ELSEVIER

Blood 142 (2023) 2720–2722

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Hypomethylating Agents Are Associated with High Rates of Hematologic Toxicity in Patients with Secondary MDS/AML That Develops after Acquired Aplastic Anemia

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Acquired aplastic anemia (AA) is an autoimmune bone marrow failure (BMF) associated with depletion of hematopoietic stem and progenitor cells. Approximately 15-20% of AA patients treated with immunosuppressive therapy (IST) develop late complications of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Little is known about managing patients with post-AA myeloid neoplasms (MN).

We hypothesized that patients with post-AA MN may be particularly susceptible to hematologic toxicities from cytotoxic therapy because of stem cell deficits. To investigate our hypothesis, we retrospectively analyzed post-AA MN patients treated at our 2 institutions over the past 15 years.

Fourteen post-AA MN patients were identified: 11 with MDS, 1 with AML, and 2 with clonal cytopenia of undetermined significance (CCUS). Patients with inherited BMF or allogeneic stem cell transplant (SCT) prior to MN diagnosis were excluded. The median age at MN was 56.5 years (range 5-75) with a median time of 5 years (range 0.25-30) between AA diagnosis and MN. At MN diagnosis, 12 of 14 patients (86%) had a partial or complete response of AA with 5 receiving cyclosporine (CSA) maintenance. Two patients (14%) were on CSA within 6 months of IST without response. After MN diagnosis, CSA was discontinued. Ten adults received hypomethylating agents (HMA) as first-line treatment in preparation for SCT. Three pediatric patients were treated with SCT with no prior HMA. One patient died before receiving treatment. The 10 post-AA patients who received HMA were matched in a 3:1 ratio with a similarly aged, randomly selected non-AA MDS cohort treated with HMA at our center during the same period (Table 1).

Compared to patients with non-AA MDS, post-AA MN patients tolerated HMA poorly with frequent, severe complications. Their median per-cycle duration of grade 4 neutropenia was longer (9 v. 1.5 days, $p = 0.044$), as was median duration of grade 4 thrombocytopenia (13 v. 0 days, $p = 0.003$). Post-AA patients notably had lower baseline platelets prior to HMA (median 36.5 v. 115 k/mL, $p = 0.007$). Following HMA, the post-AA cohort had higher rates of febrile neutropenia (80% v. 17%, RR 4.8, $p < 0.001$) and infections $\geq$ grade 3 (90% v. 13%, RR 6.8, $p < 0.001$). They also had higher rates of $\geq$ grade 3 bleeding (40% v. 7%, RR 6.0, $p = 0.026$) with 2 patients (20%) experiencing intracranial hemorrhage on HMA; no such events occurred in the non-AA cohort. Post-AA patients had more hospital admissions - 18 in 25 total chemotherapy cycles (72%) compared to 12 in 207 cycles (6%) in the matched cohort (RR 12.4, $p < 0.001$).

Post-AA MN patients had more treatment delays >2 weeks (28% v. 8% of planned treatment cycles, RR 3.4, $p = 0.01$) and dose reductions (40% v. 13%, RR 3.0, $p = 0.089$). HMA was discontinued due to treatment-emergent adverse events (TEAEs) in 70% of post-AA cases v. 3% of non-AA patients (RR 21.0, $p < 0.001$). Consequently, post-AA MN patients received fewer cycles of HMA compared to non-AA patients (median 2.5 v. 6, $p = 0.021$). Death occurred following TEAEs in 20% of post-AA MN patients; no deaths on HMA occurred in the non-AA cohort (RR 14.1, $p = 0.058$). Among surviving patients, SCT was delayed in 20% of the non-AA cohort due to TEAEs, while no delays occurred in the matched cohort. The median months from final chemotherapy cycle to SCT were 4 (range 1-12) in post-AA v. 1 (1-3) in non-AA, while median months from MN diagnosis to SCT were 8.5 (4-21) in post-AA v. 5 (4-15) in non-AA.

For all 14 post-AA MN patients, including those not treated with HMA, overall survival (OS) from MN diagnosis was 71% (95% CI 51-99) at 1 year and 56% (95% CI 34-90) at 3 years. OS of post-AA MN patients differed significantly ($p = 0.011$) based on treatment with SCT. Among the 5 who did not receive SCT, 4 died within 3 years of MN, while 1 patient is alive 13 months from diagnosis receiving supportive care after intracranial hemorrhage during the first cycle of HMA. In contrast, 7 of 9 (78%) patients who received SCT were alive 3 years after MN diagnosis. Of the 6 patients treated with SCT after HMA, 5 stopped HMA due to toxicity, all had morphologic dysplasia at SCT, and 2 were transplanted with $\geq$ 5% marrow blasts.
Our study shows that patients with MN following antecedent autoimmune AA are at high risk of severe toxicities with standard HMA regimens and have difficulty tolerating repeated cycles. Our results do not support routine use of HMA prior to SCT in this patient population and suggest that early SCT may be the most suitable strategy.

