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High dose cytarabine, mitoxantrone and L-asparaginase (HAMA) salvage for relapsed or refractory acute myeloid leukemia (AML) in the elderly

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Abstract

Acute myeloid leukemia (AML) is an aggressive malignancy that affects older patients. The role of salvage therapy in the elderly is controversial and there is little data on efficacy. Outcomes for 94 relapsed or refractory AML patients who received salvage HAMA therapy were analyzed. Of the 94 patients 66 were ≥60, including 26 patients ≥70, and 28 were <60 years old. Early mortality (30-day) was 14% (4% <60, 18% ≥60 years old). Overall, 27% of patients died during hospitalization or were discharged to hospice (11% <60, 33% ≥60 years old). CR/CRi was achieved in 41% of patients (61% <60, 33% ≥60 years old). Median survival was 6.1 months (15.7 <60, 5.2 ≥60). Patients ≥60 who achieved a CR/CRi had a median survival of 11.7 months. At 12 months 56% of patients <60 were alive versus 24% of patients ≥60. At 24 months these numbers fell to 40% and 2% respectively. In those <60 years old, 50% went on to allogeneic hematopoietic stem cell transplant (HSCT) whereas 14% of patients in the ≥60 cohort did so. In conclusion, HAMA salvage therapy results in a 33% response rate in patients ≥60 years old with acceptable toxicity.

Keywords

acute myeloid leukemia; salvage therapy; elderly patients; High dose cytarabine

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INTRODUCTION

Acute Myeloid Leukemia (AML) is a disease that primarily affects older adults and is characterized by poor survival. The incidence of AML increases with age; the median age at diagnosis is between 68 and 72 years [1, 2]. While the effect of age on outcome in AML is continuous, 60 years of age has traditionally been used as the cut point between younger and elderly patients. AML in the elderly is more aggressive and less responsive to therapy than in younger patients [3]. Older patients often have multiple comorbidities, poor performance status, and a greater incidence of high-risk cytogenetics and antecedent hematologic disorders [4]. Older adults have worse survival rates, lower complete remission (CR) rates, shorter duration of remission, and are more likely to experience treatment-related death [5]. Treatment of AML in the elderly has not matched the improvements seen for younger adults and outcomes remain unsatisfactory [6]. As life expectancy improves, AML will become an increasingly common clinical problem. AML diagnoses in older adults are projected to increase 38% by 2031, making management of AML in the elderly a critical issue [1].

Significant debate exists regarding the optimal treatment strategy for older patients with AML, ranging from supportive care alone to aggressive chemotherapy [7, 8]. Patients have varying tolerance for toxicity, treatments are rarely curative, and studies either exclude the elderly or are limited by selection bias [1, 2]. For nearly 40 years, use of an anthracycline with cytarabine has constituted the backbone of remission induction therapy [9]. However, most elderly patients who achieve a CR eventually relapse and die from AML [3]. With more than 50% of elderly AML patients experiencing relapse, they will require second-line therapy. No consensus salvage regimen has been established in this age group. Efficacy of regimens reported varies widely, with some studies in elderly patients reporting no benefit [10]. Other studies have shown better response rates and increased survival when intensive chemotherapy is used in older patients compared to best supportive care or low dose Ara-C [11]. Overall there is no consensus regarding the optimal treatment of elderly AML patients with relapsed or refractory AML and little clinical data on which to base recommendations. In the current study, we reviewed the data of 66 patients 60 years of age or older with relapsed or refractory AML who received salvage high-dose cytarabine, mitoxantrone, and L-asparaginase (HAMA) therapy. This cohort included 26 patients who were 70 years of age or older. The results were compared to a contemporary cohort of 28 patients younger than 60 years of age receiving the same therapy.

