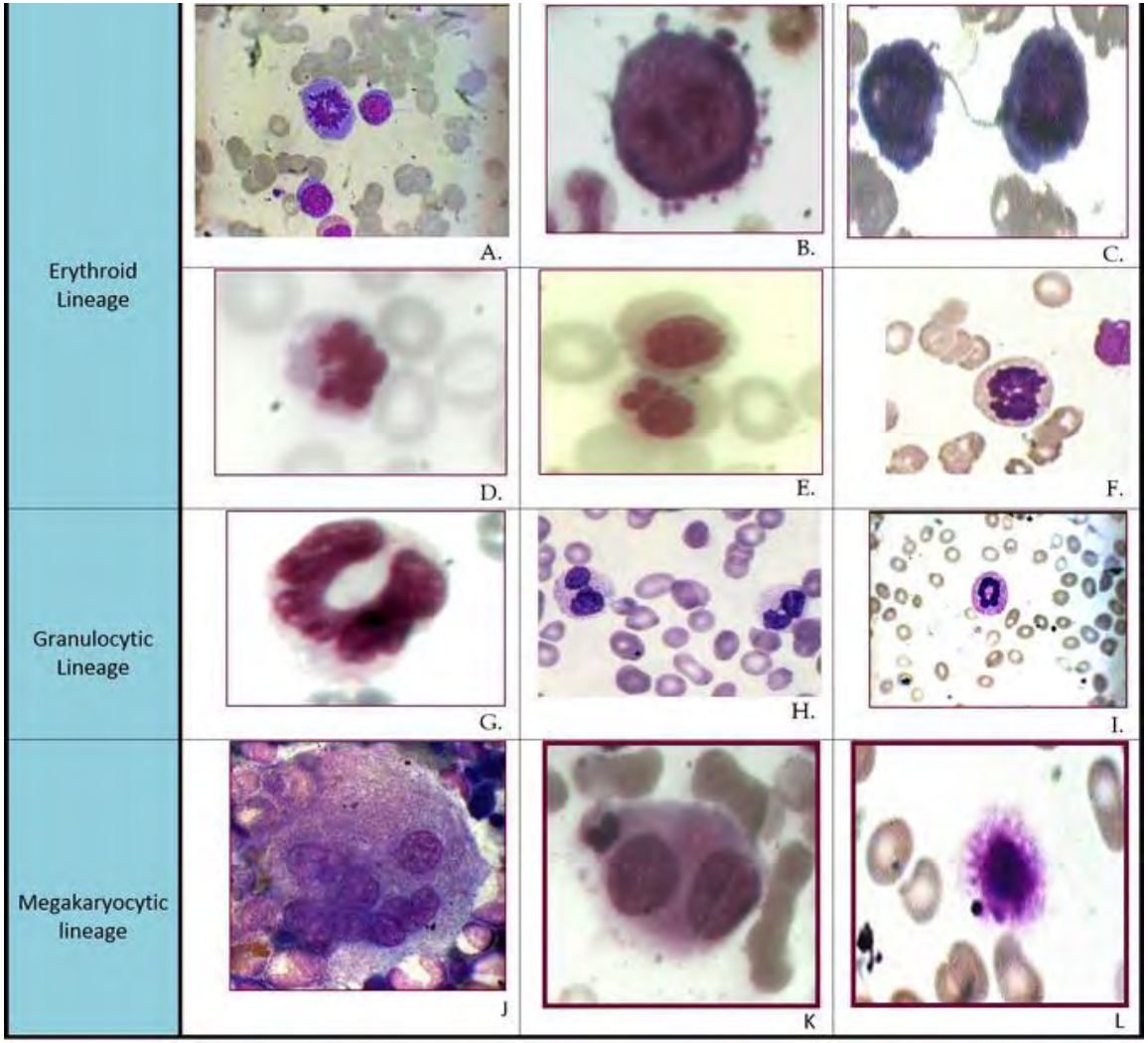
MIELODISPLASIE



Definition

- MDSs are clonal disorders of the hematopoietic stem cell characterized by ineffective hematopoiesis leading to peripheral blood cytopenias, reflecting defects in erythroid, myeloid and megakaryocytic maturation and by frequent evolution to AML.

