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Acute Myeloid Leukemia Following Myelodysplastic Syndrome and Failure of Therapy with Hypomethylating Agents: An Emerging Entity With a Poor Prognosis

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Abstract

We assessed outcome of 63 patients with acute myeloid leukemia (AML) arising from myelodysplastic syndrome (MDS) failing hypomethylating agents (HMA). Median age was 63 years. All 63 patients received at least 1 salvage regimen for AML and 35 patients (55%) received 2 or more. Of the 31 patients (49%) who received high-dose cytarabine (HDAC) at first relapse, 2 (6%) achieved complete remission (CR) and 4 (13%) CR with incomplete platelet recovery (CRp) for an overall response rate (ORR) of 19%. Of the 32 patients (51%) who received other treatments including investigational agents, 4 (12%) achieved CR and 4 (12%) CRp, for an ORR of 24%. Median response duration was 20 weeks. With a median follow up of 42 months from AML diagnosis, median survival was similar between the 2 groups (21 weeks). The 1- and 2-year survival rates were 19% and 8%, respectively. Multivariate analysis identified low albumin, HDAC treatment, and platelet count $<50\times10^9$/L as independent adverse factors for CR, and platelet count $<50\times10^9$/L and age>65 years as independent adverse factors for survival. In conclusion, outcome of AML following MDS post HMA failure is poor, and not improved with HDAC. Novel therapies directed towards this emerging entity are urgently needed.

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Authorship

Contributions: E.J, H.G., G.G.M., H.K, F.R, S.O.B and E.J. designed and performed the research and analyzed the data; H.G., X.H., S.P., S.C., M.B. and E.J. analyzed the data; G.G.M., S.V., F.R. and H.K., provided the analytical tools; and E.J., H.G., G.G.M., J.C., and H.K. wrote the manuscript.

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Keywords

myelodysplastic syndromes; acute myeloid leukemia; hypomethylating agents failure; outcomes

Introduction

The textbook knowledge of acute myeloid leukemia (AML) presents it as an entity with relatively good response to standard intensive chemotherapy and with a reasonable prognosis. Traditionally, the quoted complete response rate with intensive AML-type chemotherapy, consisting of cytarabine and anthracyclines (3+7 regimens) is 60% to 80%, and the long term survival rate is 30% to 40%.[1–4] The complete remission (CR) and survival rates are strongly dependent on several factors including age, performance status, comorbid conditions, karyotype and molecular abnormalities.[5–10] Most of this research knowledge and standard of care is based on large scale single institutional and cooperative group trials targeting younger patients (age younger than 55–60 years) with de-novo AML. Recent studies have addressed the issue of elderly AML, emphasizing the poor prognosis of these patients, their poor tolerance and high mortality with intensive chemotherapy, and the different biology of the disease in older patients.[11,12] This prompted new marrow studies and publications reporting on the outcome of older patients with AML following intensive chemotherapy and low intensity (targeted) therapies using hypomethylating agents (decitabine, azacitidine), cytotoxic therapies (clofarabine, low dose cytarabine, sapacitabine), and other targeted or investigational therapies.[13–19]

The incidence of AML is about 14,000 cases a year in the United States.[20] The success in curing patients with solid tumor is resulting in an increasing incidence of therapy related MDS and AML. This entity used to include less than 20% of patients with AML in older studies. Such patients are also usually excluded from cooperative group trials, but now consist of up to 30% to 50% of patients with AML referred to tertiary cancer centers. Their prognosis is poor with reported CR rates of 40–50% with standard AML therapy, and with cure rates of less than 10%–20%.[21–24] The incidence of MDS in the United States is reported to range from 15,000 to 45,000 cases annually, depending on the source of reporting.[20,25] The later higher figures appear to be more consistent with what is observed in oncology community practices. Recently, hypomethylating agents have become new standards of care in the treatment of MDS, improving cytopenias, producing remissions, and prolonging survival.[26–28] These include azacitidine and decitabine. This has now resulted in a significantly larger proportion of patients who benefit from these therapies, but subsequently progress to AML. Very little is known about the biology and molecular aberrations of this entity, AML following MDS and failure to hypomethylating agents. Little is also known about the response of such patients to standard AML type therapy, or to investigational therapy, in their long term prognosis. This entity is likely to soon overwhelm in numbers de-novo AML, and to produce a new and unfortunately adverse picture of the large entity of AML in relation to prognosis. Therefore it is very important to define this entity in relation to its anti AML responsiveness and prognosis, and to establish it as a separate entity to be separated from de-novo AML and from therapy related AML in ongoing clinical research trials and cooperative group trials addressing investigational

programs in AML therapy. This work reviews our experience with AML following MDS failure to hypomethylation therapy, and highlights our urgent need to define this entity molecularly and to design novel therapeutic trials addressing the particular needs of this emerging problem.