PATIENTS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board of Wake Forest University (IRB Protocol no. 22211). We reviewed the medical records for consecutive adults who received HAMA salvage chemotherapy for relapsed or refractory AML between May 1, 1999 and December 30, 2010 and treated at Wake Forest University Baptist Medical Center. Additional criteria for review were age 18 years or greater, diagnosis of AML or granulocytic sarcoma with marrow involvement, excluding M3 according to the morphologic French-American-British (FAB) classification based on bone marrow aspirate, and relapsed or refractory disease. Bi-phenotypic or undifferentiated acute leukemia was

excluded. Refractory or resistant disease was defined by morphological evidence of persistent AML in the peripheral blood or bone marrow (aspirate or biopsy) following induction chemotherapy or failure to achieve a complete remission followed by the reappearance of morphological evidence of AML. Relapsed disease was defined by reappearance of myeloid blasts in either the peripheral blood or bone marrow following a previously documented CR.

Patient characteristics reviewed included age, number of comorbidities, social history, physical exam, baseline labs on admission, history of antecedent hematologic disorder, cytogenetic risk group, length of first CR, and history of HSCT. Comorbidities captured included congestive heart failure, coronary artery disease, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, renal dysfunction, previous cancer, depression, osteoporosis, rheumatologic disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's disease), cognitive impairment, venous thromboembolism (deep venous thrombosis, pulmonary embolism), cardiac valve disease, and cirrhosis. Review of cytogenetic status included karyotypes taken from bone marrow biopsy samples taken at initial diagnosis and/or relapse. Karyotypes were divided into favorable karyotypes [t(8;21), t(16;16) or i16], unfavorable karyotypes [-5, del(5q), -7, del(7q), complex karyotype (3 or more abnormalities), or 11q23 translocation], and intermediate (all other abnormalities) as described by Byrd et al.[12].

HAMA chemotherapy

HAMA chemotherapy is given over a total of 3 days and consisted of high-dose cytarabine (HiDAC, doses ranged from 3,000 to 750 mg/m², see table 1) every 12 hours given by bolus infusion over 3 hours, for a total of 5 doses; mitoxantrone 6 mg/m² once daily immediately following doses 1, 3, and 5 of HiDAC; and L-asparaginase once at 6,000 units/m² intramuscularly following completion of the last dose of HiDAC. The dose of HiDAC administered varied by age, see table 1. There were three patients with significant baseline renal discfunction who received a dose of 750 mg/m². No growth factors were given routinely, but antivirals, antibiotics, and antifungals were given as routine prophylaxis at the physician's discretion. On day 14, bone marrow biopsies were repeated. If significant residual disease was present, patients could be retreated an abbreviated 3 day second course with 3 doses of HiDAC, 2 doses of mitoxantrone, and 1 dose of L-asparaginase. On a very few occasions patients received an identical 5-day repeat course.

Response assessment

The criteria used to define response following HAMA chemotherapy were outlined by Dohner et al. [13] including CR (neutrophils >1,000/μl, platelets >100,000/μl, and bone marrow blasts <5%) and CRi (all marrow criteria of CR but without either complete platelet or neutrophil recovery). Overall survival following HAMA salvage chemotherapy was calculated from day 1 of treatment with HAMA, until death from any cause or last follow-up.

Statistical analysis

Clinical variables tested for potential prognostic value based on pre-specified hypotheses were length of time to relapse and cytogenetic risk. Differences among variables were compared by χ^2 tests. Survival was calculated by the Kaplan-Meier method. Multivariate analyses of prognostic factors used the Cox proportional hazard method for overall survival, and the logistic regression model adjusted for age for 30-day and 60-day mortality. A p value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Patients were allocated as shown in Figure 1, and patient characteristics are summarized in Table 1. As expected, older patients had more comorbidities, therapy-related or secondary AML, and poor-risk cytogenetics. Older patients were more likely to have refractory disease and less likely to have received more than one cycle of HAMA.

Toxicity of salvage HAMA chemotherapy

Overall, 27% patients died during hospitalization or were discharged to hospice (11% of those < 60 years old, and 33% of those ≥ 60 years old). The 30-day mortality for the entire cohort was 14% (13 patients). Only one patient < 60 years old died within 30 days of HAMA treatment. The 60-day mortality rate was 22.5% (22 patients), 7.1% in patients < 60 years old and 30% in patients ≥ 60 years of age. Of the 26 patients 70 years of age or older the 30 and 60 day mortality was 23% (6/26) and 35% (9/26) respectively. Overall, 12 patients (13%) required ICU-level care during their hospitalization; 10 of these patients were ≥ 60 years old, and only 2 of the 10 lived to be discharged from the hospital compared to 2/2 patients < 60 years of age. Of the 4 patients ≥ 70 years old admitted to the ICU, none survived to be discharged from the hospital.

