Published in final edited form as:
Pediatr Blood Cancer. 2010 August ; 55(2): 248–253. doi:10.1002/pbc.22519.

MDM2 Polymorphism Increases Susceptibility to Childhood Acute Myeloid Leukemia: A Report from the Children's Oncology Group

Christine L Phillips, MD[1], **Robert Gerbing, MA**[2], **Todd Alonzo, PhD**[2], **John P Perentesis, MD**[1], **Isaac TW Harley, MS**[1], **Soheil Meshinchi, MD, PhD**[3], **Deepika Bhatla, MD**[1], **Gretchen Radloff, BS**[1], and **Stella M Davies, MB.BS PhD**[1]

[1] Division of Hematology Oncology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati, Cincinnati, OH, USA

[2] Children's Oncology Group, Arcadia, CA, USA

[3] Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, WA, USA

Abstract

Background—The variant polymorphism in the gene *MDM2*, SNP309, leads to increased level of mdm2 protein and subsequent downregulation of p53 tumor suppressor pathway. Presence of this single nucleotide polymorphism (SNP) has been associated with earlier tumorigenesis in patients with Li-Fraumeni syndrome, as well as decreased survival in patients with CLL. In addition, cells homozygous (G/G) for SNP 309 were found to have ten fold increase resistance to topoisomerase II inhibitors in vitro.

Procedure—We genotyped children (n=575) with *de novo* acute myeloid leukemia (AML) treated on three Children's Oncology Group protocols (CCG 2941/2961/AAML 03P1) for the presence of SNP309. Healthy blood donors were genotyped as control population.

Results—The variant G/G genotype was associated with an increased susceptibility to AML (OR 1.5; p=0.049). However, the presence of the variant allele at SNP309 did not modify disease response or toxicity in children treated on CCG protocols 2941/2961.

Conclusions—The variant SNP 309 influences susceptibility to pediatric AML, but does not impact overall response to therapy.

Keywords

AML; *MDM2*; SNP 309; Children's Oncology Group; susceptibility

INTRODUCTION

MDM2 is an oncogene that is overexpressed in many malignancies. [1–3]. The MDM2 protein provides negative feedback to the tumor suppressor gene, p53. Transcription of *MDM2* is activated by p53, which in turn leads to the degradation of p53. A normal interaction between the two proteins allows p53 to be maintained at low levels in normally

Corresponding author: Christine L Phillips, MD, ML 7015, Dept of Pediatrics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, Tel (513) 636–1371; Fax (513) 636–1371, christine.phillips@cchmc.org.

Conflicts of interest
The authors report no conflicts of interest.

dividing cells [4]. A single nucleotide polymorphism at position 309 (SNP 309) in the promoter region of *MDM2* results in increased affinity for transcription factor Sp1 and subsequent overexpression of MDM2, downregulation of p53 response and increased tumorigenesis [5].

Overexpression of MDM2 in cancer cell lines has been shown to lead to selective resistance to topoisomerase-II inhibiting drugs [6]. Cell lines homozygous for the variant G allele at SNP309 have a 10-fold increase in the IC_{50} of etoposide as compared to those lines with wild-type SNP 309. Although the exact mechanism is unclear, MDM2 down-regulates topoisomerase II alpha expression, causing resistance to topoisomerase II-targeting drugs such as etoposide, mitoxantrone, amsacrine and ellipticine. Furthermore, the presence of SNP 309 has been shown to reduce survival in a number of malignancies, including adults with CLL, with a 9-fold increased risk of mortality in homozygotes, likely as a consequence of reduced p53 function [7].

As a result of these findings, we hypothesized that the variant SNP 309 genotype might influence susceptibility to childhood acute myeloid leukemia (AML), as exposure to therapeutic or environmental topoisomerase II inhibitors appears to be important in etiology of childhood AML [8]. Furthermore, we hypothesized that children with AML with the variant SNP 309 would have worse treatment outcomes because of resistance to the topoisomerase II targeting agents, etoposide and daunomycin, and reduced functional p53 protein. We also hypothesized that those patients with the wild-type alleles who are more susceptible to topoisomerase II inhibitors would demonstrate more treatment related toxicity, such as longer time to hematologic recovery. To address these hypotheses, we genotyped a cohort of children with AML and examined the effect of MDM2 genotype on susceptibility and outcome of therapy.

