Tailored temozolomide therapy according to MGMT methylation status for elderly patients with acute myeloid leukemia

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Temozolomide sensitivity is determined by methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter. This study assessed whether the temozolomide dose can be tailored by *MGMT* promoter status and whether protracted, low-dose temozolomide can "prime" blasts in patients with unmethylated MGMT (unMGMT). Elderly patients with high-risk AML were stratified by *MGMT* methylation. Patients with methylated *MGMT* (mMGMT) received temozolomide 200 mg/m^2 orally for 7 days every 4 weeks, while patients with unMGMT received temozolomide 100 mg/m^2 orally for 14 days followed by 200 mg/m^2 orally for 7 days every 6 weeks. Of 36 patients (median age, 75 years), 31 (86%) had an unMGMT promoter. Overall response rate for the entire cohort was 36%. Patients with mMGMT and unMGMT had similar response rates (40% vs. 29%). Median duration of response and overall survival (OS) among responders were 29 and 35 weeks, respectively. Induction deaths (ID) occurred in 25% of patients, mostly caused by disease progression. Hematological toxicities were the most common adverse event. Toxicities were similar between patients on conventional versus protracted schedules. High HCT-CI scores were predictive of lower CR rate, higher ID, and shorter OS, while bone marrow blast count <50% at screening predicted for improved responses. Temozolomide, dosed according to *MGMT* methylation status, demonstrated modest clinical activity in elderly patients with AML, especially in those presenting with fewer comorbidities and low disease burden. The trial was registered on www.ClinicalTrials.gov as #NCT00611247. Am. J. Hematol. 87:45–50, 2012. © 2011 Wiley Periodicals, Inc.

Introduction

Acute myeloid leukemia (AML) is a disorder characterized by heterogeneous and distinct biological features with aggressive clinical behavior. Two-thirds of adults with newly diagnosed AML are older than 60 years of age [1–3]. Elderly AML patients have a poor prognosis with a median survival of approximately 2 months and less than 10 percent overall survival (OS) at 2 years [4]. In North America, the majority of elderly patients with AML are not referred to tertiary care centers and do not receive induction chemotherapy [4]. Similarly, patients with relapsed AML do poorly with low rates of and short durations of remission [5]. These observations highlight the need for more effective, patient-tailored treatment approaches for elderly patients with AML.

Temozolomide, an alkylating agent approved for the treatment of high-grade glioma, has been shown to inhibit cell growth in leukemia cell lines and leukemia xenografts [6,7]. Early studies of temozolomide in adults with leukemia determined that the maximum tolerated dose (MTD) is 200 mg/m^2/day for 7 days [8]. Subsequent studies did not confirm the initial responses seen in patients with advanced disease [9,10].

Resistance to temozolomide correlates with activity of the DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) [11]. Increased MGMT activity is associated with inferior outcomes in high-grade gliomas, [12] in vitro resistance to temozolomide in leukemia cell lines, [13] and lack of clinical responses in adult and pediatric acute leukemia [9,10]. *MGMT* promoter methylation status also appears to predict MGMT activity in acute leukemia samples with methylated MGMT (mMGMT) promoter corresponding to little to no MGMT activity, and unmethylated MGMT (unMGMT) promoter corresponding to relatively increased MGMT activity. Lastly, temozolomide resistance appears to be associated with microsatellite instability (MSI) and requires an intact mismatch repair pathway [14]. Unfortunately; *MGMT* promoter methylation is a rare phenomenon in AML, being described in approximately 10 percent of cases [15,16].

For these reasons, inactivation of MGMT activity in combination with temozolomide has been proposed as a method to increase the sensitivity of resistant tumors [17,18]. Unfortunately, most MGMT inhibitors tested have failed to improve clinical activity in temozolomide-resistant tumors [19]. Protracted administration of temozolomide may lead to a marked and sustained inactivation of MGMT leading to an "autoenhancement" of temozolomide's inherent cytotoxic potential by cumulative reduction of the leukemic blasts' capacity for MGMT-mediated DNA repair and resistance [20]. MGMT activity can be reduced by approximately 80% in patients treated with this dosing schedule [20]. Thus, we designed an exploratory clinical study to test two hypotheses: (1) Can temozolomide therapy be tailored according the MGMT methylation status in patients with AML? and (2) Can protracted doses of temozolomide (temozolomide priming) sensitize leukemic blasts to conventional doses of temozolomide in patients with unmethylated MGMT promoter?