Efficacy of salvage HAMA chemotherapy

Thirty-two patients (34%) achieved CR and 7 patients achieved a CRi (7%), for an overall response rate (ORR=CR+CRi) of 41% (Table 2). In patients under 60 years of age, 15 of 28 (54%) achieved a CR and 2 patients (7%) achieved a CRi (ORR 61%). In contrast, 17 of 66 patients (26%) ≥ 60 years of age achieved CR and 5 patients (7%) achieved a CRi (ORR 33%). In patients ≥ 70 years old 8 of 26 achieved a CR and another 2 achieved a CRi (ORR 38%). The median overall survival was 6.1 months for all patients (Figure 2). In those younger than 60 years of age, the median overall survival was 15.7 months, while for those ≥ 60 years of age, it was 5.2 months. At 12 months, 56% of patients < 60 years old were alive, compared with 24% for patients ≥ 60 years old. By 24 months, these numbers decreased to 40% and 2%, respectively (Table 2). For patients ≥ 60 years old who achieved CR, the median overall survival was 11.7 months (Table 3).

Consolidation therapy

In responding patients less than 60 years of age, post-remission therapy included 6 patients who received HAMA consolidation therapy, 3 who received autologous HSCT, 2 who

received reduced-intensity allogeneic HSCT, 7 who received full allogeneic HSCT, and 2 who received double cord transplantation. In those ≥ 60 years old, 15 of 22 patients who achieved a CR or CRi received post-remission therapy, including 6 patients (27%) who received HAMA consolidation only, 5 patients (23%) who received reduced-intensity allogeneic HSCT, and 4 patients (18%) who received full myeloablative allogeneic HSCT.

Prognostic factors

We found a strong correlation between overall survival and cytogenetic risk score ($P = 0.0016$, Figure 3); however, cytogenetic risk scores were not associated with either 30-day or 60-day mortality. Duration of CR1 was associated with improved survival (Figure 4). Patients with a CR1 duration >1 year fared significantly better than those with shorter remission duration or refractory disease. Patients with a CR1 duration of <1 year were less likely to achieve a response in both age groups (Table 2) and had a shorter median overall survival. This was only statistically significant in patients under the age of 60 but not in the elderly cohort (Figure 5). Additionally, even in elderly patients whose first remission was longer than a year there were essentially no long-term survivors.

Response to HAMA therapy was associated with a longer survival (Table 3). Patients less than 60 years of age who achieved CR/CRi after salvage HAMA had a median overall survival of 37.9 months. In patients less than 60 years old who did not achieve a CR/CRi, median overall survival was 4.9 months. Patients ≥ 60 years of age who achieved CR/CRi had a median overall survival of 11.7 months whereas patients without CR/CRi had a median overall survival of just 2 months.

Hematologic parameters including WBC count, creatinine, total bilirubin, and number of comorbidities were not significantly associated with 30- or 60-day mortality or overall survival.

DISCUSSION

The purpose of this study was to determine response rates and length of survival in elderly patients with relapsed or refractory AML who received salvage HAMA chemotherapy. There is significant controversy regarding the appropriate treatment for elderly patients with AML and many oncologists are uncomfortable offering intensive therapy, especially in the relapsed or refractory setting. This is perpetuated by a lack of clinical outcomes data for intensive salvage therapy in this age group. The purpose of this report was to report on the single institution experience of the HAMA regimen in patients over the age of 60.

