Terapia di prima linea delle Sindromi Mielodisplastiche

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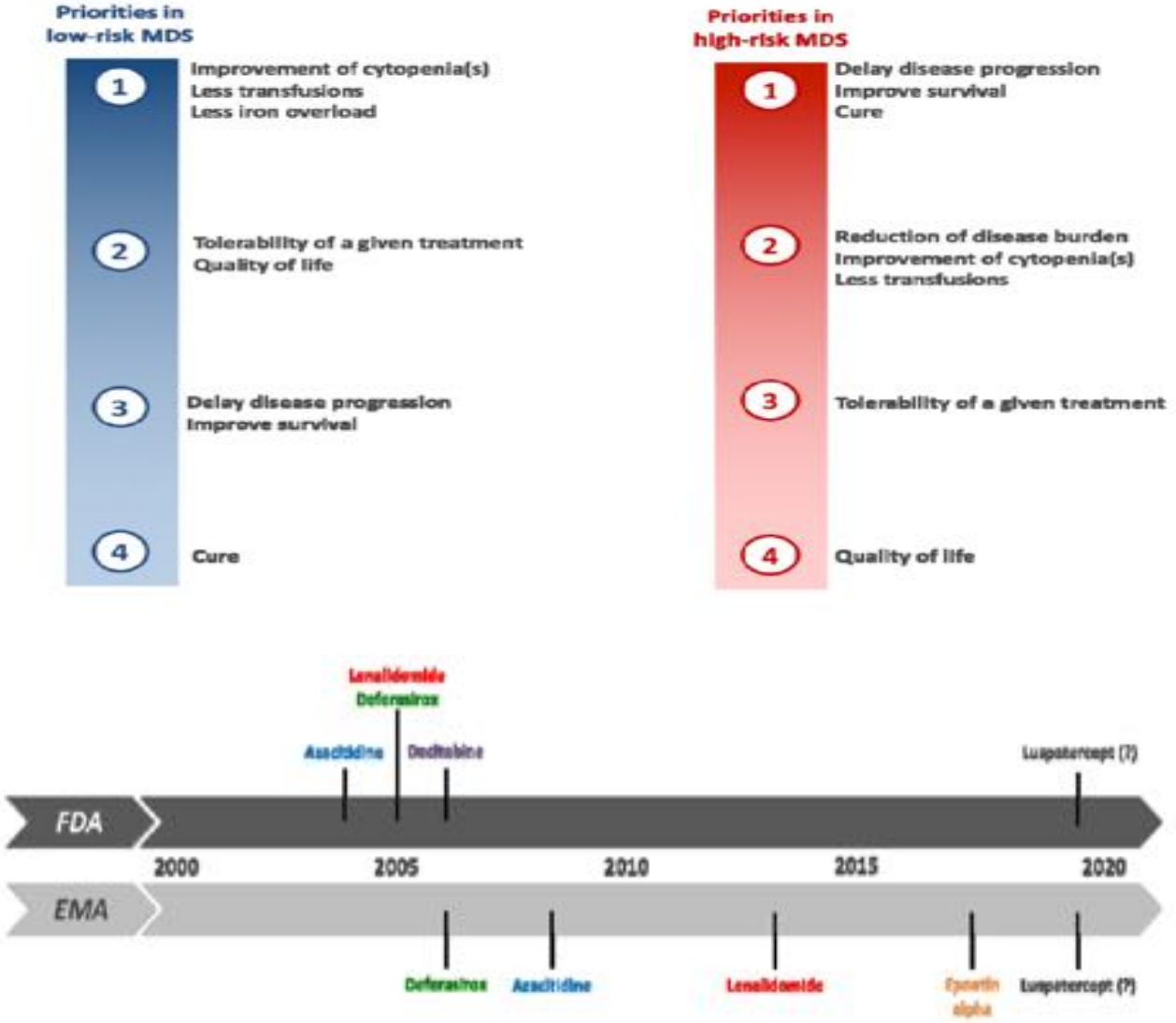
Figure 1: Priorities of therapeutic interventions in patients with MDS according to disease stage



Platzbecker U, Blood 2019

Sindromi Mielodisplastiche

Fattori che influenzano la prognosi

Individuali

- *Età*
- *PS*
- *Comorbidita'*
- *Attivita' funzionali*

Caratteristiche della malattia

- *Morfologia (WHO) ***
- *N. blasti nel midollo osseo **
- *Anomalie cromosomiche */***
- *Numero/entita'delle citopenie **
- *Trasfusione-dipendenza ***
- *LDH, fibrosi*
- *Profilo molecolare (mutazioni)*

