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A phase II Study of Decitabine and Gemtuzumab Ozogamicin in Newly Diagnosed and Relapsed Acute Myeloid Leukemia and High-risk Myelodysplastic Syndrome

Naval Daver[1], **Hagop Kantarjian**[1], **Farhad Ravandi**[1], **Elihu Estey**[3], **Xuemei Wang**[2], **Guillermo Garcia-Manero**[1], **Elias Jabbour**[1], **Marina Konopleva**[1], **Susan O'Brien**[1], **Srdan Verstovsek**[1], **Tapan Kadia**[1], **Courtney Dinardo**[1], **Sherry Pierce**[1], **Xuelin Huang**[1], **Naveen Pemmaraju**[1], **Maria Diaz-Pines-Mateo**[1], **Jorge Cortes**[1], and **Gautam Borthakur**[1]

[1]Department of Leukemia, University of Texas, MD Anderson Cancer Center

[2]Department of Biostatistics, University of Texas, MD Anderson Cancer Center

[3]Division of Hematology, University of Washington School of Medicine

Abstract

Background—Decitabine may open the chromatin structure of leukemia cells making them accessible to the calicheamicin epitope of gemtuzumab ozogamicin (GO).

Methods—110 patients (median age 70 years; range 27–89 years) were treated with decitabine and GO in a trial designed on model based futility to accommodate subject heterogeneity: Group 1: relapsed/refractory AML with complete remission duration (CRD) < 1 year (N=28, 25%); Group 2: relapsed/refractory AML with CRD ≥1 year (N=5, 5%); Group 3: untreated AML unfit for intensive chemotherapy or untreated MDS or untreated MF (N=57, 52%); and Group 4: AML evolving from MDS or relapsed/refractory MDS or MF (N=20, 18%). Treatment consisted of decitabine 20mg/m2 daily for 5 days and GO 3 mg/m2 on day 5. Post-induction therapy included 5 cycles of decitabine+GO followed by decitabine alone.

Results—CR/CRi was achieved in 39 (35%) patients; Group 1= 5/28 (17%), Group 2 = 3/5 (60%), Group 3 = 24/57 (42%), and Group 4 = 7/20 (35%). The 8-week mortality in Groups 3 and 4 was 16% and 10%, respectively. Common drug-related adverse events included nausea, mucositis and hemorrhage.

Conclusion—Decitabine and GO improved the response rate but not OS compared to historical outcomes in untreated AML ≥60 years.

Corresponding author: Gautam Borthakur, Unit 0428, 1515 Holcombe Boulevard, Houston, TX 77030. Ph: 713-563-1586, gborthak@mdanderson.org.

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Conflicts of Interest Disclosure: The other authors have no relevant conflicts of interest.

AUTHORSHIP CONTRIBUTIONS

ND and GB wrote the paper; GB and HK designed and coordinated the study; ZV, MK, JB, SO, AF, SV, TK, EJ, SF, NP, CD, JC, GB, HK enrolled the patients and conducted the research; and ND, GB, XW, SP, MD analysed the data and performed the statistics. All of the authors participated in the discussion, have reviewed and approved the current version of the manuscript.

SUPPLEMENTARY INFORMATION is available at Leukemia's website.

Keywords

Decitabine; gemtuzumab ozogamicin; acute myeloid leukemia; MDS

INTRODUCTON

Elderly patients (≥ 60–65 years) with AML have a poor prognosis attributable to having disease inherently more resistant to current standard cytotoxic agents and/or relatively poor tolerance of these agents(1–3). Elderly patients with AML also more frequently have an antecedent hematological disorder, unfavorable cytogenetics, and poorer performance status at presentation(2, 4). Among younger patients (<65 years of age), traditional induction chemotherapy (e.g., anthracycline and cytarabine) produces complete remission (CR) in approximately 50–75% of patients (5). Unfortunately, a significant number of younger patients with AML (especially those with adverse cytogenetic features, adverse molecular mutations or antecedent hematological disorder) will be refractory to induction therapy or relapse after initial response to induction therapy. The outcomes of these patients are dismal, with low response rates and poor long-term survival with salvage therapy(6–8). The development of novel agents and/or combinations for these patient groups is warranted.

