

Adult Patients With De Novo Acute Myeloid Leukemia and t(9;11)(p22;q23) Have a Superior Outcome to Patients With Other Translocations Involving Band 11q23: A Cancer and Leukemia Group B Study

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Following reports of childhood acute myeloid leukemia (AML) showing that patients with t(9;11)(p22;q23) have a better prognosis than those with translocations between 11q23 and other chromosomes, we compared response to therapy and survival of 24 adult de novo AML patients with t(9;11) with those of 23 patients with other 11q23 translocations [t(11q23)]. Apart from a higher proportion of French-American-British (FAB) M5 subtype in the t(9;11) group (83% v 43%, $P = .006$), the patients with t(9;11) did not differ significantly from patients with t(11q23) in terms of their presenting clinical or hematologic features. Patients with t(9;11) more frequently had an extra chromosome(s) 8 or 8q as secondary abnormalities (46% v 9%, $P = .008$). All patients received standard cytarabine and daunorubicin induction therapy, and most of them also received cytarabine-based intensification treatment. Two patients, both with t(9;11), underwent bone marrow transplantation (BMT) in first complete remission (CR). Nineteen patients (79%) with t(9;11) and 13 (57%) with t(11q23) achieved a CR ($P = .13$). The

clinical outcome of patients with t(9;11) was significantly better: the median CR duration was 10.7 versus 8.9 months ($P = .02$), median event-free survival was 6.2 versus 2.2 months ($P = .009$), and median survival was 13.2 versus 7.7 months ($P = .009$). All patients with t(11q23) have died, whereas seven (29%) patients with t(9;11) remain alive in first CR. Seven of eight patients with t(9;11) who received postremission regimens with cytarabine at a dose of 100 (four patients) or 400 mg/m² (2 patients) or who did not receive postremission therapy (2 patients) have relapsed. In contrast, 7 (64%) of 11 patients who received intensive postremission chemotherapy with high-dose cytarabine (at a dose 3 g/m²) (5 patients), or underwent BMT (2 patients) remain in continuous CR. We conclude that the outcome of adults with de novo AML and t(9;11) is more favorable than that of adults with other 11q23 translocations; this is especially true for t(9;11) patients who receive intensive postremission therapy.

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CYTOGENETIC STUDIES of patients with acute myeloid leukemia (AML) have shown repeatedly that the karyotype of leukemic cells at diagnosis constitutes an independent prognostic factor.¹⁻³ In adult patients with de novo AML, high rates of complete remission (CR) and prolonged durations of CR and survival have been associated with t(8;21)(q22;q22), inv(16)(p13q22), or t(16;16)(p13;q22) and, to a lesser extent, with t(15;17)(q22;q11-21), whereas such aberrations as inv(3)(q21q26) or t(3;3)(q21;q26), and del(5q) or -5 confer a poor prognosis.³ The prognostic significance of structural chromosome aberrations involving band 11q23 in AML is at present less clear. Although in

most studies, 11q23 abnormalities have been associated with an unfavorable clinical outcome,^{2,4-9} CR rates as high as 83%¹⁰ and 82%¹¹ have been observed, and one group reported no relapses in their five patients with “t(9;11) or its variants” at an almost 3-year-long follow-up.¹⁰ These discrepancies may be related to the very small number of patients in some reports, or to differences in the patients’ treatment, but they may also stem from the common practice of combining all cases with structural changes of band 11q23 into one group, thus making it impossible to discern potential differences in outcome of patients with specific translocations involving band 11q23.

Molecular studies have shown that the vast majority of AML-associated reciprocal translocations or insertions involving band 11q23 result in a rearrangement of the *ALL1* gene (also known as *MLL*, *HRX*, or *Htrx1*), mapped to this band.¹²⁻¹⁶ The only recurrent 11q23 translocation in AML that does not disrupt the *ALL1* gene, but involves a proximally located *PLZF* gene instead, is the t(11;17)(q23;q21), detected in rare cases of acute promyelocytic leukemia (APL). This abnormality appears to be a variant of the APL-specific t(15;17) because it disrupts the same gene on chromosome 17, *RARA*.¹⁷ However, when an apparently identical cytogenetically t(11;17)(q23;q21) was found in AML of French-American-British (FAB) M5 subtype, it resulted in rearrangement of the *ALL1* gene.¹⁸ To date, at least 25 distinct chromosome bands located on 14 different chromosomes have been reported to participate in reciprocal translocations or insertions involving band 11q23 and the *ALL1* gene in AML, and at least nine genes (on chromosomes 1, 4, 6, 9, 10, 17, and 19) fused with *ALL1* have been fully characterized.¹⁹ The role of these partner genes in leukemogenesis and the possible prognostic impact of distinct 11q23 translocations in AML is largely unexplored.