MATERIALS AND METHODS

Patients

The study population consisted of 458 patients with *de novo* AML treated on Childrens Cancer Group (CCG) protocols 2941 and 2961 between 1995 and 2002. Clinical data, including age, sex, white blood cell count (WBC) at diagnosis, race, presence of chloroma, CNS status, immunophenotyping and cytogenetic analysis were collected prospectively. Cases were reviewed by central pathology and were classified by the French-American-British (FAB) Cooperative Study Group criteria. All FAB categories, except FAB-M3, were eligible and treated on the same chemotherapy regimens [9–11]. In addition, 117 children with AML enrolled on the COG successor pilot study, AAML 03P1 were genotyped and included in the susceptibility analysis only. Outcome data from this subset of patients is not included in the analysis as the treatment regimen on this pilot study was different. Patients or legal guardians consented to enrollment on the therapeutic studies after approval of the study by the IRB of each participating institution, and to submission of samples for biologic studies. The genotyping study and analysis was approved by the IRB of Cincinnati Children's Hospital Medical Center. Blood samples from 496 Caucasian healthy blood donors served as controls for genotype frequencies in the normal population.

Chemotherapy Treatment Regimen

CCG-2961 was a phase III randomized trial for patients age <21 years with previously untreated acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) conducted between August 1996 and December 2002. CCG-2941 was a feasibility pilot study for the successor CCG-2961 trial and had a similar treatment plan. All patients received intensively timed induction therapy with IDA-DCTER (idarubicin, dexamethasone, cytarabine,

thioguanine, etoposide and daunomycin) given on days 0 to 3 followed by DCTER (dexamethasone, cytarabine, thioguanine, etoposide and daunomycin) given on days 10 to 13. On recovery of white blood cell and platelet counts, patients were randomly assigned to receive consolidation therapy with Regimen A i.e. DCTER or Regimen B, i.e., IDA-FLAG (idarubicin, fludarabine, cytarabine and G-CSF). Intrathecal cytarabine was used for central nervous system (CNS) prophylaxis. Following consolidation, patients with a matched related donor proceeded to allogeneic marrow transplant with ablative conditioning (busulfan and cytoxan). Those without a related donor received intensification with high-dose cytarabine and L-asparaginase (Capizzi II) and additional intrathecal cytarabine. Patients on the Capizzi II arm were further randomized to receive immune modulation with interleukin-2 or standard follow-up care. Bone marrow transplant recipients were excluded from this randomization [9–11].

Genotyping

DNA was extracted from diagnostic marrow samples using the TRIZOL(Invitrogen) reagent according to the manufacturer's directions and normalized to 10 ng/μl. A fluorescence based allelic discrimination assay (Taqman, Applied Biosystems, Foster City, CA) was used for genotyping for *MDM2* polymorphism, SNP 309 (rs2279744). PCR cycling reactions were performed in 96-well micro titer plates in a GeneAmp PCR System 9600 (Perkin-Elmer). The primers used were: Forward primer 5′CGGGAGTTCAGGGTAAAGGT 3′ and reverse primer 5′ CGACAGGCACCTGCGATAAT3′. The Fam (variant) probe was TCCCGCGCCGCAG, and Vic (wild-type) probe was CTCCCGCGCCGAAG. The thermocycling conditions were as follows: 2 step incubation at 50 C for 2 minutes and 95° C for 10 minutes followed by 50 cycles of denaturation and annealing/extension at 95° C for 15 sec and 62° C for 1 minute, respectively. Each 25 μl reaction contained 10 ng DNA, primers/probes as described above, GoldTaq polymerase, dNTP (Invitrogen), Buffer C and Rox reporter dye. Results were analyzed by the automated TaqMan allelic discrimination assay using sequence detection system 2.1 software (ABI TaqMan 7700, Applied Biosystems). Ten percent of the genotyping was repeated with 100% concordance.