Antibody drug conjugate strategies envisage one such novel approach. CD33 is expressed by myeloid blast cells in > 80% of patients with AML suggesting that antibodies to CD33 may have specific therapeutic benefit in the treatment of AML(9, 10). Gemtuzumab ozogamycin (Mylotarg®) (GO) is a humanized anti-CD33 monoclonal antibody covalently linked to a semisynthetic derivative of a potent toxin, calicheamicin(11, 12). GO has been used in combination with induction therapy in AML with improved outcomes(11, 13–17) particularly among elderly patients and those with intermediate or good-risk cytogenetics. Decitabine (Dacogen®, 5-aza-2'-deoxycytidine) exerts its antineoplastic activity by direct incorporation into DNA with subsequent inhibition of DNA methyltransferase (DNMT)(18). DNA hypomethylation from DNMT inhibition results in re-expression of tumor suppressor genes(19, 20). In a phase III study in elderly patients (≥ 60 years) with previously untreated AML, decitabine resulted in a response rate (CR/CRp) of 18%(21).

In primary AML samples, response to GO depends on *Syk* expression(22). GO binds to CD33 resulting in the phosphorylation of *Syk*, a protein kinase that docks to the intra-cytoplasmic tail of CD33. *Syk* then complexes with SHP-1, a protein phosphatase(22). Activated *Syk* in this context acts as a tumor suppressor in hematopoietic and solid tumors. DNA hypermethylation can silence *Syk* expression thereby abrogating the anti-proliferative effect of GO on AML cells(23, 24). Hypomethylating agents may restore *Syk* expression, consequently re-establishing sensitivity of AML cells to GO. Prior exposure of AML cells to hypomethylating agent such as decitabine sensitize them to GO by reducing the expression of multi-drug resistance protein-1 (MRP-1) or by enhancing DNA intercalation by calicheamicin(25). Nand et al evaluated a combination of 5-azacitidine and GO in 133 elderly patients with newly diagnosed MDS and AML(26). They divided patients into good risk (N=79) and poor risk (N=54) groups. The good-risk group included patients who were 60–69 years or had a performance status of 0 or 1; the poor-risk group included patients who

were ≥ 70 years or had a performance status of 2 or 3. Responses (CR/CRi) were seen in 44% and 35% of the good risk and poor risk patients, respectively. Median overall survival (OS) was 11 months in both risk groups. Early mortality was noted in 8% of the good risk and 13% of the poor risk patients. While these studies were ongoing, we evaluated the combination of decitabine and GO in newly diagnosed and relapsed AML and high-risk MDS patients treated at our center. Herein, the results are presented.

METHODS

Patient eligibility

Eligibility criteria included patients ≥ 18 years of age with a diagnosis of AML (other than acute promyelocytic leukemia) with refractory/relapsed disease and/or patients with newly diagnosed AML not a candidate for intensive chemotherapy in the opinion of the treating physician; previously treated, relapsed, refractory, or newly diagnosed, high-risk MDS (intermediate-2 or high by the International Prognostic Scoring System [IPSS] or ≥10% blasts)(27); and previously treated, relapsed, refractory, or newly diagnosed, with intermediate- or high-risk myelofibrosis (MF) (i.e., score ≥ 1 by the Lille scoring system) (28) or MF with symptomatic splenomegaly. Other inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3; serum creatinine ≤ 2.0 mg/dL; serum bilirubin ≤ 2.0 mg/dL; serum transaminase ≤ 2.5 times the upper limit of the normal range or or ≤ 5 times the upper limit of the normal range if the transaminase elevation was deemed related to the underlying disease. This was a single center, open-label, non-randomized study. All patients signed an informed consent form approved by the University of Texas/M. D. Anderson Cancer Center (UT/MDACC) Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki. ClinicalTrials.gov identifier: NCT00882102.

