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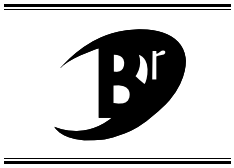

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Cytogenetics in acute leukemia

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Summary Cytogenetic analyses in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) have revealed a great number of non-random chromosome abnormalities. In many instances, molecular studies of these abnormalities identified specific genes implicated in the process of leukemogenesis. The more common chromosome aberrations have been associated with specific laboratory and clinical characteristics, and are now being used as diagnostic and prognostic markers guiding the clinician in selecting the most effective therapies. Specific chromosome aberrations and their molecular counterparts have been included in the World Health Organization classification of hematologic malignancies, and together with morphology, immunophenotype and clinical features are used to define distinct disease entities. However, the prognostic importance of less frequent recurrent aberrations in AML and ALL, both primary and secondary, is still to be determined. This review summarizes current views on clinical relevance of major cytogenetic findings in adult AML and ALL.

Introduction

The role of cytogenetics in determining the biologic basis of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) is now widely recognized. By identifying acquired chromosome aberrations that recur in AML and ALL, and providing precise chromosomal location of breakpoints in leukemia-associated translocations and inversions, cytogenetics aided in cloning of many genes whose activation or fusion with other genes contributes to the neoplastic process.[1–3] Further characterization of these genes revealed that they are often involved directly or indirectly in the development and homeostasis of normal blood cells, and that abnormal protein products of fusion genes created by specific translocations and inversions can dysregulate proliferation, differentiation or programmed cell death (apoptosis) of blood cell precursors.[1] This has paved the way to designing novel therapeutic agents targeting specific genetic abnormalities in leukemic blasts, such as imatinib mesylate, the Bcr–Abl tyrosine kinase inhibitor that suppresses proliferation of cells harboring the *BCR–ABL* fusion gene created by t(9;22)(q34;q11.2), a recurrent chromosome aberration in chronic myelogenous leukemia (CML) and ALL.[4]

Furthermore, cytogenetic analysis is now routine part of clinical practice, being an important

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tool in diagnosis and prognostication of acute leukemias. Specific chromosome aberrations and their molecular counterparts have been included in the World Health Organization (WHO) classification of hematologic malignancies, and together with morphology, immunophenotype and clinical features are being used to define distinct disease entities.[5–7] Pretreatment cytogenetic findings have been repeatedly shown to be among the most important, independent prognostic factors in both AML[8–20] and ALL.[21–26] Consequently, cytogenetic analyses are considered mandatory for analyzing outcome of many clinical trials and are currently used to stratify patients for different types of therapy.[27–29] In this review, we will summarize the clinical relevance of major cytogenetic findings in adult AML and ALL.

Acute myeloid leukemia

Clonal chromosome abnormalities, that is, an identical structural aberration or gain of the same, structurally intact chromosome detected in at least two metaphase cells or the same chromosome missing from a minimum of three cells, are consistently found in the majority of AML patients at diagnosis. However, in contrast to patients diagnosed with CML, who are invariably positive for t(9;22) or its variants, the cytogenetic picture of AML is much more complex. To date, approximately 200 different structural and numerical aberrations such as reciprocal translocations, inversions, insertions, deletions, unbalanced translocations, isochromosomes, isodicentric chromosomes, isolated trisomies and monosomies have been found to be recurring chromosome changes in AML. Many of these aberrations are very rare, being so far detected in a few patients worldwide, whereas others occur more frequently. These more common abnormalities, together with their frequencies among adults and children with AML, are presented in Table 1. A more complete list of specific AML-associated recurrent chromosome aberrations, and genes affected by their formation (if known), can be found in Refs. 27, 30–32.

The incidence of abnormal karyotypes is in general lower in adult than in pediatric de novo AML. While 55% of 4257 adults with AML enrolled onto three large cooperative studies displayed chromosome aberrations (range 53–60%), 76% of 1184 patients included in the four largest series of childhood AML had an abnormal karyotype (range 68–85%; Table 1). The reasons for such a discrepancy are unknown, but may be related to biological differences between pediatric and adult disease. This is likely reflected by varying proportions of specific chromosome aberrations in children and adults with AML. For example, balanced rearrangements, mostly reciprocal translocations, involving band 11q23 and disrupting the *MLL* gene are on average four times more common in children than in adults. The frequency of 11q23 rearrangements in patients with AML decreases appreciably with age: they are detected in 43–58% of infants aged 12 months or less,[33–35] in 39% of children aged 13–24 months,[35] in 8–9% of children older than 24 months,[35] and in just 4–7% of adults (Table 1), among whom, according to the United Kingdom Medical Research Council (MRC) study,[19] the frequency of 11q23 rearrangements goes down from 5% in patients aged 15–34 years to 2% among those aged 35–55 years and 1% in patients older than 55 years. Some other, relatively rare, recurrent aberrations are essentially restricted to young children with AML, not being detected in adult patients thus far. The t(1;22)(p13;q13), a translocation resulting in the *OTT-MAL* gene fusion and highly correlated with acute megakaryoblastic leukemia, has been to date detected exclusively in children, 96% of whom were younger than 24 months.[36,37] Interestingly, almost all infants younger than 6 months had t(1;22) as a sole aberration whereas it was predominantly part of a complex karyotype in the majority of older children ($p = 0.00004$).[36] Another aberration hitherto detected only in infants aged 20 months or younger is t(7;12)(q36;p13). This subtle translocation, involving the *ETV6* gene and almost always occurring together with trisomy 19, was often misdiagnosed as del(12p) in the past and only recently has been shown using fluorescence in situ hybridization (FISH) to be a consistent chromosome aberration in infant AML.[38,39] In contrast, t(15;17)(q22;q12-21) and t(8;21)(q22;q22), the two most common reciprocal translocations in both adults and older children with AML (Table 1), have never been detected in infants aged less than 12 months.[31] However, while the incidence of t(15;17) [and inv(16)(p13q22)/t(16;16)(p13;q22)] is similar in adults and older children, t(8;21) is twice as common in pediatric as in adult AML (Table 1). On the other hand, −5, del(5q) and other unbalanced structural abnormalities resulting in loss of material from 5q are much more frequent in adult than childhood AML. Likewise, both inv(3)(q21q26) and t(3;3)(q21;q26), which are found in 2% of adults, are extremely rare in children and have so far never been detected in a patient with de novo AML younger than 12 years.[31]

Table 1 Frequencies of the more common cytogenetic abnormalities in adult and childhood AML

Cytogenetic abnormality	Cooperative Group Study (No. of patients)				
	CALGB[c] ($n = 1311$) No. (%)	MRC[d] ($n = 2337$) No. (%)	SWOG/ECOG[e] ($n = 609$) No. (%)	Adults total[a] ($n = 4257$) No. (%)	Children[a,b] ($n = 1184$) No. (%)
None (normal karyotype)	582 (44)	1096 (47)	244 (40)	1922 (45.1)	283 (23.9)
+8	123 (9)	211 (9)	53 (9)	387 (9.1)	112 (9.5)
−7/7q−	95 (7)	209 (9)	52 (9)	356 (8.4)	62 (5.2)
−7	47 (4)	136 (6)	NA	183 (5.0)	33 (2.8)
del(7q)	19 (1)	73 (3)	NA	92 (2.5)	18 (1.5)
Loss of (7q)[f]	29 (2)	NA	NA	29 (2.2)	11 (1.3)
t(15;17)(q22;q21)	88 (7)	210 (9)	27 (4)	325 (7.6)	117 (9.9)
−5/5q−	86 (7)	183 (8)	36 (6)	305 (7.2)	14 (1.2)
−5	26 (2)	79 (3)	NA	105 (2.9)	4 (0.3)
del(5q)	42 (3)	104 (4)	NA	146 (4.0)	9 (0.8)
Loss of (5q)[f]	18 (1)	NA	NA	18 (1.4)	1 (0.1)
t(8;21)(q22;q22)	81 (6)	104 (4)	50 (8)	235 (5.5)	137 (11.6)
inv(16)(p13q22)/ t(16;16)(p13;q22)	96 (7)	53 (2)	53 (9)	202 (4.7)	70 (5.9)
−Y	58 (4)	NA	20 (3)	78 (4.1)	28 (3.8)
t/inv(11q23)	54 (4)	45 (2)	42 (7)[g]	141 (3.3)	155 (13.1)
t(9;11)(p22;q23)	27 (2)	NA	NA	27 (2.1)	54 (6.4)
abn(12p)	33 (3)	NA	NA	33 (2.5)	NA
+21	28 (2)	51 (2)	NA	79 (2.2)	60 (5.1)
abn(17p)	30 (3)	NA	12 (2)[h]	42 (2.2)	5 (2.0)
del(9q)	33 (3)	37 (2)	17 (3)	87 (2.1)	33 (2.8)
inv(3)(q21q26)/ t(3;3)(q21;q26)	12 (1)	61 (3)[i]	12 (2)	85 (2.0)	0
del(11q)	12 (1)	NA	NA	12 (0.9)	11 (1.3)
t(9;22)(q34;q11)	10 (1)	16 (1)	8 (1)	34 (0.8)	2 (0.2)
t(6;9)(p23;q34)	8 (1)	10 (<1)	11 (2)	29 (0.7)	12 (1.0)
Complex karyotype with $\geqslant$3 abn	135 (10)	NA	71 (12)	206 (10.7)	36 (14.3)
Complex karyotype with $\geqslant$5 abn	99 (8)	222 (9)	53 (9)	374 (8.8)	31 (5.2)

Abbreviations: CALGB, Cancer and Leukemia Group B; MRC, United Kingdom Medical Research Council; SWOG/ECOG Southwest Oncology Group/Eastern Cooperative Oncology Group; abn, abnormality; NA, not available.