Complicanze

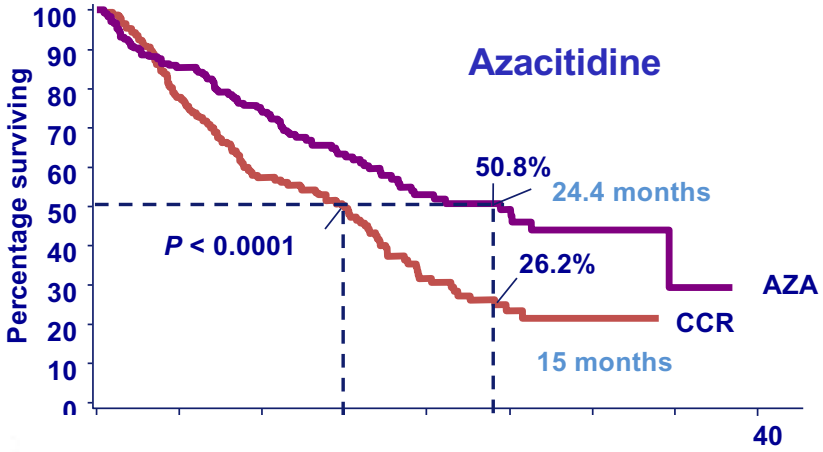
- *Anemia severa*
- *Emorragie*
- *Infezioni*
- *Evoluzione in leucemia acuta*

Terapie

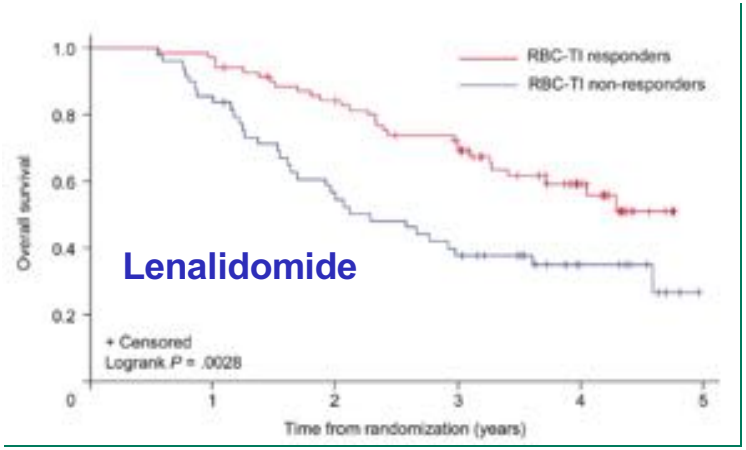
- *Trasfusioni, ferrochelazione*
- *Azacitidina, decitabina*
- *Lenalidomide, talidomide*
- *ESA*
- *Immunosoppressione*
- *Chemioterapia AML-like*
- *Trapianto allogenico*

* Parametri utilizzati per i punteggi prognostici IPSS e IPSS-R
** Parametri utilizzati per i punteggi prognostici WPSS e WPSS-R

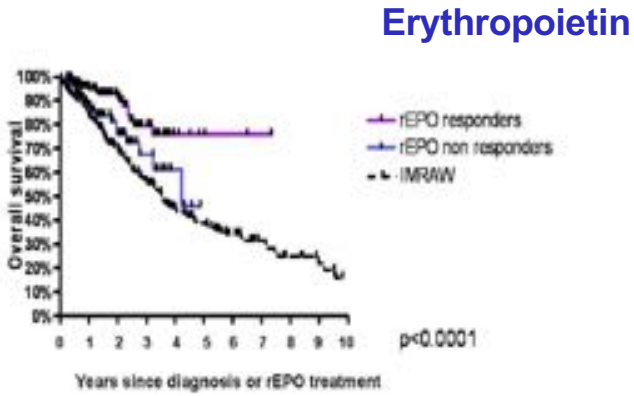
Impact of novel treatments on survival of MDS patients



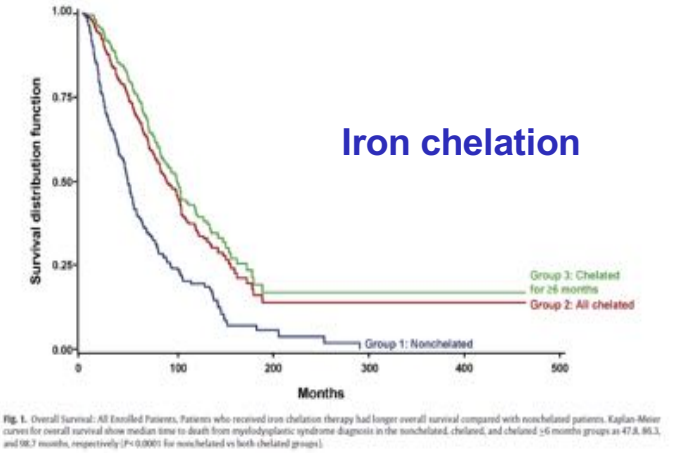
Fenaux P, et al. Lancet Oncol. 2009



Fenaux et al, Blood 2011



Park et al, Blood 2008



Lyons RM, et al. Leuk Res, 2017

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet

Luca Malcovati,[1,2] Eva Hellström-Lindberg,[3] David Bowen,[4] Lionel Adès,[5] Jaroslav Cermak,[6] Consuelo del Cañizo,[7] Matteo G. Della Porta,[1] Pierre Fenaux,[5] Norbert Gattermann,[8] Ulrich Germing,[8] Joop H. Jansen,[9] Moshe Mittelman,[10] Ghulam Mufti,[11] Uwe Platzbecker,[12] Guillermo F. Sanz,[13] Dominik Selleslag,[14] Mette Skov-Holm,[15] Reinhard Stauder,[16] Argiris Symeonidis,[17] Arjan A. van de Loosdrecht,[18] Theo de Witte,[9] and Mario Cazzola[1,2]