Treatment Regimen

The induction regimen included 5 days of decitabine at 20 mg/m^2 given intravenously (IV) over 60 to 90 minutes. The day 5 decitabine dose was followed by GO at 3 mg/m^2 given IV for one dose. Patients underwent a bone marrow aspiration on day 14 +/− 3 days. Patient's whose day 14 bone marrow showed ≥ 20% cellularity with ≥ 5% blasts received an additional course of decitabine 20 mg/m^2 IV daily for 5 days starting on day 15. Patients with response or with no obvious progression could receive post-induction therapy with up to 5 additional cycles of decitabine and GO as during induction, without the day 15 decitabine. Post-induction cycles were repeated every 4 to 8 weeks, depending on the recovery of neutrophil and platelet counts and toxicity. Patients who maintained clinically relevant response (CR or CRi) at the end of post-induction therapy could receive maintenance therapy with decitabine alone every 4–8 weeks for a total of up to 24 cycles of therapy.

Response Criteria and Definitions

Responses were according to established criteria(29). CR was defined by the presence of 5% blasts or less in the bone marrow, with greater than 1.0 × 10^9/L neutrophils and greater than

100×10^9/L platelets in the peripheral blood. CRi was as for CR, but for residual neutropenia ($<1.0 \times 10^9$/L) or thrombocytopenia ($<100 \times 10^9$/L)(30).

Statistical Design

The primary objective of this single-arm phase II study was to assess whether the combination of decitabine and GO could increase the CR rate by 10–15% as compared to historical response rates in similar patients treated at our center. Secondary objectives were to assess the overall survival (OS) and complete remission duration (CRD). Considering the heterogeneity in historical outcomes among patients based on the underlying disease, duration of prior remission and on whether they had new or relapsed disease, patients were up-front classified into four groups: Group 1: relapsed/refractory AML with CRD < 1 year; Group 2: relapsed/refractory AML with CRD ≥ 1 year; Group 3: untreated AML unfit for intensive chemotherapy or untreated MDS or untreated MF; and Group 4: AML evolving from MDS or relapsed/refractory MDS or MF. To account for the heterogeneity of expected remission rates in each group, a model-based Bayesian design(31) with interim stopping rules for futility was implemented. The flexibility of design allows for specific decisions to be made for each group such that enrollment in some groups may be stopped early due to futility while other groups with better remission rates continue to enroll patients. Specifically, for our study, if, within a given group, it was unlikely that decitabine in combination with GO would increase the CR rate by 10– 15% when compared to historical treatment, accrual to that group was to be terminated. The priors for group effects were calibrated to reflect a historical response rate of 15%, 50%, 44% and 28%, respectively, in Groups 1 through 4.

Data analysis—Unadjusted probabilities of OS and CRD were estimated using the method of Kaplan and Meier(32). A Bayesian logistic regression model was fit to assess the decitabine combined with GO treatment effect on CR rate within each group of patients, which included group indicators, treatment indicator within each group, as well as relevant clinical characteristics, such as age, white blood count, platelet count, bone marrow blast percentage, karyotype and ECOG PS. The priors for the group-specific decitabine combined with GO treatment effect were calibrated to reflect a similar response rate as historical controls within each group, but with much larger variability (i.e., non-informative priors for the experimental treatment effect). Similarly for OS, a Bayesian Weibull regression model was fit for each endpoint, with non-informative priors for all the model parameters as well as the scale parameter for Weibull distribution. All statistical analyses were carried out in Splus 8.2 and WinBugs1.4.