Predisposing factors

- **Heritable predisposition**

- Constitutional genetic disorders
- Down syndrome, Trisomy 8 mosaicism
- Familial monosomy 7
- Neurofibromatosis 1
- Germ cell tumors (embryonal dysgenesis)
- Congenital neutropenia (Kostmann syndrome or Shwachman-Diamond syndrome)
- DNA repair deficiencies
- Fanconi anemia, Ataxia telangiectasia, Bloom syndrome
- Xeroderma pigmentosum

Predisposing factors…..

- **Acquired**

- Senescence
- Mutagen exposure
- Genotoxic therapy
- Alkylators
- Topoisomerase II interactive agents
- ß-emitters (phosphorus-32)
- Autologous bone marrow transplantation
- Environmental or occupational exposure (e.g., benzene)
- Tobacco

- Aplastic anaemia
- PNH
- Polycythemia vera

Theories of Pathophysiology involved in MDS Development	Potential Targets/Components Involved	Overall Result of Abnormality
Environmental/Aging		
Aging	Increased BM apoptosis	Decreased hematopoietic stem cell pool
Environmental Exposures	Smoking Radiation Benzene Viral Infections Chemotherapy	Direct Toxicity to hematopoietic stem cells.
Telomere Abnormalities	Potential decreased telomerase and subsequent telomere shortening	•Impaired ability to renew stem cell pool. •Genetic Instability

Altered Bone Marrow Microenvironment		
Altered Bone Marrow Microenvironment Cytokines	Upregulation of: TNF-α, IFN-gamma, TGF-Beta, IL-1B, IL-6, Il-11	•Alteration of growth, differentiation, angiogenesis •Immune modulation
Alterations in Apoptosis via Signalling	•Increased TNF-α levels •FAS: Increased Apoptosis •BCL-2 alterations	•Increased apoptosis and proliferation in early stage MDS leading to hypercellular marrow with peripheral cytopenias • Decreased apoptosis and increased proliferation in later stage MDS leading to progression to AML
Increased Angiogenesis	•Increased VEG-F • Possible Increase: gFGF and EGF Angiogenin	Increased Microvessel Density (MVD): role in pathogenesis not clearly elucidated but associated with progression to AML

2016 WHO Classification of Myeloid Neoplasms

WHO Classification -- Subtypes of MDS	
MDS with single lineage dysplasia	MDS with excess blasts in transformation
MDS with ring sideroblasts	Chronic myelomonocytic leukemia (CMML-1)
MDS with multilineage dysplasia	CMML-2
MDS with excess blasts-1	Atypical chronic myeloid leukemia, *BCRABL1* negative
MDS with excess blasts-2	Chronic neutrophilic leukemia
MDS, unclassifiable	Juvenile myelomonocytic leukemia
MDS with isolated del(5q)	MDS/MPN unclassifiable
Refractory cytopenias of childhood	MDS/MPN with ring sideroblast and thrombocytosis

Arber DA, et al. *Blood*. 2016;127:2391-2405.
NCCN Guidelines. Myelodysplastic Syndromes. V1.2017.

