

Original Article

Prognostic Implications of t(10;11) Translocations in Childhood Acute Myelogenous Leukemia: A Report From the Children's Cancer Group

Jacqueline N. Casillas, MD, William G. Woods, MD, Stephen P. Hunger, MD, Loris McGavran, PhD, Todd A. Alonzo, PhD, and Stephen A. Feig, MD

Purpose: This was a retrospective analysis of outcome based on cytogenetics for a Children's Cancer Group phase 3 trial of acute myelogenous leukemia (AML) (CCG-2891).

Patients and Methods: A retrospective analysis of outcome for newly diagnosed children with AML and myelodysplastic syndrome (MDS) was performed using data collected from CCG-2891. The authors identified 11 patients whose blasts carried t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q among 470 eligible patients entered with acceptable, centrally reviewed cytogenetics. A bone marrow specimen was used for each case of cytogenetic analysis in which 20 banded (either G-banded or Q-banded) metaphases were completed on each subject. All 11 patients had characteristic monocytoid morphology (M4 or M5) and tended to be young (0.1–7.9 years; median 0.9 years).

Results: All 11 patients entered remission, but remissions tended to be short; 9 patients relapsed within 12 months (median 4 months). The relapse rate of 82% was significantly higher for this group of patients compared with 46% for the group at large. The relapse rate for this group of patients having t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q was also significantly higher compared with subjects with other 11q23 chromosomal abnormalities. The CNS relapse rate of 55% was higher for this group of patients compared with 3% for all other patients in the study. The CNS relapse rate was higher for the subjects who had t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q compared with subjects with all other chromosome 11 abnormalities. Three children survived, two in second remissions (4.7 and 6.3 years after relapse) and one in first remission (7.0 years after diagnosis). Survival and event-free survival for the patients with t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q was 27 ± 27% and 9 ± 17% at 6 years, respectively, and was not statistically different from all other patients with cytogenetics. Similarly, the survival and event-free survival for the patients with t(10;11) translocations and other rearrangements of chromosomes 10 and 11 was 27 ± 27% and 9 ± 17% at 6 years, respectively, and was not statistically different from the 11q23 group of subjects.

Conclusions: Further research is needed to determine the various changes that are occurring at the molecular level for patients with t(10;11) translocations and other rearrangements of chromosomes 10 and 11 to gain insight into the mechanisms causing this clinical phenotype associated with a poor prognosis.

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From Gwynne Hazen Cherry Memorial Laboratory, Mattel Children's Hospital at UCLA, Los Angeles, California (J.N.C., S.A.F.); AFLAC CC and Blood Disorders Service, Emory University, Dept. of Pediatrics and Children's Healthcare of Atlanta, Georgia (W.G.W.); Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida (S.P.H.); Colorado Genetics Laboratory, Department of Pathology, School of Medicine, University of Colorado Health Sciences Center, and Departments of Pathology and Pediatrics, the Children's Hospital, Denver, Colorado (L.M.); and University of Southern California Keck School of Medicine, Los Angeles, California, and Children's Oncology Group, Arcadia, California (T.A.A.).

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Address correspondence and reprint requests to Jacqueline N. Casillas, MD, UCLA School of Medicine, Department of Pediatrics, Division of Hematology-Oncology, 10833 LeConte Avenue, Room A2-410 MDCC, Los Angeles, CA 90095-1752. E-mail: jcasillas@mednet.ucla.edu Cc: smason@childrensoncologygroup.org.

Intensification of therapy has led to recent improvement in the disease-free survival of children with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).[1–3] Despite improvements in chemotherapy, the use of hematopoietic stem cell transplants, and better supportive care, treatment failure leads to mortality in half the children with AML.[4]

Several prognostic markers have been reported to identify patients, at the time of diagnosis, who may be expected to have adverse outcomes despite current intensive therapy. Although of variable importance, based on therapy used, they include an elevated white blood cell count, young age at time of diagnosis, secondary AML or prior MDS, and FAB subtypes of M4 or M5.[5–14] It has been suggested that

genetic alterations of childhood leukemia are the most important of all the prognostic indicators.[15]

