Myelodysplastisk syndrom

Klinik og behandling

LyLe, Svendborg d. 30.09.17

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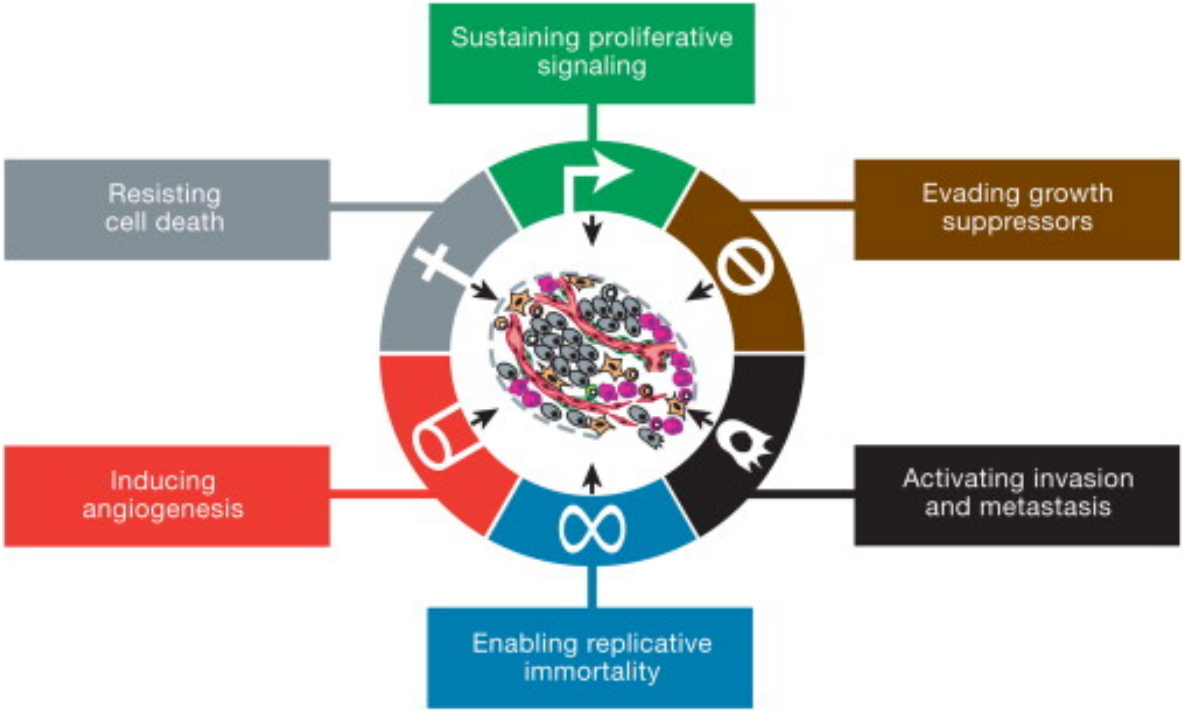
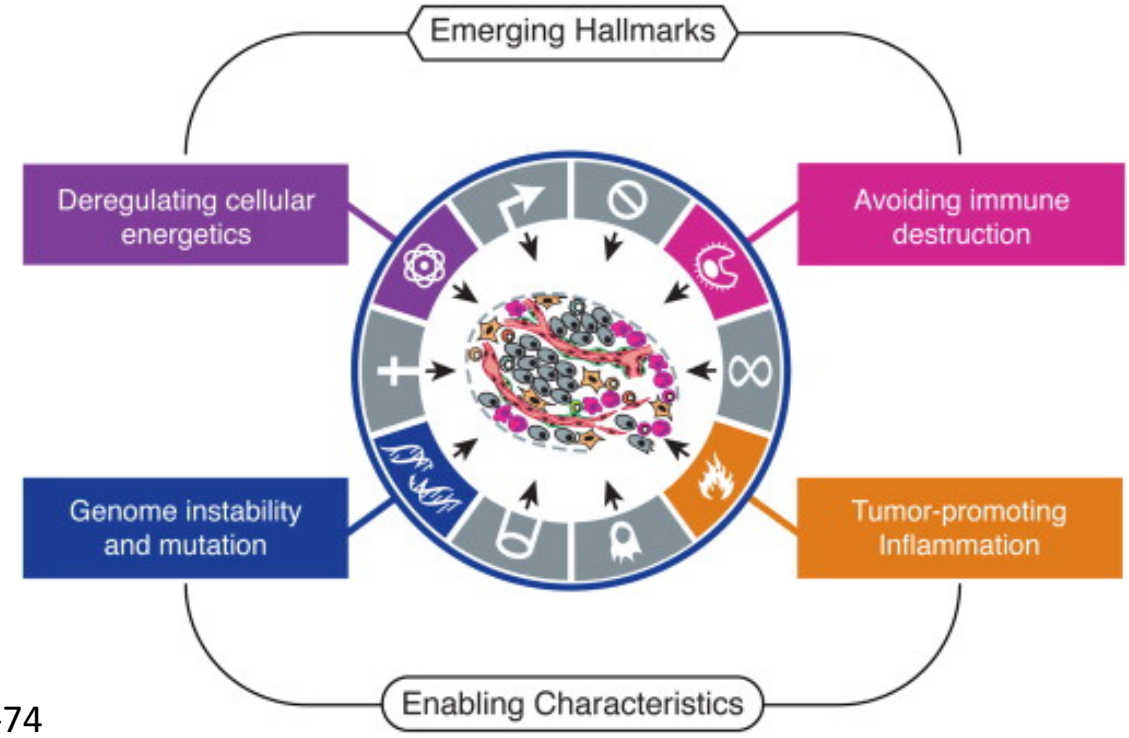
Hæmatologisk Klinik
Rigshospitalet

- Hvad er kræft?
- Arvematerialet
- Knoglemarven og den normale blodcelledannelse
- Myelodysplastisk syndrom (MDS)
  - Baggrund og tal
  - Årsager
  - Symptomer
  - Diagnostik
  - Inddeling/Klassifikation
  - Behandling
  - Prognose
  - Fremtidig behandling