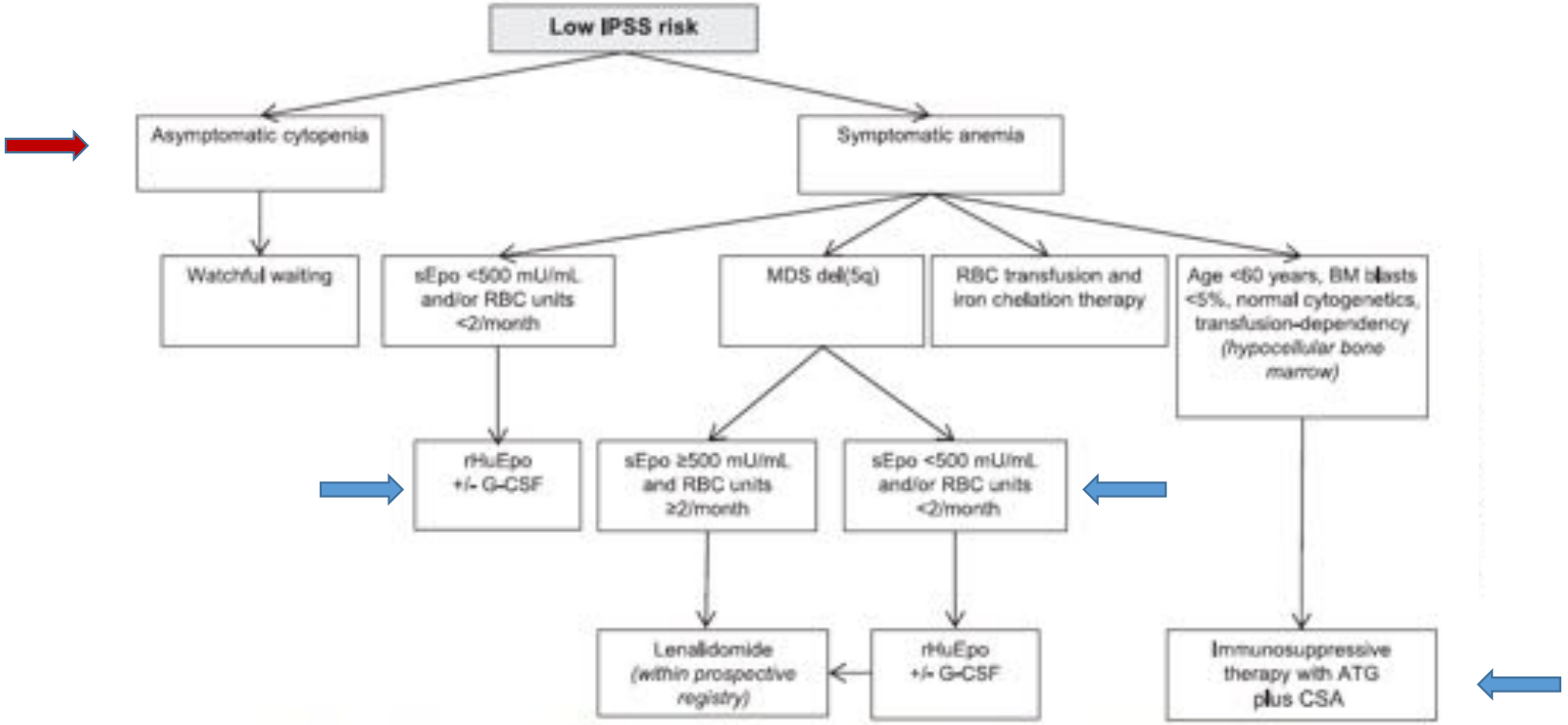
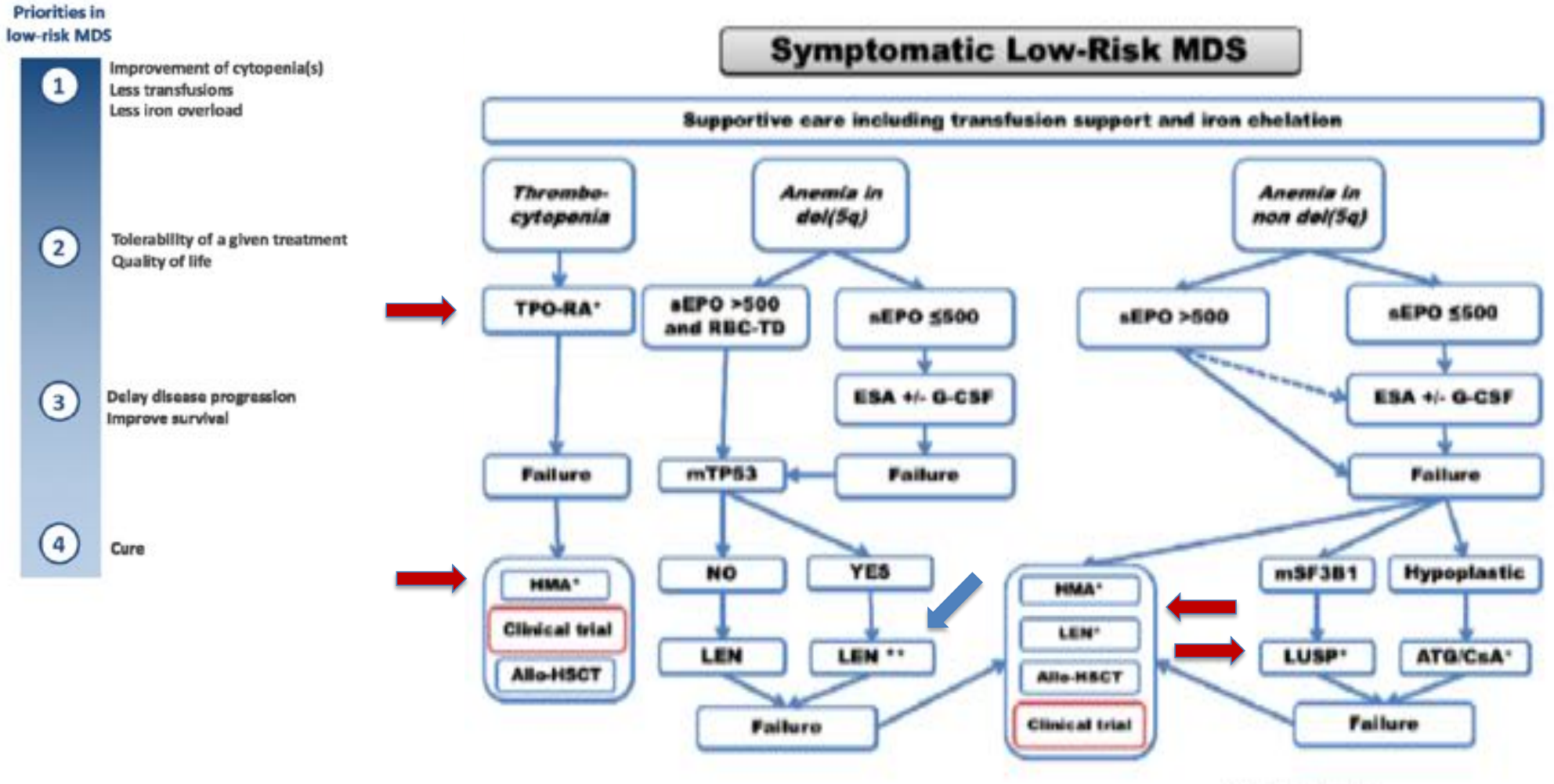