Previous studies of childhood AML have shown that pa-

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tients with t(9;11)(p22;q23) have a significantly better prognosis than those with translocations between 11q23 and other partner chromosomes [t(11q23)].²⁰⁻²² Whether a similar difference in the treatment outcome between t(9;11) and t(11q23) exists in adult patients with de novo AML is unknown. Therefore, we have compared response to treatment and survival of 24 adults with de novo AML and t(9;11) with those of 23 patients with other 11q23 translocations known to involve the *ALL1* gene. Our results indicate that adult AML patients with t(9;11) do have a more favorable outcome than patients with other translocations involving 11q23 whose prognosis is poor.

MATERIALS AND METHODS

Patients. Twenty-five patients with t(9;11)(p22;q23) and 25 patients with a reciprocal translocation (24 patients) or an insertion (one patient) between 11q23 and a chromosome other than 9 at p22 were identified among a total of 1,496 consecutive, previously untreated adult patients with newly diagnosed de novo AML who were successfully karyotyped as part of a prospective Cancer and Leukemia Group B cytogenetic study (CALGB 8461)²³ between 1984 and 1995. Three patients were excluded from this study: one with t(9;11) because she was enrolled onto CALGB 8461, but not on a CALGB treatment protocol; one with t(11;12)(q23;q13) because this translocation was present only in a sideline in addition to t(8;21)(q22;q22), a translocation of known favorable prognostic significance¹⁻³ that also was present in a stemline, without the t(11;12), thus being clearly the primary aberration in this patient; and one with t(11;17)(q23;q21) and APL because in APL, the t(11;17) represents a variant of t(15;17) and does not involve the *ALL1* gene.¹⁷ None of the patients had a previous history of a myelodysplastic syndrome.

Treatment. The patients were enrolled onto one of the following CALGB treatment protocols: 8221²⁴ (n = 1), 8525²⁵ (n = 22), 8923²⁶ (n = 4), 9022²⁷ (n = 3), and 9222 (n = 17). In all of these protocols, the induction therapy consisted of cytarabine at a dose of 200 mg/m²/d for 7 days and daunorubicin at a dose of 30 or 45 mg/m²/d for 3 days. The postremission therapy comprised cytarabine alone or in combination with other drugs depending on the protocol.²⁴⁻²⁷ Patients on protocol 9222 received as postremission therapy either three courses of high-dose cytarabine (HiDAC; 3 g/m² every 12 hours on days 1, 3, and 5 for a total of six doses) or one course of the same HiDAC regimen followed by one course of etoposide (VP-16; 1,800 mg/m²) and cyclophosphamide (50 mg/kg for 2 days) and one course of mitoxantrone (12 mg/m² for 3 days) and diaziquone (28 mg/m² for 3 days). Two patients with t(9;11) were removed from protocol to receive allogeneic bone marrow transplantation (BMT) in first remission. Four patients [three with t(9;11), and one with t(6;11)] underwent BMT after relapse.