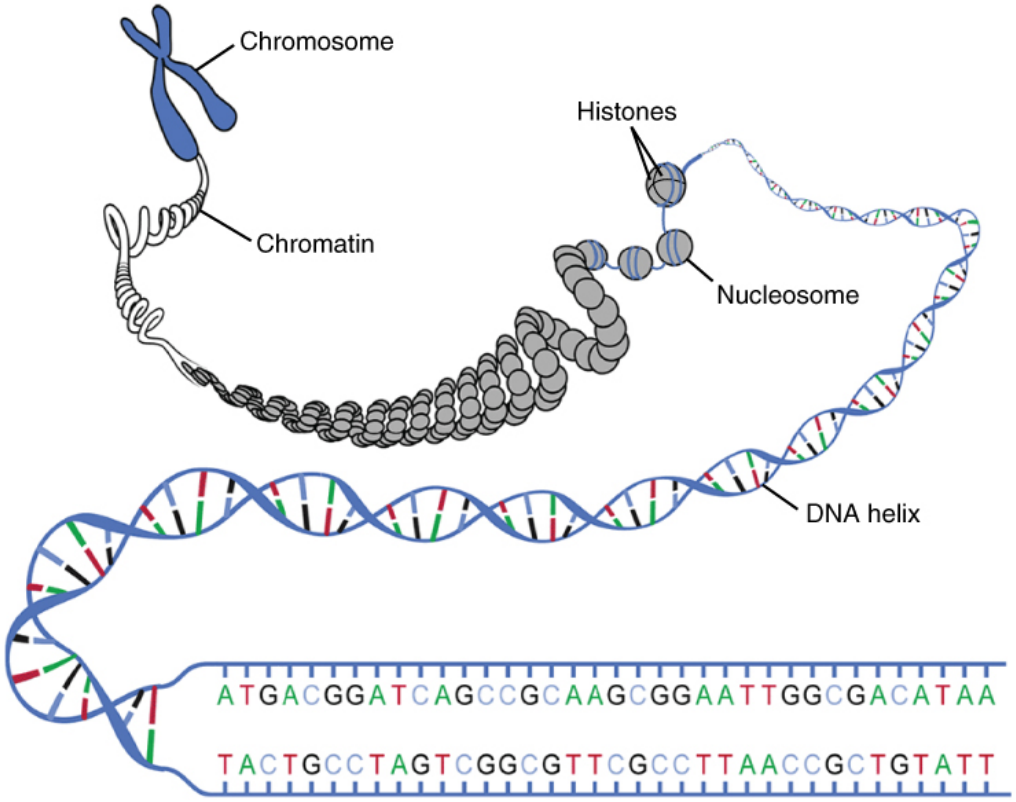
Udvikling af kræft

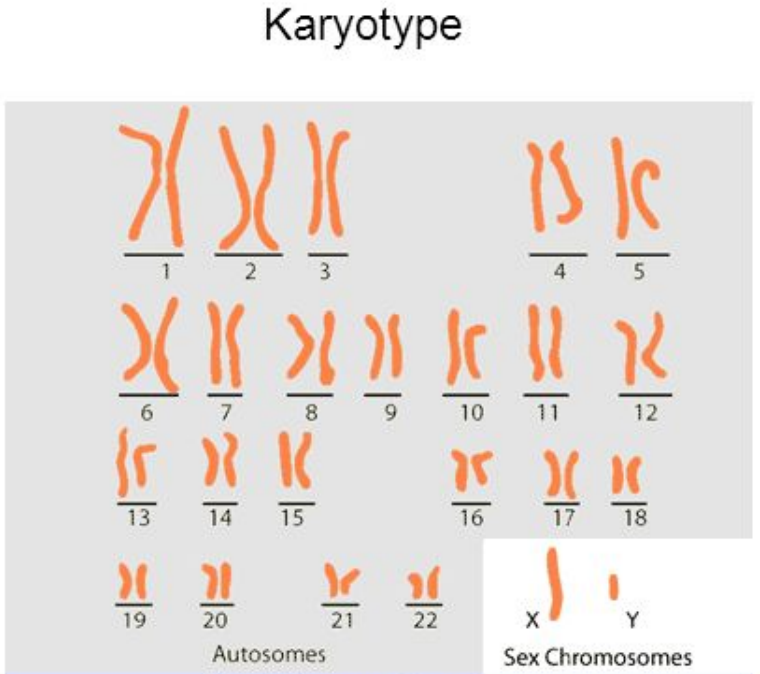


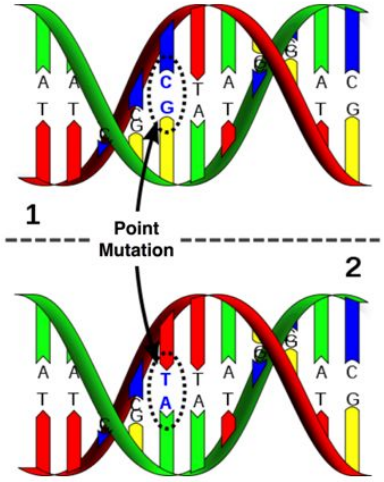


Hanahan D, Weinberg RA. *Cell*. 2011 Mar 144(5):646-74

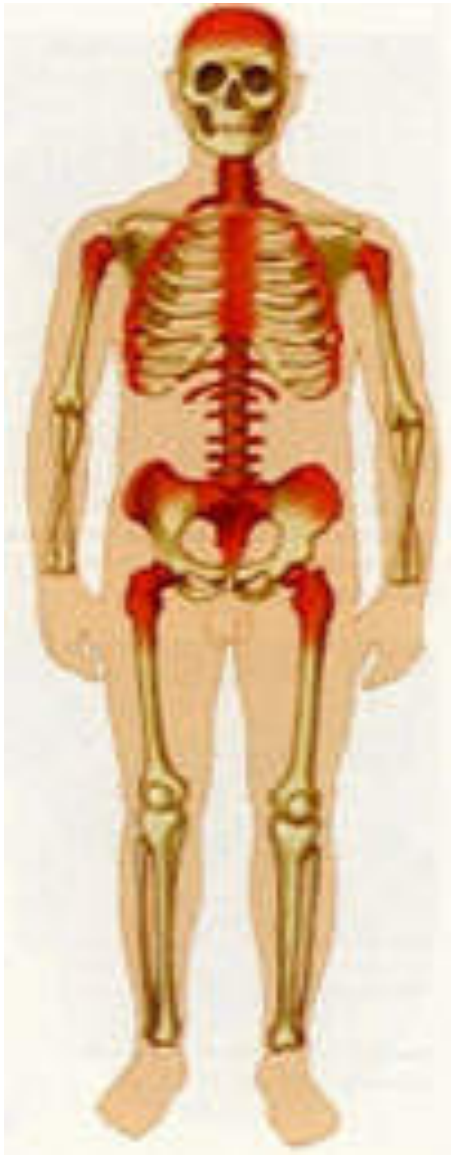
Arvematerialet

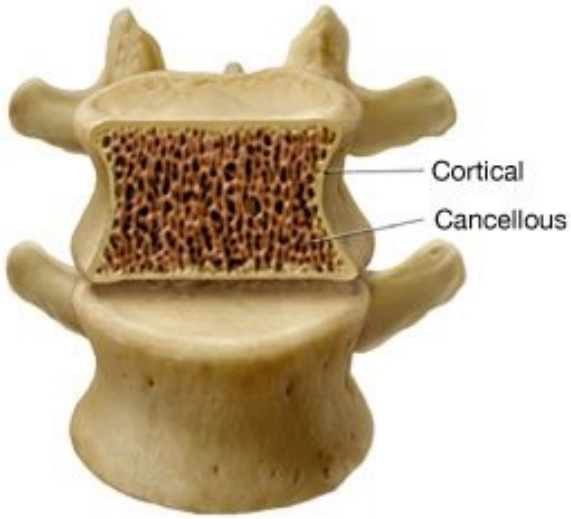


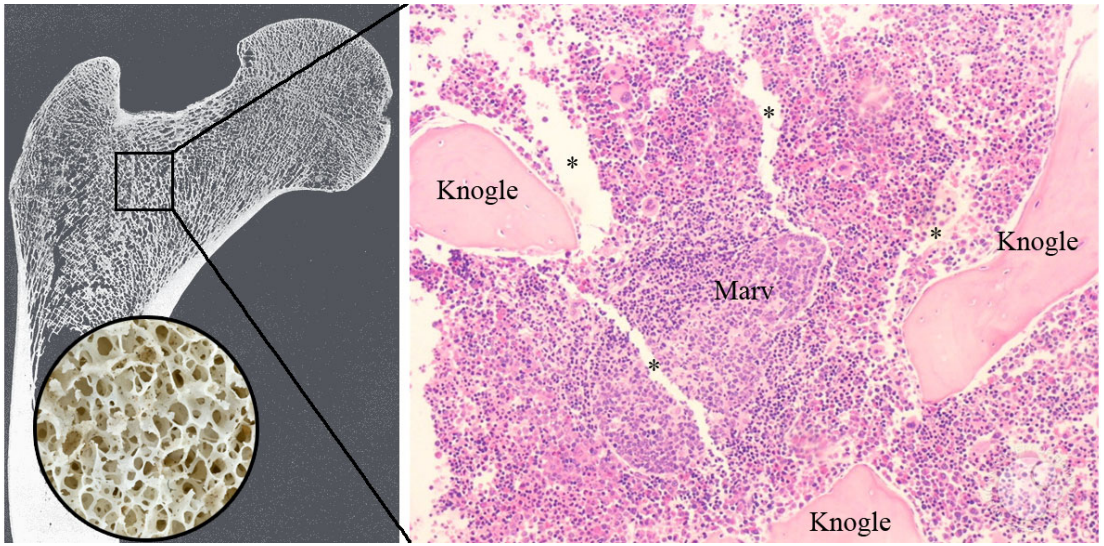




Knoglemarven

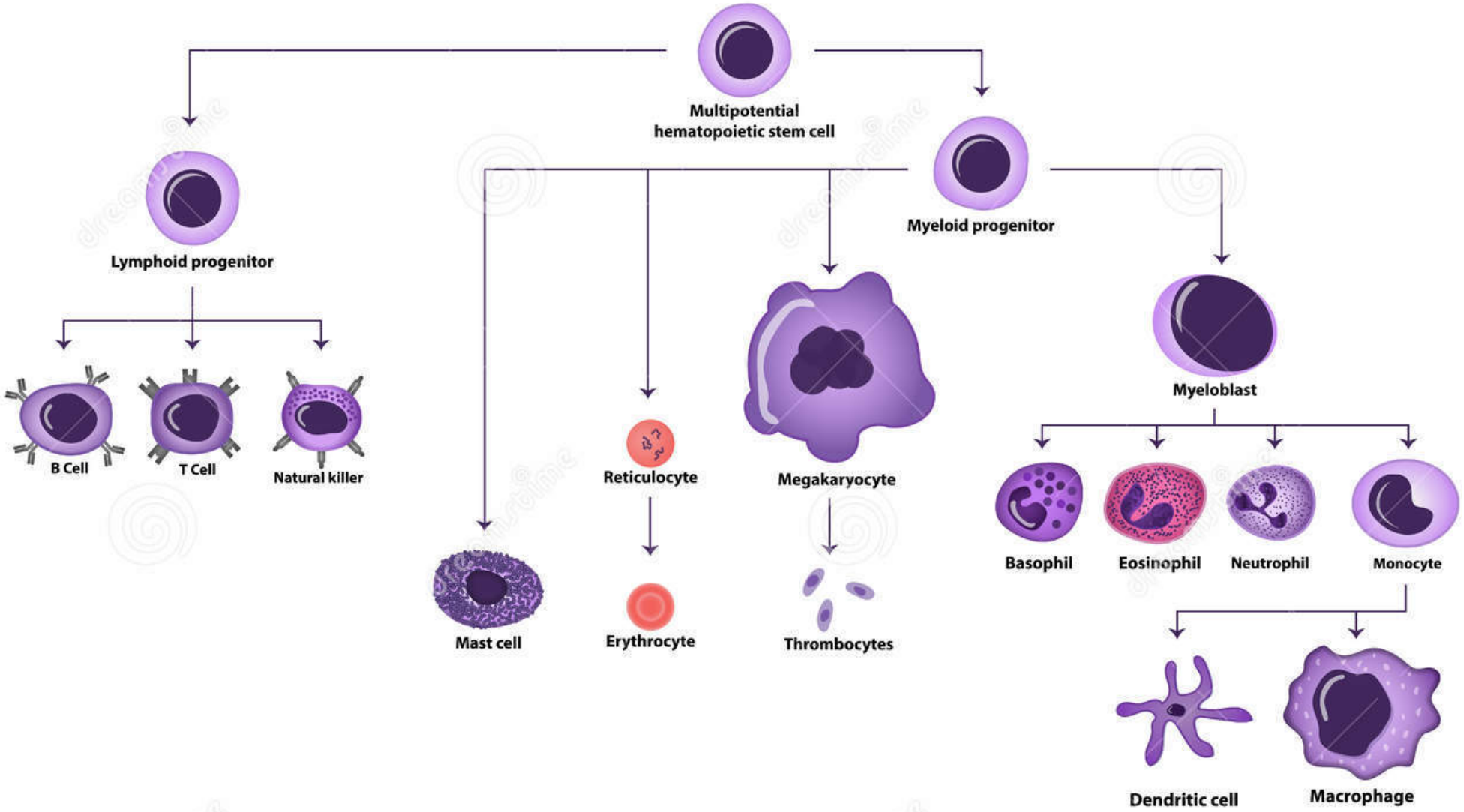






Dannelsen af blodceller

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?

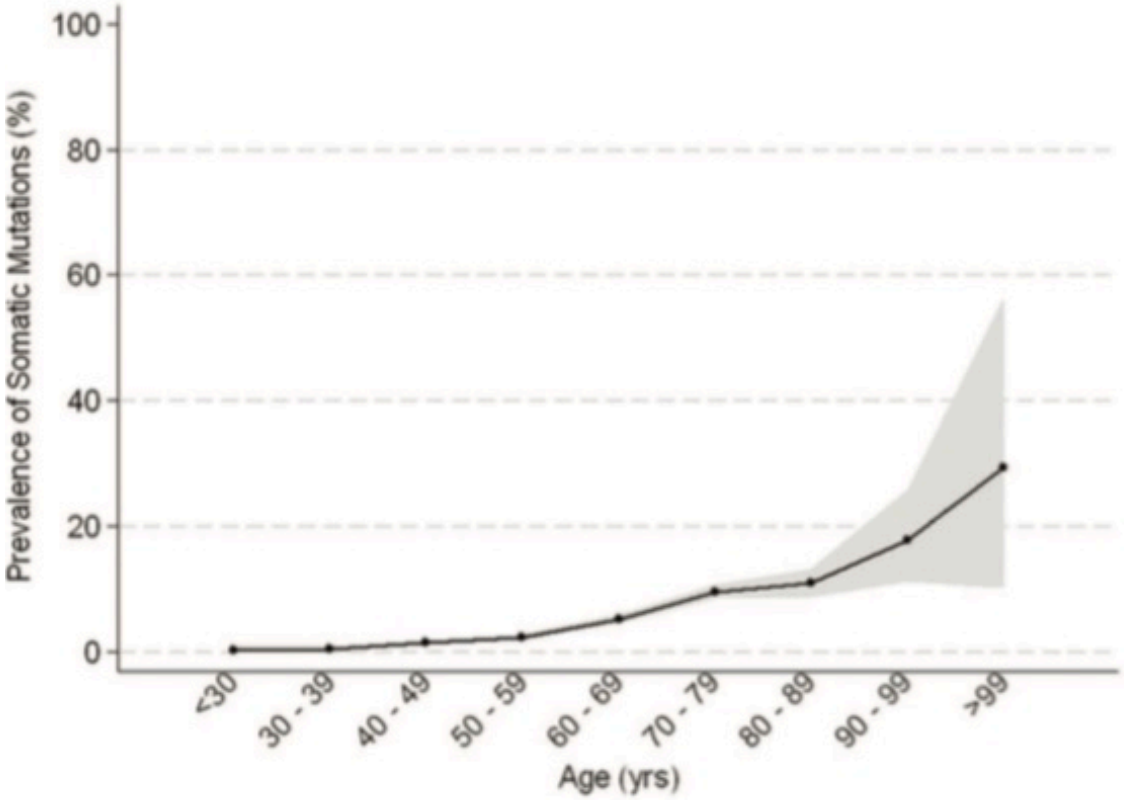
Klonal sygdom i knoglemarvens stamceller med forstyrret celle-proliferation (celledeling) og -differentiering (celle-specialisering)

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

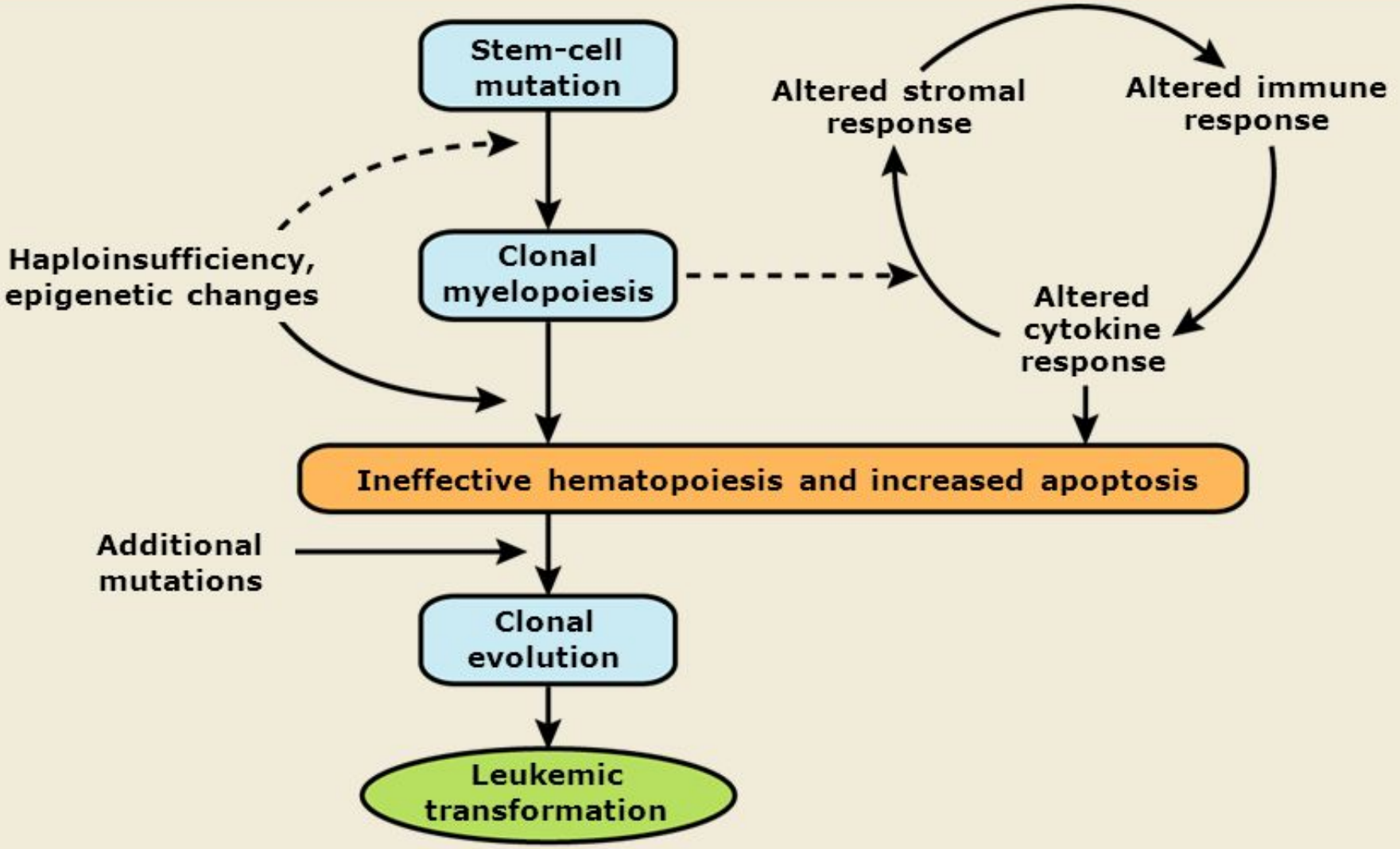


American Society of Hematology (ASH) 2015

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.

