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Case Report
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Intensive Chemotherapy Is Associated With Poor Overall Survival in Autoimmune Disease-associated Myeloid Malignancies

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Between 10% and 20% of cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are associated with prior exposure to cytotoxic chemotherapy or ionizing radiation.[1] Such therapy-related myeloid neoplasms have also been associated with treatment for nonmalignant conditions, notably autoimmune diseases (AID) such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA).[2] Furthermore, the chronic inflammatory state associated with AID has been associated with an increased risk of myeloid malignancies, independent of the treatments used.[3] A recent study of over 40,000 patients with AID showed a statistically significant 7-fold increase in therapy-related myeloid neoplasms in patients treated with azathioprine, with smaller, nonsignificant risks attributable to cyclophosphamide and mitoxantrone, but not anti-tumor necrosis factor therapy (in contrast with lymphoma).[4,5] While therapy-related myeloid neoplasms are generally associated with poor prognosis, there are limited published outcome data in the AID setting. In a single-center experience of 23 patients with AID-associated AML, most exhibited intermediate (43%) or favorable risk (26%) cytogenetics and intensive treatment (including allogeneic transplantation) was associated with a median overall survival (OS) of 68 months.[6] Of note, this cohort was relatively young (median 59 years) and the 83% of cases were female, both of which associate with more favorable prognosis in AML/MDS. This contrasts with smaller case series that associate AID-AML/MDS with poor-risk cytogenetics and short OS.[7–9]

We report the characteristics and treatment outcomes of 19 consecutive patients presenting to University College London Hospital with AML/MDS on a background of treatment for AID between August 2011 and March 2018 (Table 1). The median age at presentation with AML/MDS was 62 years (interquartile range [IQR] 50–70 years) with a secondary peak at age 19 years (n = 3). There was an equal sex distribution (M = 10, F = 9). The most common AIDs were IBD (ulcerative colitis n = 6, Crohn disease n = 1), myasthenia gravis (n = 3), and RA (n = 3). The median time from diagnosis of AID to myeloid malignancy was 10 years (IQR 76–251 months). The commonest immunosuppressive agents used were azathioprine (n = 10), methotrexate (n = 5), sulfasalazine (n = 5), and cyclophosphamide (n = 2). Three cases (patients 5, 11, and 15) had no exposure to immunosuppressive therapy associated with myeloid malignancies. Despite the presence of underlying AID, the baseline performance status of the majority of patients was good (18/19 ECOG 0), although some patients had significant comorbidities (Table 1).

Thirteen patients (68%) presented with features consistent with AML. Six patients (32%) presented with MDS (n = 3) or chronic myelo-monocytic leukemia (CMML) (n = 3). Patients exposed to azathioprine presented with both AML (n = 5) and MDS (n = 5), whereas those exposed to sulfasalazine, methotrexate, and cyclophosphamide all presented with AML. The majority of patients presented with modest peripheral leukocyte counts (median 5.3×10^9/L, IQR 2.4–11.0 $\times 10^9$/L, max 150 $\times 10^9$/L) and relatively preserved hematopoiesis (median hemoglobin 96 g/L, IQR 88–114 g/L; platelets 88 $\times 10^9$/L, IQR 26–139 $\times 10^9$/L). Median bone marrow blast percentage was 25% (IQR 12–60%). One patient presenting with AML had good-risk cytogenetics and remains in long-term complete remission (CR) after intensive chemotherapy. One patient with unopposed *NPM1* mutation died of respiratory failure during induction chemotherapy. The majority (53%) of patients exhibited poor-risk cytogenetics (n = 10). Six of seven patients tested by next-generation sequencing harbored poor-risk mutations.[10] Overall,

