Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Leukaemia Section

Review

Myelodysplastic syndrome with excess blasts

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Published in Atlas Database: June 2017

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/MyeloExcessBlastsID1798.html

Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68934/06-2017-MyeloExcessBlastsID1798.pdf

DOI: 10.4267/2042/68934

Abstract

Myelodysplastic syndrome with excess blasts (MDS-EB) represents the most clinically aggressive end of the continuum of the myelodysplastic syndromes (MDS). All MDS are characterized by clonal, ineffective hematopoiesis with maturation defects and increased apoptosis resulting in peripheral blood cytopenias, abnormal myeloid maturation (dysplasia) and variable risk of progression to bone marrow failure and/or acute myeloid leukemia. Progressive degrees of restricted myeloid maturation represented by abnormally increased numbers of morphologically-defined blasts in the blood and/or bone marrow is the key feature separating MDS-EB from the other myelodysplastic syndromes and is strongly associated with increased risk of disease progression and decreased survival. Metaphase chromosome analysis of bone marrow myeloid cells is the cornerstone of documenting clonal hematopoiesis to establish the diagnosis of MDS and for risk stratification of patients with confirmed MDS. Molecular analyses are becoming increasingly utilized for diagnosis and prognosis.

KEYWORDS

Myelodysplastic syndrome, blast, mutation, karyotype, chromosome, deletion, monosomy.

Identity

Other names

Refractory anemia with excess blasts (W.H.O. 2001, W.H.O. 2008, F.A.B. 1976, F.A.B 1982). Myelodysplastic syndrome with excess blasts is the W.H.O. 2016 s name.

Clinics and pathology

Disease

Myelodysplastic syndrome with excess blasts (MDS-EB) is a clonal disorder of hematopoietic stem cells (HSC) characterized by morphologically disordered maturation ("dysplasia") and restricted maturation of the myeloid lineages in the bone marrow resulting in ineffective hematopoiesis, cytopenias, increased blasts (5-19% of blood or bone marrow nucleated cells), and increased risk of progressive bone marrow failure and/or developing acute myeloid leukemia. Disease-specific morbidity and mortality is related to cytopenias, i.e. anemia, neutropenia, and thrombocytopenia resulting in infection and/or bleeding, due to progressive bone marrow failure and/or development of acute leukemia.

Phenotype/cell stem origin

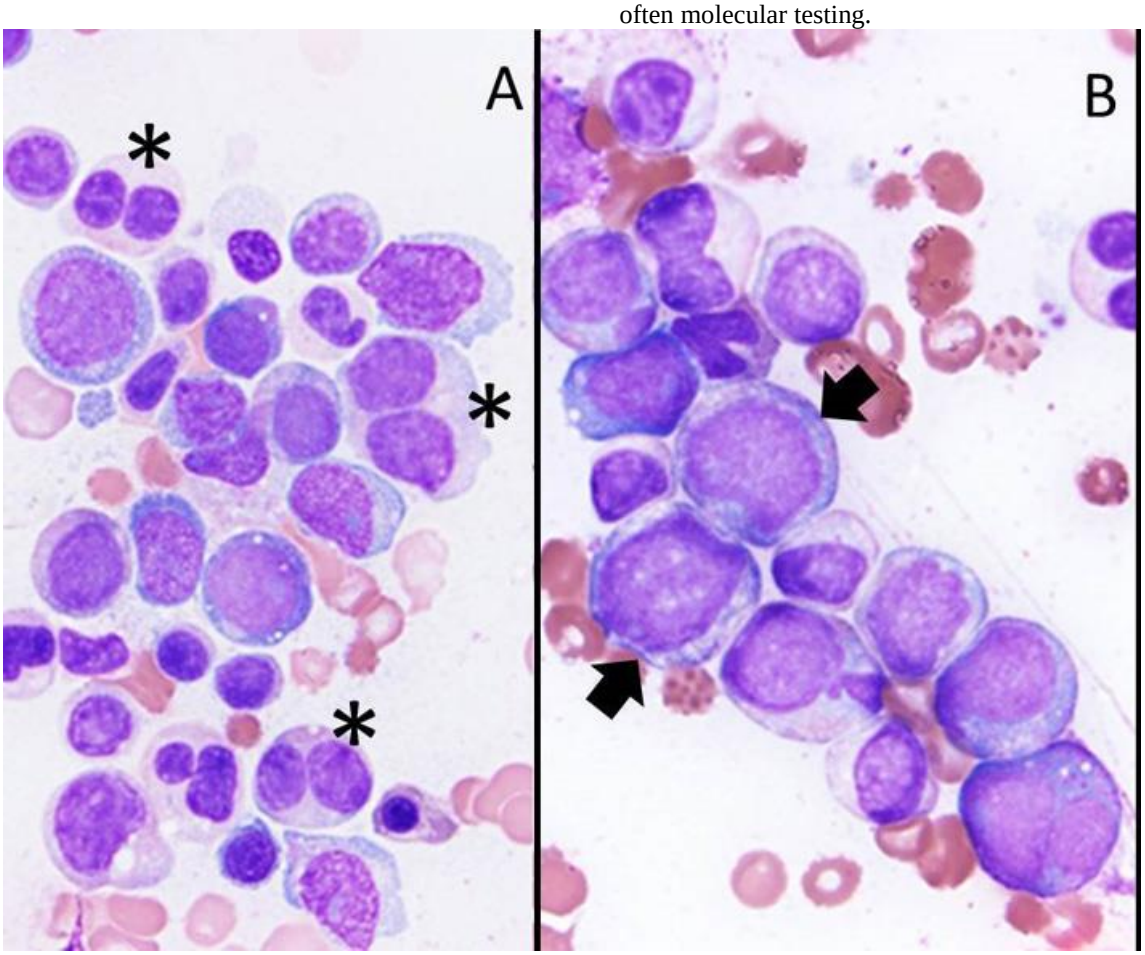
Recent work suggests that the leukemia stem cell in myelodysplastic syndromes is a specific hematopoietic stem cell with the following phenotype: Lin-, CD34+, CD38-, CD90+, and CD45RA- (Woll et al., 2014).

