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Review

Acute myeloid leukemia with myelodysplasia related changes

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder with two prominent features: i) hematopoietic progenitor cells loose the ability to differentiate normally and ii) the transformed leukemia cells show an impaired regulation of myeloid proliferation.

AML with myelodysplasia-related changes is a sub-entity of AML that has a poor prognosis. It is characterized by a history of MDS, significant morphologic dysplasia, or MDS-related cytogenetic features such as -7/del(7q) and others. Whereas the prognosis of AML is quite different with respect to genetic aberrations, the therapy - except of acute promyelocytic leukemia (APL) - is still relatively unchanged from 30 years ago. Therefore, new treatment strategies are needed.

Keywords

Acute myeloid leukemia, multilineage dysplasia, myelodysplasia related changes

Clinics and pathology

Disease

Acute myeloid leukemia with myelodysplasia related changes (AML-MRC) is a subgroup of AML. It was introduced in 2008 by the WHO classification and updated in 2016 (Weinberg et al., 2015). A diagnosis of AML-MRC requires ≥ 20% blasts and additionally one of the following three criteria:

- history of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN)
- MDS-related cytogenetic abnormalities or multilineage dysplasia (≥ 50% dysplastic cells in≥ two hematopoietic lineages) (Arber et al., 2016a).

Etiology

There are various risk factors which can cause AML in general. These risk factors can be categorized as genetic disorders, physical and chemical exposure, radiation therapy and chemotherapy. Even though many people are exposed, to various degrees, to carcinogens, only a few cases may present with a known history of carcinogen exposure. Currently, it is not fully understood why some people develop AML and some do not (Estey and Döhner, 2006). Genetically, many researchers favor the "two-hit" hypothesis first proposed by Hartmut Beug (Beug et al., 1978), and later by Gary Gilliland. This hypothesis states that for transformation, a mutation in a kinase coding gene such as RAS, KIT or FLT3 has to occur together with a class II mutation targeting a transcription of nuclear factor such as NPM1, RUNX1 or CEBPA. Today, we know about a high variation of somatic mutations and chromosomal abnormalities characterizing different types of AML. AML-MRC is often associated with the following chromosomal abnormalities (Table 1) (Deschler et al., 2006; Weinberg et al., 2015).

Epidemiology

If the WHO classification is strictly applied, 48% of all adult AML cases meet the AML-MRC criteria. It tends to affect more male and is a disease of the elderly with a median age of 68 years. Additionally, it is associated with a higher frequency of unfavorable cytogenetics and, consequently, a worse clinical outcome (Davis et al.,2013; Xu et al., 2014; Weinberg et al., 2009). AML-MRC occurs more often de novo then secondary to myelodysplasia (Vardiman and Reichard, 2015).

Cytology

AML-MRC cases commonly present with multilineage dysplasia. This is validated best with peripheral blood smears or bone marrow smears for identifying myeloid and erythroid dysplasia and bone marrow biopsy for identifying megakaryocytic dysplasia (Falini et al., 2016). Following the WHO classification an AML-MRC presents with ≥ 50 % dysplastic cells in at least two hematopoietic lineages. The dysplastic features are not unique for AML-MRC, but can be also detected in other hematopoietic diseases, such as MDS (Wu et al., 2013). Dysplastic neutrophils may exhibit a nucleus-cytoplasm dysynchrony, hypogranulation and abnormal nuclear segmentation (pseudo-Pelger-Huët anomaly), e.g. bi-nucleated segments (Weinberg et al., 2015). As mentioned, dyserythropoesis and dysmegakaryopoesis are also commonly seen. Dyserythropoesis presents with odd erythroid precusors and sometimes ring sideroblasts, as well as multinuclearity, megaloblastoid changes and karyorrhexis. Dysmegakaryopoesis commonly shows hypolobulated micromegakaryocytes, non-lobulated nuclei in megakaryocytes of all sizes and multiple widely separated nuclei (Wakui et al., 2008).