Disclosures Frey: *Sana Biotechnology:* Consultancy; *Kite Pharma:* Consultancy. **Gill:** *Kite Pharma:* Consultancy; *Carisma Therapeutics:* Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: patents, Research Funding; *Interius Biotherapeutics:* Current equity holder in private company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Asher:* Research Funding; *Currus:* Membership on an entity's Board of Directors or advisory committees; *Inndura:* Membership on an entity's Board of Directors or advisory committees; *Mission Bio:* Membership on an entity's Board of Directors or advisory committees; *NKILT:* Membership on an entity's Board of Directors or advisory committees; *Vor Bio:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Lai:** *Jazz:* Consultancy, Research Funding, Speakers Bureau; *Rigel:* Consultancy; *BMS:* Consultancy; *Genentech:* Consultancy; *Novartis:* Consultancy; *Taiho:* Consultancy; *Pfizer:* Consultancy; *Daiichi:* Consultancy; *Astellas:* Consultancy, Speakers Bureau; *AbbVie:* Consultancy. **Luger:** *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy; *Marker Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Bristol-Myers Squibb:* Honoraria; *Onconova:* Research Funding; *Astellas:* Honoraria. **Perl:** *Genentech:* Honoraria; *Rigel:* Honoraria; *Beat AML:* Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Bayer:* Research Funding; *Aptose:* Honoraria; *BerGen Bio:* Honoraria; *Syndax:* Research Funding; *Foghorn:* Consultancy; *Immunogen:* Honoraria; *Astellas:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *FujiFilm:* Research Funding; *Daiichi-Sankyo:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *BMS:* Honoraria; *Forma:* Consultancy; *Actinium:* Honoraria. **Porter:** *Tmunity:* Patents & Royalties; *Sana Therapeutics:* Consultancy, Current equity holder in publicly-traded company; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *National Marrow Donor Program:* Membership on an entity's Board of Directors or advisory committees; *Mirror Biologics:* Membership on an entity's Board of Directors or advisory committees; *Kite/Gilead:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Genentech:* Current equity holder in publicly-traded company; *DeCart:* Membership on an entity's Board of Directors or advisory committees; *Capstan Bio:* Honoraria; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Bluebird Bio:* Membership on an entity's Board of Directors or advisory committees; *Angiocrine Bio:* Membership on an entity's Board of Directors or advisory committees; *Wiley and Sons Publishing:* Honoraria. **Pratz:** *Roche:* Membership on an entity's Board of Directors or advisory committees; *Astra Zeneca:* Membership on an entity's Board of Directors or advisory committees; *Astellas:* Membership on an entity's Board of Directors or advisory committees; *Jazz Pharamceuticals:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Bristol-Myers Squibb:* Membership on an entity's Board of Directors or advisory committees; *Agios Pharmaceuticals:* Research Funding; *AbbVie:* Consultancy, Research Funding.

Table 1: Clinical Characteristics and Treatment-Emergent Adverse Events of 10 Patients with Post-Aplastic Anemia (AA) Myeloid Neoplasms (MN) and 30 Age-Matched Controls Treated with Hypomethylating Agents (HMA)