Morphologic analyses. Leukemias were classified morphologically according to the FAB Cooperative Group criteria after assessment of Wright's stains of bone marrow and/or blood smears.²⁸ The slides were reviewed in the CALGB central Leukemia Morphology and Cytochemistry Laboratory at the State University of New York Health Science Center at Syracuse. Additionally, in 21 cases with t(9;11) and 20 with t(11q23) bone marrow aspirate films or, in one case, blood smears of material previously submitted to the Laboratory were reviewed for the presence of morphologic dysplasia. One or two hundred (depending on cellularity) cells of granulocytic and erythroid lineages, and each megakaryocyte were assessed. Standard criteria for morphologic dysplasia in myelodysplastic syndromes were used.²⁹ Dysplasia was considered present in a lineage if at least 50% of the cells showed dysplastic features.³⁰

Cytogenetic studies. Pretreatment bone marrow from 45 patients or blood (from two patients) were analyzed cytogenetically in CALGB designated institutional laboratories. Chromosome studies were performed using a direct method or short-term (24- or 48-hour) unstimulated cultures. At least 20 G- or Q-banded metaphases were analyzed in each patient, with the exception of one blood sample in which 15 cells were studied. The karyotypes were interpreted according to the ISCN (1995) nomenclature.³¹ A minimum of two karyotypes from each abnormal clone were reviewed centrally by the CALGB Karyotype Review Committee.

Statistical methods. The level of significance was evaluated at the 5% level with two-sided tests. Comparisons between the two cytogenetic groups of uncensored continuous or percentage variables were performed with the Mann-Whitney test. Discrete variables were compared between cytogenetic groups with the Fisher exact test. The level of significance was adjusted to 1% for multiple comparisons of FAB subtypes and to 1.6% for multiple comparisons of outcome of induction therapy (ie, achievement of CR, death during induction, or resistant disease).

The Kaplan-Meier method³² was used to estimate the distribution of CR duration, event-free survival (EFS), and overall survival. Comparisons of survival and EFS data between the cytogenetic groups were performed with the log-rank test. The CR duration curves crossed and the modified Kolmogorov-Smirnov test³³ was required. For CR duration, as measured from the date of attainment of CR, the endpoint was the first occurrence of relapse (failure), death (failure), or continuous CR at last follow-up (censored). In accord with this definition, the two patients who received BMT in first remission were censored at the time of last follow-up. Failure endpoints for EFS were: induction failure (with EFS of 0); and relapse or death in CR (with EFS equal to CR duration). Censoring of the EFS is based on continuous CR (with EFS equal to CR duration). Survival endpoints, measured from the date of entry onto the study, were death (failure) and alive (censored). Median follow-up of the nine patients censored for survival was 33 months (range, 16 to 85 months). For CR duration, the median follow-up of the seven censored patients was 40 months (range, 15 to 84 months).

RESULTS

Cytogenetics. Among 24 patients with t(9;11), 10 (42%) had the t(9;11) as the only karyotypic abnormality, and 14 had one or more chromosome changes in addition to t(9;11). Two patients in the latter subgroup had a stemline with the t(9;11) as a sole abnormality. The most common secondary aberration was gain of an extra copy or copies of chromosome 8 or 8q; 8 patients had trisomy 8 (+8), including 4 in whom +8 was the only secondary abnormality and four in whom +8 coexisted with, respectively, +19, +i(1q), +der(9)t(9;11)(p22;q23), and, in a sideline, del(13)(q13q22); 1 patient had tetrasomy 8 together with +14 and +der(9)t(9;11); and 2 patients had pentasomy of 8q due to the presence of 2 i(8)(q10), which in 1 of these patients was accompanied by loss of chromosome 13 and an extra marker chromosome. The remaining three patients had other secondary abnormalities, including +der(9)t(9;11) as the only abnormality additional to t(9;11) in 1 patient.

The group of 23 patients with other balanced structural abnormalities involving band 11q23 comprised 7 cases with t(6;11)(q27;q23); 4 with t(11;19)(q23;p13.3); 4 with t(11;19)(q23;p13.1); 2 with complex variants of t(11;17)(q23;q11); 1 with inv ins(10;11)(p13;q23q13); and single patients with translocations between 11q23 and the

Table 1. Summary of Cytogenetic Data of Patients With Translocations Involving Band 11q23

Translocation	Sole	With Secondary Aberrations	Total
t(9;11)(p22;q23)*	10	14†	24
t(6;11)(q27;q23)	4	3†	7
t(11;19)(q23;p13.1)	4	0	4
t(11;19)(q23;p13.3)	2	2	4
t(11;17)(q23;q11)‡	0	2§	2
Other	3	3	6

* Including four cases with complex variant translocations.

† In two cases, a stemline with the translocation as a sole abnormality present.

