

Myelodysplastisk syndrom

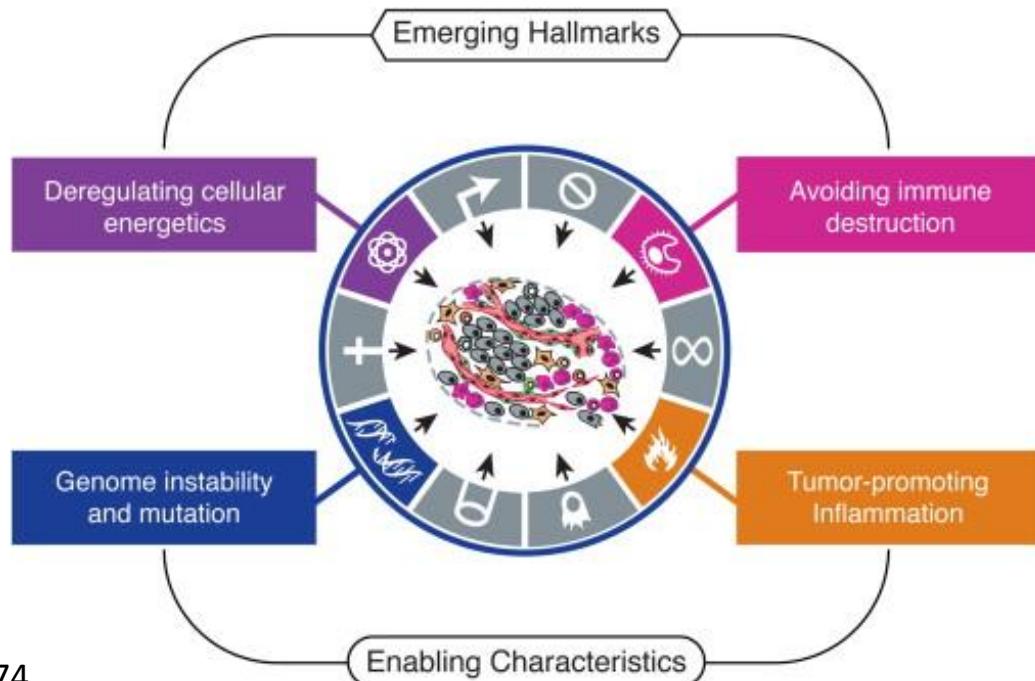
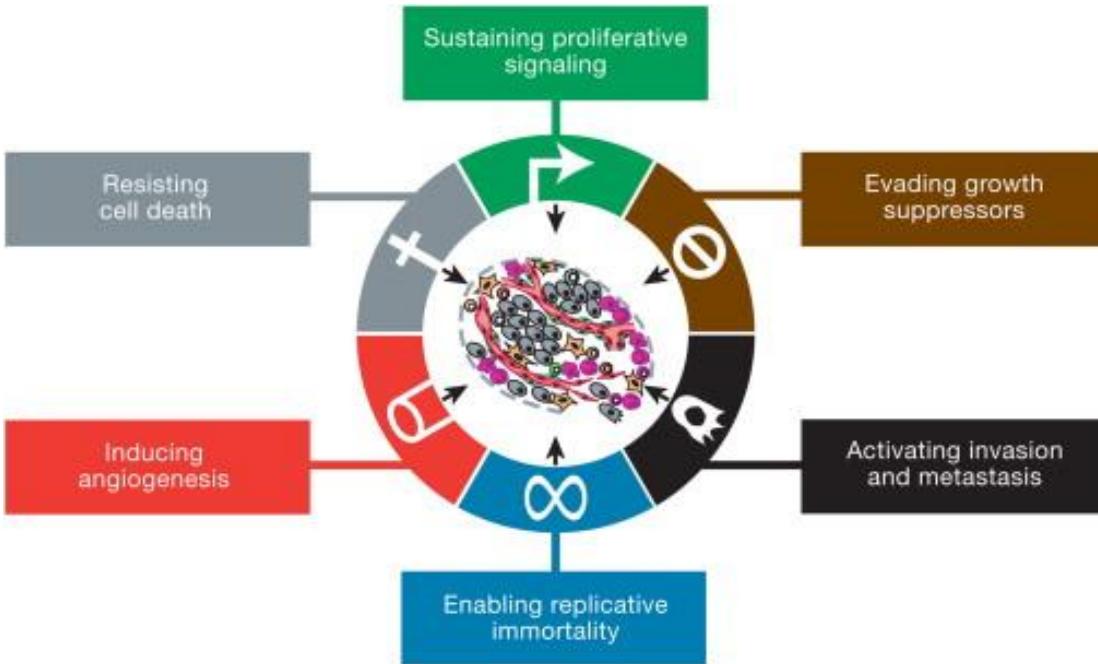
LyLe, København d. 29.09.18

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Læge, ph.d.-studerende
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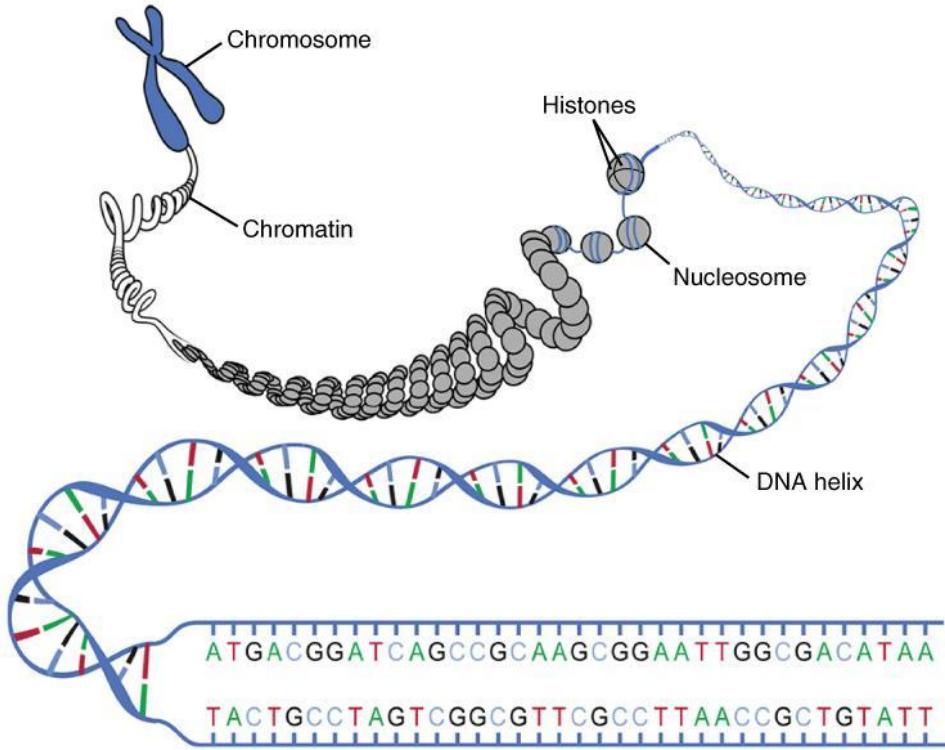
- Hvad er kræft?
- Arvematerialet
- Knoglemarven og den normale blodcelledannelse
- Myelodysplastisk syndrom (MDS)
 - Baggrund og tal
 - Årsager
 - Symptomer
 - Diagnostik
 - Inddeling/Klassifikation
 - Behandlingsprincipper