RESULTS

Study Group

A total of 110 patients were treated. Their characteristics are shown in table 1. The median age for all patients was 70 years (range, 27–89 years). Eighty-four patients had AML including 16 patients with preexisting MDS and 4 patients with preexisting myelofibrosis, 22 patients had high-risk MDS including chronic myelomonocytic leukemia in 6 patients and MDS/MPN-unclassified in 1 patient, and 4 patients had MF. Forty-four patients (40%)

had high-risk cytogenetics and 11 of 95 tested patients (12%) were *FLT3* mutated (including *ITD* and *D835*). Patients were enrolled into the four predefined groups as follows: Group 1 = 28 patients (25%) [age, 62 years (range, 26–83)]; Group 2 = 5 patients (5%) [age, 83 years (range, 64–88)]; Group 3 = 57 patients (52%) [age, 70 years (range, 42–87)] ; and Group 4 = 20 patients (18%) [age, 70 years (range, 32–82)].

Overall response and outcomes

Overall, 39 patients (35%) achieved CR/CRi with a median duration of CR/CRi of 5.8 months (range, 1 – 41). Median number of cycles for all patients was 2 (range, 1–23). Median number of cycles to CR for all patients that responded was 2 (range, 1–5). Thirty-five patients were found to have persistent blasts on the day 14 bone marrow aspirate and received an additional course of decitabine 20mg/m^2 IV daily for 5 days starting day 15.

Response and outcomes by predefined groups

Responses and outcomes by predefined groups are discussed below and are shown in table 2.

Group 1 - relapsed/refractory AML with CRD < 1 year

Twenty-eight patients with relapsed/refractory AML who had a remission lasting ≤ 1 year were treated in this group. These patients had received a median of two (range, 1–5) prior therapies for AML with a median CRD to most recent salvage regimen of 1.5 months (range, 0–12 months). CR/CRi was achieved in 5 of 28 patients (18%) with a median OS of 3.5 months and 8-week mortality of 11%. These results were comparable to a matched cohort of 440 patients with relapsed/refractory AML and CRD < 1 year treated on protocols for relapsed/refractory AML at our institution between 2001–2010, wherein the CR/CRi rate, median OS and 8-week mortality were 15%, 4.3 months (P=0.72), and 25% (P=0.18), respectively. Based on the model-based Bayesian design interim stopping rules for futility, further accrual to this cohort was closed (supplementary table 1, 2).

Group 2 - relapsed/refractory AML with a CRD ≥ 1 year

Five patients with relapsed/refractory AML who had a complete remission lasting more than 1 year were treated in this group. CR/CRi was achieved in 3 of 5 patients (60%) with a median CRD of 3 months, a median OS of 8 months, and no 8-week mortality. The small number of patients in this group precludes meaningful comparison with matched historical cohort.

Group 3: untreated AML unfit for intensive chemotherapy or untreated MDS or untreated MF

Fifty-seven patients were enrolled in this group including 40 patients with AML and 17 patients with untreated MDS or MF (including 10 MDS, 4 CMML, 1 MDS/MPN-unclassified, and 2 MF).

CR/CRi was achieved in 18 of the 40 elderly/unfit newly diagnosed AML patients (45%) with a median OS of 7.0 months and 8-week mortality of 15%. On comparison to a matched

cohort of 76 newly diagnosed AML patients who were not candidates for intensive chemotherapy and treated with hypomethylator therapy-based protocols (including single agent decitabine protocols, decitabine with or without valproate, 5-azacytidine with or without vorinostat) at our institution between 2001–2010, the CR/CRi rate, median CRD, median OS and 8-week mortality were 30% (P=0.114), 8.1 months (P=0.15) and 16% (P=0.91), respectively. Although decitabine and GO trended towards a superior response rate compared to historical data, this did not result in improved survival in this group (supplementary table 1,2). The median number of cycles administered was 3 (range, 1–23). In patients who achieved CR/CRi the median number of cycles administered was 7 (range, 1–23) and the median number of cycles to response was 2 (range, 1–5).