[a] Percentages for particular abnormalities calculated using only those studies that provided relevant data.

[b] Data from Leverger et al.[166] (130 children aged from 2 months to 16 years diagnosed with untreated AML); Raimondi et al.[167] (121 children diagnosed with de novo AML); Martinez-Climent et al.[168] (115 children and adolescents aged from 0 months to 19.2 years diagnosed with de novo AML); Raimondi et al.[169] (478 children and adolescents younger than 21 years diagnosed with de novo AML).

[c] Data from Byrd et al.;[20] the study comprised patients aged 15—86 years diagnosed with de novo AML.

[d] Data from Grimwade et al.[16] and Grimwade et al.;[19] Grimwade et al.[16] comprised 1272 patients aged 15—55 years, the majority of whom were diagnosed with de novo AML; up to 9.4% of patients had AML secondary to chemotherapy or radiotherapy or to an antecedent hematologic disorder. Grimwade et al.[19] comprised 1065 patients aged 44—91 years, 817 of whom were diagnosed with de novo AML and 248 with AML secondary to chemotherapy or radiotherapy or to an antecedent hematologic disorder.

[e] Data from Slovak et al.;[18] the study comprised patients aged 16—55 years diagnosed with untreated AML.

[f] Loss of 7q and Loss of 5q refer to unbalanced structural abnormalities, other than del(7q) and del(5q), that result in loss of material from the, respectively, 7q and 5q chromosome arms (e.g., unbalanced translocations, additions, isochromosome of 7p or 5p, etc.).

[g] Category defined as "abn 11q", might also include patients with other abnormalities of 11q including del(11q).

[h] Including three cases with i(17)(q10).

[i] Category defined as "abn 3q", might also include patients with other abnormalities of 3q.

Prognostic significance of cytogenetics in AML

The Fourth International Workshop on Chromosomes in Leukemia (4IWCL) was the first large, prospective, multi-center study that established pretreatment karyotype as an independent prognostic factor in AML.[8] Significant differences in complete remission (CR) rate, CR duration (CRD) and overall survival (OS) were demonstrated when the 716 patients were prioritized first according to the presence of t(8;21); then t(15;17); followed by −5 or del(5q), −7 or del(7q); concurrent occurrence of −5 or del(5q) and −7 or del(7q), and then abnormalities of 11q, +8 and +21. Patients without any of the above-mentioned abnormalities were classified according to the chromosome number [hypodiploid, pseudodiploid, diploid (normal) and hyperdiploid]. Cytogenetic findings so classified were independent prognostic factors for both duration of first CR and overall survival in the subset of 305 patients treated adequately.[8] In the follow-up studies, a group of patients with abnormalities of 16q22 was added, all cases with aberrations of chromosomes 5 and 7 were combined into one category, and patients with +8 and +21 included in the hyperdiploid group.[12,14,40] The multivariate analyses performed at the third follow-up of the 4IWCL, which then comprised 628 cases with de novo AML with a median follow-up of 14.7 years for patients alive, confirmed karyotype as an independent predictor of survival for all patients and for those 291 patients who received induction therapy that would be deemed standard by present-day criteria.[14]

Many studies, both smaller, performed in a single institution and large, collaborative multi-institutional ones, have confirmed that pretreatment karyotype constitutes an independent prognostic determinant for attainment of CR, CRD, risk of relapse and survival.[9–11,13,15,16,18,20] Recently, three large collaborative studies proposed prioritization schemata that assign AML patients to one of the three risk groups, favorable, intermediate or adverse, based on pretreatment cytogenetic findings.[16,18,20] The three cytogenetic risk systems share many common features, but differ with regard to some aspects (Table 2). In the MRC schema, any abnormality that is not classified as favorable or adverse, and is not accompanied by any additional chromosome aberration classified as favorable or adverse, is categorized in the intermediate-risk group. In contrast, both the Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG) and Cancer and Leukemia Group B (CALGB) schemata explicitly categorize particular abnormalities into risk groups, and leave as not classified aberrations too infrequent to be analyzed. Moreover, MRC and SWOG/ECOG classify patients with a given abnormality into one of the three risk groups once, whereas CALGB provides risk-group assignment separately for probability of induction success, cumulative incidence of relapse (CIR) and OS. Consequently, in the CALGB schema, the same abnormality [e.g., t(6;9)(p23;q34)] may be categorized in the intermediate-risk group with regard to probability of achieving a CR, in the adverse-risk group with respect to OS and not being classified with regard to CIR, because too few patients attained a CR to be analyzed.

Despite these differences, the inv(16)/t(16;16) and t(8;21), cytogenetic hallmarks of core-binding factor (CBF) AML, have been categorized in the favorable group by all three cytogenetic risk systems. However, SWOG/ECOG classified as favorable also patients with del(16q) whereas MRC and CALGB did not. We believe that patients with true del(16q) [i.e., deletions that do not represent misinterpreted inv(16) or t(16;16) and are usually found in AML with morphology other than that of acute myelomonocytic leukemia with abnormal eosinophils (AMML Eo)] should not be included in the favorable risk group, because del(16q) differs from inv(16)/t(16;16) at the molecular level, and has not been associated with a favorable outcome comparable to that of inv(16)/t(16;16).[28,41,42] Consequently, the RT-PCR and/or FISH assays detecting *CBFβ-MYH11* gene fusion should be performed in all patients with del(16)(q22) to ensure that they do not harbor a misidentified inv(16)/t(16;16).[28] Moreover, while MRC and CALGB included all patients with t(8;21) in the favorable group, irrespective of whether t(8;21) was the sole aberration or occurred together with one or more secondary abnormalities, SWOG/ECOG classified as favorable only those t(8;21)-positive patients who did not have a complex karyotype with three or more abnormalities or a secondary del(9q). The latter abnormality has been reported as a poor risk indicator in patients with t(8;21) in one study,[43] but this result was not corroborated by the MRC,[16] CALGB,[20] nor by other studies.[8,10,44] Indeed, it has been consistently reported that for patients with t(8;21) and inv(16)/t(16;16), neither the presence of secondary abnormalities, including the most frequent in t(8;21)-positive patients −Y, −X and +8, nor a complex karyotype with three or more abnormalities adversely affects clinical outcome.[8,10,16,20,44] Instead, adverse prognostic significance among t(8;21)-positive patients has been attributed to such factors as high initial white

Table 2 Risk-group assignments of patients with selected chromosome aberrations in the 3 major collaborative cytogenetic studies of adult AML