Statistical Analysis

Data were analyzed from CCG-2941 and CCG-2961 through April 2005 and October 2006, respectively for both studies. The Kaplan-Meier test was used to calculate the estimates of overall survival [OS], event-free survival (EFS) and disease-free survival (DFS) as defined in section below [12]. Estimates are reported with their Greenwood standard errors [13]. Differences in these estimates were tested for significance using the log-rank statistic [14]. Cumulative incidence estimates were used to determine relapse rate (RR) and treatment-related mortality (TRM) as detailed in previous publications [11]. Differences between RR or TRM estimates were tested for significance using Gray's test [15]. The significance of observed differences in proportions was tested using the Chi-squared test and Fisher's exact test when data were sparse with p value < 0.05 used for significance. Children lost to follow-up were censored at their date of last known contact. Data were censored 6 months prior to April 2005 for CCG 2941 or October 2006 for CCG 2961.

Definitions

Overall survival (OS) is defined as time from study entry to death from any cause. Event-free survival (EFS) is defined as time from study entry to failure at the end of two courses, relapse or death from any cause. Disease-free survival (DFS) is defined as time from the end of one course of therapy to failure at the end of two courses, relapse or death from any cause. DFS was also defined as time from the end of two courses for CR patients to relapse or death from any cause. Relapse rate (RR) is defined as time from the end of one course of therapy to failure at the end of two courses, relapse or death from progressive disease where

deaths from non-progressive disease were competing events. Treatment related mortality (TRM) is defined as time from study entry to death from non-progressive disease where failures at the end of two courses, relapses and deaths from progressive disease were competing events.

RESULTS

AML susceptibility

Genotype frequencies for the MDM2 SNP 309 polymorphism were examined in 575 children with de novo AML to determine whether genotype influences susceptibility to AML. Race is an important variable influencing SNP 309 genotype frequencies. The majority (69%) of children in our study were Caucasian, so to examine the impact of MDM2 SNP309 genotype on susceptibility to AML we compared genotype frequency of Caucasian cases with Caucasian controls only. Cases from 3 studies, CCG 2941, 2961 and 03P1 were combined to optimize sample size. Genotype frequencies differed significantly between cases and controls (p=0.049, Table I), with increased risk of AML in children with a G/G genotype (OR 1.5, CI 1.03–2.20). The genotype frequencies in the normal controls demonstrated Hardy-Weinberg proportions (Table I). However, the distribution of genotypes in the cases did not reflect Hardy-Weinberg equilibrium, in agreement with our hypothesis that the G-allele modifies risk of AML in children. No significant differences were observed with respect to age, gender or other AML prognostic factors such as cytogenetic abnormalities, WBC at diagnosis according to genotype (Table II).

MDM2 SNP 309 and Outcome

Outcomes were studied in children enrolled on CCG 2941 and 2961. Outcomes were not studied in the 117 children enrolled on COG AAML 03P1, as these children received a different treatment regimen, and outcome data are not currently mature. Overall survival (OS) was not significantly different among the genotype groups (T/T, T/G, G/G) when measured from study entry (T/T 52 ± 8%, T/G 46 ± 8%, G/G 57 ± 10%; p=0.42), the end of induction (T/T 63 ± 8%, T/G 51 ± 8%, G/G 63 ± 12%; p=0.22), or the end of course two after randomization (T/T 67 ± 9%, T/G 55 ± 9%, G/G 67 ± 12%; p=0.249). No significant differences between genotype groups were observed with respect to event-free survival (EFS), disease-free survival (DFS), relapse rate (RR) or treatment related mortality when measured from any time point (Table III).

Response to induction therapy was evaluated separately. When each genotype was examined independently, no significant differences were seen for rates of complete remission (CR) (G/G 82%, T/G 85%, T/T 75% p=0.062) (Table IV) or induction failure (G/G 7%, T/G 7%, T/T 7% p=0.984). Patients with the wild-type T/T genotype were more likely to have a partial response (10% vs G/G 6%, T/G 3% p=0.045). This difference in response, however, was not seen after course two and did not translate into difference in OS, DFS or RR.

Toxicity

Detailed toxicity data were analyzed for each course by genotype, as well as length of hospitalization (data not shown). In course one, the patients with a G/G genotype were significantly more likely to have any reported toxicity (74% vs 57% T/G or 62% T/T, p=0.026). Specifically, gastrointestinal toxicity was significantly increased in children with a G/G genotype (67% G/G vs 45% T/G or 52% T/T, p=0.002). However, this difference was not replicated in course two (p=0.842), indicating need for caution in interpreting this finding. The incidence of stomatitis was significantly increased in children with a G/G genotype (16% G/G vs 5% T/G or 6% T/T, p= 0.008). There were no differences in length of hospitalization according to genotype.