Among the 15 untreated high-risk MDS patients the CR/CRi rate, median OS and 8-week mortality were 33%, 5.7 months and 20%, respectively. On comparison to a matched cohort of 103 high-risk MDS patients treated at our institution with hypomethylator therapy-based protocols (including single agent decitabine, decitabine with or without valproate, 5-azacytidine with or without vorinostat) between 2001–2010, the CR/CRi rate, median OS and 8-week mortality were 59% (P=0.06), 19.9 months (P=0.03) and 7% (P=0.09), respectively. Thus, the response rate, OS and 8-week mortality were inferior among the patients who received decitabine in combination with GO (supplementary table 1,2).

Group 4: AML evolving from MDS or relapsed/refractory MDS or MF

Twenty patients with AML evolving from MDS (n=11) or with relapsed/refractory MDS or MF (n=9) (including 5 MDS, 2 CMML, and 2 MF) were included in this group. These patients had received a median of one (range, 1–2) prior therapy. The CR/CRi rate was 35% with a median OS of 7.2 months and 8-week mortality of 15%. This was compared to a matched cohort of 23 historical controls who had previously treated MDS that progressed to AML and were treated on-protocols at our center between 2001–2010, where the CR/ CRi rate, median OS and 8-week mortality were 13% (P=0.09), 6.5 months (P=0.37) and 22% (P=0.57), respectively. Decitabine in combination with GO improved the response rate compared to historical data but again did not improve the OS (supplementary table 1,2).

Statistical analysis

Supplementary tables 1, 2 and supplementary figures 1,2 demonstrate the covariate adjusted Bayesian posterior probabilities of decitabine with GO being superior or inferior to the historical treatment for response rate and OS, respectively within each subgroup of patient. For example, in Group 1 patients, the posterior probability of decitabine+GO having a beneficial effect on response rate as compared to historical treatments is 84.6% (supplementary table 1); and the posterior probability of decitabine+GO having a harmful effect on the OS as compared to historical treatments is only 4% (supplementary table 2). Again, in Group 3 patients, the posterior probability of decitabine+GO having a beneficial effect on the response rate as compared to the historical treatment is 71.5% (supplementary table 1), however, for the same group of patients shows that the posterior probability of decitabine with GO having a harmful effect on OS is as high as 98% (supplementary table 2). As group 3 comprised of both untreated AML (n=40) and untreated MDS (n=15) and MF (n=2) patients with different expectations of response, we analyzed effect of therapy

separately. Among patients with untreated AML (n=40), the posterior probability of decitabine with GO having a beneficial effect on the response rate is 93.5% and that of having a harmful effect on OS is 80%. On the other hand for untreated MDS patients (n=15), the posterior probability of decitabine with GO having a beneficial effect on the response rate is only 24% and that of having a harmful effect on OS is as high as 93%.

Toxicity

Neutropenic fever was the most common grade 3/4 toxicity (45%) (table 3). Grade 3/4 gastrointestinal and mucosal bleeding occurred in eight patients (7%). Other grade 3/4 non-hematological toxicities including nausea and mucositis were seen in five patients (5%). Cardiovascular events were observed in three patients including two cases of hypotension and one case of atrial fibrillation. Interestingly, no cases of treatment related grade 3–4 liver function abnormalities or veno-occlusive disease were identified.

Correlation of CD33 expression with response

Of the 110 patients enrolled, 87 were evaluable for CD33 within 3 months prior to initiation of decitabine and gemtuzumab therapy. CD33 positive was defined by a quantitative CD33 expression >/= 20%. 82/87 (94%) were positive. The median quantitative CD33 among the positive patients was 88% (range, 22–100). Only 5 patients were CD33 negative. Responses were noted in 28/79 (35%) of evaluable CD33+ patients and in 1/5 (20%) of evaluable CD33 negative patients. The small numbers preclude a truly meaningful comparison between CD33 expression and response.