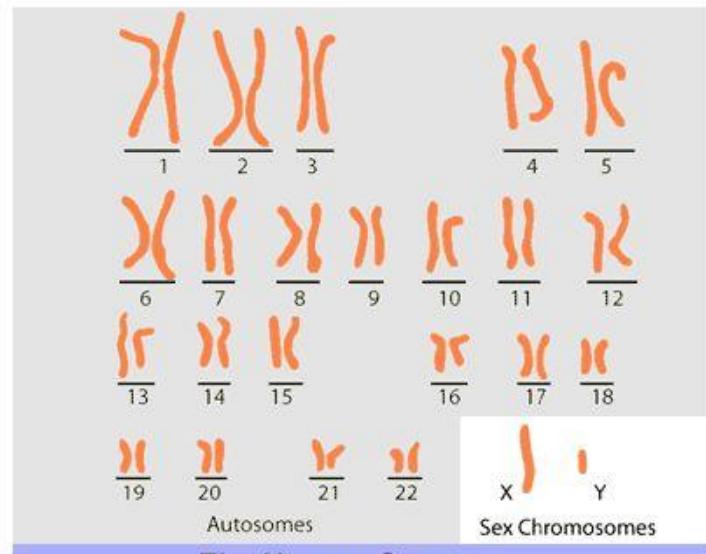
Udvikling af kræft



Arvematerialet

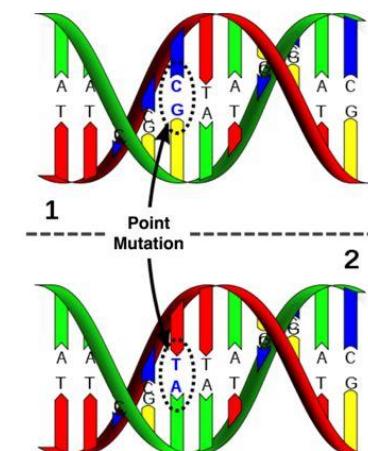


Karyotype

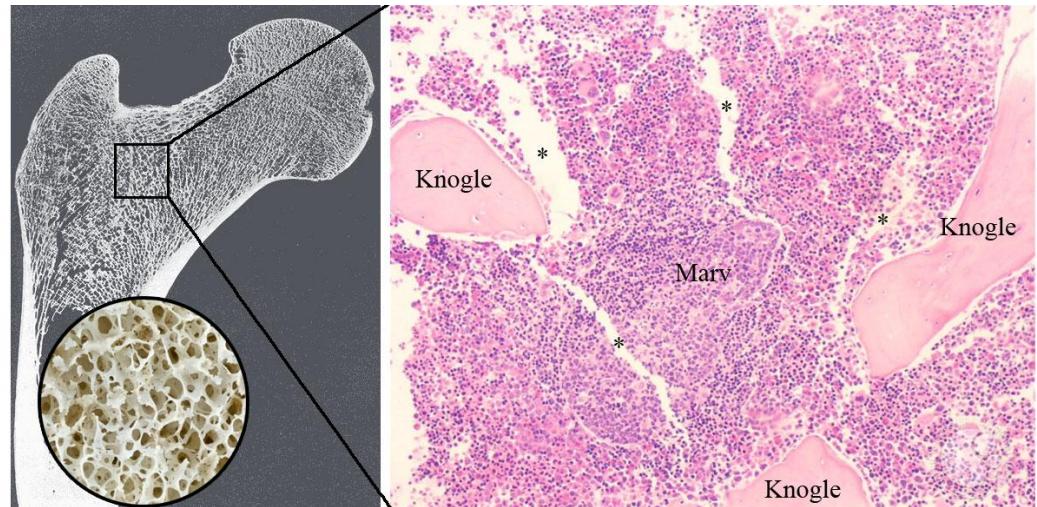
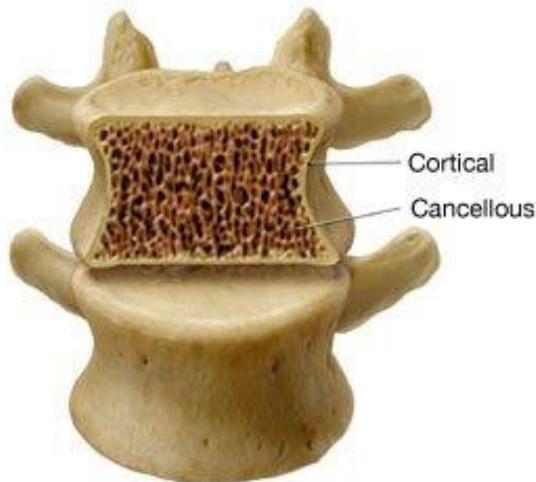


The Human Genome

The Human Genome is the total of the genetic information that is held in each human cell. It is usually made up of 46 chromosomes: 22 pairs of autosomes and 1 pair of sex chromosomes, which are usually X and X for females and X and Y for males.

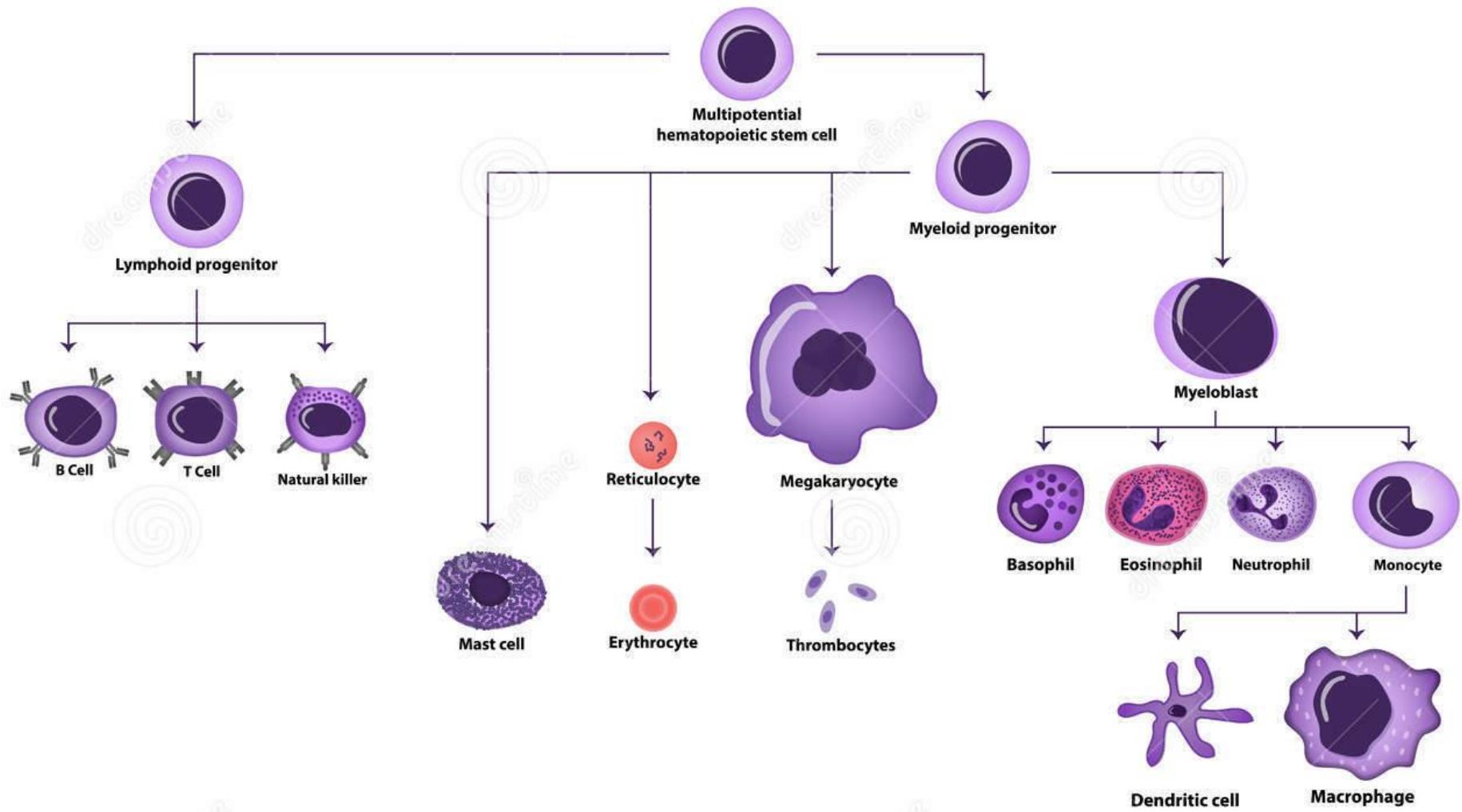


Knoglemarven



Dannelsen af blodceller

Hæmatopoiesis, græsk *haima* (blod) + *poiein* (at lave)



MDS

I tal:

- 250 nye tilfælde i Danmark om året
- Medianalder ved debut 75 år
- Hyppigst hos mænd (55-70% mænd, 30-45% kvinder)

Hvad er MDS?

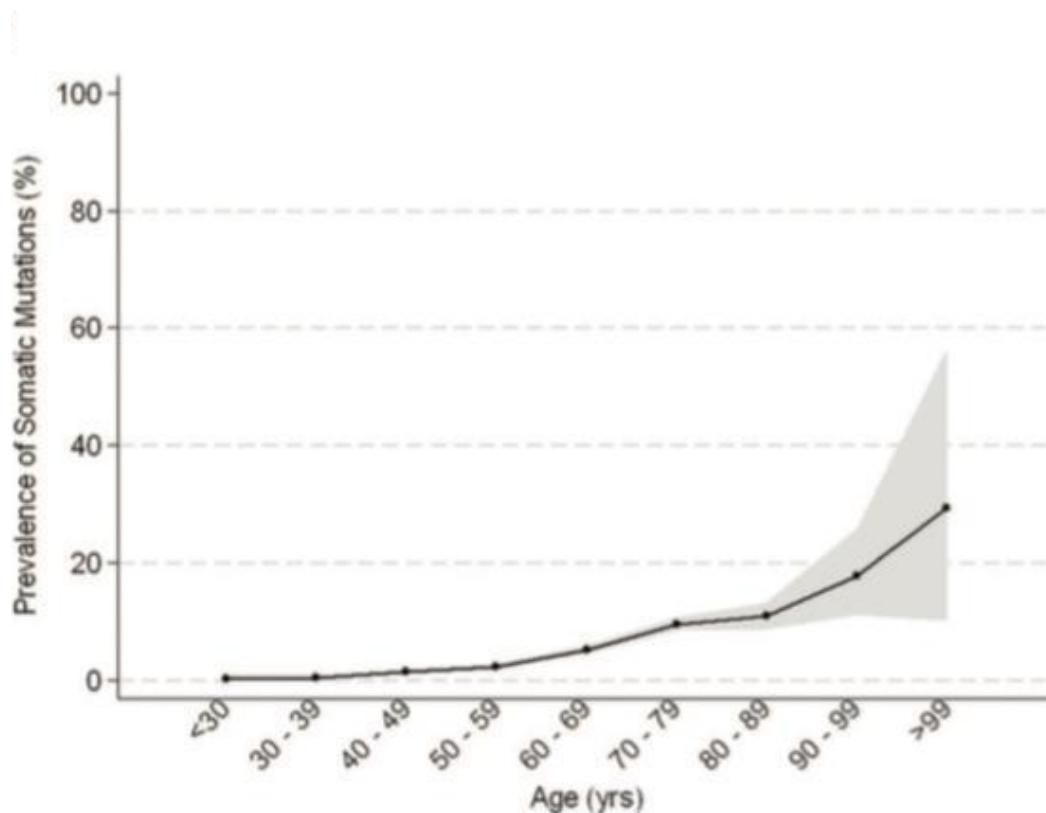
Klonal sygdom i knoglemarvens stamceller med forstyrret celledeling og celle-specialisering