Study Group and Methods

Adults with a diagnosis of AML following MDS and failure to hypomethylating agents (HMA), who were referred to MD Anderson Cancer Center, from January 2003 until the present were reviewed. All patients were treated on Institutional Review Board-approved protocols. Informed consent was obtained in accordance with the Declaration of Helsinki.

Response to therapy was documented according to standard response criteria. Response duration was calculated from the date of response documentation until date of disease relapse. Survival was calculated from the date of documentation of AML. Diagnosis of AML was based on the presence of 20% or more blasts. Univariate and multivariate analyses of prognostic factors for achievement of CR used logistic regression model and survival used the Cox proportional hazard model.

Results

Patients Characteristics

A total of 63 patients with AML following MDS and failure to HMA therapy were reviewed. Median age was 65 years (range 38 to 90 years). Thirty patients (48%) were 65 years or older, 16 (25%) were 70 or older. Twenty-five patients (39%) were female. Cytogenetic analysis was available for 58 patients (91%). Abnormal karyotypes were observed in 42 patients (66%), including adverse karyotypes consisting of chromosome 5 or 7 abnormalities in 28 patients (44%). Three or more chromosomal abnormalities (complex karyotype) were observed in 30 patients (42%). Twenty patients (32%) had complex karyotype and chromosome 5 or 7 abnormalities. At the time of MDS diagnosis, 55 patients (87%) had refractory anemia with excess blasts (RAEB), 3 patients (5%) had refractory cytopenias with multilineage dysplasia (RCMD), 2 patients (3%) had RCMD with ringed sideroblasts (RCMD-RS), 1 patient (2%) had refractory anemia (RA) and 2 patients (3%) had MDS not otherwise specified, according to the World Health Organization (WHO) classification. Equally, 13 patients (20%) had a high-risk disease according to the International Prognostic System Score (IPSS), 33 (52%) had an intermediate-2 risk disease, 16 (25%) had an intermediate-1 risk, and 1 (2%) had a low-risk disease. The median duration of MDS was 10 months (range 1 to 52 months). Prior to progression into AML, 50 patients (80%) received decitabine based regimen and 13 (20%) received azacitidine based regimen. The patient characteristics are detailed in Table 1. Response to prior HMA therapy was noted in 20 of 63 evaluable patients (32%), including CR in 18 out of 63 patients (28%) and CR with incomplete count recovery (Cri) in 2 patients (3%).

Response to induction therapy

After progression to AML, all 63 patients (100%) received at least 1 salvage regimen, 35 (55%) received 2 or more salvage regimens and 15 (24%) received 3 or more salvage

regimens. Salvage regimen and CR rates by regimen are summarized in tables 2, 3 and 4. Thirty-one patients (49%) received high-dose cytarabine (HDAC)-based regimen as first salvage and 11 (17%) as second salvage. Thirty-two patients (51%) received investigational agents at time of first relapse. Seven patients (11%) underwent an allogeneic hematopoietic stem cell transplant (ASCT) after 1st salvage therapy, 3 of them after receiving HDAC. Table 3 summarizes response to first and second salvage therapies. Of the 31 patients who received HDAC at first relapse, 2 (6%) achieved CR and 4 (13%) CR without platelet recovery (CRp), for an overall response rate (ORR) of 19%. Of the 32 patients who received other agents at first relapse, 4 (12%) achieved CR and 4 (12%) CRp, for an ORR of 24%. Of the 11 patients who received HDAC at 2nd relapse, 2 (18%) achieved CRp. Of the 24 patients who received other agents at second relapse, 3 (12%) achieved CR and 3 (12%) CRp for an ORR of 24%. Of the 16 patients with diploid cytogenetics at time of AML, 3 had a CR for an ORR of 19%. Twelve patients subsequently underwent allogeneic or cord stem transplantation, 7 as first salvage, 4 as second salvage and 1 as 3rd salvage therapy; 5 of them had active disease at time of receiving the transplant, and 7 were in CR: five after HDAC containing regimens, and 2 after other agents. The median CR duration after first salvage was 21 weeks with HDAC therapy and 20 weeks with other therapy (p=0.99) (Figure 1a). The median CR duration after second salvage was 21 weeks with HDAC therapy and 17 weeks with other therapy (p=0.78). A multivariate analysis identified 3 independent adverse factors for achieving CR (Table 5): albumin level <3 grams/dL, HDAC treatment, and platelet count $<50\times10^9$/L.