DISCUSSION

Despite the voluntary withdrawal of GO from the US market, there have been several reports of survival benefit from the addition of GO to induction therapy in AML(13–16, 33). In younger patients the benefit seems to be more clearly accentuated among patients with intermediate and/or favourable risk cytogenetics(13, 16). In older patients, the addition of GO to cytotoxic induction regimens improved the relapse risk, event-free survival and overall survival without improving the response rate or early mortality rate(14, 15). The fractionated schedules of GO in these recent studies may have allowed safe delivery of cumulative smaller doses resulting in increased efficacy when compared to the previously approved dose of 9 mg/m^2(11, 17, 34, 35). At the time we initiated this study there existed limited data regarding the use of GO in combination with lower intensity therapy such as hypomethylating agents and low-dose cytarabine.

Based on the statistical endpoints, decitabine in combination with GO improved response rate among patients with untreated AML ≥60 years of age who were unfit for chemotherapy, AML evolving from treated MDS and previously treated MDS or MF. However, this did not translate into improved survival when compared to historical data. This is similar to the recently reported MRC16 trial that showed lack of survival benefit despite improved CR rates when GO was added to low-dose cytarabine in elderly untreated AML patients(36).

An important aspect of this study is that the study design performed very well in optimally channelling accrual of patients to the arms that performed well while closing accrual to the

underperforming arms. Such a design takes into consideration the patients' heterogeneity among various prognostic subgroups in the same trial and the potential treatment-subgroup interactions. It can optimize patient allocation to effective therapy while minimizing exposure to ineffective therapy. The improved response rate among patients with newly diagnosed AML, which made up the bulk of group 3, resulted in continued accrual to this group in accordance with the flexible model-based Bayesian design. Thus, 52% of the patients accrued in our trial were in group 3. Historically, cytotoxic induction chemotherapy in elderly patients with AML and considered fit for such therapy produces a CR rate of 30–50% and an induction mortality of 25–40% (3, 6, 37, 38). The 40 treatment naïve AML patients treated with decitabine and GO in our study had an overall response rate of 45% with acceptable toxicity and lower induction mortality. These outcomes compare well to those achieved with single agent hypomethylating agents (azacytidine or decitabine) or their combinations with histone deacetylase inhibitors e.g. valproic acid or vorinostat, in comparable patients treated at our institute.

Our results with hypomethylating agent in combination with GO among treatment naïve elderly AML patients are similar to those recently reported by Nand et al(26). The scientific premise of their study was the synergy between azacytidine and GO wherein azacytidine induced increased CD33 expression and decreased P-glycoprotein expression(37–39). Azacytidine or decitabine mediated chromatin relaxation is also expected to enhance binding of calicheamicin to DNA(25). Nand et al reported a remission rate of 44% and a median survival of 11 months in 'good-risk' treatment naïve elderly AML patients (good risk = age 60–88 and PS 0–1, median age=72). Patients who did not have "good-risk" features (age 70–88 and PS 2–3, median age=75) had a remission rate and median overall survival of 35% and 11 month, respectively. Our study allowed PS of up to 3 and the median age in treatment naïve AML patients was 72 years.

In contrast, the untreated MDS patients had an inferior response rate with the combination as compared to a historical cohort of 103 high-risk MDS patients treated with hypomethylating agent-based therapies at our institution. Two factors may have contributed to inferior outcomes in the MDS patients treated with decitabine and GO. In the frontline decitabine trial conducted at our institution, the median age of patients was 5 years younger than our current cohort(40). Also for various reasons including intercurrent infections the high-risk MDS patients on the decitabine and GO cohort received a median of only 3 (range, 1–13) courses of therapy as compared to a median of 7 (range, 1–49) courses of hypomethylator-based therapy in the historical cohort. Several phase III studies implementing hypomethylator-based therapy have identified a median time to best response of approximately 3–6 months with these agents(41, 42). Thus it is quite possible that the patients in our current study received a less than optimal duration of therapy resulting in inferior response rates. Irrespective of these caveats, the combination of decitabine with GO is possibly an inferior option for patients with untreated MDS.