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Table 1

Summary of Patient Characteristics

Patient Number	M/F	Age, y	Autoimmune Diagnosis	Time From AID, mo	Immuno-suppressive Exposure	Baseline PS (ECOG)	Comorbidity	AML/MDS	Hb, g/L	WCC, 10^9/L	Peripheral blasts, 10^9/L	Neutro-phils, 10^9/L	Platelets, 10^9/L	Bone Marrow Blasts, %	Cytogenetics/ FISH	Mutations (%VAF)	Induction Treatment	Cycles	Status After Course 1	Salvage Treatment	Overall Survival, d	Dead	Cause Death
1	M	22	Ulcerative colitis	55	Azathioprine	0	Nil	CMML	88	44	6.21	5.3	43	12	−7		Fla-Ida	1	CR	Azacitidine ×1 cytarabine/idarubicin	267	Yes	Relapse: chest sepsis
2	F	68	Ulcerative colitis	79	Mesalazine, azathioprine	0	DM (T2)	MDS-EB2	89	9.14	2.29	2.84	118	14	−7		Azacitidine	6	Refractory		251	Yes	Refractory
3	M	64	Scleroderma	76	Cyclophosphamide	0	Emphysema, pulmonary fibrosis, chronic liver disease	AML	149	150	90	54	26	43			DA (60)	1	Induction death		15	Yes	Induction death: pulmonary hemorrhage
4	F	19	Ulcerative colitis	209	Sulfasalazine, azathioprine, infliximab	0	Nil	AML/myeloid sarcoma (ileopsoas)	80	2.28	0	0.71	26	50	Complex		Fla-Ida	1	Induction death		37	Yes	Induction: multiorgan failure/sepsis
5	M	84	Myasthenia, giant cell arteritis	150	Prednisolone	0	DM (T1), pernicious anemia	MDS	87	11	0	8.16	108	4	Normal		Azacitidine	8	PR	Low-dose cytarabine, hydroxycarbamide	762	Yes	Progression to refractory AML
6	F	70	Polymyositis	27	Methotrexate	0	HTN	AML	123	2.7	0	0.37	139	30			DA	1	Induction death		28	Yes	Induction death: chest sepsis
7	F	50	Rheumatoid arthritis	251	Methotrexate, sulfasalazine, anti-TNF	0	Nil	AML	114	3.7	1.22	0.37	140	73	inv16		DA DA-GO HDAC	3	CR		1220		
8	F	46	Myasthenia gravis	123	Azathioprine	0	HTN, DM (T2), asthma	AML	108	1.71	0	0.24	119	40	46 XX, 5q−, 7q−, TP53x1		FLA IDA	1	Refractory	MACE	121	Yes	Refractory: sepsis
9	F	66	Rheumatoid arthritis	251	Azathioprine, leflunomide, methotrexate, abatacept	0	Osteoporosis, active skin and previous gut vasculitis, bowel resection with colostomy	AML	123	2.4	5	0.98	327	60	46 XX - ?int del2	ASXL1 (49%), DNMT3A R882C (22%)	Azacitidine	15	CR	Intermediate cytarabine, FLA-Ida x2	648		
10	F	71	Goodpasture's, renal allograft	67	Cyclophosphamide	0	Renal transplant, HTN, hypothyroidism	AML	103	5.72	1.2	2.4	68	90	Complex (hyperdiploid, TP53 del)		Declined	0	Untreated		48	Yes	Untreated AML
11	M	82	Ulcerative colitis	97	Mesalazine	0	DM (T2), HTN, subclinical hypothyroidism	CMML	97	10	0	4.2	86	4	600 kb del including CUX1 on 7q	SRSF2 (42%), TET2 (45%)	Azacitidine	11	CR		406		
12	F	13	Ulcerative colitis	85	Azathioprine	0	Nil	Myeloid sarcoma (mediastinal)	125	9.6	0	6.57	227	0		BM relapse—EZH (31%), WT1 (26.3), KRAS (29%), TP53 (29%)	Fla-Ida	2	Refractory	DA (60)+3xGO	167	Yes	Refractory: fungal chest
13	F	62	Ulcerative colitis	315	Azathioprine, balsalazide, infliximab, vedolizumab	0	Nil	CMML	91	4	0	2.24	20	12	42XX, monosomal, complex-7, 5q−	TP53 (83%)	Azacitidine	5	Refractory	Venetoclax	183	Yes	Refractory
14	M	58	Systemic lupus erythematosus	242	Azathioprine, hydroxychloroquine, corticosteroid	0	APLS with 2 strokes, no residual deficit; severe mixed aortic valve disease	MDS-EB2	80	1.68	0	0.6	20	15	del 7q, gain 1q, +8	U2AF1 (24%), BCOR (53%), RUNX1 (25%), BCORL1 (51%), IDH2 R140Q (22%)	Azacitidine	6	CR		275	Yes	Neutropenic sepsis/heart failure
15	M	66	Ankylosing spondylitis	506	Phenylbutazone, sulfasalazine, adalimumab	0	HTN, IHD	AML	109	2.7	0	0.22	63	22	Complex monosomal (including TP53 del)		Azacitidine	6	Refractory		155	Yes	Refractory
16	M	74	Myasthenia gravis	123	Azathioprine	1	DM (T2), HTN	AML	89	1.35	0	0.6	88	22	FISH 5q−, +8, MLL amplification		Azacitidine	2	Refractory		91	Yes	Refractory: sepsis
17	M	58	Mixed connective tissue disease	76	Methotrexate, sulfasalazine	0	Nil	AML	134	17	0.83	10	169	25	FISH MECOM rearrangement, −7, +8	DNMT3A R882H (47%), IDH2 R140W (46.7%), TET2 (48%), EZH2 (17%), RUNX1 (20%), ASXL1 (50%), CSF3R (52%), CBL (47%), U2AF1 (47%)	CPX351	1	Induction death		34	Yes	Refractory: respiratory failure
18	M	54	Crohn disease	567	Azathioprine, adalimumab	0	Anastomotic stricture, active proctitis	AML	96	11.69	8.56	0.47	101	95	46 XY, 20q−, 7q32-ter deletion	BCOR (95%), RUNX1 (43%)	DA (60)+ GO DA (50), HDAC	3	CR	RIC allograft	350		
19	M	55	Rheumatoid arthritis	84	Methotrexate, sulfasalazine, hydroxychloroquine	0	Nil	AML	86	5.3	4.45	0.21	13	90	Normal	NPM1	FLAG-Ida	1	Induction death		24	Yes	Respiratory failure/pneumonitis

APLS = antiphospholipid syndrome, CMML = chronic myelo-monocytic leukaemia, DM = diabetes mellitus (T1: type 1; T2: type 2), FISH = fluorescence in situ hybridization, GO = gemtuzumab ozogamicin, Hb = hemoglobin concentration, HDAC = high-dose cytarabine, HTN = hypertension, IHD = ischemic heart disease, PR = partial remission, PS = performance status, RIC = reduced intensity conditioning, TNF = tumor necrosis factor, VAF = variant allele frequency, WCC = white cell count.