Patients and Methods

The phase 2 study was reviewed and approved by the Stanford Office of Human Medical Subjects and according to the precepts established by the Helsinki Declaration. All patients provided signed

Additional Supporting Information may be found in the online version of this article.

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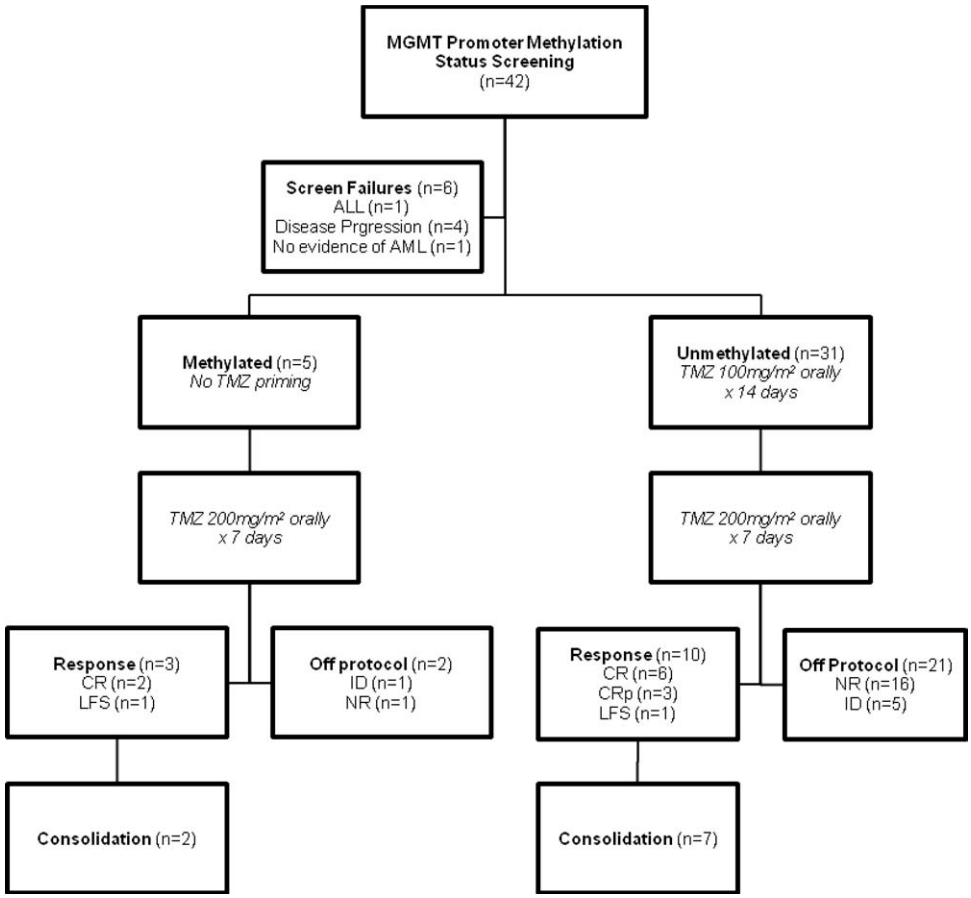

Figure 1. Clinical trial scheme and stratification of patients. TMZ, temozolimide; ALL, acute lymphoblastic leukemia; CR, complete remission; CRp, complete remission with incomplete count recovery; LFS, leukemia free state; MGMT-O^6, methylguanine-DNA methyltransferase; ID, induction death; NR, no response.

informed consent. The trial was registered on www.ClinicalTrials.gov as #NCT00611247.

Patient eligibility. Patients, who were age 60 years or older, with histologically confirmed AML, as defined by the WHO classification [21] were considered eligible. Previously untreated patients had to fulfill, at least one of the following high-risk criteria: adverse and intermediate risk cytogenetics according to SWOG criteria, [22] or secondary AML (antecedent hematologic disorder or therapy-related AML). Patients with relapsed or refractory AML, those deemed unfit by the referring physician for conventional induction chemotherapy and those unwilling to receive such treatment were also eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, serum creatinine $<$2.0 mg/dl, adequate liver function (serum bilirubin $\leq$ 1.5 mg/dL, ALT/AST $\leq$ 3x the institutional upper limit of normal for age). Transfusion support was performed according to standard practices. Hydroxyurea was permitted up to 24 hours before the start of therapy if needed for cytoreduction. No other systemic chemotherapy or investigative agents were permitted within 4 weeks of study entry or during the study period. All screening bone marrow biopsies were performed at Stanford Hospital and the diagnosis of AML confirmed.

