11q23 rearrangements in de novo childhood acute myeloid leukemia

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Identity

Note
Clinical aspects of 11q23 abnormalities in de novo childhood acute myeloid leukemia (AML) are described.

Disease and pathology

Disease
Childhood acute myeloid leukemia and 11q23/MLL rearrangement

Phenotype/cell stem origin
Leukemic cells with 11q23 abnormalities typically disrupt the MLL gene; they frequently have a myelomonoblastic or monoblastic morphology (FAB M4, M5) with accompanying myeloblastic immunophenotype of moderate CD45, low SSC, CD13+, CD33+, CD34+, CD117+, HLA-DR+ and monoblastic immunophenotype of bright positive CD45, low SSC, CD11b+, CD11c+, CD13+, CD14+, CD33+, CD64+, CD4+, CD56+, HLA-DR+. Additional cytogenetic lesions are present in approximately 50% of patients with an 11q23/MLL rearrangement, with trisomy 8 being the most frequent (18%). (See Table 1).

Etiology
There is strong molecular evidence that 11q23 abnormalities in pediatric leukemia occur in utero. The MLL gene has an important role in normal hematopoietic growth and differentiation. Abnormalities in this region can occur very early in hematopoietic stem cell development. In utero exposure to natural or synthetic substances that inhibit topoisomerase II (e.g., genistein, catechins, flavonoids) may result in acute leukemia. It has been suggested that rearrangement of the MLL gene leads to the inhibition of apoptosis and leukemogenesis. Acute leukemias of myeloid (AML) and lymphoid (ALL) lineage have 11q23/MLL rearrangements but show a different predilection for translocation partners, which are thought to be responsible in part for development of the phenotype of each type of leukemia. The brief latency of infant acute leukemias involving 11q23/MLL rearrangements suggests that the MLL fusions need some additional cooperating mutations to cause leukemia. Recent array comparative genomic hybridization (aCGH) and high-throughput genomic studies have confirmed these findings.
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Table 1. Occurrence of different MLL rearrangements according to the French American British (FAB) morphology type in an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML. * Patients with a clearly indicated sub-band were classified in their respective categories; other patients for whom data on subband or translocation partner were insufficient were classified as noted. Data obtained from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).

Table 2. Occurrence of different MLL rearrangements by age at diagnosis in an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML. * Percentage within the indicated age group. ¶ Patients with a clearly indicated sub-band were classified in their respective categories; other patients for whom data on subband or translocation partner were insufficient were classified as noted. Data obtained from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).

Table 3. Occurrence of different MLL rearrangements by clinical parameters in an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML. * Percentage within the 11q23 abnormality group. ¶ Patients with a clearly indicated sub-band were classified in their respective categories; other patients for whom data on subband or translocation partner were insufficient were classified as noted. Data obtained from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).
Epidemiology

Depending on the method of detection, the overall incidence of 11q23 abnormalities among children with AML ranges from 15% to 25%. In children younger than 2 years, the peak incidence of 11q23/MLL gene rearrangements is 50%-60%. By contrast, the incidence of 11q23 abnormalities in adults with AML is approximately 5%, and these abnormalities are rarely seen in patients older than 60 years. Also, patients with second leukemias, especially those administered prior epipodophyllotoxin II treatment, have a high incidence of 11q23 aberrations, but these are not dealt with in detail here. An estimated 5%-10% of MLL rearrangements in AML are subtle or cryptic and need to be detected by fluorescence in situ hybridization (FISH) using the MLL probe, preferentially in a sequential G-banded and FISH metaphase to identify the partner chromosome. Most of the following information was obtained from a large international collaborative retrospective study consisting of 756 pediatric patients with 11q23 abnormalities and AML in which the overall 5-year event free survival (EFS) rate was 44%. (See Table 2).

Clinics

Children with 11q23/MLL rearranged AML often present with high white blood cell counts (WBC), central nervous system (CNS) involvement and organomegaly. (See Table 3).

Treatment

In most pediatric AML protocols, patients with 11q23/MLL rearrangements are treated according to intermediate-risk stratification. Stem cell transplantation is not generally advised in first complete remission. A recent study, however, showed significant benefit of matched sibling donor stem cell transplantation for 11q23-rearranged pediatric AML patients in first complete remission in the AML-BFM 98 protocol.