Aberration	Risk group assignment[a]				
	CALGB[b]			MRC[c]	SWOG/ECOG[d]
	CR rate	CIR	OS		
t(8;21)(q22;q22)	Favorable	Favorable	Favorable	Favorable	Favorable[e]
inv(16)(p13q22)/ t(16;16)(p13;q22)	Favorable	Favorable	Favorable	Favorable	Favorable
t(15;17)(q22;q21)	NA	NA	NA	Favorable	Favorable
del(9q)	Intermediate	Intermediate	Favorable/ Intermediate[f]	Intermediate	Adverse
None (Normal)	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
-Y	Intermediate	Intermediate	Intermediate	Other numerical	Intermediate
del(5q)	Intermediate	Not classified	Intermediate	Adverse	Adverse
Loss of 7q	Intermediate	Not classified	Intermediate	Other structural	Unknown
t(9;11)(p22;q23)	Intermediate	Intermediate	Intermediate	Intermediate[g]	Adverse[m]
+11	Intermediate	Intermediate	Intermediate	Other numerical	Unknown
del(11q)	Intermediate	Not classified	Intermediate	Other structural	Adverse[m]
+13	Intermediate	Intermediate	Intermediate	Other numerical	Unknown
del(20q)	Intermediate	Not classified	Intermediate	Other structural	Adverse[h]
abn(12p)	Adverse	Not classified	Intermediate	Other structural	Intermediate/ Unknown[i]
+21	Intermediate	Adverse	Intermediate	Intermediate	Unknown
+8 sole	Intermediate	Intermediate	Adverse	Intermediate	Intermediate
+8 with 1 other abn	Intermediate[j]	Intermediate	Adverse	Intermediate[k]	Intermediate
t(6;9)(p23;q34)	Intermediate	Not classified	Adverse	Other structural	Adverse
t(6;11)(q27;q23)	Intermediate	Not classified	Adverse	Intermediate[g]	Adverse[m]
t(11;19)(q23;p13.1)	Intermediate	Not classified	Adverse	Intermediate[g]	Adverse[m]
t(9;22)(q34;q11)	NA	NA	NA	Other structural	Adverse
-7	Intermediate	Adverse	Adverse	Adverse	Adverse
inv(3)/t(3;3)	Adverse	Not classified	Adverse	Adverse[l]	Adverse
complex ≥3	Adverse	Adverse	Adverse	Not classified	Adverse
complex ≥5	Adverse	Adverse	Adverse	Adverse	Adverse
-5	Not classified	Not classified	Not classified	Adverse	Adverse
del(7q)	Not classified	Not classified	Not classified	Intermediate	Adverse
abn(11q23)	Not classified	Not classified	Not classified	Intermediate	Adverse[m]
+22	Not classified	Not classified	Not classified	Intermediate	Unknown
abn(17p)	Not classified	Not classified	Not classified	Other structural	Adverse
abn(20q)	Not classified	Not classified	Not classified	Other structural	Adverse
del(16q)	Not classified	Not classified	Not classified	Other structural	Favorable
+6	Not classified	Not classified	Not classified	Other numerical	Intermediate
abn(21q)	Not classified	Not classified	Not classified	Other structural	Adverse

Abbreviations: CALGB, Cancer and Leukemia Group B; MRC, United Kingdom Medical Research Council; SWOG/ECOG Southwest Oncology Group/Eastern Cooperative Oncology Group; CR, complete remission; CIR, cumulative incidence of relapse; OS, 5-year overall survival; abn, abnormality; NA, not available.

[a]For the convenience of the reader, risk group assignments of particular abnormalities are depicted in color: green for "favorable", blue for "intermediate" and probably intermediate by virtue of being "other structural" or "other numerical" in the MRC classification, red for "adverse" and brown for "not classified" or "unknown".

Table 2 (*continued*)

[b]Data from Byrd et al.;[20] 1213 adults with de novo AML analyzed. Patients with t(15;17) and t(9;22) were excluded from the analysis because therapy with ATRA or imatinib mesylate, respectively, is now considered a standard treatment option for these AML subtypes. All patients with t(8;21) and inv(16)/t(16;16) were classified in the favorable and those with t(9;11) in the intermediate risk categories regardless of whether t(8;21), inv(16)/t(16;16) and t(9;11) occurred alone or together with any secondary aberration or as part of a complex karyotype (defined as the presence of three or more aberrations). All other patients with a complex karyotype were classified as having adverse risk. Consequently, risk-group assignments of all other aberrations concerned only those patients who had a given aberration occurring alone or with only one additional abnormality other than t(8;21), inv(16)/t(16;16) and t(9;11).[20]

[c]Data from Grimwade et al.[16] Of the 1612 patients analyzed, 1493 were diagnosed with de novo AML and 119 with secondary AML. The patient population included 340 children aged 0—14 years and 1272 adults aged 15—55 years. Patients with t(8;21), inv(16)/t(16;16) and t(15;17) were classified in the favorable risk group irrespective of whether t(8;21), inv(16)/t(16;16) and t(15;17) occurred alone or in conjunction with other abnormalities. Adverse abnormalities were classified as such regardless of whether they occurred alone or in conjunction with intermediate-risk or other adverse-risk abnormalities. Intermediate group comprised cytogenetic abnormalities not classified as favorable or adverse in the absence of accompanying favorable or adverse cytogenetic changes[16].

[d]Data from Slovak et al.;[18] 609 adults aged 16—55 years with untreated AML analyzed.

[e]Provided t(8;21) is not part of a complex karyotype or is not accompanied by del(9q). Both complex karyotype and del(9q) were classified in the adverse prognostic category.

[f]Favorable for a group of 13 patients with del(9q) that included six who underwent SCT off-protocol; intermediate for non-transplanted patients treated with chemotherapy only.

[g]Would be included in "abnormal 11q23" category.

[h]Would be included in "abn 20q" category.

[i]del(12p) classified as intermediate, other rearrangements affecting 12p presumably classified as unknown.

[j]The abnormality accompanying +8 is other than t(8;21), t(9;11) and inv(16) or t(16;16).

[k]Intermediate provided the abnormality accompanying +8 is not classified as favorable or adverse.

[l]Would be included in "abn 3q" category.

[m]Would be included in "abn 11q" category.

blood cell count (WBC) or absolute granulocyte count, the presence of granulocytic sarcomas, expression of the neural cell adhesion molecule CD56 on leukemic blasts and high WBC index.[44] The WBC index [i.e., WBC $\times$ (% of marrow blasts/100)], which divides patients into three subgroups (low index, <2.5; intermediate index, 2.5—20; high index, $\geqslant 20$) that differ with respect to clinical outcome, has been found in a recent large study to be the only prognostic factor for CRD, disease-free survival (DFS) and overall survival of patients with t(8;21) in multivariate analysis.[44]

The outcome of adults with CBF AML can be improved substantially by intensive post-remission therapy with high-doses of cytarabine (HDAC).[17] Furthermore, patients with t(8;21) who received three or four cycles of HDAC on CALGB treatment protocols had superior projected 5-year DFS (71% versus 37%) and survival (76% versus 44%) rates compared with those who were administered only one cycle of HDAC followed by sequential treatments with cyclophosphamide/etoposide and mitoxantrone/diaziquone with or without filgrastim.[45] The efficacy of repeated courses of HDAC for AML patients with t(8;21) has been confirmed by others.[46] Likewise, the 5-year CIR was significantly decreased in patients with inv(16)/t(16;16) receiving 3—4 cycles of HDAC as compared with those receiving one HDAC course (43% versus 70%) [Byrd et al., unpublished results]. This improved outcome is likely related to an increased sensitivity of the leukemic cells carrying inv(16)/t(16;16) or t(8;21) to cytarabine. Tosi et al.[47] have shown a significant increase in incorporation of cytarabine into nuclear DNA in vitro and cytarabine induced apoptosis in blasts from patients with inv(16) compared to cells from patients with other chromosome aberrations or a normal karyotype. Another study revealed that samples from patients with inv(16)/t(16;16) and those with t(8;21) had the highest in vitro proliferative activity which was closely correlated with an increased incorporation of the active moiety of cytarabine, AraC triphosphate, into the DNA.[48]

The three major cytogenetic risk classifications agree that prognosis of patients with inv(3)(q21q26) or t(3;3)(q21;q26), -7 and a complex karyotype is poor (Table 2). The definition of complex karyotype differs, though, with the MRC characterizing this category as "the presence of a clone with at least five unrelated cytogenetic abnormalities", and SWOG/ECOG and CALGB, as well

as the German AML Study Group,[49] as three or more abnormalities. A multi-center Italian study defined complex karyotype as "the presence of a clone with more than three cytogenetic abnormalities".[50] Byrd et al.[20] compared the outcome of patients with three or four abnormalities [other than t(8;21), inv(16)/t(16;16) or t(9;11)(p22;q23)] with that of patients with five or more abnormalities. Although patients in the former group were younger and had significantly better CIR and 5-year OS than patients with five or more abnormalities, the CR rate and OS of patients with three or four abnormalities were significantly lower and the CIR significantly higher than those of patients included in the cytogenetically normal group. Only one patient in the group with three or four abnormalities remained in remission at 5 years. Thus, the authors concluded that these data justify combining patients with three or four abnormalities with patients who have five or more abnormalities into one complex karyotype category defined by the presence of three or more abnormalities.[20]

It has been striking in the CALGB series that all or almost all patients with −5, del(7q), −17/17p−, −18, and −20 had a complex karyotype, thus precluding assessment of the prognostic significance of these abnormalities independently from complex karyotype. In the MRC study, the outcome of patients with del(7q) that was not part of a complex karyotype with $\geqslant$ 5 abnormalities and was not accompanied by −5/del(5q) or abn(3q) did not differ significantly from outcome of patients with a normal karyotype.[16] Their findings are consistent with earlier observations suggesting that patients with del(7q) without coexisting aberrations of chromosome 5 may have prolonged survival.[40,51] In the CALGB series, most patients with del(5q) had a complex karyotype and very poor prognosis. However, a relatively small group of patients with del(5q) in a non-complex karyotype was classified as having intermediate risk with regard to CR rate and OS.[20]