Treatment and study design. We determined the methylation status of the MGMT promoter in leukemic blasts that served as the basis for treatment stratification in all patients prior to initiation of therapy. Patients with mMGMT promoter (temozolomide sensitive) received conventional doses of temozolomide 200 mg/m^2 orally for 7 days [8]. Patients achieving a CR could receive TMZ 200 mg/m^2 for 5 days every 4 weeks for five more cycles. Patients with an unMGMT promoter (temozolomide resistant) received a protracted, low dose of temozolomide (100 mg/m^2 orally for 14 days) [20] designed to inhibit MGMT activity and prime the leukemic blasts. This was immediately followed by conventional doses of temozolomide 200 mg/m^2 orally for 7 days [8] (Figure 1). Patients achieving a CR received up to five cycles of consolation (14 days of protracted doses followed by 5 days of conventional doses of TMZ) every 6 weeks. Treatment was performed on an outpatient basis. Bone marrow biopsies were repeated 3 weeks after completion of the first cycle of therapy for response assessment. While receiving conventional doses of temozolomide patients were pretreated with antiemetic prophylaxis. Patients were eligible to receive a second, similar, cycle of induction therapy if they achieved less than CR but at least a partial response after the first cycle. Patients in CR after a first or second induction cycle were eligible to receive up to five cycles of consolidation therapy. Consolidation therapy was also stratified based on the *MGMT* promoter status. Patients with mMGMT promoters received temozolomide 200 mg/m^2 orally for 5 days every 4–5 weeks. Those with unMGMT promoters were treated with similar doses of priming temozolomide 100 mg/m^2 orally for 14 days followed immediately by temozolomide 200 mg/m^2 orally for 5 days every 6–7 weeks. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Nonhematologic toxicities were defined as any grade 3 or 4 adverse event possibly, probably, or definitely related to temozolomide. Patients who received at least one dose of temozolomide were eligible for safety and efficacy assessment.

Response assessment. European LeukemiaNet response criteria were used to determine treatment outcomes [23]. They were classified as CR [bone marrow blasts $<$5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $>1.0 \times 10^9$/L; platelet count $>100 \times 10^9$/L; independence of red cell transfusions), CRi (all CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L) or thrombocytopenia ($<100 \times 10^9$/L)], morphologic leukemia-free state (LFS) (bone marrow blasts $<$5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required), and relapse (bone marrow blasts $>$5%; or reappearance of blasts in the blood; or development of extramedullary disease). All other responses, including partial response, were considered resistant disease. Induction death was defined as death from all causes occurring within the first 6 weeks of initiation of therapy. Patients with delayed peripheral blood count recovery, defined as absence of recovery of blood counts in the absence of active AML for more than 7 weeks

TABLE I. Patient Baseline Characteristics ($N = 36$)

Characteristic	Methylated MGMT promoter	%	Unmethylated MGMT promoter	%
Number of patients	5	14	31	86
Age, years				
Median	77		75	
Range	66–83		64–87	
≥70	4	80	26	84
Female	2	40	11	36
Race				
White	4	80	22	71
Asian	0	0	7	23
Ethnicity				
Hispanic or Latino	1	20	2	6
ECOG performance status				
0	1	20	5	16
1	3	60	21	68
2	1	20	5	16
HCT-CI Score				
0-2	4	80	26	84
≥3	1	20	5	16
Disease status				
Presence of AHD	0	0	15	48
Prior MDS	0	0	8	26
Prior MPD	0	0	6	19
Prior MPD/MDS	0	0	1	3
Relapsed/Refractory	2	40	5	16
de novo AML	3	60	11	35
Median WBC count ($10^3/\mu L$)	1.5 (1.3–56)		1.8 (0.5–53.3)	
Median serum LDH (U/L)	171 (149–864)		200 (82–1164)	
Karyotype				
Unfavorable/intermediate	4	80	30	96
Normal	3	60	13	42
Favorable	1	20	1	4
Molecular Markers				
FLT3-ITD/TKD	1/0	20/0	2/1	6/3
NPM1/CEBPα mutations	2/0	40/0	3/3	10/10
IDH1/IDH2 mutations	0/1	0/20	4/2	13/6

HCT-CI, HCT-specific comorbidity index; ECOG, Eastern Cooperative Oncology Group; AHD, antecedent hematologic disorder; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; AML, acute myeloid leukemia; MGMT-O^6, methylguanine–DNA methyltransferase; WBC, white blood cell; PB, peripheral blood.