Definition of sideroblasts

- **Type 1**
  <5 siderotic granules
- **Type 2**
  ≥5 siderotic granules (not perinuclear)
- **Ringed**
  ≥5 perinuclear granules (usually 1/3 or more of the nucleus)

← Perinuclear siderotic granules

Mufti GJ et al. Haematologica 2008; 93:1712-7

Clinical Features

- 4/100000 incidence

- Discovered by chance
- ½ of patients are over 70yrs and < 25% are less than 50 years

- Symptoms of anemia, infection, easy bruising and bleeding
- Splenomegaly uncommon unless in CMML MDS

Management

Before management, consider:

- ✓ Age
- ✓ General fitness
- ✓ Severity of the condition
- ✓ Prognosis
- ✓ If the disease is stable or has progressed

Box 8.1 Treatment options in myelodysplastic syndrome

- Observation
- Supportive care
  - Red cell and/or platelet transfusions
  - Antibiotics
  - Haemopoietic growth factors
- Immunosuppressive therapy
- Low dose chemotherapy
- Intensive chemotherapy
- Transplantation
  - Autologous
  - Allogeneic
    - Mycloablative
    - Non-myeloablative

Revised International Prognostic Scoring System Risk Stratification[5]

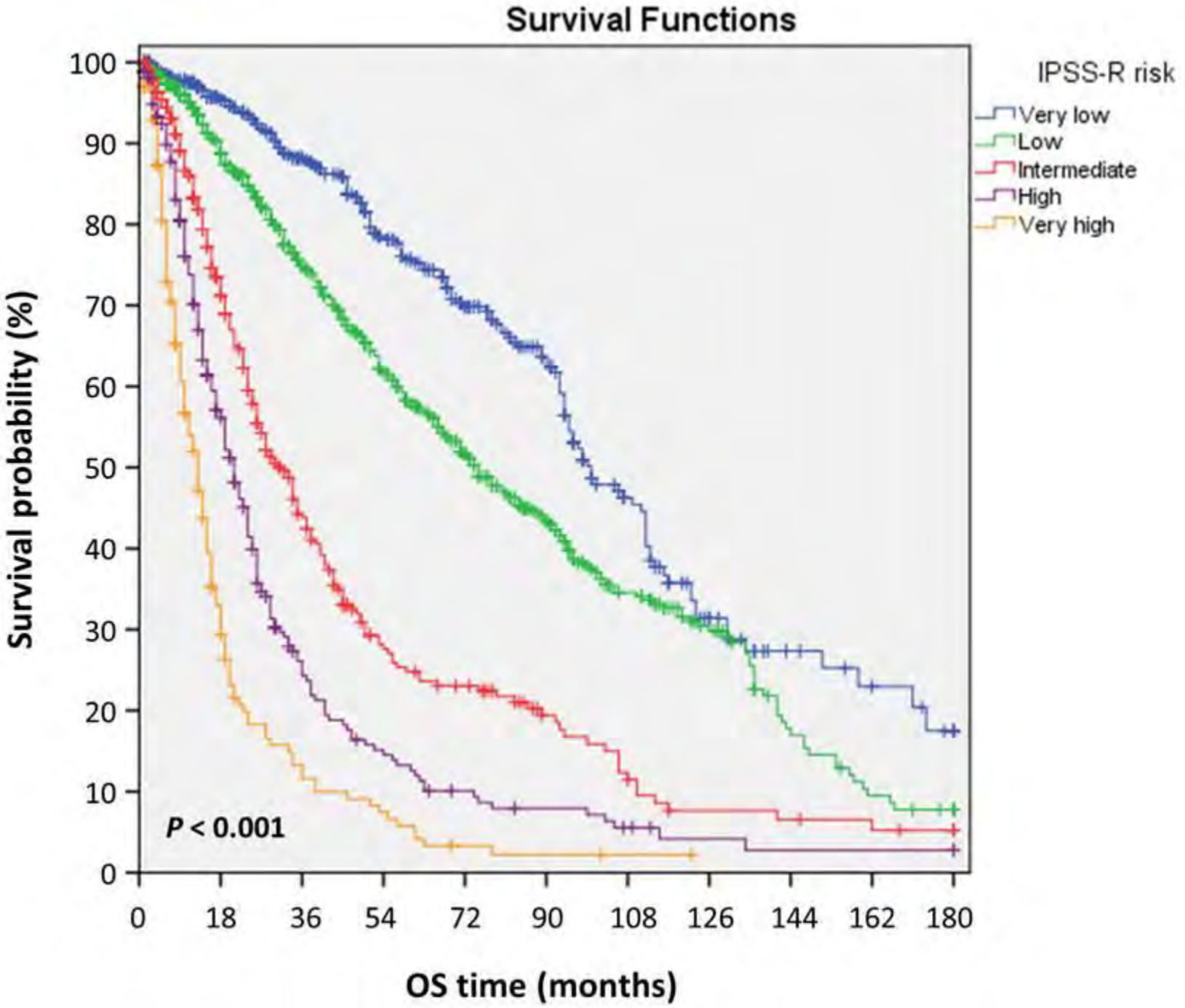
IPSS-R Prognostic Category	Score						
	0	0.5	1	1.5	2	3	4
Cytogenetics[a]	Very good		Good		Inter	Poor	Very poor
Bone marrow blasts (%)	≤2		>2-<5		5-10	>10	
Hemoglobin (g/dL)	≥10		8-<10	<8			
Platelets ($\times 10^9$/L)	≥100	50-<100	<50				
ANC ($\times 10^9$/L)	≥0.8	<0.8					