Karyotypic abnormalities associated with malignancy may present a unique opportunity to assess prognosis but may also indicate novel therapeutic approaches to patients whose cancer cells carry a specific genetic marker if the molecular mechanism is understood. This has formed the basis of promising therapy with all-trans-retinoic acid in most patients with acute promyelocytic leukemia and PML-RARα fusion and tyrosine kinase inhibitors in patients with Philadelphia chromosome-positive chronic myelogenous leukemia.[16–19]

We report the identification of a karyotypic marker, t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q [t(10;11) & other], that confers a poor prognosis in children with AML. This subset of patients was identified retrospectively in the analysis of outcome in the 2891 study of the Children's Cancer Group (CCG-2891). The translocation and other rearrangements identified in this group of patients involve the short arm of chromosome 10 and the long arm of chromosome 11. Several different gene fusion events have previously been identified in leukemia patients with translocations between 10p and 11q, including *MLL-AF10, MLL-ABI-1*, and *CALM-AF10*.[20–22] The breakpoint associated with the oncogene *ABI-1* is on chromosome 10p11.2, a human homolog to mouse Abl-interactor 1(*Abi-1*). There are reports of heterogeneity in the breakpoints involved that yield the MLL-AF10 fusion transcript in the t(10:11) group. They include breakpoints on 10p11-15 and on 11q13-23.[20–24] We did not perform molecular studies to differentiate between these different molecular subtypes of t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q, but we did observe similar clinical features and a greatly increased risk of treatment failure in AML patients with this cytogenetic abnormality. It is recognized, however, that given the heterogeneity of the karyotypic changes in this study population, it is highly unlikely that they result in similar transcriptional (or other) oncogenic events. However, given that leukemogenesis most likely represents a multistep process, the homogeneity of the clinical presentation and course of disease suggests that the karyotypic changes involving the short arm of chromosome 10 and the long arm of chromosome 11 may be a starting point to understand various changes that are occurring at the molecular level.

METHODS

Study Design

CCG-2891 was a phase 3 randomized prospective treatment protocol for newly diagnosed children with AML and MDS. The era of patient accrual was from October 1989 to April 1995. Patients were randomized to receive induction chemotherapy by intensive or standard timing, followed by matched related marrow transplant (if a donor was available); if no donor was available, the patient was randomized to receive an autologous purged (with 4-HC) marrow transplant or intensive consolidation chemotherapy. The details of therapy as well as the overall clinical outcome of induction therapy and post-induction therapy have been previously reported.[4,25]

Cytogenetic Analysis

A bone marrow specimen was used for each case of cytogenetic analysis. At each CCG institution, both a direct preparation and a short-term unstimulated culture were completed. A complete analysis of 20 banded (either G-banded or Q-banded) metaphases was done on each subject's bone marrow specimen. The chromosomes in each metaphase cell were counted and then each chromosome was examined to determine if the banding pattern was normal or abnormal either using microscopic examination or photographic prints. Identification of clones was determined by following the Second International Workshop on Chromosomes in Leukemia as stated in the General Report.[26] The karyotypes were designated according to the International System for Human Cytogenetic Nomenclature.[27] Each case was reviewed by at least two members of the CCG Cytogenetics Committee at biannual meetings using the photographic karyotypes.

Statistical Analysis

Analyses compare patients with [t(10;11) & other] to patients whose blasts did not have these rearrangements using data obtained through August 10, 2000. The significance of observed differences in proportions were tested using the χ^2 statistic. Patients lost to follow-up were censored at their last known point of study, with a cut off of February 10, 2000. Estimates of overall survival from study entry and event-free survival, defined as the time from study entry to induction failure, marrow relapse, CNS relapse, or death, were calculated using the Kaplan-Meier method. Differences in survival and event-free survival were tested for significance using the log-rank statistic.[28] Relapse rates were estimated using cumulative incidence estimates, with death and other competing risks censored.[29]

Ethics Review and Consent

Informed consent was obtained for each subject in accordance with each institution's policies developed by its institutional review board (IRB) and approved by the Department of Health and Human Services. The approval of the protocol was obtained by each individual institution's IRB committee.

