall survival.

($P=0.062$, 1-year relapse free survival (RFS): 50±25% vs. 0%, Fig. 1A). The 1-year OS (overall survival) of the 5 patients responsive to pre-emptive therapy versus the other 5 unresponsive patients were 100% versus 30±23.9% ($P=0.132$, Fig. 1B). Three patients (3/10, 30%) died of disease relapse (all the 3 cases were from the unresponsive group). The most common adverse events in the study population were hematological, with grade 3/4 neutropenia and thrombocytopenia reported in 50% and 70% of patients, respectively. Infections were the most common non-hematological events, with neutropenic fever occurring in 40% of patients. Gastrointestinal events occurred in 30% of patients. No tumor lysis syndrome was observed.

As the National Comprehensive Cancer Network guidelines recommended, if the MRD is persistently positive, patients should consider receiving allo-HSCT. Patients who could not receive allo-HSCT may choose other treatment regimens for the elimination of the MRD. Single AZA treatment is an option for patients with persistent positive MRD, with a modest major response (MRD negativity) rate of only 35.8%.[4] Venetoclax-based regimens may enhance the efficacy of the pre-emptive treatment, but so far there is only one report about the elimination of NPM1 mutant MRD in combination with venetoclax and low-intensity chemotherapy in AML, and studies about the efficacy of venetoclax-based regimens in the pre-emptive therapy of persistent FCM or molecular MRD positive patients are even less reported. In this study, venetoclax-based regimens were effective in the pre-emptive therapy of MRD positive AML patients, and the major response (MRD negativity) rate is 50%, which is higher than the single AZA therapy, and the relapse-free survival of responsive patients was significantly prolonged.

Moreover, there were another 36 refractory and relapsed (R/R) AML patients who were treated with venetoclax-based regimens (most of whom were treated with venetoclax plus combined intensified chemotherapy) as the salvage therapy in our center, and the complete remission (CR) rate of the 36 cases was 50% (detail data was not published), though the CR rate of R/R patients was similar with the pre-emptive therapy efficacy of MRD positive patients, but patients received pre-emptive therapy had slighter side effects than R/R patients received salvage therapy. According to the outcome of the study, the venetoclax-based regimens is worthy to be explored in the future. In consideration of the high relapse rate, we recommend that persistent MRD positive patients who could not receive allo-HSCT should receive venetoclax-based pre-emptive therapy, which could prolong the relapse-free survival if initially responsive. Several disadvantages of the study include its retrospective nature, small sample size, and short follow-up time. Thus, a large-scale prospective clinical study is warranted in the future to validate the outcomes.

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