Similar to elderly patients unfit for standard induction, patients with AML refractory to induction chemotherapy or with short remission have dismal outcomes with salvage chemotherapy(43). The response rates become progressively worse in patients failing multiple salvages. The 28 patients with relapsed/refractory AML and a CRD < 1 year

(median of 1.5 months) treated on our trial had received a median of two prior salvage regimens (range, 1 to 5). CR/CRp was achieved in 18% of these patients with a median OS of 4 months. These results are similar to a matched cohort of 440 patients treated on salvage studies at our institution. Of note, the combination of GO with “3+7’ as first salvage in a small group of younger patients with AML has shown promising results(44). These results need to be confirmed in larger studies in this patient population.

In summary, decitabine in combination with GO may be a suitable regimen in newly diagnosed AML patients who are not candidates for intensive induction therapy. However, the regimen produced inferior outcomes in the small cohort of treatment naïve high-risk MDS patients evaluated. In patients with relapsed/refractory AML decitabine and GO may be a viable alternative to more intensive chemotherapy based salvage regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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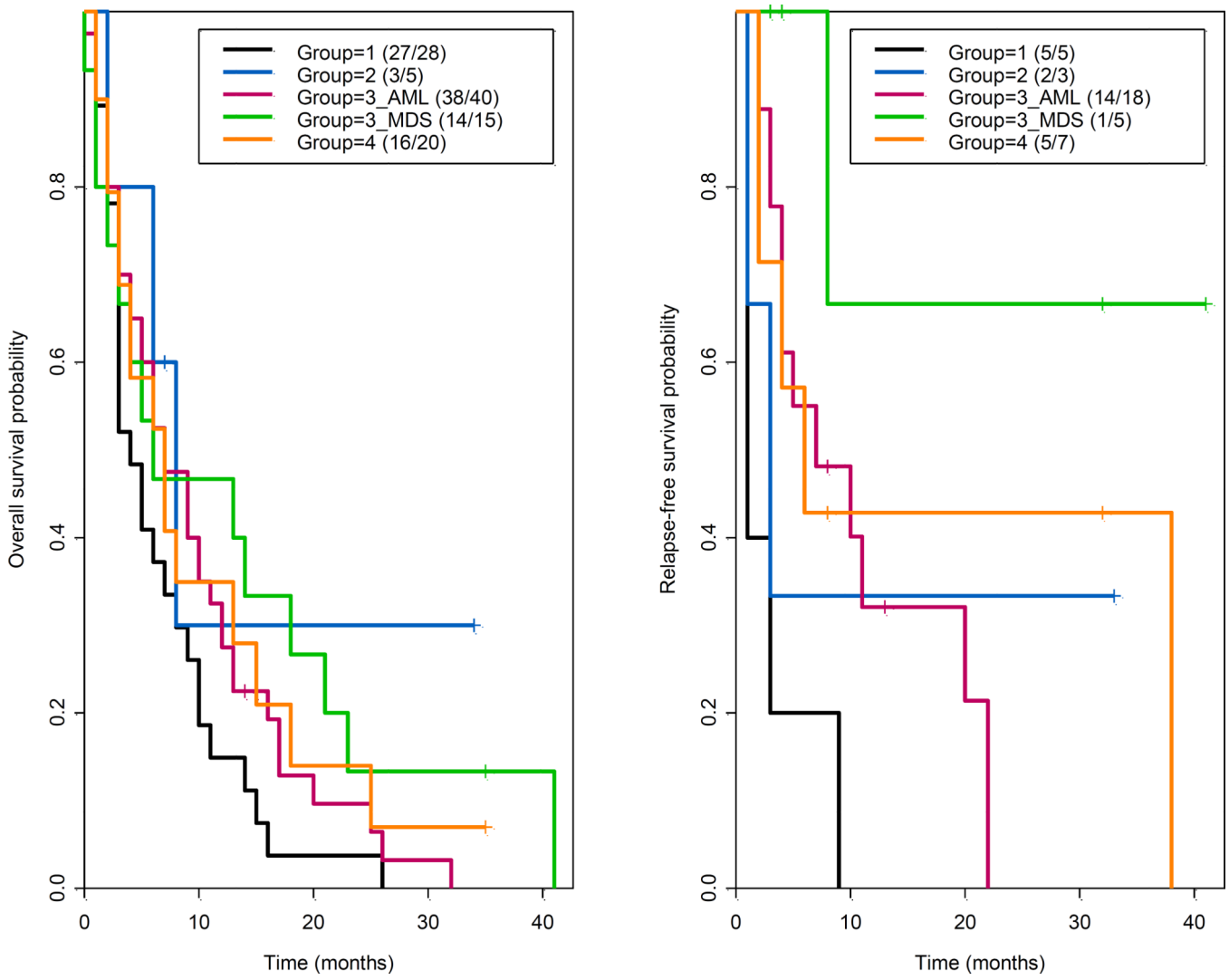