Characteristics	Post-AA MN treated with HMA* (n = 10)	Non-AA MDS treated with HMA (n = 30)	P-value
Median Age at MN diagnosis**, years [Range]	62.5 [49-75]	62 [46-75]	0.656
Female Sex, n [%]	5 [50%]	10 [33%]	0.457
Diagnosis, n [%]			N/A
AML	1 [10%]	0	
MDS	8 [80%]	30 [100%]	
CCUS	1 [10%]	0	
IPSS-R, n [%]			0.511
Very High	1 [10%]	8 [27%]	
High	2 [20%]	8 [27%]	
Intermediate	4 [40%]	8 [27%]	
Low	1 [10%]	2 [7%]	
Very Low	1 [10%]	0	
Unknown	1 [10%]	4 [13%]	
Median Cellularity at MN Diagnosis, % [Range]	55 [30-65]	65 [10-95]	0.365
Median Blasts at MN Diagnosis, % [Range]	3.5 [0-14]	5 [0-20]	0.115
Median ANC Prior to HMA, cells/µl [Range]	1310 [40-5800]	1500 [30-10,500]	0.092
Median Hgb Prior to HMA, g/dL [Range]	10.3 [7.2-13.6]	9.6 [6.2-14.4]	0.055
Median Platelets Prior to HMA, k/µl [Range]	36.5 [10-255]	115 [6-477]	**0.007**
Received SCT after HMA, n [%]	6 [60%]	15 [50%]	0.721
Median Months MN Diagnosis to SCT [Range]	8.5 [4-21], n=6	5 [4-10], n=15	0.452
Median Months Last Chemo to SCT [Range]	4 [1-12], n=6	1 [1-3], n=15	0.171
Median Marrow Blasts at SCT, % [Range]	4 [0-32], n=6	1 [0-5], n=15	0.084
Hematologic Toxicity While on HMA			P-value
Median Days per Cycle ANC < 500 cells/µl [Range]	9 [0-40]	1.5 [0-33.5]	**0.048**
Median Days per Cycle Hgb < 8.0 g/dL [Range]	5.5 [0-21]	4 [0-21]	0.270
Median Days per Cycle Platelets < 25 k/µl [Range]	13 [0-35]	0 [0-21]	**0.009**
Median Cycles HMA [Range]	2.5 [1-13]	6 [1-41]	**0.021**
Treatment Emergent Adverse Events (TEAEs)			Risk Ratio (P-value)
Patients with Grade 3-4 Bleeding Events, n [%]	4 [40%]	2 [7%]	**6.0 (0.026)**
Intracranial Bleeding Events, n [%]	2 [20%]	0 [0%]	14.1 (0.058)
Patients with Grade 3-4 Infections, n [%]	9 [90%]	4 [13%]	**6.8 (<0.001)**
Patients with Febrile Neutropenia, n [%]	8 [80%]	5 [17%]	**4.8 (<0.001)**
TEAEs leading to dose reduction, n [%]	4 [40%]	4 [13%]	3.0 (0.089)
Cycles delayed > 2 weeks, n [%]	7 of 25 total cycles [28%]	17 of 207 total cycles [8%]	**3.6 (0.007)**
Treatment stopped due to toxicity, n [%]	7 [70%]	1 [3%]	**21.0 (<0.001)**
Patients needing admission for TEAEs, n [%]	9 [90%]	10 [33%]	**2.7 (0.003)**
Hospitalizations (% of cycles requiring admission)	18 [72%]	12 [6%]	**12.4 (<0.001)**
Patients with TEAEs delaying SCT, n [%]	2 [20%]	0	14.1 (0.058)
Patients who died from TEAEs, n [%]	2 [20%]	0	14.1 (0.058)

* The table does not include 4 patients with post-AA MN, who did not receive HMA. Of these patients, 3 were pediatric and went to SCT without chemotherapy; 1 was an adult who died of presumed sepsis prior to therapy.

** AA was diagnosed using standard criteria, which required exclusion of inherited bone marrow failure. Non-AA MN patients were a randomly selected subset of age-matched patients treated with HMA at the University of Pennsylvania over the same time period as post-AA patients.

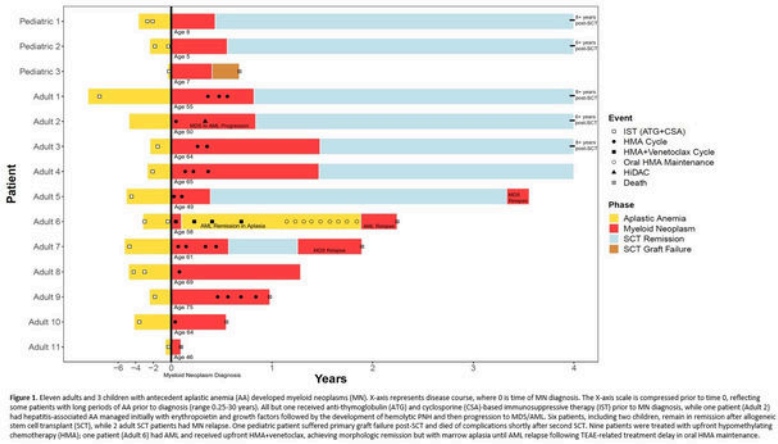

Figure 1. Eleven adults and 3 children with antecedent aplastic anemia (AA) developed myeloid neoplasms (MN). X-axis represents disease course, where 0 is time of MN diagnosis. The X-axis scale is compressed prior to time 0, reflecting some patients with long periods of AA prior to diagnosis (range 0.25-30 years). All but one received anti-thymoglobulin (ATG) and cyclosporine (CSA)-based immunosuppressive therapy (IST) prior to MN diagnosis, while one patient (Adult 2) had hepatitis-associated AA managed initially with erythropoietin and growth factors followed by the development of hemolytic PNH and then progression to MDS/AML. Six patients, including two children, remain in remission after allogeneic stem cell transplant (SCT), while 2 adult SCT patients had MN relapse. One pediatric patient suffered primary graft failure post-SCT and died of complications shortly after second SCT. Nine patients were treated with upfront hypomethylating chemotherapy (HMA); one patient (Adult 6) had AML and received upfront HMA+venetoclax, achieving morphologic remission but with marrow aplasia until AML relapse following TEAE-related treatment delay in oral HMA maintenance.

Figure 1

https://doi.org/10.1182/blood-2023-179383