Patients with various balanced abnormalities involving band 11q23 have been grouped into one cytogenetic category in both the SWOG/ECOG and MRC study, and classified, respectively, as having adverse and intermediate prognosis (Table 2). However, mounting evidence suggests that outcome of patients with translocations involving band 11q23 depends on the partner chromosome involved, with t(9;11)(p22;q23)-positive patients having a more favorable prognosis that places them in the intermediate-risk group.[20,52] Remarkably, a recent study of 298 infants and children with de novo AML found that t(9;11) was the most important, favorable prognostic factor for patients treated on protocols used at St. Jude Children's Research Hospital.[53] Zwaan et al.[54] suggested that the superior outcome of the t(9;11)-positive patients may be explained by enhanced sensitivity of their leukemic blasts to several chemotherapeutic drugs. In this study, bone marrow or blood samples from children with AML and t(9;11) were significantly more sensitive in vitro to cytarabine, etoposide, the anthracyclines and 2-chlorodeoxyadenosine than samples from patients with various other chromosome aberrations. When compared with a subgroup of childhood AML patients harboring other 11q23 translocations, including t(6;11)(q27;q23), t(9;11)-positive samples were significantly more sensitive for cytarabine and doxorubicin, and borderline more sensitive for etoposide.[54] The survival of adults with t(6;11) and t(11;19)(q23;p13.1) studied by CALGB was significantly shorter than that of the cytogenetically normal group, and, consequently, t(6;11) and t(11;19)(q23;p13.1) were assigned to the adverse-risk group for OS. For patients with other, less frequent 11q23 translocations, the definitive assignment of risk category will be possible only once enough patients are analyzed in large prospective studies.[20]

The most common trisomies in de novo AML are, in decreasing order of frequency, +8, +22, +13, +21 and +11.[20] Trisomy 22 is a non-random secondary aberration accompanying inv(16)/t(16;16) and is rarely seen as the only chromosome abnormality.[31] Although each of the remaining trisomies can be found as a secondary aberration, +8, +13, +11 and +21 are also detected recurrently as the only (isolated) karyotypic changes at diagnosis, with a frequency among adults with de novo AML of 4% for sole +8, 1% each for sole +13 and +11, and 0.4% for sole +21.[55] With regard to the impact of recurrent trisomies on clinical outcome, most data have been gathered for trisomy 8, but results have been somewhat inconsistent. CR rates of patients with +8 have differed widely, from 29%[11] to 91%,[51] as have CRD and survival among studies,[32] and consequently patients with +8 have been classified either in the intermediate or adverse-risk category. In some reports, this cytogenetic group included both patients with isolated +8 and those who in addition to +8 had other aberrations that may have affected response to treatment and outcome. It has been repeatedly shown that prognosis of AML patients with +8 indeed depends on whether +8 occurs as an isolated abnormality or is accompanying other aberrations.[16,20,56–58] In the latter situation, +8 does not appear to adversely affect the favorable outcome of patients with t(15;17), inv(16)/t(16;16) and t(8;21).[16,20,56,57] In contrast,

patients with +8 and a complex karyotype and/or such unfavorable aberrations as del(5q) or −7 usually have very poor outcome. In one recent study, patients with +8 and unfavorable chromosome aberrations (according to the SWOG/ECOG classification) had significantly worse OS than other patients with unfavorable aberrations who lacked +8 in their karyotype.[58] On the other hand, isolated +8 has been considered to bestow either intermediate or unfavorable prognosis (Table 2). The conflicting results might be associated with variation in the age of the patients analyzed in different series,[30] but may also stem from differences in proportion of patients who underwent stem cell transplantation (SCT). Farag et al.[55] reported that prognosis of patients with an isolated +8, +11, +13 and +21 was dependent on SCT. While these isolated trisomies constituted an independent adverse prognostic factor for OS in non-transplanted patients, in those receiving SCT in first remission, the 5-year OS was not different than that of transplanted patients with a normal karyotype thus changing the risk stratification of isolated trisomies from adverse to intermediate.[55] Prospective studies are required to confirm this finding.

Patients with a normal karyotype are the single largest cytogenetic subset of adult AML. They are classified in the intermediate prognostic category, because their CR rates, CRD and survival probabilities are usually lower than those of adequately treated patients with t(8;21), inv(16) or t(15;17), but higher than patients with unfavorable chromosome aberrations.[16,20,51] However, this group is highly heterogeneous at the molecular level, and is likely composed of subsets with varying prognoses.

A small fraction of patients determined to have a normal karyotype by conventional cytogenetic analysis may carry gene fusions typically associated with recurrent translocations or inversions. Occasionally, this happens because the presence of a chromosome aberration is not recognized by the cytogenetic laboratory, especially when the quality of chromosome preparation is suboptimal and the missed rearrangement subtle, e.g., t(11;19)(q23;p13.1), t(15;17), or inv(16). However, in other patients, the gene fusion results from a cryptic rearrangement involving segments smaller than the length of a single band and thus unrecognizable by standard cytogenetic analysis. For instance, cryptic insertions of a very small segment from 17q containing the *RARα* gene into the locus of the *PML* gene on chromosome 15q have been repeatedly detected using FISH in patients with acute promyelocytic leukemia (APL) and a normal karyotype.[59] Grimwade et al.[59] estimates that insertions leading to formation of the *PML-RARα* fusion gene, most of which are cryptic, account for approximately 4% of all patients with APL. Because marrow of patients with cryptic *PML-RARα* fusions has a typical APL morphology, and such patients share the favorable prognosis of those with the standard t(15;17),[59] karyotypically normal patients suspected of having APL should be tested for the presence of the *PML-RARα* fusion gene by reverse transcription-polymerase chain reaction (RT-PCR), Southern blot analysis or/and FISH, and, if found positive, treated with regimens containing all-*trans*-retinoic acid (ATRA). Similarly, rare patients with the *CBFβ-MYH11* fusion gene but without microscopically detectable abnormalities of chromosome 16[60,61] and those with the *RUNX1-CBFA2T1* (*AML1-ETO*) fusion gene and normal chromosomes 8 and 21[62,63] should likely be grouped together with other patients with CBF AML. Of note, as demonstrated by two large prospective series,[28,63] patients truly positive for the *CBFβ-MYH 11* and *Runx1-CBFA2T1* gene fusion transcripts in the absence of cytogenetically detectable aberrations of chromosomes 16, and 8 and 21, respectively, are rare and their frequencies are much lower than those indicated by two retrospective studies.[64,65].

It is also rather unlikely that a large proportion of cytogenetically normal patients with de novo AML harbor hidden aberrations detectable only by FISH-based techniques. In a series of 102 adult AML patients tested by FISH using a comprehensive set of genomic DNA probes capable of detecting major AML-associated aberrations, only three patients were found to harbor, respectively, inv(16), −Y and del(12p).[66] In retrospect, only the del(12p) appeared to represent a truly cryptic aberration.[66] Cuneo et al.[67] did not find any occult chromosome anomaly among 55 adults with de novo AML aged 15—60 years who were studied by FISH using probes detecting −5, −7, +8, and deletions of 5q31, 7q31, 12p13/*ETV6*, 17p13/*TP53* and 20q11. The authors did identify, however, chromosome aberrations in interphase cells of 3 of 21 (14%) AML patients aged 62—80 years and in 5 of 6 (83%) patients with AML secondary to an antecedent MDS. In four of these patients, FISH analysis of metaphase cells revealed submicroscopic del(5)(q31) (three cases) and del(7)(q31) (one case).[67] To date, application of multi-color FISH-based techniques that use chromosome painting probes, such as spectral karyotyping (SKY) and multiplex FISH (M-FISH), to study AML patients with a normal karyotype has failed to discover any novel hidden rearrangement, akin to the cryptic t(12;21)(p13;q22) in childhood pre-B ALL, which, due to the juxtaposition of similarly banded regions, can be discerned microscopically only by FISH.[68–71] On the other hand, a new recur-

Table 3 Molecular genetic rearrangements reported to affect clinical outcome of AML patients with a normal karyotype or those classified in the intermediate prognostic category