Figure 1. Therapeutic algorithm for adult patients with primary MDS and low IPSS score. BM, bone marrow; sEpo, serum erythropoietin.

Figure 1: Priorities of therapeutic interventions in patients with MDS according to disease stage



Platzbecker U, Blood 2019

* Still not approved
**Intensified disease surveillance

British Journal of Haematology, 1998, 101, 1070–1074

A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes

Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes*

*Writing committee: Pierluigi Rossi Ferrini, Alberto Grossi, Alessandro M. Vannucchi, Giovanni Barosi, Roberta Guarnone, Nadia Piva, Pellegrino Musto, Enrico Balleari.

Summary. To evaluate the effect of recombinant human erythropoietin (rHuEpo) on the haemoglobin level and transfusion requirement in low-risk myelodysplastic syndromes (MDS), 87 patients were enrolled in a randomized double-blind placebo-controlled study. 44 patients were assigned to epoetin α (150 U/kg/d s.c. for 8 weeks) and 43 to placebo arms. MDS types were homogeneous in both groups: refractory anaemia (RA) 47·7–48·8%, refractory anaemia with ringed sideroblasts (RAS) 20·5–25·6%, refractory anaemia with excess of blasts (RAEB) (blasts < 10%) 31·8–25·6%.

14/38 evaluable patients responded to epoetin α versus 4/37 to placebo ($P = 0·007$). 50% of RA responded to epoetin α versus 5·9% to placebo ($P = 0·0072$); RAS 37·5% v 18·2% ($P = 0·4$) and RAEB 16·7% v 11·1% ($P = 1·00$). 60% of non-pretransfused patients responded to epoetin α (Hb 8·35 ± 0·73 to 10·07 ± 1·87 g/dl), whereas a slight decrease was observed in the placebo group (8·4 ± 0·66 to 8·19 ± 0·92 g/dl) ($P = 0·0004$). Percentage of transfused patients was similar in both arms. Basal erythropoietin (Epo) serum levels > 200 mU/l predicted for a non-response. At week 4 sTfR levels were increased > 50% in responders ($P = 0·013$), whereas an increase < 18% predicted for non-response ($P = 0·006$). Leucocyte and platelet counts were not influenced by epoetin α treatment. Adverse events occurred in 31·8% of the rHuEpo-treated versus 42·9% of the placebo-treated patients ($P = 0·2$), and seven patients did not complete the course. In conclusion, rHuEpo was effective in the treatment of low-risk MDS. RA subtype, no transfusions prior to rHuEpo therapy, and low basal Epo levels were associated with higher probability of response. Soluble transferrin receptor level at the fourth week was an early predictor of response.

