Blood Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Acute megakaryocytic leukemia: What have we learned

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ARTICLE INFO

Available online xxxx

Keywords:
Acute megakaryocytic leukemia
AML M7
Molecular features
Clinical outcomes
Allogeneic hematopoietic stem cell transplant
Polyploidization
Novel therapies

ABSTRACT

Acute megakaryocytic leukemia (AMegL) is a biologically heterogenous subtype of acute myeloid leukemia (AML) that arises from megakaryocytes. Improvements in the accuracy of diagnosing AMegL as well as interest in the molecular analysis of leukemias have led to an increased amount of data available on this rare AML subtype. In this review, we will analyze the diverse molecular features unique to AMegL and how they have influenced the development of novel treatment strategies, including polyploidization. The review will also consider the data available on clinical outcomes in AMegL and how it is a poor individual prognostic factor for AML. Finally, the role of allogeneic hematopoietic stem cell transplant in AMegL will be explored.

1. Introduction

Acute megakaryocytic leukemia (AMegL) is a biologically heterogeneous subtype of acute myeloid leukemia (AML) that arises from primitive megakaryocytes. AMegL was first described in 1931 by Von Boros but was rarely reported in subsequent years due to a lack of consistent diagnostic criteria [1]. In 1978, Breton-Gorius et al. utilized ultrastructural identification techniques with platelet peroxidase (PPO) to identify small megakaryocytes and increase the accuracy of diagnosing AMegL [2]. AMegL was then added to the French–American–British (FAB) classification as AML M7 in 1985 providing precise diagnostic criteria [3]. AMegL has a bimodal age distribution with peaks in children age 1–3 and adults in their fifties and sixties [4]. AMegL comprises 3–10% of all AML cases in children and carries a poor prognosis, except in children with Down Syndrome (DS) whom have an excellent prognosis [5–7]. In fact, AMegL is the most common form of AML in children with DS and is 400-fold more likely than in other children [7–11]. In contrast, AMegL in adults is a rare subtype of AML comprising only ~1% of AML cases in clinical trials and population-based data and carries a poor overall prognosis [12–15].

De novo AMegL often presents clinically with a low WBC and normal or increased platelet count on CBC and is frequently reported with extramedullary manifestations [15–18]. Additionally, AMegL can be seen in association with primary mediastinal germ cell tumors [19–21]. Bone marrow (BM) biopsy of AMegL reveals a proliferation of abnormal megakaryoblasts in addition to extensive fibrosis [14,22]. Immunohistochemistry stains and flow cytometry have significantly improved the ability of clinicians to accurately diagnose AMegL. Treatment of AMegL is with traditional chemotherapies used for other AML subtypes, while hematopoietic stem cell transplant has been investigated as a post-remission therapy in AMegL. Despite complete remission (CR) rates that are similar to other AML subtypes, the overall median overall survival for AMegL is very poor at 18–40 weeks [12–15].

This perspective will explore the diverse molecular and immunophenotypic characteristics of AMegL. We will review how AMegL is a poor individual prognostic factor for AML by looking at the data available on clinical outcomes in AMegL. Finally, we will consider the role of allogeneic hematopoietic stem cell transplant in post-remission treatment, while also exhibiting the need for novel strategies in the treatment of AMegL.

2. Pathophysiology and molecular features of acute megakaryocytic leukemia

AMegL arises from primitive megakaryoblasts and is comprised of megakaryocytes at different levels of maturation. Leukemogenesis of AMegL is complex and heterogenous in adults and children. In adults, AMegL can be *de novo* or secondary to leukemic transformation of a prior hematologic disorder. Secondary AMegL is frequently reported from the transformation of chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocytosis (ET), or primary myelofibrosis [23–25]. Interestingly, the complexity of karyotypes seen in adult *de novo* AMegL has prompted the question of whether more AMegL is secondary to myeloproliferative neoplasms than is currently reported [26].