Table 4

Table 4. Outcomes of patients by univariate analysis of different MLL rearrangements and as per clinical and laboratory parameters, from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML. Abbreviations: pEFS, probability of event free survival; pCIR, probability of cumulative incidence of relapse; pOS, probability of overall survival; SE, standard error; WBC, white blood cell count. * P-values of indicated abnormality as compared to 11q23/MLL-rearranged pediatric AML patients with other additional cytogenetic abnormalities. ‡ Patients with a clearly indicated sub-band were classified heir respective categories; other patients for whom data on subband or translocation partner were insufficient were classified as noted. Data obtained from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).
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Table 5. Hazard ratios from multivariate analysis of different MLL rearrangements and according to additional cytogenetic aberrations, from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML. Abbreviations: EFS, event free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; P, P-value; ACAs, additional cytogenetic aberrations. * P<0.05; † P<0.01. ¶ Patients with a clearly indicated sub-band were classified in their respective categories; other patients for whom data on subband or translocation partner were insufficient were classified as noted. Data obtained from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).

Prognosis
The prognostic significance of 11q23 abnormalities in children with AML is unclear, but it appears to depend on the partner gene involved and additional chromosomal aberrations. Most of the work presented here is from an international collaborative retrospective study consisting of 756 pediatric patients with 11q23 abnormalities and AML in which the overall 5-year EFS rate was 44%. The outcome of the subgroups varied greatly; for example, patients with a t(1;11)(q21;q23) had an excellent outcome (5-year EFS, 92%) whereas those with a t(6;11)(q27;q23) had the worst outcome (5-year EFS, 11%). Subgroups t(10;11)(p12;q23), t(4;11)(q21;q23), and t(10;11)(p11.2;q23) had a 5-year EFS of 31%, 29%, and 17%, respectively. The prognosis of the most commonly occurring partner t(9;11) is controversial and will be described later. In this retrospective study, patients younger than 10 years had a more favorable prognosis than those 10 years or older (EFS of 46% and 34%, respectively) (P=0.006).

The presence of specific additional cytogenetic aberrations was significantly correlated with outcome. Patients with trisomy 19 and structural additional cytogenetic aberrations had a 5-year EFS of 17% and 32%, respectively, whereas patients with the most frequent specific additional aberration trisomy 8 had a 5-year EFS of 53%. (See Table 4 and Table 5).

Cytogenetics

Cytogenetics morphological

t(9;11)(p22;q23)
- The t(9;11)(p22;q23) is the most frequent 11q23/MLL abnormality in pediatric AML, occurring in approximately 50% of patients.
- The fusion gene resulting from this translocation involves MLL and AF9 (MLLT3).
- Additional cytogenetic aberrations have been detected by conventional karyotyping in approximately 47% of patients with t(9;11)(p22;q23). The most frequently recurring additional aberration is trisomy 8 (~24%).
- There is no consensus on the outcome of patients with t(9;11). A 5-year EFS of 50% and a 5-year OS of 63% were reported in an international retrospective study. However, the Nordic countries (NOPHO) and St. Jude Children's Research Hospital (St. Jude), Memphis, TN, USA, have reported that patients with t(9;11)(p22;q23) had better prognosis than patients with other translocation partners, with a 7-year EFS of 86% in the
NOPHO-AML93 trial and a 5-year EFS of 65% in the 4 consecutive St Jude trials (1980 to 1997).
- In some protocols, treatment of t(9;11)(p22;q23) is done according to low-risk stratification, but this approach is controversial.

**t(10;11)(p12;q23)**
- The t(10;11)(p12;q23) is the second most frequent 11q23/MLL abnormality in pediatric AML, accounting for approximately 13% of all cases of 11q23/MLL rearranged pediatric AML.
- However, this percentage is underestimated, because in many instances the generation of the fusion gene is cryptic or complex (see below). It is difficult to accurately establish the breakpoints of 10p in many translocations involving 10p and 11q23.
- The fusion gene resulting from this translocation involves MLL and AF10 (MLLT10).
- To generate an MLL-AF10 fusion, the translocation of chromosome 10 and chromosome 11 has to include at least one inversion. Most t(10;11)(p12;q23) cases are identified by conventional karyotyping, but structural aberrations can be very complex. These aberrations include insertions of 11q material onto the 10p arm and vice versa, some of which are also cryptic. In some instances, FISH using the subtelomeric probes for 10p and 11q can clarify the nature of the abnormality. RT-PCR is also a very useful method to detect the MLL-AF10 fusion transcript.
- In approximately 50% of the t(10;11)(p12;q23) cases, additional cytogenetic aberrations have been detected by conventional karyotyping. The most frequently recurring additional aberration is trisomy 8 (~7%); diverse structural additional aberrations have been detected (36%) and can affect other chromosomes.
- A 5-year EFS of 31% and a 5-year OS of 45% were reported in a large international retrospective study.