Rearrangement[a]	Age group	Prognostic relevance[b]	No. pts with/no. pts without rearrangement	Reference number
		Normal karyotype		
PTD *MLL*	Adults	CR rate and OS: no significant difference	11/87	72
		CRD: significantly shorter for PTD *MLL*+ patients	7/61	
PTD *MLL*	Adults	Median survival: significantly shorter for PTD *MLL*+ patients compared with that of age-matched karyotypically normal control group	15/30	73
		Relapse-free interval: significantly shorter for PTD *MLL*+ patients compared with that of age-matched karyotypically normal control group	9/17	
PTD *MLL*	Adults 16–60 years	CR rate and OS: no significant difference	18/203	75
		CRD: significantly shorter for PTD *MLL*+ patients	16/158	
PTD *MLL*	Adults 16–60 years	EFS: significantly shorter for PTD *MLL*+ patients	5/25	29
FLT3 ITD	Adults 16–60 years	CR rate: no significant difference	67/125	84
		CRD: significantly shorter for *FLT3* ITD+ patients	47/95	
		OS: significantly shorter for *FLT3* ITD+ patients	67/125	
FLT3 Asp835	Adults 16–60 years	CR rate and OS: no significant difference	28/125	84
		CRD: no significant difference	23/95	
FLT3 ITD versus *FLT3* Asp835	Adults 16–60 years	CR rate and OS: no significant difference	67/28	84
		CRD: no significant difference	47/23	
FLT3 ITD	Adults	CR rate: no significant difference	16/37	88
		OS: significantly shorter for *FLT3* ITD+ patients	16/37	
		CRD: significantly shorter for *FLT3* ITD+ patients	8/28	
FLT3 ITD	Adults 20–59 years	CR rate and OS: no significant difference	23/59	80
		DFS: significantly shorter for *FLT3* ITD+ patients	17/51	
$FLT3^{ITD/-}$	Adults 20–59 years	CR rate: no significant difference	8/59	80
		OS: significantly shorter for $FLT3^{ITD/-}$ patients	8/59	
		DFS: significantly shorter for $FLT3^{ITD/-}$ patients	6/51	
$FLT3^{ITD/WT}$	Adults 20–59 years	CR rate and OS: no significant difference	15/59	80
		DFS: no significant difference	11/51	
$FLT3^{ITD/-}$ versus $FLT3^{ITD/WT}$	Adults 20–59 years	CR rate: no significant difference	8/15	80
		OS: significantly shorter for $FLT3^{ITD/-}$ patients	8/15	
		DFS: no significant difference	6/11	

Table 3 (*continued*)

Rearrangement[a]	Age group	Prognostic relevance[b]	No. pts with/no. pts without rearrangement	Reference number
		Intermediate-risk prognostic group[c]		
FLT3 ITD	Adults <60 year	CR rate: no significant difference	66/217	85
		DFS: no significant difference	46/139	
		Probability of relapse: significantly higher for *FLT3* ITD+ patients	46/139	
FLT3 ITD or *FLT3* TKD	Adults <60 year	OS: significantly shorter for *FLT3* ITD+/*FLT3* TKD+ patients	76/172	85
FLT3 ITD mutant/wt allele ratio >0.78	Adults <60 year	OS: significantly shorter for *FLT3* ITD patients with mutant/wt allele ratio >0.78	29/192	85
		DFS: significantly shorter for *FLT3* ITD patients with mutant/wt allele ratio >0.78	23/152	
		Probability of relapse: significantly higher for patients with mutant/wt allele ratio >0.78	23/152	
FLT3 ITD mutant/wt allele ratio >0 ⩽0.78	Adults <60 year	OS: no significant difference	30/192	85
		DFS: no significant difference	25/152	
		Probability of relapse: no significant difference	25/152	
FLT3 ITD mutant/wt allele ratio >0.78 versus >0 ⩽0.78	Adults <60 year	OS: significantly shorter for *FLT3* ITD patients with mutant/wt allele ratio >0.78	29/30	85
		DFS: significantly shorter for *FLT3* ITD patients with mutant/wt allele ratio >0.78	23/25	
		Probability of relapse: significantly higher for patients with mutant/wt allele ratio >0.78	23/25	
FLT3 ITD	Adults	EFS: significantly shorter for *FLT3* ITD+ patients	118/288	86
		OS: no significant difference	109/251	
		DFS: no significant difference	44/94	
FLT3 ITD	Adults 15—74 years	OS: significantly shorter for *FLT3* ITD+ patients	10/34	77
FLT3 ITD	Adults	EFS: no significant difference	15/65	89
		DFS: no significant difference	17/54	
FLT3 ITD or *FLT3* Asp835	Adults	EFS: no significant difference	27/65	89
		DFS: no significant difference	26/54	
FLT3 ITD	Adults 16—88 years	DFS: significantly shorter for *FLT3* ITD+ patients	15/40	78
FLT3 ITD	Adults 15—85 years	OS: significantly shorter for *FLT3* ITD+ patients	123[d]	76
N-RAS point mutation	Adults 15—85 years	OS: significantly shorter for patients with *N-RAS* point mutation	123[d]	76
GSTM1$^-$ or/and *GSTT1*$^-$	Adults 19—75 years	CR rate: significantly lower for *GSTM1*$^-$/*GSTT1*$^-$ patients	51/44	94
		EFS: significantly shorter for *GSTM1*$^-$/*GSTT1*$^-$ patients	31/36	
		OS: significantly shorter for *GSTM1*$^-$/*GSTT1*$^-$ patients	51/44	

[a] Unless otherwise indicated, all comparisons are between patients with a given gene rearrangement and those without (wild-type allele); PTD *MLL*, partial tandem duplication of the *MLL* gene; *FLT3* ITD, internal tandem duplication of the *FLT3* gene; $FLT3^{ITD/WT}$ cases of AML with the *FLT3* ITD in combination with the *FLT3* wild-type (WT) allele; $FLT3^{ITD/-}$, cases of AML with the *FLT3* ITD lacking a *FLT3* WT allele; *FLT3* Asp835, activating point mutations of D835 within the activation loop of the *FLT3* gene; *FLT3* TKD, activating point mutations in codon 835 or 836 of the *FLT3* gene; $GSTM1^{-}$ or/and $GSTT1^{-}$, homozygous deletions resulting in null genotypes at the glutathione *S*-transferase *GSTM1* or/and *GSTT1* loci.

[b] CR, complete remission; CRD, CR duration; EFS, event-free survival; OS, overall survival.

[c] Intermediate-risk prognostic group defined as follows: Thiede et al.[85] — normal karyotype and chromosome aberrations other than those conferring high risk [i.e., −5/del(5q), −7/del(7q), hypodiploid karyotypes (besides isolated −Y or −X), inv(3q), abn 12p, abn 11q, +11, +13, +21, +22, t(6;9); t(9;22); t(9;11); t(3:3) and multiple aberrations (= 3 independent aberrations)] and those conferring low risk [i.e., t(8;21) and t(8;21) combined with other aberrations]; Schnittger et al.[86] — normal karyotype and aberrations other than t(15;17), t(8;21), inv(16)/t(16;16), t(11q23), t(6;9), t(1;3), inv(3)/t(3;3), t(3;12), t(3;21), t(8;16) and −5/−7/7q−; Abu-Duhier et al.[77] and Voso et al.[94] — normal karyotype and +8, +21, +22, del(7q), del(9q), abnormal 11q23 and all other structural/numerical abnormalities without additional favorable [i.e., t(8;21), t(15;17) and inv(16)] or adverse [i.e., −5, −7, del(5q), abnormal 3q and complex karyotype with 5 or more abnormalities] cytogenetic changes; Moreno et al.[89] — normal karyotype and aberrations other than −5/del(5q), −7/del(7q), abn 3q, complex aberrations ($\geqslant$ 3 independent aberrations), t(9;22), t(6;9); t(8;21) and inv(16); Rombouts et al.[78] — normal karyotype and aberrations other than t(15;17), t(8;21), inv(16), t(6;9), alterations in the 11q23 region, del(5), del(7) or deletions of the q-arms of these chromosomes, and complex karyotype with more than 3 abnormalities; Kioyi et al.[76] — normal karyotype and aberrations other than t(8;21), inv(16), t(9;22), 11q23 alterations, del(5) or del(7).