Figure 1.
Kaplan-Meier estimates for overall survival and relapse-free survival by study group

Table 1

Patient characteristics

N=110	
Characteristic	**N (%)/ Median [Range]**
Age	70 [27–89]
Males	63 (57)
Diagnosis at enrollment	
AML [De-novo=64, Preexisting MDS=20]	84 (76)
MDS [MDS=15, CMML=6, MDS/MPN-U=1]	22 (20)
MF	4 (4)
ECOG performance status	1 [0–3]
White Blood Cell Count × 10^9/L	2.5 [0.3–121.9]
Hemoglobin, g/dL	9.3 [6.9–31.9]
Platelets × 10^9/L	37 [3–816]
Percentage of bone marrow blasts	32 [0–96]
Cytogenetics	
High-risk cytogenetics	44(40)
Non high-risk cytogenetics	57(52)
FLT3 mutations (95 evaluated patients)	
FLT3 mutated	11(10)
FLT3 non-mutated	81(76)

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome, CMML, chronic myelomonocytic leukemia, MDS/MPN-U, myelodysplastic/myeloproliferative neoplasm unknown, MF, myelofibrosis

Table 2

Outcomes by predefined groups

Group	CR/ CRi N (%)	Median CR duration (Months)	Median overall survival (Months)	8-week mortality N (%)
1. (R/R AML < 1 yr remission)	5/28 (18%)	1	3.5	3 (11%)
2. R/R AML > 1 yr remission)	3/5 (60%)	3	8	0 (0%)
3. Untreated AML	18/40 (45%)	7	7.0	6 (15%)
Untreated MDS	5/15 (33%)	Not reached	5.7	3 (20%)
4. MDS evolving to AML or relapsed/refractory MDS/MF	7/20 (35%)	6	7.2	3 (15%)

Abbreviations: AML; acute myeloid leukemia, yr, year; MDS; myelodysplastic syndrome; MF; myelofibrosis, CR, complete remission; CRi, complete remission with incomplete count recovery

Table 3

Toxicity profile for all 110 patients

Toxicity	Grade 2 N	Grade 3 N	Grade 4* N	Hospitalizations for grade 3/4 N (%)
Gastrointestinal				
Nausea	1	2		2/2 (100%)
Mucositis		2	1	1/3 (33%)
Infection				
Neutropenic infection	3	21	4	26/28 (93%)
Non-neutropenic infection		2	1	1/3 (33%)
Febrile neutropenia		50		50/50 (100%)
Hemorrhage				
Gastrointestinal hemorrhage		7		7/7 (100%)
Other Mucosal (Oral)		1		1/1 (100%)
Cardiac				
Hypotension	1	1		1/2 (50%)
Atrial fibrillation		1		1/1 (100%)
Metabolic				
Elevated alkaline phosphate	1			0/1