Hvad er symptomerne ved MDS?

Forpustethed
Hjertebanken
Brystsmerter
Dårlig kondition
Træthed
Svimmelhed
Hovedpine

Mangel på røde blodlegemer

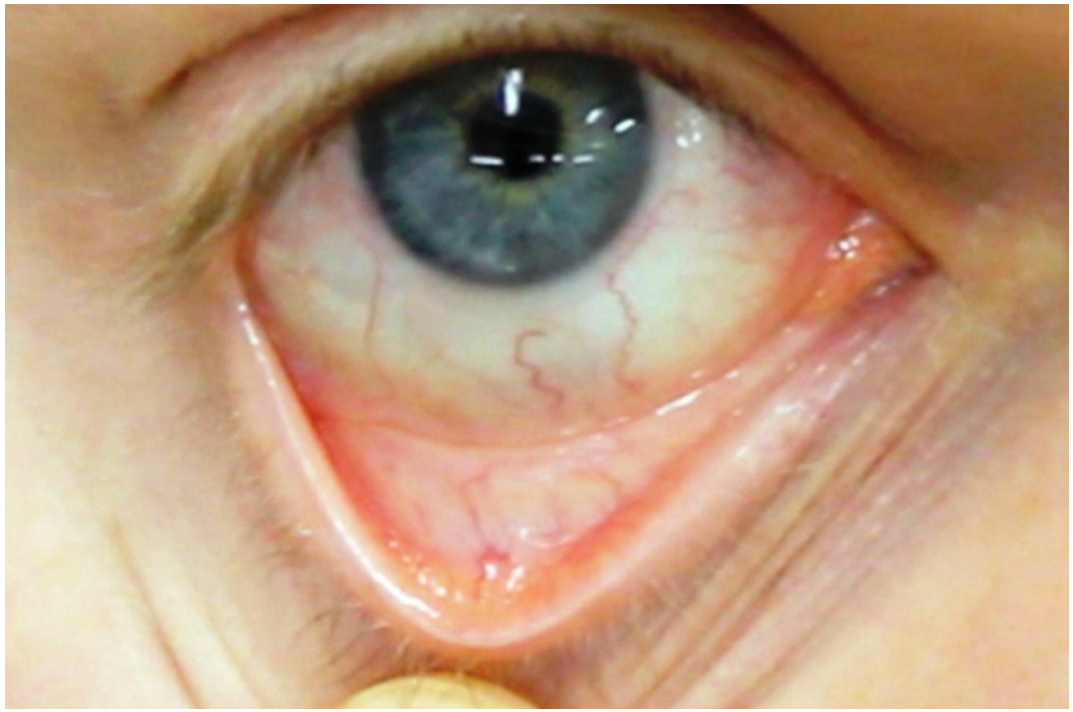
Hyppige og/eller langvarige infektioner

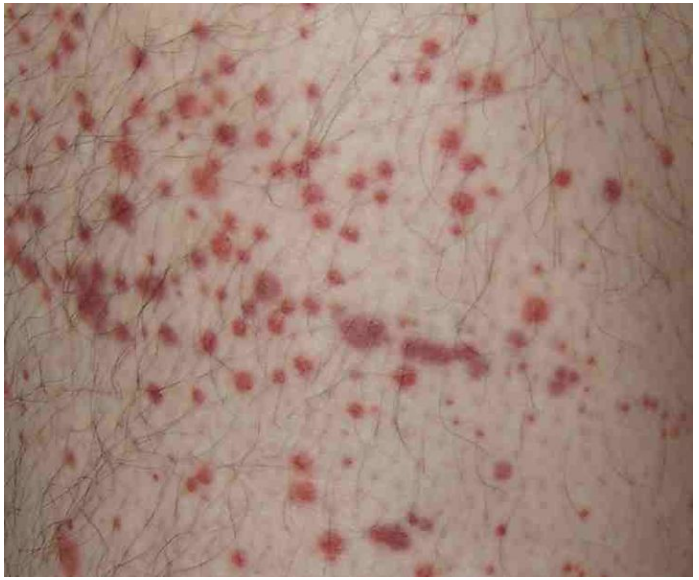
Mangel på hvide blodlegemer

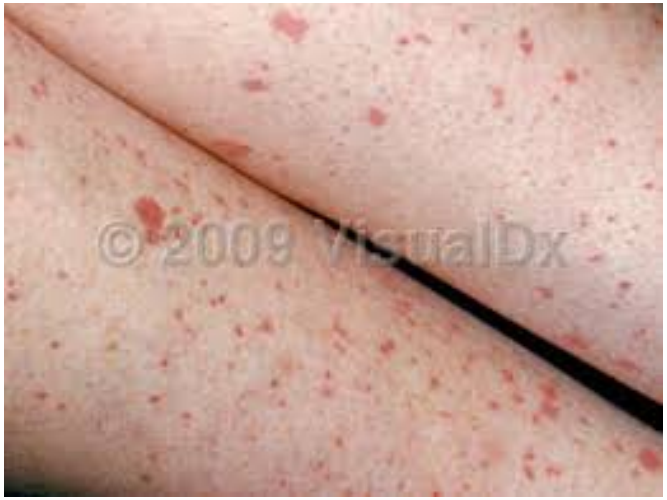
Tendens til blå mærker og røde pletter
Blodet lang tid om at størkne
Blødning fra slimhinder

Mangel på blodplader

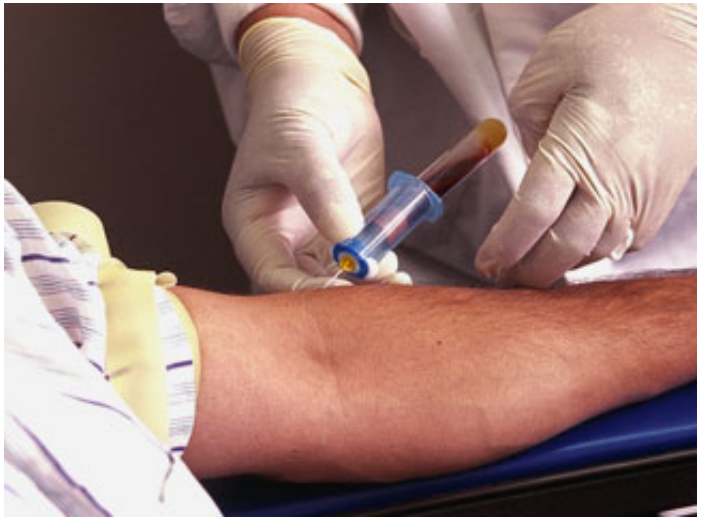
Hvad kan man observere ved MDS?







Hvordan stilles diagnosen?



- Blodprøver + udstrygning af perifert blod
- Knoglemarvsundersøgelse

- Udelukkelse af andre årsager til cytopeni/dysplastiske ændringer
  - Vitaminmangel (vitamin B_{12}, 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 i en eller flere blodcellelinier
- Morfologiske tegn på betydelig dysplasi (≥ 10% af forstadier til røde blodlegemer, granulocytter eller megakaryocytter) uden anden forklaring
- < 20% blaster

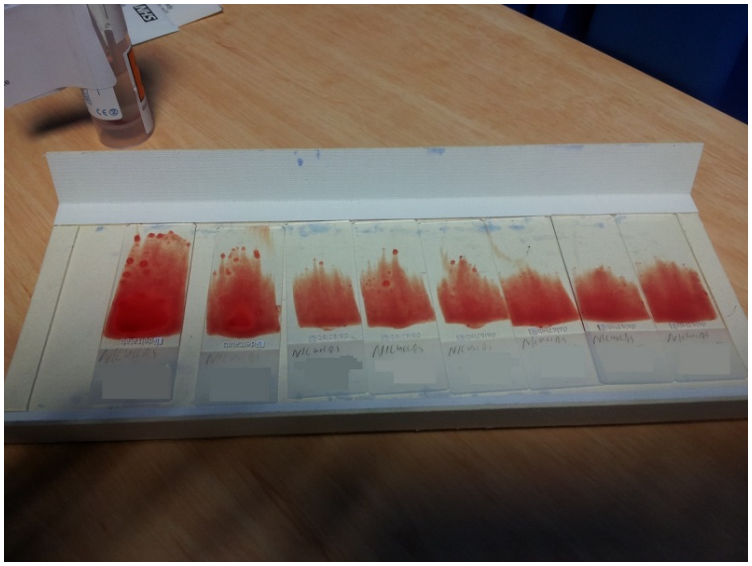
Når MDS er diagnosticeret:

- Serum-erythropoietin
- Ferritin-koncentration
- Evt. HLA-DR15-bestemmelse
- Evt. HLA-bestemmelse

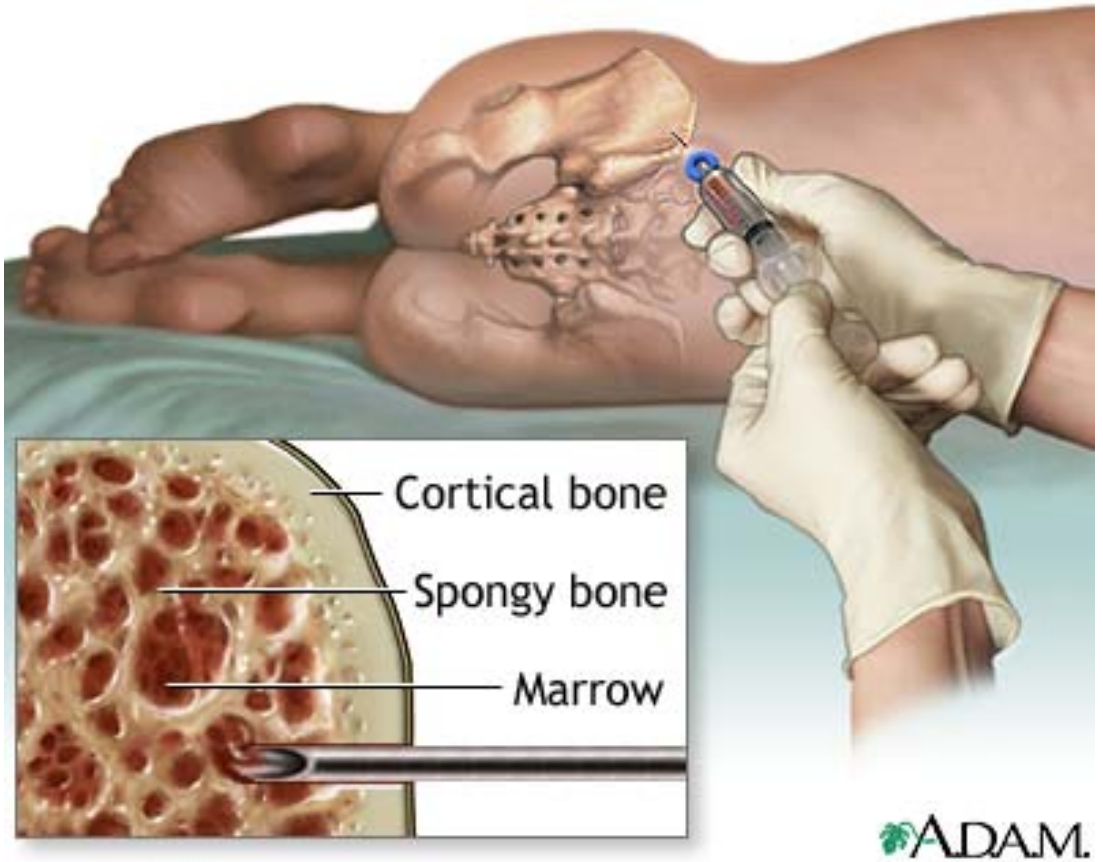
Knoglemarvsundersøgelse

- Knoglemarvsaspirat - udstryg og koagel
- Knoglespange - imprint og "snit"
- Perifert blod - udstryg