**t(10;11)(p11.2;q23)**
- The t(10;11)(p11.2;q23) is a rare 11q23/MLL abnormality mainly found in young children with AML. However, in the large retrospective study, 3 of 12 (25%) patients were older than 2 years.
- The fusion gene resulting from this translocation involves MLL and ABI1.
- In approximately 58% of t(10;11)(p11.2;q23) cases, additional cytogenetic aberrations have been detected by conventional karyotyping, all cases displaying at least one additional structural aberration.
- A 5-year EFS of 17% and a 5-year OS of 27% were reported in a large international retrospective study.

**t(6;11)(q27;q23)**
- The t(6;11)(q27;q23) occurs in approximately 5% of all pediatric patients with 11q23/MLL rearranged AML. However, this incidence is underestimated as the DNA exchanged in this translocation is very subtle and may go undetected or be misclassified as a del(11)(q23).
- The fusion gene resulting from this translocation involves MLL and AF6 (MLT4). RT-PCR is also a very useful method to identify the MLL-AF6 fusion transcript.
- In approximately 46% of t(6;11)(q27;q23) cases, additional cytogenetic aberrations have been detected by conventional karyotyping. The most frequent recurring additional aberrations are trisomy 8 and trisomy 21 (~17% each) and additional structural aberrations (~26%).
- A 5-year EFS of 11% and a 5-year OS of 22% have been reported in a large international retrospective study; t(6;11)(q27;q23) thus represents the subgroup with the worst outcome in pediatric 11q23/MLL rearranged AML, but the reason for the very poor survival rate is unknown.

**t(11;19)(q23;p13)**
- Translocations of chromosome 11q23 with chromosome 19p13 occur in approximately 12% of pediatric patients with 11q23/MLL rearranged AML. Two common translocation partners are present on 19p13: ELL on 19p13.1 and ENL (MLLT1) on 19p13.3. In approximately 33% of pediatric AML cases, resolution of the karyotype can be insufficient to define the sub-band with certainty, and for this publication these patients are grouped as t(11;19)(q23;p13).
- A 5-year EFS for patients with a t(11;19)(q23;p13), t(11;19)(q23;p13.1), and t(11;19)(q23;p13.3) of 49%, 46% and 46% respectively, and a 5-year OS of 49%, 61% and 47%, respectively, have been reported in a large international retrospective study.

**t(1;11)(q21;q23)**
- The t(1;11)(q21;q23) occurs in approximately 3% of all pediatric patients with 11q23/MLL rearranged AML.
- The fusion gene resulting from this translocation involves MLL and AF1q (MLLT11).
- In approximately 25% of t(1;11)(q21;q23) cases, additional cytogenetic aberrations have been detected by conventional karyotyping, all cases displaying at least one additional structural aberration.
- A 5-year EFS of 17% and a 5-year OS of 27% were reported in a large international retrospective study.
Figure 1. Survival curves of different MLL rearrangements, from an international retrospective study of 756 pediatric patients with 11q23/MLL rearranged AML (Balgobind et al., Blood 2009).
Cytogenetics molecular

Approximately 5% to 10% of cases of AML and an MLL gene rearrangement are not detectable by conventional cytogenetic methods. Currently, commercially available dual-color MLL break-apart probes are available that allow FISH evaluation of rearrangement in the interphase nuclei and identification of the partner/derivative chromosome on metaphase chromosomes. In rare instances, segments of the MLL probe may be deleted when generating the rearrangement; thus FISH may also detect a concurrent deletion of 3'MLL and rarely of 5'MLL. As mentioned throughout, molecular cytogenetic methods have shown that the frequency of MLL gene rearrangements exceeds that of 11q23 translocations detected by conventional cytogenetic method alone. In AML cases in which aberrations affect the 11q23 band, a complementary FISH study should be done to determine whether a rearrangement of MLL is present, as in rare cases an 11q23 translocation may involve genes other than MLL. In AML patients with normal karyotypes or without an identified type II aberration [such as t(8;21), t(15;17) or inv(16)], FISH might identify a cryptic MLL rearrangement. Because the translocation partners for 11q23 are numerous and markedly heterogeneous, additional molecular methods may be needed to further assess the partner genes for MLL. RT-PCR is suitable to evaluate the most frequently observed MLL fusion transcripts, and, if positive, can also be useful for following the status of the patient's minimal residual disease. In other cases, long-distance inverse PCR on genomic DNA can aid the finding of uncommon or novel translocation partners.

MLL-partial tandem duplication is a separate entity that can only be identified by PCR or other techniques, and is not discussed here.

Genetic lesions also occur frequently in 11q23/MLL rearranged pediatric AML. In approximately 43% of cases, a mutation in one of the RAS-pathway coding genes, FLT3 or KIT, has been identified.

References


This article should be referenced as such: