Azacitidine in the Treatment of Pediatric Therapy-related Myelodysplastic Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation

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Summary: We herein present a case of pediatric therapy-related myelodysplastic syndrome (t-MDS) with complex karyotype who was treated with azacitidine (AZA) for AML1-EVI1 fusion transcript as minimal residual disease after allogeneic hematopoietic stem cell transplantation (HSCT). The patient was started on AZA 41 days after the HSCT without having achieved complete remission. After 9 cycles of AZA, the AML1-EVI1 fusion transcript disappeared, and there was no manifestation of graft versus host disease during AZA treatment. Preemptive AZA treatment for minimal residual disease has an acceptable safety profile and appears to be an effective strategy for preventing or substantially delaying hematological relapse in pediatric patients with high-risk myelodysplastic syndrome after HSCT.

Key Words: therapy-related myelodysplastic syndrome, azacitidine, allogeneic transplantation, AML1-EVI1

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Therapy-related myelodysplastic syndrome or acute myeloid leukemia (t-MDS/AML) is a well-recognized complication of cancer treatment. The major factors contributing to t-MDS/AML are exposure to alkylating agents, epipodophyllotoxin, and radiation therapy. Patients with t-MDS/AML generally have an inferior outcome because of the more progressive clinical course compared with patients with de novo disease, with a lower complete remission (CR) rate and a shorter duration of CR.1,2

Accumulated data indicate that the clinical and subclinical organ toxicities due to prior cancer therapy are also risk factors that limit the success of subsequent therapy. Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment for t-MDS/AML. Nevertheless, in patients eligible to undergo allogeneic HSCT, disease relapse still remains a major cause of treatment failure.

Azacitidine (AZA), a hypomethylating agent, is the first drug that has shown a significant survival advantage compared with conventional care regimens in patients with higher-risk MDS. The effect of AZA in t-MDS/AML is not established, but the recent report showed that by comparison with de novo MDS/AML, AZA received AZA for at least 1 cycle (median 4 cycles), t-MDS/AML had a similar response rate (38% vs. 45% in de novo MDS/AML).3

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fludarabine; 30 mg/m² on days −5 to −2, and melphalan; 70 mg/m² on days −3 to −2, and the graft versus host disease (GVHD) prophylaxis was performed using cyclosporine alone. Engraftment was achieved on day 10, and acute GVHD (skin grade II) was observed. A CR and complete donor chimerism were obtained in the BM, and monosomy 7 and trisomy 8 were no longer detected by FISH, but an AML1/EVI1 fusion transcript was detected by RT-PCR.

Forty-one days after the peripheral blood stem cell transplantation, the patient was started on low-dose AZA subcutaneously; 5 doses of 32 mg/m² after withdrawal of cyclosporine, based on recent reports. After 3 cycles of low-dose AZA every 4 weeks, there was no hematological toxicity, and a CR had been maintained, but an AML1/EVI1 fusion transcript was detected by RT-PCR.

Disruption of chromosome 3q26 is a rare but recurrent cytogenetic aberration that occurs in AML or MDS, and among several types of 3q26 aberrations, the most common are inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and t(3;21)(q26.2;q22). Shaoying and colleagues have reported clinicopathologic, cytogenetic, and survival data for 17 MDS/AML patients associated with t(3;21)(q26.2;q22) (12 patients had t-MDS, 4 patients had t-AML, and 1 patient had de novo AML). They described that MDS/AML associated with t(3;21)(q26.2;q22) usually showed marked multilineage dysplasia and frequent association with −7 and a complex karyotype, furthermore, all 17 patients died with 1- and 2-year survival rates of 35% and 6%, respectively.7

Chromosome 3q26.2 abnormalities have been shown to activate EVI1 expression. EVI1 plays an important role in pathogenesis by promoting myeloid proliferation and blocking differentiation. Vazquez et al have confirmed that EVI1 overexpression is an adverse prognostic factor in AML patients and the total absence of EVI1 expression might have a prognostic impact on the outcome of AML patients, and that this pattern may be regulated by epigenetic mechanisms involving DNA methylation.

Previous clinical studies in patients with MDS and AML after allogeneic HSCT have shown that low doses of AZA (8 to 40 mg/m²/d for 5 d every 4 wk) as salvage or maintenance therapy could be a potential treatment option to prevent or delay hematological relapse.4,5 So we herein presented a case of pediatric t-MDS with −7/8/−t(3;21)(q26.2;q22) that was treated with 9 cycles of AZA for minimal residual disease (MRD) (AML1/EVI1 fusion transcript) after allogeneic HSCT. The patient received 3 cycles of low-dose AZA (32 mg/m²/d) on days 1 to 5, and 6 cycles of higher-dose AZA (75 mg/m²/d) on days 1 to 5, with repeated cycles beginning on day 29.

The hematological toxicity and infectious complications associated with AZA treatment were reversible and acceptable, and no other toxicities were recognized. The use of AZA was not associated with exacerbation of GVHD. After 9 cycles of AZA, AML1/EVI1 fusion transcript disappeared and AZA was discontinued. The patient has been free from recurrence for over 26 months after the HSCT.
and over 14 months after the discontinuance of AZA, although he did not achieve a CR before HSCT.

The German RELAZA trial evaluated the efficacy of AZA in the setting of MRD-triggered preemptive therapy to prevent or delay hematological relapse in patients with MDS or AML after allogeneic HSCT. After only 4 cycles of AZA (75 mg/m²/d for 7 d), the MRD was diminished or stabilized in 80% of patients (16 of 20 patients) in the absence of a hematological relapse. Nevertheless, for 65% of patients, a hematological relapse after the initial response could not be finally prevented; 13 patients eventually relapsed, but the time to relapse was considerably prolonged.5

There is no previous data proven that the AML1/EVI1 gene translocation was eliminated by the AZA therapy. However EVI1 expression may be regulated by epigenetic mechanisms involving DNA methylation,6 so the use of AZA may have been useful for the EVI1-induced leukemogenesis in this patient.

Furthermore, recent results suggest that AZA treatment of allotransplanted mice mitigates deleterious GVHD while preserving the beneficial graft-versus-leukemia effect, because AZA induces FOXP3 expression in naive T cells, which in turn induces the production of a regulatory T-cell population.9,10

Preemptive AZA treatment for MRD has an acceptable safety profile and appears to be an effective strategy in pediatric patients with high-risk MDS after HSCT. There are little data available about AZA therapy after HSCT in pediatric MDS/AML, and therefore, further studies are needed.

REFERENCES