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Review Article

11q23/MLL Acute Leukemia : Update of Clinical Aspects

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Rearrangements of the *MLL* gene located at 11q23 are common chromosomal abnormalities associated with acute leukemia (AL), especially infant and secondary leukemia after previous treatment with DNA topoisomerase II inhibitors. 11q23/MLL abnormalities have been widely recognized as an important prognostic factor in AL. Over 70 chromosome partners of 11q23 have been identified to date, at least 50 of which have been cloned and characterized at the molecular level. Recent studies showed that the prognosis of 11q23/MLL AL varies widely according to the partner gene, the leukemia cell lineage, the age of the patient and the treatment administered. Special strategies are needed to treat 11q23/MLL AL, including allogeneic hematopoietic stem cell transplantation, according to the fusion partner. The development of novel methodologies, including new molecular therapeutic targets, is also needed to improve the prognosis of 11q23/MLL AL. The present article provides an update on the current status of prognosis and treatment of 11q23/MLL AL according to the fusion partner. 〔*J Clin Exp Hematopathol 50(2) : 91-98, 2010*〕

Keywords: hematopoietic stem cell transplantation, mixed-lineage leukemia, acute myeloid leukemia, acute lymphocytic leukemia, 11q23

INTRODUCTION

A number of chromosomal aberrations have been reported in hematological malignancies. Recent studies have demonstrated that several chromosomal abnormalities and molecular rearrangements are strongly associated with distinct clinical subgroups, and are predictive of both clinical features and therapeutic responses. The 11q23 abnormalities are frequent cytogenetic abnormalities found in some adult[1-3] and pediatric[4-6] patients with primary acute leukemia (AL), and also in the majority of patients with secondary AL after previous treatment with DNA topoisomerase II inhibitors.[7,8] In the WHO classification, AL with 11q23 abnormalities involving the *mixed-lineage-leukemia (MLL)* gene comprises one category of recurring genetic abnormalities. The *MLL* gene consists of at least 36 exons, encoding a nuclear protein of 3,969 amino acids with a molecular weight of almost 430 kDa, which is thought to function as a positive regulator of gene expression in early embryonic development and hematopoiesis. In 11q23 abnormalities, the *MLL* gene is translocated within a cluster breakpoint of an 8.3-kb region spanning exons 5-11.[9] Over 70 chromosome partners of 11q23 have been identified to date, at least 50 of which have been cloned and characterized at the molecular level.[10] *MLL* gene translocations result in the production of a chimeric protein in which the amino-terminal portion of the *MLL* gene is fused to the carboxy-terminal portion of the fusion partner gene. This has led to a model of leukemogenesis in which the MLL fusion protein may confer gain-of-function or neomorphic properties, or may interfere with the normal function of MLL.[11] Fig. 1 shows the structure of the MLL protein. All MLL fusion proteins retain the amino-terminal portion containing AT hooks and the CxxC domain of MLL, thus preserving DNA binding activity. In contrast, a region with transactivating potential, the plant homeodomain (PHD) fingers, and the suppressor of variegation-enhancer of zeste-trithorax (SET) domain, which mediates histone H3 lysine 4 (H3K4) methylation, are lost. Although loss of the carboxy-terminal regions of MLL in chimeric oncoproteins would be predicted to result in abrogation of transactivation and histone methyltransferase (HMT) functions, transforming MLL fusion proteins function as transcriptional regulators and induce aberrant expression of downstream MLL targets, including HOX genes, EPHA7, MEIS and PBX.[12] The precise mechanism for this aberrant transcriptional activity is not known but involves the formation of a transcriptional core complex by the remaining N-terminal part of MLL and the fusion-partner portion of the chimeric MLL oncoprotein.[12]

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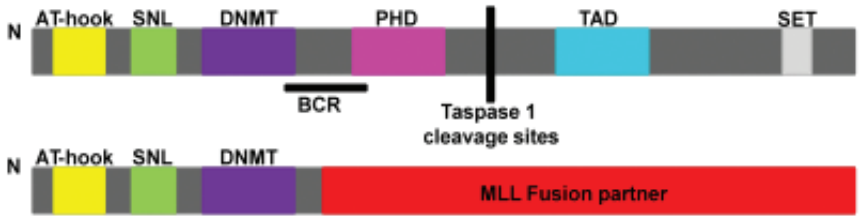

Fig. 1. Structure of the MLL protein. Location of MLL protein domains in relation to BCR, PTD and fusion partners. AT-hook [DNA binding motif that binds adenosine-thymidine (AT)-rich DNA], speckled nuclear localization sites (SNL), DNA methyl-transferase domain (DNMT), plant homeodomains (PHD), transactivation domain (TAD), and suppresser variegation/Enhancer of zeste/Trithorax (SET) domain. Cleavage by Taspase (Threonine-aspartase) 1 divides MLL into NH 2- and COOH-terminal fragments.