Keywords: anaemia, myelodysplastic syndromes, erythropoietin, transfusion, transferrin receptor.

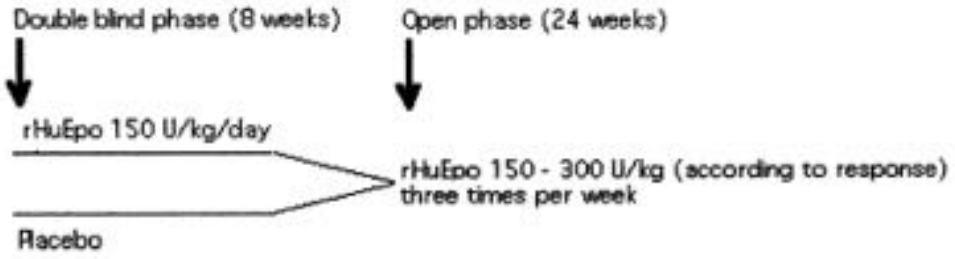


Fig 1. Treatment plan of low-risk MDS with rHuEpo.

Table III. Double-blind phase.

Response to rHuEpo: per protocol analysis

	Epoetin α	Placebo	P
Partial	9/38	4/37	
Full	5/38	0/37	
Total	14/38 (36·8%)	4/37 (10·8%)	0·007*

*Cochran Mantel Haenszel statistic

Response according to RAS subgroups

RA 50% epoetin α versus 5·9% placebo ($P = 0·0072$)
RAS 37·5% epoetin α versus 18·2% placebo ($P = 0·4$)
RAEB 16·7% epoetin α versus 11·1% placebo ($P = 1·00$)

Response according to transfusion need prior to therapy

Pre-transfused 5/27 (21·7%) epoetin α versus 4/28 (14·3%) placebo ($P = 0·72$)
Non pre-transfused 9/11 (82%) epoetin α versus 0/9 (0%) placebo ($P = 0·0008$)

ORIGINAL ARTICLE

A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes

U Platzbecker[1], A Symeonidis[2], EN Oliva[3], JS Goede[4], M Delforge[5], J Mayer[6], B Slama[7], S Badre[8], E Gasal[8], B Mehta[8] and J Franklin[8]

The use of darbepoetin alfa to treat anemia in patients with lower-risk myelodysplastic syndromes (MDS) was evaluated in a phase 3 trial. Eligible patients had low/intermediate-1 risk MDS, hemoglobin ⩽10 g/dl, low transfusion burden and serum erythropoietin (EPO) ⩽500 mU/ml. Patients were randomized 2:1 to receive 24 weeks of subcutaneous darbepoetin alfa 500 μg or placebo every 3 weeks (Q3W), followed by 48 weeks of open-label darbepoetin alfa. A total of 147 patients were randomized, with median hemoglobin of 9.3 (Q1:8.8, Q3:9.7) g/dl and median baseline serum EPO of 69 (Q1:36, Q3:158) mU/ml. Transfusion incidence from weeks 5–24 was significantly lower with darbepoetin alfa versus placebo (36.1% (35/97) versus 59.2% (29/49), $P=0.008$) and erythroid response rates increased significantly with darbepoetin alfa (14.7% (11/75 evaluable) versus 0% (0/35 evaluable), $P=0.016$). In the 48-week open-label period, dose frequency increased from Q3W to Q2W in 81% (102/126) of patients; this was associated with a higher hematologic improvement–erythroid response rate (34.7% (34/98)). Safety results were consistent with a previous darbepoetin alfa phase 2 MDS trial. In conclusion, 24 weeks of darbepoetin alfa Q3W significantly reduced transfusions and increased rates of erythroid response with no new safety signals in lower-risk MDS (registered as EudraCT#2009-016522-14 and NCT#01362140).

Leukemia (2017) **31**, 1944–1950; doi:10.1038/leu.2017.192

Leukemia (2018) 32:2648–2658
https://doi.org/10.1038/s41375-018-0118-9

ARTICLE

Myelodysplastic syndrome

A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS

Pierre Fenaux[1] · Valeria Santini[2] · Maria Antonietta Aloe Spiriti[3] · Aristoteles Giagounidis[4] · Rudolf Schlag[5] · Atanas Radinoff[6] · Liana Gercheva-Kyuchukova[7] · Achilles Anagnostopoulos[8] · Esther Natalie Oliva[9] · Argiris Symeonidis[10] · Mathilde Hunault Berger[11] · Katharina S. Götze[12] · Anna Potamianou[13] · Hari Haralampiev[14] · Robert Wapenaar[15] · Iordanis Milionis[16] · Uwe Platzbecker[17]

Received: 26 September 2017 / Revised: 21 December 2017 / Accepted: 14 February 2018 / Published online: 30 March 2018

Abstract

Erythropoiesis-stimulating agents are first choice for treating anemia in low-risk MDS. This double-blind, placebo-controlled study assessed the efficacy and safety of epoetin-α in IPSS low- or intermediate-1 risk (i.e., low-risk) MDS patients with Hb ≤ 10.0 g/dL, with no or moderate RBC transfusion dependence (≤4 RBC units/8 weeks). Patients were randomized, 2:1, to receive epoetin-α 450 IU/kg/week or placebo for 24 weeks, followed by treatment extension in responders. The primary endpoint was erythroid response (ER) through Week 24. Dose adjustments were driven by weekly Hb-levels and included increases, and dose reductions/discontinuation if Hb > 12 g/dL. An independent Response Review Committee (RRC) blindly reviewed all responses, applying IWG-2006 criteria but also considering dose adjustments, drug interruptions and longer periods of observation.