There were no significant P values ($P < 0.05$) between patients on the methylated MGMT versus unmethylated MGMT group (log-rank P value).

upon completion of therapy were eligible for up to two distinct dose reductions. For patients with mMGMT, dose reductions were temozolomide 200 mg/m^2 for 5 days and temozolomide 150 mg/m^2 for 5 days. For patients with unMGMT, dose reductions were 100 mg/m^2 for 14 days followed by 200 mg/m^2 for 5 days and 100 mg/m^2 for 10 days followed by 200 mg/m^2 for 5 days.

Molecular markers in AML, MGMT promoter methylation, and MSI assay. Methods for sequence analysis of molecular markers, MGMT promoter methylation and MSI assay are described in Supporting Information 1. Genomic DNA from pretreatment bone marrow aspirates was extracted and amplified. Bone marrow aspirate MSI was compared with DNA obtained from buccal mucosa from the same patient.

Statistical analysis. A two-stage minimax design was used [24]. If ≤9 of 36 patients achieved CR, the hypothesis that the overall response rate (ORR) is 30% was to be rejected with 50% probability of early termination. Survival was measured from the day of temozolomide treatment to death from any cause. Disease free survival was measured only in responding patients as the length of time after achievement of a response during which a patient survives with no sign of the disease. Univariate analyses were performed by χ^2 and Fisher's exact tests. Distributions of OS and disease free survival were estimated by the Kaplan-Meier method. All tests were two-sided, with a significance level of 0.05.

Results

Forty-two patients fulfilling the inclusion criteria were enrolled between February, 2008 and November, 2009. Prior to initiation of temozolomide therapy, two patients were excluded because the AML diagnosis could not be confirmed (one patient had no evidence of AML and one patient had acute lymphoblastic leukemia). Four (9.5%) patients were excluded due to disease progression and death prior to start of therapy.

Baseline characteristics of the study population

The patient baseline characteristics according to the *MGMT* methylation status are detailed in Table I. The median time to start of therapy was 12 days (range, 11–14 days). For the entire cohort ($n = 36$), there were 23 (64%) males and the median age was 75 years (range, 64–88 years). Only 6 (17%) patients were younger than 70 years of age and 22% of patients were older than 80 years of age. The *MGMT* promoter was found to be unmethylated in 31 of 36 (86%) patients. Fourteen (39%) patients had newly diagnosed AML, 83% (30/36) had an ECOG performance status of 0-1 and a hematopoietic cell transplantation comorbidity index (HCT-CI) between 0-2. No patients with secondary AML (s-AML) had a mMGMT promoter. Median WBC count at presentation was $1.9 \times 10^3/\mu L$ and only 17% (6/36) of patients had a WBC $>10 \times 10^3/\mu L$. Intermediate (normal karyotype, $n = 16$) or unfavorable risk karyotype was found in 34/36 patients (94%) and *FLT3-ITD*, *FLT3-TKD*, *NPM1* or *CEPBA* mutations were uncommon (Table I). *IDH1* (R132) and *IDH2* (R140) mutations were found in two and three patients, respectively. MSI was not detected in any of the 36 patients in this study. No differences were noted between the baseline characteristics of patients with mMGMT versus unMGMT promoter (Table I).

Response assessment according to *MGMT* methylation and baseline bone marrow blast

The ORR for the entire cohort was 36% including 30% CR plus CRi (Table II). All responses were noted after the first induction cycle. There were five (14%) patients who died while in aplasia prior to response assessment. When stratified by the *MGMT* methylation, overall and complete response rates were statistically similar in patients with mMGMT versus unMGMT promoter (60% vs. 32%) and 40% vs. 19%, respectively. No differences in the CR/CRi rate were noted among patients with de *novo*, secondary or

TABLE II. Rates of Overall Response, Resistant Disease, and Induction Deaths According to the MGMT Methylation Status

Response assessment	All patients (n = 36)	%	Methylated MGMT promoter (n = 5)	%	Unmethylated MGMT promoter (n = 31)	%
Overall response	13	36	3	60	10	32
CR	8	22	2	40	6	19
CRp	3	8	0	0	3	10
LFS	2	6	1	20	1	3
Resistant disease	17	47	1	20	16	51
Induction death	9	25	1	20	8	22