A number of chemotherapeutic salvage regimens have been developed, each with limited efficacy, and none has emerged as the clear standard of care [14]. Salvage HiDAC chemotherapy remains a standard component of treatment for relapsed and refractory AML. The landmark Southwest Oncology group trial (SWOG-8326) evaluated 210 patients from 1985-1992 with relapsed and refractory AML who were randomized to HiDAC or HiDAC plus mitoxantrone (HM). Those on the HM regimen were more likely to achieve CR than those given HiDAC alone (44% versus 32%) [15]. The HAMA regimen added L-asparaginase and reduced the number of doses of cytarabine based on preclinical studies

conducted at our institution [16] and a randomized study demonstrating synergy between HiDAC and L-asparaginase [17]. This regimen is the primary salvage regimen used at the Comprehensive Cancer Center of Wake Forest University.

Older AML patients who received salvage HAMA ranged in age from 60-84 years including 26 patients > 70 years old (average and median age of the > 60 cohort was 68). These patients achieved a CR+CRi rate of 33% and their median overall survival was 5.2 months. These results are comparable to studies of younger patients with relapsed AML. A retrospective study that compared CLAG and MEC for relapsed/refractory AML (average patient age of 55 years) reported CRs of 37.6% and 23.8%, respectively. The overall survival for CLAG was 7.3 months and MEC was 4.5 months [18]. The classic I trial looked at HiDAC with or without clofarabine in relapsed AML patients older than 55. The combination arm resulted in a response rate of 46% and a median survival of 6.6 months very similar to the results of our > 60 cohort despite including patients less than 60 years old [19]. Thus the HAMA regimen resulted in similar CR rates and overall survival in an elderly population and argues that intensive salvage can be given to older patients.

In a recent comparison of the efficacy of elacytarabine versus 7 commonly used salvage regimens for patients with relapsed AML, only 22% of patients achieved a CR or CRi and median survival was only 3.4 months [20]. Again, the median age of the patients in that study was 59, significantly younger than in our elderly cohort. These results suggest that the HAMA regimen can result in superior outcomes in patients over 60 years old. It is important to note however that despite a 33% response rate, only one patient was alive 24 months after relapse stressing the general palliative nature of salvage therapy in this age group. While some might argue these data suggest the futility of intensive therapy for relapsed elderly AML patients we would point out the fact that elderly patients achieving a response had a longer median survival and although intensive chemotherapy is associated with a transient decrease in quality of life studies suggest it rebounds to baseline levels following its completion [21].

Treatment-related toxicity is usually higher in elderly patients and a barrier to potential intensive chemotherapy. Our results confirm a difference in mortality based on age, with a 60-day mortality rate of 7.1% in patients younger than 60 years old, compared to 30% in those over 60 years of age. By comparison, the 30-day mortality rate for CLAG was 9.4% and for MEC, 10.9% [18]. In our study, the 30-day mortality rate for older patients was 18.2%. A more meaningful endpoint may be the percentage of patients who either died while hospitalized or were discharged to hospice. In our study 27% of all patients either died or were discharged to hospice, and they were more likely to be over 60 years old (11% of those <60 years old versus 33% of those > 60 years old).

Other than age, duration of first remission and cytogenetics are considered important prognostic variables in relapsed AML. Our study demonstrated that cytogenetics correlated with improved overall survival ($p = 0.0016$), but not early mortality. Our study also confirmed the results of previous studies that achieving CR/CRi is correlated with overall survival. In our elderly patients who received salvage HAMA, those who achieved CR/CRi had a median overall survival time of 11.7 months, compared to 2.1 months for those who

did not. Importance of achieving CR/CRi was also demonstrated in our patients <60 years old; in this group, the median overall survival times were 37.9 and 4.9 months for those who did and did not achieve CR/CRi, respectively.

The current study has several limitations. It is a retrospective study from a single institution. Performance status could not be evaluated, since it was not routinely documented in the medical record. While the number of cycles each patient received was well documented, duration of the additional cycles (i.e. 1.5 vs 3 days) often was not.

In conclusion, the prognosis of elderly patients with relapsed or refractory AML remains poor, and no consensus salvage regimen exists. Based on our results, salvage HAMA chemotherapy in elderly AML patients with relapsed or refractory disease is a viable palliative option. This study provides an additional data set to inform discussions with these patients. A frank discussion with patients at the time of relapse, regarding the risks and benefits of intensive therapy versus less intensive approaches, is needed to ensure that patients can make the most informed decision possible. Finally, there is an urgent need for randomized, prospective trials of intensive chemotherapy versus lower-intensity regimens like azacytidine in patients over 60 years of age. We believe HAMA could serve as a standard, intensive, chemotherapy approach in such a study.