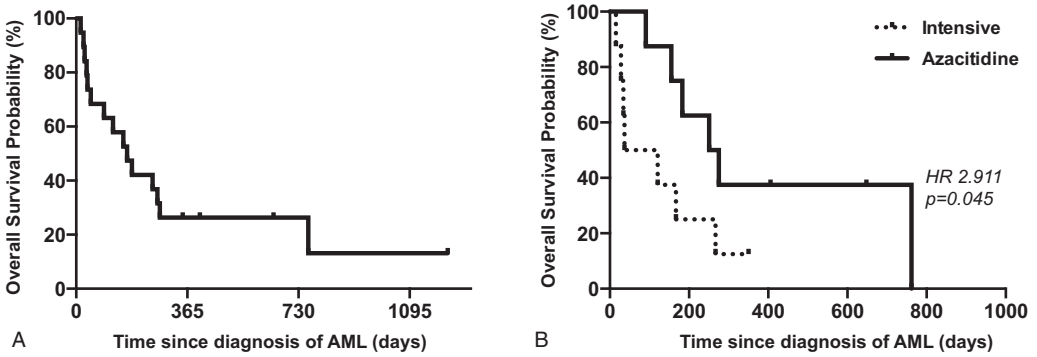

Figure 1. Analysis of overall survival outcomes. (A) Overall survival probability of all patients with AID associated myeloid neoplasms (median = 167 days, n = 19). (B) Overall survival probability comparing induction treatment with intensive multiagent chemotherapy (n = 8) to the demethylating agent azacitidine (n = 8) in cytogenetically intermediate/poor-risk AML/MDS secondary to AID (79 vs 263 days, HR 2.911, 95% CI 0.87–9.73, $P = 0.045$). AID = autoimmune disease, AML = acute myeloid leukemia, CI = confidence interval, HR = hazard ratio, MDS = myelodysplastic syndrome.

the majority of patients (68%, n = 13) harbored an adverse cytogenetic or molecular marker, with 21% intermediate-risk (n = 4, including 2 with no cytogenetic/molecular results) and 11% (n = 2) good-risk.

Ten patients were treated with intensive induction chemotherapy, including both favorable risk patients (median age 52 years, AML [n = 9]). Eight patients received nonintensive treatment with azacitidine (median age 67, range 58–84, MDS/CMML n = 6) and 1 patient declined treatment. Of the patients undergoing an intention-to-treat with intensive induction chemotherapy, only 3 (30%) received more than 1 cycle of first-line treatment, with 50% of these patients dying within 40 days of diagnosis, principally from sepsis and/or respiratory failure. Three patients treated intensively received re-induction chemotherapy at relapse, none of whom achieved CR. One patient treated with intensive chemotherapy responded sufficiently to proceed to allogeneic bone marrow transplantation. By contrast, the median number of cycles of azacitidine administered at time of analysis was 6 (range 2–15). Two patients who progressed on azacitidine underwent salvage treatment: patient 9 successfully achieved a second CR with intensive chemotherapy; patient 13 was treated with venetoclax, but died of refractory AML. Overall, CR was achieved in a total of 6 patients (3/10 intensive, 3/8 azacitidine).

Median OS for all patients was surprisingly poor at 167 days (Fig. 1A). Unexpectedly, AID-AML/MDS patients treated with intensive chemotherapy demonstrated a significant survival disadvantage over those treated nonintensively with azacitidine (median OS 79 vs 263 days, hazard ratio 2.911, 95% confidence interval 0.87–9.73, $P = 0.045$) (Fig. 1B).

Our experience suggests that AID-AML/MDS is associated with adverse prognostic factors and a median OS shorter than expected in secondary-AML/MDS. Patients with intermediate/poor-risk AID-AML/MDS treated with intensive chemotherapy have markedly high induction mortality, low rates of CR and dismal OS. By contrast, the demethylating agent azacitidine was not associated with significantly reduced OS in AID patients and should be considered as a less toxic alternative to intensive chemotherapy in this cohort. This is the second-largest published cohort of AID-AML/MDS treatment outcomes, with results that are markedly inferior to those from the larger Philadelphia series.[6] This disparity likely relates to biases in retrospective series, such as differences in age or gender. Further studies are required to identify AID-AML/MDS patients who benefit from intensive induction chemotherapy and investigate novel curative treatment strategies, in particular whether azacitidine can provide a safe and effective bridge to allogeneic transplantation. Lastly, as high-dose chemotherapy is increasingly used to treat advanced AID, our experience suggests that clinicians should exercise caution and proactively report adverse outcomes.

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