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Transfusional Iron Overload in MDS

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Disclosures

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Off Label Usage:

Nothing to Disclose

Objectives:

- Measurements of iron overload
- Why address iron overload in MDS
- Relevant targets of iron reduction in MDS
- Summary/conclusions

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- **Measurements of iron overload**
- Why address iron overload in MDS
- Relevant targets of iron reduction in MDS
- Summary/conclusions

Currently available measures of iron overload in clinical practice.

Diagnostic tool	Characteristics	Advantages	Disadvantages
Calculation of transfusion iron burden	Provide a direct quantitative estimate of the body iron burden	Easy to calculate, inexpensive	Unreliable in patients with bleeding or chelation therapy
Serum ferritin level	Indirect serologic estimation of body iron burden	Widely available; easy to perform; low-cost; repeatable	Unreliable in patients with inflammation, liver function deficiency, and ascorbate deficiency
Serum transferrin saturation	High sensitivity and specificity in untransfused patients	Widely available; easy to perform; low-cost; repeatable	No quantitative correlation to iron burden
SQUID	Direct instrumental estimation of hepatic iron concentration	Noninvasive, repeatable	Expensive; not widely available; not validated; significant underestimation; not applicable to the heart
MRI R2	Indirect instrumental estimation of tissue iron concentration	Noninvasive, repeatable; validated in the liver	Expensive, not widely available; reliable up to LIC of 15mg/g DW; not applicable for cardiac assessment
MRI T2*	Indirect instrumental estimation of tissue iron concentration	Noninvasive; repeatable; validated in the heart; provides cardiac functional information	Expensive, not widely available; complex, requires skilled radiologist
Liver biopsy	Provides a direct estimation of iron overload	Validated and quantitative method to estimate hepatic iron concentration (gold standard)	Invasive (cannot be employed in many patients with hematologic malignancies)
Non-transferrin bound iron (NTBI)/labile plasma iron (LPI) ★	Research tool at present	Noninvasive method; estimates generation of the toxic iron fraction	Not validated and not widely available. Not currently useful in clinical practice
Serum hepcidin level	Research tool at present	Noninvasive method that identifies patients at high risk of iron loading	Not widely available. Not currently useful in clinical practice

Modified from Alessandrino EP et al; Am J Hematol. 2011;86(10):897-902; Leitch HA et al; Crit Rev Oncol Hematol 2017;113:156-170 & Leitch HA et al; Leuk Res. 2018 Nov;74:21-41.

Therapeutic Objectives for MDS Patients

Treatment goals	Lower risk	Higher Risk
Hematologic improvement/Reduce RBC transfusion requirements	√	√
Improve quality of life	√	√
Extend overall survival and delay AML progression	?	√
Alter disease's natural history	?	√

Treatment options for MDS

Therapeutic options are determined by risk score

Treatment	Comment
Lower risk MDS	
ESAs[1–3]	Most effective in patients with low serum erythropoietin (EPO) level and low transfusion burden
Lenalidomide[1,4]	Transfusion-dependent patients with LR-MDS and del(5q) after ESA failure
IST[2]	For patients with features indicating a high probability of response to IST
HMAs[2]	May be a second-line option for selected cytopenic LR patients in some jurisdictions
Supportive care[2]	RBC transfusions (+ iron chelation)*, platelet transfusions, growth factors
Luspatercept	For MDS-RS
Investigational agents	
Stem cell transplantation	
Higher risk MDS	
HMAs ± other	Venetoclax, investigational agents
Supportive care	
Stem cell transplantation	

*Management of iron overload should be a consideration in all treatment groups

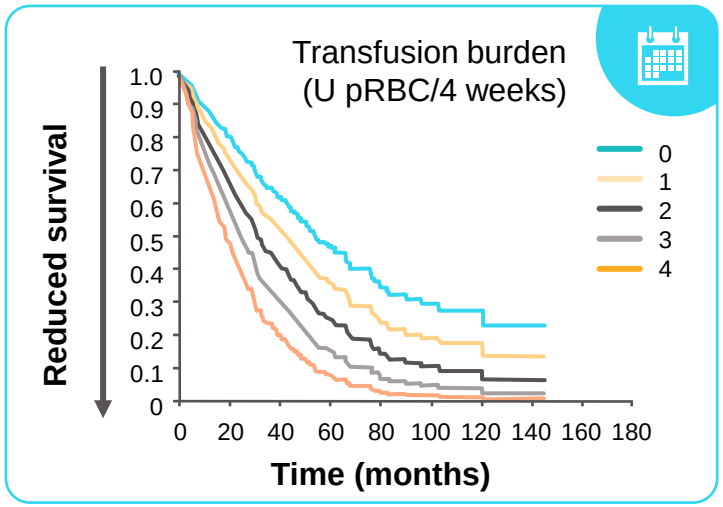
EPO: epoetin; HMAs: hypomethylating agents; IST: immunosuppressive therapy

1. Fenaux P, et al. Br J Haematol 2019. doi: 10.1111/bjh.16206. Epub ahead of print; 2. Raj K, et al. Postgraduate Haematology. John Wiley & Sons, Ltd., 2016. p.438–73; 3. Hellstrom-Lindberg, E. 2008. Myelodysplastic Syndromes. 1st ed. Remedica. London; 4. Fenaux P, et al. Blood 2011;118:3765–76.

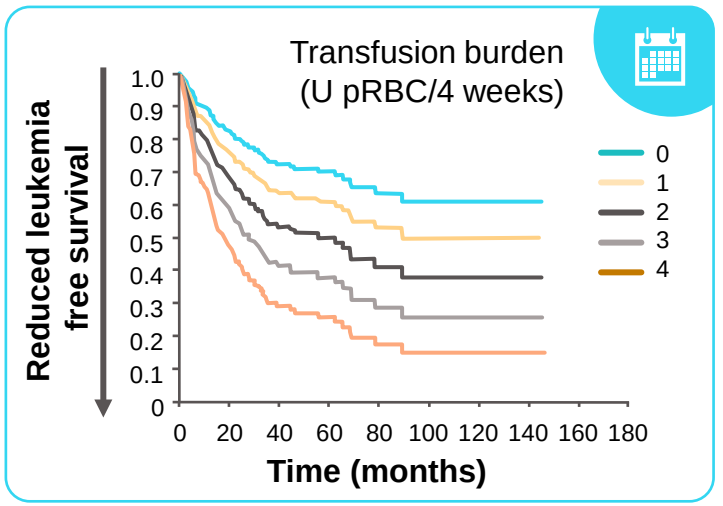
Transfusion dependency in LR-MDS is associated with inferior OS

The effect of transfusion dependency is more noticeable in patients with LR MDS & is associated with the severity of transfusion requirement[1]

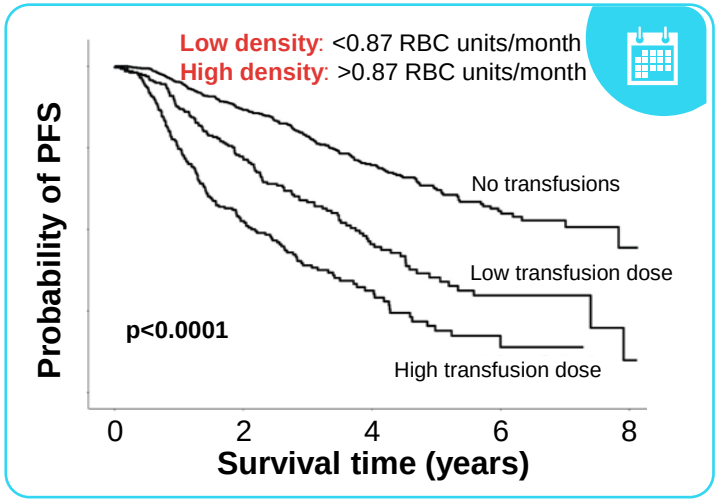
Overall survival (HR=1.36; p<0.001)[1]



Leukemia free survival (HR=1.40; p<0.001)[1]



Progression-free survival[2]



Malcovati et al.

EUMDS

EUMDS: European LeukemiaNet MDS Registry;
PFS: progression-free survival; pRBC: packed red blood cells

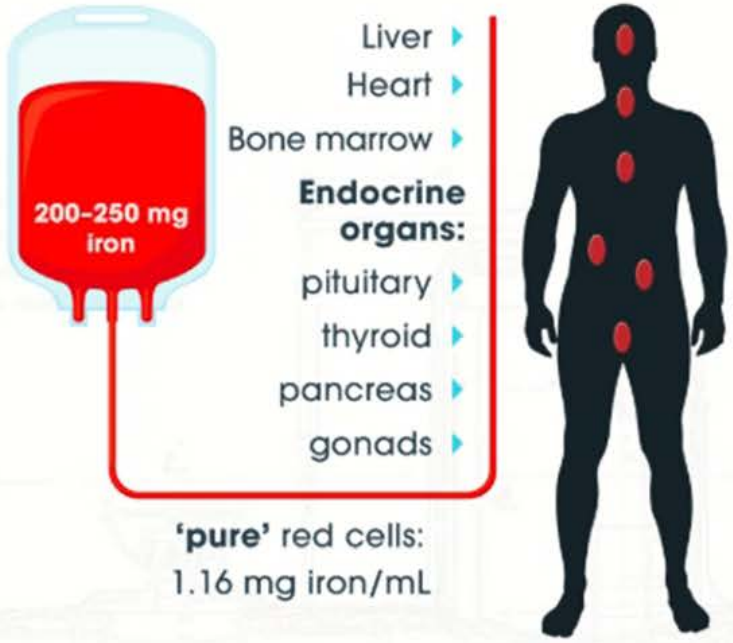
1. Malcovati L, et al. Haematologica 2006;91:1588-90; 2. de Swart L, et al. Haematologica 2019;104. Epub ahead of print

Fe accumulation | Organ endpoints | Oxidative stress | Hematopoiesis | Infections | AML progression | Event-free survival | Overall survival | HR MDS

Iron accumulation from transfusion therapy

Moderate transfusion requirement:

- 2 units/month
- ~ 100 units/4 years
- 100 units: ≥ 20g iron
- Iron is deposited in tissues & organs & causes toxicity
- Recent data from the EUMDS show that even receiving 0.87U/month is associated with inferior outcomes[1]

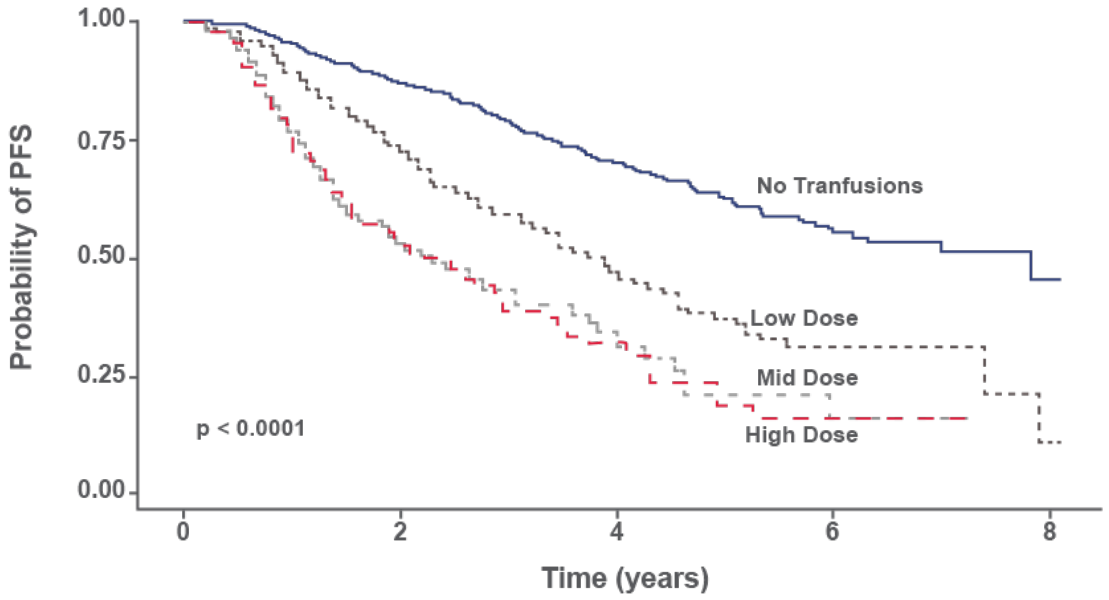


EUMDS, European LeukemiaNet MDS Registry; mg, milligrams; g, grams; U, units. de Swart L, et al. 2019 Haematologica; doi 10.3324/haematol.2018.212217.

Impact of Transfusions (?iron?) on Prognosis (Cont'd)

- de Swart et al. demonstrated that RBC transfusion dose density (units per month) is inversely correlated with PFS[1]
- The negative effect on PFS occurs even at transfusion densities below 1 units/month[1]
- MDS-related causes of death increased from 28% in the non-transfused group to 39% and 48% in patients with mid and high transfusion burden[1]

Progression-free survival stratified by transfusion densities[1*]



Number at risk					
No	751	447	220	71	4
Low	242	145	51	13	1
Mid	131	49	14	3	0
High	143	61	17	1	0

*Low dose defined as >0 to <0.75 units per month, mid dose defined as 0.75 – 1.75 units per month, high dose defined as >1.75 units per month
PFS, progression-free survival; RBC, red blood cell
[1]de Swart, et al. Haematologica. 2020;105(3):632-639.

Transfusion Iron Burden

- Guidelines recommend starting iron chelation once a patient has received >20U or >50U RBC (generally with a ferritin >1000 or >2500)[1-9]
- However, these numbers are extrapolated from the experience with beta thalassemia major in the era of deferoxamine
- Data are needed to determine the best transfusion burden to start iron chelation
- Given that achievable chelator dose may be limited by side effects

[1]Alessandrino EP, et al. Haematologica 2002;87(12):1286–306. [2]Bowen D et al.. Br J Haematol 2003;120(2):187–200. [3]Gattermann N, et al. Hematol Oncol Clin North Am 2005;19(Suppl 1):18–25. [4]Suzuki T, et al. Int J Hematol 2008;88(1):30–5. [5]Valent P, et al. Eur J Clin Invest 2008;38(3):143–9. [6]Greenberg PL, et al. J Natl Compr Canc Netw 2006;4(1):58–77. [7]Mittelman M, et al. Isr Med Assoc J 2008;10(5):374–6. [8]Wells RA, et al. Leuk Res 2008;32(9):1338–53. [9]Leitch HA et al. Leuk Res. 2018 Nov;74:21-41.

Measurements of Organ Iron

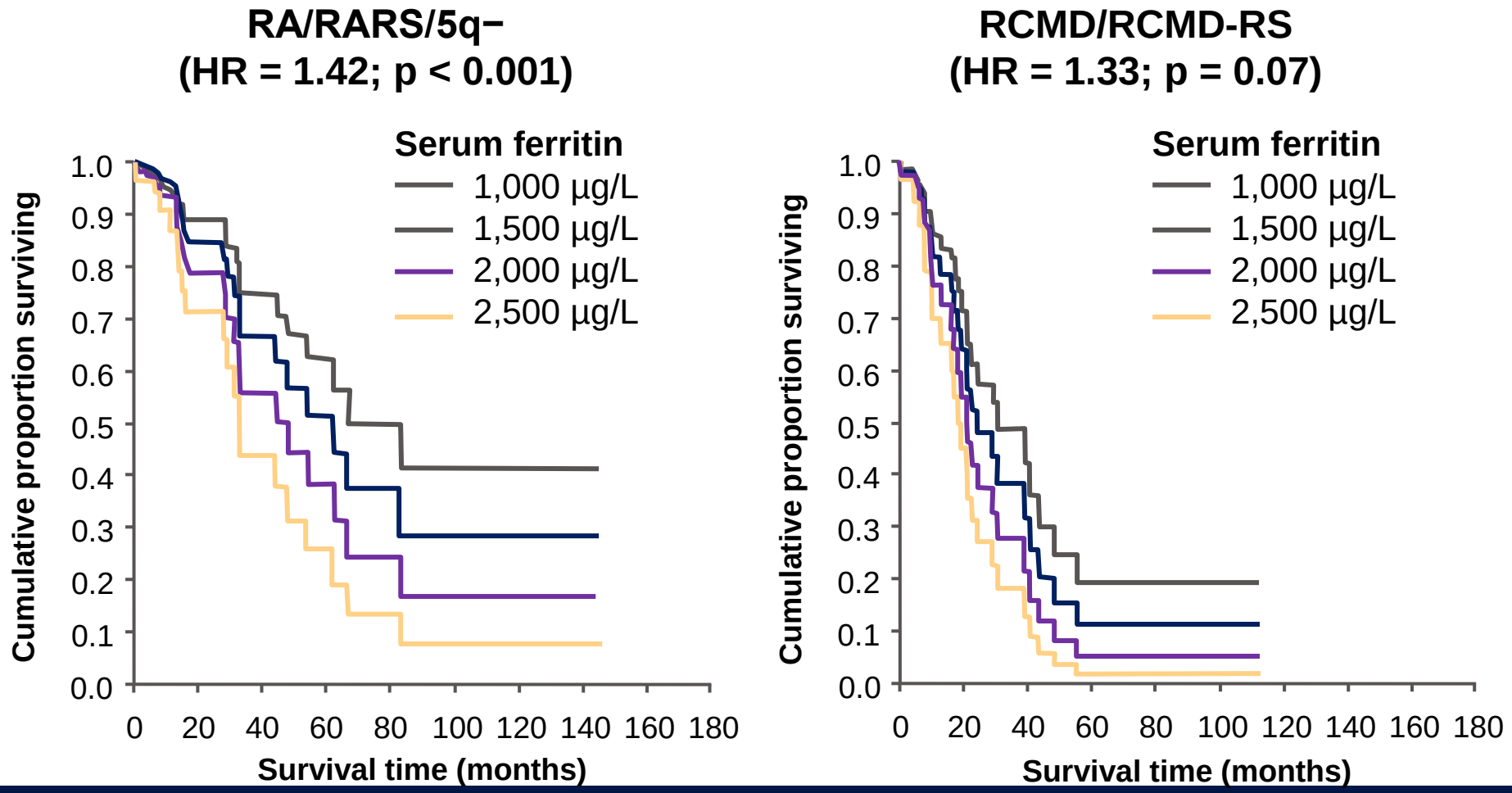
- Liver biopsy – is rarely done in patients with MDS due to neutropenia, thrombocytopenia and risk of infection and bleeding
- Preclinical and clinical data show that organ iron can be offloaded using chelation, with improvement in liver function tests[1,2]
- Imaging – Clinical data indicating a benefit of iron reduction in the organs are inconsistent in the SCT setting

[1]Vlachodimitropoulou E, et al.Blood. 2017 Oct 26;130(17):1923-33. [2]Gattermann N, et al. Haematologica. 2012 June 2012;97(1):138, Abstract 344.

Serum ferritin

- The vast majority of data in MDS address serum ferritin level
- Most data are retrospective and examine overall survival
- Other endpoints examined include:
  - organ events (cardiac, hepatic)
  - infection risk
  - hematologic improvement
  - outcomes in higher risk MDS
  - clinical endpoints around SCT

Overall survival of transfusion-dependent patients by serum ferritin level



RA = refractory anaemia; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ringed sideroblasts.

Malcovati L, et al. Haematologica. 2006;91:1588-90.

Levels of evidence and grades of recommendations

- Levels of evidence:
  - I, randomized controlled trials;
  - II-1, controlled, non-randomized trials;
  - II-2, cohort studies, preferably from more than one center;
  - II-3, comparison to historical controls, dramatic results of uncontrolled studies;
  - III, expert opinion.
- Grading of recommendations:
  - A, based on good evidence;
  - B, fair evidence; and
  - C, conflicting evidence

Canadian Task Force on Preventive Health Care, e-Appendix 1: definitions of levels of evidence and grades of recommendations of the Canadian Task Force on Preventive Health Care, Can. Med. Assoc. J. (2004) [cited 2018 April 29]; Available from: http://www.cmaj.ca/content/suppl/2004/03/15/170.6.976.

Relevant clinical endpoints around iron overload and iron chelation therapy in MDS.

Clinical endpoints considered[1]	Evidence level	Recommendation grade
IOL in MDS may contribute to:		
• **Organ dysfunction (cardiac, hepatic)**	II-2	NA
• Infections	II-2	NA
• Marrow failure	NA	NA
• Decreased overall survival	II-2	NA
• AML progression	II-2	NA
• Clinical endpoints around SCT[2]	II-2	NA
Iron chelation therapy may improve:		
• **Organ dysfunction**	II-3	B
• Infection risk	II-2	B
• Effective hematopoiesis	II-2	A
• Overall Survival	II-2	C
• Outcomes in higher risk MDS	III	B
• Clinical endpoints around SCT	II-2	B

[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Studies examining IOL & organ endpoints in TD IPSS LR MDS (cardiac, hepatic, endocrine)

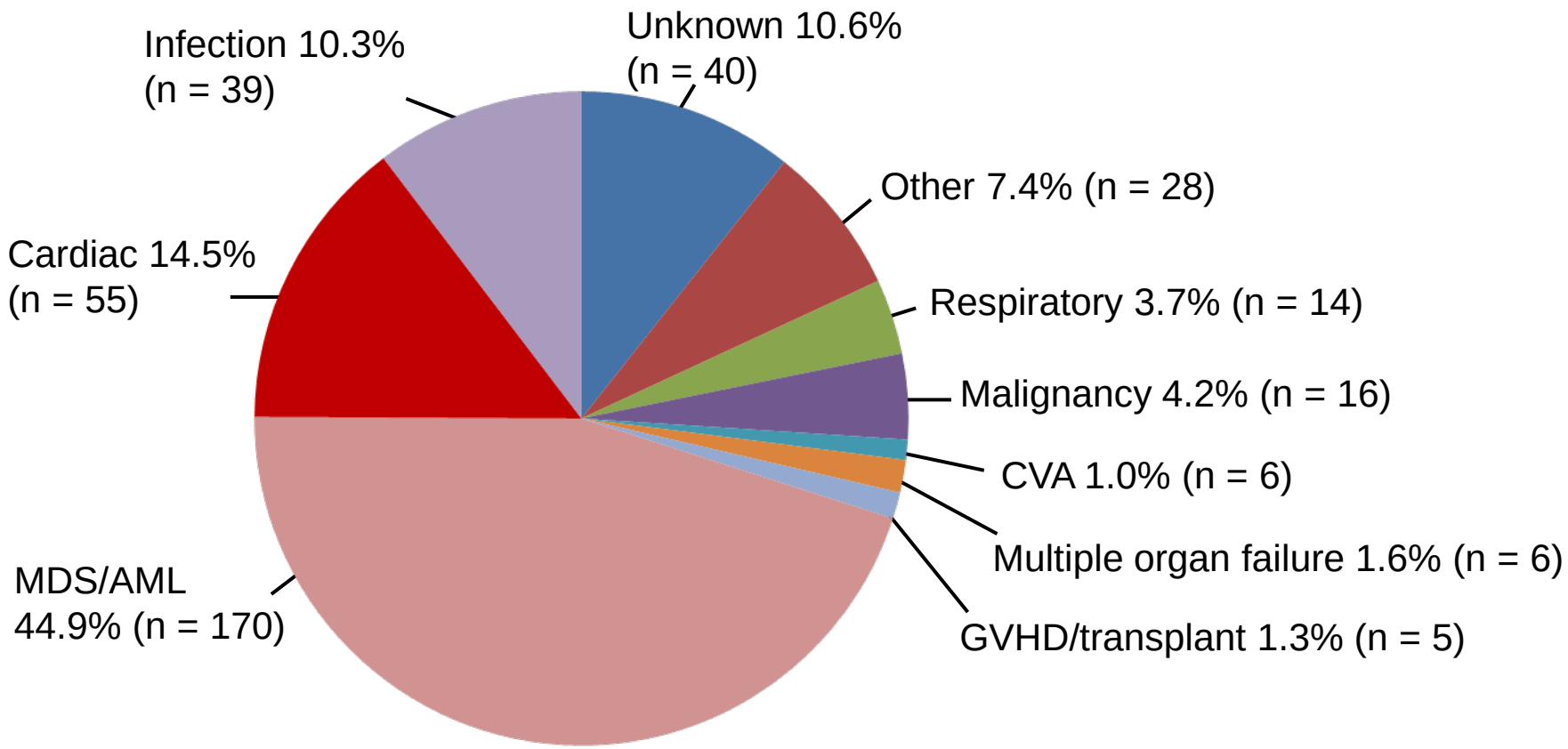
Study	N	IOL measure	Endpoint	Findings
Schaefer 1981	15	Median RBCU 120	organs	Elevated LFTs (87%), portal fibrosis (66%), Cardiomegaly (50%), CHF (27%), arrhythmias (53%), abnormal GTT (100%)
Jaeger 1992	46	Median RBCU 79	organs	Elevated LFTs (24%) Cardiac siderosis (43%), CHF deaths (30%), arrhythmias (22%) DM (11%)
Cazzola 1988	26	Median RBCU 64	organs	Elevated LFTs (69%) CHF (31%) Impaired GTT/DM (77%)
Takatoku 2007	152	Median RBCU ≈100	organs	Elevated LFTs (90%), hepatic failure (7%)1 CHF (24%)[1]
Ferte 2006	21	Median RBCU 81	heart	Cardiomegaly (43%), CHF 966%)

[1]present at death CHF, congestive heart failure; DP, disease progression; GTT, glucose tolerance test; HR, hazard ratio; IOL, iron overload; IPSS-R; International Prognostic Scoring System-Revised; LFT, liver function tests (transaminases); n, number; p, probability; RBCU, red blood cell units; SF, serum ferritin; TD, transfusion dependent; TI, transfusion independent.

Modified from Wells RA et al. Leuk Res 2008 Sep;32(9):1338-53.

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Cardiac disease is a leading cause of non-leukaemic death in MDS patients

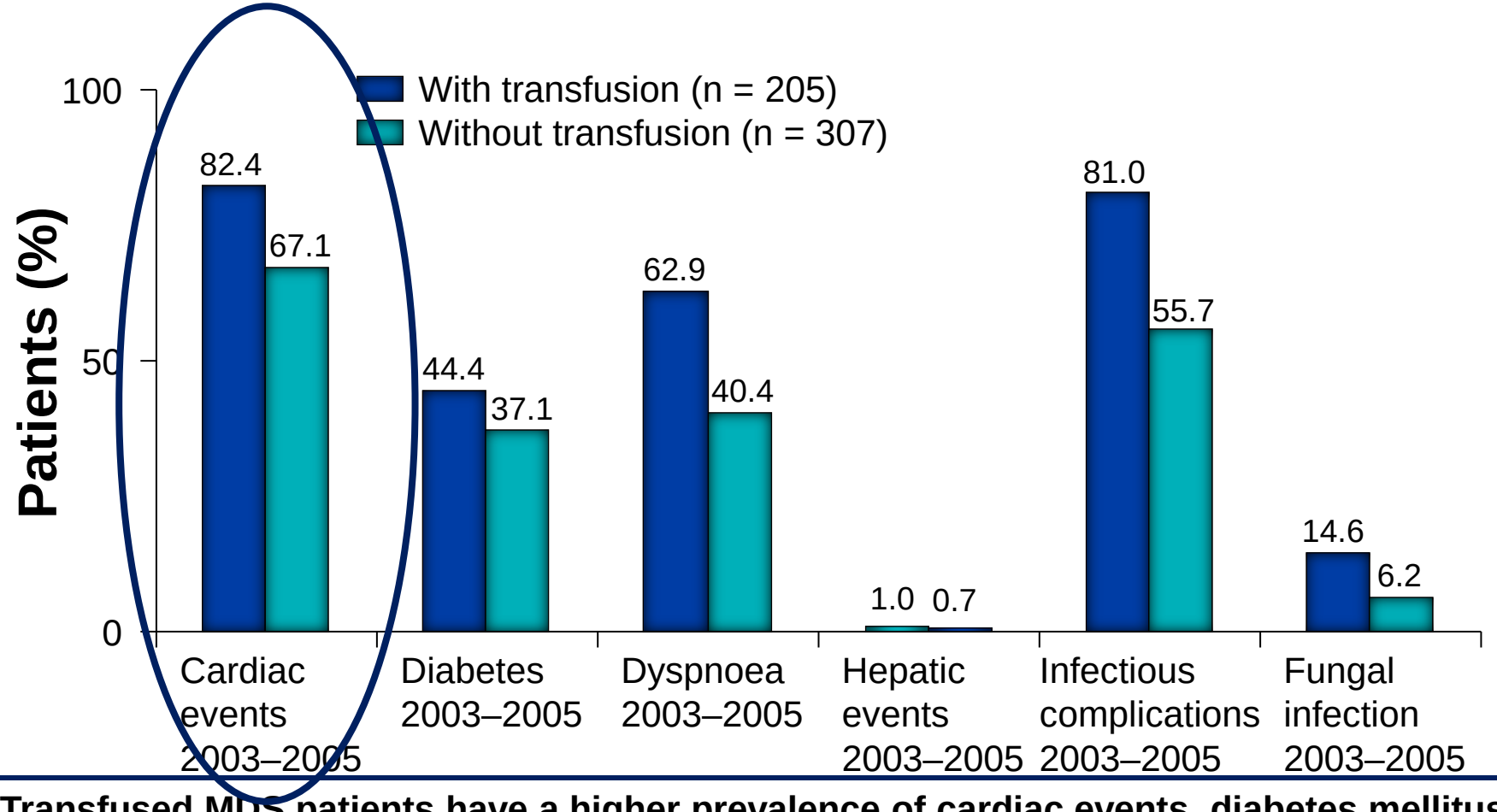


AML, acute myeloid leukaemia; CVA, cerebrovascular accident;

GVHD, graft-versus-host disease.

Marek BJ, et al. Blood. 2013;122:abstract 2775.

Prevalence of comorbidities in transfusion-dependent MDS: Cardiac



Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients

Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52.

CLOSE X

Cardiac events in transfused lower IPSS risk MDS

- Cardiac events included clinical episodes of CAD, CHF & ARR[1]
- Median TTCE was 7 & 20 months for ICT & non-ICT patients[1]
- In MVA, receiving ICT remained significant for TTCE (p=0.03)[1]
- For a detailed discussion of the contribution of IOL to atherosclerosis, see Vinchi et al (2014)[2]

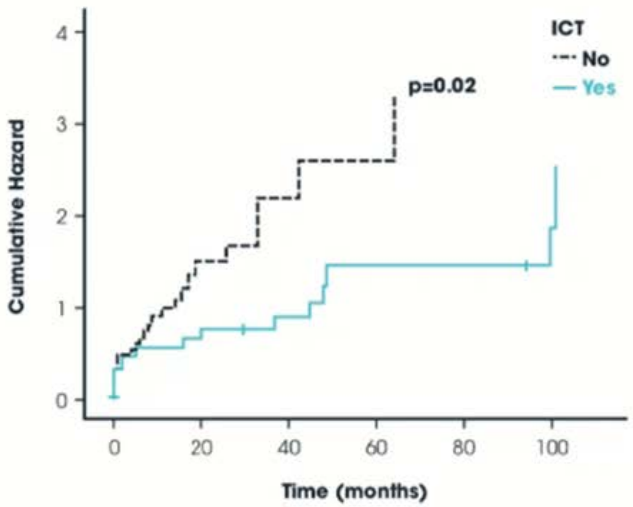


Figure Delayed time from RBC transfusion dependence to first cardiac event in lower IPSS risk MDS patients receiving iron chelation therapy

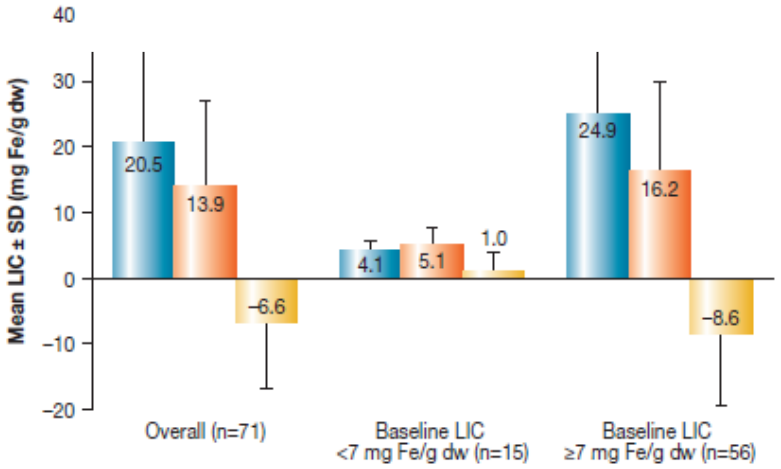
Wong CAC & Leitch HA. Leuk Res. 2019 Aug;83:106170.

ARR, arrythmia; CAD, coronary artery disease; CHF, congestive heart failure; ICT, iron chelation therapy; MVA, multivariate analysis; TD, transfusion dependence; TTCE, time to cardiac event. [1]Wong CAC & Leitch HA. Leuk Res. 2019;83:106170. [2]Vinchi F, et al. Front Pharmacol. 2014;5:1-20.

MDS pooled analysis: Deferasirox reduces iron overload & improves liver function

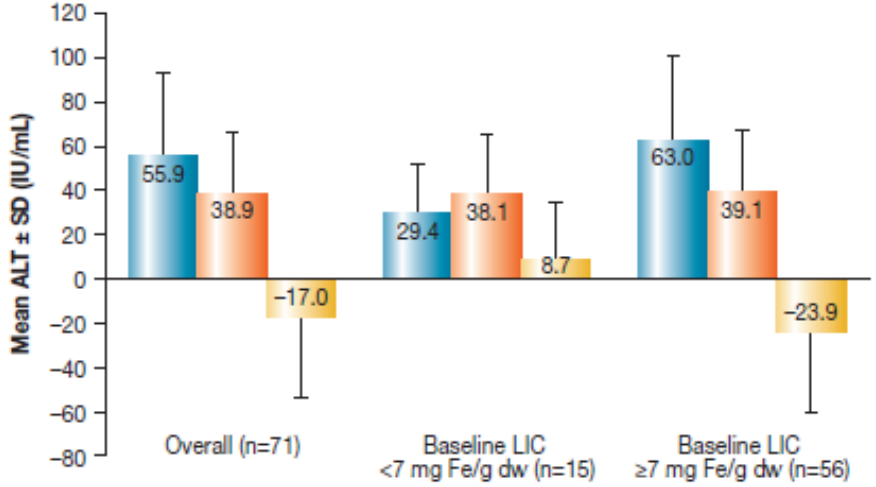
EPIC, US02, Studies 108 & 2204

Mean LIC baseline to EOS



- Proportion of patients with LIC ≥7 mg Fe/g dw reduced from 78.9% at baseline to 59.2% at EOS
- Among patients with baseline LIC ≥7 mg Fe/g dw, 58.9% achieved an LIC decrease of ≥30%
- Most patients had elevated baseline SF:
  - ≤2500 ng/mL – 48.4%
  - >2500 -≤5000 ng/mL – 35.5%
  - >5000 ng/mL – 16.1%

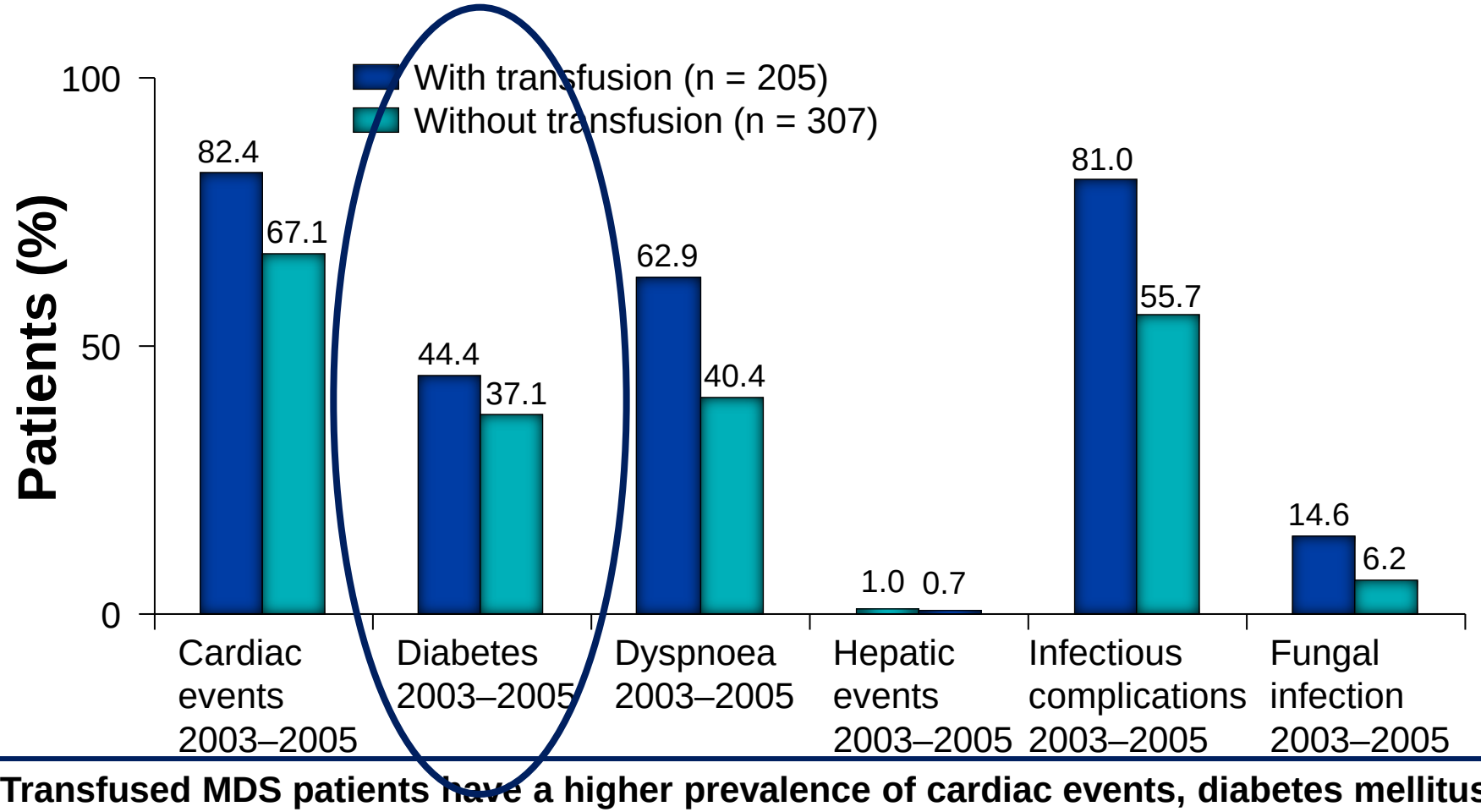
Mean ALT baseline to EOS



- Patients with baseline LIC ≥7 mg Fe/g dw: 32.1% normal ALT at baseline vs 71.4% at EOS

Gattermann N, et al. Haematologica. 2012 June 2012;97(1):138, Abstract 344.

Prevalence of comorbidities in transfusion-dependent MDS: Endocrine



Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients

Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52.

Relevant clinical endpoints around iron overload and iron chelation therapy in MDS.

Clinical endpoints considered[1]	Evidence level	Recommendation grade
IOL in MDS may contribute to:		
• Organ dysfunction (cardiac, hepatic)	II-2	NA
• **Infections**	II-2	NA
• Marrow failure	NA	NA
• Decreased overall survival	II-2	NA
• AML progression	II-2	NA
• Clinical endpoints around SCT[2]	II-2	NA
Iron chelation therapy may improve:		
• Organ dysfunction	II-3	B
• **Infection risk**	II-2	B
• Effective hematopoiesis	II-2	A
• Overall Survival	II-2	C
• Outcomes in higher risk MDS	III	B
• Clinical endpoints around SCT	II-2	B

[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Iron overload may increase infections in MDS – preclinical:

- An iron rich environment enhances the growth of microorganisms.
  - Yersinia is a recognized cause of infection in transfused patients[1].
- NTBI augmented the growth of Staphylococcus aureus in the serum of hemodialysis patients receiving iv iron[2].
- HFE-deficient mice had increased susceptibility to Mycobacterium avium[3].
- IOL can lead to functional impairment of neutrophils, macrophages & NK cells, including phagocytic capacity[4-8].

[1]Cantinieaux B, et al. J Lab Clin Med. 1988;111(5):524-8. [2]Barton Pai A, Am J Nephrol. 2006;26(3):304-9. [3]Gomes-Pereira S, et al. Infect Immun. 2008;76(10):4713-9. [4]Cantinieaux B, et al. Eur J Haematol 1987;39(1):28-34. [5]Cantinieaux B, et al. J Lab Clin Med.1999;133(4):353-61. [6]van Asbeck BS, et al. J Immunol.1984;132(2):851-6. [7]van Asbeck BS, et al. J Infect. 1984;8(3):232-40. [8]Nairz M, et al. Front Pharmacol. 2014;5:152.

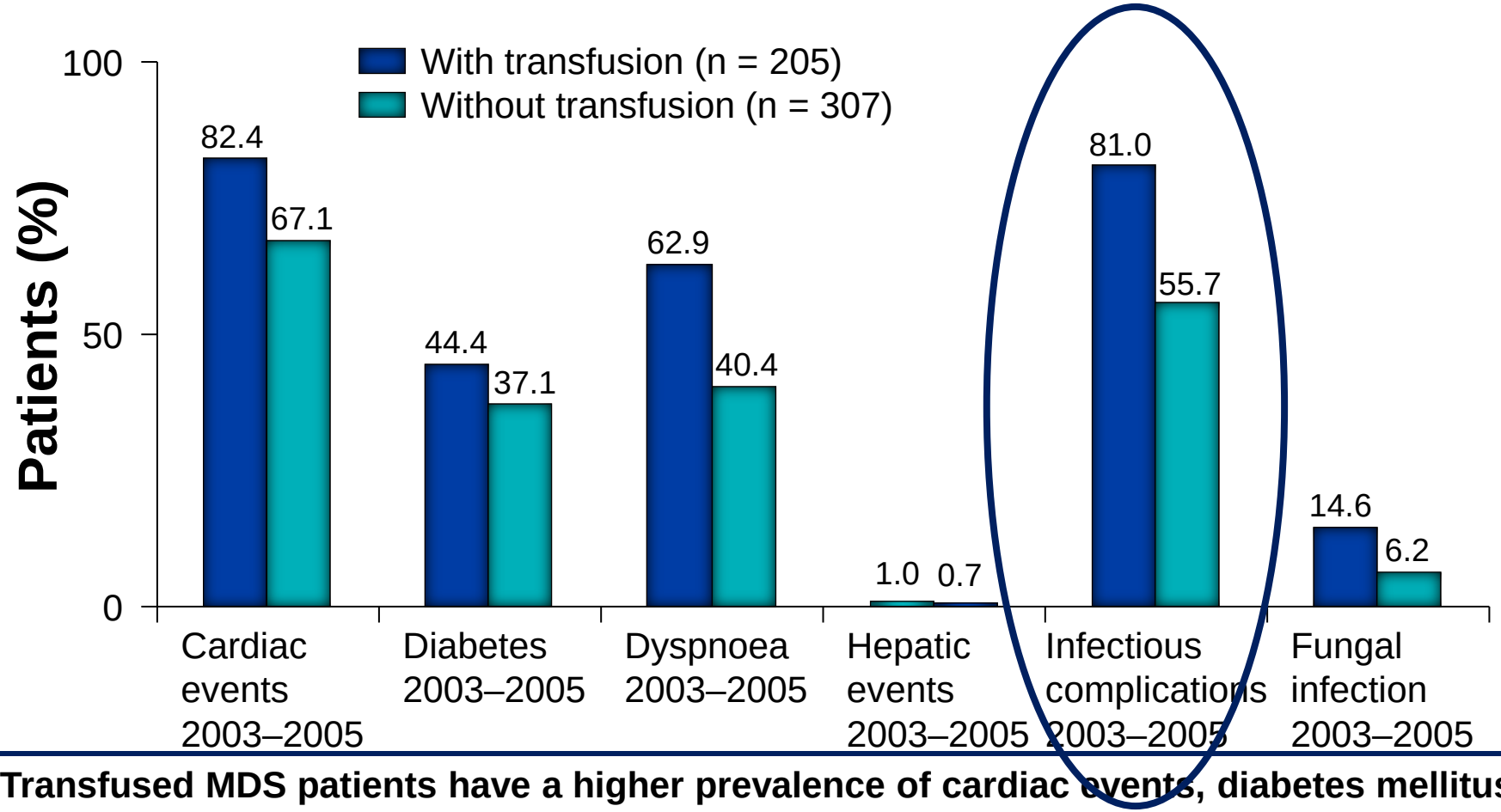
Iron overload may increase infections in MDS – clinical:

- In NTDT patients, a risk factor for severe bacterial infections (sepsis, meningitis, organ abscess) was SF >1000ng/mL[1].
- Several studies in HSCT for hematologic malignancies identify IOL (elevated pre-SCT SF, hepcidin level, or LIC) as a risk factor for significant infections (bloodstream infections, infectious deaths, bacterial infections, invasive mold infections, severe infections)[2-16].
- A US Medicare Registry analysis indicated that MDS patients who were TD had a higher rate of infections than those who were TI (81 vs 55.7%, $p<0.001$)[17].
- In MDS, though factors such as neutropenia and pre-existing neutrophil dysfunction must be taken into account as contributing to infection risk, the data suggest that IOL may increase infectious risk.

[1]Teawtrakul N, et al.. Int J Infect Dis. 2015;39:53-6. [2]Platzbecker U, et al. Biol Blood Marrow Transplant. 2008;14(11):1217-25. [3]Kataoka K, et al. Biol Blood Marrow Transplant. 2009;15(2):195-204. [4]Sivgin S, et al. Neoplasma. 2012;59(2):183-90. [5]Tachibana T, et al. Int J Hematol. 2011;93(3):368-74. [6]Altes A, et al. Bone Marrow Transplant. 2004;34(6):505-9. [7]Garcia-Vidal C, et al. Clin Infect Disease: 2008;47(8):1041-50. [8]Kanda J, et al. Haematologica. 2008;93(10):1550-4. [9]Ozyilmaz E, et al. Bone Marrow Transplant. 2010;45(10):1528-33. [10]Storey JA, et al. J Hematol Oncol. 2009;2:44. [11]Miceli MH, et al. Bone Marrow Transplant. 2006;37(9):857-64. [12]Pullarkat V, et al. Bone Marrow Transplant. 2008;42(12):799-805. [13]Virtanen JM, et al. Eur J Haematol. 2013;91(1):85-93. [14]Wermke M, et al. Lancet Haematol. 2018 May;5(5):e201-e210. [15]Busca A, et al. Biol Blood Marrow Transplant. 2010;16(1):115-22. [16]Altes A, et al. Ann Hematol. 2007;86(6):443-7. [17]Goldberg SL, et al. J Clin Oncol. 2010;28(17):2847-52.

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Prevalence of comorbidities in transfusion-dependent MDS: Infections



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Infections

- An iron rich environment enhances the growth of microorganisms. IOL leads to functional impairment of neutrophils, macrophages & natural killer cells[1-7].
- In SCT for hematologic malignancies, IOL (elevated pre-SCT SF, hepcidin level, or LIC) is a risk factor for significant infections[8].
- An analysis from the US Medicare Registry indicated that TD MDS had a higher rate of infections than TI (81 vs 55.7%, p<0.001)[9].
- In 138 RBC TD lower IPSS risk MDS, median time to first infection (TTI) in patients not receiving ICT was shorter (7.8 vs 27 months for ICT patients, p<0.0001)[10].

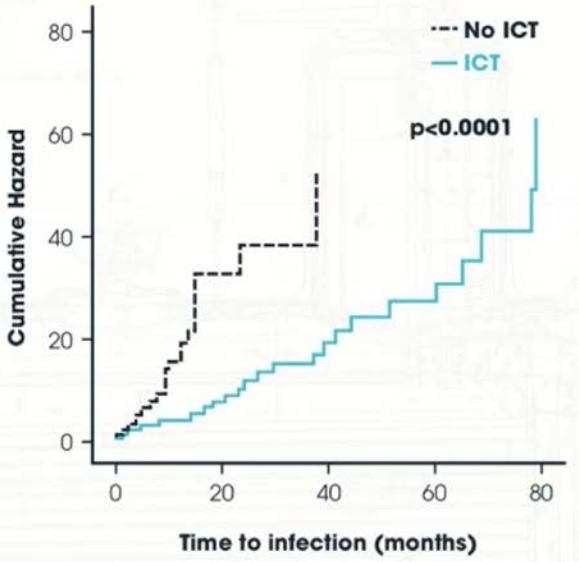

Figure Time from first RBC transfusion to first infection in patients with lower IPSS risk MDS not receiving or receiving iron chelation therapy[9].

Wong CAC, et al. Leuk Res. 2018 Apr;67:75-81.

ICT, iron chelation therapy; IOL, iron overload; LIC, liver iron concentration; SCT, stem cell transplantation; SF, serum ferritin; TD, transfusion dependent; TI, transfusion independent; TTI, time to infection. [1]Cantinieaux B, et al. J Lab Clin Med. 1988;111:524-8. [2]Barton Pai A, et al. Am J Nephrol. 2006;26:304- 9. [3]Cantinieaux B, et al. Eur J Haematol. 1987;39:28-34. [4]Cantinieaux B, et al. J Lab Clin Med. 1999;133:353-61. [5]van Asbeck BS, et al. J Immunol. 1984;132:851-6. [6]van Asbeck BS, et al. J Infect. 1984;8:232-40. [7]Nairz M, et al. Front Pharmacol. 2014;5:152. [8] Leitch HA, et al. Crit Rev Oncol Hematol. 2017 May;113:156-170. [9]Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52. [10]Wong CAC, et al. Leuk Res. 2018;67:75-81.

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• Infections	II-2	NA
• **Marrow failure**	NA	NA
• Decreased overall survival	II-2	NA
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Iron chelation therapy may improve:		
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• **Effective hematopoiesis**	II-2	A
• Overall Survival	II-2	C
• Outcomes in higher risk MDS	III	B
• Clinical endpoints around SCT	II-2	B

[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Iron overload contributes to marrow failure in MDS - preclinical

- Erythropoiesis was impaired in vitro in MDS patients with SF >250ng/mL; p=0.0012)[1].
- Hematologic reconstitution of normal donor cells was delayed in IOL recipients ($p<0.05$)[2].
- The bone marrow hematopoietic microenvironment was impaired in mice with IOL
  - with decreased expression of CXCL-12, kit-ligand, VCAM-1, IGF-1 and serum EPO & TPO.
  - This led to impaired interactions between stromal and HSPC, and impaired hematopoiesis[2].
  - The proliferation of mouse bone marrow mesenchymal cells was also impaired by IOL[3].
- Some hypothesize that SF may have inflammatory, angiogenic, matrix remodeling and immunomodulatory properties, which may explain some observations[4].
- In summary, multiple pre-clinical data give biological plausibility to a suppressive effect of IOL on hematopoiesis.

[1]Hartmann J, et al. Leuk Res 2013;37(3):327-32. [2]Taoka, et al. Int. J. Hematol. 95 (February (2)) (2012) 149–159. [3]Zhang Y, et al., PLoS One 10 (3) (2015) E0120219.
[4]Raaijmakers M.H.,Cell Stem Cell 14 (June (6)) (2014) 695–697.

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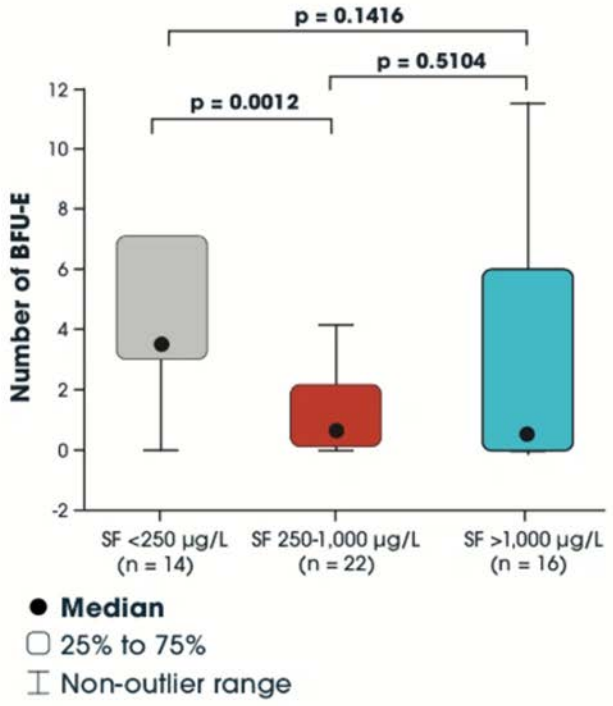
Bone marrow failure



Hartmann J, et al. Leukemia Research. 2013 Mar;37(3):327-32.

Hartmann J, et al. Leukemia Research. 2013 Mar;37(3):327-32.

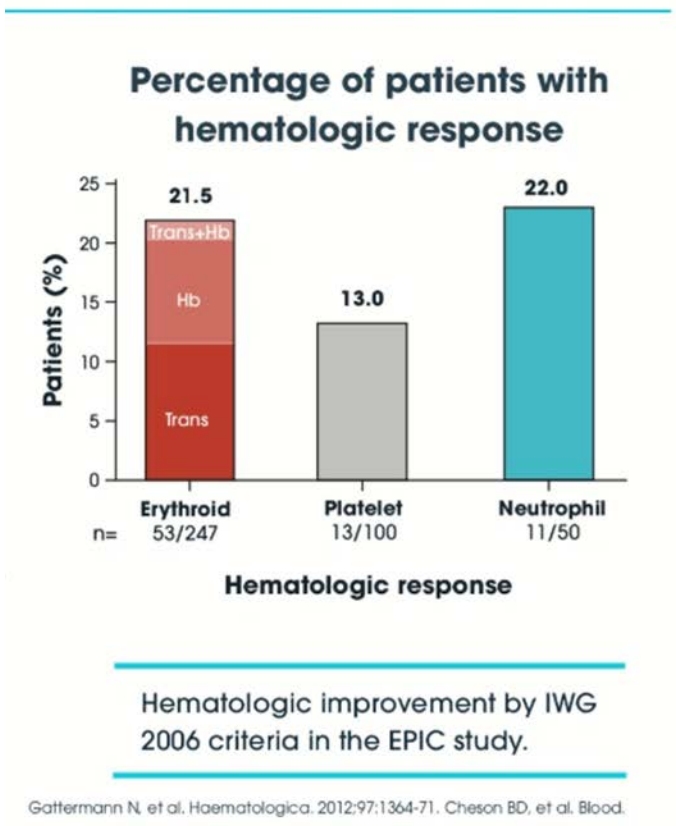
BFU-E, burst-forming units erythroid; EPIC, Evaluation of Patients' Iron Chelation with Exjade; IWG, International Working Group; SF, serum ferritin. Gattermann N, et al. Haematologica. 2012;97:1364-71. Cheson BD, et al. Blood. 2006;108:419-25.

IOL/Marrow Failure: Oxidative Stress

- Measures of cellular oxidative DNA damage were elevated with RBC transfusion[1].
- Plasma nitrite & malonaldehyde, a secondary product of lipid peroxidation, showed a significant increase in patients with MDS & IOL ($p<0.05$)[2].
  - Both were positively correlated with the SF level.
- The clonogenic capacity of HSPC was inhibited by ROS[3]
  - an effect which was attenuated by the antioxidant NAC or the iron chelator DFX.

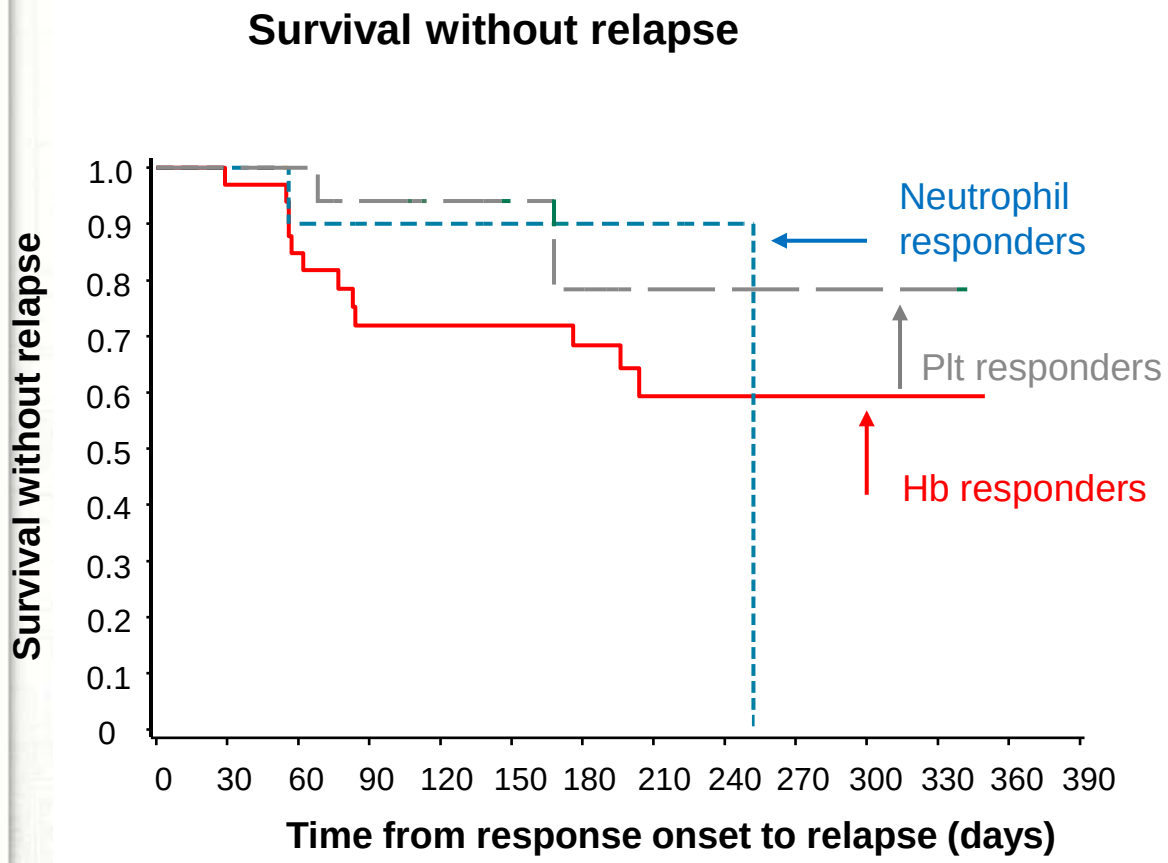
[1]Kobune M, et al., Blood 122 (November (21)) (2013) 959. [2]de Souza, G.F., et al., J. Clin. Pathol. 66 (November (11)) (2013) 996–998. [3]Chai X, et al., Zhongguo Yi Xue Ke Xue Yuan Xue Bao 35 (October (5)) (2013) 547–552.

Hematological responses in MDS patients treated with DFX: an EPIC post-hoc analysis using IWG 2006 criteria



Hematologic improvement by IWG 2006 criteria in the EPIC study.

Gattermann N, et al. Haematologica. 2012;97:1364-71. Cheson BD, et al. Blood.



Gattermann N, et al. Haematologica. 2012 Sep;97(9):1364-71.

Studies examining hematologic improvement in transfusion dependent lower IPSS risk MDS patients receiving ICT.

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Study	N (RBC, NEUTS, PLTS)	Erythroid response	Neutrophil response	Platelet response	Reference
Jensen 1996[1]	5	5 TI	NR	NR	[174]
Cilloni 2011[2]	57	45.6%	NR	NR	[187]
List 2012	173 52 77	15%	15%	22%	[186]
Gattermann 2012	247 50 100	21.5%	22%	13%	[183]
Nolte 2012	50	11%	NR	NR	[185]
Angelucci 2012	152	TI in 12% at 12 months	NR	NR	[255]
Breccia 2015	40	45.6	NR	NR	[256]
Maurillo 2015[3]	105	7.1	7.1	5.9	[191]
Rose 2016	57	19% at 12 months	NR	NR	[257]
Messa 2017[4]	98	45.6	NR	NR	[258]

AA, aplastic anemia; AML, acute myeloid leukemia; DFX, deferasirox; DFO, deferoxamine; mo, months; N, number; NEUTS, neutrophils; NR, not reported; PLTS, platelets; PMF, primary myelofibrosis; RBC, red blood cell;

Relevant clinical endpoints around iron overload and iron chelation therapy in MDS.

Clinical endpoints considered[1]	Evidence level	Recommendation grade
IOL in MDS may contribute to:		
• Organ dysfunction (cardiac, hepatic)	II-2	NA
• Infections	II-2	NA
• Marrow failure	NA	NA
• **Decreased overall survival**	II-2	NA
• **AML progression**	II-2	NA
• Clinical endpoints around SCT[2]	II-2	NA
Iron chelation therapy may improve:		
• Organ dysfunction	II-3	B
• Infection risk	II-2	B
• Effective hematopoiesis	II-2	A
• **Overall Survival**	II-2	C
• Outcomes in higher risk MDS	III	B
• Clinical endpoints around SCT	II-2	B

[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Studies examining IOL & overall and leukemia-free survival in TD lower IPSS risk MDS.

Study	N	IOL measure	Endpoint	Findings
Malcovati 2006	467	Per +1 RBCU/4wk Per +500SF >1000ng/mL	OS, LFS OS	HR 1.36, 1.40, p<0.0001 HR 1.42, p<0.001
De Swart 2012	1000	TD	Mortality rate Without DP With DP	 TI, 5%; TD, 24% TI, 32%; TD, 66%
Hiwase 2017	408	TD	OS	TD at any point is associated with inferior OS independent of the IPSS-R (p<0.0001)

[1]present at death CHF, congestive heart failure; DP, disease progression; GTT, glucose tolerance test; HR, hazard ratio; IOL, iron overload; IPSS-R; International Prognostic Scoring System-Revised; LFS, leukemia free survival; LFT, liver function tests (transaminases); n, number; OS, overall survival; p, probability; RBCU, red blood cell units; SF, serum ferritin; TD, transfusion dependent; TI, transfusion independent. Modified from Wells RA et al. Leuk Res 2008 Sep;32(9):1338-53.

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Studies examining overall survival in transfusion dependent patients with lower IPSS risk MDS by receipt of iron chelation therapy.

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41

Study	N	Design	Endpoint	Non-chelated patients	Chelated patients	p value	Reference
Leitch 2008	178	Retrospective	Median OS	40 mo	Not reached	**0.003**	[201]
			4-year OS	43%	64%	**0.003**	
Rose 2010	97	Prospective follow-up	Median OS	53 mo	124 mo	**<0.0003**	[203]
			Median OS: adequate vs weak ICT	NA	124 vs. 85 mo	**<0.001**	
			Cardiac mortality	34.5%	37%	NS	
Neukirchen 2012	188	Matched pair analysis	Median OS	49 mo	75 mo	**0.002**	[204]
Komrokji 2011	97	Retrospective	Median OS	34 mo	59 mo	**0.013**	[205]
Delforge 2012	186	Retrospective	Median OS	37 mo	126 mo	**<0.001**	[252]
			Cardiac mortality	NR	NR	NS	
Zeidan 2015[2]	3926	Retrospective, registry	Median OS	47 wk	110 wk	**0.003**	[139]
			HR for death, 14-26 wks on DFX	1	0.77		
			HR for death, ≥53 wks on DFX	1	0.34	<0.001	
Remacha 2012, 2015	263	Retrospective	Median OS	105 mo	133 mo	<0.001	[165, 253]
			Cardiac EFS	90 mo	137 mo	0.017	
Leitch 2012	268	Retrospective	Median OS, non-RARS	44 mo	NR	**<0.001**	[202]
			Median OS, RARS	73.8 mo	134.4 mo	**0.025**	
Lyons 2017[4]	599	Prospective, registry	Median OS	47.8 mo	All 86.3 mo ICT >6 mo, 98.7 mo	**<0.0001**	[254]
			New or progressive cardiac condition	NR	NR	NS	
Langemeijer 2016[5]	765	Prospective, registry	Adjusted HR (for superior OS)			**0.006**	[208]
			TR		1.5		
			SF	1	1.6		
Mainous 2014[6]	1562	Meta-analysis	Pooled OR (for superior OS)	1	1.984	**<0.001**	[206]
Leitch 2017[7]	239	Prospective, registry	Median OS	2.1 y	5.2 y	**<0.001**	[207]
			MVA	HR for death2.0		**0.03**	

Canadian MDS (Prospective) Registry Analysis

- In 219 patients with IPSS LR-MDS, 83 received ICT and OS was measured from time of RBC TD
- 4 measures of frailty, comorbidity & disability at TD did not differ between ICT and non-ICT groups

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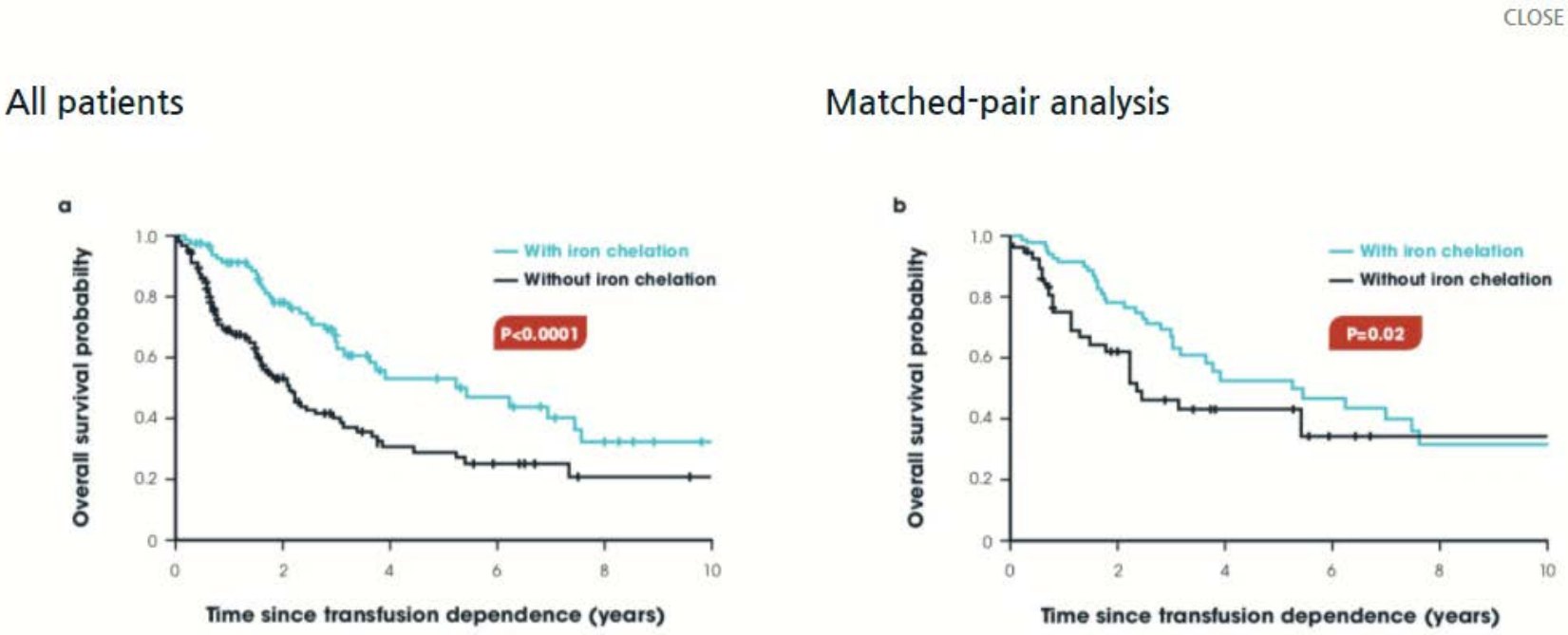


Figure. Overall survival in lower IPSS risk MDS from red blood cell transfusion dependence by receipt of iron chelation therapy a) in all patients; b) in patients matched 1:1 for age (≤50, 51-60, 61-65, 66-70, 71-75, 76-80, and >80 years), IPSS-R score (very low + low, intermediate, and high + very high), number of RBC units/month transfused (0, >0-≤2, >2-≤4, >4-≤6, & >6), and time from MDS dx until RBC transfusion dependence (0, >0-<6, >6-36, >36 months).

Leitch HA, et al. Br J Haematol. 2017 Oct;179(1):83-97.

Event-free survival: TELESTO

- Enrollment reduced by 2/3
- Mean age of patients only 60 years
- Half of placebo patients dropped out and subsequently received ICT

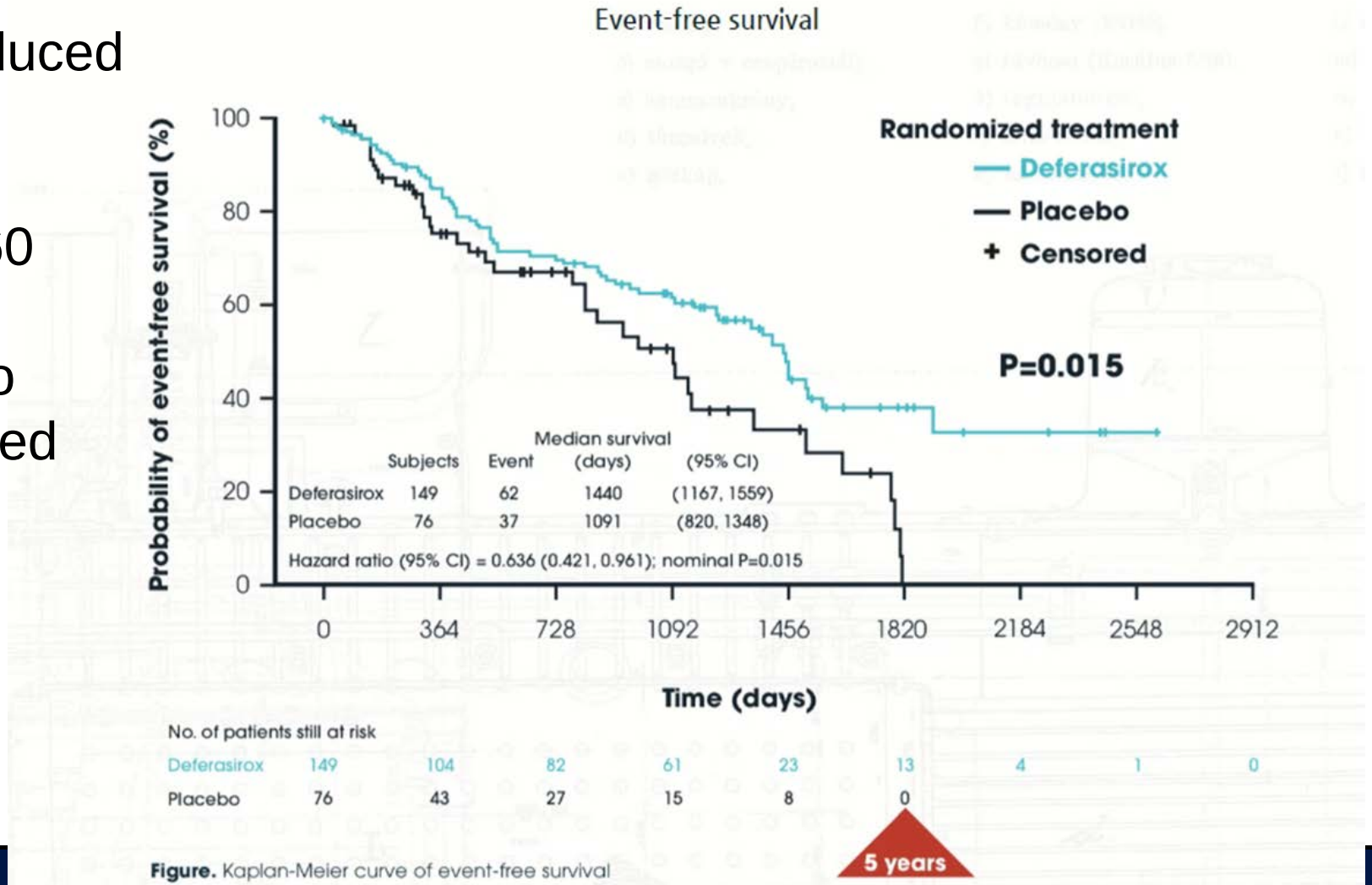


Figure. Kaplan-Meier curve of event-free survival

Angelucci E, et al. Ann Intern Med. 2020;172(8):513-522.

Relevant clinical endpoints around iron overload and iron chelation therapy in MDS.

Clinical endpoints considered[1]	Evidence level	Recommendation grade
IOL in MDS may contribute to:		
• Organ dysfunction (cardiac, hepatic)	II-2	NA
• Infections	II-2	NA
• Marrow failure	NA	NA
• Decreased overall survival	II-2	NA
• AML progression	II-2	NA
• Clinical endpoints around SCT[2]	II-2	NA
Iron chelation therapy may improve:		
• Organ dysfunction	II-3	B
• Infection risk	II-2	B
• Effective hematopoiesis	II-2	A
• Overall Survival	II-2	C
• **Outcomes in higher risk MDS**	III	B
• Clinical endpoints around SCT	II-2	B

[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

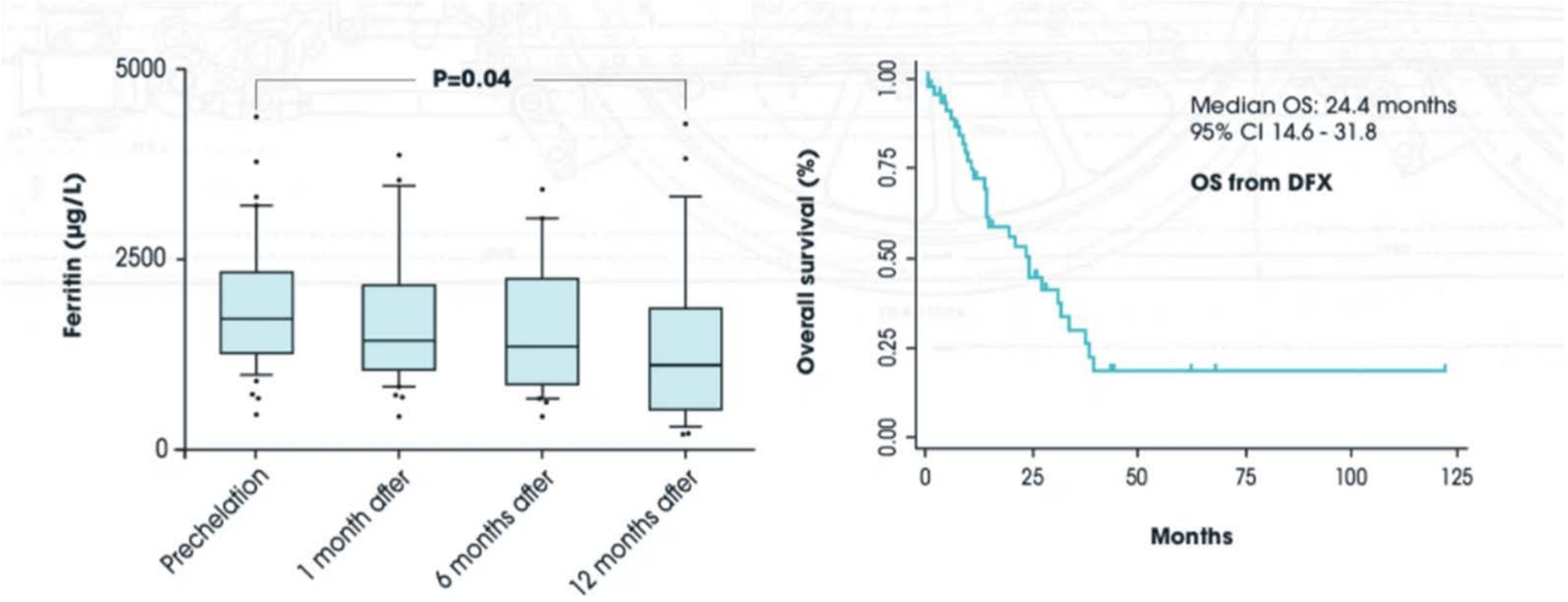
Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Iron Chelation Therapy in Transfusion-Dependent, Higher Risk MDS

- 2 studies of ICT in patients receiving novel agents
- A retrospective study (n=51) transfusion-dependent, intermediate-to-very high IPSS-R risk MDS, receiving DFX
- 36 (71%) received azacitidine (AZA) concomitantly
  - 8 (16%) grade 2-3 toxicities (renal or GI), 4 (8%) required interruption
  - During DFX; ≥temporary clinical benefits occurred in 22
  - 4 successfully underwent allo-SCT following DFX
  - Median SF decreased from 1709 to 1100ng/mL at 12 months (P=0·02)
  - 17 had abnormal transaminases that improved/normalized on DFX in 8
  - **1 became transfusion independent with DFX alone**

*Approximately 14mg/kg/day

ICT in HR-MDS



Musto P, et al. Br J Haematol. 2017;177(5):741-750.

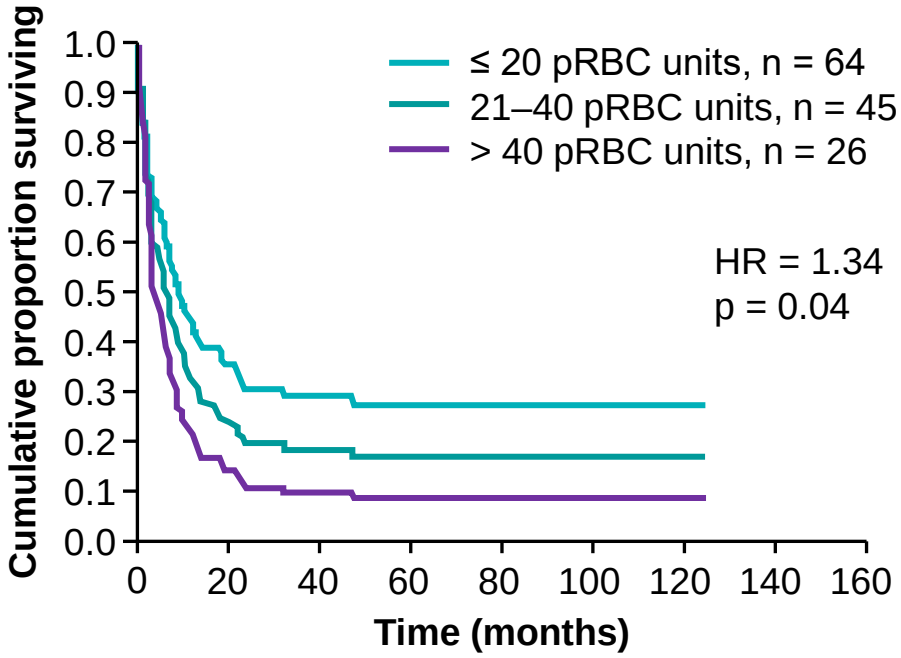
Relevant clinical endpoints around iron overload and iron chelation therapy in MDS.

Clinical endpoints considered[1]	Evidence level	Recommendation grade
IOL in MDS may contribute to:		
• Organ dysfunction (cardiac, hepatic)	II-2	NA
• Infections	II-2	NA
• Marrow failure	NA	NA
• Decreased overall survival	II-2	NA
• AML progression	II-2	NA
• **Clinical endpoints around SCT[2]**	II-2	NA
Iron chelation therapy may improve:		
• Organ dysfunction	II-3	B
• Infection risk	II-2	B
• Effective hematopoiesis	II-2	A
• Overall Survival	II-2	C
• Outcomes in higher risk MDS	III	B
• **Clinical endpoints around SCT**	II-2	B

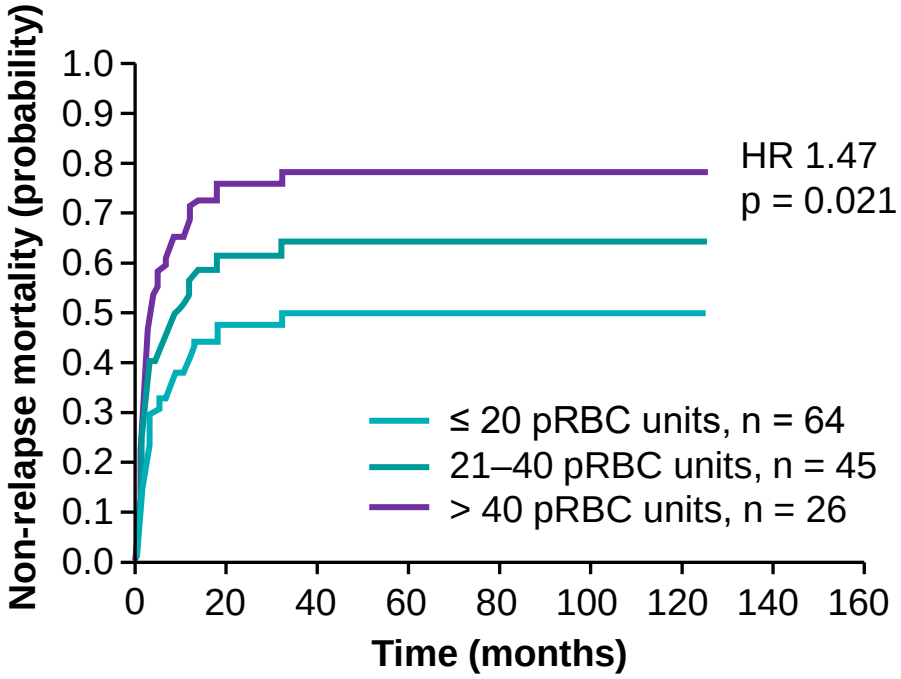
[1]in lower risk MDS except where specified [2]for hematologic malignancies including MDS AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; MDS, myelodysplastic syndrome; NA, not applicable; SCT, hematopoietic stem cell transplantation. Levels of evidence: I, randomized controlled trials; II-1, controlled, non-randomized trials; II-2, cohort studies, preferably from more than one center; II-3, comparison to historical controls, dramatic results of uncontrolled studies; and III, expert opinion. Grading of recommendations: A, based on good evidence; B, fair evidence; and C, conflicting evidence (reference [25]).

Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.

Retrospective: Impact of transfusion burden prior to SCT on OS and NRM post-SCT (n=357)



Overall survival by transfusion burden prior to SCT

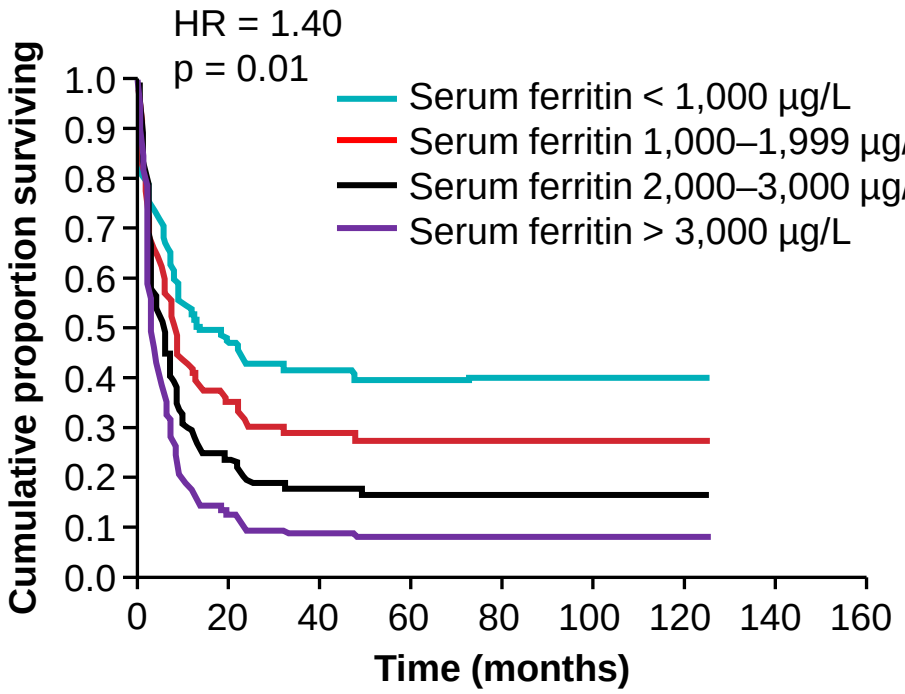


Non-relapse mortality by transfusion burden prior to SCT

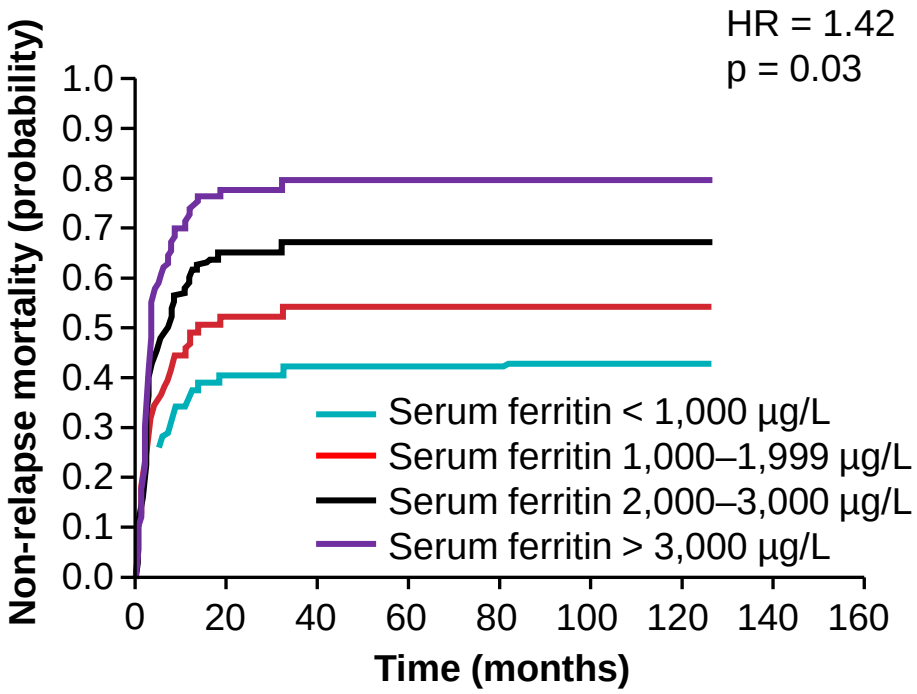
OS and NRM for < 20 units was not significantly different compared with transfusion-independent patients

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Impact of ferritin level prior to SCT on OS and NRM post-SCT (n = 129)



Overall survival by ferritin level prior to SCT



Non-relapse mortality by ferritin level prior to SCT

The impact of serum ferritin remained unchanged when the model was adjusted for albumin level

Alessandrino EP, et al. Haematologica. 2010;95:476-84

Table 4. Studies examining an impact of IOL in SCT for hematologic malignancies, and including a multivariate analysis or receiver operator curve (ROC) analysis. For retrospective analyses, studies of ≥50 patients were included; for prospective analyses, ≥25 patients.

Analysis	SCT	N	Diseases	IOL	Infection	Relapse	NRM	TRM	OS	other	Comments	Reference
Retro	MA	543	Multiple	Pre SF				0.002 (for MDS)	<0.00125	SOS 0.05, aGVH NS	Included albumin	Armand 2007
Retro	Allo NOS	172	MDS, AML	Pre SF	0.032 BSI				NS			Platzbecker 2008
Retro	MA & RIC	217	MDS	Pre SF		NS	0.03		0.01		Still sig adj for albumin NS in RIC	Alessandrino 2010
				TD pre			0.023		0.003			
Retro	Allo NOS	101	Multiple	Pre SF	NS	NS		0.003	0.001	SOS NS		Lee 2009
Retro	MA & NMA	264	Multiple	Pre SF	Infectious deaths 0.01		0.01@5y	0.05@5y		organ failure deaths 0.02		Kataoka 2009
Retro	Allo NOS	1448	Multiple	?pre SF				0.03@2y	≤0.005		NRM NS for NMA	Sorror 2009
Retro	MA	222	Multiple	Pre SF		0.003 RFS			0.003			Mahindra 2009
Retro	MA & RIC	477	Multiple	Pre SF	NS							Dadwal 2015
Retro	Allo NOS	84	Multiple	Pre SF	<0.023	0.039 DFS			0.023	Engraftment, aGVH NS		Sivgin 2012
Retro	MA	230	Multiple	Pre SF					<0.001		ROC analysis	Bazuaye 2012
Retro	MA & RIC	114	AML, MDS	Pre SF	)100 BSI 0.02						Time to engraftment 0.03	Tachibana 2011
Retro	Allo NOS	261	AL, MDS	Pre-SF		≤0.031 DFS			≤0.043			Tachibana 2012
Retro	MA & RIC	158	Multiple	Pre SF				0.04	0.002			Michallat 2013
Retro	Allo NOS	290	Multiple	Pre SF				Increased (PNR)	<0.02		OS sig @ 0-6, 6-12, 12-24 & 25-60 mo	Meyer 2013
Retro	MA & RIC	309	Multiple	Pre SF		0.015, 0.002 RFS		0.023	0.013			Wahlin 2011
Retro	MA, RIC, NMA	3917	Multiple	Pre SF			0.002 for SF >2500		0.02, 0.001 for SF >1000, >2500			Vaughn 2015
Retro	MA	59	Multiple	LIC at necropsy	Invasive aspergillus 0.012							Altes 2004
Retro	MA[1]	1248	Multiple	Pre(?) SF	nvasive mold <40d 0.02							Garcia-Vidal 2008
Retro	RIC	99	MDS, AML[2]	Pre SF		NS, DFS NS		NS	0.03			Lim 2010
Retro	NMA	64	multiple	Pre SF		NS	NS		0.01	aGVH NS		Mahindra 2009
Retro	Allo NOS & ASCT	55	Multiple	Pre hepcidin	bacterial 0.007							Kanda 2008
Retro	MA & ASCT	148	Multiple	Pre SF	Pulm fungal 0.045							Ozyilmaz 2010
Retro	MA, NMA & ASCT	427		Pre SF						SOS 0.04		Maradei 2009
Retro	MA, NMA & ASCT	77	Multiple	BMIS	0.02 IRM			0.03	0.01		SF, RBC TR, BM iron stores.	Storey 2009
Retro	ASCT	315	HL & NHL	Pre SF		0.049, 0.021 RFS			0.002			Mahindra 2008
Retro	ASCT	367	MM	BMIS	Severe <0.001							Miceli 2006

Leitch HA et al. Crit Rev Oncol Hematol. 2017 May;113:156-170.

Table 4 (continued)

Analysis	SCT	N	Diseases	IOL	Infection	Relapse	NRM	TRM	OS	other	Comments	Reference
Meta-analysis	MA & RIC	276	Multiple	SF pre			0.026 RIC		0.036		Including CRP	Armand 2014
Pro	MA	45	MDS, AL	SF, LIC by MRI		SF, LIC NS	SF, LIC NS		SF p=0.042LIC NS	LIC NS	Including CRP	Armand 2012[3]
Pro	MA & RIC	190	Multiple	SF pre	0.032 BSI			0.004	0.013@100d	0.001 severe GVH		Pullarkat 2008
Pro	MA & RIC	190	AML, AL	Pre SF	NS@100d	NS	NS	EFS NS	0.017	Grade II-IV aGVH NS		Tanaka 2015
Pro	MA & RIC	67	Multiple	LIC by MRI	0.003 severe			LIC NS	LIC NS			Virtanen 2013[3]
Pro	Allo NOS	133	AML, MDS	LIC by MRI, LPI	0.023 bacteremia LPI		D100 0.002 LPI					Wermke 2015
Pro	MA & RIC	88	MDS, AML	Pre SF, LIC by MRI, LPI			0.016 LIC		0.038 LIC			Wermke 2012[3]
Pro	MA & RIC	102	Multiple	Post SF, LIC by SQUID	0.006 IFI							Busca 2010
Pro	MA & RIC	88	Multiple	Pre SF, LIC by MRI			SF 0.03 LIC NS		SF 0.05 LIC NS			Trottier 2013[3]
Pro	Allo NOS & ASCT	25	Multiple	Pre SF, TS				0.01	≤0.02	Grade III-IV aGVH ≤0.01		Altes 2002
Pro	MA, RIC & ASCT	50	Multiple	Pre SF, TS >80%	0.006, 0.012 invasive aspergillus					Severe mucositis SF 0.03		Altes 2007

[1]predominantly [2]secondary [3]included in meta-analysis Abbreviations: AA, aplastic anemia; AE, adverse events; AL, acute leukemia; Allo, allogeneic; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; AST, aspartate aminotransferase; BM, bone marrow; BMIS, bone marrow iron score; BSI, bloodstream infection; bx, biopsy; CR, complete remission; CRP, C-reactive protein; CSP, cyclosporine; D, day; DFS, disease-free survival; EFS, event-free survival; GVH, graft versus host; Hb, hemoglobin; IFI, invasive fungal infection; IOL, iron overload; IRM, infection related mortality; LIC, liver iron concentration; LFT's, liver function tests; LLN, lower limit of normal; LPI, labile plasma iron; MA, myeloablative; MDS, myelodysplastic syndrome; mo, months; MRI, magnetic resonance imaging; NMA, non-myeloablative; MVA, multivariate analysis; n, number; NOS, not otherwise specified; NRM, non-relapse mortality; NS, not significant; OS, overall survival; p, probability; pro, prospective; RBCU, red blood cell units; retro, retrospective; RFS, relapse free survival; RI, relapse incidence; RIC, reduced intensity conditioning; ROC, receiver-operator curve; SCT, stem cell transplantation, SF, serum ferritin; SOS, sinusoidal obstructive syndrome; SQUID, Superconducting Quantum Interference Device; TD, transfusion dependent; TI, transfusion independent; TR, transfusion requirement; TRM, transplant-related mortality; TS, transferrin saturation

Leitch HA, et al. Crit Rev Oncol Hematol. 2017 May;113:156-170.

Iron Overload Prior to SCT: LIC

- 4 *prospective* studies examined LIC & outcomes in SCT

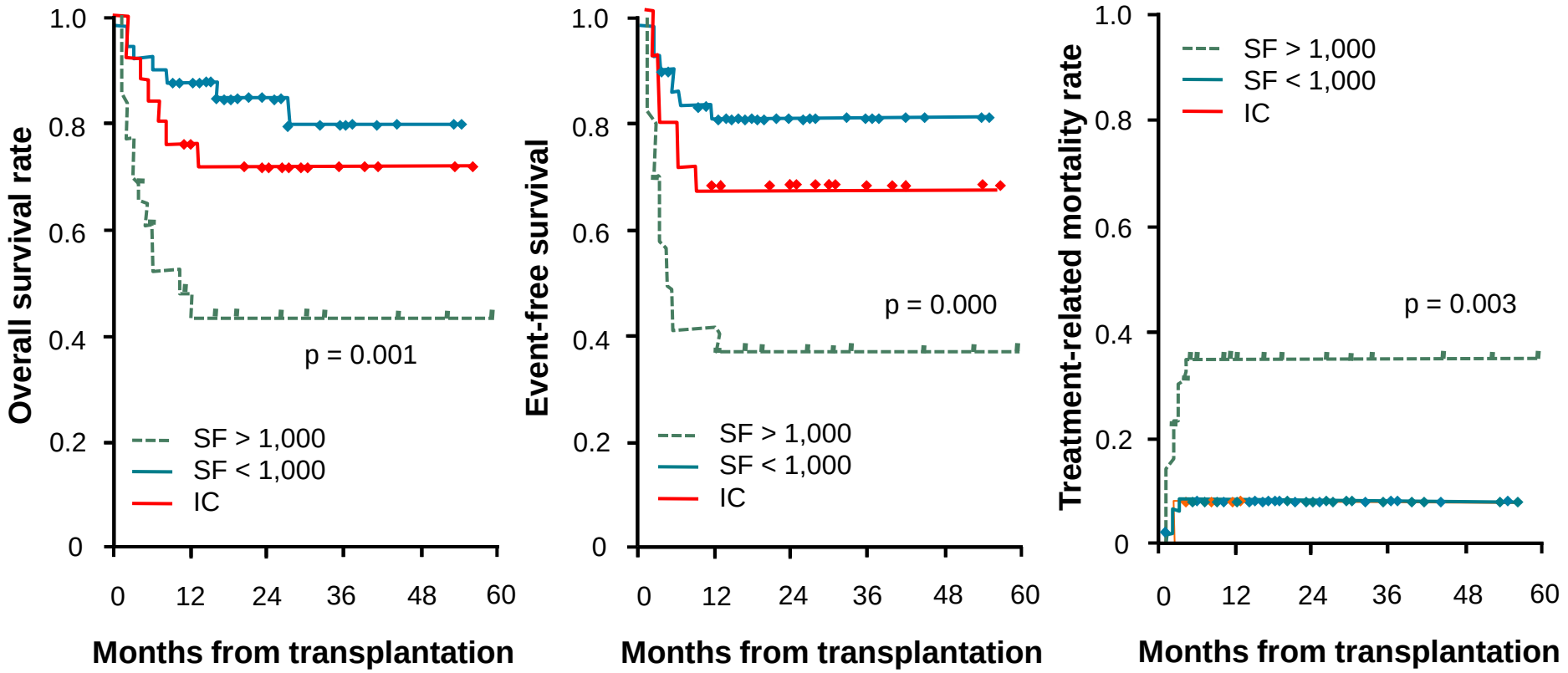
Studies examining an association between elevated *LIC* and clinical outcomes in SCT

		Clinical outcome, p-value				
Study	N	Severe infection	NRM	OS	GVH	relapse
Armand	48	-	NS	NS	NS	NS
Virtanen	67	**0.0003**	-	-	-	-
Trottier	88	-	NS	NS	-	-
Wermke	133	-	**0.016**	**0.038**	-	-

- A *meta-analysis* was conducted from these 4 studies[4]
  - The HR for mortality with LIC >7mg/gDW (primary endpoint) was **NS** (p=0.18)
  - [But SF >1000 ng/mL *was* significant for OS (p=0.036)]

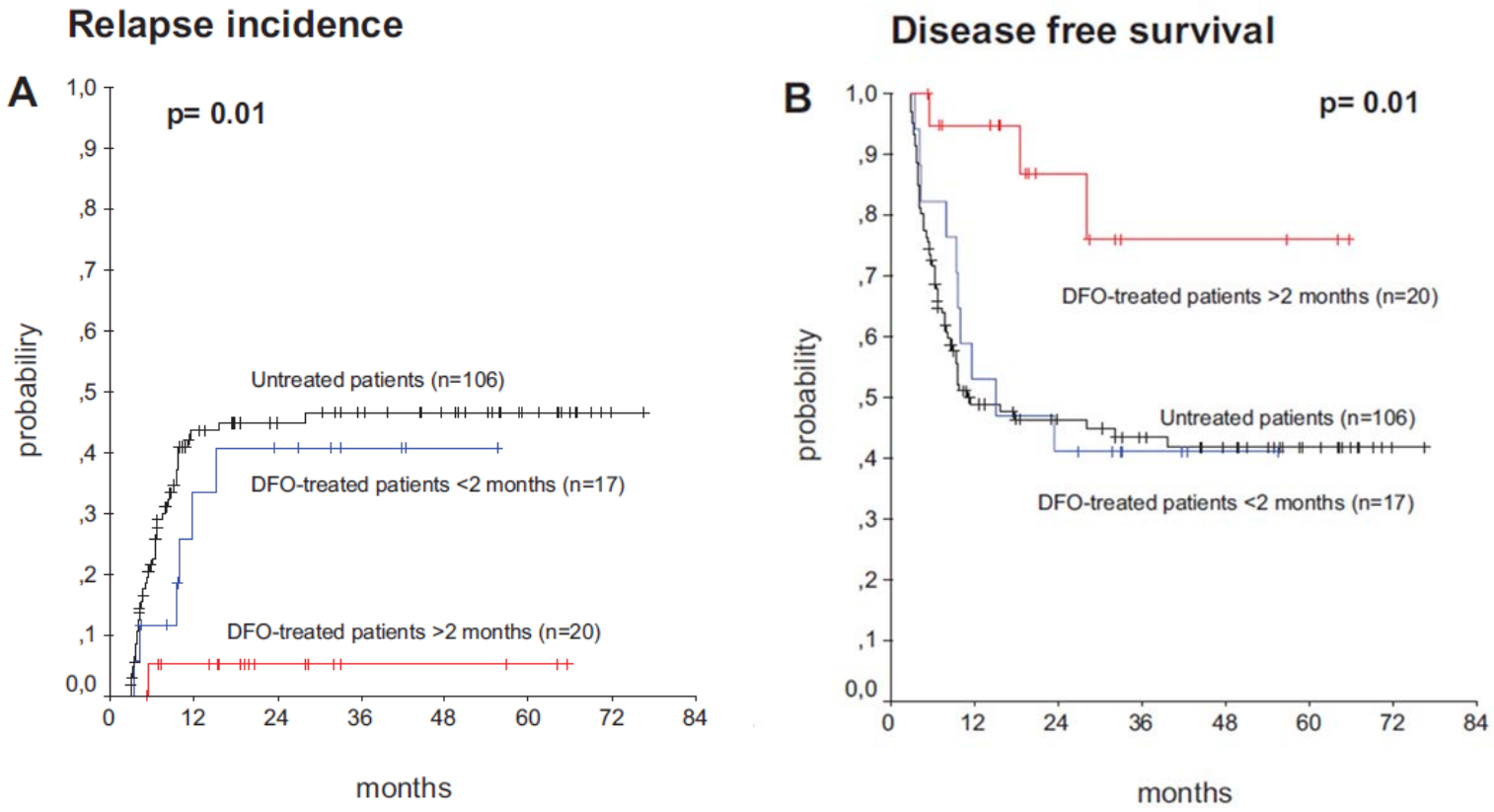
[1]Virtanen JM, et al. Eur J Haematol. 2013;91(1):85-9 [2]Trottier BJ, et al. Blood. 2013;122(9):1678-84. [3]Wermke M, et al. Clin Cancer Res. 2012;18(23):6460-8. [4]Armand P, et al. Biol Blood Marrow Transplant. 2014;20(8):1248-51.

Iron chelation *prior* to SCT (n = 101)



SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of SCT;
SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of SCT, without ICT;
IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before SCT.

Iron Chelation Therapy (deferoxamine) Post-SCT

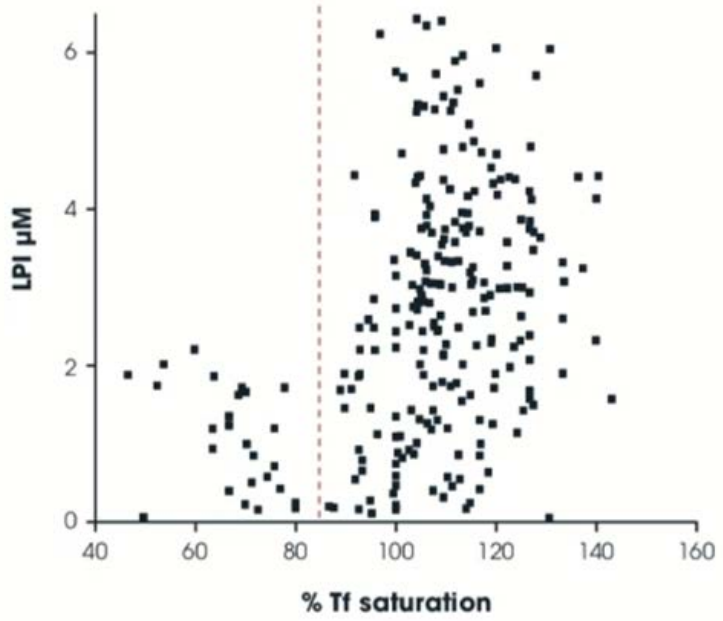


Kaloyannidis P, et al. Transplantation. 2010;89(4):472-9.

Iron-Induced Oxidative Stress

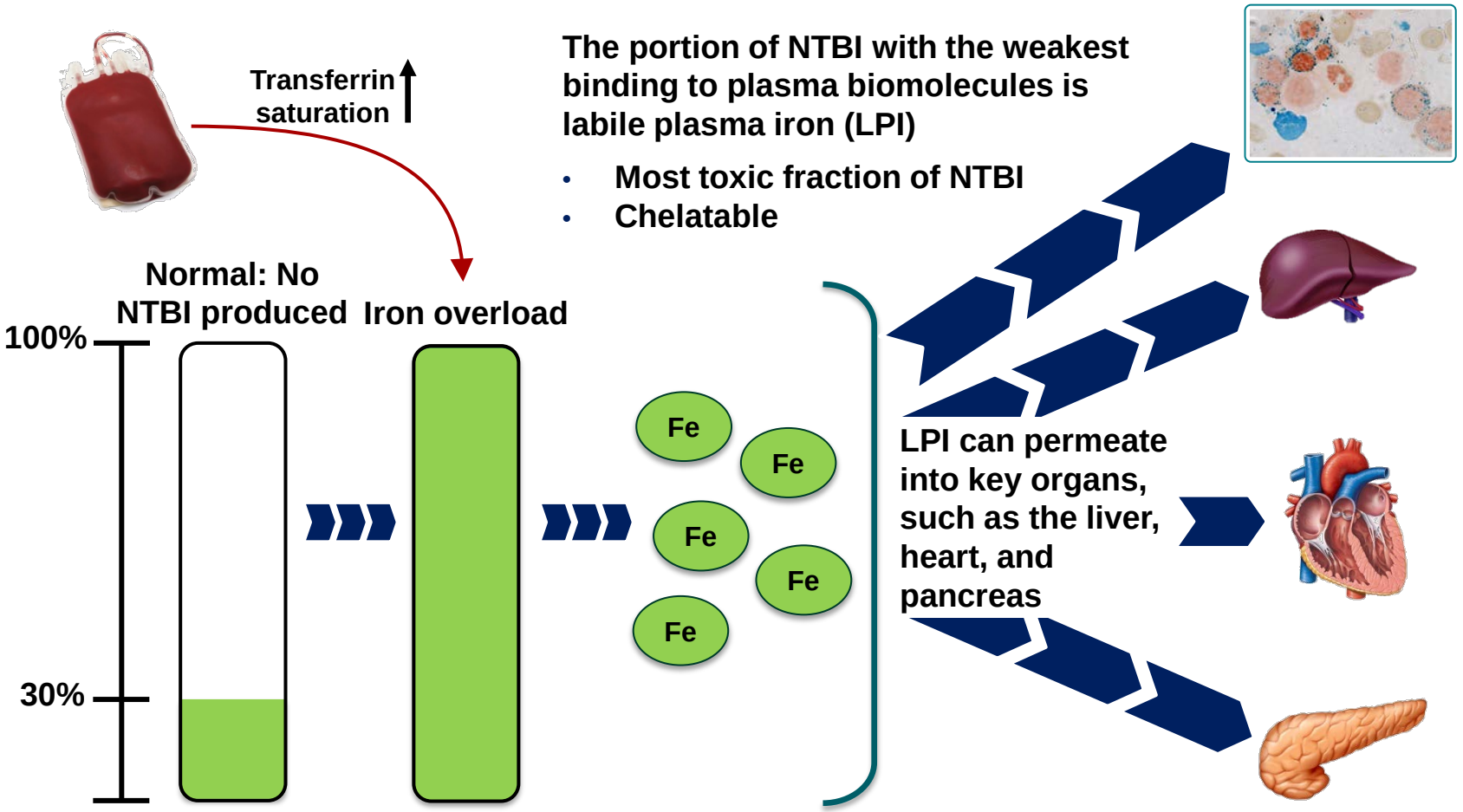
CLOSE X

LPI Appear at a Transferrin Saturation Over 80%



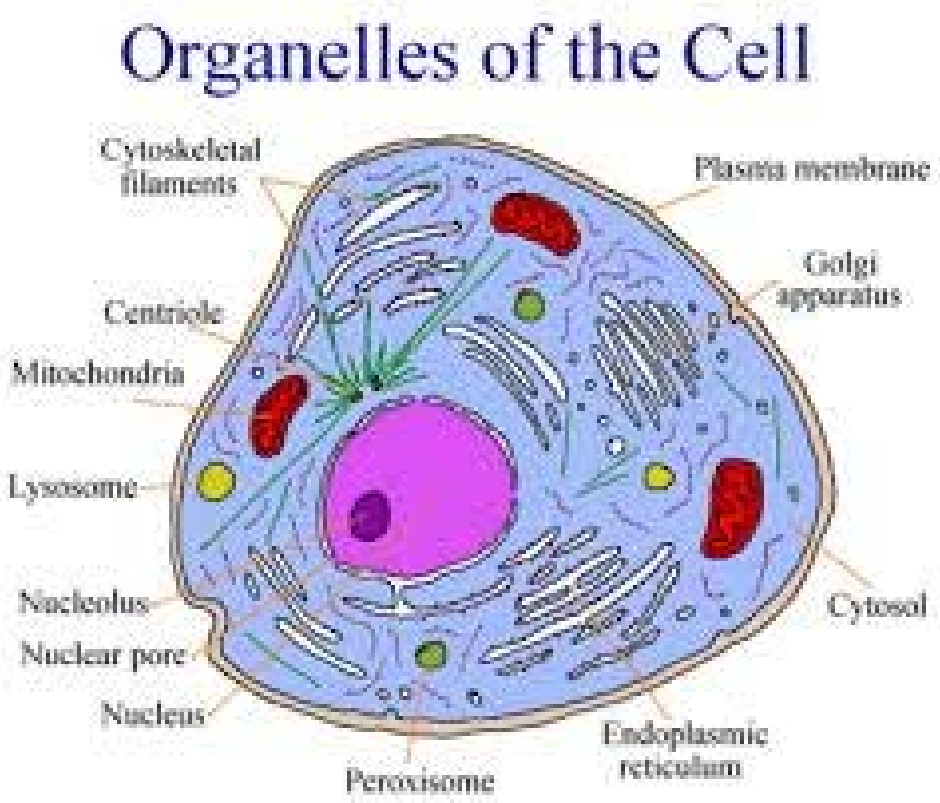
LPI, labile plasma iron; Tf, transferrin; µm, micromolar. Figure courtesy of E. Rachmilewitz.

Non-transferrin-bound iron



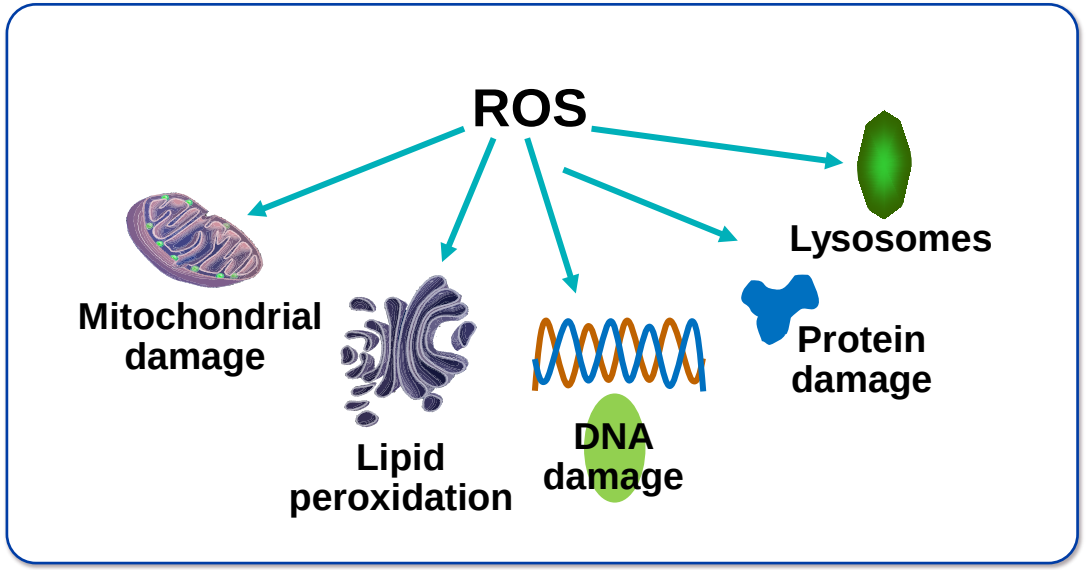
Structure of the cells of our body

- Proteins
  - Enzymes – do the work
  - Structural proteins
- Lipids
  - Plasma membrane – cell integrity
  - Lysosomes – sequester toxic substances
  - Golgi – process proteins
- Nucleic acids
  - DNA – stores genetic code
  - RNA – translates the genetic code to proteins
- Mitochondria
  - the powerhouse of the cell



Cellular Targets of Labile Iron

- **Ability to transfer electrons**
  (Fenton reaction: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\cdot}OH$)
- **Production of free O_2 radicals:**



ROS may be toxic

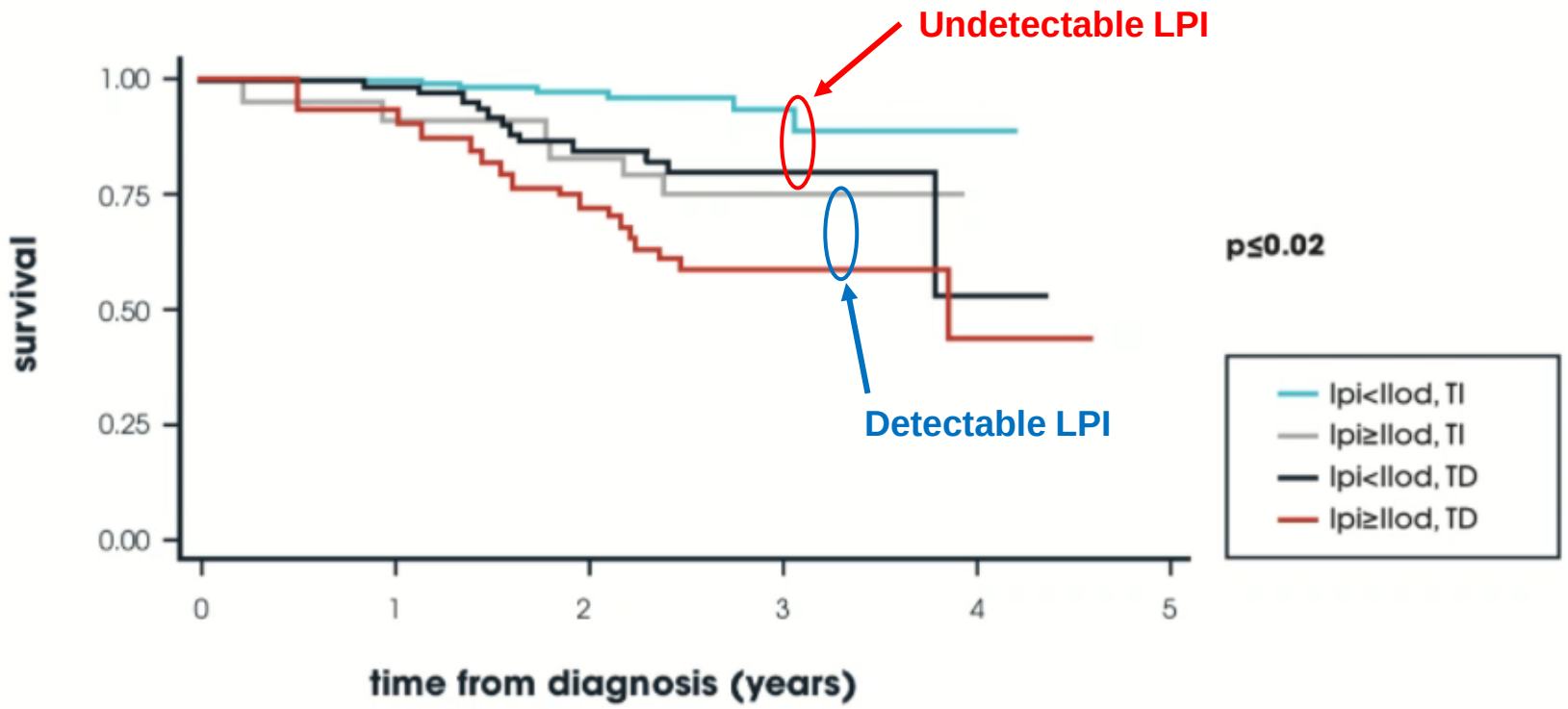
Gattermann N, Rachmilewitz EA. Ann Hematol. 2011;90:1-10.

ROS = Reactive Oxygen Species

LPI in Lower-Risk MDS

EUMDS Registry, n=247

- Impact of LPI on survival stratified by transfusion status as a time dependent variable (censored at time of starting chelation)

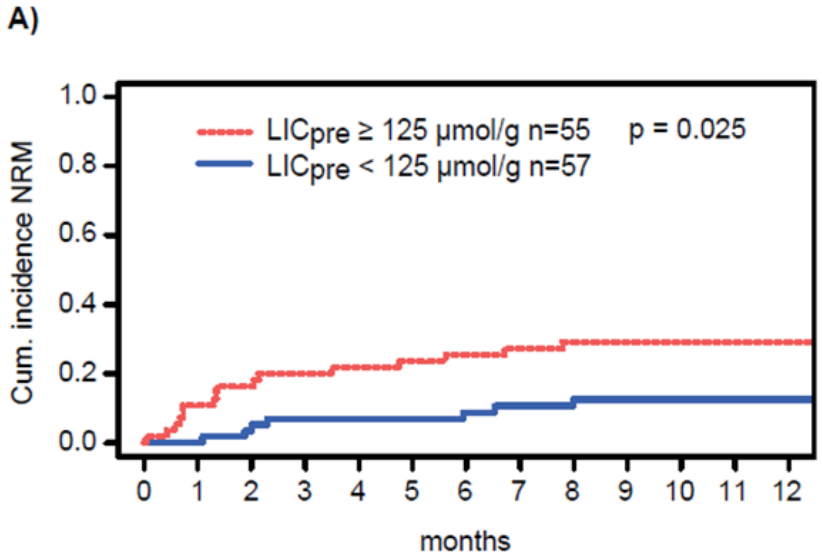


Number at risk						
lpi<llod, TI	165	126	73	29	1	0
lpi≥llod, TI	22	23	21	12	0	0
lpi<llod, TD	52	60	43	8	2	0
lpi≥llod, TD	8	31	32	11	2	0

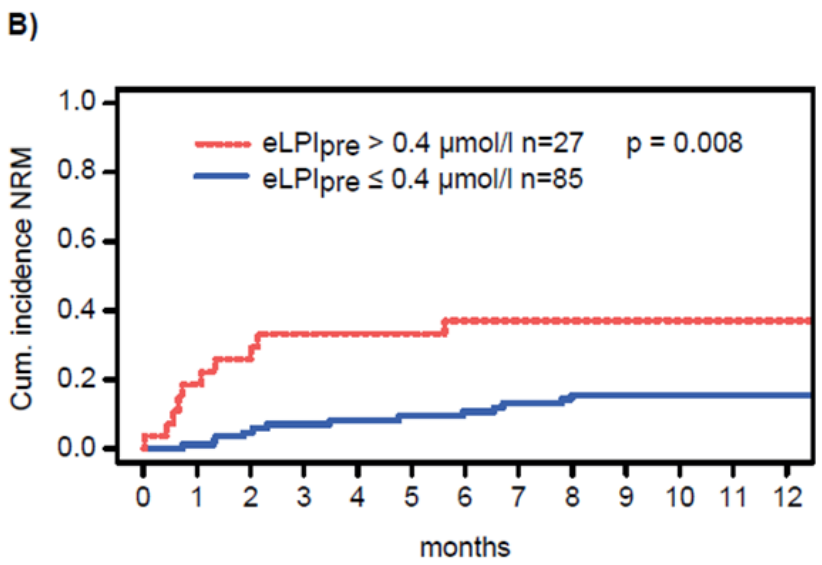
ALLIVE: Non-Relapse Mortality

- By including nitrolotriacetic acid (NTA) in the assay at concentrations too low to affect transferrin-bound iron, iron bound to substances such as citrate and albumin can be mobilized, allowing its measurement as **enhanced LPI (eLPI)**

NRM BY pre-SCT LIC



NRM BY pre-SCT *eLPI*

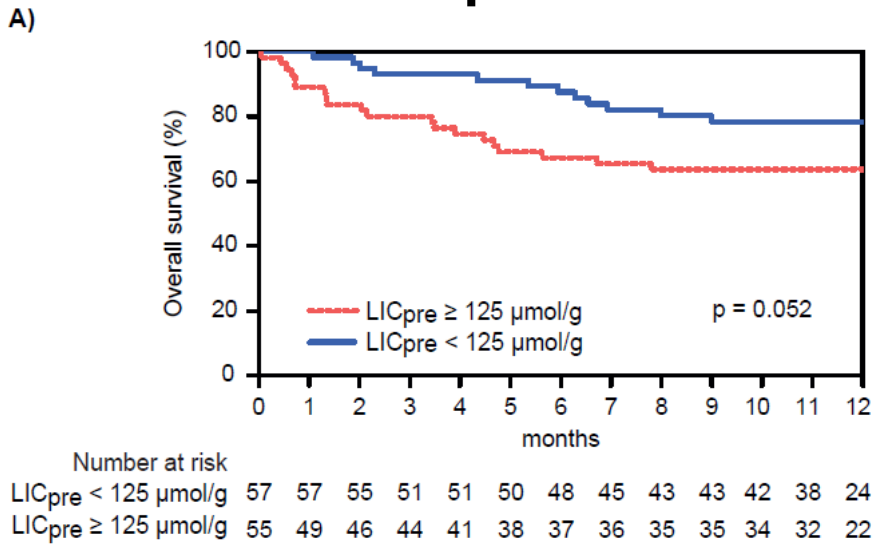


- Elevated pre-SCT eLPI was an independent predictor of NRM (p=0·0082) & OS (p<0·0001) in multivariate analysis

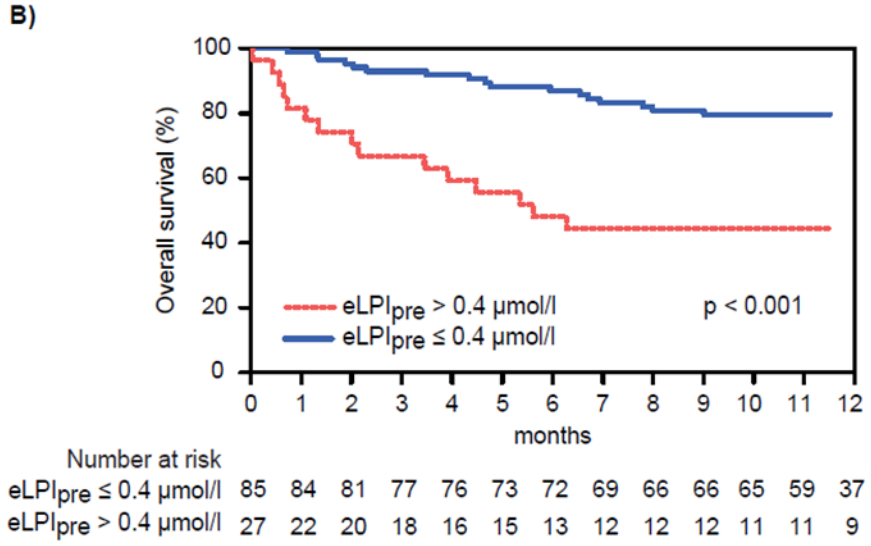
Wermke M, et al. Lancet Haematol. 2018;5(5):e201-e210.

ALLIVE: Overall Survival

OS BY pre-SCT LIC

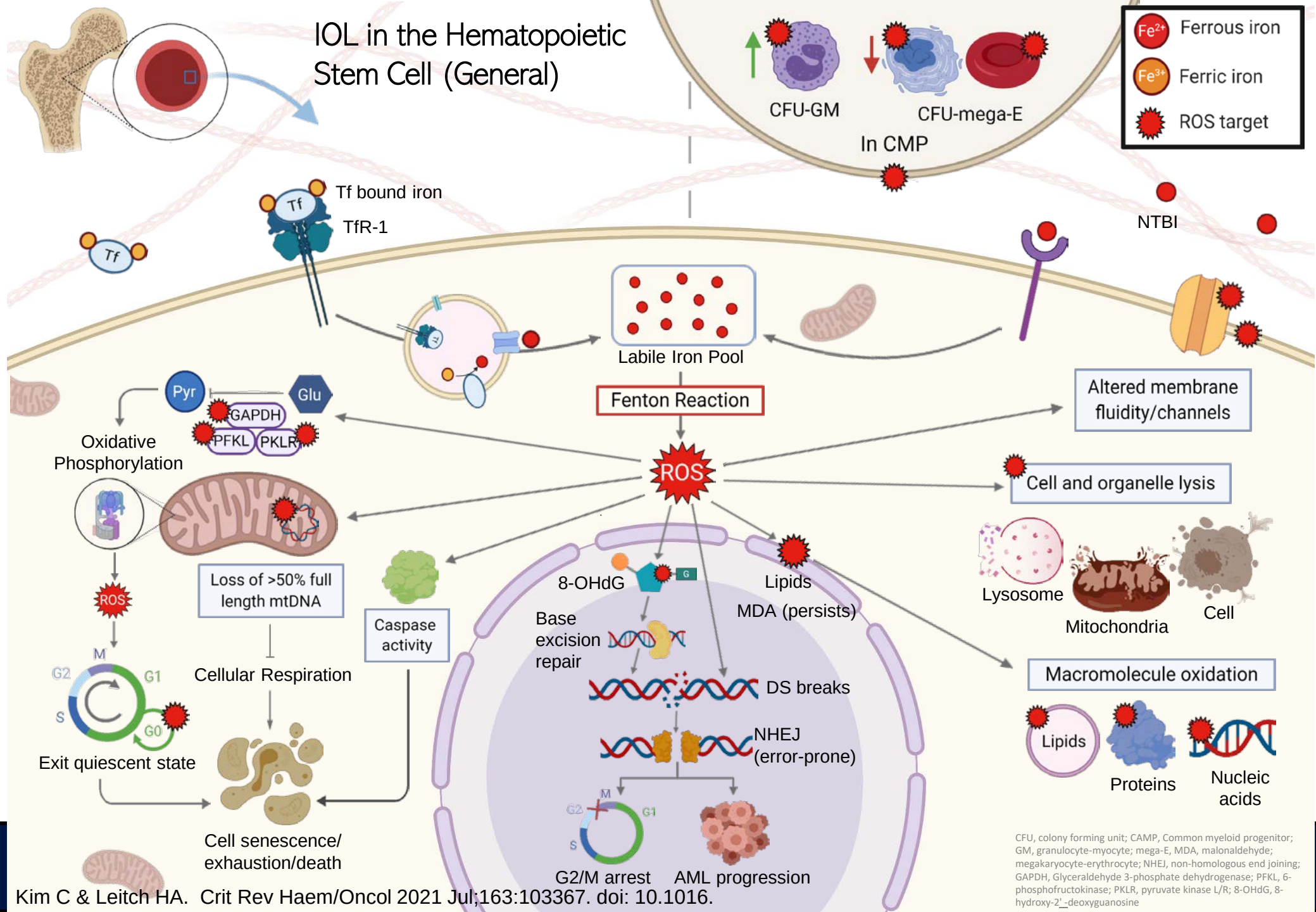


OS BY pre-SCT *eLPI*



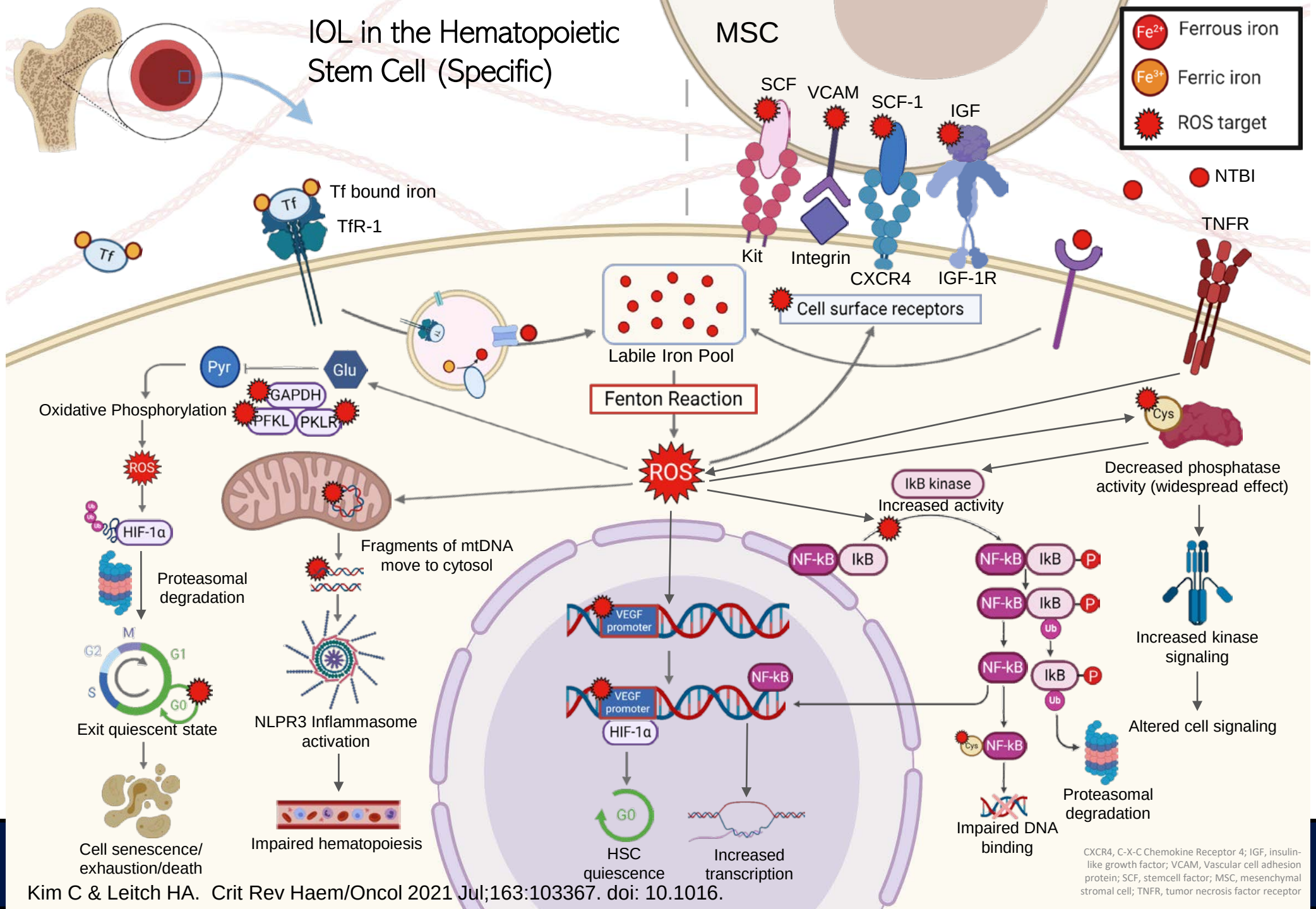
Wermke M, et al. Lancet Haematol. 2018;5(5):e201-e210.

IOL in the Hematopoietic Stem Cell (General)



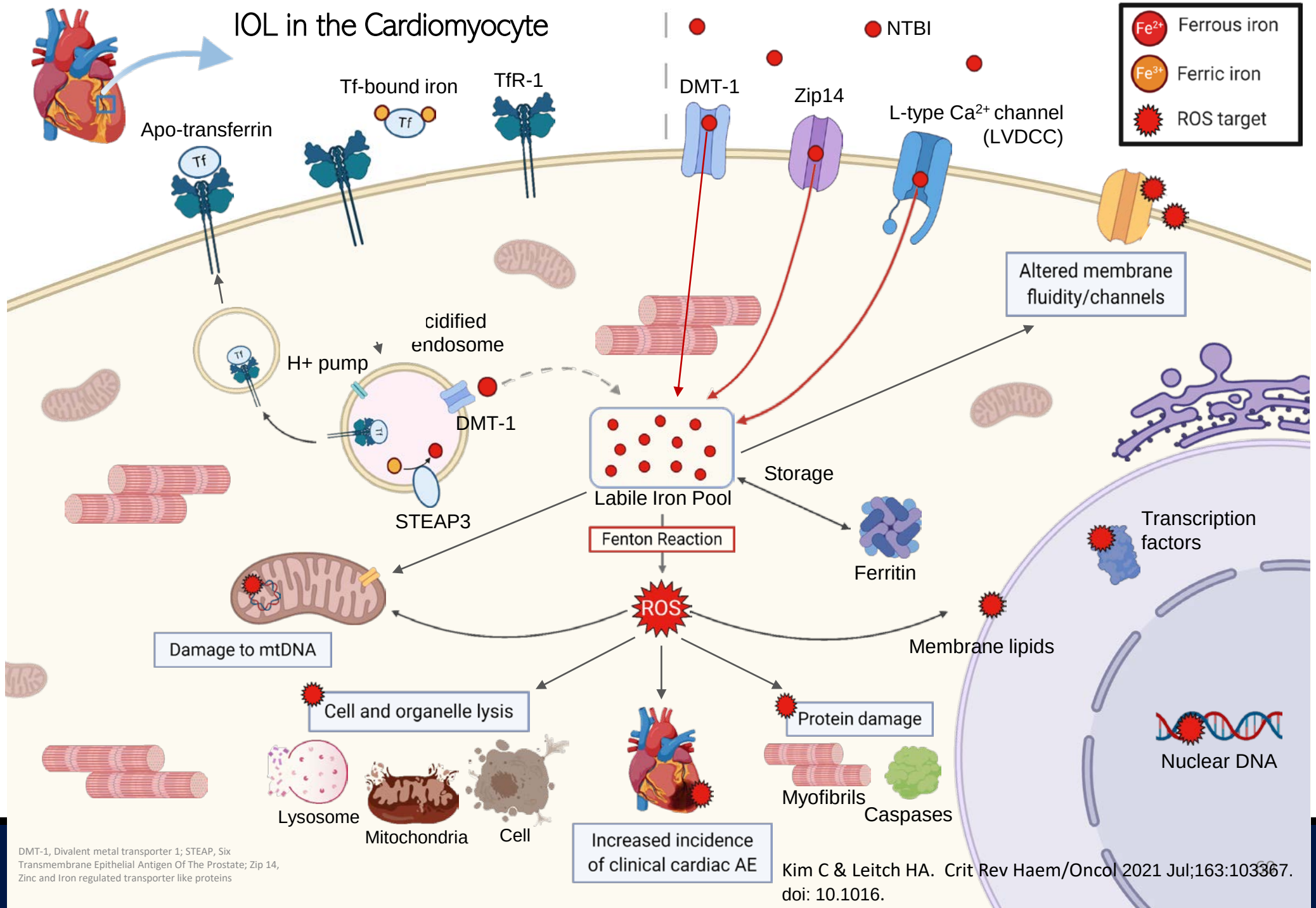
CFU, colony forming unit; CAMP, Common myeloid progenitor; GM, granulocyte-myocyte; mega-E, MDA, malonaldehyde; megakaryocyte-erythrocyte; NHEJ, non-homologous end joining; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; PFKL, 6-phosphofructokinase; PKLR, pyruvate kinase L/R; 8-OHdG, 8-hydroxy-2'_-deoxyguanosine

Kim C & Leitch HA. Crit Rev Haem/Oncol 2021 Jul;163:103367. doi: 10.1016.



CXCR4, C-X-C Chemokine Receptor 4; IGF, insulin-like growth factor; VCAM, Vascular cell adhesion protein; SCF, stemcell factor; MSC, mesenchymal stromal cell; TNFR, tumor necrosis factor receptor

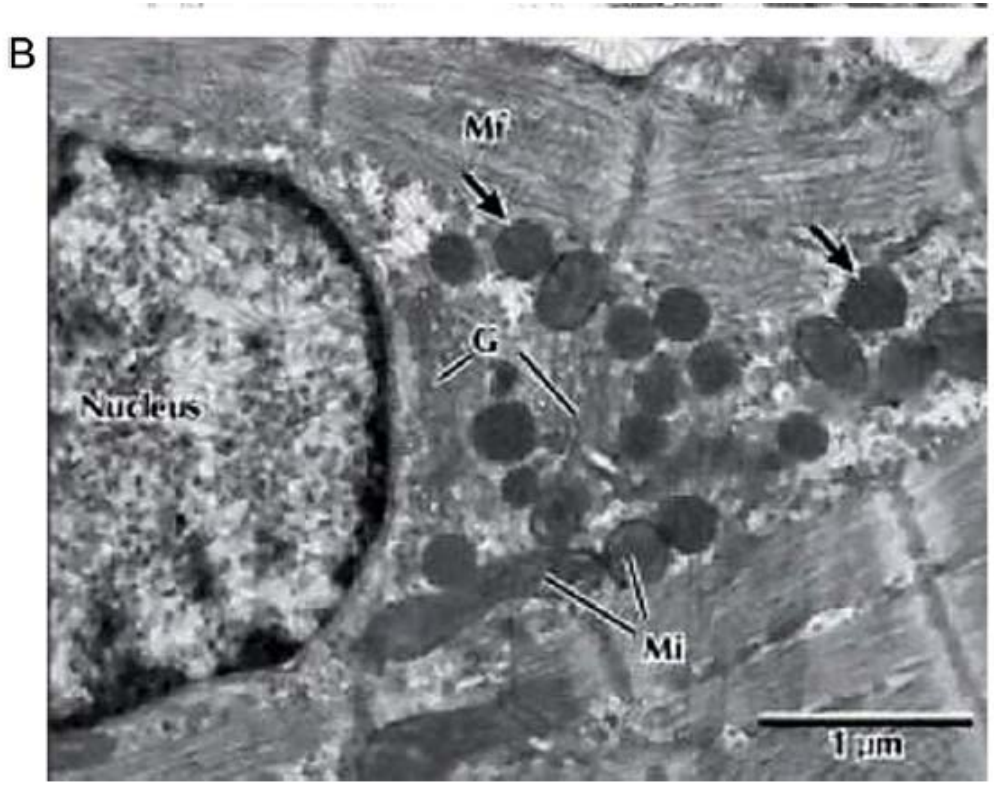
Kim C & Leitch HA. Crit Rev Haem/Oncol 2021 Jul;163:103367. doi: 10.1016.



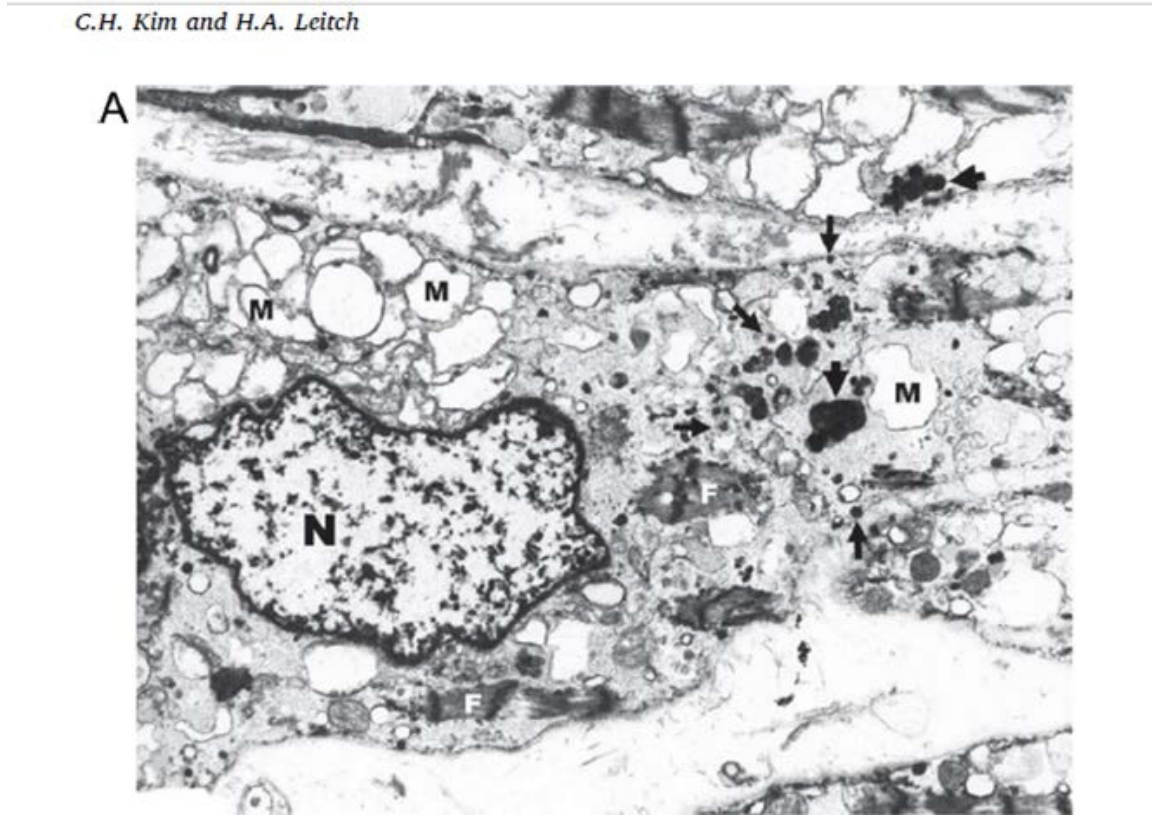
DMT-1, Divalent metal transporter 1; STEAP, Six Transmembrane Epithelial Antigen Of The Prostate; Zip 14, Zinc and Iron regulated transporter like proteins

Kim C & Leitch HA. Crit Rev Haem/Oncol 2021 Jul;163:103367. doi: 10.1016.

Electron micrographs of cardiomyocytes



Normal cell



IOL cell from BTM

Kim C & Leitch HA. Crit Rev Haem/Oncol 2021 Jul;163:103367. doi: 10.1016.

Objectives:

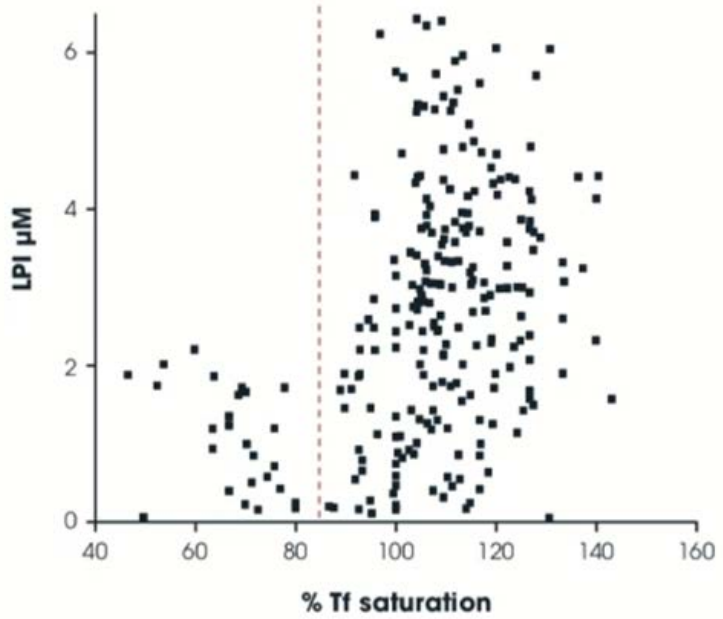
- Measurements of iron overload
- Why address iron overload in MDS
- **Relevant targets of iron reduction in MDS**
- Summary/conclusions

So what targets to use with iron reduction?

- Probably all of them:
  - Clinical:
    - Transfusion burden
    - Organ function
    - Hematologic improvement
  - Laboratory:
    - Serum ferritin level
    - Organ iron
    - Measures of oxidative stress: NTBI, LPI, eLPI, ROS, measures of cellular oxidative damage
      - These measures while straightforward are not validated or standardized between laboratories
      - Moreover, not all oxidative species are created equal, for example there are several types of ROS & which is most related to clinical status is currently unclear
      - However….

CLOSE X

LPI Appear at a Transferrin Saturation Over 80%

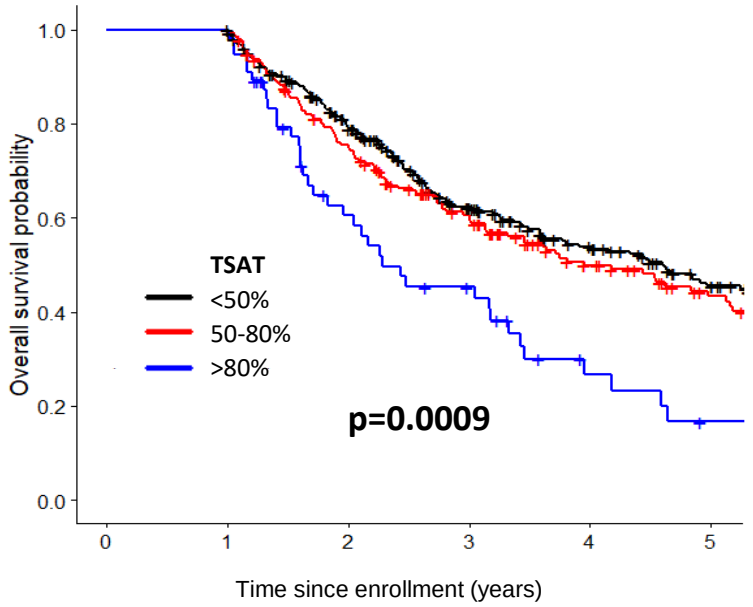


LPI, labile plasma iron; Tf, transferrin; µm, micromolar. Figure courtesy of E. Rachmilewitz.

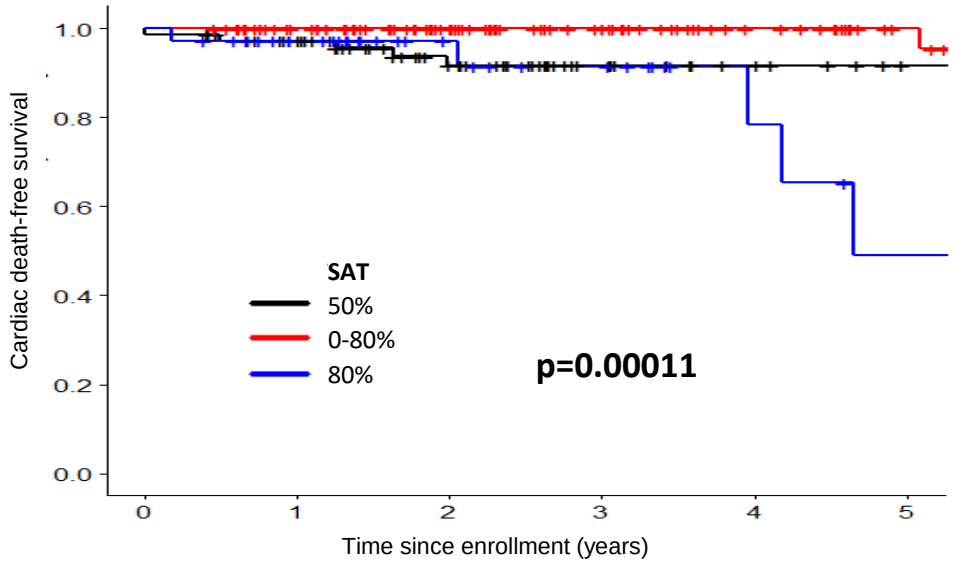
High transferrin saturation predicts inferior clinical outcomes in patients with MDS

- 718 patients from the Canadian MDS (MDS-CAN) patient registry

Overall Survival



Cardiac Death-Free Survival



Teichman J et al, Haematologica. 2022 Aug 18. doi: 10.3324/haematol.2022.280723. Online ahead of print. PMID: 35979720

What about endpoints?

Starting points

Proposed in 2008

Table 4
Proposed classification system for severity of iron overload in MDS.

Serum ferritin level (ng/mL)	Organ function[a]	
	Normal (A)	Abnormal (B)
501–1000	1A	1B
1001–2500	2A	2B
2501–5000	3A	3B
>5000	4A	4B

Criteria for organ dysfunction: Cardiac, left ventricular ejection fraction <50%; Hepatic, abnormal transaminase levels, hepatic fibrosis or cirrhosis; Pancreatic endocrine, impaired glucose tolerance.
Adapted from Suzuki et al., Int J Hematol 2008; 88: 30–35. With permission from the International Journal of Hematology, Springer Press.
[a] Cardiac, liver and pancreatic endocrine related to iron overload; organ dysfunction progresses as ferritin or transfusion burden increases.

Proposed right now

PROPOSED criteria for severity of Iron Overload in MDS

	Ferritin ng/mL	TSAT or LPI	Cardiac Imaging msec	Hepatic Imaging LIC (g/mgDW)
Negligible IOL	≤500	normal	>20	<3
Mild	501-1000	<50% or UN	>20	<5
Moderate	1000-2500	50-80% or UN	>20	5-7
Severe	>2500	>80% or DET	<20*	>7**

*OR cardiac dysfunction: LVEF <50% **OR hepatic dysfunction: AST/ALT >2xULN, fibrosis, cirrhosis
DET, detectable; DW, dry weight; LIC, liver iron concentration; LPI, labile plasma iron; TSAT, transferrin saturation; UN, undetectable

Disclaimer: This is open for discussion!!!

Endpoints

Proposed in 2008

Table 5
Proposed response criteria for the therapy of iron overload.

Response	Criteria
Complete (CR)	Decrease in SF to <2000 ng/mL AND Decrease in SF by ≥500 ng/mL
Minor (MiR)	Decrease in SF to <2000 ng/mL BUT Decrease in SF by <500 ng/mL
Stable iron load (SIL)	SF constantly elevated BUT <4000 ng/mL
No Response (NR)	Increase in SF of ≥500 ng/mL OR SF constantly >4000 ng/mL

Abbreviation: SF, serum ferritin.
Adapted from Valent P et al., Eur J Clin Invest 2008; 38(3): 143–149. With permission from Wiley-Blackwell.

Proposed right now

PROPOSED response criteria for therapy of IOL in MDS	
Complete	Decrease ≥1 category to negligible IOL
Very Good Partial	Decrease ≥1 category to Mild IOL
Partial	Decrease >1 category to moderate
Stable	No change in category
Progression	Worsening of IOL by ≥1 category

Disclaimer: This is open for discussion!!!

How to keep track of all this data?

MDS CLEAR PATH

This tool is designed to help streamline the continuum of care for MDS patients, from diagnosis and staging through to treatment.

It features a comprehensive algorithm, which is the outcome of a Canada-wide physician consensus on best practices in MDS management. Ultimately it will serve to support physicians at key decision points in their treatment of MDS patients.

START FRANÇAIS

The content of this program is supported by an unrestricted educational grant from Celgene Inc.

The MDS Clear Path has been developed and approved by a Steering Committee with the input of over 60 Canadian physicians. Members of this Steering Committee are Dr. Richard Wells, Dr. Heather Leitch, Dr. Harold Olney and Dr. April Shamy. The opinions expressed are solely those of the Steering Committee members. The content is specifically intended to be used by qualified physicians/medical professionals, to assist them in the management of MDS patients. The MDS Clear Path does not substitute, nor is it intended to substitute for the medical advice of an appropriately qualified and licensed physician or other healthcare provider. Use of the application is undertaken entirely on your own responsibility as a healthcare professional. The information provided here is for educational and informational purposes only. In no way should it be considered as offering medical advice. The digital formats of the MDS Clear Path have been completed by The Adpharm Inc. (a healthcare communications company) through funding from Celgene Inc. The sole purpose was to deliver the content of the original MDS Clear Path in a user friendly, digital format. No content was modified in the transition to a digital format. All digital formats are the property of Celgene Inc. This presentation may include indications and treatment regimens which are not authorized in Canada. Please refer to current product monographs for complete indication and safety information.

Canadian Guidelines for the Management of Iron Overload in MDS

Leukemia Research 74 (2018) 21–41

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Iron overload in myelodysplastic syndromes: Evidence based guidelines from the Canadian consortium on MDS

Heather A. Leitch[a,*], Rena Buckstein[b], Nancy Zhu[c], Thomas J. Nevill[d], Karen W.L. Yee[e], Brian Leber[f], Mary-Margaret Keating[g], Eve St. Hilaire[h], Rajat Kumar[i], Robert Delage[j], Michelle Geddes[k], John M. Storring[l], April Shamy[m], Mohamed Elemary[n], Richard A. Wells[b]

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[b] Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
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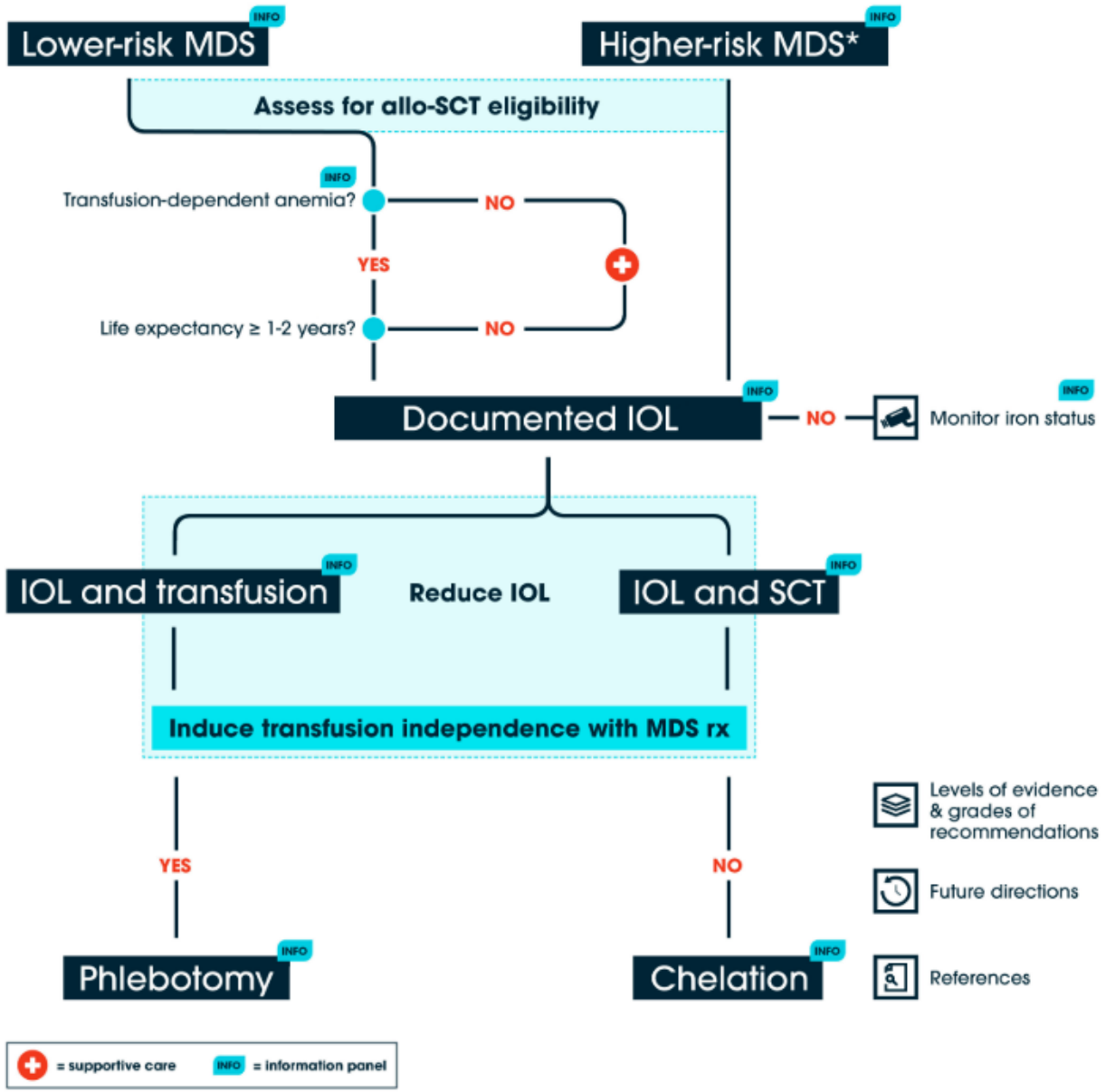
[d] Leukemia/BMT Program of British Columbia, Division of Hematology, Vancouver, BC, Canada
[e] Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[f] McMaster University, Hamilton, Ontario, Canada
[g] Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, Canada
[h] Centre d'Oncologie, Dr-Leon-Richard, Moncton, New Brunswick, Canada
[i] Hematology/Oncology, CancerCare Manitoba, Winnipeg, Manitoba, Canada
[j] Hematology Department, Centre Hospitalier Universitaire, Laval University, Quebec, QC, Canada
[k] Department of Medicine/Hematology, Foothills Medical Centre, Calgary, Alberta, Canada
[l] McGill University Health Centre, Montreal, Quebec, Canada
[m] Sir Mortimer B Davis Hospital, McGill University, Montreal, Quebec, Canada
[n] Saskatoon Cancer Center, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

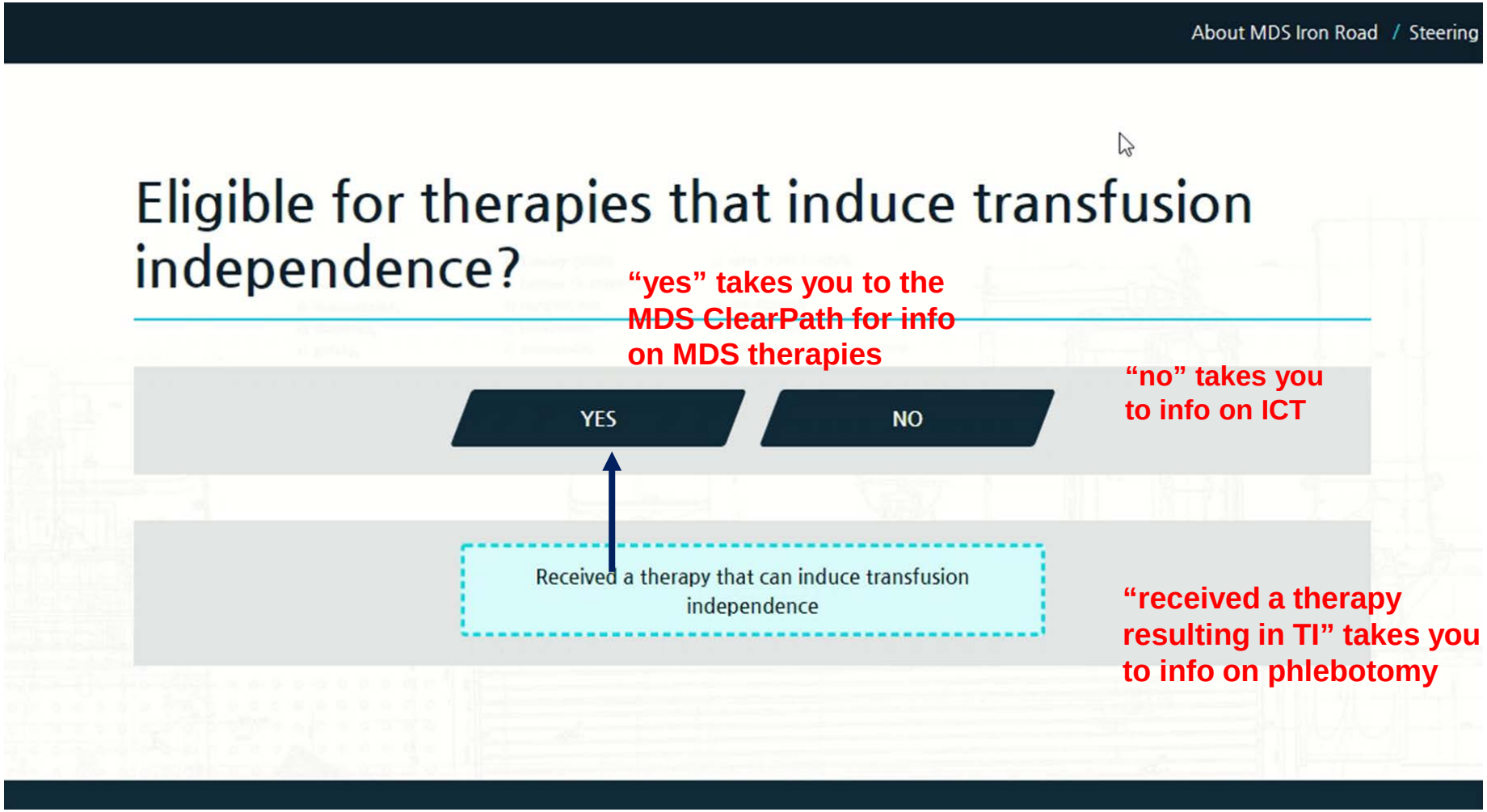
This tool is designed to help streamline the care of MDS patients with iron overload (IOL). It features comprehensive information on clinical endpoints impacted by and IOL reduction, the outcome of a Canada-wide physician consensus on best practices in IOL management in MDS. It will support physicians in their treatment of MDS patients with IOL.

CCMDS|CCSMD

Canadian guidelines for the management of iron overload in MDS



IR Express:

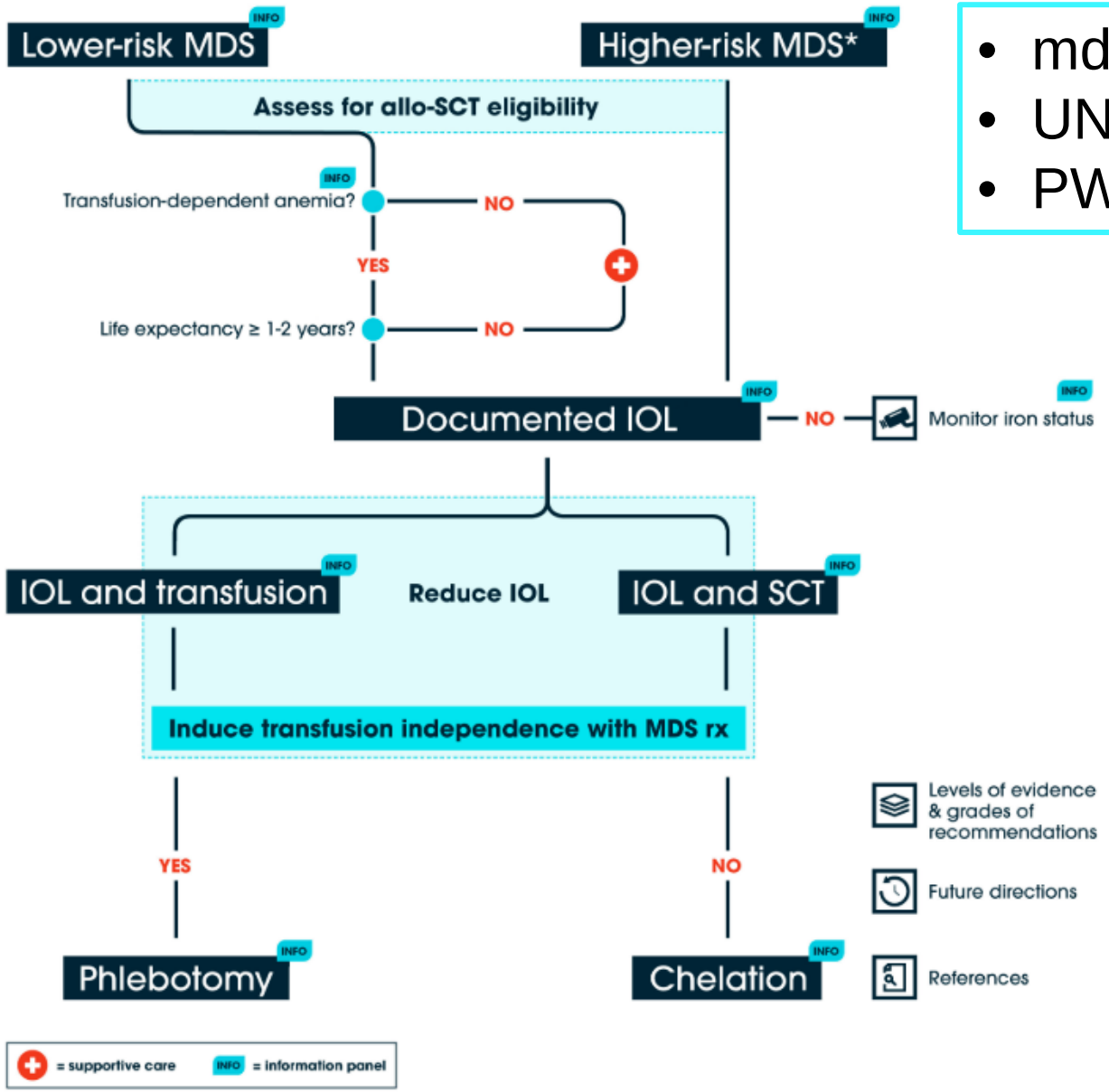


“yes” takes you to the MDS ClearPath for info on MDS therapies

“no” takes you to info on ICT

“received a therapy resulting in TI” takes you to info on phlebotomy

Canadian guidelines for the management of iron overload in MDS



- mdsironroad.org
- UN: ironroad
- PW: makeirongreatagain

Objectives:

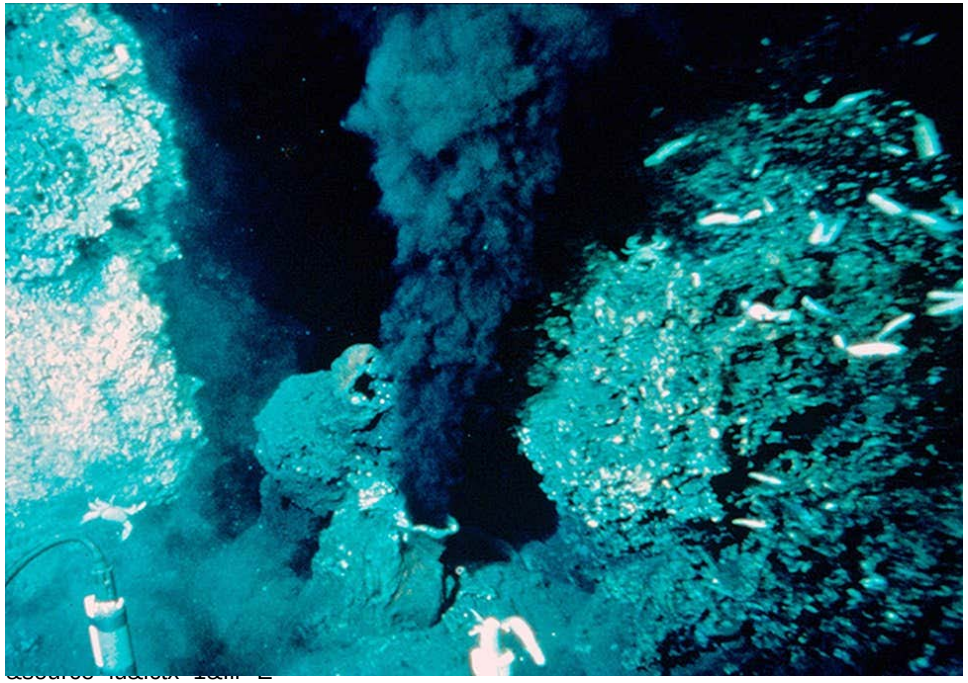
- Measurements of iron overload
- Why address iron overload in MDS
- Relevant targets of iron reduction in MDS
- **Summary/conclusions**

Summary/Conclusions:

- There is increasing evidence that control of iron load is of clinical benefit in MDS
  - The number of chelators we have access to is limited
  - Use of these chelators may be limited by side effects
- In future, we will hopefully have access to more therapeutic options to ***modify disease course*** in MDS
  - This in turn will ***induce transfusion independence***
  - which will minimize iron overload and optimize overall survival & QOL
- Reduce IOL with iron chelation where MDS therapies are not available & phlebotomies are not feasible
- Take into account RBC transfusion history, ferritin level, organ imaging & function, and measures of oxidative stress

What the Internet is Saying About Iron Overload

- "Iron is the new cholesterol"[1]
  - Iron is central to many processes & disorders.
  - "Such is the Faustian bargain that has been struck by life on this planet. Oxygen & iron are essential for energy production but may also conspire to destroy the delicate order of our cells. 'Life was designed to exist at the very interface between iron sufficiency and deficiency.'"
- Iron is an ancient signaling molecule[2]
  - Iron was involved in signaling billions of years before the existence of ATP
  - "Environmental conditions in porous hydrothermal vents — where heated, mineral-laden seawater spews from cracks in the ocean crust — created a gradient in positively charged protons that served as a 'battery' to fuel the creation of organic molecules & proto-cells."



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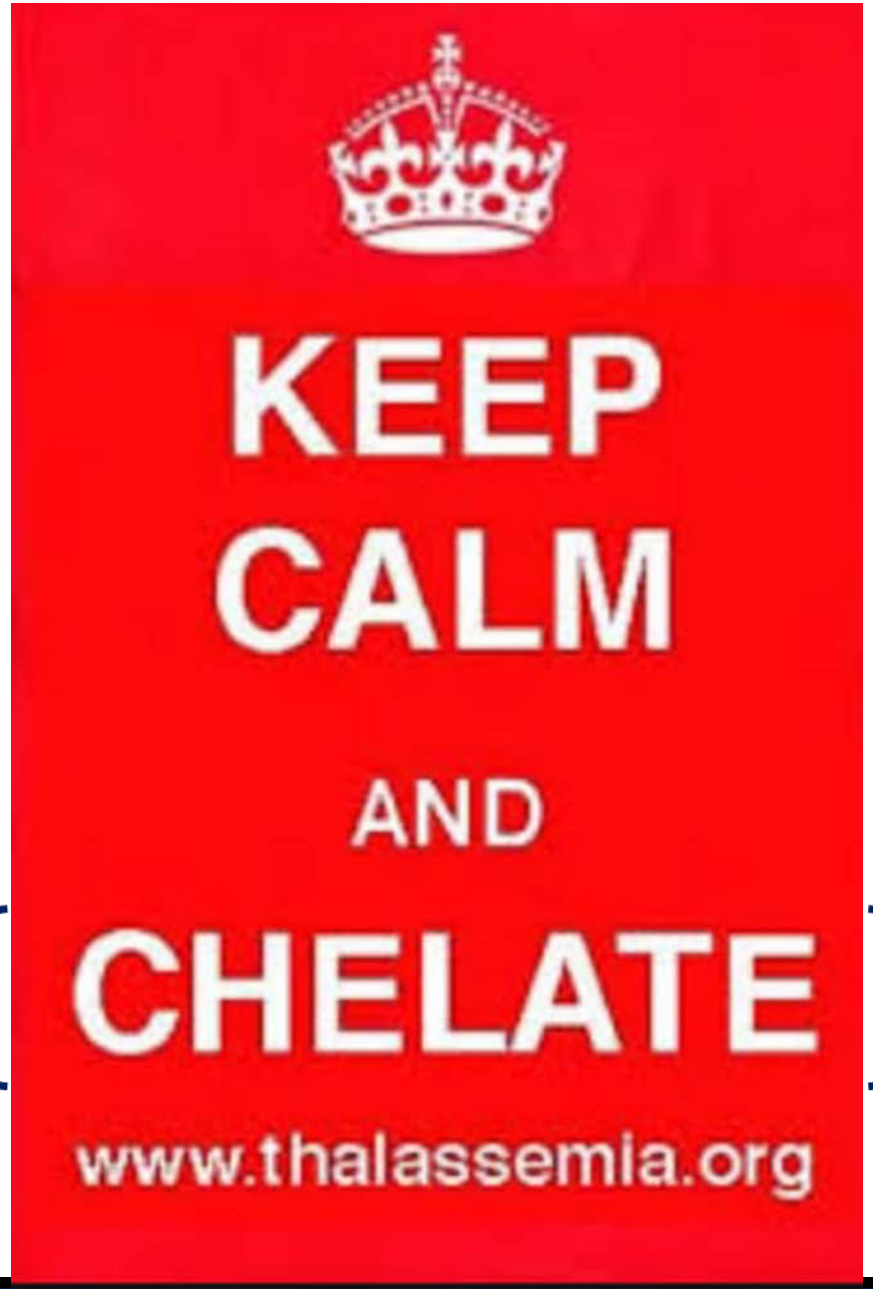
[1]Dalton C. 2018 **http://getpocket.com/explore/item/iron-is-the-new-cholesterol**. [2]Ghose T. 2013 **https://www.livescience.com/26173-hydrothermal-vent-life-origins.html**.

Future directions

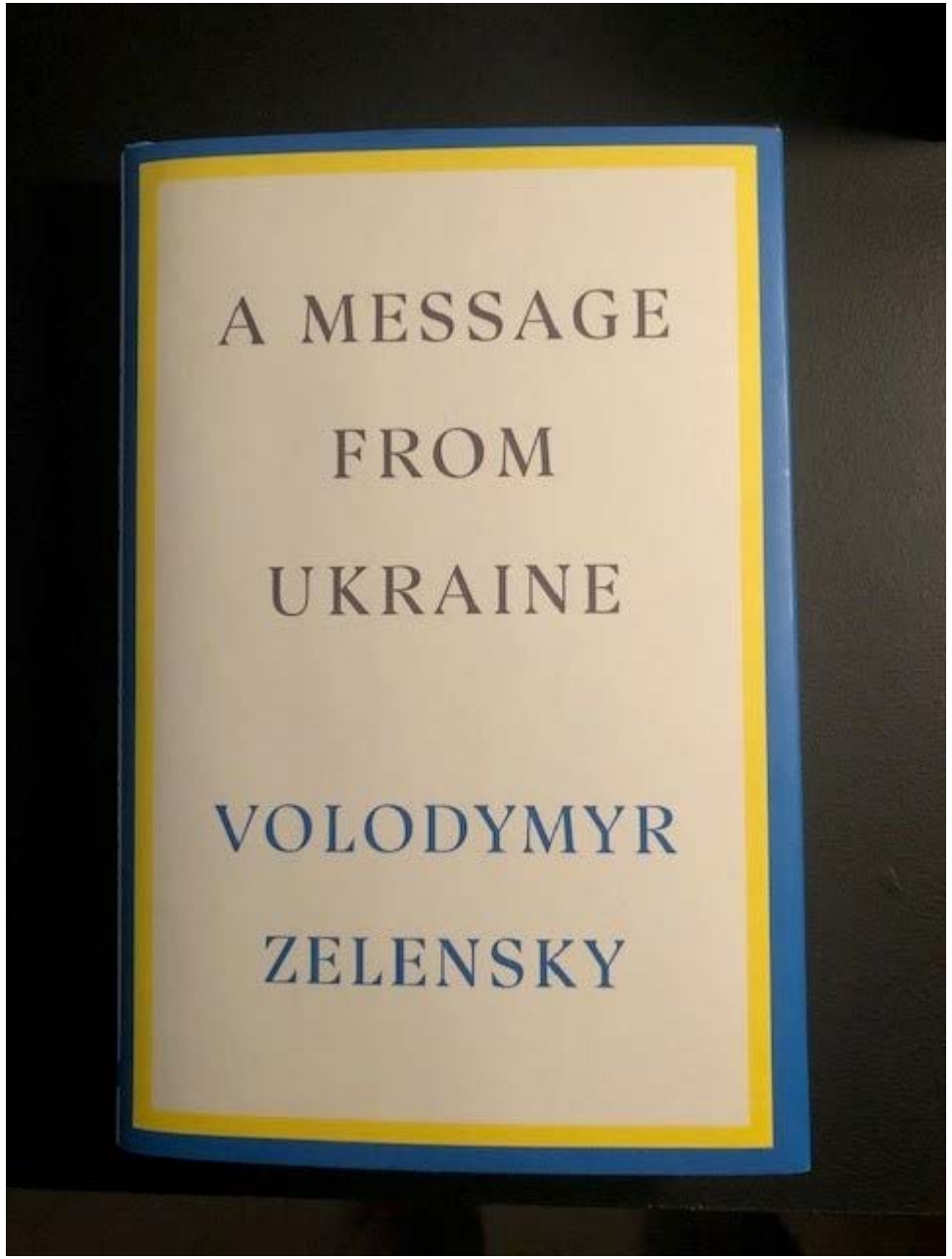
Research agenda addressing iron overload and iron chelation therapy in MDS.

- Clarify the contribution of iron toxicity to symptoms and risk in MDS.
- Does ICT improve overall survival in lower risk MDS?
- Does ICT decrease organ complications in lower risk MDS?
- What clinical markers predict for hematologic improvement with ICT in lower risk MDS?
- Does ICT decrease infection risk in lower risk MDS?
- Which subgroups of lower risk MDS patients benefit most from iron reduction?
- Is there value to early intervention/prevention of iron overload vs rescuing damaged tissue?
- Is there a benefit to chelating to a lower iron burden?
- Is there a benefit to combining standard of care with ICT for MDS?
- Does ICT delay progression to AML?
- Should ICT be offered to selected patients with higher risk MDS?
- Should ICT be offered to MDS patients undergoing SCT?
- Can combinations of chelators be used safely and effectively in MDS?
- Develop newer chelators with fewer side effects.
- Which measures of IOL best predict clinical endpoints? Do these add to the prognostic value of existing scoring systems for MDS?

AML, acute myeloid leukemia; ICT, iron chelation therapy; IOL, iron overload; SCT, stem cell transplantation; vs, versus. From: Leitch HA, et al. Leuk Res. 2018 Nov;74:21-41.



REDUCE IRON OVERLOAD


A MESSAGE
FROM
UKRAINE
VOLODYMYR
ZELENSKY

Questions?

QUESTIONS & DISCUSSION