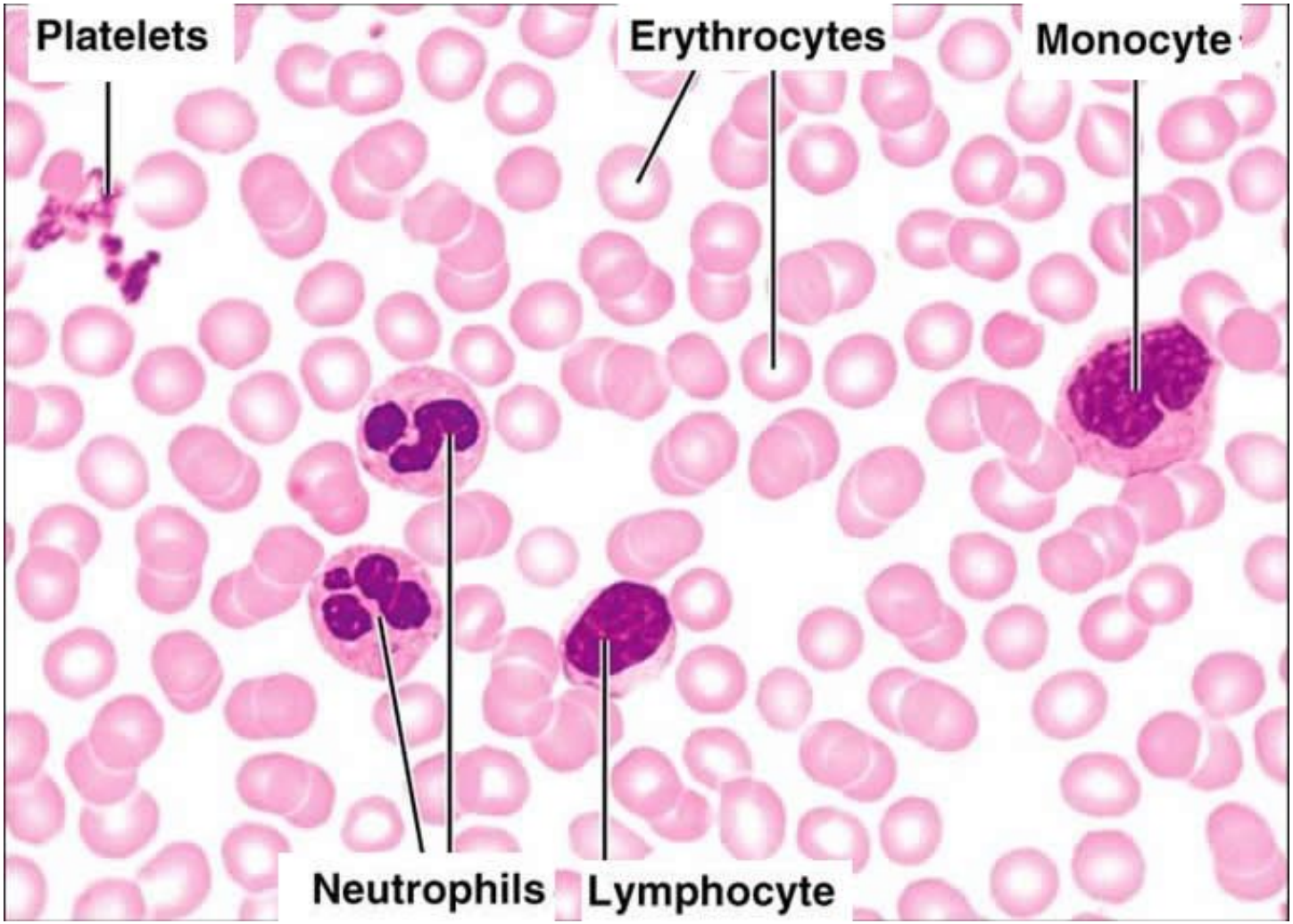
- Kromosomundersøgelse
- Markørundersøgelse



1 cm

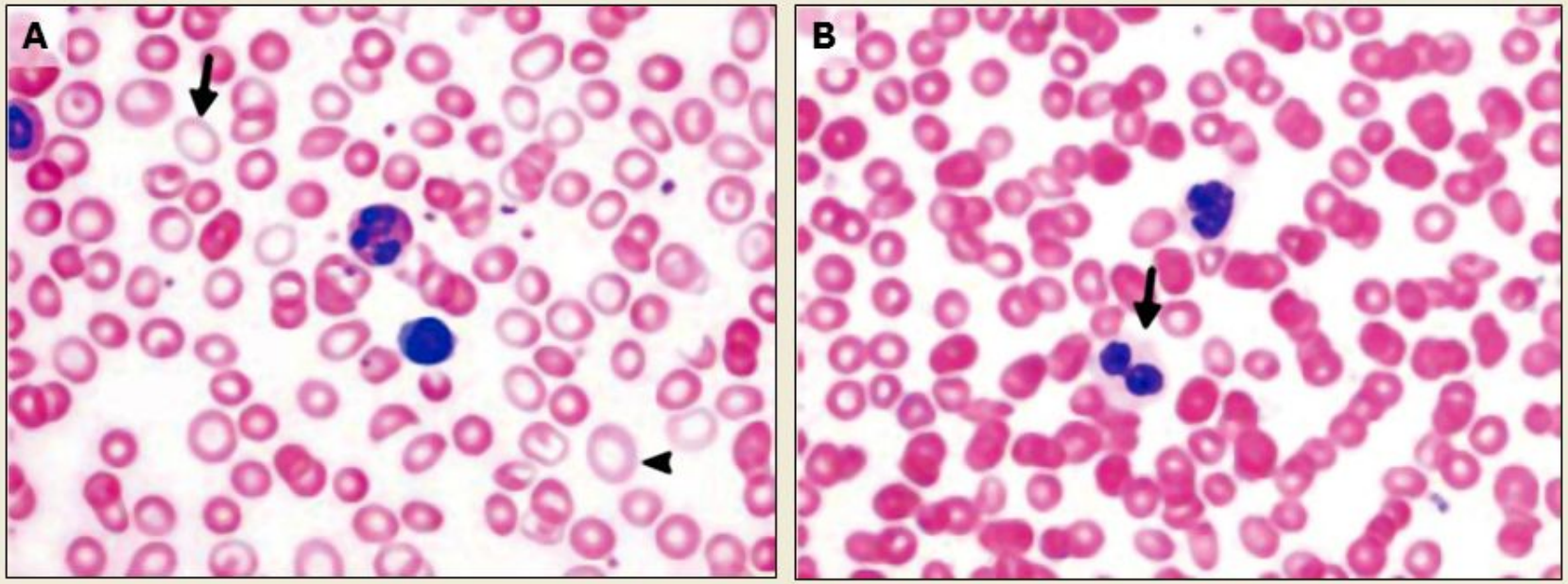


Normalt blodbillede i mikroskopet



MDS i mikroskopet

Perifert blod



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

Typiske fund i perifert blod:

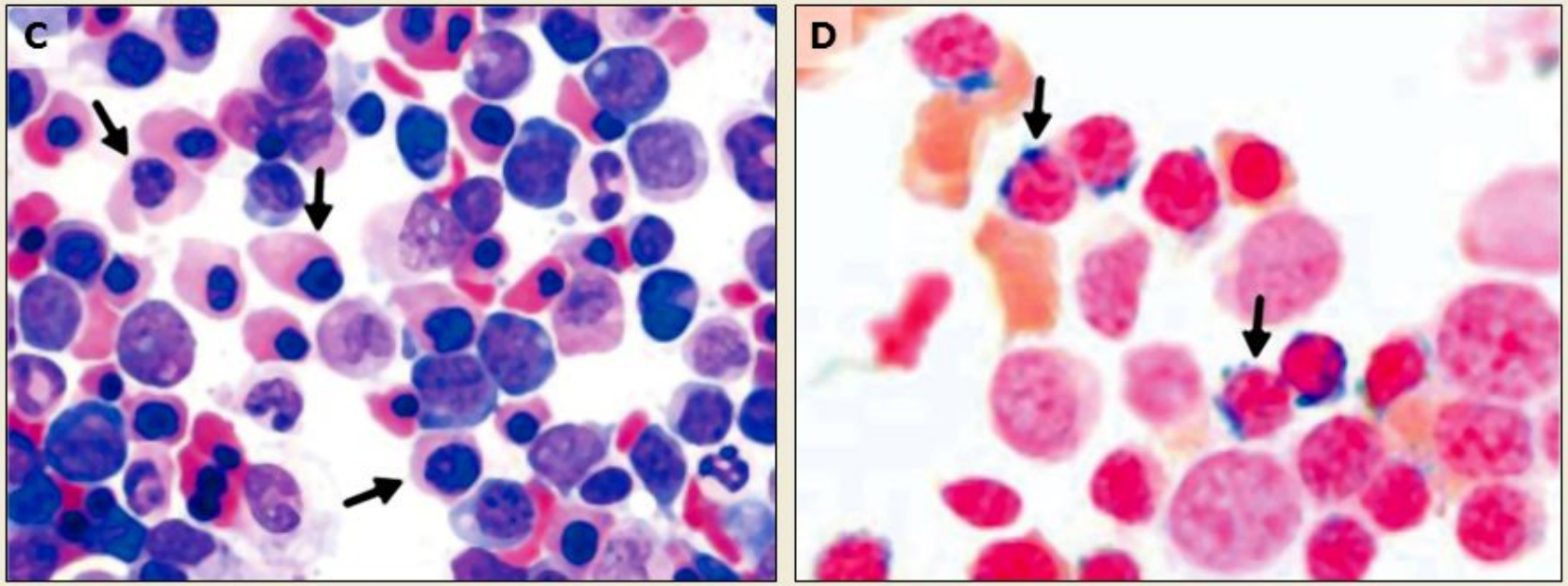
Røde blodlegemer: Varierende størrelse, store celler, abnorm form (oval, ellipsoid), to cellepopulationer, kerneholdige celler

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.

Typiske fund i knoglemarv:

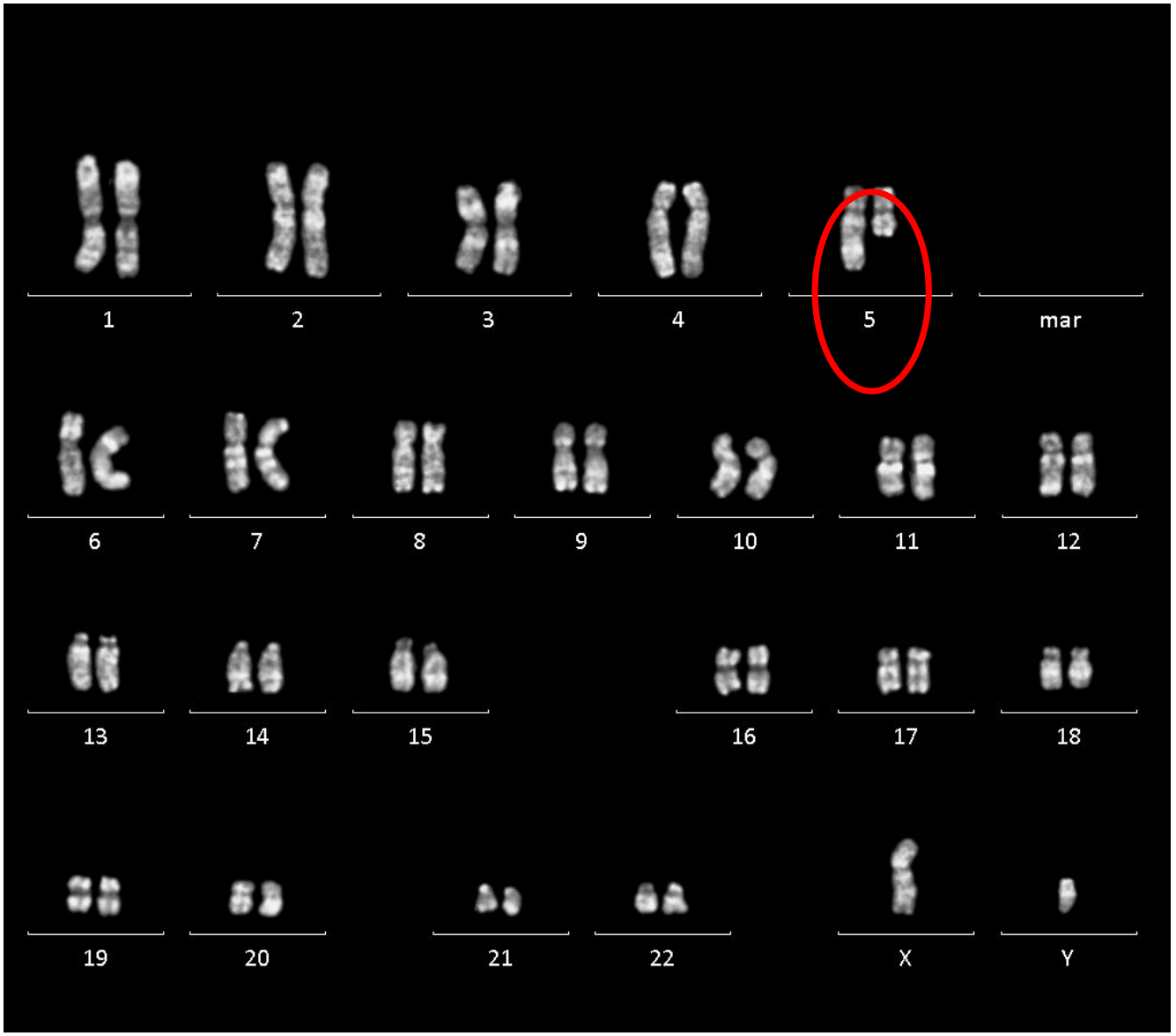
Oftest øget cellularitet, ofte mild-moderat fibrose

Erythropoiesen: Abnormt store celler, kernefragmentering, flere kerner, vakuoler, ringsideroblaster (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 ringsideroblaster 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 ringsideroblaster af erythroide celler i knoglemarv
- Procentdel blaster i blod og knoglemarv
- Kromosomafvigelser
- Antal cytopenier

WHO-klassifikation 2008 af MDS

Subtype	Dysplasi	Blaster i blod	Blaster i knoglemarv	Ringsideroblaster	Cytogenetik
5q− - syndrom	Mest DysE	< 1%	< 5%	< 15%	Del(5q) isoleret
RA, RN, RT, RCUD	DysE, N, T	< 1%	< 5%	< 15%	Variabel
RARS	Mest DysE	0	< 5%	> 15%	Variabel
RCMD	2−3 linier	Sjældent	< 5%	< 15%	Variabel
RAEB-1	1−3 linier	< 5%	5–9%	< 15%	Variabel
RAEB-2	1−3 linier	5–19% ± Auer-stave	10–19% ± Auer-stave	< 15%	Variabel
MDS-U	1 linie	< 1%	< 1%	< 15%	Variabel

RA, refractory anemia; RN, refractory neutropenia; RT, refractory thrombocytopenia; RCUD, refractory cytopenia with unilineage dysplasia; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; MDS-U, myelodysplastic syndrome, unclassified; DysE, dyserythropoiesis; N , neutropenia; T, thrombocytopenia

Swerdlow SH, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon: IARC Press; 2008:109-38.