DISCUSSION

In this study, we analyzed the frequency of a functional promoter polymorphism (SNP 309) in the gene MDM2 in a large group of children with AML treated on a cooperative group study. Our findings indicate that the presence of this genetic variant modifies susceptibility to leukemia. Children with the G/G genotype have an increased susceptibility to AML. We initially hypothesized, based on *in vitro* data that this variant modifies sensitivity to topoisomerase II inhibitors, that the homozygous variant genotype would decrease susceptibility to AML. Therapeutic topoisomerase II inhibitors such as etoposide are a potent cause of secondary AML. In addition, natural topoisomerase inhibitors exist in the environment, particularly in fruits and vegetables which contain quercetin, beverages such as tea, cocoa and red wine which contain catechins, and soy, which is a sources of genistein [8]. Increasing levels of maternal consumption of dietary topoisomerase II inhibitors are associated with an increased risk of de novo infant AML with MLL rearrangement [8]. Therefore, we speculated that the homozygous variant G/G genotype would offer a protective effect against natural topoisomerase inhibitors due to its resistance to topoisomerase II inhibitors and decrease susceptibility to AML. However, our data do not support this hypothesis, but rather demonstrate that the homozygous variant genotype increases susceptibility to AML. The variant G allele of MDM2 has increased binding of the transcription factor Sp1, leading to increased expression of MDM2, and reduced expression of p53, reducing susceptibility of the cell to p53 induced apoptosis. Increased risk of AML in children with the homozygous variant genotype may be due to a failure of apoptosis in cells that have received DNA damage, so preserving potential oncogenic mutations. Our finding of increased risk of malignancy in association with the homozygous variant genotype is in agreement with a number of prior studies. Studies of solid tumors including renal cell carcinoma, colorectal cancer, pancreatic cancer, gastric carcinoma, lung cancer, soft tissue sarcoma and neuroblastoma have reported an increased risk of malignancy in persons with a homozygous variant genotype, with odds ratios typically between 1.5 and 2.0 [16–23]. More recently, this genotype was found to be associated increased susceptibility to AML in an older cohort of patients (median age 35) [24].

We also hypothesized that the presence of the SNP 309 variant allele might modify response to therapy, as the variant has been shown to modulate sensitivity to topoisomerase II inhibitors, and the homozygous variant genotype has been associated with inferior survival in a number of solid tumors [2,18,19,22,25–27]. Our data showed no differences in survival according to MDM2 genotype. These data do not support our original hypothesis, as we expected an inferior response to therapy in persons with the variant genotype. We saw some minor increase in toxicity in patients with the G/G genotype, but caution is needed in interpreting these data also as data regarding 37 specific toxicities were collected, and these may also be chance findings. It is notable that our study of outcome is the first to include a group of patients all treated with chemotherapy on a uniform clinical trial, allowing us a better opportunity to directly examine the impact of genotype on chemotherapy response, rather than perhaps other biological features of solid tumors that modify survival, as many adult patients with solid tumors do not receive chemotherapy.

Our data contrast with a report of a very significant effect of SNP 309 genotype on outcome of therapy in adults with CLL [7]. In CLL, deletion or reduced function of p53 is associated with more aggressive disease and reduced survival [7]. The SNP 309 variant G allele causes over-expression of MDM2 protein and reduction in production of p53 in CLL, leading to a more aggressive disease course, similar to that seen in patients with CLL with deleted or mutated p53. The difference between this study and our results may indicate lesser importance for p53 status in response to chemotherapy in children with AML compared with CLL.

Multiple comparisons were made in the analysis of outcomes and toxicities, and the majority of the observations were negative. Great caution must be used in interpreting the somewhat limited positive findings of increased toxicity in this analysis as they may represent the consequence of multiple comparisons alone. The significant finding of increased susceptibility to AML was based on a simple analysis of genotype frequency in cases vs. controls. These observations regarding the influence of genotype and susceptibility to AML, were also based on a priori hypothesis that susceptibility would be modified and can be regarded with more confidence. However, in common with all association studies, these observations need to be repeated in a independent dataset for confirmation