Revised International Prognostic Scoring System Stratification by Score[5]

Score	IPSS-R Risk Group
≤1.5	Very low
>1.5-3	Low
>3-4.5	Intermediate
>4.5-6	High
>6	Very high

The revised International Prognostic Scoring System (R-IPSS) Cytogenetic Scoring System:

Prognostic subgroup	Cytogenetic abnormalities
Very good	–Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	–7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex (3 abnormalities)
Very poor	Complex (> 3 abnormalities)


Survival Functions
IPSS-R risk
Very low
Low
Intermediate
High
Very high
Survival probability (%)
100
90
80
70
60
50
40
30
20
10
0
P < 0.001
0
18
36
54
72
90
108
126
144
162
180
OS time (months)

TO TREAT OR NOT?

- Only if there are symptoms resulting from anemia or other cytopenia or perhaps pre-symptomatic anemia or severe thrombocytopenia.

TO TRANSPLANT OR NOT?

- The only curative modality in the t/t of pts with MDS is allogeneic HSCT.
- Patients can reasonably safely be transplanted in the standard (myeloablative) fashion up to age 55 to 60 years.
- Recent data suggest that lower risk patients (according to the WHO or WPSS) do very well with allogeneic transplantation, whereas those with 5% to 20% marrow blasts have only a 25% to 28% 5-year overall survival.
- It is appropriate to refer young patients with MDS with a relatively poor prognosis for an allogeneic transplantation.

HEMATOPOIETIC GROWTH FACTORS?

- A several-month trial of erythropoietin is a reasonable option in anemic pts, mainly in those with low-risk disease and baseline serum erythropoietin levels less than 500 IU/ml.
- If no benefit is seen or if a response has waned, the drug s/b stopped.
- 25% of patients will respond (reduce their transfusion requirement by at least 50% or increase hemoglobin by 1 g/dL).
- Response can take 8 weeks or more.

TO CHELATE OR NOT?

- It is reasonable to use deferasirox at a starting dose of 20 mg/kg per day in chronically transfused patients who, by virtue of low IPSS scores, are expected to live for many years.

Is 5q- present?

- Approx. 5% of pts : "5q- syndrome" → middle-aged to older females with profound anemia, well-preserved platelet counts, and 5q- as a sole karyotypic abnormality in a diagnostic bone marrow specimen.

- DOC : Lenalidomide
  - Immunomodulatory thalidomide congener
  - 67% rate of transfusion independence and major increase in hemoglobin.
  - S/E : Myelosuppression , DVT/PE

Table 3. Responses to lenalidomide in 5q− and non-5q− MDS patients

	Non-5q−	5q−
Transfusion independence	26%	67%
Median hemoglobin rise	3.2 g/dL	5.4 g/dL
Median time to response	4.8 weeks	4.6 weeks
Complete cytogenetic response	10%	44%

Modified from List et al[45] and Raza et al[46] with permission.

