LETTER TO THE EDITOR

Hypomethylating agents are associated with high rates of hematologic toxicity in patients with secondary myeloid neoplasms developing after acquired aplastic anemia

Authors

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SUPPLEMENTAL APPENDIX for

Hypomethylating agents are associated with high rates of hematologic toxicity in patients with secondary myeloid neoplasms that develop after acquired aplastic anemia.

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Supplemental Table S1. Characteristics of 9 post-aplastic anemia myeloid neoplasm patients undergoing allogeneic stem cell transplant

Characteristic	Value
Total patients, n	9
Median age at SCT, years [Range]	51 [5-66]
Median time from MN diagnosis to SCT, months [Range]	6 [3-21]
Donor, n [%]	
Matched sibling	4 [44%]
Fully matched unrelated	2 [22%]
Mismatched unrelated	1 [11%]
Haploidentical	
Child	1 [11%]
Parent	1 [11%]
Conditioning regimen, n [%]	
Pediatric (n = 3)	
Flu-Cy-TBI + rATG	2 [67%]
Bu-Cy-Thiotepa + rATG	1 [33%]
Adult (n = 6)	
Cy-TBI	1 [17%]
Flu-Bu	2 [33%]
Flu-Cy-TBI	1 [17%]
Clo-Bu	1 [17%]
Flu-Bu-Mel + rATG	1 [17%]
GVHD Prophylaxis, n [%]	
Tacrolimus + methotrexate	3 [33%]
Tacrolimus + MMF	1 [11%]
PTCy + tacrolimus + MMF	1 [11%]
T-cell depletion only	2 [22%]
TCD + tacrolimus + MMF	1 [11%]
TCD + tacrolimus + MMF + PTCy	1 [11%]
Day +100-120 marrow response, n [%]	
Complete remission	4 [44%]
Complete remission with incomplete hematologic recovery	3 [33%]
Morphologic remission	1 [11%]
Patient deceased	1 [11%]
Acute GVHD, n [%]	
Any	2 [22%]
≥ Grade 2	1 [11%]
Chronic GVHD, n [%]	
Any	5 [56%]
Requiring systemic immunosuppression	5 [56%]

Abbreviations: SCT, stem cell transplant; MN, myeloid neoplasm; Flu, fludarabine; Cy, cyclophosphamide; TBI, total body irradiation; rATG, rabbit anti-thymocyte globulin; Bu, busulfan; Clo, clofarabine; Mel, melphalan; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; TCD, T-cell depletion

Supplemental Table S2. Hematologic toxicities and treatment-emergent adverse events in 9 post-AA MDS and 30 non-AA MDS patients treated with HMA

Hematologic parameters and HMA cycles			
Parameter	**Post-AA MDS [n = 9]**	**Non-AA MDS [n = 27]**	**P-value**
Median days per cycle ANC < 0.5 x10^3/µl [Range]	9 [0-40]	0.7 [0-33.5]	**0.016**
Median days per cycle Hgb < 8.0, g/dL [Range]	3.5 [0-21]	4.3 [0-21]	0.239
Median days per cycle platelets < 25, x10^3/µl [Range]	13.2 [0-35]	0 [0-21]	**0.003**
Total cycles HMA, median [Range]	2.0 [1-5]	6 [2-41]	**<0.001**
Treatment-emergent adverse events			
Adverse Event	**Post-AA MDS [n = 9]**	**Non-AA MDS [n = 27]**	**Risk Ratio [P-value]**
Patients with grade 3-4 bleeding events, n [%]	4 [40%]	2 [7%]	**6.0 [0.024]**
Patients with intracranial bleeding events, n [%]	2 [20%]	0 [0%]	14.0 [0.060]
Patients with grade 3-4 infections, n [%]	8 [89%]	4 [13%]	**6.0 [<0.001]**
Patients with febrile neutropenia, n [%]	7 [78%]	3 [11%]	**7.0 [<0.001]**
TEAEs leading to dose reduction, n [%]	3 [33%]	4 [13%]	2.3 [0.333]
Cycles delayed > 2 weeks, n [%]	4 [28%] n = 21 cycles	10 [8%] n = 186 cycles	**3.5 [0.040]**
Patients stopping treatment due to toxicity, n [%]	7 [70%]	1 [3%]	**21 [<0.001]**
Hospital admissions, n [percentage of cycles requiring hospitalization]	14 [67%]	9 [5%]	**13.8 [<0.001]**
Patients with TEAEs leading to delay in SCT, n [%]	2 [20%]	0	14.0 [0.060]
Patients with who died from TEAEs, n [%]	2 [20%]	0	14.0 [0.060]

Note: Bold values denote statistical significance.

Abbreviations: AA, aplastic anemia; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; ANC, absolute neutrophil count; Hgb, hemoglobin; TEAE, treatment-emergent adverse event

Supplemental Figure S1. Clonal evolution of 14 patients with aplastic anemia who subsequently developed secondary myeloid neoplasms.

Proportion of all post-aplastic anemia myelodysplastic syndrome patients with specified (**A**) clonal somatic mutations and (**B**) clonal cytogenetic abnormalities detected in bone marrow at baseline, following immunosuppressive therapy (IST), at myeloid neoplasia (MN) diagnosis, and post-chemotherapy or stem cell transplant.