‡ Both t(11;17) are complex, three- and four-way translocations, respectively.

§ In one case, a stemline with the translocation as a sole abnormality present.

|| Including one case with ins(10;11).

following bands: 1q32, 4q21, 17q21, 17q25 and 22q11 (Table 1). All translocations listed above have been reported to involve the *ALL1* gene.^{16,34,35} The patients were not studied systematically by molecular genetic techniques for detecting the presence of *ALL1* gene rearrangements. However, we performed Southern analysis of DNA obtained from a diagnostic sample in the AML patient with t(11;17)(q23;q21) because this translocation in APL involves the *PLZF* gene instead of *ALL1*. This analysis showed that the *ALL1* gene was rearranged in this patient (data not shown).

In 13 (57%) patients with t(11q23), the 11q23 translocation was found to be the sole cytogenetic abnormality. The remaining 10 patients with t(11q23) had additional chromosome changes including three patients who also had a stemline with an isolated t(11q23). The only secondary aberration detected in more than 1 case with t(11q23) was trisomy 8 found in 2 patients, both of whom had t(11;19)(q23;p13.3) as the primary chromosome abnormality.

The proportions of patients with and without secondary aberrations did not differ between the cytogenetic groups—58% of patients with t(9;11) had secondary aberrations versus 44% of t(11q23) patients ($P = .39$). However, an extra copy or copies of chromosome 8 or 8q as secondary cytogenetic changes were significantly more common in patients with t(9;11) than in the t(11q23) group (46% v 9%, $P = .008$).

Presenting hematologic and clinical characteristics. Presenting clinical and hematologic features of the patients with t(9;11) and t(11q23) are summarized in Table 2. There were no significant differences between the cytogenetic groups in sex distribution, age, hemoglobin levels, white blood cell counts, platelet counts, percent blood or bone marrow blasts, the presence of myelodysplastic features, organomegaly or the percent of patients who had Auer rods in their marrow blasts. There was also no difference between the two groups when the proportions of patients with high white blood cell counts ($>50 \times 10^9/L$) were compared (33% v 43%, $P = .56$). Patients with t(9;11) had AML of FAB M5 subtype more frequently than patients with t(11q23) (83% v 43%, $P = .006$). However, when both AML subtypes with a mono-

Table 2. Comparison of Pretreatment Clinical and Hematologic Characteristics of the Patients With t(9;11) and t(11q23)

Characteristic	t(9;11) (n = 24)	t(11q23)* (n = 23)	P
Sex (% females)	63	48	.39
Age (median, yr)	44	39	.76
FAB (%)			.02
M1	0	13	
M2	4	4	
M4	8	30	.07†
M5	83	43	.006†
AML‡	4	9	
Hemoglobin (median, g/dL)	10.2	9.6	.94
Platelets (median, $\times 10^9/L$)	48.5	49.0	.86
WBC (median, $\times 10^9/L$)	9.4	29.7	.23
% Blood blasts (median)	47	64	.17
% Bone marrow blasts (median)	90	88	.21
Auer rods (% positive)	13	26	.29
MDF§ (no. positive/no. evaluated)			
Erythroid	0/13	0/17	1.0
Megakaryocytic	2/5	1/6	.55
Granulocytic	3/10	4/12	1.0
Organ involvement (% positive)			
Skin	4	14	.34
Gum hypertrophy	21	36	.33
Splénomegaly	8	5	1.0
Hepatomegaly	21	9	.42
Lymphadenopathy	17	18	1.0

* t(11q23), translocations involving the band 11q23 other than t(9;11).

† Based on multiple comparisons with the level of significance adjusted to .01.

‡ AML, acute undifferentiated leukemia or acute myeloid, FAB unclassifiable leukemia on central review.

§ MDF, myelodysplastic features.

cytic component (FAB M4 and M5) were combined, there was no significant difference between the two cytogenetic groups (92% v 74%, $P = .14$).