Table 1. Frequent rearrangements of 11q23/MLL*

Type of 11q23/MLL rearrangement	%/MLL	Age predominance	Disease
t(4;11) (q21;q23) (MLL-AF4)	30%	Infants and children	B-ALL
t(6;11) (q27;q23) (MLL-AF6)	5%	Children and young adults	ALL (M4/M5)
t(9;11) (p23;q23) (MLL-AF9)	25%	(−)	ALL (M4/M5)
t(11;19) (q23;p13.1) (MLL-ELL)	5%	Adults	ALL (M4/M5)
t(11;19) (q23;p13.3) (MLL-ENL)	5%	Infants	ALL (M4/M5) Biphenotypic ALL

(−), none ; *, modified from reference 59

11q23/MLL FUSION PARTNER INFLUENCES THE PROGNOSIS OF 11q23/MLL AL

Large-scale studies performed in 1998 and 1999 indicated that 11q23/MLL acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) have poor prognoses.[13,14] Although 11q23/MLL AML was categorized as having an intermediate prognosis in the 2002 WHO classification,[15] large-scale studies published around the same time indicated that this disease has a poor prognosis.[16,17] These studies assessed the prognosis of 11q23/MLL AL without separating populations into adults and children. Recent studies have shown that the prognosis of 11q23/MLL AL is dependent on the 11q23 fusion partner,[18-29] and that the prognosis of AL with 11q23 according to the fusion partner is different between adults and children.[30-33]

Frequency of 11q23/MLL fusion partner in AL

The 11q23 fusion partners observed most frequently in AML are t(6;11) (q27;q23) (MLL-AF6), t(9;11) (p23;q23) (MLL-AF9), t(10;11) (p12;q23) (MLL-AF10) and t(11;19) (q23;p13.1) (MLL-ELL),[10] while those in ALL are t(4;11) (q21;q23) (MLL-AF4) and t(11;19) (q23;p13.3) (MLL-ENL) (Table 1).[10]

Prognosis of 11q23/MLL AL according to fusion partner

Table 2 presents a summary of prognostic data in adults and children with individual 11q23 fusion partners, and the findings regarding 11q23/MLL AL with different fusion partners are discussed in the following paragraphs.

1) ALL with t(4;11) (q21;q23) (MLL-AF4)

The most prevalent MLL rearrangement in ALL generates the MLL/AF4 fusion gene owing to the t(4;11) (q21;q23) chromosomal translocation.

ALL with t(4;11) (q21;q23) has a bimodal age distribution with a major peak incidence in early infancy, and accounts for over 50% of ALL cases in infants less than 6 months of age, 10-20% in older infants, 2% in children and up to 7% in adults. Despite recent improvements in the overall treatment outcome for ALL patients, MLL/AF4 fusion is still associated with a dismal prognosis.[34] The complete remission (CR) rate in children is as high as 88%, but the median overall survival (OS) is only 10 months, indicating an extremely poor prognosis.[34-37] In adult patients with ALL, the CR rate is

Table 2. Prognosis of 11q23/MLL AL*

Type of 11q23/MLL rearrangement	Adult AML	Adult ALL	Childhood AML	Childhood ALL
t(4;11) (q21;q23) (MLL-AF4)	–	poor	poor	poor
t(6;11) (q27;q23) (MLL-AF6)	poor	–	poor	–
t(9;11) (p23;q23) (MLL-AF9)	controversial (poor/intermediate)	–	controversial (good/intermediate)	poor
t(11;19) (q23;p13.1) (MLL-ELL)	poor	–	intermediate	–
t(11;19) (q23;p13.3) (MLL-ENL)	–	–	intermediate	poor (B-lineage) good (T-lineage)

–, not reported ; *, modified from reference 59

75%, but the prognosis is also poor, with median OS of 7 months.[38-40]

2) ALL with t(9;11) (p23;q23) (MLL-AF9)

ALL with t(9;11) (p23;q23) is encountered more frequently in children than in adults. The 5-year event-free survival (EFS) rate is 38% in infants younger than 1 year old and 50% in children aged 1-9 years old, showing a similarly poor prognosis to ALL with t(4;11) (q21;q23).[41] Clinical studies have not been performed in adults.