Survival

With a median follow-up of 42 months from transformation into AML, 5 (8%) patients remained alive, 3 of them in CR following ASCT. The median survival of the total study group was 5 months (range 1 to 75 months) (Figure 1b). The estimated 1-year survival and 2-year survival rates were 19% and 8%, respectively. Survival overall by type of therapy (intensive versus other treatments) is shown in Figure 1c. There was no difference in OS between the 2 groups: the median OS was 25 weeks for HDAC and 20 weeks for other therapies (p=0.76). The 8 week overall mortality was 23% with intensive chemotherapy and 21% with other therapies (p=0.93). A multivariate analysis identified patients' age >65 years and platelet count $<50\times10^9$/L as independent factors associated with worse survival.

Discussion

Our analysis highlights this emerging entity, AML following MDS and failure to hypomethylation therapy, as an important one for several reasons: 1) the poor prognosis of these patients with current standard of care; 2) the need to understand the differences between the pathophysiology of this entity versus Denovo AML and therapy related AML; 3) the need to consider this entity as separate in investigational trials in ongoing and future investigational trials of AML; 4) the urgent need to develop novel and unique therapies for this entity based on understanding of its pathophysiology.

In Denovo AML, the CR rate ranges from 60% to 80% and the long term survival rate is about 40%, particularly in younger patients. The entity of AML following MDS and failure

to hypomethylation therapy is shown in this study to be associated with the CR rate of 10%, an ORR of 23%, a median survival rate of 5 months, and an estimated survival rate of 19% at 1 year. The incidence of Denovo AML is 12,000 cases annually in the United States.[25] There are no existing estimates of the annual incidence of AML following MDS and failure on hypomethylating agents. Based on an MDS incidence of 15,000 to 45,000, a median survival of 2 to 3 years in MDS (hence an approximate relevance rate of 30,000 to 120,000) and an AML transformation rate of about 50%, the estimated incidence of AML following MDS and failure on hypomethylation therapy would be anywhere from 15,000 to 60,000 cases. This overwhelming number may overshadow Denovo AML in incidence, and will, in the next few years result in perceived degrees in the CR rate of AML in general and in the perceived survival rates, unless we identify this disease as a separate entity. Little is known about the pathophysiology and molecular evolution of AML from MDS. Efforts are ongoing to decipher these molecular pathways and to compare them to those involved in Denovo AML and in therapy related AML. These ongoing research efforts, involving whole genome profiling, and additional profiles of the transcriptome, proteome, and epigeno of these three AML entities, are urgently needed, in order to understand the evolutionary pathways and to develop better, hopefully targeted therapies, addressing these molecular pathways. Finally, it is very clear that this emerging entity, AML following MDS and failure on hypomethylation agents is quite distinct from Denovo AML, does not respond to standard AML therapies, does not also seem to respond well to existing investigational therapies. This entity needs to be separated from Denovo AML in ongoing large institutional and multi institutional-cooperative trials of AML therapy, in order not to erroneously result in the false adverse picture of AML compared to previous decades. Urgent efforts are needed to develop hopeful potential future therapies for patients with AML following MDS and hypomethylation failure. While ASCT may be one potential existing curative approach, it may have to be implemented earlier in the course of MDS, before transformation to AML, to improve the results.[29] Consideration of post transplantation maintenance therapy and immune modulation strategies are needed.[30] Regardless, as in our experience, ASCT appears to benefit only a minority of patients, highlighting the need to discover novel therapies for this entity.

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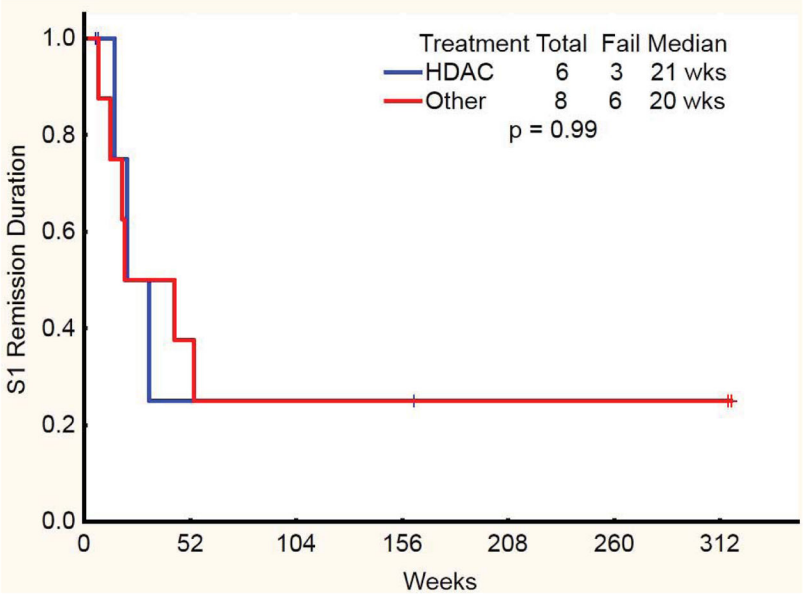
Figure 1a:



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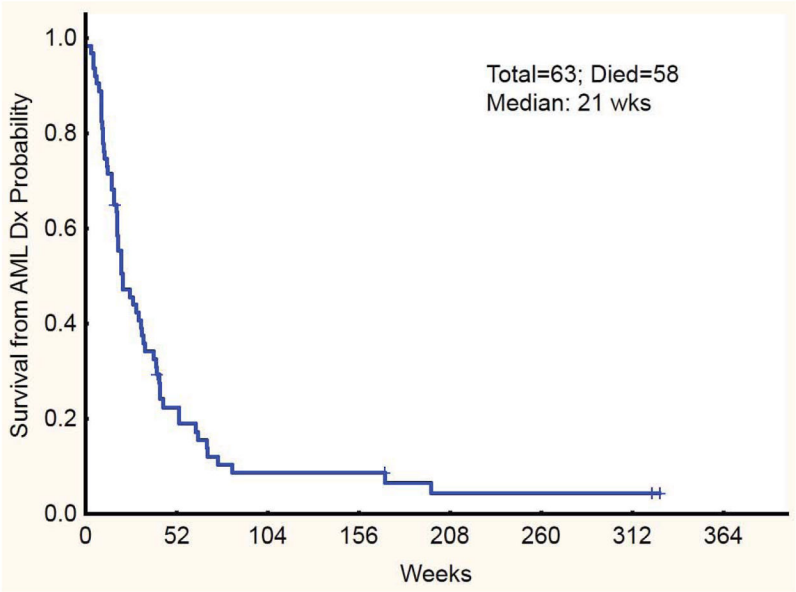

Figure 1c:

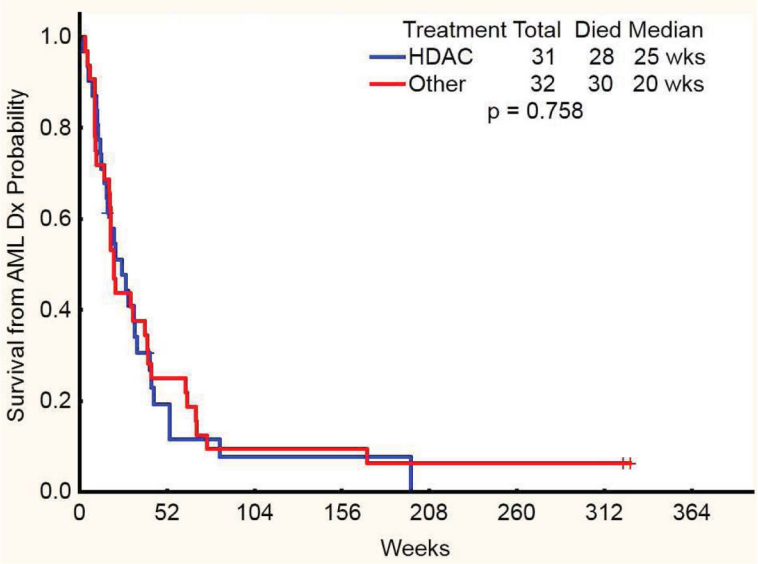

Figure 1.

Figure 1a: Duration of complete response after AML therapy at first salvage

AML, acute myeloid leukemia; S1, first salvage; HDAC, high dose Ara-C; Other, other therapies; Wks, Weeks

Figure 1b: Survival from time of AML diagnosis post HMA failure

AML, acute myeloid leukemia; HMA, hypomethlating agent; Dx, diagnosis; Wks, Weeks

Figure 1c: Survival from time of AML diagnosis post HMA failure (by type of therapy)

N, number of patients; Wks, weeks; AML Dx, diagnosis of acute myeloid leukemia, HDAC, high dose Ara-C; Else, other therapies