Treatment outcome. All patients were treated according to one of five CALGB protocols.²⁴⁻²⁷ The distribution of the different protocols (Table 3) and postremission therapy did not differ significantly between the cytogenetic groups. Specifically, intensification with HiDAC alone or in combination with other drugs was given to 47% of the patients with

Table 3. Response to Treatment of the Patients With t(9;11) and t(11q23)

Outcome*	t(9;11)	t(11q23)†	P
Treatment protocol (%)			
CALGB 8221, 8525	42	57	.58
CALGB 8923	8	9	
CALGB 9022, 9222	50	35	
CR rate (%)	79	57	.13
CR duration (median, mo)	10.7	8.9	.02
EFS (median, mo)	6.2	2.2	.009
Survival (median, mo)	13.2	7.7	.009

* CR, complete remission; EFS, event-free survival.

† t(11q23), translocations involving band 11q23 other than t(9;11).

t(9;11) who achieved CR and 54% of patients with t(11q23) who responded to induction therapy ($P = 1.0$).

Patients with t(9;11) were more likely to achieve CR compared with patients with t(11q23), but the difference did not reach statistical significance (79% v 57%, $P = .13$). Likewise, there was no significant difference between the cytogenetic groups in proportions of patients who died during remission induction therapy (21% v 26%, $P = .74$). There was a suggestion that patients with t(11q23) who survived induction therapy were more likely to have resistant disease (0% v 17%, $P = .05$). Among patients who did not achieve CR, 5 with t(9;11) and 6 with t(11q23) died during remission induction therapy, and 4 patients with t(11q23) had resistant disease and died.

The duration of CR was significantly longer for patients with t(9;11) compared with the t(11q23) group ($P = .02$; median, 10.7 months v 8.9 months) (Fig 1A), as was the EFS ($P = .009$; median, 6.2 months v 2.2 months) (Fig 1B). The overall survival of the t(9;11) group was also significantly longer than that of patients with t(11q23) ($P = .009$; median, 13.2 months v 7.7 months) (Fig 1C). All patients with t(11q23) have died, whereas seven (29%) patients with t(9;11), including two who underwent BMT in first CR, remain alive in first CR.

The analysis of postremission therapy administered to patients with t(9;11) showed that 7 patients who received regimens with cytarabine at a dose of 100 (4 patients) or 400 mg/m² (2 patients) or who did not receive postremission therapy (1 patient) relapsed, and 1 additional patient who did not receive postremission therapy died in remission at 1.8 months after diagnosis. In contrast, 7 (64%) of 11 patients who received intensive postremission treatment remain in continuous CR, including both patients who underwent BMT in first CR, and 5 of 9 (56%) patients who received regimens with HiDAC alone (1 patient) or in combination with VP-16, cyclophosphamide, mitoxantrone, and diaziquone (4 patients). Among 13 complete responders with t(11q23), 4 received regimens with HiDAC alone, 3 with HiDAC in combination with VP-16, cyclophosphamide, mitoxantrone, and diaziquone, 3 with cytarabine at a dose 400 mg/m², and 3 with cytarabine at a dose 100 mg/m². All of these patients relapsed and died.

Because almost one half of t(9;11) patients had an extra copy or copies of chromosome 8 or 8q as secondary abnormalities, we compared CR rates, CR duration, and survival of patients with ($n = 11$) and without ($n = 13$) extra chromosome(s) 8 or 8q in addition to t(9;11). The CR rate was similar for both subgroups of patients ($P = 1.0$, 82% v 77%). Likewise, neither CR duration ($P = .53$; median, 26.5 months v 9.6 months) nor survival ($P = .61$; median, 12.3 months v 14.2 months) differed significantly between the two subgroups. Thus the presence of an extra copy or copies of chromosome 8 or 8q does not appear to confer a worse prognosis in patients with t(9;11) as a primary aberration.