Forskelligartede sygdomme, men alle kendetegnet ved:

- Ineffektiv udvikling af modne blodceller
- Tiltagende cytopeni(er) – for lave niveauer af modne celler i blodet
- Dysplasi af en eller flere linier (ændret form/udseende i mikroskopet)
- Variabelt antal blaster (men < 20%)
- Normal eller abnorm cytogenetik
- Øget risiko for videreudvikling til akut myeloid leukæmi; prognosen variabel

Hvorfor får man MDS?

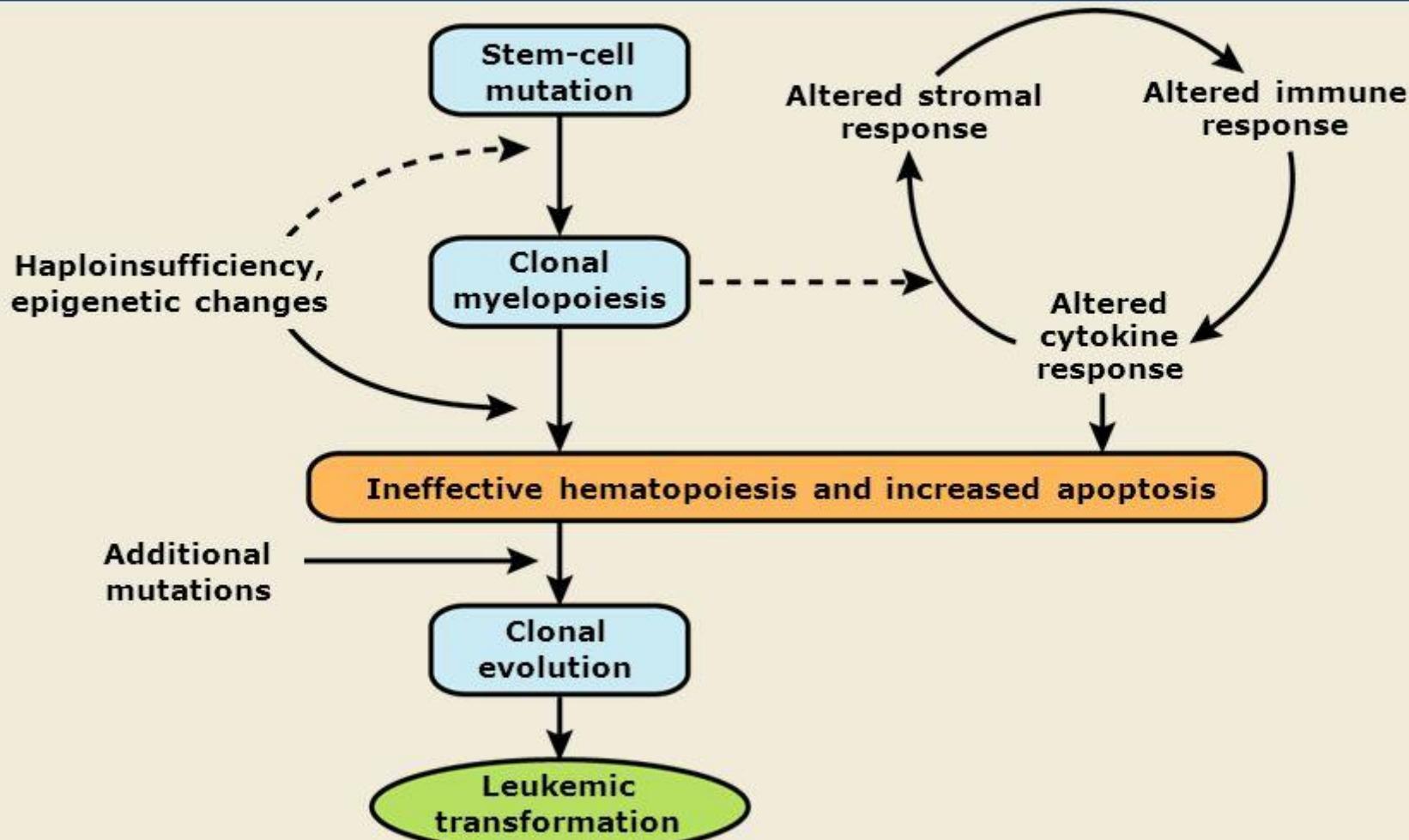
- Primær MDS (80%; ukendt årsag)
- Sekundær MDS - behandlingsrelateret MDS (strålebehandling, kemoterapi mm.)
- Familiær MDS (arvelig) – sjælden



CHIP – Clonal Hematopoiesis
of Indeterminant Potential

ICUS – Idiopathic Cytopenia
of Undetermined
Significance

Putative Pathogenic Mechanisms and Their Interaction in the Myelodysplastic Syndromes



Adapted from Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.
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Hvad er symptomerne ved MDS?

Forpustethed

Hjertebanken

Brystsmerter

Dårlig kondition

Træthed

Svimmelhed

Hovedpine



Mangel på røde blodlegemer

Hyppige og/eller langvarige infektioner



Mangel på hvide
blodlegemer

Tendens til blå mærker og røde pletter

Blodet lang tid om at størkne

Blødning fra slimhinder



Mangel på blodplader

Hvad kan man observere ved MDS?



Hvordan stilles diagnosen?

- Blodprøver + udstrygning af perifert blod
- Knoglemarvsundersøgelse
- Udelukkelse af andre årsager til lave blodcelletal og abnorme blodceller
 - Vitaminmangel (vitamin B₁₂, folinsyre) eller anden mangeltilstand (jern)
 - Inflammatoriske sygdomme
 - Anden kræftsygdom
 - Virusinfektioner (HIV, parvovirus B19)
 - Forgiftningstilstande (bly, arsenik, visse medikamenter)