Epidemiology

Myelodysplastic syndromes may affect individuals of any age, gender or ethnicity. Accurate measurement of the incidence of myelodysplastic syndromes, including MDS-EB, is very difficult to obtain due to underreporting and underdiagnosing, but clearly shows a marked increase incidence with age. Some estimates are as high as 63.9 / 100,000 in people ≥85 y.o. (Cogle et al., 2015). The median age of diagnosis is around 71 years (Pfeilstöcker et al., 2016).

Clinics

Patients may present with asymptomatics cytopenias identified on routine laboratory testing or due to symptoms related to cytopenias, e.g. fatigue or exercise intolerance due to anemia, infections due to neutropenia and/or bleeding due to thrombocytopenia. Diagnosis requires examination of blood and bone marrow for morphological features of disordered maturation of myeloid lineages ("dysplasia") and enumeration of blast cells in blood and marrow correlated with genetic and often molecular testing.



Bone marrow aspirate smear from a patient with MDS-EB (Wright-Geimsa, 1000X). A. Extensive dysgranulopoiesis with marked nuclear-to-cytoplasmic dyssynchrony, numerous "Pelgeroid" segmented neutrophils with bilobed nuclei and hypogranular cytoplasm (∗) and giant forms. B. Increased blasts (arrows).

Cytogenetics

Metaphase chromosome analysis remains a crucial pillar in the diagnosis and prognosis of patients with MDS. Overall, about 40-50% of all individuals with de novo MDS will show a clonal chromosomal abnormality at the time of diagnosis (Greenberg 2012). Not surprisingly, the likelihood of identifying a clonal chromosomal abnormality is correlated with the severity of the disease, e.g. about 32 %patient's with MDS with single-lineage dysplasia and

Chromosomal abnormalities in myelodysplastic syndromes are myriad, but the most common are unbalanced resulting in net loss/gain of chromosomal material, such as monosomy, deletions and/or unbalanced translocations, and trisomy. Specifically, the incidence of common chromosomal abnormalities in MDS with an abnormal karyotype is: del(5q) (30%), -7/del(7q) (21%), +8 (16%), -18/18q- (7%), 20q- (7%), -5 (6%), -Y (5%), -17/17p- (including isochromosome (17q)) (5%), +Mar (5%), +21 (4%), inv/t(3q) (4%), -13/13q- ID: 1096 (4%), +1/+1q (3%), -21 (3%), +11 (3%), 12p- (2%), t(5q) (2%), 11q- (2%), and t(7q) (2%). MDS-EB is enriched for unfavorable risk abnormalities (i.e. ≥ 3 abnormalities or any chromosome 7 abnormality) as compared to MDS with <5% blasts. (Haase 2017)

The most recent multinational study of prognosis in MDS created a Revised International Prognostic Scoring System (IPSS-R) (Greenberg et al.,2012) stratified chromosomal abnormalities into 5 categories: Very good, good, intermediate, poor and very poor as follows: (Schanz et al, 2012).