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Figure 1. Schema of trial. Patients with relapsed or refractory AML treated at our institution with HAMA salvage therapy were identified and eligibility assessed.

Survival of Entire cohort

Figure 2. Survival rates for the entire cohort. Kaplan-Meier curves for all patients treated with HAMA are shown.

Figure 3.

Survival of cohort by cytogenetic risk category. Kaplan-Meier curves for patients are shown for patients in the good, intermediate and poor cytogenetic risk categories. P value was determined by Log-Rank test.

Figure 4.

Survival of cohort by duration of CR1. Kaplan-Meier curves for patients are shown for patients with CR1>1 and <1 year. P value was determined by Log-Rank test.

A.**Survival of <60 CR1>vs<1yr** **B.****Survival of 60+ CR1>vs <1yr** **Figure 5.**

Survival of cohort by duration of CR1 in both the younger and older cohorts. A) Kaplan-Meier curves for patients <60 years old are shown divided by length of CR1. B) Kaplan-Meier curves for patients ≥60 years old are shown divided by length of CR1. P values were determined by Log-Rank test.

Table 1

Characteristics of the 94 patients

	Age	
Characteristics	< 60 (N=28)	60 (N=66)
Median age (range)	50.5 (20, 59)	68 (60,84)
Male (%)	16/28 (57%)	36/66 (55%)
No. Caucasian (%)	22/28 (79%)	62/66 (94%)
Median Duration of CR1 (months)	12.3	7.2
Charlson Comorbidity Index		
0	24/28 (86%)	34/66 (51%)
1	3/28 (11%)	18/66 (27%)
2	1/28 (3.0%)	11/66 (17%)
3	0/28 (0.0%)	2/66 (3%)
4	0/28 (0.0%)	1/66 (2%)
Refractory disease (%)	2/28 (7%)	23/66 (35%)
Therapy-related AML	1/28 (4%)	10/66 (15%)
Antecedent hematologic disorder	4/28 (14%)	21/66 (32%)
Cytogenetic Risk Score		
Not available	6/28 (21%)	22/66 (33%)
Good risk	5/22 (23%)	2/44 (5%)
Intermediate risk	14/22 (64%)	29/44 (65%)
Poor risk	3/22 (14%)	13/44 (30%)
Cytarabine dose 3.0 gm/m ²	24/28 (86%)	1/66 (2%)
Cytarabine dose 2.0 gm/m ²	1/28 (3%)	41/66 (62%)
Cytarabine dose 1.5 gm/m ²	1/28 (3%)	17/66 (26%)
Cytarabine dose 1.0 gm/m ²	2/28 (6%)	4/66 (6%)
>1 cycle of HAMA	16/28 (57%)	30/66 (45%)

Table 2

Response and survival by age group

Age at initiation of HAMA therapy	<60	60	Overall
Response (CR or CRi)	17/28 (61%)	22/66 (33%)	39/94 (41%)
CR1 <1 year and response	5/16 (31.3%)	17/48(35.4%)	22/64 (34.4%)
Death in 12 months	11 (39%)	52 (79%)	63 (67%)
Lost to follow-up	1	1	2
Estimated survival at 12 months	56.3%	23.7%	34.0%
Death in 24 months	18 (64%)	65 (98.5%)	83 (88%)
Lost to follow-up	3	2	5
Estimated survival at 24 months	39.7%	1.9%	14.0%
Median survival (months)	15.7	5.2	6.1

Values presented are N (%). Overall survival calculated in months from HAMA treatment.

Table 3

Survival by response status and age group

Age	<60			60		
Response (CR or CRi)	N	Deaths	Median OS (Months)	N	Deaths	Median OS (Months)
No	11	10	4.9	44	42	2.1
Yes	17	9	37.9	22	22	11.7

Values presented are Kaplan-Meier survival estimates. OS calculated in months from date of HAMA treatment.