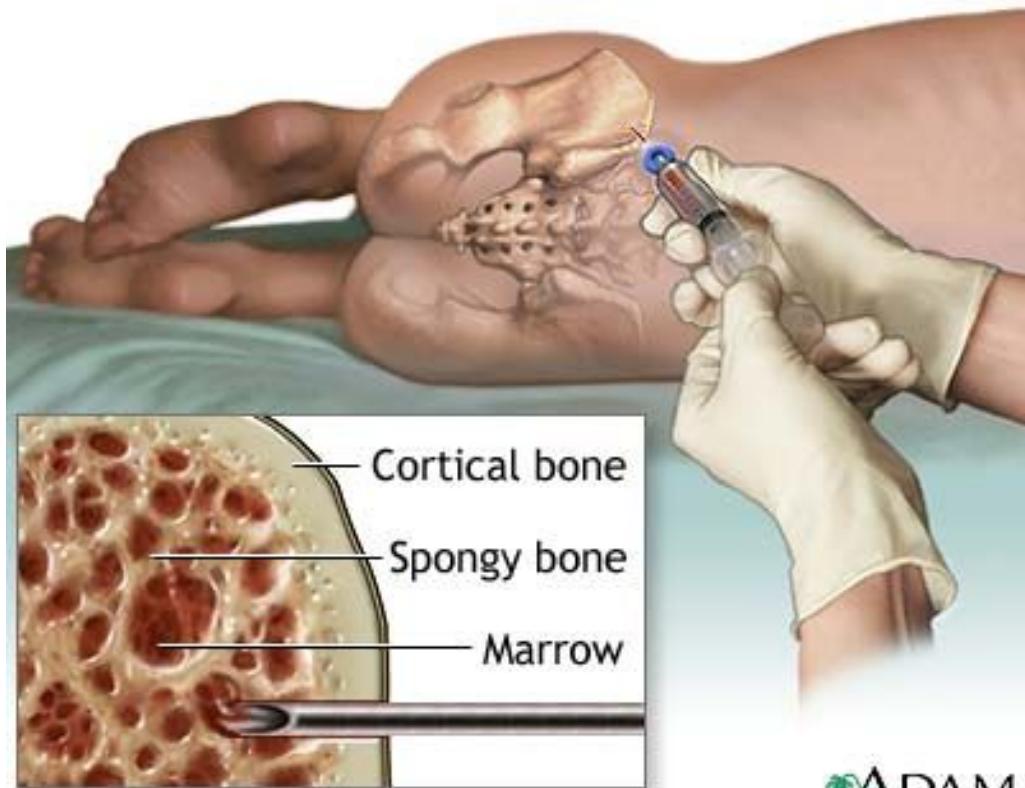
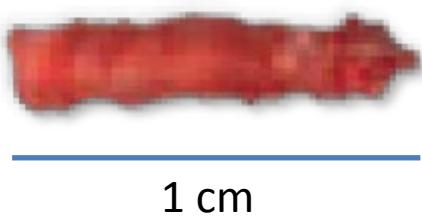
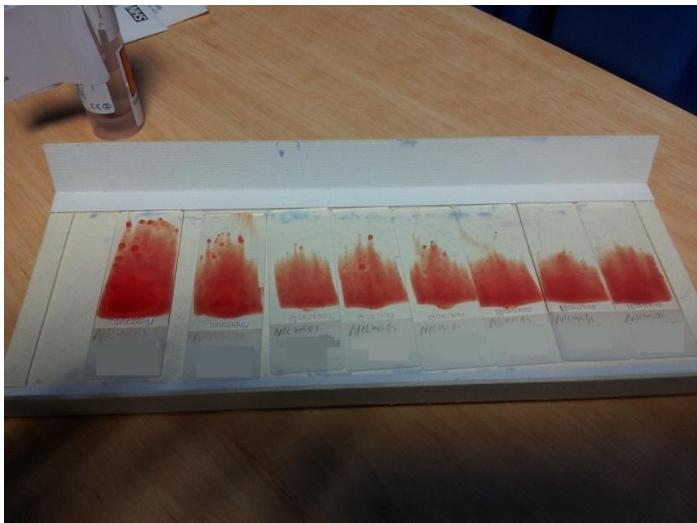
Hvordan stilles diagnosen?

Tre centrale karakteristika:

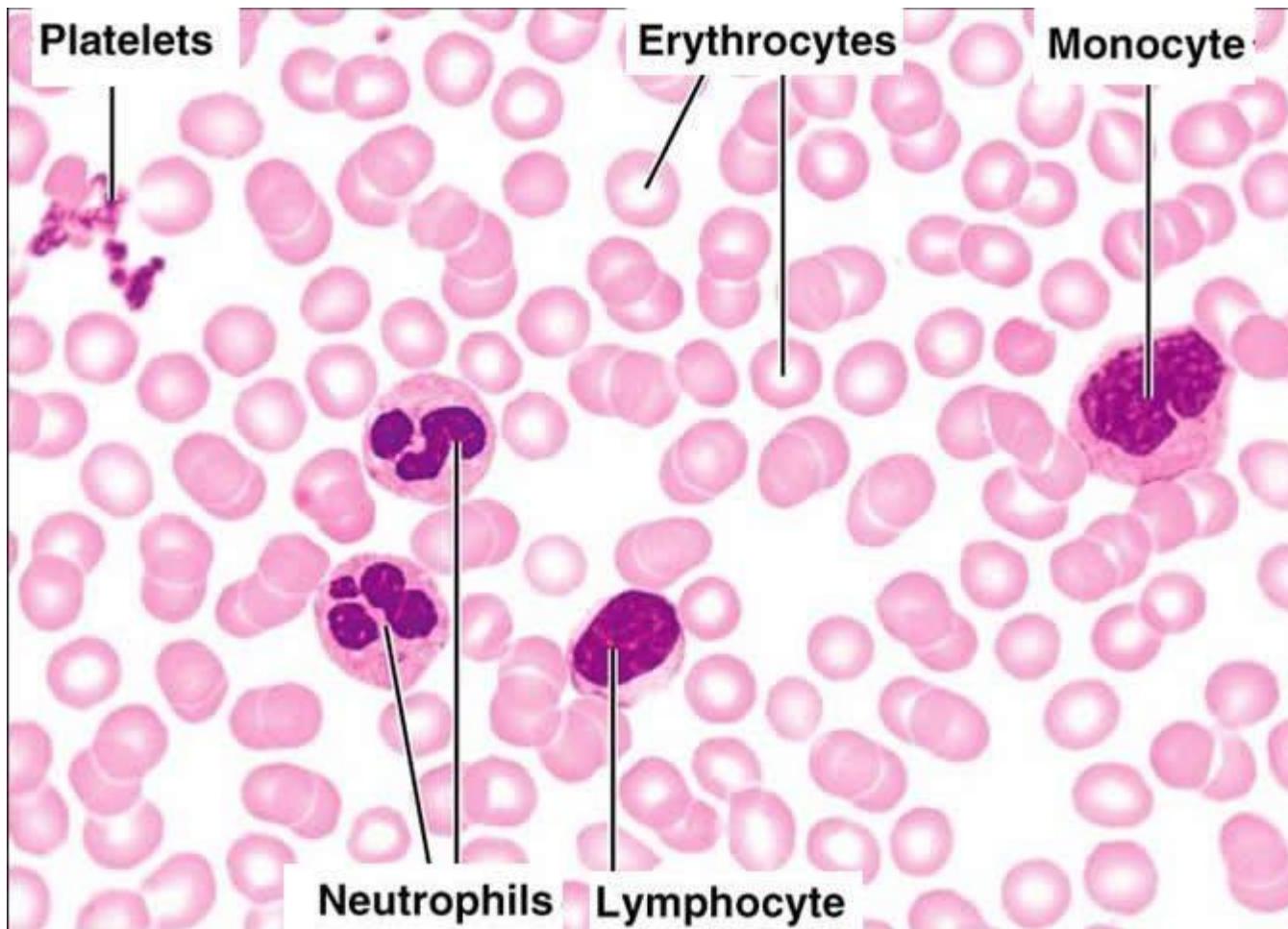
- Uforklaret cytopeni (for få blodceller) i en eller flere blodcellelinier
- Unormalt udseende af knoglemarvsceller (dysplasia; $\geq 10\%$ af forstadier til røde blodlegemer, granulocytter eller megakaryocytter) uden anden forklaring
- $< 20\%$ blaster

Knoglemarvsundersøgelse

- Knoglemarvsaspirat - udstryg og koagel
- Knogle'splint' - imprint og "snit"
- Perifert blod - udstryg
- Kromosomundersøgelse
- Markørundersøgelse

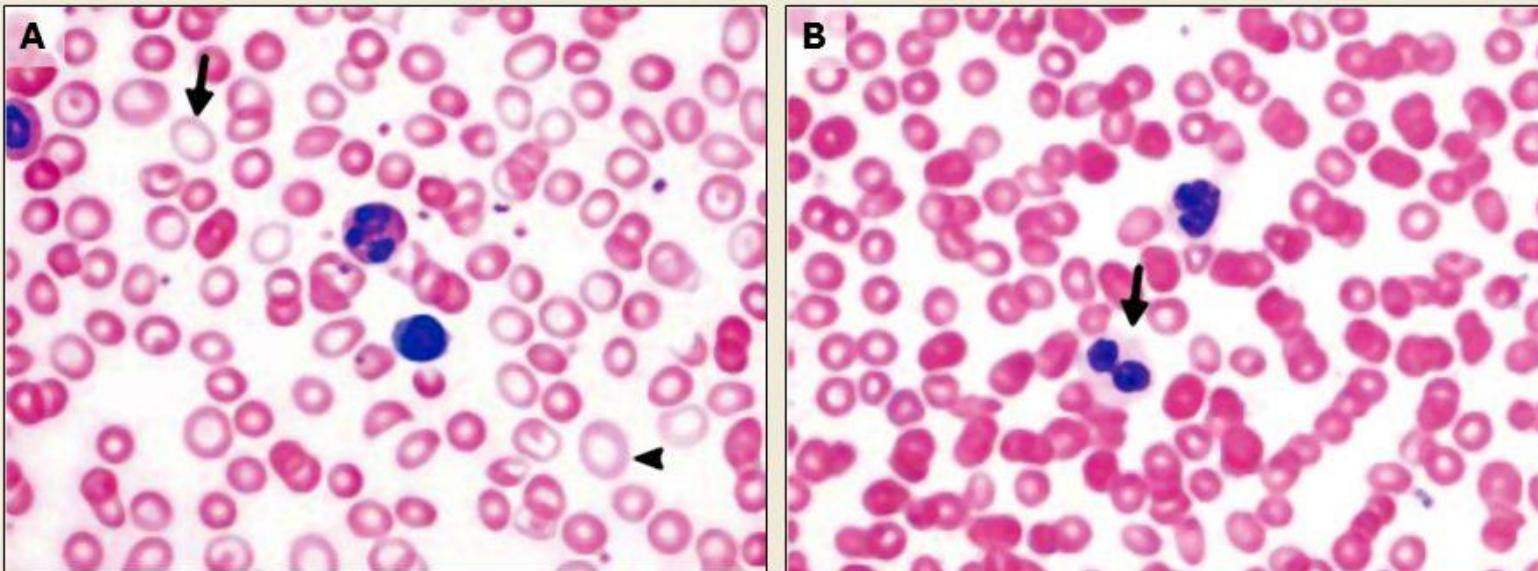


Normalt blodbillede i mikroskopet



MDS i mikroskopet

Perifert blod



Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.
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Typiske fund i perifert blod:

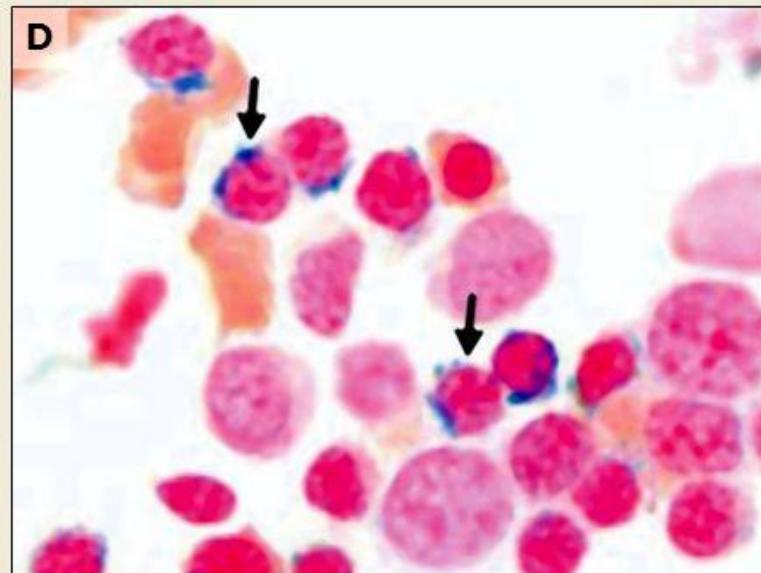
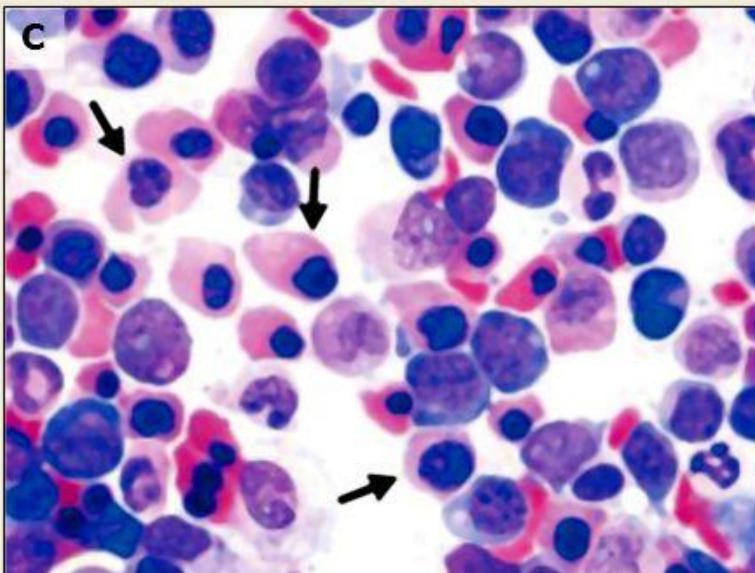
Røde blodlegemer: Varierende størrelse, store celler, abnorm form (oval, ellipsoid), to cellepopulationer, kerneholdige celler

Granulocytter: Nedsat kerne-lobulering, kerner med abnorm form (ringform), kromatinklumper, nedsat antal granula, blastceller

Blodplader (trombocytter): Mindre eller større, ændret granulering (dog oftest normale)

MDS i mikroskopet

Knoglemarv



Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.
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Typiske fund i knoglemarv:

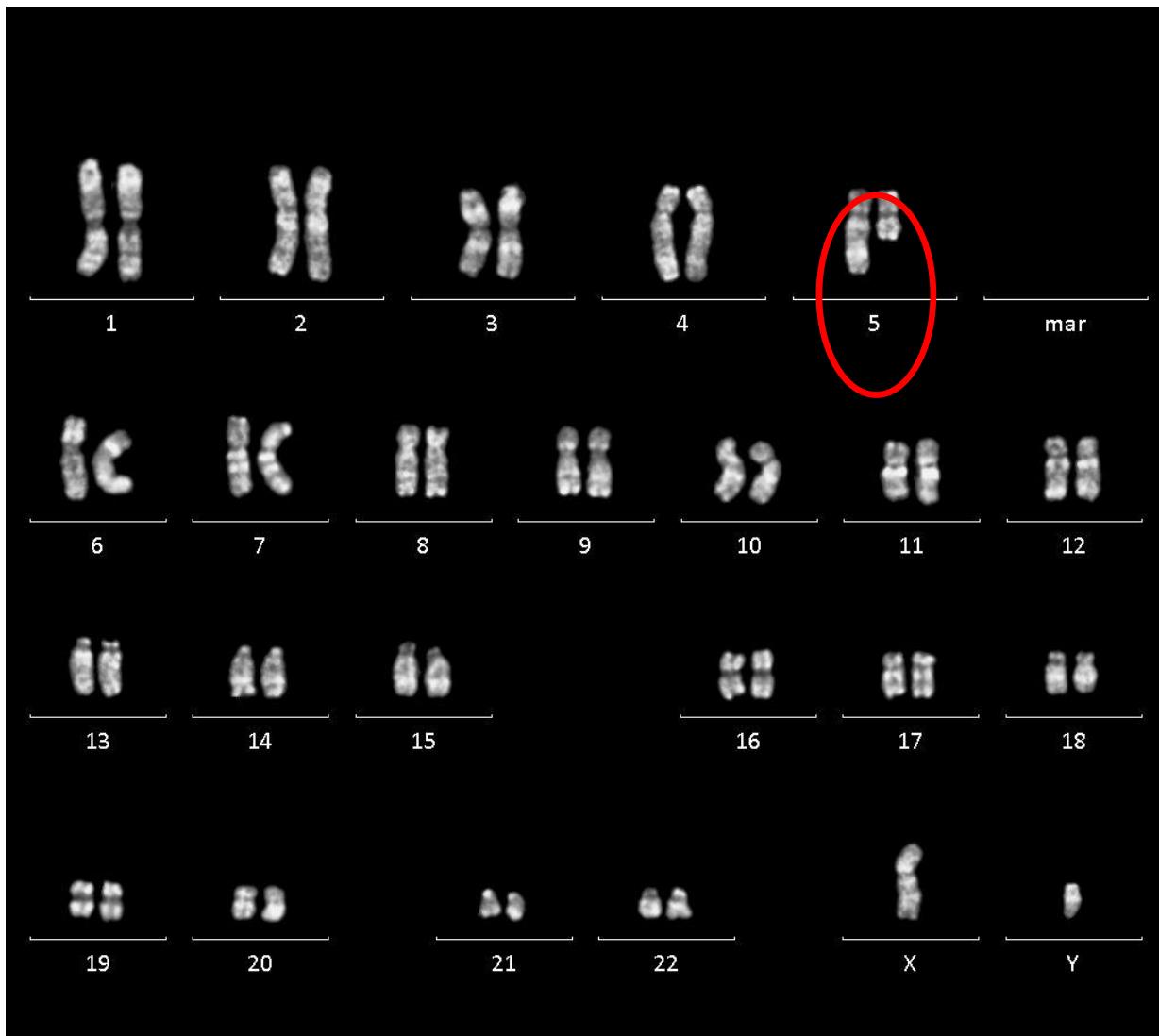
Oftest øget cellularitet, ofte mild-moderat fibrose

Erythropoiesen: Abnormt store celler, kernefragmentering, flere kerner, vakuoler, ringsideroblater (pile i figur D)

Granulopoiesen: Abnormt store celler, nedsat/øget antal granula, abnorm kerneform

Thrombopoiesen: Store megakaryocytter (MKC) med ikke-lobulerede kerner, små MKC, nedsat antal granula i MKC, forandringer af MKCs kerner

Kromosomundersøgelse



Inddeling af MDS

WHO-klassifikation 2008

Inddeling i 7 overordnede typer på baggrund af:

- Antal dysplastiske cellelinier
- Procentdel ringsideroblaste af erythroide celler i knoglemarv
- Procentdel blaster i blod og knoglemarv
- Kromosomafvigelser

WHO-klassifikation 2016

Inddeling i 6 overordnede typer på baggrund af:

- Antal dysplastiske cellelinier
- Procentdel ringsideroblaste af erythroide celler i knoglemarv
- Procentdel blaster i blod og knoglemarv
- Kromosomafvigelser
- **Antal cytopenier**

2016 WHO myelodysplastic syndrome subtypes

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/ \leq 5% [¶]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1 to 3	<15%/ \leq 5% [¶]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	\geq 15%/ \geq 5% [¶]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1 to 3	\geq 15%/ \geq 5% [¶]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1 to 3	1 to 2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0 to 3	1 to 3	None or any	BM 5 to 9% or PB 2 to 4%, no Auer rods	Any
MDS-EB-2	0 to 3	1 to 3	None or any	BM 10 to 19% or PB 5 to 19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1 to 3	1 to 3	None or any	BM <5%, PB = 1%, [△] no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1 to 3	<15% [◊]	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1 to 3	1 to 3	None	BM <5%, PB <2%	Any

BM: bone marrow; PB: peripheral blood; MDS: myelodysplastic syndrome

* Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9/L$; and absolute neutrophil count, $<1.8 \times 10^9/L$. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. Peripheral blood monocytes must be $<1 \times 10^3/L$.