Treatment

The therapy of AML-MRC is based on regular AML-therapy with a risk-adapted chemotherapy including induction chemotherapy ("7+3"; daunorubicine plus cytarabine) and postinduction therapy, such as high-dose cytarabine or in high-risk patients, allogeneic transplantation in first remission. Using regular assessments, lab studies including cytogenetics and molecular analyses, the patient can be assigned to a risk group and treatment and prognosis can be determined and the decision between curative chemotherapy/allogeneic stem cell transplantation, palliative chemotherapy and best supportive care can be made (Estey and Döhner, 2006). Chemotherapy can be separated into two main parts. First, the induction therapy with the attempt to reach complete remission. Second, the consolidation therapy to prolong the complete remission. If the patient displays characteristics of high risk AML, a hematopoietic stem cell transplantation (HSCT) must be considered (Kumar, 2011). As AML-MRC frequently fulfills the high-risk criteria such as: 3(q21q26) abnormalities, RPN1/MECOM (EVI1), del(5q), del(7q), t(6;9), other 11q23 abnormalities, 17p abnormalities, or complex aberrant karyotypes described as at least 3 unrelated abnormalities excluding cases with t(8;21), inv(16), and t(15;17), an allogeneic stem cell transplantation will be the post-induction therapy of first choice in most adults (Vardiman and Reichard, 2015).

Prognosis

The myelodysplastic changes and MDS associated chromosomal abnormalities of AML-MRC are associated with a worse prognosis and lower rates of event-free survival and overall survival. However, it was shown that there is no difference in prognosis between patients with AML-MRC with a history of MDS and the remaining cases of AML-MRC (Weinberg et al., 2009; Arber et al., 2003). Besides, AML-MRC with the absence of cytogenetic abnormalities seem to have a better prognosis (Weinberg et al., 2009). Additionally, AML-MRC with NPM1 mutations and with or without cytogenetic abnormalities show a better prognosis (Haferlach et al., 2009). This was also shown for CEBPA mutations (Vardiman and Reichard, 2015). Therefore AML-MRC with NPM1 or CEBPA mutations are excluded from the AML-MRC category in the WHO classification 2016 (Arber et al., 2016). The prognosis of AML-MRC particularly in context of multilineage dysplasia remains controversial (Vardiman and Reichard, 2015). In patients who have undergone allogenic HSCT there is no prognostic difference in AML-MRC patients compared to AML not otherwise specified (AML-NOS) (Ikegawa et al., 2016).

Cytogenetics

Cytogenetics morphological

Following the WHO classification, cases of AML with MDS-related cytogenetic abnormalities meet the criteria of AML-MRC. MDS and AML-MRC may show complex karyotype and with predominantly unbalanced chromosomal abnormalities (Vardiman and Reichard, 2015; Miesner et al., 2010). A complex karyotype is defined as three or more unrelated chromosomal abnormalities and is differentiated into unbalanced and balanced chromosomal abnormalities (see Figure 1). A complex karyotype can lead to aberrant expression pattern of regulating genes and is often associated with a poor prognosis. Likewise, it is assumed that autosomal monosomy (2 or more autosomal monosomies or 1 autosomal monosomy plus one or more other chromosomal abnormalities) is associated with a poor prognosis.