3) ALL with t(11;19) (p23;q13.3) (MLL-ENL)

ALL with t(11;19) (p23;q13.3) also occurs mainly in children, especially in infants younger than 1 year old. Studies have shown a 5-year EFS of 26% in infants younger than 1 year old, 67% in children aged 1-9 years and 60% in children aged 10 years or older, indicating a relatively poor prognosis in infants younger than 1 year old but relatively good prognosis in children aged 1 year old or older.[41] The prognosis of children with T-lineage ALL is also relatively good among those with ALL with t(11;19) (p23;q13. 3).[42] There have been no reports of clinical studies regarding this variant in adult patients.

4) A4) AML with t(6;11) (p27;q23) (MLL-AF6)

The Cancer and Leukemia Group B (CALGB) study indicated an extremely poor prognosis of AML with t(6;11) (p27; q23) in a small number of adult cases (n = 16), as indicated by the 2-year survival rate of 13% and median EFS of 9 months.[30] In a previous study in a population of adult Japanese patients, the 1-year EFS was 22.2% and the 2-year OS was 33.7%, indicating a similarly poor prognosis to that in the CALGB study.[43] The prognosis of children with AML with t(6;11) (p27;q23) is also very poor. The results of an international retrospective study performed in 2009 indicated a 5-year OS and EFS of patients with t(6;11) (p27;q23) of 22% and 11%, respectively.[44]

5) AML with t(9;11) (p23;q23) (MLL-AF9)

AML with t(9;11) (p23;q23) has been reported to have a 5-year OS of 64.9% in children, indicating a relatively good prognosis.[45] However, the results of an international retrospective study performed in 2009 showed that the 5-year OS and EFS of patients with t(9;11) (p22;q23) were 63% and 50%, respectively, and therefore did not confirm a favorable prognosis.[44] There is also controversy regarding the prognosis of adult cases of AML with t(9;11) (p23;q23), with different authors reporting poor[32] or intermediate prognosis.[33] In an analysis of adult Japanese patients, the 1-year EFS and 2-year OS were 27.7% and 32.1%, respectively, showing a poor prognosis.[43]

6) AML with t(11;19) (q23;p13.1) (MLL-ELL)

In adult Japanese subjects, AML with t(11;19) (q23; p13.1) showed a 1-year EFS and 2-year OS of 12.8% and 10.7%, respectively, indicating an extremely poor prognosis.[43] Pediatric AML with t(11;19) (q23;p13.1) showed intermediate prognosis. The results of an international retrospective study in 2009 showed that the 5-year OS and EFS of patients with t(11;19) (q23;p13.1) were 61% and 46%, respectively.[44]

TOPICS OF TREATMENT OF 11q23/MLL AL

IndiIndication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for 11q23/MLL AL

The indication for allo-HSCT has been problematic in clinical treatment of 11q23/MLL AL. Until 2007, evaluation of allo-HSCT in patients with 11q23/MLL AL in CR was

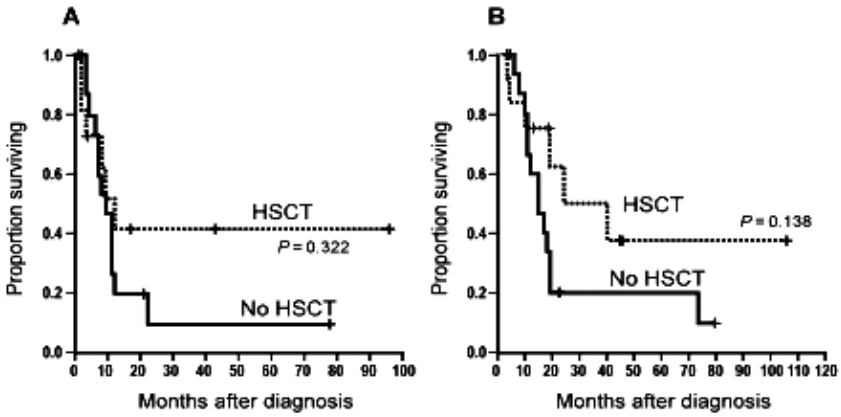

Fig. 2. Disease-free survival (DFS) (*A*) and overall survival (OS) (*B*) of adult acute myeloid leukemia in 11q23 patients aged < 60 years in first complete remission with allo- hematopoietic stem cell transplantation (HSCT) vs. no HSCT (modified from reference 43).