¶ If SF3B1 mutation is present.

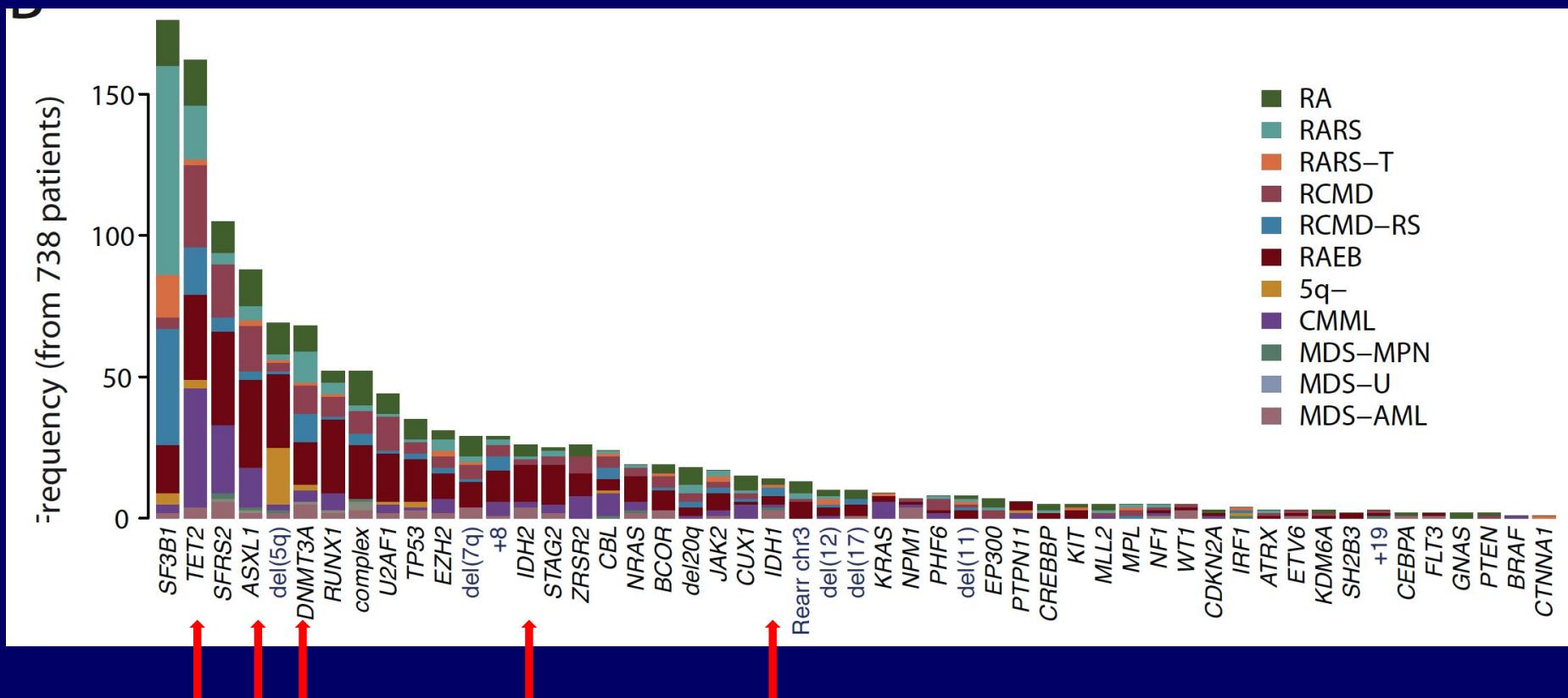
△ One percent peripheral blood blasts must be recorded on at least 2 separate occasions.

◊ Cases with $\geq 15\%$ ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

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Spektrum af mutationer

- 738 MDS-patienter, 111 gener
- > 90% har mindst én ‘driver’-mutation



Vil ny teknologi gøre det lettere at diagnosticere MDS?

- Kortlægning (sekventering) af de 20 gener, der hyppigst har genfejl (mutationer) ved erhvervet MDS
- Gen-panel:
DNMT3A, TET2, IDH1, IDH2, EZH2, ASXL1, TP53, NRAS, KRAS, CBL, JAK2, GATA2, CEBPA, RUNX1, SF3B1, U2AF1, SRSF2, ZRSR2, SETBP1, ETV6



IPSS-R

Revised international prognostic scoring system (IPSS-R) in myelodysplastic syndrome

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

Risk group	IPSS-R score
Very low	≤1.5
Low	>1.5 to 3.0
Intermediate	>3 to 4.5
High	>4.5 to 6
Very high	>6

Overlevelse

Transformation til AML

AML: acute myeloid leukemia; MDS: myelodysplastic syndrome.

* Cytogenetic definitions:

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, double not including del(5q) or -7/del(7q), or independent clones.

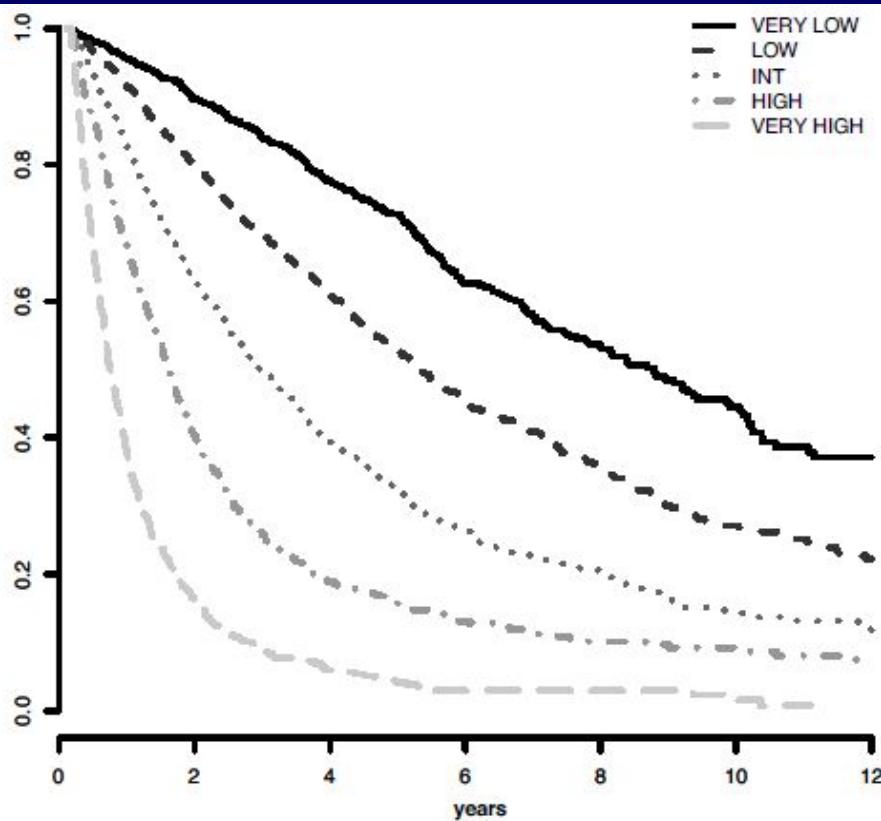
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.

Very poor: Complex: >3 abnormalities.