CR, complete remission; CRp, complete remission with incomplete count recovery; LFS, leukemia free state; MGMT, O^6, methylguanine–DNA methyltransferase

relapsed AML (21% vs. 28% vs. 40% $P = 0.24$). As the incidence of induction deaths (ID) were similar in both groups, apparent lower overall response rates were primarily caused by a higher rate of resistant disease in unMGMT promoter group (51% vs. 20%). No differences in the median age, type of AML, *MGMT* promoter methylation status, ECOG performance status, or molecular markers were noted between responders and nonresponders (data not shown). However, responding patients were more likely to have a normal karyotype (61% vs. 35%, $P = 0.3$) and lower risk HCT-CI scores (100% vs. 65%, $P = 0.2$). Finally, no significant differences in the rate of OR, ID, and RD (resistant disease) were noted between different types of AML (*de novo*, relapsed, or s-AML) (data not shown).

Driven by the observation that >80% of responders had a baseline bone marrow blast counts <50%, we determined the effect of bone marrow blast count at diagnosis on the outcome of these AML patients. The median baseline bone marrow blast count was significantly lower in responding patients compared with those without response (38.7% vs. 54.2%, Student t test $P = 0.02$). In fact, patients with bone marrow blasts at screening <50% were significantly more likely to respond to temozolomide than those presenting with baseline bone marrow blasts >50% (CR rate 58% vs. 12%, Fisher's exact test $P = 0.006$)

Overall and disease free survival according to *MGMT* methylation status

The median duration of follow-up from first dose of temozolomide for all patients was 25 weeks (range, 1–110 weeks). The median duration on active study for all patients was 6 weeks (range, 1.5–51 weeks). The median duration of response for the 13 responders was 30 weeks (range, 7–92) and 38% of responders were still alive 12 months after achieving a CR (Figure 2). For the entire cohort of patients, the median OS was 11.5 weeks (range, 1.5–110 weeks) (mean 24 weeks). When patients were stratified based on the *MGMT* promoter methylation status, median duration on study and overall follow-up were longer in patients with methylated *MGMT* promoter (10 weeks vs. 6 weeks; and 32 weeks vs. 23 weeks). No differences in the median OS (20 weeks vs. 10 weeks) or median duration of response (8 weeks vs. 35 weeks) were noted. The median number of consolidation cycles for the 13 responding patients was 2 (range, 0–5). Four responding patients with incomplete peripheral blood count recovery (CRi-2 and LFS-2) did not receive temozolomide consolidation therapy (two received no therapy and two received demethylating agent after being removed from the protocol for lack of peripheral blood count recovery).

Treatment-associated toxicity

All patients started their treatment in the outpatient setting. The all-cause 30-day and induction mortality rates were 19% and 25%, respectively. All induction deaths were deemed to be unrelated to the treatment (disease progression, 17%; and sepsis, 8%). The majority of adverse events (AEs) was recorded during the induction phase of therapy (65%) and was considered unrelated to therapy (78%). Approximately 40% (14/36) of patients never required admission to the hospital during induction therapy. Grade 3 or 4 hematological toxicity was noted in approximately 85% of patients. Neutropenic sepsis occurred in 17% of patients. Median time to recovery for neutrophil and platelet from the end of induction was 18 days and 23 days, respectively. Drug-related hematologic toxicities were difficult to distin-