limited to a few reports on children, such as a report by Pui *et al*. on children with ALL with t(4;11) (q21;q23).[40] In 2009, we reported the prognosis of adult patients with 11q23/MLL AL to evaluate the effects of allo-HSCT.[42] Recently, the German Acute Myeloid Leukemia Intergroup also evaluated the impact of allo-HSCT in a larger adult population.[46]

1) Allo-HSCT for 11q23/MLL AML

A study population examined by Tamai *et al*. included 51 adult Japanese patients with 11q23/MLL AML, of whom allo-HSCT was performed in 12 of 39 patients in the first CR (matched, related donor : n = 8, matched, unrelated donor : n = 4). The other patients in the first CR underwent high-dose Ara-C therapy at least twice. The prognosis of patients who underwent allo-HSCT (< 60 years old, n = 12) was compared with that of those receiving chemotherapy (n = 18) to evaluate the effects of allo- HSCT in the first CR of 11q23/MLL AML. The 1-year disease-free survival (DFS) and 2-year overall survival (OS) in patients who underwent allo-HSCT were 41.5% and 62.5%, while those for patients receiving chemotherapy were 20.0% and 20.0%, respectively. These data did not differ significantly between the groups, but the allo-HSCT group tended to show a favorable prognosis (DFS : P = 0.322;OS : P = 0.138) (Fig. 2).[43] Krauter *et al*. also evaluated the effects of allo-HSCT in 49 adult patients up to 60 years old with 11q23/MLL AML. Relapse-free survival and overall survival rates were significantly better (DFS : P = 0.03, OS : P = 0.05) for patients who received allo-HSCT than for those receiving chemotherapy or autologous-HSCT as consolidation therapy (Fig. 3).[46] Garrido *et al*. reported that the effects of allo-HSCT were limited in an 11q23/MLL AML patient population including

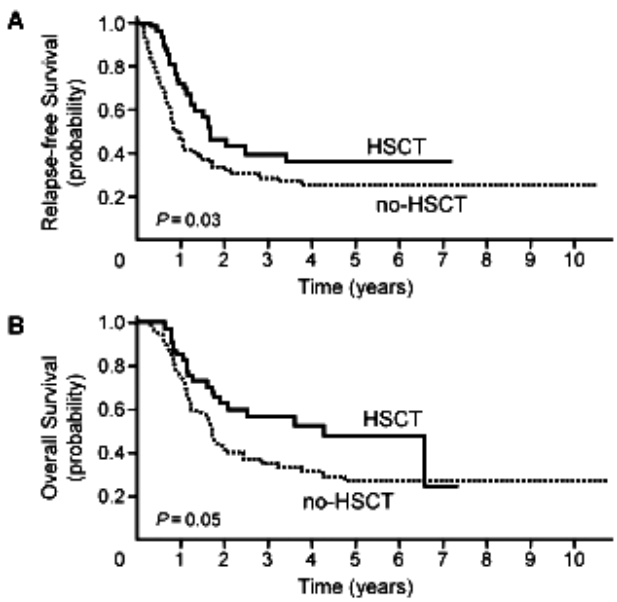

Fig. 3. Relapse-free survival (*A*) and overall survival (OS) (*B*) of adult acute myeloid leukemia in 11q23 patients aged < 60 years in first complete remission with allo- hematopoietic stem cell transplantation (HSCT) vs. no HSCT (modified from reference 46).

all age groups and after second CR or for those with refractory disease.[47] These studies suggested that treatment strategies including allo-HSCT should be considered in cases of AML with 11q23 abnormalities during the first CR. Studies of treatment for relapse of 11q23/MLL AML after allo-HSCT have been limited to case reports only. Gemtuzumab ozogamicin (GO) + donor lymphocyte infusion (DLI)[48] and intensive chemotherapy + DLI[49] are effective, but further

evaluation in larger cohorts is required.