IMMUNOSUPPRESIVE THERAPY (IST)

- Indications of IST
  - HLAD15 positive,
  - Younger,
  - Lower platelet count irrespective of marrow cellularity
  - Hypocellularity and
  - Low IPSS score

- IST options
  - ATG
  - Cyclosporine
  - Anti-CD52 monoclonal antibody : alemtuzumab

ROLE OF HYPO-METHYLATING AGENTS

- Indication : High-risk patient who is not a candidate for HSCT.
- Epigenetic modulators : believed to act through demethylating mechanism → alter gene regulation → allow differentiation to mature blood cells from the abnormal MDS stem cell.
- Azacitidine and decitabine are two epigenetic modifiers.

- Azacitidine is usually administered S/C 75 mg/m2 daily for 7 days, at 4-week intervals, for at least four cycles before assessing for response.
- Decitabine is usually administered by continuous IV infusion in regimens of varying doses and durations of 3 to 10 days in repeating cycles.
- The major toxicity of azacitidine and decitabine is myelosuppression, leading to worsened blood counts.

Vidaza è indicato per il trattamento di pazienti adulti non eleggibili al trapianto di cellule staminali emopoietiche (HSCT) con:

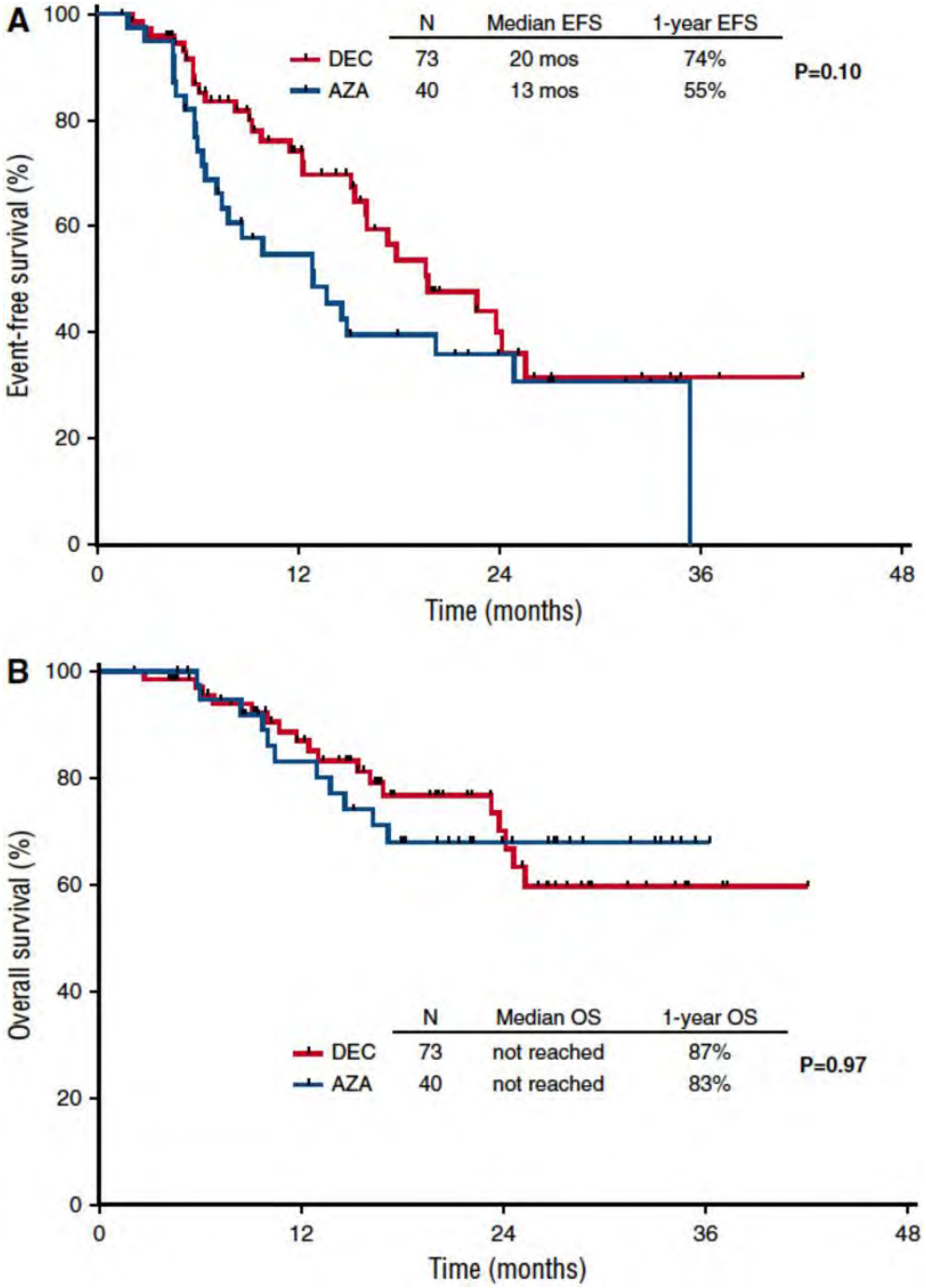
sindromi mielodisplastiche (SMD) a rischio intermedio 2 e alto secondo l'International Prognostic Scoring System (IPSS),