DISCUSSION

Earlier studies on the prognostic significance of chromosome aberrations in adults with AML did not separate patients with t(9;11) from those with other 11q23 translocata-

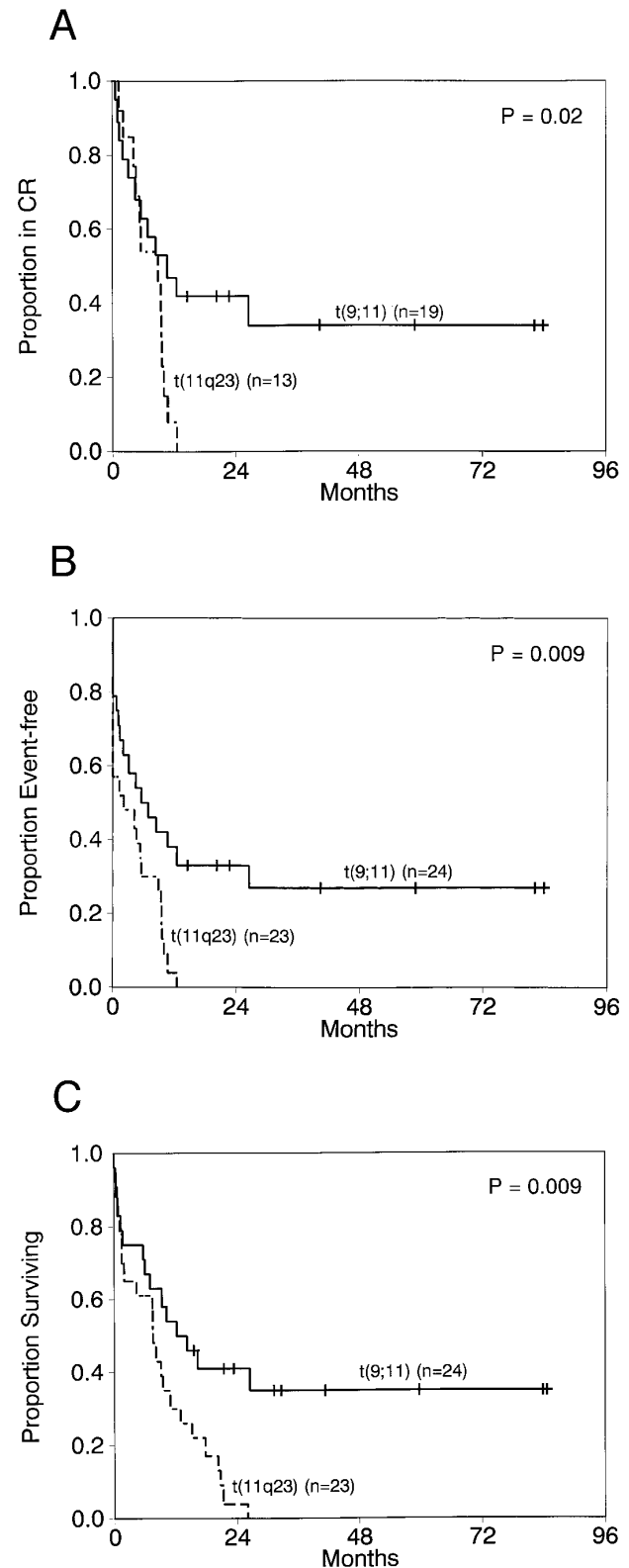


Fig 1. Comparison of outcome for adult de novo AML patients with t(9;11) and with other translocations involving band 11q23 [t(11q23)] at diagnosis. (A) Shows probability of remaining in CR, (B) shows probability of EFS, and (C) shows probability of survival for patients with t(9;11) compared with those with t(11q23).

tions,^{4-9,11} and sometimes also combined deletions⁶⁻⁸ or other structural aberrations involving band 11q23⁸ with 11q23 translocations. Furthermore, in recent molecular studies correlating *ALL1* gene rearrangements with clinical, biologic, and outcome data in patients with AML, all patients positive for *ALL1* gene rearrangements detected by Southern analysis have been considered as one uniform group.^{36,37}

In the current cytogenetic study of a relatively large patient population with a relatively long median follow-up, we have shown for the first time that adult patients with de novo AML and t(9;11) have a significantly better clinical outcome compared with that of adults with translocations between 11q23 and other chromosomes. Our findings are in agreement with previous studies of childhood AML showing a favorable prognosis of patients with t(9;11), but not of those with other 11q23 translocations.²⁰⁻²² Thus in de novo AML, t(9;11) appears to confer a more favorable prognosis than other 11q23 translocations regardless of patient's age. Our results and others²⁰⁻²² also indicate that both in adult and childhood AML, a demonstration of the *ALL1* gene rearrangement alone, without simultaneous identification of the partner chromosome by either cytogenetic analysis and/or reverse transcriptase-polymerase chain reaction (RT-PCR) method, is not sufficient for predicting clinical behavior in patients with translocations involving band 11q23.