A total of 130 patients were randomized (85 to epoetin-α and 45 to placebo). The ER by IWG-2006 criteria was 31.8% for epoetin-α vs 4.4% for placebo ($p < 0.001$); after RRC review, the ER was 45.9 vs 4.4% ($p < 0.001$), respectively. Epoetin-α reduced RBC transfusions and increased the time-to-first-transfusion compared with placebo.

Thus, epoetin-α significantly improved anemia outcomes in low-risk MDS. IWG-2006 criteria for ER may require amendments to better apply to clinical studies.

bjh review

Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1–risk myelodysplastic syndrome: a systematic literature review

Sophie Park,[1] Peter Greenberg,[2] Aylin Yucel,[3] Caroline Farmer,[4] Frank O'Neill[3] Cisio De Oliveira Brandao,[3] and Pierre Fenaux[5]

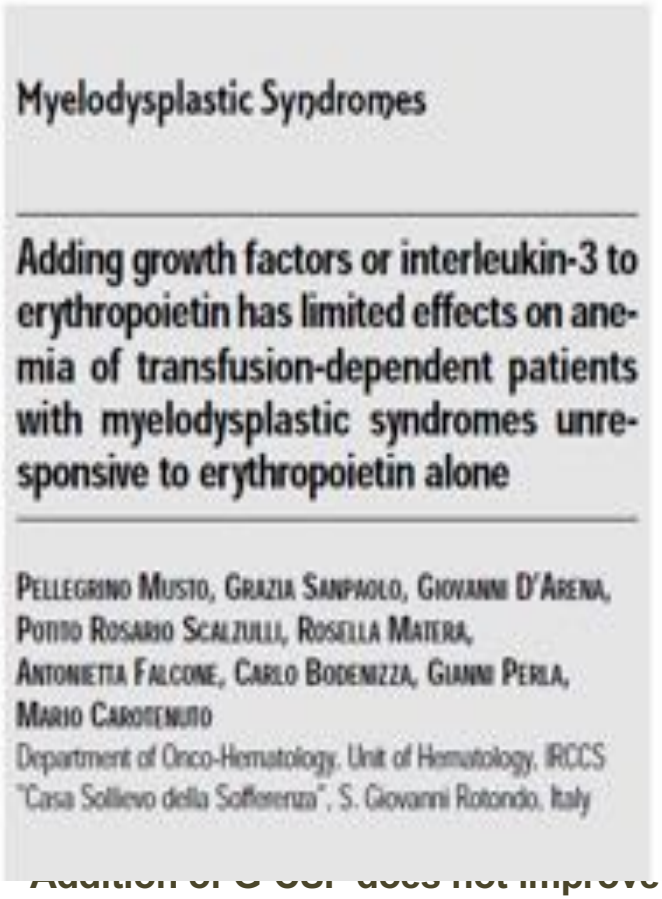
- **Systematic literature review** to identify randomized and non-randomized prospective studies reporting on clinical efficacy/effectiveness, patient-reported quality of life (QoL), and safety.
- Retrospective studies for darbepoetin alfa specifically and to ascertain the feasibility of completing an indirect network **meta-analysis comparing epoetin and darbepoetin alfa.**
- Overall, 53 articles reporting on **35 studies** were included.
- The studies indicated a **clinical benefit of ESAs,**observed across key clinical outcomes.
- ESAs showed consistent **improvement in erythroid response rates (ESA-naiive, 45–73%; previous ESA exposure, 25–75%) and duration of response.**
- Comparative studies demonstrated **similar progression to AML** and several showed **improved OS and QoL.**
- **Limited safety concerns** were identified.
- This analysis confirmed **ESA therapy should be the foremost first-line treatment of anaemia in most patients with lower-risk MDS who lack the 5q deletion.**

Study	Intervention
Randomized controlled trials	
Jang *et al* (2015)	DA
Platzbecker *et al* (2017a)	DA
Balleari *et al* (2006)	Epo beta
Fenaux *et al* (2018)†	Epo alfa
Ferrini *et al* (1998)	Epo alfa
Greenberg *et al* (2009)	Epo alfa
Single-arm trials	
Gabrilove *et al* (2008)	DA
Gotlib *et al* (2009)	DA
Kelaidi *et al* (2013a)	DA
Mannone *et al* (2006)	DA
Musto *et al* (2005)	DA
Nilsson-Ehle *et al* (2011)	DA
Oliva *et al* (2010)	DA
Stasi *et al* (2005)	DA
Villegas *et al* (2011)	DA
Latagliata *et al* (2008)‡	Epo (brand NR)
Spiriti *et al* (2005)	Epo alfa (brand NR)
Stasi *et al* (1999)	Epo alfa
Stasi *et al* (2002)	Epo alfa
Stasi *et al* (2004)	Epo alfa
Van Kamp *et al* (1991)	Epo alfa
Prospective observational trials	
Balleari *et al* (2011)	Epo alfa
Economopoulos *et al* (2005)	Epo (brand NR)
Retrospective observational trials	
Giraldo *et al* (2006)	DA
Kelaidi *et al* (2013b)	DA