RESULTS

A total of 1,096 patients were enrolled onto the study. Only those patients with de novo AML (n = 887) were selected for this analysis. Patients with MDS, Down syndrome, secondary AML, and chloromas were excluded from

TABLE 1. *Complete karyotypes observed among 11 pediatric patients with AML and [t(10;11) & other]*

Subject	Karyotype (11q23 translocations and other chromosomal rearrangements)
1	46,XX,inv ins(10;11)(p13;q23q21)[2]/46,XX[18]
2	46,XX,–1, +dic(1;19)(p13;q13.1),del(9) (q12q34), t(10;11)(p13;q23)[7]/47,idem, +1[12]/46,XX[3]
3	46,XX,inv ins(10;11)(p13;q23q21)[20]
4	46,XX,t(10;11;16)(p12,q23;p11.2)[20]
5	47,XY,?ins(10;11)(p15;q14q23),+mar[20]
6	46,XY,t(10;11)(p11.2;q23)[20]
7	45,XY,del(1)(p34),–10,t(10;11)(p11.2;q23)[23]
8	46,XX,t(10;11)(p11.2;q23)[18]/46 XX[15] t(10;11)(p13;q21):
9	46,XY,t(10;11)(p13;q21)[15]/46,XY[5]
10	46,XY,t(10;11)(p13;q21[17]/46,XY[7]
11	46,XX,t(10;11)(p13;q21)[13]/46,XX[7]

this analysis (n = 209). Of the 887 eligible de novo AML patients, 470 had confirmed adequate cytogenetic specimens available for evaluation. Among the 470 eligible patients with confirmed adequate cytogenetic specimens, 11 were identified whose leukemia cells carried a [t(10;11) translocation & other]. Of those 11 abnormal karyotypes involving chromosomes 10 and 11, 8 involved 11q23 breakpoints and 3 involved the t(10;11)(q22;q23) translocation (Table 1).

The clinical description of each of the 11 subjects with an abnormal karyotype involving chromosomes 10 and 11 warrants further discussion, because the majority of these subjects also had other clinical characteristics that would place them into a poor prognostic group (Table 2). Two patients had M4 morphology and nine patients had M5 FAB morphology. Eight of the 11 patients were less than 2 years of age (range 0.1–7.9 years; median 0.9 years). Eight of the patients received the intensive timing induction, which was subsequently shown to have superior long-term outcome, while three patients received standard timing induction.[25] The median white blood cell count at presentation was 28.8×10^3/uL.

Despite the presence of clinical poor prognostic indicators, all 11 patients entered initial remission promptly. One of the 11 subjects had an HLA-identical sibling and underwent a bone marrow transplant (BMT). This patient developed chronic graft-versus-host disease and died of an infection 3 years after BMT. Of the remaining 10 patients without an available identical sibling donor, one was randomized to autotransplantation. This patient relapsed and died 4 months after transplantation.

The remaining nine subjects were randomized to receive continued chemotherapy (CC). Eight of these nine subjects relapsed between 1 and 12 months after initiation of CC. Four of these patients relapsed and died before continued chemotherapy could be completed. There was one bone marrow relapse, one CNS relapse, and two relapses in combined sites (bone marrow and CNS). Of the remaining four subjects who were randomized to CC, two have died and two are surviving after further therapy (second complete remission) at 6.1 and 7.5 years after diagnosis. One subject remains in first complete remission without evidence of disease 7.0 years after diagnosis (see Table 2).

Survival (Fig. 1) and event-free survival (Fig. 2) for the [t(10;11) & other] patients, 27 ± 27% and 9 ± 17% at 6 years, respectively, was not statistically different from patients with all other cytogenetics, 46 ± 5% ($P = 0.37$) and 35 ± 5% ($P = 0.28$). Only one patient remains in initial remission (7 years after diagnosis). The overall risk of relapse was significantly higher in the [t(10;11) & other] group compared with patients with other cytogenetics (82% vs. 46%, $P = 0.029$). In addition, the rate of CNS relapse in the [t(10;11) & other] group was 55% compared with 3% for all other patients in the study ($P < 0.001$).