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http://dx.doi.org/10.1016/j.blre.2015.07.005
0268-960X/

Clinical diagnosis of AMegL from BM histology has historically been challenging, as it is difficult to differentiate from acute panmyelosis with myelofibrosis (APMF); however, the diagnostic criteria of FAB classification system and the advent of flow cytometry have drastically improved the diagnostic sensitivity for AMegL [27–29]. The diagnosis of AMegL is challenging due to extensive fibrosis of the BM secondary to activating fibroblast factors produced by megakaryocytes [30]. The extensive fibrosis seen in AMegL causes inadequate BM aspirates (dry taps) leading to more frequent failure of cytogenetic analysis and difficulty in determining the exact number of blast present in the BM, which is required for distinguishing AMegL from APMF [13–15]. When dry taps become an issue, touch preparations from BM biopsy are often used to obtain adequate sample for counting blast number and for immunohistochemistry (IHC) staining [31]. For IHC staining of blasts, Orazi et al. noted that blasts in AMegL only stained positive for CD34 in 60% of cases unlike APMF whose blasts always stain positive for CD34 [31]. In IHC staining, AMegL is usually negative for myeloperoxidase (MPO) and is often differentiated from APMF by expressing megakaryocyte specific antigens. Megakaryocyte specific antigens on IHC include CD41 (GPIIb/IIIa), CD42b (GPIb), CD61 (GPIIIa), and vWF (factor VIII) (Table 1) [31–33]. vWF has historically been the most frequently used IHC stain for megakaryoblasts, but vWF expression can be decreased in poorly differentiated blasts making CD42b an ideal IHC stain for AMegL [31]. AMegL also usually stains positive for reticulin marking fibrosis but this does not help decipher AMegL from APMF [13]. On flow cytometry, megakaryoblasts in AMegL are positive for markers of megakaryocytic lineage, such as CD41 or CD61 [34]. Interestingly, AMegL in children with DS has a distinct immunophenotype with CD7, an atypical expression of lymphoid associated antigens, CD11b, and CD36 positive that is not seen in other subtypes of AMegL [35,36].

When AMegL is compared with other AML subtypes, the karyotype is more complex with a higher incidence of abnormalities and even a different distribution of karyotypes between adults and children [26,37]. Two distinct cytogenetic abnormalities are seen in AMegL in children: one in children with DS (DS-AMegL) and the other in children without DS who develop AMegL in infancy (non-DS-AMegL). The most common cytogenetic abnormality seen in non-DS-AMegL is t(1;22)(p13;q13) [38,39]. This translocation results in the fusion of RBM15 on chromosome 1p13 to the MLK1 gene on chromosome 22q13, which is referred to as the OTT-MAL (RBM-MLK) fusion gene [40].

DS-AMegL is unique and of particular research interest because it originates during fetal life and is considered a potentially tractable model of multistep leukemogenesis [41,42]. 5–10% of perinatal infants with DS experience transient abnormal myelopoiesis (TAM), which is an abnormal myeloproliferation disorder that is morphologically indistinguishable from AMegL but is usually self-limiting and resolves within 3–4 months of birth [43]. However, 20–30% of DS children with TAM during infancy will go on to develop AMegL [44]. Trisomy 21 alone has been shown to cause a trilineage perturbation in all blood lineages in fetal as well as neonatal hematopoiesis, but the molecular basis for this observation is not well understood and thought to be extremely complex [41]. Wechsler et al. discovered that all cases of TAM have a N-terminal truncating mutation in the 5′ coding exon of GATA1, a DNA-binding transcription factor on the X chromosome, in addition to trisomy 21 [45]. The GATA1 mutation disappears at remission of TAM and is thought to be disease specific for DS-AMegL [46]. While trisomy 21 with a GATA1 mutation is sufficient for development of TAM, Yoshida et al. showed that cohesin gene mutations are present in 23/49 cases of DS-AMegL and 0/41 cases of TAM [44,47]. This finding implies a prominent role for cohesin as a third genetic hit required for the transformation of TAM to DS-AMegL. Cohesin is a multi-protein complex made of 4 subunits responsible for cohesion of sister chromatids following DNA replication until cleavage during mitosis [44]. AMegL in DS has an excellent prognosis and is highly chemo-sensitive making the genetic differences between AMegL in DS and non-DS children of therapeutic interest.