DA, darbepoetin alfa; Epo, epoetin; NR, not reported.

 doi: 10.1111/bjh.15707

Meta-analysis of erythroid response to ESAs: role of doses and combination with G-CSF



Myelodysplastic Syndromes

Adding growth factors or interleukin-3 to erythropoietin has limited effects on anemia of transfusion-dependent patients with myelodysplastic syndromes unresponsive to erythropoietin alone

Pellegrino Musto, Grazia Sanpaolo, Giovanni D'Arena, Potito Rosario Scalzulli, Rosella Matera, Antonietta Falcone, Carlo Bodenizza, Gianni Perla, Mario Carotenuto
Department of Onco-Hematology, Unit of Hematology, IRCCS "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Italy

original paper

haematologica 2001; 86:44-51
http://www.haematologica.it/2001_01/0044.htm

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Addition of G-CSF does not improve the results

Santini V Semin Haematol 2012; 49(4):295-303
Santini V Oncologist 2011; 16 Suppl 3:35-42;
Nilsson-Ehle et al, EurJ Haematol 2011,87 244

Modified from Moyo V et al *Ann Hematol* 2008 87:527–536
and Mundle S, et al. *Cancer* 2009;115:706-715.

Effects of different (standard vs higher) doses of erythropoietin in patients with myelodysplastic syndromes: a (retrospective) propensity-score matched analysis

	Standard dose 208 pts EPO 40.000 UI weekly (S cohort)	**Higher doses** 104 pts EPO 40.000 IU twice/w (H cohort)	**p**
Hb pre-treatment (median)	9.1 mg/dL	8.9 mg/dL	P=0.9
IPSS score			
low/intermediate 1 (%)	92	95	
Intermediate 2/ high (%)	8	5	P= 0.6
Transfusion-dependency			
No dependency (%)	74	75	
Dependency (%)	26	25	P=0.9
EPO at diagnosis (median)	69 IU	79 UI	P=0.3

Erythroid response

Overall survival

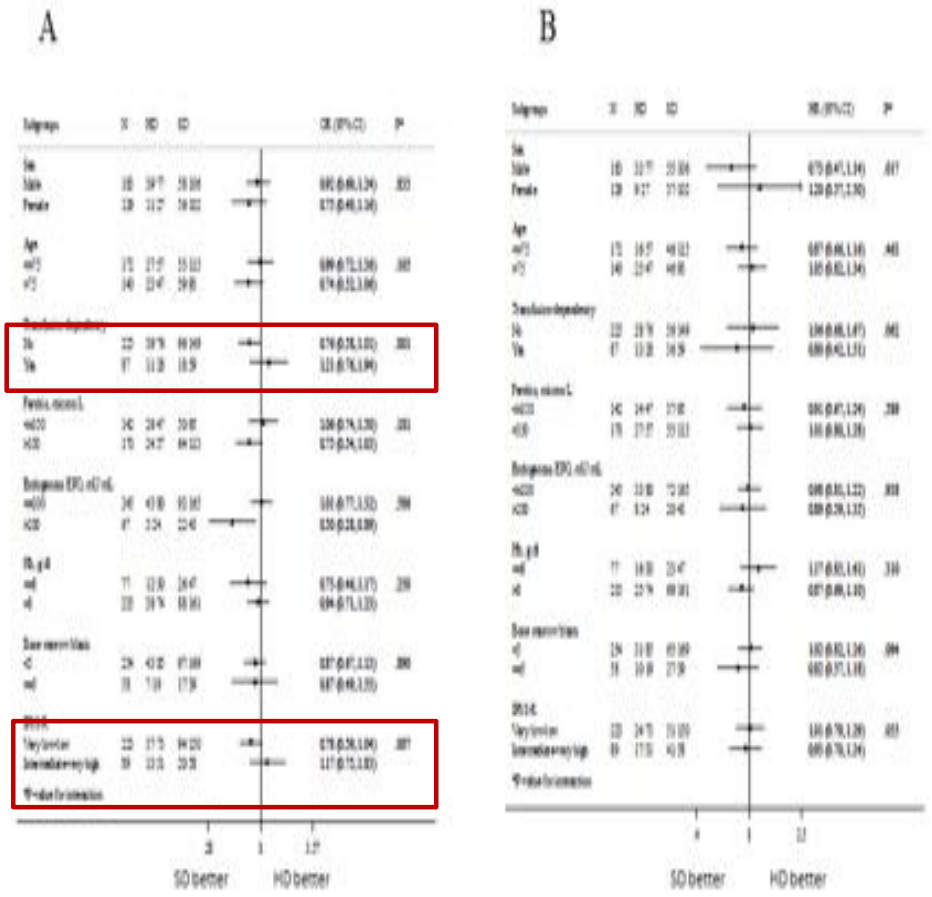


Figure 3

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Balleari et al, Cancer Medicine, in press