WHO-klassifikation 2016 af MDS

Seks overordnede typer:

- MDS med dysplasi i en enkelt linie (tidligere refractory cytopenia with unilineage dysplasia inkl. RA, RN, and RT) – < 5%
- MDS med multilinie-dysplasi (tidligere RCMD) – 70%
- MDS med ringsideroblaster inkl. undergrupper med dysplasi i en enkelt linie og i flere linier (tidligere RARS) – < 5%
- MDS med isoleret del(5q) – 5%
- MDS med overskud af blaster ('Excess Blasts'; MDS-EB; tidligere RAEB) med yderligere underinddeling i MDS-EB-1 and MDS-EB-2 baseret på blastprocenten eller +/- Auer-stave – 25%
- MDS, uklassificeret – < 5%

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%/<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%/<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	≥15%/≥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	≥15%/≥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%,Δ 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 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. Peripheral blood monocytes must be <1 × 10^9/L.

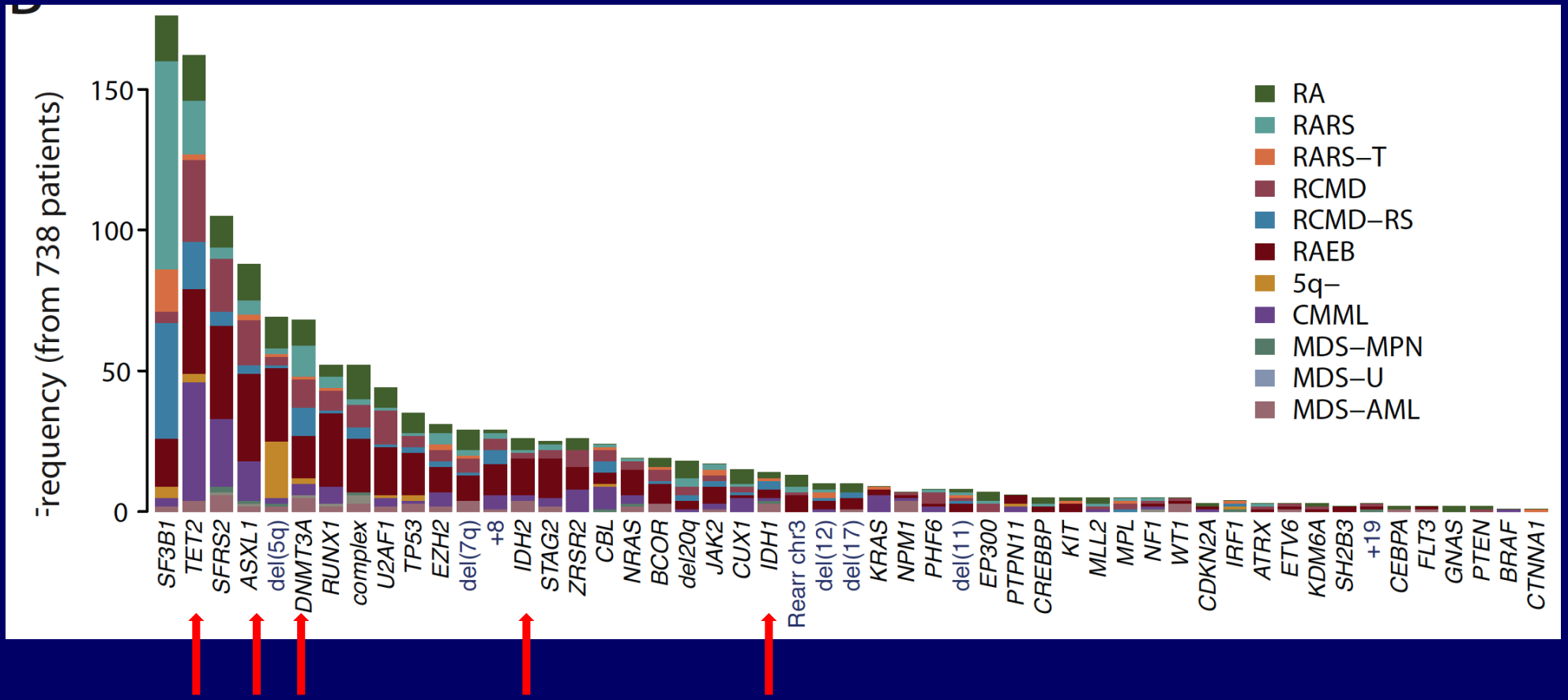
¶ If *SF3B1* mutation is present.

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

◇ Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Spektrum af mutationer

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



Papaemmanuil, *Blood*, 2013

Vil ny teknologi gøre det lettere at diagnosticere MDS?

- Sekventering af de 20 hyppigst muterede gener 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

Hvad er prognosen?

IPSS

International prognosis scoring system (IPSS) in myelodysplastic syndrome

Variable	Score				
	0	0.5	1	1.5	2
Bone marrow blasts (percent)	<5	5 to 10	-	11 to 20	21 to 30
Karyotype*	Good	Intermediate	Poor	-	-
Cytopenias¶	0/1	2/3	-	-	-
Risk group	**IPSS score**				
Low	0				
Intermediate-1	0.5 to 1				
Intermediate-2	1.5 to 2				
High	2.5 to 3.5				

* Karytope definitions:
Good: Normal;-Y; del (5q); del (20q).
Poor: Complex (≥3 abnormalities); abnormal chromosome 7.
Intermediate: All others.
¶ Cytopenia definitions:
Red blood cells: Hemoglobin <10 g/dL (100 g/L).
White blood cells: Absolute neutrophil count <1800/microL.
Platelets: Platelet count <100,000/microL.

Adapted from: Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89:2079. Erratum in Blood 1998; 91:1100.

UpToDate®

Overlevelse

Transformation til AML

IPSS-R

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

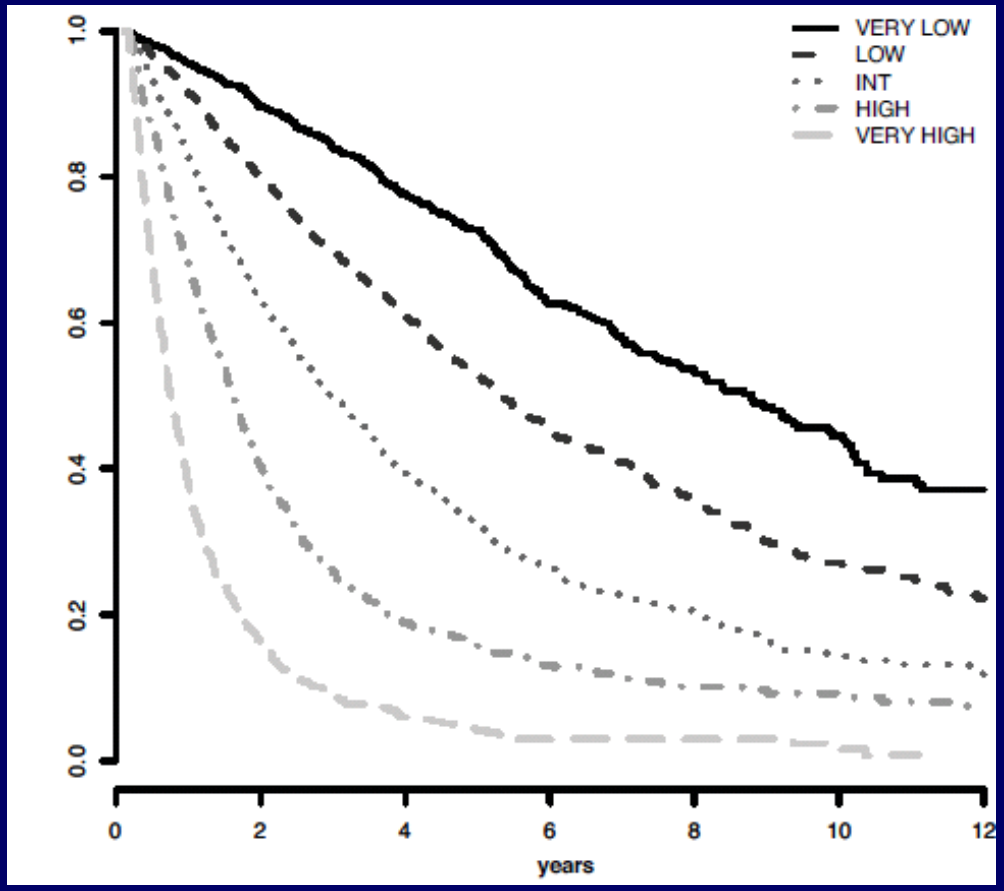
Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8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

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.