Acknowledgments

This work was supported by Hyundai Hope on Wheels Scholarship (CLP), Bear Necessities Pediatric Cancer Foundation Grant (CLP), NIH T32 GM063483 (ITWH), R01 CA93552-01 (SMD), R21 CA10262-01, R01 CA114563-01, (SM) and COG Grant CA 98543. A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at: http://www.childrensoncologygroup.org/admin/grantinfo.htm

References

1. Rayburn E, Zhang R, He J, Wang H. MDM2 and human malignancies: expression, clinical pathology, prognostic markers, and implications for chemotherapy. Curr Cancer Drug Targets. 2005; 5:27–41. [PubMed: 15720187]
2. Boersma BJ, Howe TM, Goodman JE, et al. Association of breast cancer outcome with status of p53 and MDM2 SNP309. J Natl Cancer Inst. 2006; 98:911–919. [PubMed: 16818855]
3. Turbin DA, Cheang MC, Bajdik CD, et al. MDM2 protein expression is a negative prognostic marker in breast carcinoma. Mod Pathol. 2006; 19:69–74. [PubMed: 16258514]
4. Arva NC, Gopen TR, Talbott KE, et al. A chromatin-associated and transcriptionally inactive p53-Mdm2 complex occurs in *mdm2* SNP309 homozygous cells. J Biol Chem. 2005; 280:26776–26787. [PubMed: 15908423]
5. Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the *MDM2* promotor attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell. 2004; 119:591–602. [PubMed: 15550242]
6. Nayak MS, Yang J-M, Hait WN. Effect of a single nucleotide polymorphism in the Murine Double Minute 2 promoter (SNP309) on the sensitivity to topoisomerase II-targeting drugs. Cancer Res. 2007; 67:5831–5839. [PubMed: 17575151]
7. Gryshchenko I, Hofbauer S, Stoecher M, et al. *MDM2* SNP309 is associated with poor outcome in B-cell chronic lymphocytic leukemia. J Clin Oncol. 2008; 26:2252–2257. [PubMed: 18467716]
8. Spector LG, Xie Y, Robison LL, et al. Maternal diet and infant leukemia: The DNA topoisomerase II inhibitor hypothesis: A report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev. 2005; 14:651–655. [PubMed: 15767345]
9. Lange BJ, Dinndorf P, Smith FO, et al. Pilot study of idarubicin-based intensive-timing induction therapy for children with previously untreated acute myeloid leukemia: Children's Cancer Group Study 2941. J Clin Oncol. 2004; 22:150–156. [PubMed: 14701777]
10. Aplenc R, Alonzo TA, Gerbing RB, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2006; 108:74–80. [PubMed: 16537811]
11. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG 2961, a Children's Oncology Group Phase 3 Trial for untreated pediatric acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2008; 111:1044–1053. [PubMed: 18000167]
12. Kaplan E, Meier P, Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–481.
13. Greenwood, M. The natural duration of cancer. Report on Public Health and Medical Subjects. Vol. 33. His Majesty's Stationery Office; London England: 1926.