Table 1

Patients characteristics

Parameter	Category	N (%); Median [ ]	
Age (years)	≥ 70	16 (25); 63 [38–90]	
PS (ECOG)	0	14 (22)	
	1	49 (78)	
Karyotype	Diploid	16 (25)	
	Chromosome 5 or 7 abnormality	28 (44)	Not complex: 8 (12)
			Complex: 20 (32)
	Miscellaneous	14 (22)	Not complex: 8 (12)
			Complex: 6 (10)
	ND/Insufficient	5 (9)	
Hemoglobin (g/dl)	<10	36 (57)	
Platelets ($\times 10^9$/L)	<50	30 (48)	
	>50	33 (52)	
Albumin (g/dl)	<3	1(2); 4.2 [2.3–5]	
Creatinine (mg/dl)	1.3–2.0	8 (13); 0.9 [0.5–2.0]	
Type of MDS based on the WHO classification	RAEB	55 (87)	
	RCMD	3 (5)	
	RCMD-RS	2 (3)	
	RA	1 (2)	
	MDS-NOS	2 (3%)	
IPSS	Low	1 (2)	
	Intermediate 1	16 (25)	
	Intermediate 2	33 (52)	
	High	13 (20)	
MDS treatment prior to transformation into AML	Azacitidine based	13 (20)	
	Decitabine based	50 (80)	

N, Number of patients; ECOG PS, Easter Cooperative Oncology Group performance status; WHO, World Health Organization; IPSS, international prognostic scoring system; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts, RCMD, refractory cytopenias with multilineage dysplasia; RCMD-RS refractory cytopenias with multilineage dysplasia with ringed sideroblasts (RCMD-RS); RA, refractory anemia; MDS-NOS, MDS not otherwise specified; AML, acute myeloid leukemia

Table 2

Therapy for AML at 1st salvage and 2nd salvage

Therapy for AML	Type of treatment	N (%)
Salvage 1	HDAC combinations	31 (49)
	Clofarabine-based	10 (16)
	HMA-based	5 (8)
	Miscellaneous	9 (14)
	Phase one agents	8 (13)
Salvage 2	HDAC combinations	11 (31)
	Clofarabine-based	3 (8)
	HMA-based	5 (14)
	Miscellaneous	7 (20)
	Phase one agents	9 (26)

AML, acute myeloid leukemia; N, number of patients; HDAC, high dose Ara-C; HMA, hypomethylating agent

Table 3

Response to therapy for AML

	N (%)					
Parameter	**All treatments**		**HDAC**		**Other**	
	1st salvage (N=63)	**2nd salvage (N=35)**	**1st salvage (N=31)**	**2nd salvage (N=11)**	**1st salvage (N=32)**	**2nd salvage (N=24)**
OR	14 (23)	8 (23)	6 (19)	2 (18)	8 (24)	6 (24)
CR	6 (10)	3 (9)	2 (6)	0 (0)	4 (12)	3 (12)
CRp	8 (13)	5 (14)	4 (13)	2 (13)	4 (12)	3 (12)
Death (week 1–8)	14 (23)	11 (31)	7 (23)	5 (45)	7 (21)	6 (25)
Week 1–4	6 (10)	4 (11)	3 (10)	2 (18)	3 (9)	2 (8)
Week 5–8	8 (13)	7 (20)	4 (13)	3 (27)	4 (12)	4 (17)
Resistant	35 (54)	16 (46)	18 (58)	4 (36)	17 (55)	12 (50)

AML, acute myeloid leukemia; N, number of patients; HDAC, high dose Ara-C; CR, Complete remission; CRp, complete remission without platelet recovery; ORR, overall response rate

Table 4

Response to different types of therapy at 1st and 2nd salvage

Parameter	Category	N. of responses (%)
1st salvage	HDAC combinations	6 (19)
	Clofarabine-based	4 (40)
	HMA-based	0 (0)
	Miscellaneous	3 (33)
	Phase one	1 (13)
2nd salvage	HDAC combinations	2 (18)
	Clofarabine-based	0 (0)
	HMA-based	0 (0)
	Miscellaneous	5 (71)
	Phase one	1 (11)

N, number; HDAC, high dose Ara-C; HMA, hypomethylating agent

Table 5

Prognostic factors for achievement of complete remission and for overall survival by multivariate analysis

	Complete remission		Overall survival	
Parameter	**P-value**	**Odds ratio**	**P-value**	**Hazard ratio**
HDAC	0.04	2.1	0.28	1.4
Age >65 years	0.07	2	0.05	1.9
Platelets $>50\times10^9$/L	0.004	0.4	0.01	0.5
Albumin <3 gr/dl	0.02	13	0.08	6.3

HDAC, high dose Ara-C