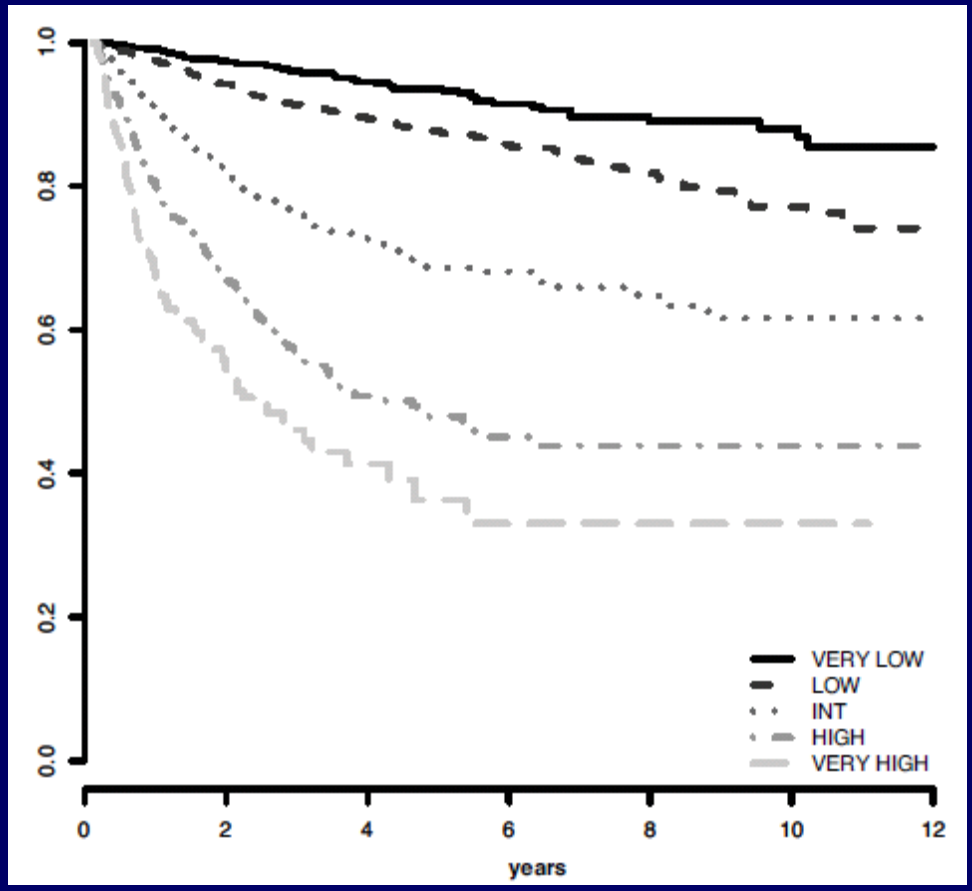
IPSS-R

Overall survival



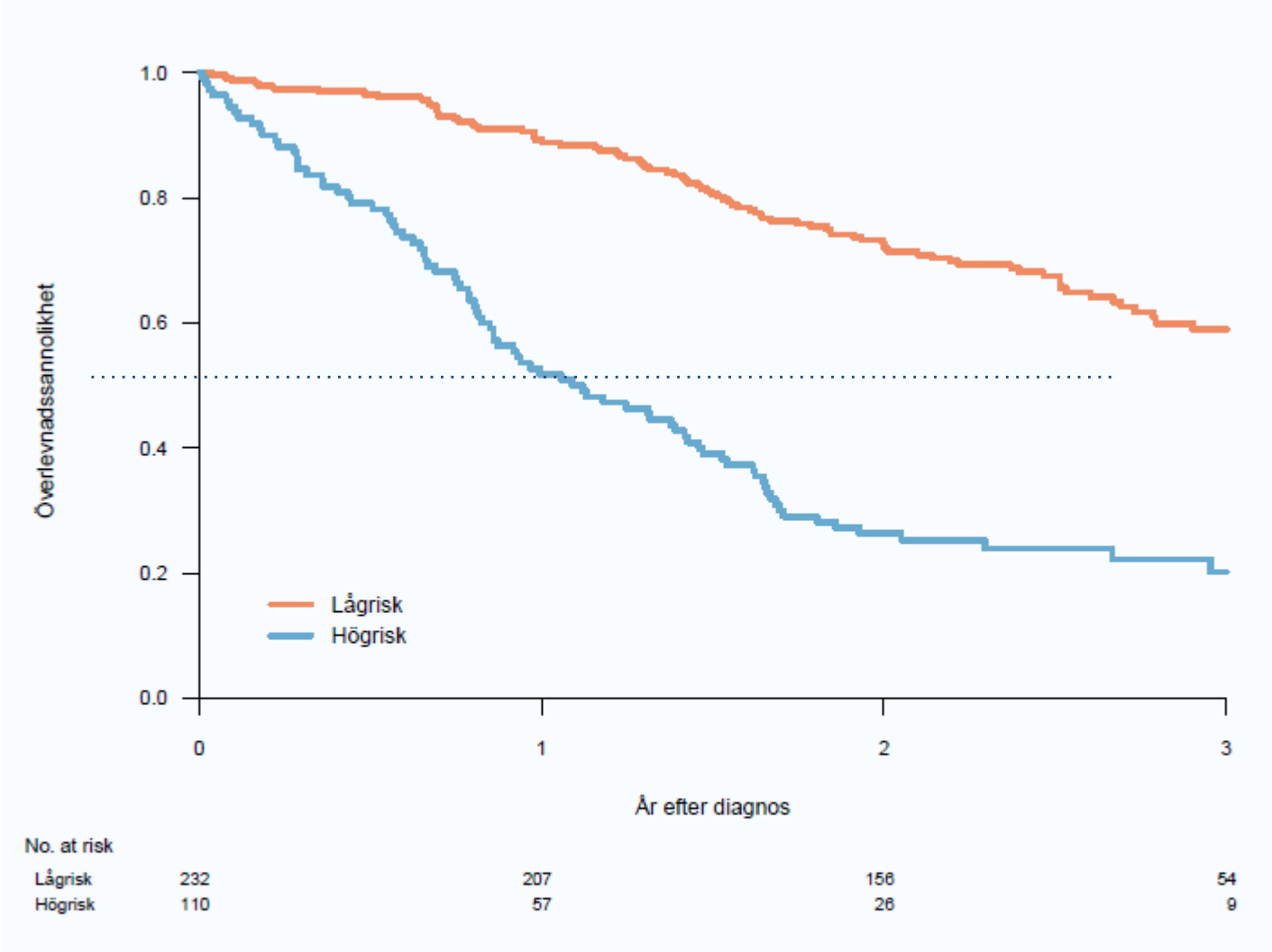
AML evolution

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, hypometylerende medikamenter, immundæmpende behandling, lenalidomid
- Høj-intensitetsbehandling intensiv kombinations-kemoterapi, knoglemarvstransplantation

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 Allogenetic Bone Marrow Transplantation for Myelodysplastic Syndromes: Delayed Transplantation for Low Risk Myelodysplasia is Associated with Improved Outcome. *Blood* 2004.

Høj-dosis kemoterapi

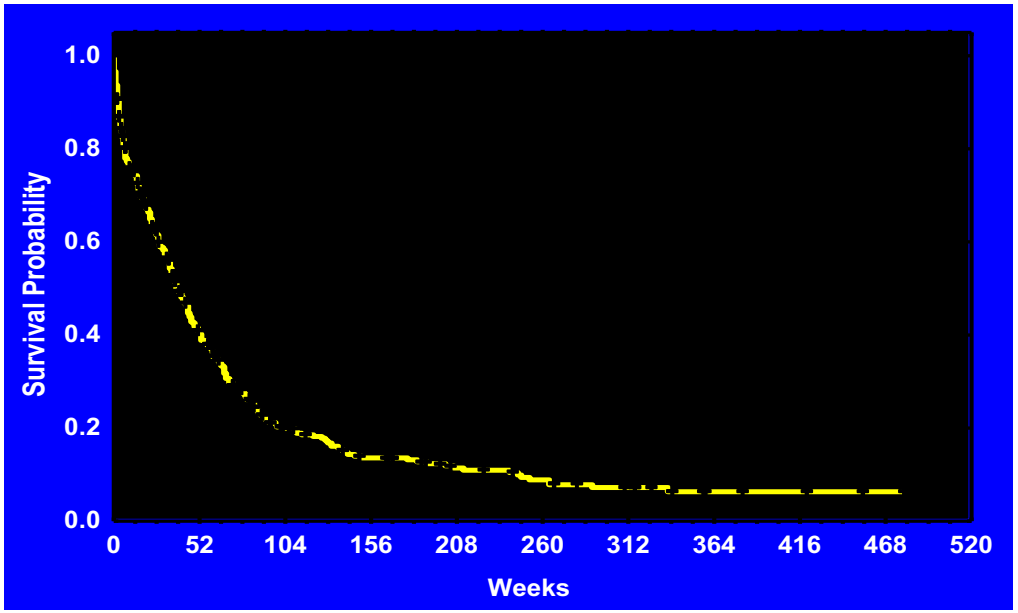
> 10% blaster i knoglemarv, alder < 60 år, godt funktionsniveau, 'good risk'-cytogenetik

- Få randomiserede studier
- Små studier, oftest fra ét center – forskellige MDS-subtyper og cytogenetik
- Retrospektive sammenligninger med "supportive care"
- Omkring 1100 patienter behandlet i publicerede studier

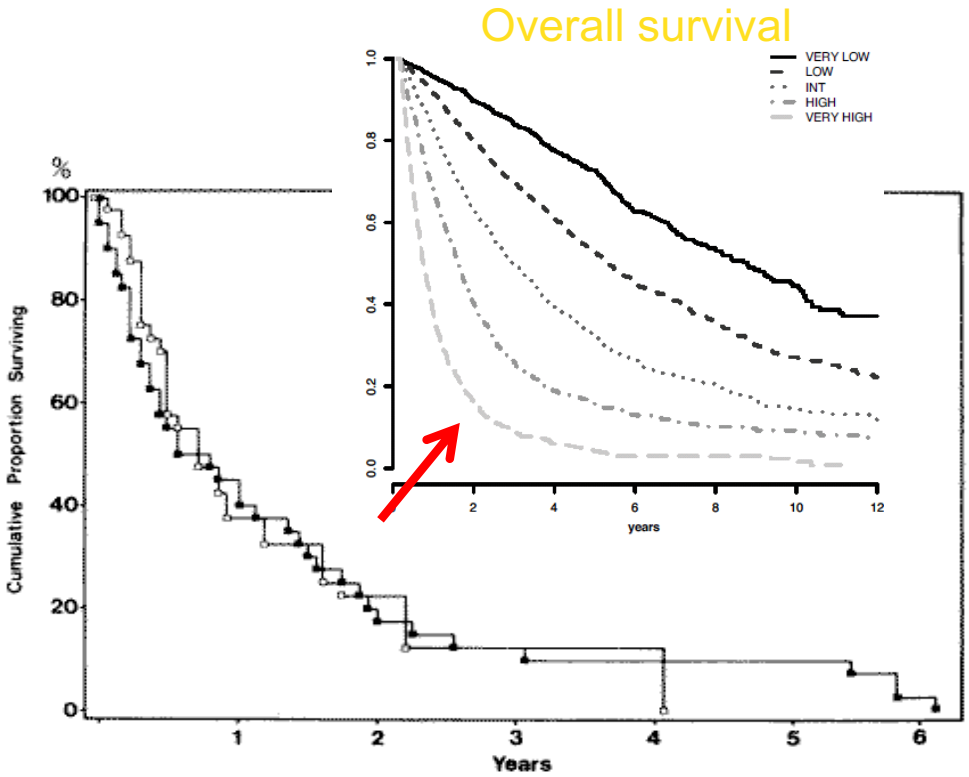
Høj-dosis kemoterapi

- AML-lignende terapi (cytarabin, etoposid, idarubicin)
- Komplet remission hos 40-60% (hos 85% med AML)
- Kort varighed af remissionen (< 12 mdr.)
- MDS-patienter (medianalder > 70 år) tåler høj-dosis kemoterapi dårligt
- Behandlingsinduceret død 8-27%
- Lange hospitalsophold
- Meget få langtidsoverlevere (‘good risk’-cytogenetik)

Høj-dosis kemoterapi



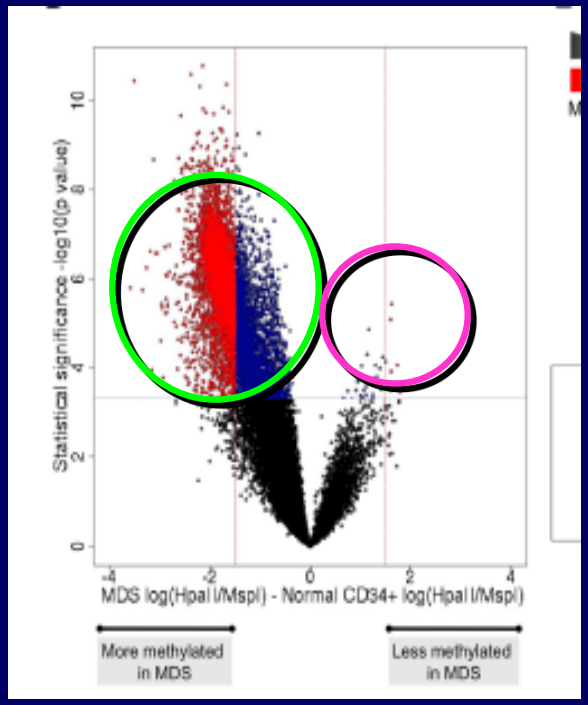
MD Anderson, Estey; Survival MDS 1990-2000 Given Intensive Chemotherapy



Aul et al, 1989 (Cancer); Non-randomized comparison Low-dose Ara-C vs Supportive care

Generelt ikke bevist, at høj-dosis kemoterapi ændrer naturhistorien af MDS

DNA-metylering: MDS vs. nCD34+



Hvorfor mere metylering i MDS?
Mutationer i
TET2 ~ 25%
DNMT3A ~ 8%
IDH ~ 8%
Aldersrelaterede ændringer i metylering

Mere metylering i MDS | Mindre metylering i raske celler

14 MDS | 8 normale CD34+

Figueroa, M *et al. Blood* 2009, 114 3448-3458

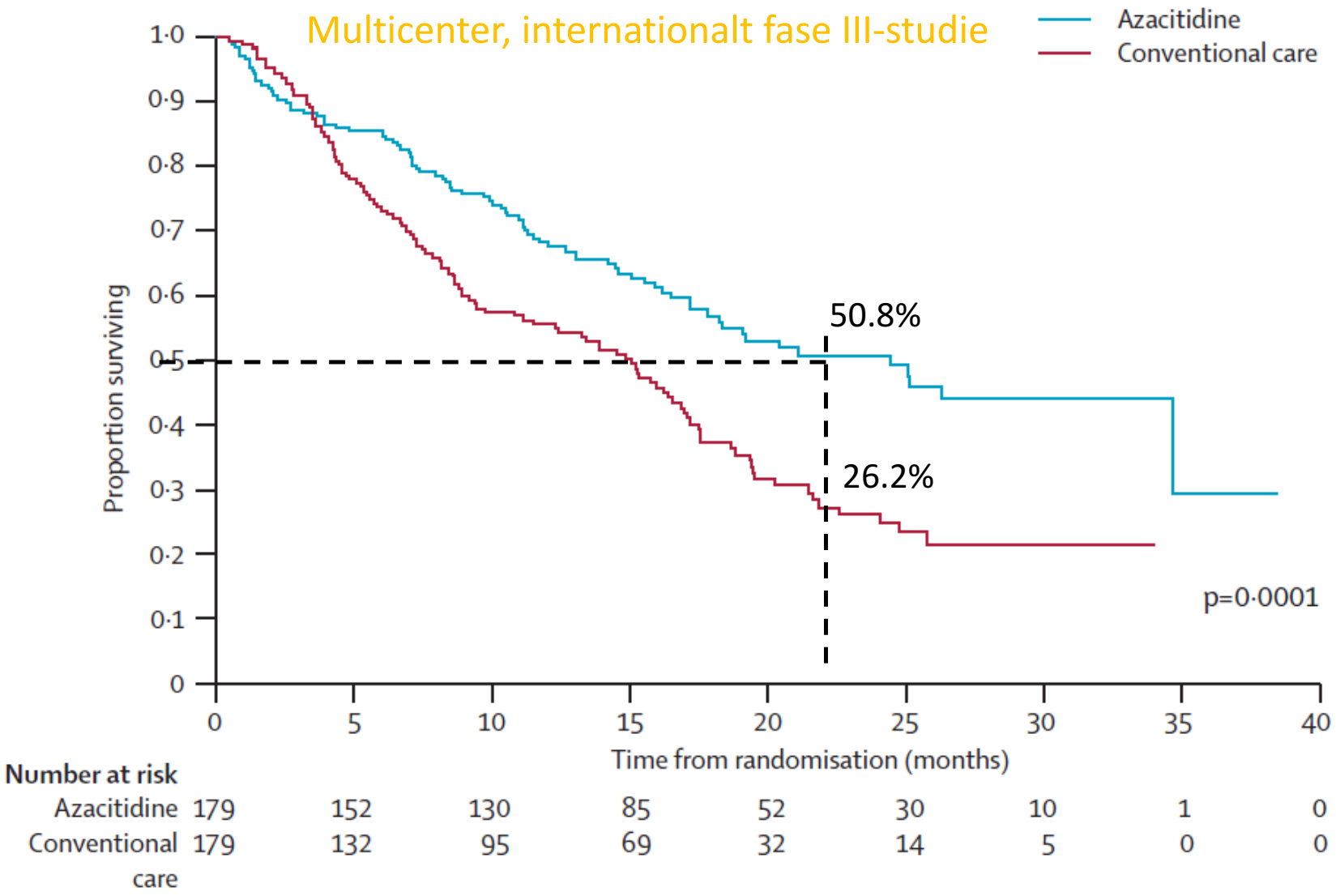
Azacitidin (Vidaza®)