14. Kalbfleisch, J.; Prentice, R. The Statistical Analysis of Failure Time Data. New York: John Wiley; 1980.
15. Gray R. A Class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988; 16:1141–1154.
16. Hirata H, Hinoda Y, Kikuno N, et al. *MDM2* SNP 309 polymorphism as risk factor for susceptibility and poor prognosis in renal cell carcinoma. Clin Cancer Res. 2007; 13:4123–4129. [PubMed: 17634539]
17. Menin C, Scaini MC, De Salvo GL, et al. Association between MDM2-SNP 309 and age at colorectal cancer diagnosis according to p53 mutation status. J Natl Cancer Inst. 2006; 98:285–288. [PubMed: 16478747]
18. Asomaning K, Reid AE, Zhou W, et al. MDM2 promoter polymorphism and pancreatic cancer risk and prognosis. Clin Cancer Res. 2008; 14:4010–4015. [PubMed: 18559624]
19. Ohmiya N, Taguchi A, Mabuchi N, et al. *MDM2* promoter polymorphism is associated with both an increased susceptibility to gastric carcinoma and poor prognosis. J Clin Oncol. 2006; 24:4434–4440. [PubMed: 16983111]
20. Lind H, Zienolddiny S, Ekstrom PO, et al. Association of a functional polymorphism in the promoter of the *MDM2* gene with risk of nonsmall cell lung cancer. Int J Cancer. 2006; 119:718–721. [PubMed: 16496380]
21. Zhang X, Miao X, Guo Y, et al. Genetic polymorphisms in cell cycle regulatory genes *MDM2* and *TP53* are associated with susceptibility to lung cancer. Hum Mutat. 2006; 27:110–117. [PubMed: 16287156]
22. Cattelani S, Defferrari, Marsilio S, et al. Impact of a single nucleotide polymorphism in the *MDM2* gene on neuroblastoma development and aggressiveness: Results of a pilot study on 239 patients. Clin Cancer Res. 2008; 14:3248–3253. [PubMed: 18519749]
23. Bond GL, Hirshfield KM, Kirchhoff T, et al. *MDM2* SNP 309 accelerates tumor formation in a gender-specific and hormone dependent manner. Cancer Res. 2006; 66:5104–5110. [PubMed: 16707433]
24. Xiong X, Wang M, Wang L, et al. Risk of *MDM2* SNP 309 alone or in combination with the *p53* codon 72 polymorphism in acute myeloid leukemia. Leuk Res. 2009; 33:1454–1458. [PubMed: 19423162]
25. Han JY, Lee GK, Jang DH, et al. Association of *p53* codon 72 polymorphism and *MDM2* SNP 309 with clinical outcome of advanced nonsmall cell lung cancer. Cancer. 2008; 113:799–807. [PubMed: 18618574]
26. Heist RS, Zhou W, Chirieac LR, et al. *MDM2* polymorphism, survival and histology in early-stage non-small-cell lung cancer. J Clin Oncol. 2007; 25:2243–2247. [PubMed: 17538168]
27. Tu HF, Chen HW, Kao SY, et al. *MDM2* SNP 309 and *p*53 codon 72 polymorphisms are associated with the outcome of oral carcinoma patients receiving postoperative irradiation. Radiother Oncol. 2008; 87:243–252. [PubMed: 18423915]

Table I

MDM2 SNP 309 Genotype and Susceptibility to AML (CCG 2941/2961 and AAML 03P1)

	g/g		t/g		t/t			
	N	%	N	%	N	%	Hardy Weinberg Proportion p-value	Chi-square p-value, cases vs controls
Caucasian cases	78	18.1	178	41.2	176	40.7	0.007	0.049
Caucasian controls	62	12.8	229	47.2	194	40.0	0.661	

Table II

Demographics of Patient Population

De novo patient characteristics for patients on CCG-2941 and CCG-2961							
	g/g (n=91)		t/g (n=183)		t/t (n=184)		
	N	%	N	%	N	%	p-value
Study							
CCG-2941	8	9%	17	9%	12	7%	0.599
CCG-2961	83	91%	166	91%	172	93%	
Gender							
Male	50	55%	108	59%	95	52%	0.363
Female	41	45%	75	41%	89	48%	
Age [yrs]							
Median [range]	10.4	[0.17 – 19.7]	10.0	[0.01 – 20.9]	10.3	[0.20 – 19.5]	0.829
0–2 y	14	15%	51	28%	47	26%	0.070
3–10 y	34	37%	53	29%	49	27%	0.179
11–21 y	43	47%	79	43%	88	48%	0.640
Race							
White	55	60%	128	70%	132	72%	0.142
Black	1	1%	9	5%	28	15%	<0.001
Hispanic	28	31%	30	16%	14	8%	<0.001
Asian	4	4%	7	4%	3	2%	0.334
Other	3	3%	8	4%	7	4%	0.901
Unknown	0		1		0		
Hepatomegaly	23	25%	69	38%	59	32%	0.113
Splenomegaly	22	24%	64	35%	64	35%	0.150
WBC ($\times 10^3/\mu L$]) - median [range]	22.7	[1.0 – 684.0]	22.5	[1.0 – 648.2]	17.7	[0.3 – 860.0]	0.351
BM Blasts %	70	[6 – 100]	72	[0 – 100]	70	[1 – 100]	0.417
Platelets ($\times 10^3/\mu L$) - median [range]	45	[2 – 800]	49.5	[5 – 610]	46.5	[3 – 452]	0.593
Hemoglobin (gm/dL)- median [range]	7.8	[2.8 – 30.7]	8.3	[0.4 – 20.4]	8.5	[1.8 – 27.1]	0.315
Days hospitalized, Course 1 - median [range]	37	[4 – 150]	35.5	[1 – 79]	35	[2 – 105]	0.363