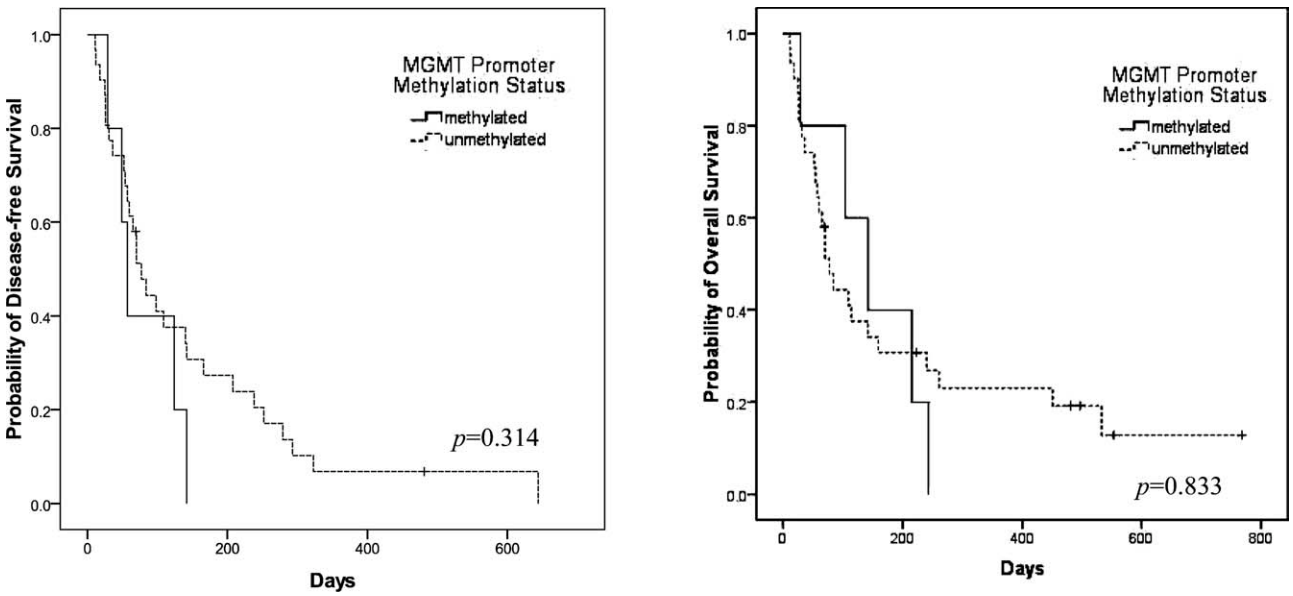

Figure 2. Kaplan Meier curve for overall survival and disease free survival according to MGMT promoter methylation status.

TABLE III. Grade 3/4 Drug-Related Non-Laboratory Adverse Events Reported in >10% of Patients ($N = 36$)

	All grades		No. of patients at maximum grade		
Adverse event	No. of patients	%	3	4	5
Infection	11	31	10	1	0
Febrile neutropenia	11	31	6	2	3
Fatigue	8	22	8	0	0
Pain	6	17	5	1	0

guish from disease-related cytopenias. Grade 3 or 4 nonhematological toxicity was noted in 38% and 8% of patients. Nonspecified infection (31%), fatigue (22%) and pain (11%) were the most commonly reported severe AEs. Other toxicities occurred in less than 10% of patients (Table III). There were 24 cycles of post-remission therapy administered; grade 4 neutropenia occurred during one cycle, and grade 3 thrombocytopenia occurred during four cycles. Grade 3/4 myelosuppression was relatively short with median duration of less than 2 weeks. Three patients required dose reduction of temozolomide due to delayed peripheral blood count recovery while still in CR1.

Outcomes according to HCT-CI stratification

Determining the impact of comorbidities on the outcome of elderly patients with AML is extremely complex. In order to address this issue, patients were scored for their comorbidities according to the HCT-CI at the time of study enrollment [25]. Thirty (83%) patients received a score of 2 or less at the time of enrollment. There were no significant differences in the median age, presenting WBC count and type of AML (*de novo* vs. s-AML) in the two groups. All patients with high HCT-CI scores had cytogenetic abnormalities (three unfavorable risk, two intermediate, and one favorable), while 16/30 patients with low risk HCT-CI scores had a normal karyotype. The overall response rate for patients with low HCT-CI scores was 43% (13/30), while none of the patients with high risk scores responded to therapy ($P = 0.044$, Pearson chi-square). Induction deaths were noted more frequently in patients with high-risk scores (17% vs. 67%, respectively) ($P = 0.01$, Pearson chi square). Finally, OS was also shorter in patients with high risk HCT-CI scores ($P = < 0.01$, by t test).