[d] Intermediate-risk prognostic group included 123 patients, but numbers of patients with and without *FLT3* ITD and *N-RAS* point mutation were not provided.

rent AML-associated cryptic translocation, t(5;11)(q35;p15.5), was recently discovered by Brown et al.[71] who used a 12-color FISH assay (termed M-TEL) capable of detecting subtle subtelomeric rearrangements that are below the resolution of G-banding. The t(5;11), which results in the *NUP98-NSD1* gene fusion, was found in 2 of the 61 (3%) patients with a normal karyotype.[71]

The presence of an exclusively normal karyotype in a diagnostic marrow sample does not mean that cytogenetically normal leukemic blasts harbor no acquired genetic alterations. A variety of genetic abnormalities discernible only by molecular genetic techniques, such as Southern analysis, RT-PCR or direct sequencing, have been reported. These include partial tandem duplication of the *MLL* gene (PTD *MLL*);[29,72–75] internal tandem duplication of the *FLT3* gene (*FLT3* ITD);[76–89] activating point mutations of D835 within the activation loop of the *FLT3* gene (*FLT3* Asp835 mutation);[84,85,89,90] point mutations of the *N-RAS*,[76,81] *CEBPA*,[91] and *RUNX1* (*AML1*) genes;[92] deletions and point mutations of the *PU.1* gene;[93] homozygous deletions resulting in null genotypes at the glutathione *S*-transferase *GSTM1* and *GSTT1* loci;[94] and overexpression of the *BAALC*,[95] and *EVI1* genes.[96] The molecular abnormalities shown to influence prognosis of AML patients with a normal karyotype and of those comprising the intermediate-risk cytogenetics group (which usually contains a large proportion of karyotypically normal patients) are provided in Table 3. All four studies examining the prognostic significance of the PTD *MLL* in patients with a normal karyotype agree that the presence of PTD *MLL* significantly shortens the patients' CRD or event-free survival (EFS);[72–75] in one study, OS of patients with PTD *MLL* was also significantly shorter than that of an age-matched karyotypically normal control group.[73] The prognostic impact of *FLT3* ITD, the most common gene rearrangement in AML, is more controversial. Some studies investigating patients with a normal karyotype or those comprising the intermediate-risk cytogenetics group found no significant difference in the DFS,[85,86,89] EFS[89] and OS[80,86] between patients with and without *FLT3* ITD. In other studies, patients with *FLT3* ITD had significantly worse CRD,[84,88] DFS,[78,80] EFS[86] and OS.[76,77,88] These differences among studies may be attributed to several factors, including varying numbers of patients studied, differences in age of the patients, differing definitions of the intermediate-risk group (see footnote to Table 3) and thus disparate proportions of patients with particular "intermediate-risk" chromosome aberrations, and distinct induction and post-remission therapies

administered to patients in different studies. Additionally, some studies did not separate patients who had *FLT3* ITD in combination with the *FLT3* wild-type allele from those with the *FLT3* ITD who lacked a *FLT3* wild-type allele. Two groups have recently demonstrated that only patients with the latter genotype (or a high mutant/wt ratio, greater than 0.78) had a significantly shorter DFS and OS than patients without *FLT3* ITD.[80,85] Importantly, *FLT3* ITD is also common in APL patients with t(15;17), but hitherto has not been shown to predict prognosis in these patients.[87,88,97] This underscores the importance of assessing prognostic value of novel gene rearrangements in the context of cytogenetically defined groups of patients with AML.

Acute lymphoblastic leukemia

The first comprehensive study of the cytogenetics of adult ALL was the Third International Workshop on Chromosomes in Leukemia,[21] which showed that adult ALL cytogenetics have biologic and prognostic significance. Four cytogenetic classification schemata were defined: (1) according to the presence of normal and abnormal metaphases: NN — all metaphase cells normal, NN + Ncl — normal cells and non-clonal abnormalities, AN — normal cells and clonal abnormalities and AA — only abnormal metaphases; (2) according to the modal chromosome number, dividing the patients with an abnormal karyotype into six groups, $\leqslant 35$, 36—45, 46 (pseudodiploid), 47—50, 51—60 and >60 chromosomes, and grouping patients with no clonal abnormalities in the "46 normal" category; (3) normal, abnormal with a translocation identified and abnormal without an identified translocation; (4) the Lund classification.[21] The Lund classification was comprised of 10 hierarchical groups, t(9;22)(q34;q11.2) or a Philadelphia chromosome (Ph), t(4;11)(q21;q23), t(8;14)(q24;q32) or del(8q), other 14q+ abnormalities, del(6q), and normal karyotype, with the remaining cytogenetically abnormal patients classified by modal chromosome number as hypodiploid, pseudodiploid, low hyperdiploid (47—50 chromosomes) and high hyperdiploid (>50 chromosomes). By the Lund classification, survival was longest for patients with high hyperdiploidy and for those with normal karyotypes. Patients with t(4;11), t(8;14), 14q+, hypodiploidy and low hyperdiploidy had the shortest survival times. Remission rates were lowest in patients with hypodiploidy, t(9;22), t(4;11), t(8;14) and 14q+. Importantly, the karyotype was independent of other known prognostic factors in a multivariate analysis, although other clinical features were associated with modal number. Older age was more common in patients with low hyperdiploidy, and patients with a normal karyotype were more likely to be younger and have T-cell disease. Higher WBC was associated with pseudodiploidy, hypodiploidy, t(4;11) and t(9;22). With 6-year follow-up, patients with FAB L1, WBC $\geqslant 50{,}000/\mu l$ *and* high or low hyperdiploidy, normal metaphases or with a del(6q) were most likely to have achieved a cure; however, the karyotype did not add prognostic significance for disease-free survival to age, WBC and immunophenotype.[24] Additional reports have confirmed these observations, the clinical significance of some abnormalities has been further elucidated, and the molecular basis and biological consequences of many aberrations have been described. Below we will summarize the significance of the cytogenetics of adult ALL described since the International Workshops, particularly the more common abnormalities. Mature B-cell ALL will not be considered.

The frequency of abnormal karyotypes in adult ALL is slightly higher than in pediatric ALL; 64—85%[25,26,98–100] and 60—69%[101,102] of successful cases, respectively. The frequencies of different ploidy groups and some aberrations, however, differ between children and adults, as does treatment outcome (Table 4). The overall survival rate for adults is 22—38%,[25,99,103] whereas children have a 75—80% survival rate.[104–107] The frequency of Ph+ ALL increases with age, whereas the frequency of high hyperdiploid ALL decreases with age. Less than 6% of children with ALL have a t(9;22), whereas up to 40% of adults aged $\geqslant 40$ years with ALL are Ph+, a poor prognostic feature regardless of age.[25,108] In contrast, less than 12% of adults[23,25,98,100] but 25% of children[101,102,109,110] have high hyperdiploidy, a good prognostic feature. The different outcomes for adults compared with children with ALL may be partially a result of the different frequencies of specific abnormalities.

A t(9;22) is the most common recurring abnormality in adult ALL, occurring in 11—29% of patients included in series comprising both B- and T-ALL,[25,26,98] and in 37% of patients diagnosed with B-cell precursor ALL (c-ALL and pre-B ALL) who were studied by RT-PCR.[103] Most ($\sim$97%) Ph result from a standard t(9;22); only $\sim$3% are variant translocations. Patients with Ph+ ALL present with a high WBC (23,500/μl versus 11,550/μl),[103] have B-lineage disease, a typical immunophenotype of CD34+/CD10+/CD19+,[111] and myeloid markers in up to 71% of adult cases.[112] The remission rate usually is similar to the overall ALL remission rate,[113] although has been lower in some studies.[103] Progno-

Table 4 Frequencies of cytogenetic aberrations in adult and childhood ALL and their prognostic relevance

Abnormality	Adults		Children	
	Frequency[a]	Prognosis[a]	Frequency[a]	Prognosis[a]
None (normal chromosomes)	15–36%[25,26,98–100,128]	Intermediate–good[26,98,127]	31–40%[101,102]	Intermediate–good[101,102]
High hyperdiploidy	2–11%[23,25,98,100]	Good[25,26,98,100,127]	23–26%[101,102,109,110]	Good[101,102]
Low hyperdiploidy	10–15%[25,98,129]	Good[25]	10–11%[101,102]	Intermediate[101,102]
Near-triploid/ near-tetraploid	3–5%[25,100]	Intermediate[25]	1%[110,126]	
	Near-triploidy: 3%[98]	Near-triploidy: Poor[98]		Near-triploidy: Good[102,126]
	Near-tetraploidy: 2%[98]	Near-tetraploidy: Excellent[98]		Near-tetraploidy: Adverse[126] Intermediate[102]
Pseudodiploidy	31–50%[25,98,100,129]	Poor[25]	18–26%[101,102]	Intermediate[101,102]
Hypodiploidy	4–9%[25,98,100,129]	Poor[25,98]	6%[101,102]	Modal number = 45: Intermediate[101] Modal number = 30–45: Intermediate[102] Modal number <45: Poor[101]
Near-haploidy	Rare[100]	Not known	<1%[101,102]	Poor[101,102]
t(9;22)(q34;q11.2)	11–29% overall[25,26,98] 37% of B-ALL by RT-PCR[100]	Poor[26,103,129,131,170]	2–6%[102,108,171]	Poor[102,171,172]
t(4;11)(q21;q23)	3–7%[25,26,98,100,130,131]	Poor[26,133]	2%[102 d]	Poor[173]
t(1;19)(q23;p13.3)	2–3%[25,98,100,135]	Poor[98,100,127,137] Good[25]	4–5%[174,175]	Excellent[102] Intermediate[174]
t(12;21)(p13;q22)	0–3%[150–152]	Not known	20–25%[147–149]	Good in most studies[147–149]
Abnormal 9p	6–30%[25,26,98,100,129]	Intermediate[25,26,98]	7–11%[102,176]	Adverse[138,176] Not prognostic[102]
Abnormal 12p	4–6%[25,26,98,100]	Favorable[25,26] Unfavorable[98]	7–9%[102,177]	Not prognostic[102,177]
del(6q)	3–16%[25,26,129]	Not prognostic[132] Intermediate[98] Adverse[145]	6–9%[102,178]	Not prognostic[102,178]
del(7p)/del(7q)/ monosomy 7	6–11%[26,98b]	Not prognostic[155] Poor[26,132]	4%[110]	Adverse[110]
del(5q)	<2%[155]	Not prognostic[155]	1%[179]	Adverse[179]
+8[c]	10–12%[26,98]	Poor[26]	2%[Unpublished data from CCG c]	Unknown
14q11	5–7% overall or 26% of T-ALL[26,98]	Excellent, especially t(10;14) (q24;q11)[26,98]	3–4% overall or 17–22% of T-ALL[180,181]	Not Prognostic[180,181]
t(10;14)(q24;q11)	2–3%[98]			