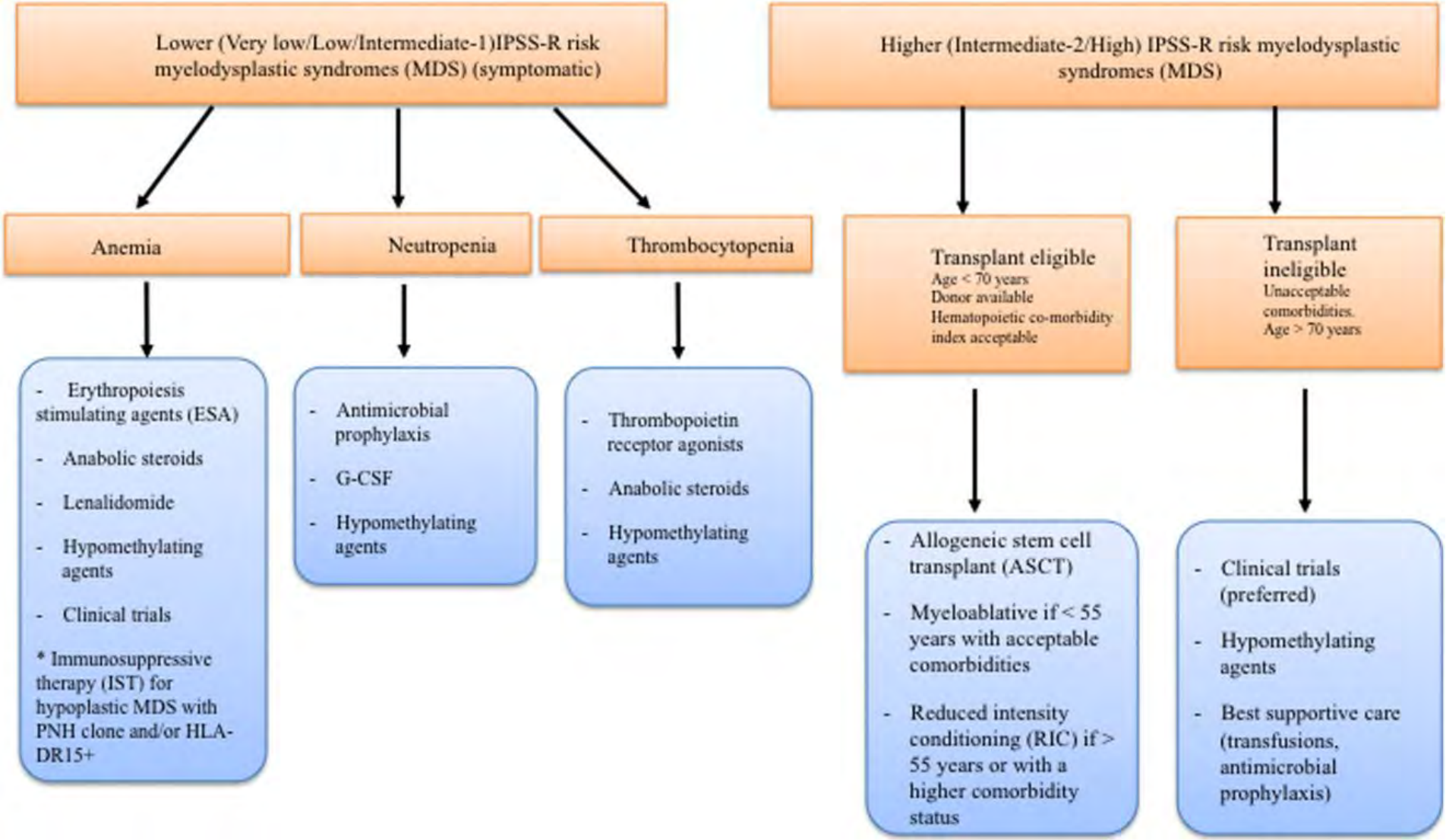
leucemia mielomonocitica cronica (LMMC) con il 10-29% di blasti midollari senza disordine mieloproliferativo,