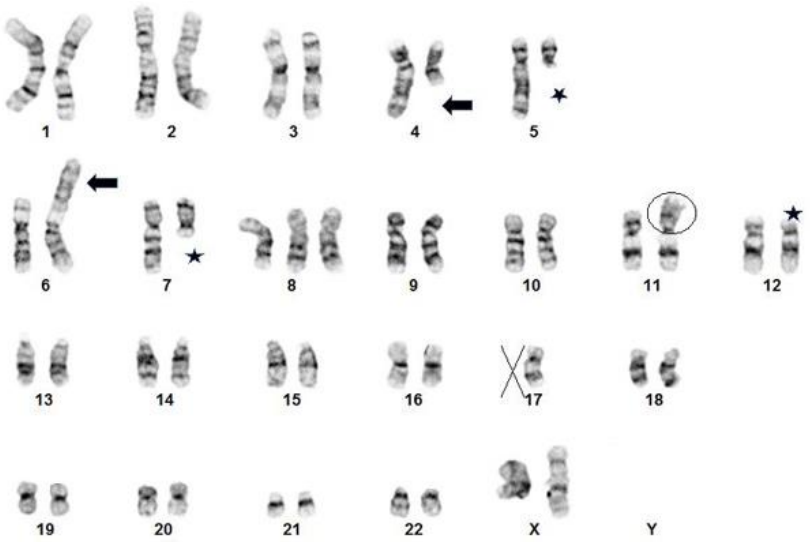

Figure 1. Karyotype analysis with MDS related cytogenetic abnormalities: 46,XX,t(4;6)(q21;23),del(5)(q11.2q35),del(7)(q11.2q36),+8,add(11)(p15),del(12)(p12p13),-17. Commonly seen in MDS is the deletion of 5 and 7 (stars) and/or monosomy 17 (cross) (Miesner et al., 2010).

The most common monosomies in AML and MDS are monosomies 5 and 7 which are known for its poor prognosis (Takahashi, 2011; Cazzola et al., 2013). Table 1 shows the commonly occurring balanced and unbalanced chromosomal abnormalities.

Complex Karyotype	>3 unrelated abnormalities, none of which are included in the AML with recurrent genetic abnormalities subgroup
Unbalanced abnormalities	-7/del(7q) -5/del(5q) i(17q)/t(17p) -13/del(13q) del(11q) del(12p)/t(12p) idic(X)(q13)
Balanced abnormalities	t(11;16)(q23;p13.3) t(3;21)(q26.2;q22.1) t(2;11)(p21;q23) t(1;3)(p36.3;q21.1) t(5;12)(q33;p12) t(5;7)(q33;q11.2) t(5;17)(q33;p13) t(5;10)(q33;q21) t(3;5)(q25;q34)

Table 1. Cytogenetic abnormalities for AML with myelodysplasia-related features (modified from Vardiman and Reichard et al. 2015).

Common gene arrangements and their effects are displayed in Table 2. According to the 2016 WHO classification the MDS related cytogenetic abnormality del(9q) is no longer considered a AML-MRC defining abnormality. Since del(9q) commonly occurs together with NPM1 or bi-allelic CEBPA mutations it is also associated with a better outcome. The same is true for trisomy 8, del(20q) and loss of chromosome Y (Pabst et al., 2009; Wu et al., 2013).

Gene arrangement	Effect
5q33	activation of the platelet-derived growth factor- β (PDGFRB)
3q26 (MECOM (EVI1) locus)	Impaired EVI1 expression (poor prognosis)
3q21 (GATA2 locus)	Impaired EVI1 expression (poor prognosis)
11q23 (KMT2A (MLL) locus)	Clonal evolution and disease progression in acute leukemia
t(3;5)	fusion product NPM1 / MLF1

Table 2. Common gene arrangements in AML-MRC (Vardiman and Reichard, 2015; Arber et al., 2003; Heldin and Lennartsson, 2013; Zuo et al., 2016; Lim et al., 2010)

Genes involved and proteins

As mentioned in Prognosis, the NPM1 mutation can present with multilineage dysplasia and is associated with a better outcome. However, there are no genetic somatic mutations fully specific for AML-MRC. As the subcategory AML-MRC represents almost 50% of all AML cases there can be found all common somatic mutations of AML concomitantly. In case of an AML-MRC with a history of MDS commonly mutated genes in MDS should also be considered, e.g. SF3B1 which is associated with the formation of ring sideroblasts in MDS (Malcovati et al., 2014). Somatic mutations have prognostic value and are assumed to play a critical role in leukemogenesis.

They can affect signal transduction, DNA methylation, chromatin modification, transcriptional regulation, RNA splicing and cohesion- complexes. The most commonly mutated genes in AML are FLT3, NPM1, CEBPA besides many more (Cancer and Atlas, 2013; Malcovati et al., 2014). Following the 2016 WHO classification an AML-MRC with presence of NPM1 and bi-allelic CEBPA mutation is not considered a AML-MRC anymore as these gene mutations are associated with a better outcome (Arber et al., 2003; Haferlach et al., 2009; Pabst et al., 2009) In contrast FLT3 mutations are associated with genetic abnormalities and a worse clinical outcome (Bibault et al., 2015).

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