The reasons for the significant difference in outcome between t(9;11) and other 11q23 translocations are unknown. In children, translocations involving 11q23 other than t(9;11) have been more frequently associated with extreme hyperleukocytosis at presentation,^{20,21} coagulation abnormalities,²⁰ and skin²¹ and central nervous system (CNS) involvement than t(9;11).^{20,21} In contrast, none of the adults reported herein had symptomatic CNS involvement, and there was no significant difference in leukemic infiltration of the skin or leukocyte count between the two cytogenetic groups. A comparison of other presenting clinical and hematologic characteristics between the t(9;11) and t(11q23) groups did not show any significant differences that could explain the observed difference in CR duration, EFS, or survival. Likewise, induction therapy was similar for all patients in both cytogenetic groups, as was the distribution of postremission therapies. Thus the major factor influencing prognosis in adults with 11q23 translocations appears to be the type of the translocation, ie, whether it involves chromosome 9 at p22 or not, presumably due to differences in the leukemogenic properties of fusion proteins coded by chimeric genes created by various translocations.

In our study, as in other published reports,³⁸ extra copy(ies) of chromosome 8 or 8q were the most common abnormalities secondary to t(9;11). However, the frequency of cases with +8 or extra 8q, 46%, observed by us was more than twice as high as that in patients with t(9;11) reported by others.^{3,38} Moreover, in our series, +8 or extra 8q was significantly more common in patients with t(9;11) than in the t(11q23) group. Interestingly, both of the two cases with +8 in the latter group had as the primary chromosome abnormality t(11;19)(q23;p13.3). This translocation involves the *ENL* gene mapped to 19p13.3 that encodes a protein related to and 56% identical structurally to the protein coded by

AF9, the gene disrupted by the t(9;11).¹⁹ Thus, it is possible that the pattern of secondary aberrations in AML with 11q23 translocations may be dependent to some extent on the type of 11q23 partner chromosome/gene, with a secondary +8 or extra 8q being nonrandomly associated with translocations disrupting related genes on chromosomes 9 and 19.

Trisomy 8 as a secondary aberration appears to be widespread among different types of leukemia and solid tumors,³⁹ but its pathogenetic and prognostic role is largely unknown. Recent studies have suggested that in de novo AML and APL, respectively, an additional chromosome 8 or 8q does not influence treatment outcome.^{9,40} Although the numbers of t(9;11) patients with and without +8 or extra 8q in our study were too small to establish conclusively whether extra 8 or 8q has any prognostic impact, the similar remission duration and survival in the two aforementioned subgroups of patients suggest that a secondary gain of chromosome 8 or 8q at diagnosis might not be an adverse prognostic factor in patients with t(9;11), as well.

Although our patients with t(9;11) fared better than those with t(11q23), almost two thirds of t(9;11) patients have relapsed to date. The complete responders with t(9;11) who remain in CR appear to differ from those who relapsed in the type of postremission therapy they received. While 7 of 8 patients who were administered regimens with cytarabine at a dose 100 mg/m² or 400 mg/m² or who did not receive postremission chemotherapy relapsed, 5 of 9 (56%) patients who received intensification regimens with HiDAC remain in first CR, as do both patients who underwent BMT in first CR. These preliminary findings suggest that intensive postremission therapy in first CR may be especially beneficial in adult patients with t(9;11), and that the intensification chemotherapeutic regimens containing HiDAC alone or in combination with other drugs, including VP-16, which has been shown to be particularly effective in childhood myelomonocytic and monocytic leukemias,⁴¹ should be assessed prospectively in such patients. If their efficacy is confirmed, these regimens may become the therapy of choice in adults with de novo AML and t(9;11) at diagnosis for whom allogeneic BMT is not possible. For patients with translocations between 11q23 and other chromosomes, whose prognosis is poor when treated with current regimens, alternative therapeutic approaches should be explored.

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APPENDIX

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