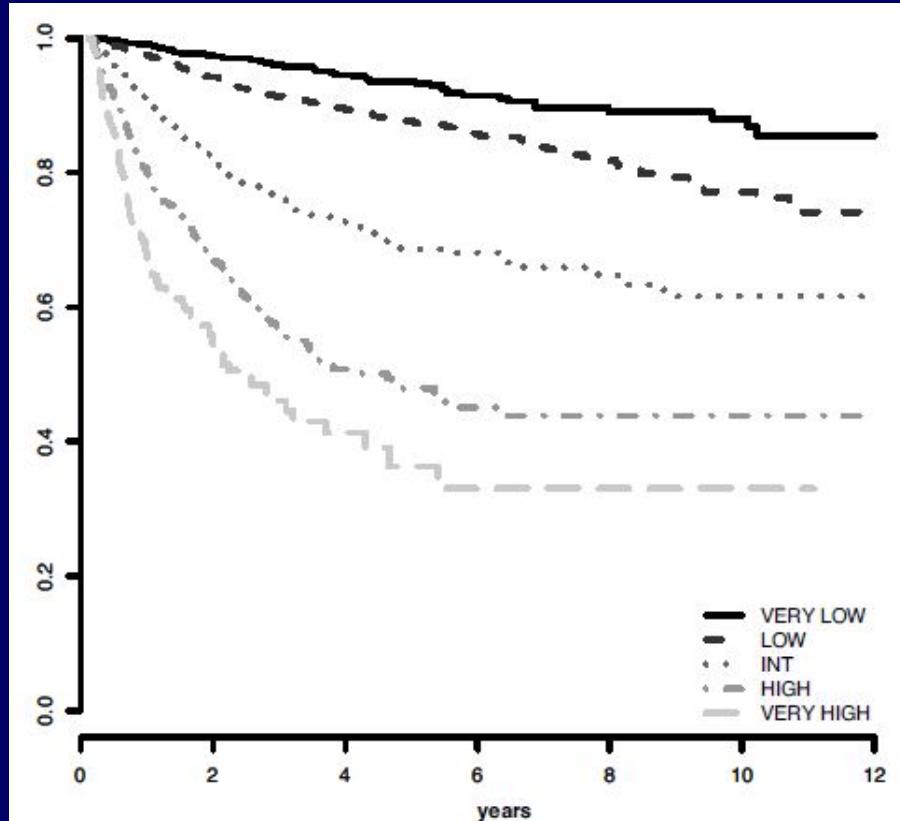
This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012. Copyright © 2012 the American Society of Hematology.

IPSS-R

Overall survival

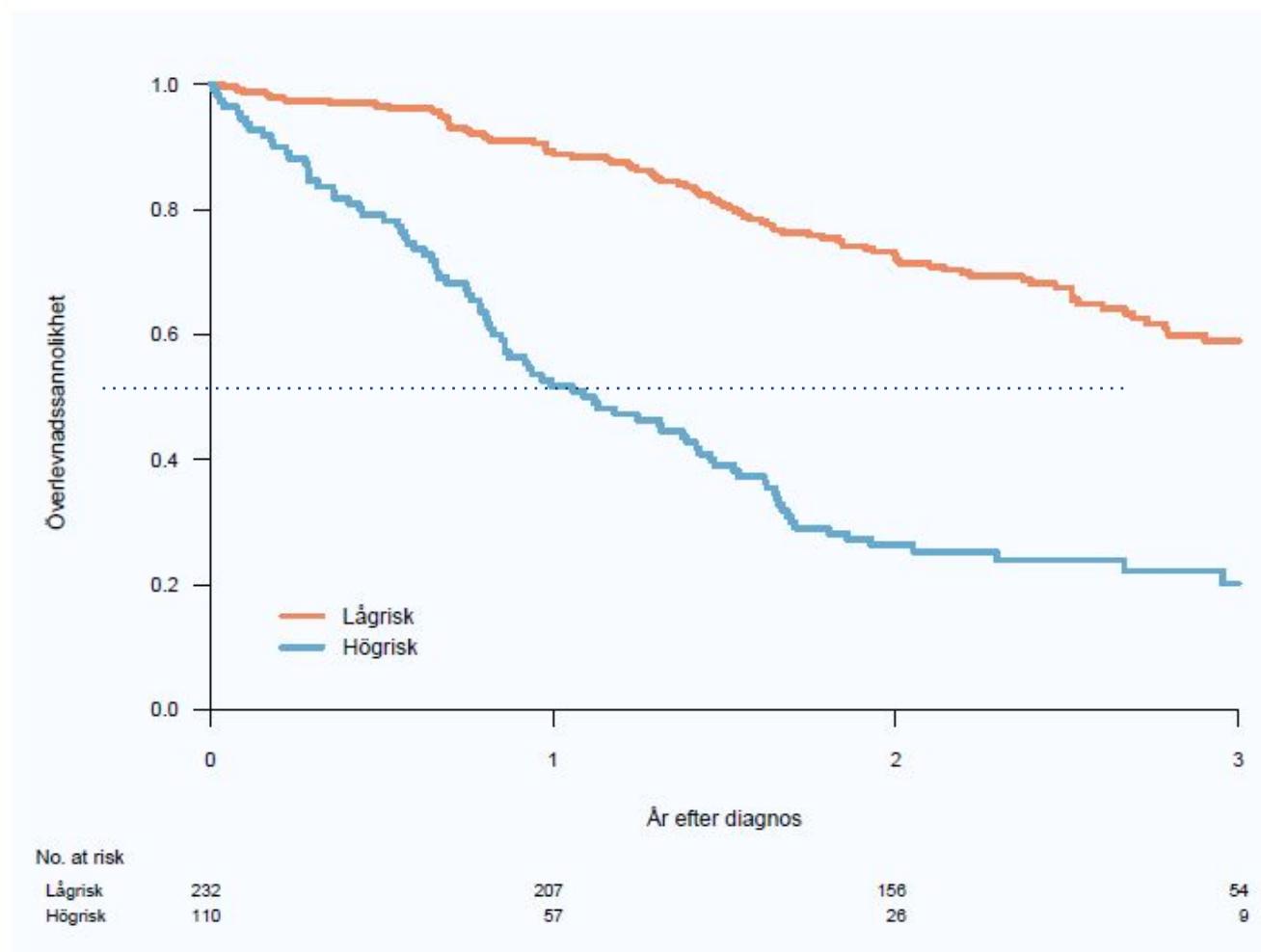


AML evolution 25% of the population



- Lav-risiko MDS
 - IPSS Low-risk
 - IPSS Intermediate-1
- Høj-risiko MDS
 - IPSS Intermediate-2
 - IPSS High-risk

Swedish INCA; Low-risk + Int-1 vs. Int-2 + High-risk



Figur 11. Total överlevnad uppdelat på Lågrisk-MDS och Högrisk-MDS för MDS enbart, diagnosår 2009-2010.

Målet med MDS-behandling

- Helbredelse
 - Risikogruppe
 - Alder
 - Andre sygdomme
 - Findes der en donor
- Forlænge livet
- Forbedre blodværdierne/mindske symptomer (røde og hvide blodlegemer, blodplader)
- Forbedre livskvalitet
- Lindrende behandling

Forskellige niveauer af behandling

- "Watch and wait" + vaccinationer, rygeophør
- **Understøttende behandling** antibiotika, transfusioner med blodprodukter
- **Lav-intensitetsbehandling** hæmatopoietiske vækstfaktorer, epigenetisk behandling, immundæmpende behandling, lenalidomid
- **Høj-intensitetsbehandling** intensiv kombinations-kemoterapi, knoglemarvstransplantation

Behandlingsrespons

Stringente kriterier bruges primært i kliniske forskningsprojekter

- Hæmatologisk respons **forlænget levetid?**
- Knoglemarvsrespons **forlænget levetid ved komplet remission**
- Cytogenetisk response
- Stabil sygdom
- Sygdomsprogression (stigende knoglemarvs blastprocent eller tiltagende cytopeni)



Strange new trend at the office. People putting names on food in the company fridge. Today I had a tuna sandwich named Kevin.



Tak for jeres tid!

Nyd frokosten, vi ses bagefter.

Høj-risiko MDS

Høj (> 4,5-6) eller meget høj (> 6) risiko IPSS-R-score

Transplantation – hvornår?

Overlevelse (år)

	Umiddelbart transplanteret	Transplanteret efter 2 år	Transplanteret ved progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

From Cutler C, et al. A Decision Analysis of Allogeneic Bone Marrow Transplantation for Myelodysplastic Syndromes: Delayed Transplantation for Low Risk Myelodysplasia is Associated with Improved Outcome. *Blood* 2004.