Discussiosn

The results of this exploratory study indicate that single agent temozolomide is modesty active and relatively well tolerated in elderly patients with AML with high-risk features. The overall response rates (ORR) observed in our cohort compare favorably with those previously reported using single agent temozolomide in AML [10,25]. The phase I clinical trial of temozolomide in relapsed/refractory AML demonstrated an ORR of 21% (4/19 patients), [25] while Brandwein et al. reported an ORR of 15% (CR rate of 11%) in elderly AML patients with identical pretreatment features to patients included in our cohort [10]. Similarly, in heavily pretreated children with acute leukemia (AML and ALL), the ORR was 13% (PRs in 2/16 patients) [9]. Interestingly, responses following 7 days of temozolomide were limited to patients with no MGMT expression and/or methylated *MGMT* promoter. Although, patients with methylated *MGMT* promoter represented ~15% of our patients (similar rates of *MGMT* methylation have been previously reported), [25] the ORR for this group of patients was 60%. These findings suggest that pre-treatment *MGMT* methylation status screening may identify temozolomide-sensitive patients. Furthermore, patients with lower disease burden, defined as <50% bone marrow blasts at diagnosis, had a respectable CR rate of 58% compared to a CR rate of 12% in patients with >50% blasts. These results are similar to those recently reported by Fehniger et al. with single agent Lenalidomide in elderly patients with AML, where patients with blast count <50% had a CR rate of 60% compared to 6% in those patients with higher disease burden at baseline. [26]

Unfortunately, the *MGMT* promoter is unmethylated in the majority of patients with AML, rendering these individuals resistant to the conventional 7 days of temozolomide. In fact in previous studies, no responses have been demonstrated in children or adults with unmethylated *MGMT* promoter and/or MGMT protein expression (the only responding patient in previous reports had weak expression of MGMT protein and no assessment of MGMT promoter methylation status) [27,28]. Our results suggest that extended administration of low dose temozolomide may sensitize leukemic blasts to conventional doses of temozolomide in this temozolomide-refractory patient population.

Recently, several lower-intensity therapies have been developed as induction for the treatment of older patients with AML deemed unfit for conventional induction chemotherapy. Although comparison of results between studies is limited by both known and unknown variables and biases, a few results are worthy of mention. When compared with hydroxyurea, low-dose cytarabine produced higher CR rates and longer survival [29]. Demethylating agents, such as 5-azacitidine and decitabine, have consistently demonstrated CR rates of 15%–25% [30–32]. Single agent clofarabine in elderly patients with AML show CR rates of approximately 45% and acceptable treatment related mortality, although the median OS of the non-responders for these trials (15 weeks) was longer than reported in population studies of elderly AML [33,34]. Tipifarnib, the only other oral agent recently explored for AML patients unfit for induction, produced CR rates of less than 15% and median survival of 3 months [35,36]. Patients with relapsed or refractory AML (19% of patients in our cohort) were usually excluded from these studies.

We noted a relatively high induction and 30-day mortality rate; however, this likely reflects the poor baseline outcome for these patients. The reported median survival for patients with newly diagnosed AML and 75-84 years of age is only 2 months [4]. Ten percent of the patients screened for this trial had disease progression precluding start of therapy. Similar mortality rates have been reported in octogenarian patients receiving supportive care only (21% 7-day mortality and 39% 30-day mortality) [36] as well as the "low intensity" approach used on the British MRC AML 14 trial (30-day mortality 26%) [29]. Toxicities were consistent with those seen in this patient population and difficult to distinguish from disease-related complications. To address this issue further, we calculated the expected induction death rate for the cohort of patients with untreated AML (*de novo* or sAML), [37] and determined the expected and observed 60-day mortality (27% vs. 31%) were not significantly different.

Despite evidence of clinical benefit with our tailored temozolomide regimen, some unanswered questions remain. For example, this study does not address the optimal schedule for temozolomide priming, which AML patients are more likely to benefit from temozolomide, and whether clinical responses correlate with inhibition of MGMT activity in leukemia blasts. However, the response rates demonstrated in this study compare favorably to prior studies using conventional dosing of temozolomide which warrants further evaluation of the priming regimen in future AML studies and other MGMT-expressing malignancies, such as melanoma, colorectal, and breast cancers [38,39]. Also, responses seen in patients in the unMGMT promoter group may simply represent exposure to higher cumulative

doses of TMZ instead of suppression of MGMT activity by protracted doses of TMZ. Finally, a recent report has shown that the expression of MGMT in leukemic blasts correlates poorly with the methylation status of the *MGMT* promoter [40]. These findings suggest that a proportion of patients in the unMGMT promoter group could have low MGMT expression level and therefore would be likely to respond to the conventional temozolomide schedule.

In summary, determination of pretreatment *MGMT* promoter methylation status may allow for differential temozolomide treatment in elderly patients with AML. Although, temozolomide has modest anti-leukemic activity in this high-risk cohort, selection of patients with lower disease burden may improve overall responses in these patients.

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