- Hypometylerende medikament
- Potentielle effekter: Forbedret overlevelse, hæmatologisk respons, forbedret livskvalitet
- Bivirkninger: Marvsuppression, feber, kvalme, reaktioner på indstikssted
- Dosering: subkutan injektion 75 mg/m^2 dgl. i 7 dage / 28 dage

Azacitidine (Vidaza®)

Høj-risiko MDS

Multicenter, internationalt fase III-studie



Fenaux *et al*. *Lancet Oncology* 2009

Lav-risiko MDS

Meget lav (≤ 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

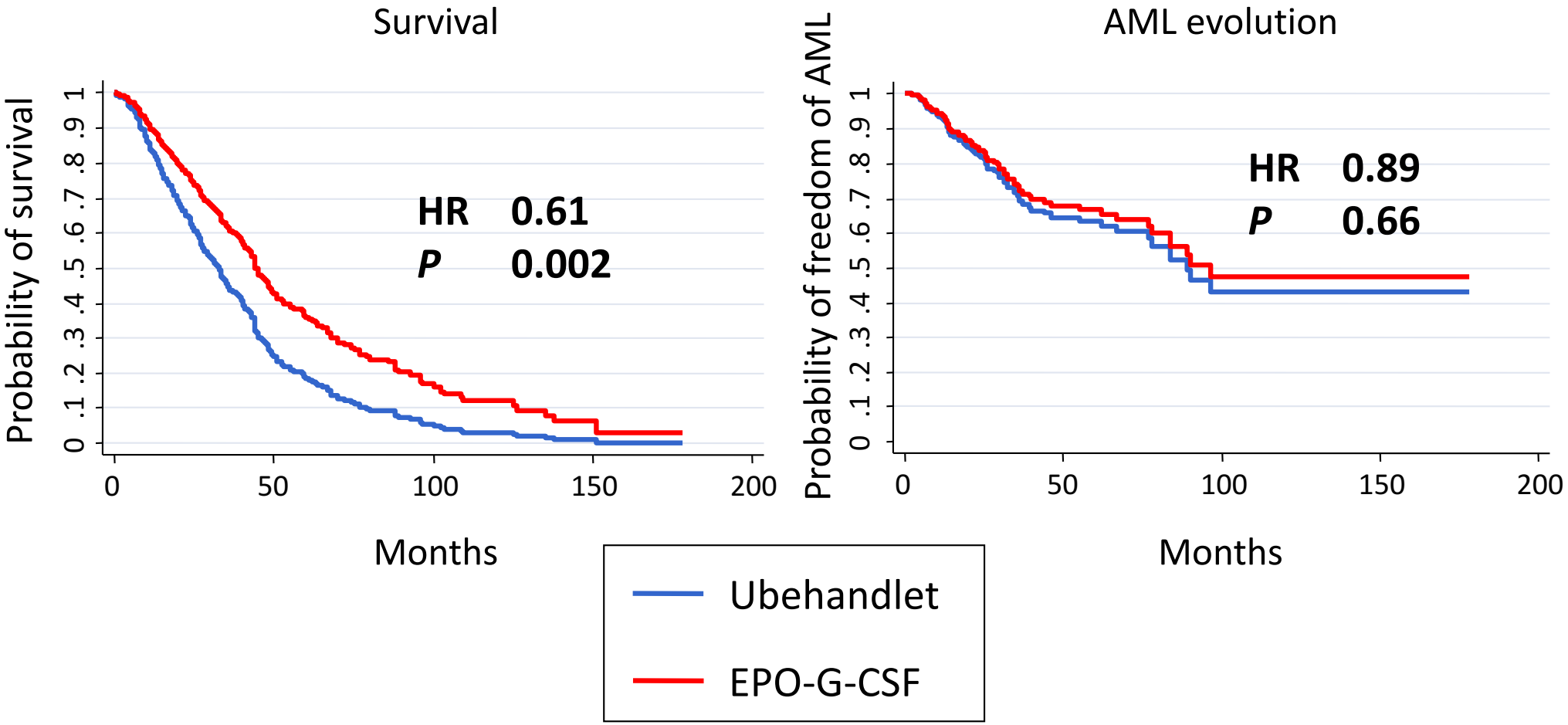
- Overvej immundæmpende behandling – antithymocyt-globulin (ATG) +/- ciclosporin (Sandimmun®) hos yngre patienter (< 60 år, hypoplastisk knoglemarv, HLA-DR15-positive)

EPO: f.eks. Darbepoetin 300 *µ*g/uge hver 2. uge

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

Jadersten et al. JCO. 2008

Behandling med EPO-G-CSF er associeret med forbedret overlevelse



Jadersten *et al. JCO*. 2008

Beslutningsmodel for behandling med EPO + G-CSF

Variabel	Værdi	Score	Værdi	Score
Transfusionsbehov	**< 2 U/m**	**0**	**≥ 2 U/m**	**1**
Serum-EPO	**< 500 U/l**	**0**	**≥ 500 U/l**	**1**

Sandsynlighed for respons:
Total-score 0: 74%; Score 1: 23%; Score 2: 7%

Prædiktiv værdi af model: $p < 0.001$

Hellström-Lindberg, *BJH,* 2003

Lav-risiko MDS: Immunsuppression (ATG+/-ciclosporin) - hvem responderer?

		Proportion resp.	(%)	
MDS-subtype	RA	17 / 37	46	p=0.003
	RAEB/RARS	4 / 20	20	
Alder	< 60 years	15 / 21	71	p=0.005
	> 60 years	13 / 39	33	
Karyotype	Normal	14 / 29	48	p=0.02
	Abnorm	6 / 29	21	
Marvmorfologi	Hypocellulær	11 / 30	37	p=0.002
	Normal	7 / 21	33	
	Hypercellulær	3 / 16	19	

HLA-DR15

NIH data

Immunsuppression i lav-risiko MDS

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

Jernkelerende behandling

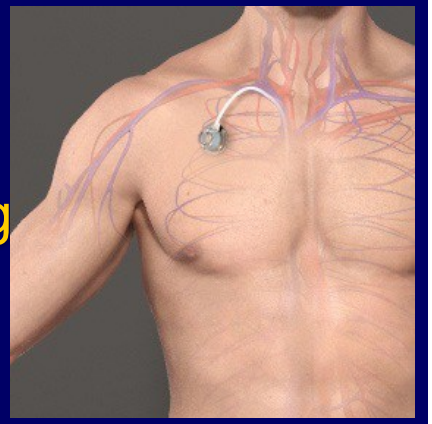
- Hvilke patienter?
  - Lav-risiko MDS RA, RARS, del(5q) (RCMD, mere fremskreden MDS)
  - Lang forventet levetid
  - Vedvarende transfusionsbehandling
  - Kandidater til knoglemarvstransplantation - forebyggende

- Serum-jernniveau, der indikerer behandling
  - Ved ~>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%

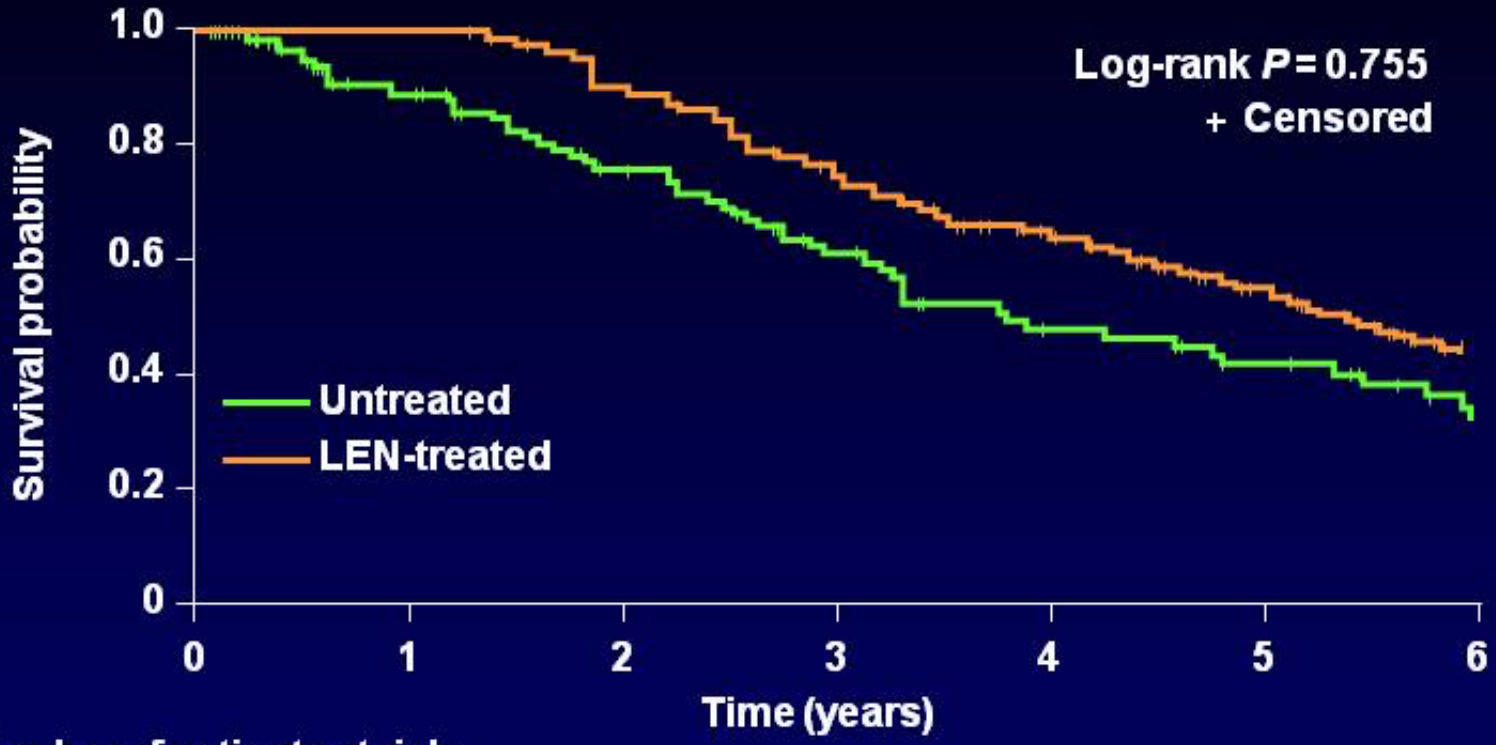
Retrospektive studier viser længere overlevelse i lav-risiko MDS-patienter; dog ingen studier af langtidseffekten

- Deferasirox (Exjade®), oral
  - 1 x dagligt peroralt doseret efter vægt
  - Maveproblemer
  - Må ikke anvendes ved nedsat nyrefunktion (regelmæssig måling af lever- og nyretal)

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 megakaryocytmorfologi
- Bivirkninger: Marvsuppression, 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

MDS-003/-004 vs Multicenter Registry: OS (Kaplan-Meier Estimator With Left Truncation)



Number of patients at risk

LEN-treated	125	87	66	48	31	24	14
Untreated	–	53	101	125	135	127	101

	LEN-treated	Untreated
2-year cumulative probability	90%	74%
5-year cumulative probability	54%	41%
Median OS, years (95% CI)	5.2 (4.5–5.9)	3.8 (2.9–4.8)

CI, confidence interval; OS, overall survival.