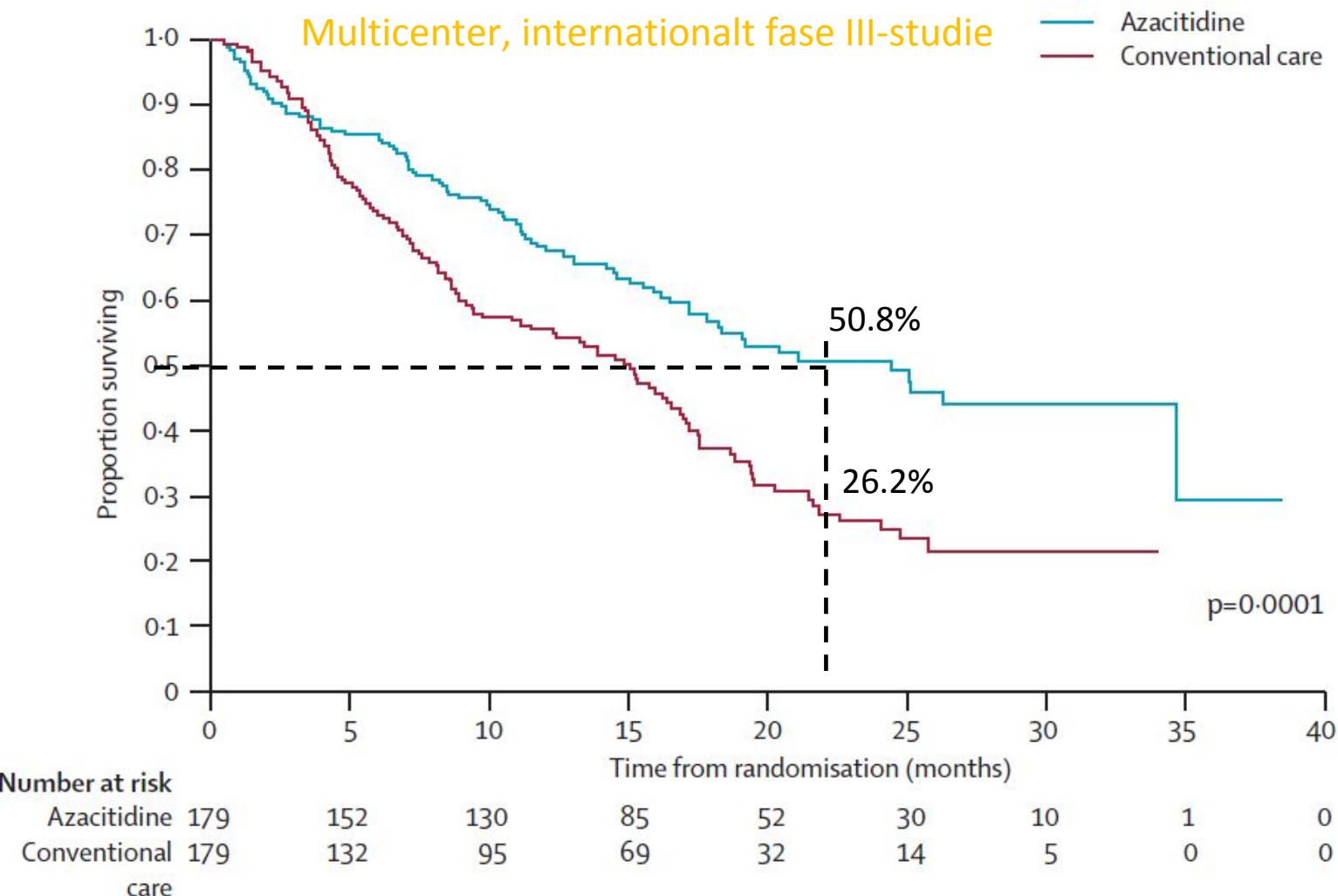
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Azacitidin (Vidaza®)

- Hypometylerende medikament
- **Potentielle effekter:** Forbedret overlevelse, hæmatologisk respons, forbedret livskvalitet
- **Bivirkninger:** Marv suppression, feber, kvalme, reaktioner på indstikssted
- Dosering: subkutan injektion 100 mg/m^2 dgl. i 5 dage / 28 dage

Azacitidine (Vidaza®)

Høj-risiko MDS



Lav-risiko MDS

Meget lav ($\leq 1,5$), lav ($> 1,5-3$) eller intermediær ($> 3-4,5$) risiko IPSS-R-score

Vækstfaktorer – Erythropoiesis stimulating agent, e.g. erythropoietin (EPO)

- WHO 2008 subtyper: RA, RARS, RAEB-1
- Lav serum-erythropoietin (≤ 500 mU/ml)
- Start med EPO alene, tilføj granulocyte-colony stimulating factor (G-CSF) efter 8 uger ved manglende respons
- Overvej immundæmpende behandling – antithymocyt-globulin (ATG) +/- ciclosporin (Sandimmun®) hos yngre patienter (< 60 år, hypoplastisk knoglemarv, HLA-DR15-positive)

EPO: f.eks. Darbepoetin 300 µg/uge hver 2. uge

G-CSF: Dosis tilpasset neutrofilocytallet – f.eks. Zarzio 60 mio. IE hver 2. uge

Immunsuppression i lav-risiko MDS

- Aktiv RA/RCMD
- Kort transfusionsafhængighed
- < 70 år
- HLA-DR15
- Hypoplastisk knoglemarv

Jernkelerende behandling

- Hvilke patienter?
 - Lav-risiko MDS RA, RARS, del(5q) (RCMD, mere fremskreden MDS)
 - Lang forventet levetid
 - Vedvarende transfusionsbehandling
 - Kandidater til knoglemarvstransplantation - forebyggende
- Serum-jernniveau, der indikerer behandling
 - Ved $\sim >25$ blodtransfusioner eller serum-ferritin 1500-2000 g/l

Gattermann *et al*, *Hem / Oncol Clinics (Suppl)*, 2005

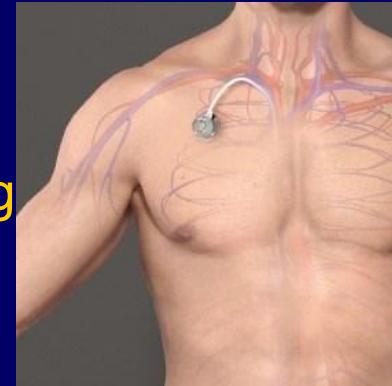
Bennett *et al*, *Am J Hematol*, 2008

Wells *et al*, *Leuk Res*, 2008

Nordic Guidelines 2008 (www.nordicmds.org)

Jernkelerende midler

- Deferoxamin (Desferal®), subkutan/iv infusion
 - Subkutan infusion over 8-12 timer 5-7 dage om ugen, alternativt intravenøst via Port-a-Cath (PAC) over 4-5 dag
- Deferipron (Ferriprox®), oral
 - 3 x dagligt peroralt
 - Neutropeni 1-2%
- Deferasirox (Exjade®), oral
 - 1 x dagligt peroralt doseret efter vægt
 - Maveproblemer
 - Må ikke anvendes ved nedsat nyrefunktion (regelmæssig måling af lever- og nyretal)



Retrospektive studier viser længere overlevelse i lav-risiko MDS-patienter; dog ingen studier af langtidseffekten

Lenalidomid (Revlimid®)

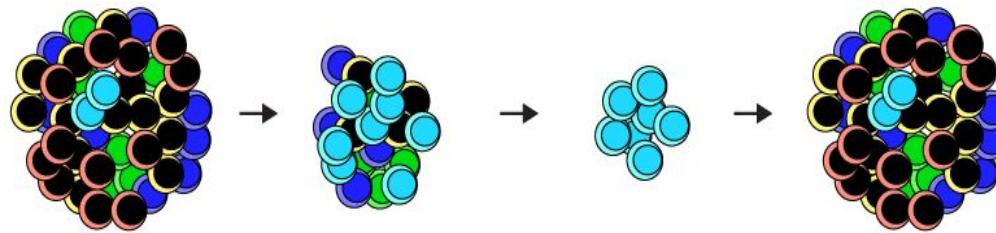
- Immunmodulerende medikament (IMiD)
- Ældre med IPSS low- and Int-1 risk med **5q-** med transfusionsafhængig anæmi, når EPO (+/- G-CSF) ikke har effekt
- **Potentielle effekter:** Stigning i hæmoglobin, stigning i antallet af blodplader og neutrofilocytter (mindre hyppigt), genoprettelse af normal karyotype, genoprettelse af normal megakaryocytmorphologi
- **Bivirkninger:** Marv suppression, evt. øget risiko for transformation til AML
- Dosering: kapsel 10 mg x 1 dgl. i 21 dage / 28 dage (evt. 5 mg x 1 dgl.)
- Til start skal blodprøver tjekkes ugentligt

Fremtidig behandling

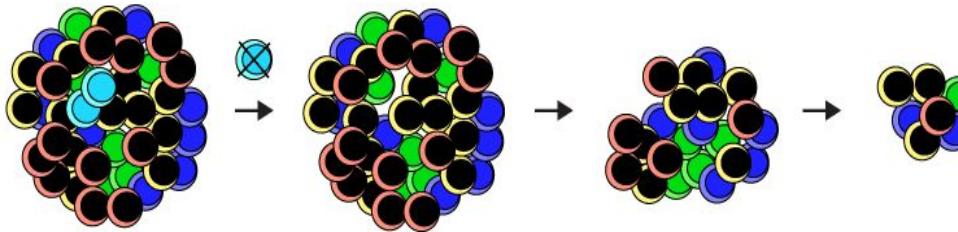
- Navlesnors-stamcelletransplantation
- Haploidentisk transplantation
- Nye hypometylerende lægemidler
- Immun-checkpoint-inhibitor i kombination med hypometylerende lægemidler
- Behandling rettet mod cancer-stamceller?
- Skræddersyet behandling

Behandling rettet mod cancer-stamceller?

a) Conventional therapy



b) CSC-specific treatment



Skræddersyet behandling tilpasset den enkelte patient?