When compared with children, adults with AMegL have a larger diversity of cytogenetic abnormalities. The most frequently seen abnormalities in adults are inv(3)(q21;q26), aberrations of chromosome 5 and 7, and t(9;22)(q34;q11) [13–15,26]. The inv(3)(q21;q26) abnormality is frequently seen in patients with preceding myeloproliferative neoplasms and is associated with increased or normal platelet counts [48]. Dastugue et al. found that adults with AMegL had a higher incidence of complex karyotypes and unrelated, abnormal karyotypes than other *de novo* AML. They also noted that unbalanced abnormalities in chromosomes 5 and 7 make up specific subgroups of adults with AMegL [26]. These findings are remarkably similar to the criteria required for diagnosis of AML with myelodysplastic-related (MDS) changes. AML with MDS-related cytogenetics predicts inferior outcomes, which could partially explain the poor overall survival seen in adults with AMegL [49]. The complexity and heterogeneity of alterations seen in AMegL would also raise concern for chromosome 17p or p53 mutations, but no studies to date have explored this possibility. In adults with synchronous hematological neoplasia and primary mediastinal germ-cell tumors, a cytogenetic abnormality, isochromosome 12p, has been identified in the mediastinal tumor and leukemic blasts [50,51]. The association and shared cytogenetic abnormality suggest a common origin of the tumors.

3. Clinical outcomes

Since AMegL is a rare subtype of AML with a historically challenging diagnosis, limited data on the natural history, treatment, and prognosis of AMegL exist in the literature. In the past fifteen years, three large case series have been published on the treatment and outcomes of AMegL in adults in large academic centers, which are summarized in Table 2 [13–15]. Additionally, a recent, large population-based study utilizing the SEER database introduced data on five year overall survival of AMegL in the general population [12]. All four of these studies revealed consistent results that highlight the need for a renewed, novel approach to the prognosis and treatment of AMegL in adults. The incidence of AMegL in adults is ~1% with a younger median age (~50 years) in academic centers than other AML subtypes. Induction therapy of AMegL in adults has been with an anthracycline plus cytarabine based regimen, which is traditionally utilized for other AML subtypes. Complete remission

Table 1
Laboratory modalities to aid in the diagnosis of AMegL.

Modality	Marker	Positivity	Cell lineage
Immunohistochemistry	Myeloperoxidase (MPO)	Negative	Myeloid
	vWF (Factor VIII)	Positive	Megakaryocyte
	GPIIb/IIIa (CD41)	Positive	Megakaryocyte
	GPIb (CD42b)	Positive	Megakaryocyte
	GPIIIa (CD61)	Positive	Megakaryocyte
	Reticulin	Positive	Reticular fiber
Immunophenotype	Myeloperoxidase (MPO)	Negative	Myeloid
	GPIIb/IIIa (CD41)	Positive	Megakaryocyte
	GPIIIa (CD61)	Positive	Megakaryocyte
	CD7	Pos in DS	Lymphoid

Table 2
Summary of clinical outcomes for the largest series of adult AMegL patients.

	Oki et al. [13]	Pagano et al. [14]	Giri et al. [11]	Tallman et al. [12]
# of AML M7 patients	37	24	304	20
Median age (years)	56 (21–78)	51 (15–76)	68 (18–92)	43 (18-70)
Complete remission	16 (43%)	12 (50%)	N/A	10 (50%)
Median OS (weeks)	23	40	18	41
5 year OS	N/A	10%	11%	N/A
Presence of chrom 3 abnorm	6 (16%)	2/11 (18%)	N/A	4/8 (50%)

Please cite this article as: Hahn AW, et al, Acute megakaryocytic leukemia: What have we learned, Blood Rev (2015), http://dx.doi.org/10.1016/j.blre.2015.07.005