Behandlingsrespons

Stringente kriterier bruges primært i kliniske forskningsprojekter

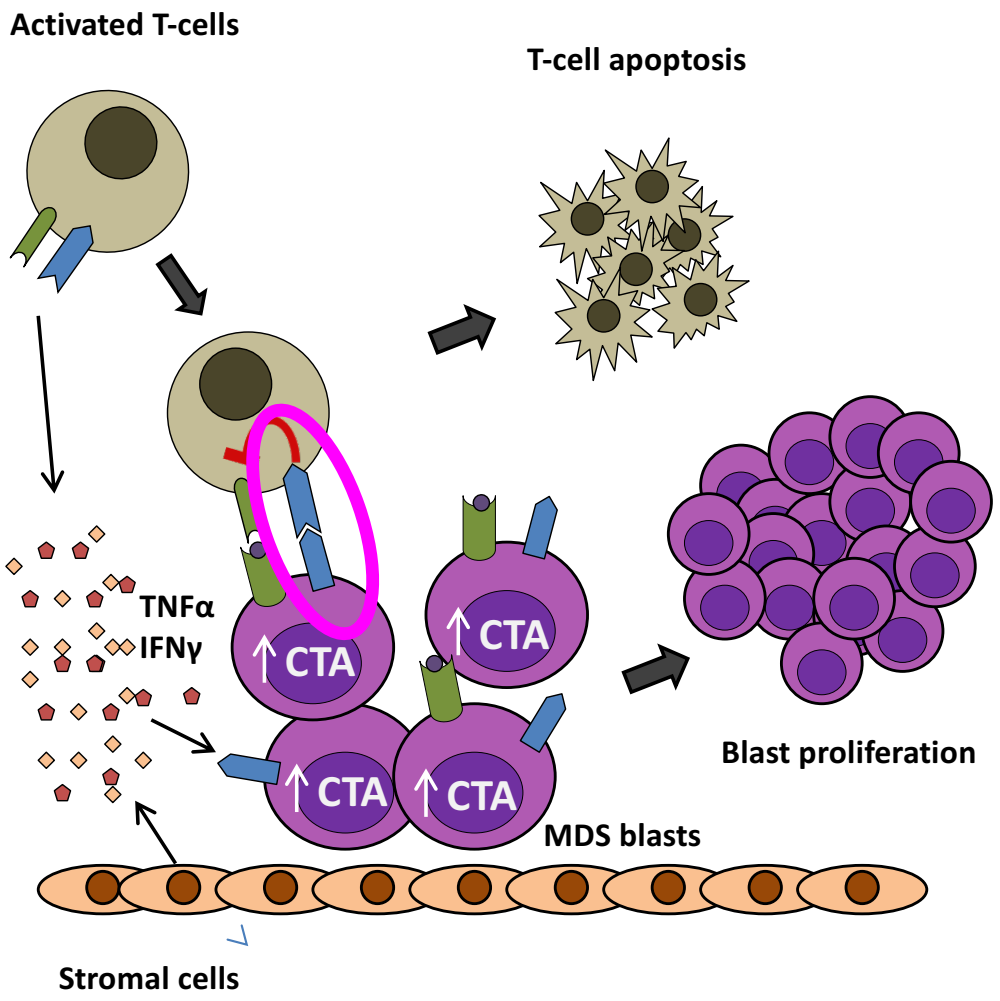
- Hæmatologisk respons forlænget levetid?
- Knoglemarvsrespons forlænget levetid ved komplet remission
- Cytogenetisk response
- Stabil sygdom
- Sygdomsprogression (stigende knoglemarvs blastprocent eller tiltagende cytopeni)

Fremtidig behandling

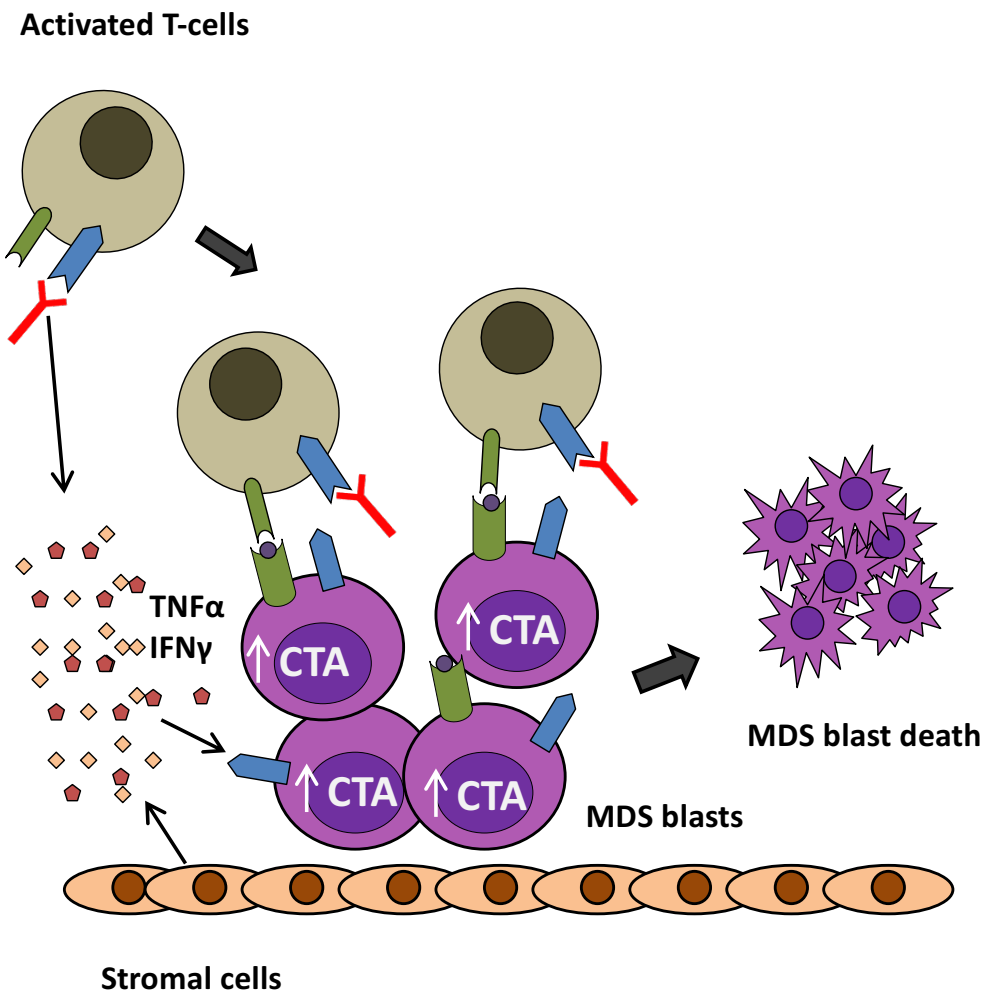
- Navlesnors-stamcelletransplantation
- Haploidentisk transplantation
- Nye hypometylerende lægemidler
- Immun-checkpoint-inhibitor i kombination med hypometylerende lægemidler
- Behandling rettet mod cancer-stamceller?
- Skræddersyet behandling

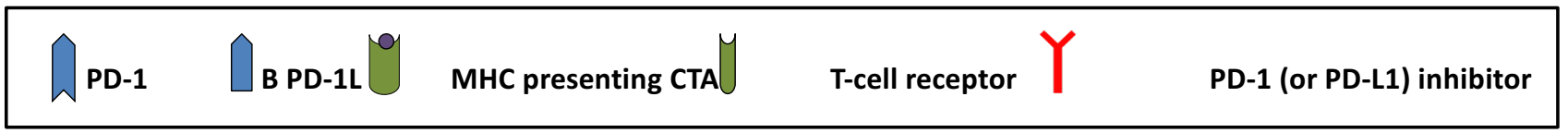
Illustration of the hypothesis

A. Beh med Guadecitabine (”Vidaza lignende ”)

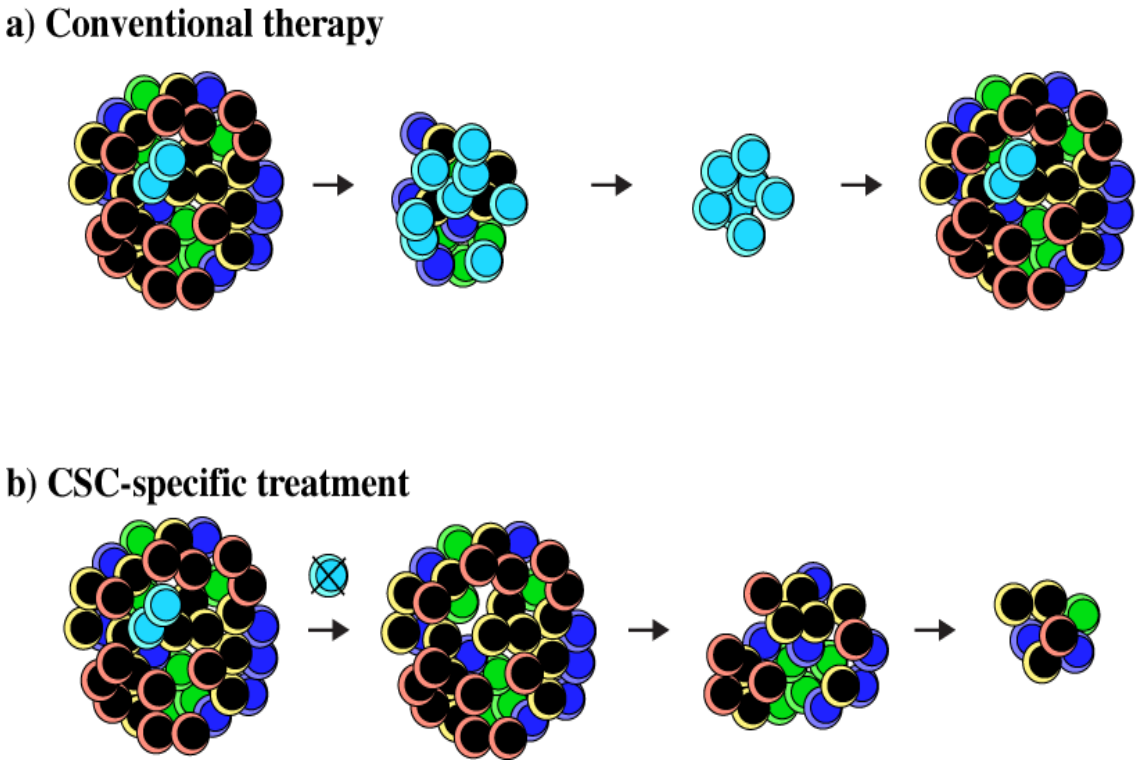


B. Beh med Guadecitabin og Immun check point inhibitor

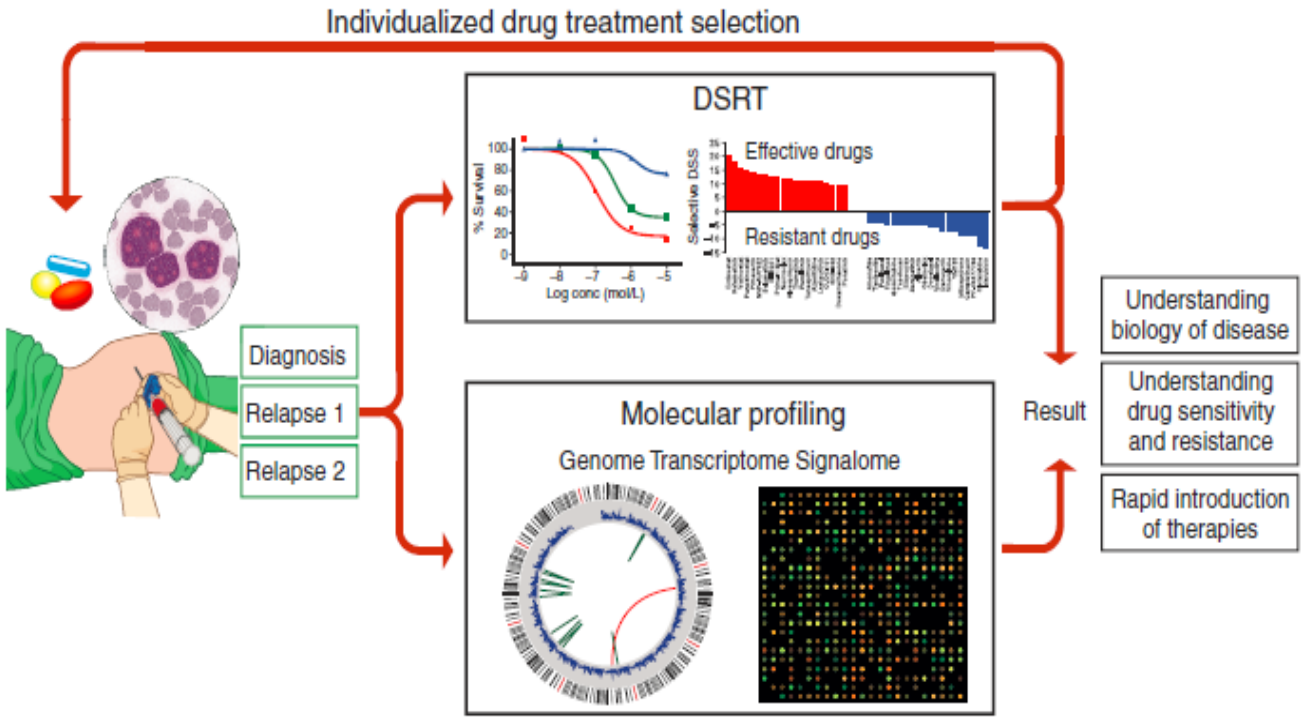




Behandling rettet mod cancer-stamceller?



Skræddersyet behandling tilpasset den enkelte patient?



NYT regime: Fludarabin / Treosulfan (FT) MA - med reduceret toxicitet (RTC)

- Ruutu T *et al.* *Haematologica* 2011
- 45 MDS-patienter
- Medianalder: 50 år (range, 22-63 år)