Comparisons were made with the subjects who had [t(10;11) & other] to the all other cytogenetics group to determine if subjects with abnormalities involving chromosomes 10 and 11 in the study did poorly because of having clinical markers associated with a poor prognosis, such as

TABLE 2. *Clinical characteristics and outcome of patients with [t(10;11) & other] AML*

Subject	Age (yrs)	WBC at DX ($x10^3$/μL)	FAB	CNS at DX	ST vs. IT	CR1 achieved	Post remission therapy	Time to relapse (mos)	Site of relapse	Status
11q23 subjects										
1	2.7	103.6	M5	–	IT	+	Chemo	8	CNS+BM	Dead
2	2.6	2.5	M5	–	IT	+	Chemo	12	CNS+BM	CR2
3	0.5	28.8	M5	+	ST	+	Chemo	5	BM	Dead
4	0.3	20.2	M5	–	IT	+	Chemo	1	BM	Dead
5	1.1	50.7	M4	–	IT	+	Chemo	<1	CNS+BM	Dead
6	0.7	8.0	M5	–	IT	+	Auto BMT	4	BM	Dead
7	1.0	52.9	M5	+	IT	+	Chemo	1	CNS	Dead
8	0.9	198	M4	+	IT	+	Chemo	10	CNS+BM	CR2
t(10;11)(p13;q21) Subjects										
9	0.7	3.3	M5	–	ST	+	Chemo	3	CNS+BM	Dead
10	0.1	149.1	M5	+	IT	+	Chemo	N/A	N/A	NED
11	7.9	23.2	M5	–	ST	+	Chemo	5	BM	Dead

WBC, white blood cell count; ST, standard timing induction chemotherapy; IT, intensive timing induction chemotherapy; BM, bone marrow; CR1, first complete remission; CR2, second complete remission; NED, no evidence of disease; Allo BMT, allogeneic bone marrow transplant; Auto BMT, autologous BMT.

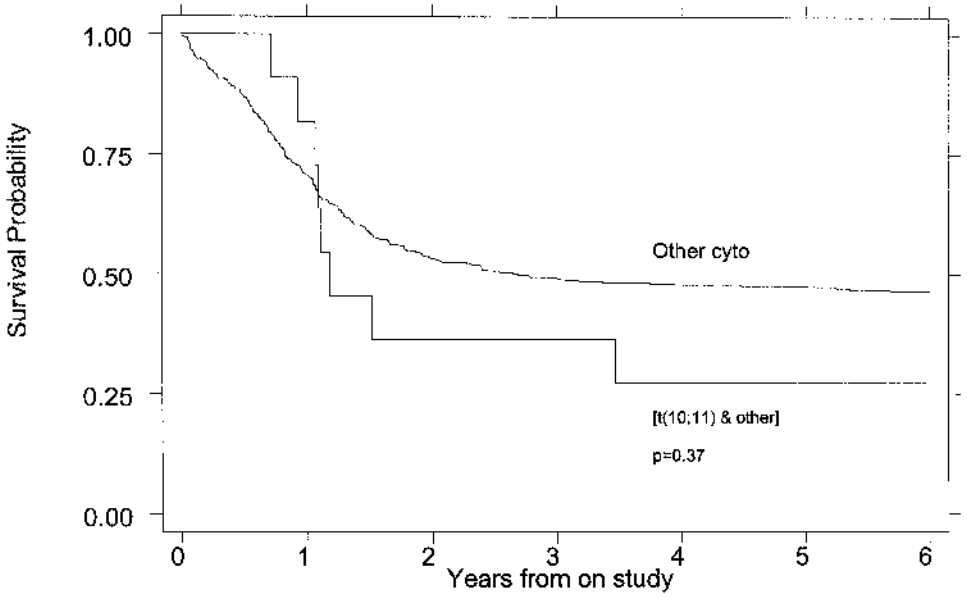

FIGURE 1. Overall survival curve.

