Optimizing Transfusion Support for Patients with Myelodysplastic Syndrome

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QUEST Quality Utilization Efficacy Safety Transfusion

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Disclosure

- Presenter: Dr. Yulia Lin
- Relationships with commercial interests: None

Case Study

- 72 M with myelodysplastic syndrome (MDS) and severe anemia, not responding to treatment
- The hematologist asks…..
  - Are there transfusion guidelines for outpatients?
  - Any blood bank testing or measures that I need to order to help my patient?

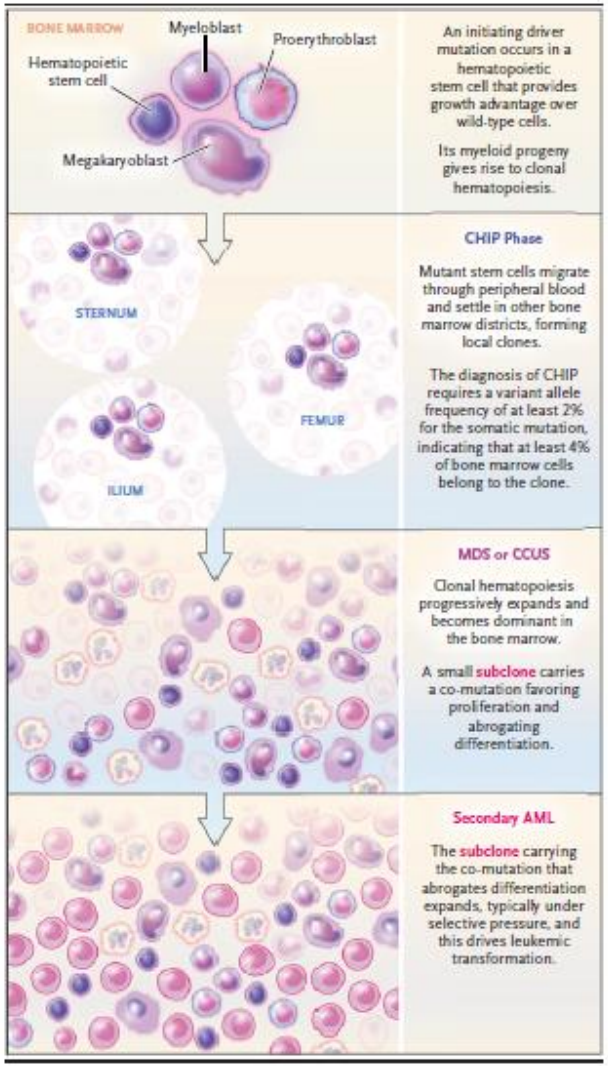
Objectives

At the end of the presentation, attendees will be able to:

- Compare the approach to transfusion in patients with MDS with the approach to transfusion in hospitalized patients
- Explain the quality of life considerations for transfusion in patients with MDS
- Discuss the potential complications of transfusion in patients with MDS, their prevention and their management

What is MDS?

- Myeloid neoplasm
- Clonal proliferation
- Abnormal (*dys*) formation (*plasis*) of hematopoietic stem cells (*myelo*)
- Ineffective hematopoiesis, cytopenias, risk of evolution to AML
- Incidence 4-5 per 100,000 persons per year *(likely underestimated)*
- Median age: 70 years



Cazzola et al. NEJM 2020;383:1358-74

MDS and Transfusion Burden

- 2nd leading indication for transfusion amongst hematologic diseases and ~ 7.2% of transfused pts

- Most patients with MDS become transfusion-dependent
  - 2311 pts in 1st 4 yrs after diagnosis (Swedish study)

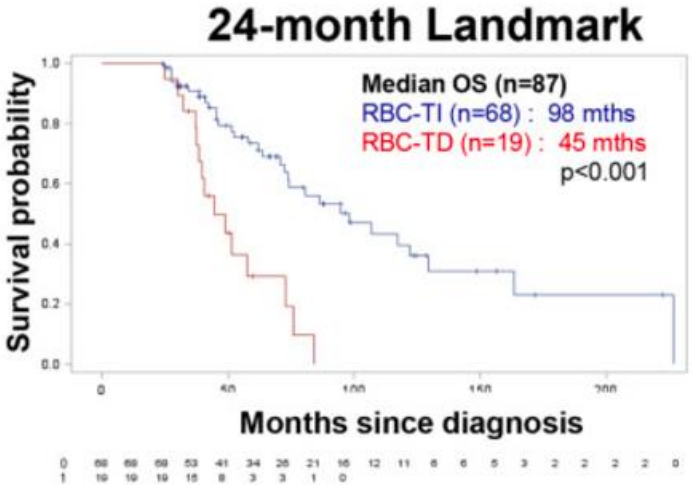
IPSS-R	RBCs in 1st 4 y	PLTs in 1st 4 y	Cost ($USD)
Very low	25	4	$ 8,805
High risk	171	66	$80,106

(Note: RBC unit $169 USD)

Zhao et al. Vox Sanguinis 2020 Nov 18; epub ahead of print

Impact of Transfusion on MDS

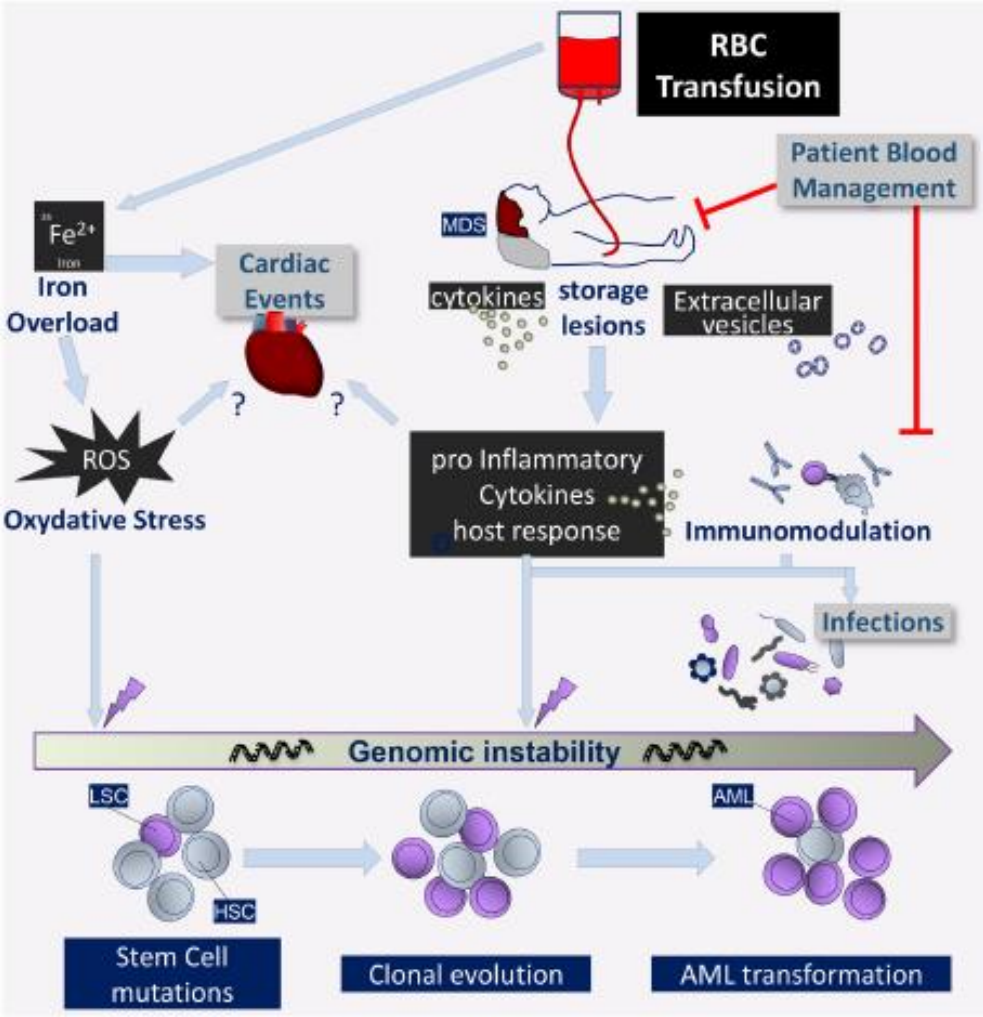
- Transfusion dependence associated with worse outcomes
  - ↓ overall survival
  - ↑ progression to AML
  - ↑ non-leukemic death (infection, bleeding, CV events)
  - ↑ cost of illness, medical costs (hospitalization, ER visit ~ 3x higher)
  - ↓ quality of life: physical, emotional and social domains



Braga Lemos et al. Eur J Haematol 2021; Epub ahead of print (Systematic Review)
Hiwase et al. AJH 2017;92:508-14

Transfusion & MDS

- Iron toxicity: cardiac toxicity, infections (impaired CD4, CD8 T cells), oxidative stress
- Transfusion: iron, microvesicles, inflammatory mediator
- Transfusion reactions



Kaphan et al. Blood Reviews 2020;41:100649

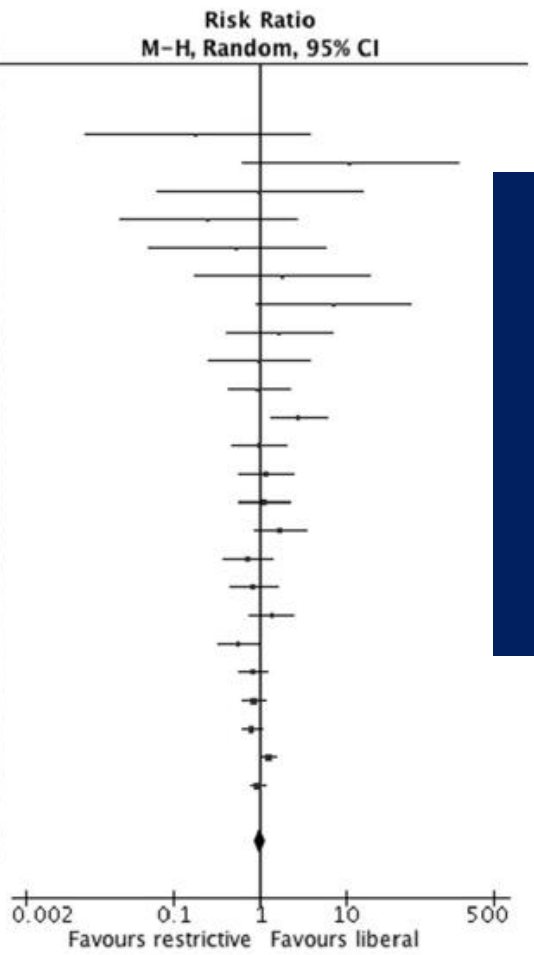
Fig. 2. Physiopathogenesis of the effects of RBC transfusions in MDS patients: hypotheses.

Are there transfusion guidelines for outpatients with MDS?

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Laine 2017	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Blair 1986	0	26	2	24	0.2%	0.19 [0.01, 3.67]
Foss 2009	5	60	0	60	0.3%	11.00 [0.62, 194.63]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06, 15.47]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02, 2.69]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05, 5.58]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18, 18.70]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89, 55.01]
Parker 2013	5	100	3	100	1.1%	1.67 [0.41, 6.79]
Bush 1997	4	50	4	49	1.2%	0.98 [0.26, 3.70]
Hébert 1995	8	33	9	36	2.7%	0.97 [0.42, 2.22]
de Almeida 2015	23	101	8	97	3.2%	2.76 [1.30, 5.87]
Lacroix 2007	14	320	14	317	3.4%	0.99 [0.48, 2.04]
Hajjar 2010	15	249	13	253	3.4%	1.17 [0.57, 2.41]
Palmieri 2017	16	168	15	177	3.8%	1.12 [0.57, 2.20]
Gregersen 2015	21	144	12	140	3.9%	1.70 [0.87, 3.32]
Walsh 2013	12	51	16	49	4.2%	0.72 [0.38, 1.36]
Jairath 2015	14	257	25	382	4.2%	0.83 [0.44, 1.57]
Murphy 2015	26	1000	19	1003	4.7%	1.37 [0.76, 2.46]
Villanueva 2013	19	416	34	417	5.3%	0.56 [0.32, 0.97]
Carson 2011	43	1009	52	1007	7.9%	0.83 [0.56, 1.22]
Mazer 2017	74	2427	87	2429	10.2%	0.85 [0.63, 1.15]
Hébert 1999	78	418	98	420	11.4%	0.80 [0.61, 1.04]
Bergamin 2017	84	151	67	149	12.6%	1.24 [0.99, 1.55]
Holst 2014	168	502	175	496	14.4%	0.95 [0.80, 1.13]
Total (95% CI)		**7792**		**7889**	**100.0%**	**1.00 [0.86, 1.16]**
Total events	641		660			

Heterogeneity: Tau² = 0.03; Chi² = 34.44, df = 23 (P = 0.06); I² = 33%

Test for overall effect: Z = 0.02 (P = 0.99)



26 trials
15,681 pts
30 day
mortality
OR 1.00
(0.86, 1.16)

Carson et al. Am Heart Journal 2018;200:96-101

AABB RBC Guideline 2016

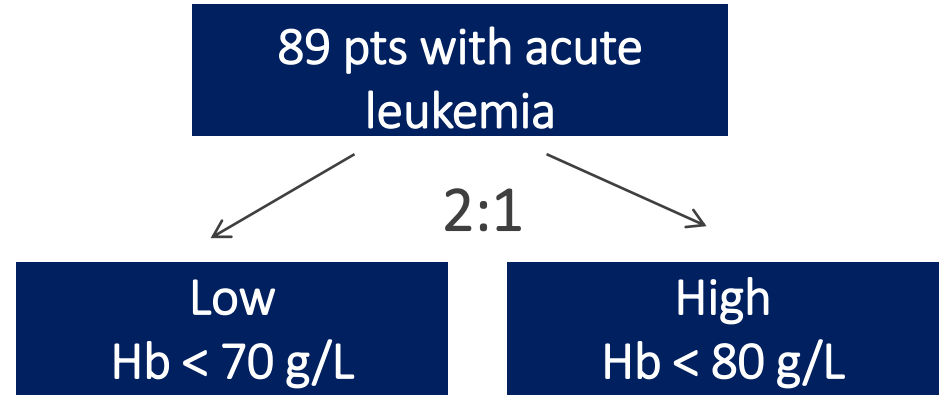
- Transfusion not indicated until hemoglobin
  - 70 g/L for hemodynamically stable hospitalized patients
  - 80 g/L for orthopedic surgery, cardiac surgery or with preexisting cardiovascular disease

- Recommendations do not apply to acute coronary syndrome, severe thrombocytopenia (heme onc), and chronic transfusion dependent anemia

Carson et al. JAMA 2016;316:2025-35

Inpatients – Acute Leukemia

Feasibility Trial
Excluded: ACS, known active blood loss with hemodynamic instability

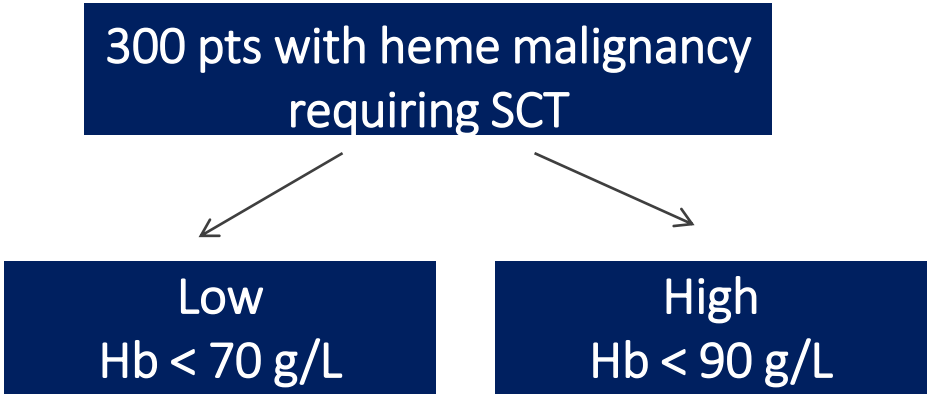


Mean Hb pre (g/L)	68	77	
Mean Hb post (g/L)	77	86	
RBC units, median (IQR)	8 (6-11)	10 (8-12)	P=0.01
Fatigue (NCI score out of 10)	4.8	4.5	P=NS
Bleeding	32%	37%	P=NS

DeZern AE et al. Transfusion 2016;56:1760-7

Transfusion in Stem cell transplant

Multicentre, non-inferiority RCT at 4 Canadian Centres. Transfused 2 units at a time.*



Mean Hb pre (g/L)	70.9	84.6	P<0.0001
RBC units, median (IQR)	2.7 (SD 4.8)	5.0 (6.1)	P=0.0004
FACT-BMT Baseline	108	103	Difference non-inferior
FACT-BMT Day 100	113	108	

No difference in secondary outcomes including TRM, hospital LOS, ICU admission, hospital re-admission

Tay et al. J Clin Oncol 2020;13:1463-73.

What is different about outpatients?

- MDS pts are often older with comorbidities
- Prescribers and patients may have differing views on important transfusion related outcomes or impact on QoL
- Patients may want less disruption to daily life and fewer hospital visits

Wood EM, McQuilten ZK. Hematology 2020:167.

What can we use to guide transfusion in outpatients with MDS?

Consensus Surveys of MDs

Hematology patients - US

TABLE 2. Most common reported Hb level thresholds for RBC transfusions in hospitalized and ambulatory patients*

Threshold	Inpatient (n = 130)	Ambulatory (n = 121)
7 g/dL	61 (47)	37 (31)
7.5 g/dL	7 (5.4)	16 (13)
8 g/dL	46 (35.4)	57 (47)
Only if bleeding or symptomatic	4 (3)	1 (0.8)
Other	12 (9.2)	10 (8.2)
8.5 g/dL	1	1
9 g/dL	0	1
No specific threshold	5	4
Hematocrit instead of Hb	6	4

*Data are reported as number (%).

MDS patients – Australia & NZ

- Commonest thresholds
  - Asymptomatic 50 y.o. <70 g/L
  - Symptomatic 50 y.o. < 80 g/L
  - Patient with prior MI < 90 g/L
  - 80 y.o. pt < 80 g/L
- Commonest post transfusion Hb target 90-100 g/L

Pine et al. Transfusion 2017;57:289-95
Mo et al. Internal Medicine Journal 2017; 47:695-8

Consensus Minimum Hb

- Modified Delphi method of 13 expert MDS clinicians
  - 100% consensus that given no end organ effects of anemia, patients with MDS can safely forgo transfusion with hemoglobin 75 g/L or higher

Tanasijevic et al. Leuk & Lymphoma 2020;61: 2900-4

What should the goals of RBC and platelet transfusion be in MDS?

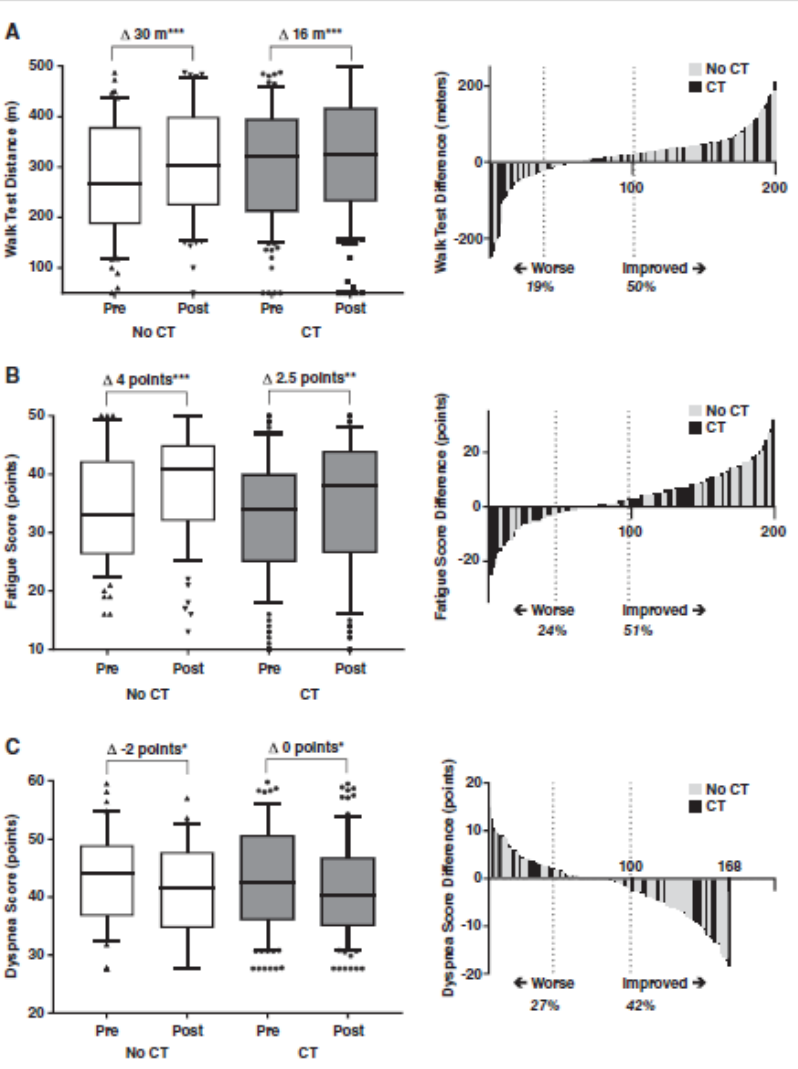
Table 1. Goals of RBC and platelet transfusion in MDS

Transfusion type	Goal of transfusion	Measured by	Desired outcomes
Red cell transfusion	• Improve acute and chronic symptoms of anemia (fatigue, dyspnea, chest pain, palpitations, effects on cognitive function) • Minimize major complications of (severe) anemia • Improve functional outcomes	• Hemoglobin and hematocrit • Functional measures using standardized tool (eg, fatigue score, walk distance, grip strength) or self-report	• Control of symptoms • Better functional status in activities of daily living • Increased ability to participate in work or social and community interests
Platelet transfusion	• Improve symptoms of thrombocytopenia (patient experience of skin bruising and other bleeding) • Minimize major complications of (severe) thrombocytopenia • Improve functional outcomes	• Platelet count • Bleeding assessments (eg, standardized tool or self-report)	• Improved health-related QoL

Wood EM, McQuilten ZK. Hematology 2020:167.

RETRO Study

- Effect of transfusion on outpatient functional status
- 208 pts with benign or malignant hematology/ oncology diagnosis
- Predictors of response
  - Hb ≥ 80 g/L x 1 week post
  - No recent cancer therapy within 4 weeks
  - No hospitalization during study period



Lezin et al. Transfusion 2019;59:1934-43

Ask the Patients…

- Web-based survey in the US, Canada and UK: 475 TD-RBC MDS pts

Median Hb threshold 80g/L
40% pts preferred higher Hb;
15% lower Hb

Fatigue, SOB most common symptoms and had most negative impact

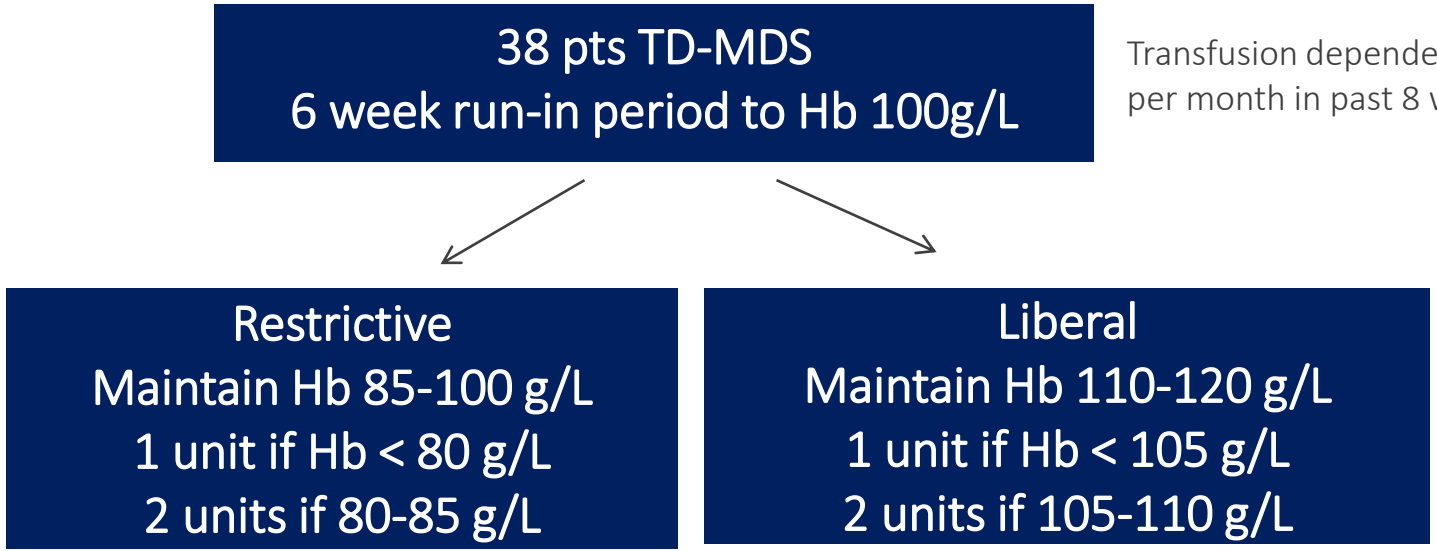
While majority felt better, 20% felt worse post transfusion for 1-2 days and 7% no change

31% experienced undue financial hardship due to transfusion dependence

Starkman, Buckstein et al. ASH Abstract 2018; Blood 2018;132(Suppl1):3092

REDDS-1 Study

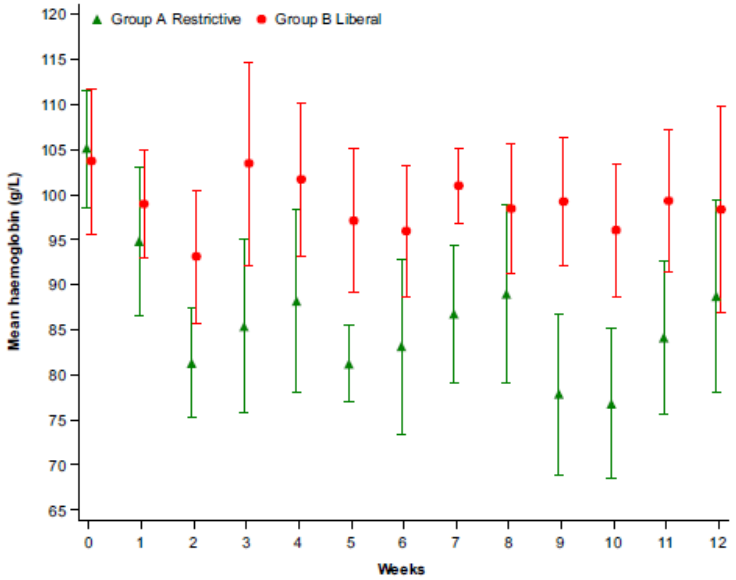
- Pilot: RBC transfusion thresholds and QOL in MDS in UK/Aus/NZ



Pilot study deemed feasible with ≥ 70% compliance in both arms (86% vs 99%)

Stanworth et al. BJH 2020;189:279-290

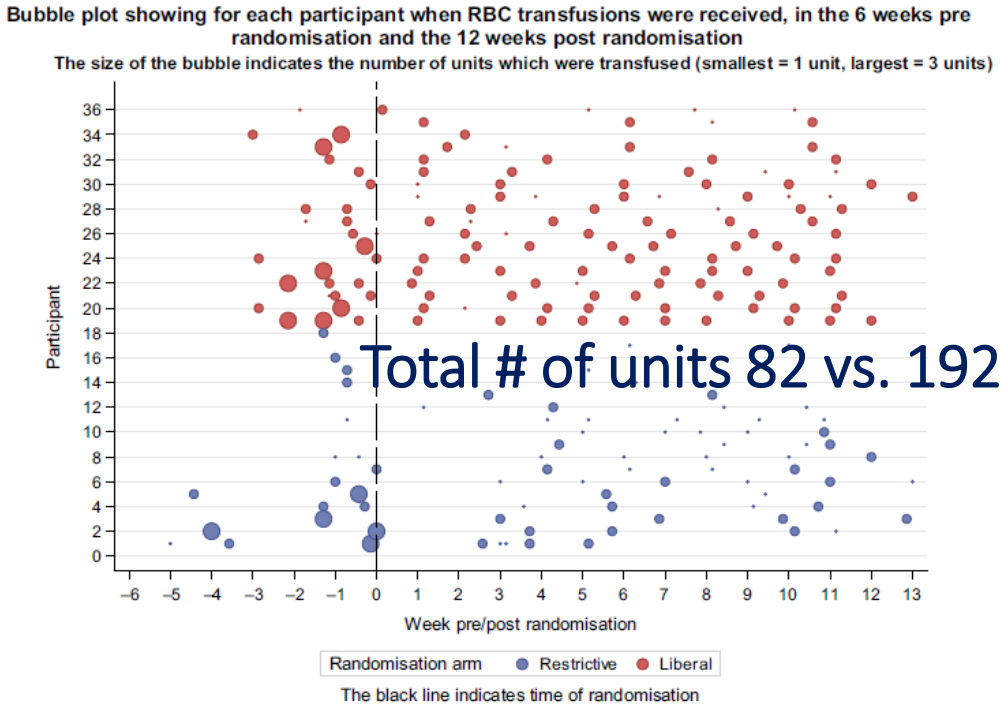
REDDS-1 Pilot Study



The number of haemoglobin measurements included at each time point

Randomisation arm	0	1	2	3	4	5	6	7	8	9	10	11	12
Group A Restrictive	27	12	3	12	15	7	5	11	11	7	8	7	12
Group B Liberal	28	14	8	12	16	10	10	10	14	13	9	11	11

Pre-tx Hb 80 vs. 97 g/L



Total # of units 82 vs. 192

Stanworth et al. BJH 2020;189:279-290

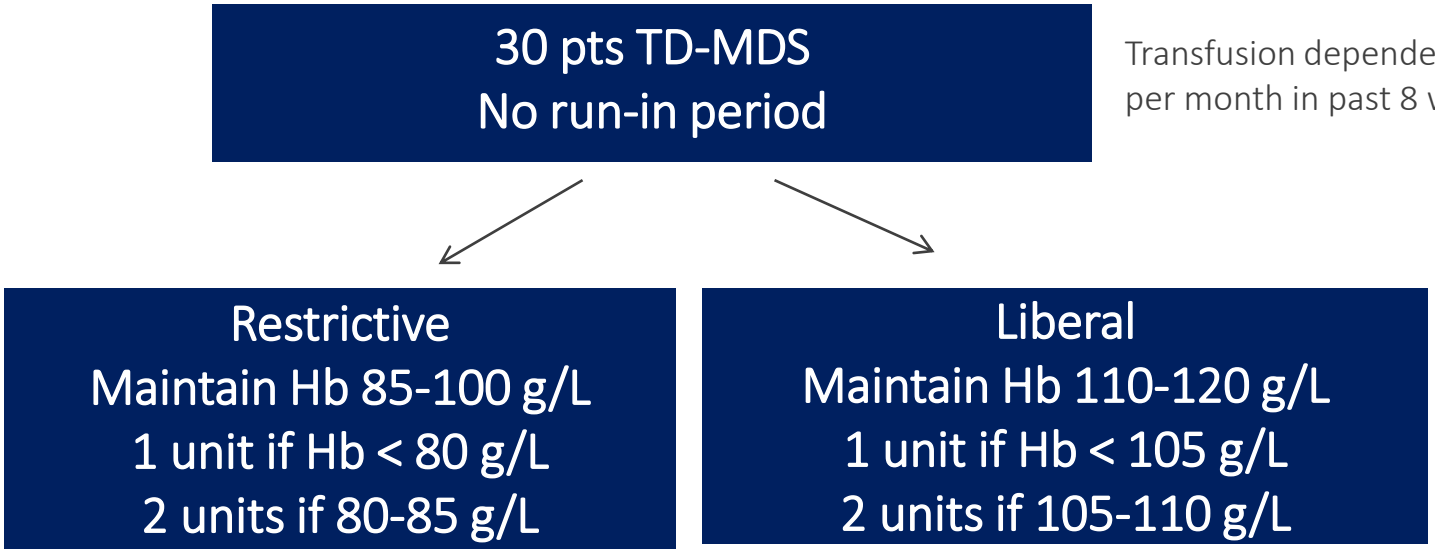
REDDS-1 Pilot Study - QoL

	Restrictive (n=20)	Liberal (n=18)	Overall (n=38)
EQ-5D-5L: Descriptive part (Higher=better)	0.76 (0.51-0.81)	0.83 (0.69-0.86)	0.78 (0.68-0.86)
EORTC: Physical functioning (Higher=better)	61 (50-86)	69 (48-94)	68 (50-86)
EORTC: Global health scores (Higher=better)	63 (60-75)	70 (53-87)	68 (56-76)
EORTC: Fatigue (Lower=better)	38 (33-54)	34 (14-66)	37 (21-63)
EORTC: Dyspnoea (Lower=better)	42 (31-64)	25 (1-77)	40 (12-67)

Stanworth et al. BJH 2020;189:279-290

ENHANCE-RBC Study

- Pilot: RBC transfusion thresholds and QoL in MDS in Toronto/Hamilton



Buckstein et al. Blood 2020;136(Supplement):3-4

Pre-txn Hb
101 vs. 90 g/L

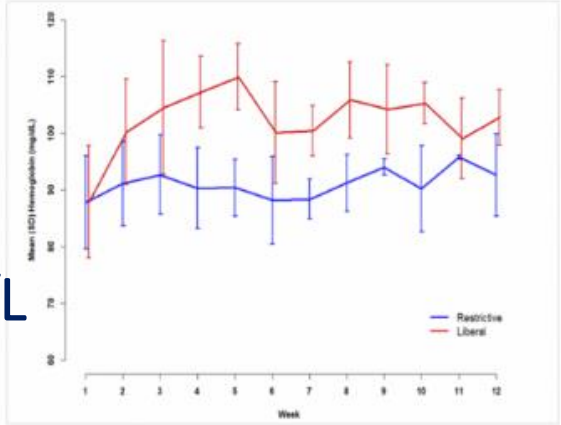


Figure 1. Mean Hb (SD) at weeks 1-12 in patients from 2 treatment arms

QOL

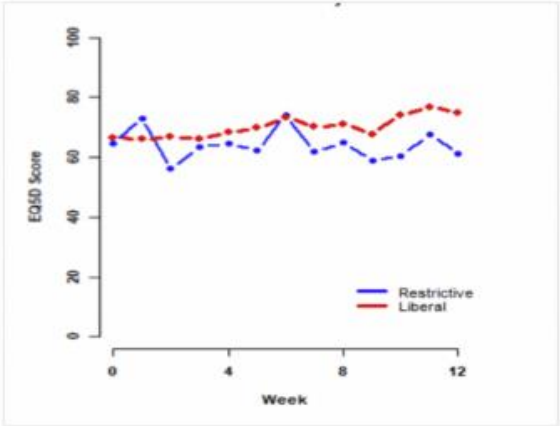


Figure 2. Mean (EQ-5D) visual analog score over 12 weeks from 2 treatment arms

Table 1.

	Liberal Arm, n=15 (IQR)	Restrictive Arm, n=13 (IQR)	P Value
# CBC	16 (14-20)	12 (10-14)	0.01
# CBC after 4 week run-in	8 (7-12)	7 (5-8)	0.04
# transfusion visits	8(7-9)	5 (4-7)	0.001
# RBC units overall	12 (12-16)	9 (8-12)	0.02
# RBC units after 4 week run in	7 (6-9)	6 (4-8)	0.07
Days between transfusions	9 (8-15)	15 (11-22)	<.0001
Mean change in ferritin ug/L	803	155	0.003
New allo-antibody	1	0	0.3
Febrile non hemolytic reaction	1	0	0.3

Buckstein et al. Blood 2020;136(Supplement):3-4

What can we use to make the transfusion experience safer and better for the patient?

Iron Overload

- Ineffective iron metabolism due to ineffective erythropoiesis
- Secondary to transfusion
- Screen: Ferritin > 1000 mcg/L and > 15-20 RBC units

- Iron overload associated with reduced survival
- TELESTO RCT trial of iron chelation: median EFS 3.9 y vs 3 y with placebo (HR 0.64; 95%CI 0.42-0.96)

Volpe et al. Ther Adv Hematol 2021;12:1-10
Angelucci et al. Ann Intern Med 2020;172:513-22

Transfusion Reactions

Table 1 Adverse transfusion reactions observed in transfused patients with aplastic anaemia or myelodysplastic syndrome from 1 January 2010 to 30 June 2016 in the Auvergne-Rhône-Alpes region

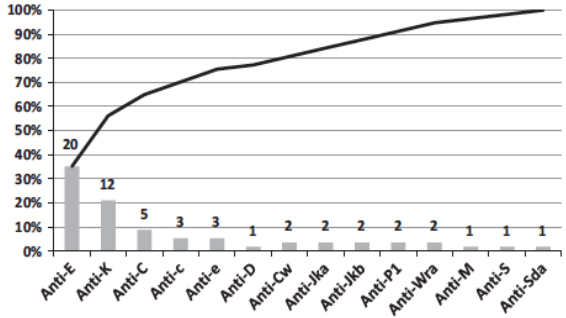
Type of adverse transfusion reaction	Myelodysplastic syndrome (193)	Auvergne-Rhône-Alpes (7174)
Febrile non-haemolytic transfusion reaction	56 (29·0)	1767 (24·6)
Post-transfusion red blood cell alloimmunization	43 (22·3)	2346 (32·7)
Allergic reaction	33 (17·1)	978 (13·6)
Suspected transfusion-transmitted bacterial infection	16 (8·3)	693 (9·7)
Transfusion-associated circulation overload	8 (4·1)	237 (3·3)

[a]Number of adverse transfusion reactions.
[b]Percentage.

Moncharmont P et al. Vox Sanguinis 2019;114:349-354

Alloimmunization & MDS

- Rates of alloimmunization: 11% - 57% *(smaller studies report higher rates)*
  - 75% antibodies in Rh, Kell blood group systems
  - Associated with ↑ RBC units *(70% by 20 units)*
  - ↓ with disease modifying therapies
  - ↑ transfusion intensity post alloimmunization



- Rates of autoantibodies: 4-10% (40-45% DAT+)
  - More common in alloimmunized pts

Singhal D et al. Haematologica 2017;102:2021-9
Lin Y et al. Vox Sanguinis 2017;112:79-86
Chhetri et al. Haematologica; 2019;104:e453

Alloimmunization & MDS

- Consequences
  - Delayed hemolytic transfusion reactions
  - Autoantibodies: pathological → autoimmune hemolysis
  - Delayed serologic transfusion reactions
  - Challenge to resolve in Transfusion Lab
  - Longer time to prepare RBC units for transfusion

Singhal D et al. Haematologica 2017;102:2021-9

Prevention

- MDS Registry : Compared pts receiving transfusion at site with prophylactic antigen matching for RhCEK vs not

Alloimmunization	Rh/K matching site	No matching site	P value
Clin significant alloAbs	11%	23%	0.06
Rh/K alloantibodies	7%	22%	0.008

  - No pt receiving Rh/K matched developed Rh/K alloantibody (0 vs. 18%)

- Alloimmunization still occurs: plt transfusion, non Rh/K alloabs

Lin Y et al. Vox Sanguinis 2017;112:79-86

Case Study

- 72 M with myelodysplastic syndrome (MDS) and severe anemia, not responding to treatment
- The hematologist asks…..
  - Are there transfusion guidelines for outpatients?
  - Any blood bank testing or measures that I need to order to help my patient?

Case Study - Summary

- No current guidelines for MDS outpts
- Reasonable: Hb 70-80 g/L and adjust considering comorbidities, QOL
- Consider prophylactic Rh/K matching for transfusion dependent pts
- Explore ways to simplify the process: same day crossmatch, home G&S
- Explore ways to capture QOL and what is important to patients

What about chronic platelet transfusion in MDS outpatients?

What about MDS outpatients?

- Thrombocytopenia = adverse prognostic factor in MDS
- Death from bleeding in MDS ~ 9-13%

- MDS registry in Australia
  - 50% required at least 1 plt transfusion
  - 9% required HLA matched platelets for platelet refractoriness

Bowen et al. Editorial. Transfusion 2020;60:2164-7
Cheok et al. Transfusion 2020;60:2192-8

Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia

See Editorial, pages 1–2

Susan Nahirniak [a,*], Sherrill J. Slichter [b], Susano Tanael [c], Paolo Rebulla [d], Katerina Pavenski [e], Ralph Vassallo [f], Mark Fung [g], Rene Duquesnoy [h], Chee-Loong Saw [i], Simon Stanworth [j], Alan Tinmouth [k], Heather Hume [l], Arjuna Ponnampalam [m], Catherine Moltzan [n], Brian Berry [o], Nadine Shehata [p], for the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

Annals of Internal Medicine

CLINICAL GUIDELINE

Platelet Transfusion: A Clinical Practice Guideline From the AABB

Richard M. Kaufman, MD; Benjamin Djulbegovic, MD, PhD; Terry Gernsheimer, MD; Steven Kleinman, MD; Alan T. Tinmouth, MD; Kelley E. Capocelli, MD; Mark D. Cipolle, MD, PhD; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Brenda J. Grossman, MD, MPH; Paul D. Mintz, MD; Barbara A. O'Malley, MD; Deborah A. Sesok-Pizzini, MD; Aryeh Shander, MD; Gary E. Stack, MD, PhD; Kathryn E. Webert, MD, MSc; Robert Weinstein, MD; Babu G. Welch, MD; Glenn J. Whitman, MD; Edward C. Wong, MD; and Aaron A.R. Tobian, MD, PhD

- Prophylactic transfusion at < 10×10^9/L

Nahirniak et al. Transfusion Med Reviews 2015;29:3-13

Kaufman et al. Ann Int Med 2015;162:205-13

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

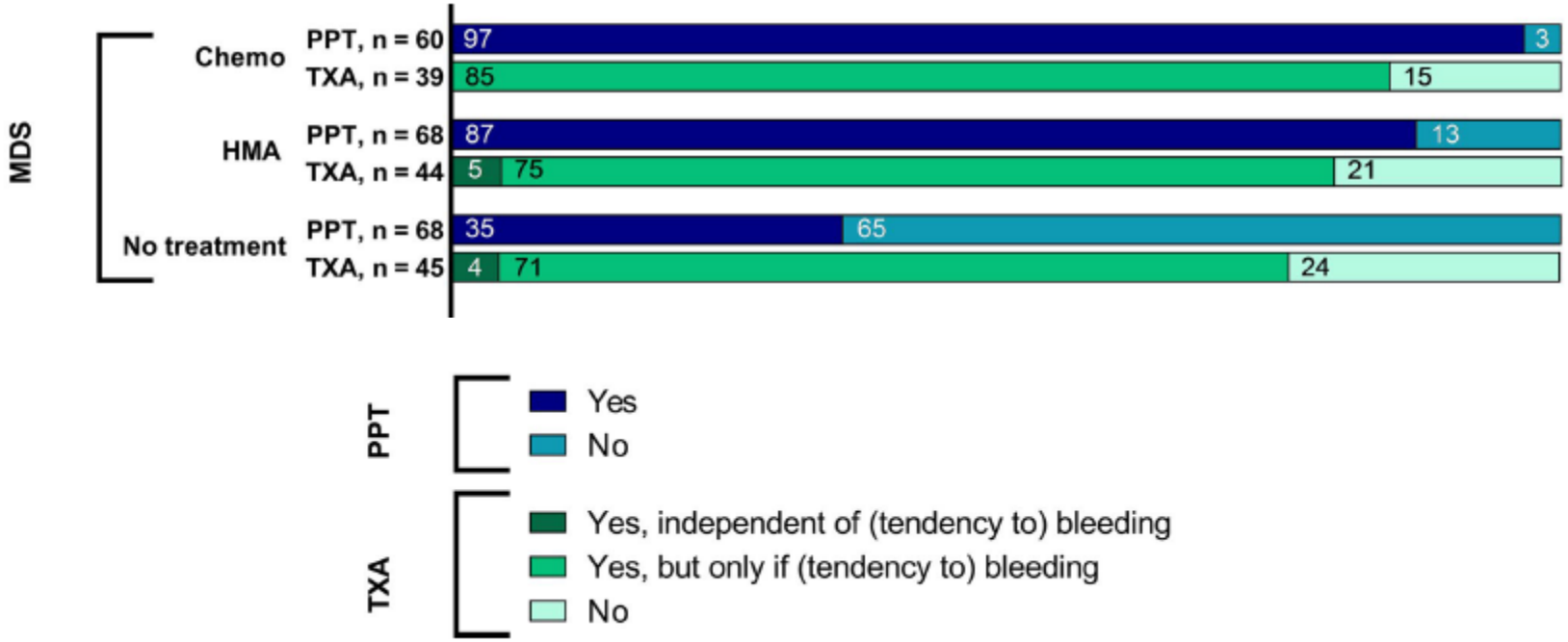
Charles A. Schiffer, Kari Bohlke, Meghan Delaney, Heather Hume, Anthony J. Magdalinski, Jeffrey J. McCullough, James L. Omel, John M. Rainey, Paolo Rebulla, Scott D. Rowley, Michael B. Troner, and Kenneth C. Anderson

- Prophylactic platelet transfusion at < 10 x 10^9/L
  - Patients receiving therapy for hematologic malignancies
  - Allogeneic stem cell transplantation

- Therapeutic platelet transfusion
  - Autologous SCT: similar rates of bleeding with decreased platelet usage when patients transfused at first sign of bleeding rather than prophylactically (experienced centers)
  - Chronic stable severe thrombocytopenia (MDS, aplastic anemia) not receiving active treatment

Schiffer et al. JCO 2018;36:283-99

Survey in Netherlands



Cornelissen et al. Eur J Haematol 2021;106:362-70

MDS & Thrombocytopenia

- MDS Registry: 586 registry pts at a single site
  - 99 pts (17%) had persistent plt < 20 x 10^9/L; median OS 0.9 yrs

Bleeding	TXA alone N=28	TXA + Proph N=39	Proph alone N=19	No tx N= 13
Any bleeding event	86%	74%	89%	85%
Grade 3	7%	10%	11%	0
Grade 4	11%	5%	5%	0
Therapeutic plts	32%	--	--	23%

  - No significant difference in grade 3-4 bleeding → retrospective
  - 71% in group 1 and 4 received no plt transfusions

Vijenthira et al. Leuk Res 2019;76:76-81

Tranexamic Acid in Heme

- RCT: TXA vs. placebo every 8 hrs during chemo / HSCT

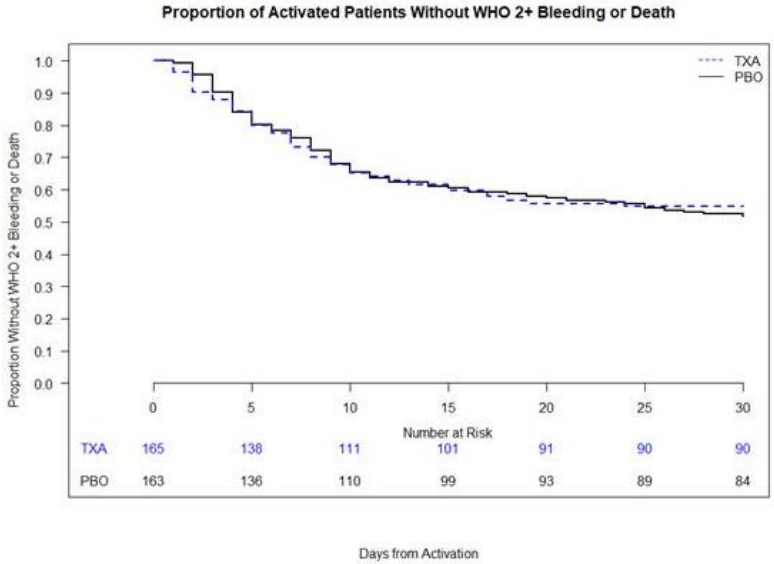


Figure 1. Kaplan-Meier plot of the proportion of patients without WHO 2+ bleeding or death within 30 days following activation.

Gernsheimer et al. ASH Abstract 2020

Summary

- MDS patients carry a significant transfusion burden with impact on quality of life, prognosis and resource utilization
- Evidence for transfusion indications is developing
  - How can we tell if we are over / undertransfusing pts in the outpatient setting?

- Time to focus on the outpatient setting: optimize outcomes, care and the experience for patients

Thank you!

- Rena Buckstein
- Christine Cserti-Gazdewich