In contrast to acute myeloid leukemia (AML), balanced reciprocal translocations are conspicuously uncommon in MDS-EB.

IPSS-R Cytogenetic Risk Categories		
Very Good:	*Single:*	del(11q), -Y
Good:	*Single:*	Normal, del(5q), del(12p), del(20q)
	Double:	including del(5q)
Intermediate:	*Single:*	del(7q), +8, i(17q), +19, any other, independent clones
	Double:	any other
Poor:	*Single:*	inv(3)/t(3q)/del(3q)
	Double:	including -7/del(7q)
	Complex:	3 abnormalities
Very poor:	*Complex:*	Greater than 3 abnormalities

I.

Genes

As about 40% of patients with MDS-EB will have normal metaphase chromosomes, many investigators have sought to use higher-resolution molecular techniques to identify diagnostic, prognostic and predictive molecular aberrations.

The use of FISH for as an adjunct to metaphase chromosome analysis in MDS is controversial. Many physicians routinely request a panel of interphase FISH probes to common and/or clinically significant abnormalities (e.g. -5/5q-, +8, -7/7q-, 20q-, 17p/TP53) a priori for all patients with suspected or confirmed MDS. However, several studies have shown essentially no additional clinically useful information is discovered with this technique if the metaphase study is adequate. Interphase FISH may be useful for specimens without adequate metaphases. Metaphase and/or interphase FISH may also be helpful to clarify subtle abnormalities of metaphase spreads.

Array comparative genomic hybridization (aCGH) and single nucleotide polymorphism array (SNP array) are particularly attractive methods to interrogate the entire genome at a fairly fine resolution to identify the gains and/or losses of chromosomal material that are common in MDS. Additionally, SNP arrays can identify copy-neutral loss of heterozygosity (CN-LAH) which can functionally inactivate tumor suppressor genes, similar to gross monosomies and deletions. These techniques have been shown to confirm most, but not all chromosomal abnormalities concurrently identified in metaphase chromosome analysis. They also detect additional abnormalities in genes or regions implicated in the pathogenesis or prognosis of patients with myeloid neoplasia. The precise clinical significance of detecting these submicroscopic chromosomal abnormalities in patients with MDS is currently under extensive study.

Sequence level techniques, including targeted sequencing of specific genes or broader whole-genome sequencing (WGS) may be used to document clonal hematopoiesis and to provide prognostic and predictive data to patients with established MDS. Targeted sequencing techniques will identify mutations in up to 90% of all MDS patients. Commonly mutated genes include: SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2 (Haferlach et al., 2014). The clinical significance of specific mutations is currently evolving (Bejar et al, 2017).

In patients with MDS-EB, the issue of clonality is rarely a question, but the predictive information about which therapies may work for an individual patient may prove highly beneficial, such as mutations of IDH1 /IDH2 that can be targeted by specific drug therapies. In addition, these techniques

have identified novel genetic abnormalities and mechanisms, e.g. chromothripsis, which are improving our understanding of the mechanisms of disease development and progression (Abaigar et al., 2016).

Treatment

Treatment options for patients with MDS-EB include a broad spectrum of options from supportive care, low-intensity therapies, to high-intensity therapies +/- stem cell transplantation. Given that the incidence of MDS-EB is highly positively correlated with age, it is no surprise that many patients will have significant comorbidities and decreased performance status at the time of diagnosis, which are likely to limit their tolerance of higher-intensity chemotherapy and stem cell transplant.

Supportive care options are aimed at ameliorating or lessening symptoms and improving quality of life, such as RBC transfusion to improve symptoms of decreased oxygen carrying capacity or platelet transfusions for bleeding events. Antifibrinolytics may benefit patients who are unresponsive to platelet transfusion. Some patients may also respond to colony stimulating factors such as erythropoietin, granulocyte colony stimulating factor, granulocyte-monocyte stimulating factor and thrombopoietin mimetics.

Low intensity therapeutic options mostly center hypomethylating agents such as 5' azacytidine or decitabine or low-dose cytotoxic chemotherapies such a as cytosine arabinoside. Some patients will respond to immunosuppression (ATG) and/or biological response modifiers (lenalidomide) suggesting an immune-mediated etiology in some individuals.