FAB classification and age, or due to the rearrangements. The all other cytogenetics group included 114 subjects with a normal 46XX or 46XY karyotype. There were 121 subjects with a favorable karyotype, which included t(8;21)(q22;q22), inv(16)(p13;q22) or t(16;16)(p13;q22), and t(15;17)(q22;q21). There were three t(11;19)(q23;p13) patients. There were 66 patients with other 11q23 abnormalities and 42 patients with all other karyotypic abnormalities. Thirty-eight percent of the all other cytogenetics group had FAB M4/M5 morphology. Twenty percent of the other cytogenetic group were less than 2 years of age, and 10% of the other cytogenetics group were FAB M4/M5 and less than 2 years of age. The relapse rate (Fig. 3) for the [t(10;11 & other] group was 82% compared with 45% for patients with FAB M4/M5 who had other cytogenetics ($P = 0.007$). The CNS relapse rate for the [t(10;11) & other] group was 55% compared with 4% for the patients with FAB M4/M5 with other cytogenetics ($P < 0.001$) and 8% for patients less than 2 years old who had all other cytogenetics ($P < 0.001$). Overall and event-free survival curves were then compared for the two groups, [t(10;11) & other] versus all other cytogenetics. The comparisons did not reveal statistical significance, but the number of cases was small and statistical power was limited.

In addition, comparisons of the patients with the [t(10:11) & other] were made to patients who had other 11q23 abnormalities, since it has been previously described that translocations involving this locus confer a poor prognosis.[30] The results are summarized in Table 3. There was a significantly higher relapse rate for the [t(10;11) & other] group compared with those patients with other 11q23 abnormalities (82% vs. 45%, $P = 0.045$). In addition, there

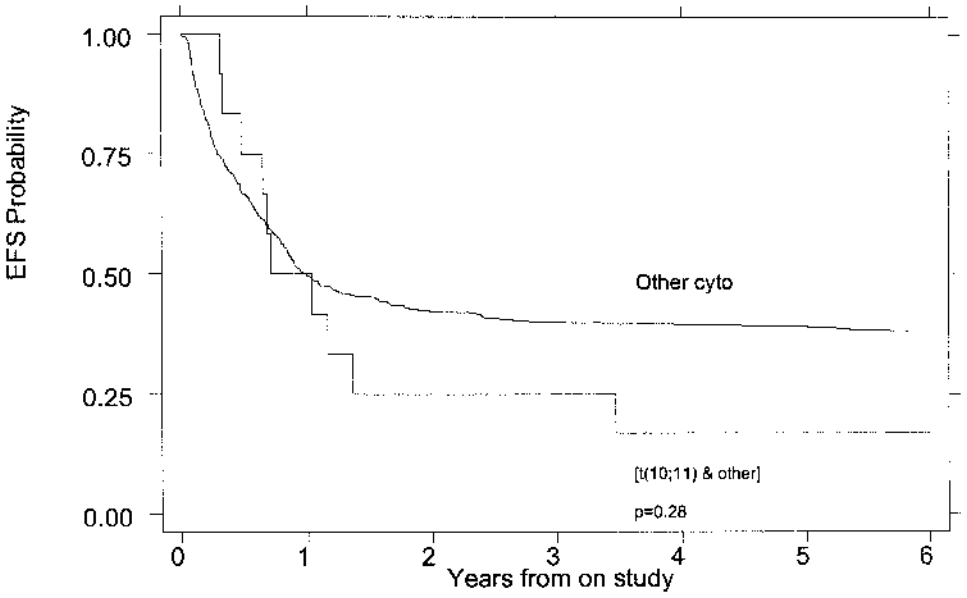

FIGURE 2. Event-free survival curve.