De novo patient characteristics for patients on CCG-2941 and CCG-2961							
	g/g (n=91)		**t/g (n=183)**		**t/t (n=184)**		
	N	**%**	**N**	**%**	**N**	**%**	**p-value**
Days hospitalized, Course 2 - median [range]	34	[6 – 100]	34	[5 – 109]	34	[5 – 127]	0.585
CNS involvement at study entry							
Yes	6	7%	9	5%	9	5%	0.817
No	85	93%	173	95%	174	95%	
Unknown	0		1		1		
Chloroma at study entry							
Yes	7	8%	27	15%	14	8%	0.051
No	84	92%	156	85%	170	92%	
Unknown	0		0		0		
FAB Classification							
M0	5	6%	12	7%	10	5%	0.873
M1	14	16%	24	13%	31	17%	0.631
M2	29	32%	48	27%	48	26%	0.563
M4	27	30%	46	26%	50	27%	0.754
M5	9	10%	41	23%	31	17%	0.031
M6	4	4%	2	1%	4	2%	0.217
M7	2	2%	6	3%	8	4%	0.649
De novo (NOS)	1		4		2		
Cytogenetics							
Normal	16	31%	22	21%	27	23%	0.362
t(8;21)	6	12%	12	12%	25	21%	0.111
Abnormal 16	7	14%	12	12%	9	8%	0.402
Abnormal 11	10	20%	25	24%	24	20%	0.706
t(6;9)(p23;q34)	2	4%	1	1%	2	2%	0.432
−7/7q-	1	2%	2	2%	5	4%	0.549
−5/5q-	2	4%	1	1%	1	1%	0.269
+8	1	2%	6	6%	11	9%	0.199

De novo patient characteristics for patients on CCG-2941 and CCG-2961									
	g/g (n=91)		t/g (n=183)		t/t (n=184)				
	N	%	N	%	N	%	p-value		
+21	0	0%	1	1%	1	1%	0.788		
Pseudodiploid	5	10%	15	15%	8	7%	0.157		
Hyperdiploid	0	0%	4	4%	4	3%	0.378		
Hypodiploid	1	2%	2	2%	2	2%	0.987		
No data	40		80		65				

Table III

Outcomes of Therapy According to Genotype.

2941/2961 de novo	g/g		t/g		t/t		g/g vs t/g vs t/t
	N	% ± 2SE%	N	% ± 2SE%	N	% ± 2SE%	p
5yr OS from study entry	91	57 ± 10	183	46 ± 8	184	52 ± 8	0.421
5yr EFS from study entry	91	45 ± 10	183	36 ± 7	184	43 ± 7	0.472
5yr OS from end of course 1	72	63 ± 12	150	51 ± 8	135	63 ± 8	0.220
5yr DFS from end of course 1	72	54 ± 12	150	41 ± 8	135	52 ± 9	0.124
5yr RR from end of course 1	72	30 ± 11	150	45 ± 8	135	38 ± 9	0.126
5yr TRM from end of course 1	72	16 ± 9	150	14 ± 6	135	10 ± 5	0.614
5yr OS from end of course 2	58	67 ± 12	130	55 ± 9	122	67 ± 9	0.249
5yr DFS from end of course 2	58	58 ± 13	130	45 ± 9	122	56 ± 9	0.131
5yr RR from end of course 2	58	32 ± 12	130	47 ± 9	122	40 ± 9	0.126
5yr TRM from end of course 2	58	10 ± 8	130	8 ± 5	122	5 ± 4	0.389

Table IV

Response to Induction Therapy According to Genotype

	g/g		t/g		t/t		g/g vs t/g vs t/t
	N	%	N	%	N	%	p-value
Phase 1 (course 1) response							
CR	72	82%	150	85%	135	75%	0.062
PR	6	7%	6	3%	18	10%	0.045
Fail	6	7%	12	7%	13	7%	0.984
Death	4	5%	8	5%	13	7%	0.477
Unevaluable	3		7		5		
Phase 2 (course 2) cumulative response							
CR	58	73%	130	78%	122	70%	0.261
PR(M1)	4	5%	3	2%	5	3%	0.367
Fail	8	10%	14	8%	26	15%	0.148
Death	10	13%	20	12%	21	12%	0.993
Unevaluable	11		16		10		