High intensity treatments are similar to those used for acute myeloid leukemia such as intensive induction chemotherapy, e.g. idarubicin/daunorubicin, cytarabine/fludarabine, topoisomerase inhibitors, etc. +/- allogeneic stem cell transplantation.

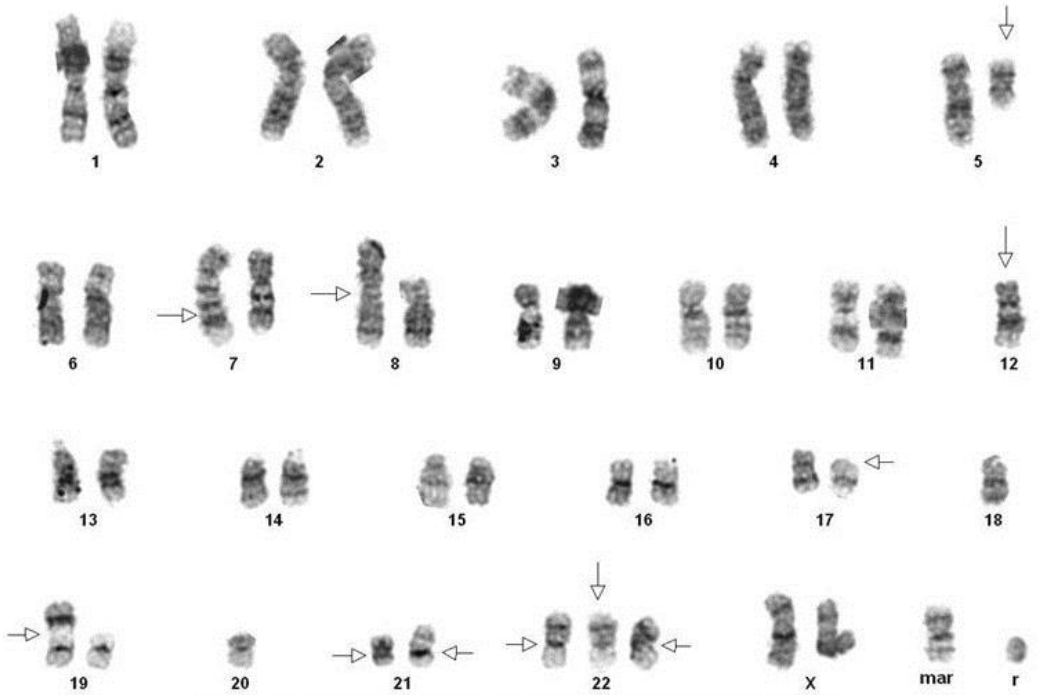
Evolution

MDS-EB is usually a clinically and genomically unstable disease state with a very high rate of progression to death due to bone marrow failure and/or acute myeloid leukemia (>20% blasts). Cytogenetic evolution often accompanies and/or precedes clinical and morphological progression.

Prognosis

The prognosis for patients with MDS has been studied intensively leading to several risk stratification models, e.g. IPSS, IPSS-R and IPSS-RA (ie, IPSS-R including age),the original WHO classification-based Prognostic Scoring System (WPSS) applying transfusion need, its modification using hemoglobin thresholds (WPSS 2011) and its modification including age (WPSS-A), and the Lower-Risk Prognostic Scoring System (LR-PSS). (Pfeilstoeker et al., 2016) The most commonly used system in clinical practice is the IPSS-RA. (Greenberg et al, 2012) These systems all incorporate chromosomal analysis with clinical and morphological features. Most patients with MDS-EB will be stratified into higher-risk categories with median overall survival about 9 months to 2 years and about 50-90% risk of progression to AML within 5 years.

Cytogenetics



Abnormal karyogram from the bone marrow of a patient with MDS-EB showing a highly complex karyotype with numerous monosomies and unbalanced translocations resulting in net loss of chromosomal material. Common abnormalities associated with MDS include del(5q), -7q, del(17p), -18, -20 are illustrated. Karyogram and interpretation provided by Rhett P. Ketterling, M.D., Mayo Medical Laboratories, Rochester, MN, USA.

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This article should be referenced as such:

Bayerl MG. Myelodysplastic syndrome with excess blasts. Atlas Genet Cytogenet Oncol Haematol. 2018; 22(8):346-351.