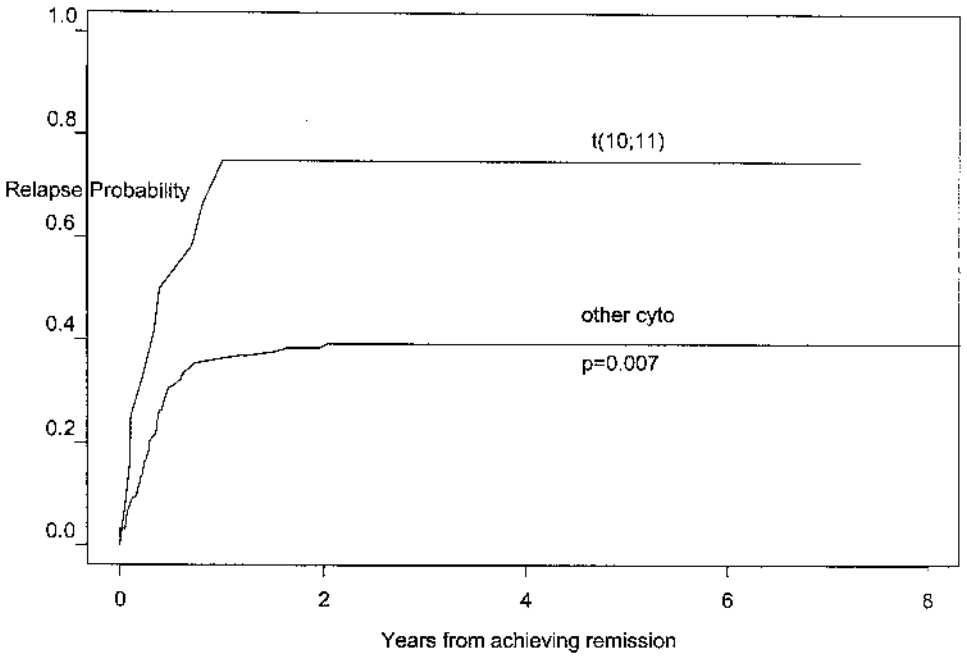

FIGURE 3. Relapse rate for [t(10;11 & other] patients versus other cytogenetics group with FAB M4/M5 morphology.

was a significantly higher CNS relapse rate for the [t(10;11) & other] group compared with patients with other 11q23 abnormalities (55% vs. 6%, $P < 0.001$). There was not a statistically significant difference in the overall survival and event-free survival between the two groups. The only statistically significant difference in the clinical features between the two groups was age at presentation. The patients who carried the [t(10;11) & other] were younger at presentation (median 0.9 years vs. 2.0 years, $P = 0.012$).

DISCUSSION

AML remains a challenge because of variable survival outcomes. Previous studies have described various clinical and biologic findings associated with a poor prognosis in AML. While several studies have described clinical features and molecular characteristics of patients with AML and a t(10;11) translocation, this is the first report from a large, prospective clinical trial describing the outcome with this cytogenetic abnormality.[20–24,31–34] Children enrolled in this trial, who had a [t(10;11) & other], had similar clinical features. All [t(10;11) & other] patients had monocytoid morphology (M4 or M5) (100% vs. 38%, $P \leq 0.001$). In addition, [t(10;11) & other] patients tended to be young (8/11 patients were <2 years old; median 0.9 vs. median 8.2, $P < 0.0001$). There were no induction failures, but the risk of relapse was significantly higher in the [t(10;11) & other] group compared with the all other cytogenetics group (82% vs. 46%, $P = 0.029$). The risk of relapse was also significantly higher in the [t(10;11) & other] group compared with the 11q23 group (82% vs. 45%, $P = 0.045$). The time to relapse was very short, and the latest relapse occurred within 12 months of diagnosis. Four relapses occurred before consolidation chemotherapy could be completed. Another unique feature of the relapses in the subjects with a [t(10;11) & other] was the very high risk of CNS relapse. While CNS relapse was not common in the all other cytogenetics group (3%), there was a significantly higher frequency (55%) among the [t(10;11) & other] patients ($P < 0.0001$). More specifically, the CNS relapse rate for the [t(10;11) & other] group was 55% compared with 4% for the patients with FAB M4/M5 with all other cytogenetics ($P < 0.001$). CNS relapse was also less frequent in the 11q23 group compared with the [t(10;11) & other] group, 6% versus 55%, respectively ($P \leq 0.001$).