leucemia mieloide acuta (LMA) con 20-30% di blasti e displasia multilineare, secondo la classificazione dell'Organizzazione Mondiale della Sanità (OMS),

LMA con blasti midollari > 30% secondo la classificazione dell'OMS.

Dacogen è indicato per il trattamento di pazienti adulti con nuova diagnosi di leucemia mieloide acuta (LAM) “de novo” o secondaria in base alla classificazione dell’Organizzazione Mondiale della Sanità (OMS), e che non siano candidabili alla chemioterapia di induzione standard.


A
100
80
60
40
20
0
Event-free survival (%)
0
12
24
36
48
Time (months)
N
Median EFS
1-year EFS
DEC
73
20 mos
74%
AZA
40
13 mos
55%
P=0.10
B
100
80
60
40
20
0
Overall survival (%)
0
12
24
36
48
Time (months)
N
Median OS
1-year OS
DEC
73
not reached
87%
AZA
40
not reached
83%
P=0.97


Lower (Very low/Low/Intermediate-1)IPSS-R risk myelodysplastic syndromes (MDS) (symptomatic)
Anemia
Neutropenia
Thrombocytopenia
- Erythropoiesis stimulating agents (ESA)
- Anabolic steroids
- Lenalidomide
- Hypomethylating agents
- Clinical trials
* Immunosuppressive therapy (IST) for hypoplastic MDS with PNH clone and/or HLA-DR15+
- Antimicrobial prophylaxis
- G-CSF
- Hypomethylating agents
- Thrombopoietin receptor agonists
- Anabolic steroids
- Hypomethylating agents
Higher (Intermediate-2/High) IPSS-R risk myelodysplastic syndromes (MDS)
Transplant eligible
Age < 70 years
Donor available
Hematopoietic co-morbidity index acceptable
Transplant ineligible
Unacceptable comorbidities.
Age > 70 years
- Allogeneic stem cell transplant (ASCT)
- Myeloablative if < 55 years with acceptable comorbidities
- Reduced intensity conditioning (RIC) if > 55 years or with a higher comorbidity status
- Clinical trials (preferred)
- Hypomethylating agents
- Best supportive care (transfusions, antimicrobial prophylaxis)