[a] Superscript numbers denote reference numbers identifying articles that contain data on a given abnormality frequency and clinical outcome of patients with this aberration.
[b] In Wetzler et al.[26], only patients with monosomy 7 were included.
[c] Non-high hyperdiploid cases; CCG, Children's Cancer Group.
[d] Excluding infants.

sis is poor with traditional therapy and may be increasingly poor with increasing age.[100] However, two studies showed a markedly reduced risk of relapse and increased survival for younger Ph+ ALL patients who underwent allogeneic SCT from HLA-matched related donors in first CR and were conditioned with regimens that included fractionated total body irradiation and high-dose

etoposide.[114,115] Additionally, newer biological therapy with imatinib mesylate, a drug powerfully effective in CML, another leukemia with t(9;22), also may be effective in ALL when combined with chemotherapy or other approaches. This drug competitively inhibits the abnormal protein produced in Ph+ disease,[116] and may help to improve the outcome in Ph+ ALL. Early studies of Ph+ patients with ALL or CML with lymphoid blast crisis who had no response to standard treatment or who relapsed after standard treatment showed an initial 70% response rate to this therapy, but the responses have been of short duration.[4] In a subsequent study of 48 patients with relapsed or refractory Ph+ ALL, imatinib induced complete hematologic and marrow responses in 29% of patients but development of resistance and subsequent disease progression were rapid, thus necessitating further studies of the efficacy of imatinib in combination with other chemotherapeutic agents in Ph+ ALL patients.[116]

The genes involved in the t(9;22) are *ABL* on chromosome 9 and *BCR* on chromosome 22. The 5′ portion of *BCR* is joined to the 3′ portion of *ABL* to form a chimeric gene, *BCR-ABL*. Two different breakpoints in *BCR* give rise to proteins of different sizes. The major breakpoint cluster region (M-bcr) spans *BCR* introns 12—16, and when fused with *ABL* results in a 210-kDa protein. This is the typical rearrangement in CML and in 24—50% of adult Ph+ ALL,[113,117] but is rare in pediatric Ph+ ALL.[118] The minor breakpoint (m-bcr) occurs 5′ of the M-bcr in the first intron of *BCR*, and when fused with *ABL*, codes for a 190-kDa protein.[119] This breakpoint occurs in 50—77% of adult Ph+ ALL[103,117] and over 90% of pediatric Ph+ ALL.[120] The proportion of patients with breakpoints in M-bcr increases with increasing age.[121] Both proteins are tyrosine kinases, but the m-bcr product has stronger transforming potency in transfection assays and in transgenic mice.[117] Comparisons of adults with Ph+ ALL with m-bcr and M-bcr breakpoints rarely show differences in the presence of additional cytogenetic aberrations, WBC, age, or outcome;[117,122,123] although one study showed that patients with M-bcr breakpoints were older[103] and another study of allogeneic transplants showed that patients with an m-bcr breakpoint had an increased risk of relapse compared with those with an M-bcr breakpoint.[124]

Cytogenetic abnormalities in addition to a t(9;22) occur in 41—86% of adult ALL at diagnosis;[117,122] most frequently loss of a chromosome 7 or its short arm (7p), an additional der(22)t(9;22), abnormalities of 9p, gain of a chromosome 8 or X, duplication of 1q and high hyperdiploidy.[117,122] No pretreatment clinical factors have been associated with the presence of additional abnormalities.[122] Outcome has been reported as no different,[122,125] or dependent on the specific aberration in addition to t(9;22), with hyperdiploid patients having a better outcome and those with monosomy 7 or deletions of 9p having a particularly poor outcome.[117]

High hyperdiploidy is rare in adult ALL (2—11%)[23,25,98,100] compared with pediatric ALL (25%).[101,102,109,110] Near-triploidy and near-tetraploidy are more frequent in adult than in pediatric ALL.[25,100,110,126] High hyperdiploidy in adults is associated with younger age and normal WBC. Outcome for adult high hyperdiploid patients is somewhat improved compared with other ploidy groups, but does not show the excellent outcome observed in children.[25,26,98,100–102,109,110,127] Structural abnormalities are frequent in high hyperdiploid cases, most commonly a t(9;22). Patients with high hyperdiploidy and t(9;22) have outcomes similar to other Ph+ patients.[98,125] Clinical features and outcome in patients with high hyperdiploidy and other recurring translocations also are similar to those of patients with the translocations and pseudodiploidy or low hyperdiploidy.[25] Low hyperdiploidy is distinct from high hyperdiploidy both in chromosome pattern and in clinical features. Recent studies show an improved outcome for patients with low hyperdiploidy compared with patients with $\leqslant$46 chromosomes.[25] Normal, diploid karyotypes occur in 15—36% of adult ALL[25,26,98–100,128] and are associated with an intermediate[26] or an improved outcome.[26,98,126] Only 4—9% of adult ALL are hypodiploid.[25,98,100,129] Patients with hypodiploidy are somewhat younger than those with normal karyotypes, and most have B-lineage ALL. Severe hypodiploidy with modal numbers of 30—44 is more frequent in adult ALL than is near-haploidy with chromosome numbers below 30. These patients have a poor outcome.[25,98] Recurrent structural abnormalities occur in 60—70% of pseudodiploid patients,[25,98] and the prognosis of these patients reflects the prognosis of the recurrent abnormality. When all pseudodiploid patients are considered, their outcome is worse than that of patients with normal chromosomes or with hyperdiploidy.[25]

A common recurring translocation in adult ALL is t(4;11)(q21;q23). Although particularly common in infant ALL, it also occurs in 2% of pediatric[102] and 3—7% of adult ALL.[25,26,98,100,130,131] It is associated with an immunophenotype of TdT+/HLA-DR+/CD34+/CD10−/CD19+,[111,132] a high WBC, a high frequency of circulating blasts and an increased frequency of central nervous system disease.[132] The t(4;11) predicts a poor prognosis.[26,133] Secondary abnormalities in addition to t(4;11) are

common, particularly i(7)(q10) and trisomy 6; outcome does not appear to differ for these patients compared with those with t(4;11) as a sole abnormality.[130] The gene involved on chromosome 11 is *MLL*, which has multiple translocation partners. In t(4;11), *MLL* is rearranged with *AF4*, the most common partner gene of the *MLL* gene in ALL. Other 11q23 (*MLL*) translocations also occur and overall, *MLL* translocations are found in up to 7% of adult ALL,[26,98] occurring in both de novo and in therapy-related disease.[134]

Translocation (1;19)(q23;p13.3) occurs in 2—3% of adult ALL[25,98,100,135] and, as in pediatric ALL, can be either balanced or an unbalanced der(19)t(1;19) with two normal chromosomes 1. Most cases are pseudodiploid, although some are high hyperdiploid. The rearrangement results in a chimeric *E2A-PBX1* gene in 95% of cases with $\leqslant$50 chromosomes, but in only 25% of cases with $>$50 chromosomes.[136] Nearly all cases are pre-B ALL; that is, the cells have cytoplasmic *mu* immunoglobulin, but not surface immunoglobulin, and are CD9+/CD10+/CD19+/CD22+/CD34—. Low WBC is common, and the patients tend to be younger.[98] Outcome is poor in most studies of adults,[98,100,127,137] although not all.[25]