TABLE 3. *Comparisons of the [t(10;11) & other] patients versus all other patients with 11q23 abnormal cytogenetics*

	(10;11) rearrangements (n = 11)	11q23 (n = 69)	*P* value
Relapse rate	82%	45%	0.045
CNS relapse rate	55%	6%	<0.001
EFS at 6 years	9 ± 17%	41% ± 12%	0.089
OS at 6 years	27% ± 27%	48 ± 12%	0.350
Median age	0.9 years	2.0 years	0.012
Median WBC	28.8 × 10E^3/uL	48 × 10E^3/uL	0.489
FAB M4/M5	100%	83%	0.201
Intensive induction	73%	57%	0.511

Many studies have found that sentinel cytogenetic abnormalities are powerful predictors of outcome in patients with AML. The three most common reciprocal translocations in AML are the t(8;21)(q22;q22), t(16;16)(p13;q22), and t(15;17)(q22;q21). Each is present in approximately 10% to 15% of patients with AML, and all generally have been associated with a better-than-average treatment outcome. Translocations between chromosome 11q and 10p are another recurring abnormality in AML.[35] To date, three types of translocation events have been characterized molecularly. The *MLL* gene, located at 11q23, was shown to be

TABLE 4. *Karyotypes observed in the all other cytogenetics group*

Karyotype	Frequency (n)
Normal/constitutional	114
t(15;17)	31
t(8;21)	53
Abnormal 16	37
Abnormal 11	69
t(9;11)	33
t(11;19)	3
Other 11q23	33
t(6;9)(p23;q34)	5
–7/–7q–	18
–5/5q–	6
+8	34
+21 (not constitutional)	9
Pseudodiploid	61
Hyperdiploid	14
Hypodiploid	8

fused to a new chromosome 10 gene termed *AF10* in a patient with AML and a t(10;11)(p12;q23).[36] Subsequent studies demonstrated that the *MLL-AF10* fusion occurs in many patients with leukemia and a t(10;11), most of whom have AML of the FAB M5 subtype.[20,37–40] These translocations often involve rearrangements between three or more chromosomes or include inversions of 10p or 11q, such as ins(10;11)(p12;q23q13). These complex rearrangements are needed to produce in-frame MLL-AF10 fusion protein because *MLL* and *AF10* are in opposite transcriptional orientations. *MLL* has also been found to be fused to a different chromosome 10 gene, *ABI-1*, by a t(10;11)(p11.2;q23) in a patient with M4 AML.[21] The third molecular event arising from a t(10;11) is fusion of *AF-10* to the chromosome 11 gene *CALM*, which was originally described in diffuse histiocytic cell line U937 and has subsequently been detected in patients with both ALL and AML.[20,41–46] Overall, it is difficult to distinguish between these three different molecular events by standard cytogenetics, with the exception that the ins(10;11)(p12;q23q13) appears to be specific for the *MLL-AF10* fusion.[24] Although we did not perform molecular studies to differentiate between these different molecular subtypes of t(10;11) translocations and rearrangements involving chromosomes 10 and 11, we did observe similar clinical features and a clinical course of increased risk of treatment failure with significantly increased risk for CNS disease in AML patients. This suggests that the [t(10;11) & other] cytogenetic abnormality can be used as a starting point for future investigation and may involve the underlying gene fusions described above or other fusion products that have not yet been identified.

The most significant limitation of this study, as previously discussed, is the description of only the standard cytogenetics identified on routine karyotypes without molecular-level analysis. Recognition of clinical and standard cytogenetic associations, however, is often the first step in understanding that a homogeneous clinical phenotype has resulted from a common mechanism at the molecular level. In addition, just as the heterogeneous group of clinical and biologic markers (e.g., age, white blood cell count, prior history of MDS, and FAB classification) have been shown to be useful in the assessment of the prognosis of AML patients, the heterogeneous t(10;11) reciprocal translocations or other complex rearrangements involving 10p and 11q described in this study have also been shown to result in an exceptionally high risk of relapse. It will be important for future studies to define the molecular abnormalities present in AML patients with t(10;11) complex rearrangements or other complex rearrangements involving chromosomes 10 and 11. This should lead to improvements in risk group stratification and has the potential to identify well-defined subsets of patients for novel molecularly targeted therapies.

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