2) Allo-HSCT for 11q23/MLL ALL

The MLL96/MLL98 study in Japan suggested the efficacy of allo-HSCT for pediatric 11q23/MLL ALL,[50] but Pui *et al*. found no beneficial effect of allo-HSCT in a large-scale study of ALL with t(4;11) (q21;q23), which accounts for the majority of ALL-positive 11q23 chromosomal abnormalities in children (Fig. 4).[41] The Interfant-99 trial suggested that infants with MLL rearrangements, younger age and very high white blood cell (WBC) count may benefit from stem cell transplantation.[51] Therefore, the therapeutic value of childhood allo-HSCT for 11q23/MLL ALL remains controversial. In addition, the application of allo-HSCT for 11q23/MLL ALL in children has decreased globally because of late-phase complications, which are more serious than those in adult patients, and due to recent improvements in the clinical results of chemotherapy in children and anticipation of new targeted molecular therapeutic modalities. The accumulation of data from larger numbers of cases is necessary to determine the appropriateness of a similar shift in therapy in adult patients.

New Therapeutic Agents

Conventional chemotherapy and improved hematopoietic stem cell transplantation may be insufficient to improve the prognosis of patients with 11q23/MLL AL. Therefore, the development of novel methodologies, including new molecular therapeutic targets, is necessary. The FMS-like tyrosine kinase 3 (FLT3) gene is expressed on pro/pre-B cells and plays an important role in early-phase differentiation of B cells.[52] A recent investigation indicated that ~80% of patients with infantile 11q23/MLL ALL exhibit high-level expression of wild-type FLT3, and the mutated activation loop (mutated D835/I836) of the TK2 domain in the FLT3 gene was confirmed in about 15% of such patients.[53-55] Thus, FLT3 is a potentially useful molecular therapeutic target for infantile 11q23/MLL ALL.[56,57] At present, the Children's Oncology Group (COG) in the USA is engaged in a randomized comparative study to examine the efficacy of concomitant therapy with the FLT3 inhibitor Lestaurtinib (CEP-701) along with chemotherapy (COG AALL0631 study). In addition, a phase I/II study with PKC412, another FLT3 inhibitor, in patients with recurrent disease is currently in the planning stages in Europe. In addition to FLT3 inhibitors, the use of DNA demethylating agents, such as 5-aza-2'-deoxycytidine (decitabine), is also under investigation. Stam *et al*. reported demethylation of 5' CpG islands of FHIT, a tumor-suppressor gene, in all samples from patients with infantile 11q23/MLL ALL, and that expression of FHIT induced apoptosis.[58] Other agents, such as human DOT1-like (hDOT1L), protein arginine methyltransferase 1 (PRMT1), HOX genes, EPHA7, MEIS1 and PBX, GSK-3, RAS, heat shock protein (HSP)-90 or MCL-1, are candidates for new therapeutic targets of 11q23/MLL AL. Thus, a number of new therapeutic agents have been developed for use in 11q23/MLL AL, mainly in the USA and European countries, and favorable results are expected.

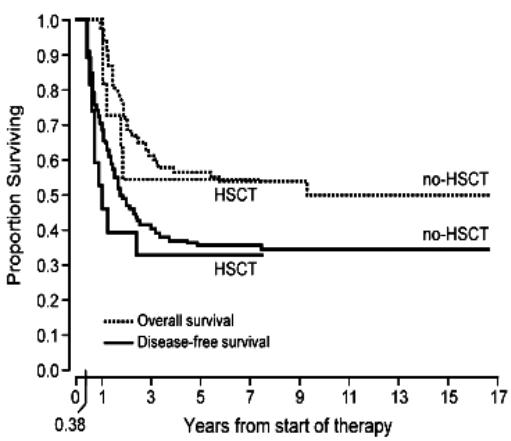

Fig. 4. Mantel-Byar estimates of disease-free survival with a landmark of 0.38 years, and Kaplan-Meier estimates of survival with a landmark of 1 year in patients with t(4;11) (modified from reference 41).

CONCLUSION

Chromosomal translocations leading to MLL gene fusion are common events in patients with AL, and are particularly common in infants with AL and patients with secondary leukemia. MLL fuses with numerous partner genes and the identity of fusion partner genes influences the prognosis of 11q23/MLL AL.

Special strategies are needed to treat 11q23/MLL AL, including allogeneic hematopoietic stem cell transplantation, according to the fusion partner. The development of novel methodologies, including new molecular therapeutic targets, is also needed to improve the prognosis of 11q23/MLL AL.

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