Abnormalities of 9p that result in loss of genetic material [abn(9p)], including deletions, unbalanced translocations and chromosomal losses, are recurrent in ALL. Abn(9p) occurs in both T- and B-lineage ALL, with some studies indicating a higher frequency in T-lineage[138] and some in B-lineage ALL.[139] Abn(9p) appears to be similar in adult and pediatric ALL.[132] Cytogenetically, 6—30% of adult ALL patients have an abn(9p), and more show loss by molecular technologies.[25,26,98,100,129] Prognosis is intermediate.[25,26,98] Interestingly, several dicentric chromosomes recur in ALL; most involve chromosome arm 9p and result in partial loss of the p-arm. Dic(9;20)(p11—13;q11) has a good prognosis,[140] as does dic(9;12)(p11—13;p11—12) even though most patients with the latter have at least one adverse feature.[141] Dic(9;12) is more frequent in younger patients and is rare in adults.[132] Abnormalities in addition to dic(9;12) are common, but complex karyotypes are rare.[141] Isochromosome 9q, which results in loss of 9p, also is recurrent in ALL.[142] The most common region of loss is 9p21, and deletion of the *p16^{INK4a}* gene (also called *CDKN2A* or *MTS1*) appears to be the significant loss. Both hemizygous and homozygous deletions occur, with no apparent difference in clinical features or outcome.[139] The neighboring gene *p15^{INK4b}* (*MTS2*) also is lost frequently and may contribute to the pathogenesis of ALL.[139] Loss of expression of *p15^{INK4b}* and of *p16^{INK4a}* may occur through methylation of the remaining allele in some patients with hemizygous loss.[143,144]

Recent studies have failed to show a prognostic significance for del(6q)[132], have shown an intermediate outcome,[98] or an adverse outcome.[145] Patients with del(6q) tend to be younger than those with normal 6q.[145] Deletion of 6q may be a sole abnormality or part of a complex karyotype. An isolated del(6q) has been associated with hyperleukocytosis and T-ALL.[145] Breakpoints vary, with band 6q21 most frequently cited as containing the smallest region of deletion.[132,145] It is assumed that an as yet unidentified tumor suppressor gene is lost as a result of the deletion.

Rearrangements of 12p occur in 4—6% of adult ALL,[25,26,98,100] frequently as part of a complex karyotype. Translocations with many different partner chromosomes have been reported, as well as partial loss of 12p, resulting from both deletions and unbalanced translocations. Patients with 12p abnormalities tend to be younger and have a favorable prognosis in some studies,[25,26] but not in all.[98] One recently described aberration of 12p is the cryptic t(12;21)(p13;q22), resulting in fusion of *ETV6* (*TEL*) and *AML1* (*RUNX1*, *CBFA2*), in pre-B ALL.[146] It occurs in up to 25% of children aged 1—10 years,[147—149] but in only 0—3% of adult ALL.[150—153] In children, it usually is associated with an excellent prognosis,[147,149,151] although not always.[154] Because it is infrequent in adult ALL, its prognostic significance in adults remains to be determined.

Other less frequently recurring cytogenetic abnormalities in adult ALL include trisomy 8 and partial or complete monosomy for chromosomes 5 (—5/5q—) and 7 (—7/7q—).[26,132,155] They are often secondary to t(9;22) and in those cases are associated with the poor outcome of Ph+ ALL.[155] Patients with —5/5q— tend to be younger and frequently have T-ALL.[156] Cases with —5/5q—/—7 without t(9;22) have remission and survival rates similar to patients with normal chromosomes 5 and 7,[98,155] although in another study patients with —7 and +8 who were Ph-negative fared as poorly as the Ph+ patients.[26]

T-ALL occurs in 14—28% of adult ALL.[25,26,98,100] Although the cytogenetics of T-lineage and B-lineage ALL overlap, there are distinct differences between them. In the three largest series of adult ALL,[25,26,98] the proportion of cytogenetically normal cases was consistently higher in T-ALL than in B-lineage ALL (range of 24—43% versus 13—32%, respectively). About one-third of T-ALL have a translocation involving one of the T-cell receptor genes (*TCR*), resulting in over-expression of a gene juxtaposed to a *TCR* (Table 5). A breakpoint in 14q11.2, the location of α-*TCR* and δ-*TCR*, is the

Table 5 Breakpoints and genes recurrently rearranged with T-cell receptor genes in T-ALL

Chromosome breakpoint	Gene involved
1p32	*SCL* (*TAL-1* or *TCL-5*)
1p35-p34.3	*LCK*
8q24	*PVT1* and *cMYC*
9q34.3	*TAN-1*
10q24	*HOX11*
11p13	*RBTN2 (TTG2)*
11p15.5	*RBTN1 (TTG1)*
19p13.2-p13.1	*LYL1*

most common *TCR* breakpoint, but breakpoints in 7q35 (β-*TCR*) and 7p15 (γ-*TCR*) also recur. The most common *TCR* rearrangement in adult ALL is t(10;14)(q24;q11.2), which results in overexpression of the *HOX11* gene.[98] It appears to be a primary aberration and is associated with a favorable outcome.[98] Few studies of a recurrent δ-*TCR* rearrangement in children, t(1;14)(p32;q11.2), have been reported in adults.[31] This translocation juxtaposes δ-*TCR* and *SCL* (also called *TAL1* or *TCL5*), resulting in over-expression of *SCL*. A cryptic deletion of chromosome 1 in which *SCL* is juxtaposed to *SIL* also results in overexpression of *SCL*. In pediatric T-ALL, t(1;14) occurs only in about 3% of cases, but the *SIL-SCL* deletion occurs in 6—26%, making the combination of the two rearrangements the most common abnormality in pediatric T-ALL.[157] The frequency of these rearrangements in adult ALL has not been widely studied.

A cryptic t(5;14)(q35;q32) occurs in 20—30% of pediatric T-ALL;[158,159] it is less common in adults. The translocation results in over-expression of *HOX11L2* (5q35), although the breakpoint is actually in *RanBP17*, distant from *HOX11L2*. The abnormal expression of *HOX11L2* is thought to result from abnormal control of the gene by *CPT12*, located at 14q32.[158]

Translocation (4;11)(q21;p15.5) is a rare abnormality that occurs in T-ALL,[160,161] frequently in association with a del(12p). It is more frequent in children and young adults, thus far with poor outcomes. The rearrangement fuses *NUP98* from chromosome 11 with *RAP1GDS1* from chromosome 4 to encode nrg, a fusion protein.[160,161]

Concluding remarks

During the last 30 years, cytogenetic analyses of patients with AML and ALL have discovered a great number of recurrent chromosome abnormalities. Several of the more common abnormalities have been associated with specific laboratory and clinical characteristics, and are being used as diagnostic and prognostic markers that can guide the clinician in selecting the most effective treatment regimens. However, the prognostic importance of less frequent recurrent aberrations, both primary and secondary, is still unknown. Continuing cytogenetic studies are thus necessary to accrue enough patients with these rarer abnormalities to define conclusively their impact on CR rates, remission duration and survival, and to resolve discrepancies in prognostic categorization of some of the more frequent aberrations that currently exist among the major cytogenetic risk-assignment systems. Such studies will likely uncover new recurrent aberrations as they are still being identified by both classical cytogenetic methods and, increasingly, by molecular-cytogenetic techniques such as FISH, spectral karyotyping (SKY), multiplex-FISH (M-FISH) and multiplex FISH telomere assay (M-TEL).[38,39,68,71,158,159,162–165] Moreover, it is well known that prognostic factors depend on the type of therapy used. A cytogenetic or molecular genetic abnormality conferring an adverse prognosis with one therapeutic regimen may lose its unfavorable prognostic impact when another treatment is used. Therefore there is a constant need for large prospective studies correlating karyotype with selected molecular genetic markers, gene expression profiles, immunophenotype, other biologic parameters and clinical outcome in patients treated with both current therapies and those receiving novel therapeutic agents.

Practice points

- Cytogenetic analysis should be performed in all newly diagnosed patients with AML or ALL.
- Patients may be stratified to different therapies based on results of standard cytogenetic analysis, FISH and/or molecular genetic investigations (RT-PCR).

Research agenda

- Continuing correlation of recurrent chromosome aberrations with response rates, response duration, survival and cure in groups of AML and ALL patients treated with current and novel induction and post-induction regimens.
- Ascertainment of prognostic significance of the less common recurrent abnormalities in AML and ALL that are currently arbitrarily assigned to the intermediate-risk group or not categorized at all.

- Further correlation of specific cytogenetic findings with biological and clinical features of acute leukemias to define unique disease entities that will be incorporated into the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues in the future.
- Molecular genetic detection of submicroscopic mutations in patients belonging to cytogenetically defined groups (e.g., normal karyotype) that may provide additional clinically relevant information.

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