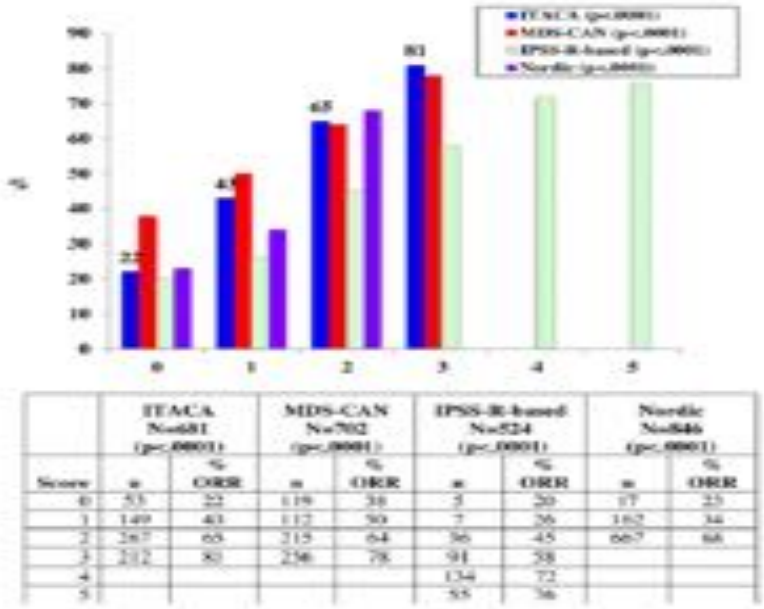
Received: 19 June 2017 | Revised: 27 June 2017 | Accepted: 29 June 2017
DOI: 10.1002/ajh.24642

RESEARCH ARTICLE

WILEY AJH

ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems

Rena Buckstein[1] | Enrico Balleari[1] | Richard Wells[1] | Valeria Santini[1] | Alessandro Sanna[1] | Chiara Salvetti[1] | Elena Crisà[1] | Bernardino Allione[1] | Paolo Danise[1] | Carlo Finelli[1] | Marino Clavio[1] | Antonella Poloni[1] | Flavia Salvi[1] | Daniela Cilloni[1] | Esther Natalie Oliva[1] | Pellegrino Musto[1] | Brett Houston[1] | Nancy Zhu[1] | Michelle Geddes[1] | Heather Leitch[1] | Brian Leber[1] | Mitchell Sabloff[1] | Thomas J. Nevill[1] | Karen W. Yee[1] | John M. Storring[1] | Janika Francis[1] | Luca Maurillo[1] | Roberto Latagliata[1] | Maria Antonietta Aloe Spiriti[1] | Alessandro Andriani[1] | Anna Lina Piccioni[1] | Luana Fianchi[1] | Susanna Fenu[1] | Svitlana Gumenyuk[2] | Francesco Buccisano[1]



Score	ITACA N=681 (p<.0001) n	% ORR	MDS-CAN N=702 (p<.0001) n	% ORR	IPSS-R-based N=524 (p<.0001) n	% ORR	Nordic N=846 (p<.0001) n	% ORR
0	55	22	139	38	5	20	17	35
1	149	43	117	50	7	26	162	34
2	267	65	215	64	36	45	667	66
3	212	80	236	78	91	58		
4					134	72		
5					55	36		

FIGURE 1 Response according to predictive scores.

- 996 ESA-treated patients were identified in 3 MDS registries in Italy and Canada (FISM 555, GROM 233, and MDS-CAN 208).
- Nordic, MDS-CAN, and IPSS-R-based ESA scores were calculated and documented ESA responses compared.

- Overall response rate (ORR) was 59%.
- The database was randomly divided into balanced derivation (n. 463) and validation (n. 462) cohorts.
- The 'ITACA' score had the highest discriminating power of response

TABLE 3 Response rates according to ITACA score in both derivation and validation sets

	Derivation set N=345 ESA ORR		Total	Fisher exact P-value	Validation set N=336 ESA ORR		Total	Fisher exact P-value
Score	No	Yes		<.0001	No	Yes		<.0001
0	20 (77%)	6 (23%)	26		21 (78%)	6 (22%)	27	
1	43 (57%)	33 (43%)	76		42 (57%)	31 (42%)	73	
2	46 (33%)	92 (67%)	138		46 (36%)	83 (64%)	129	
3	16 (15%)	89 (85%)	105		23 (21%)	84 (78%)	107	
Total	125	220	345		132	204	336	

Abbreviations: ORR, overall response rate.

Note: Score = 0: Transfusion-dependence, INT-1/INT-2 IPSS and EPO≥100; Score = 3: Transfusion-independence, Low IPSS and EPO<100

Am J Hematol. 2017;92:1037–1046.

Thalidomide abolishes transfusion-dependence in selected patients with myelodysplastic syndromes

Among 25 transfusion-dependent patients with myelodysplastic syndromes (MDS) receiving up to 300 mg/d thalidomide p.o., 5 became transfusion-free within 4-9 weeks and for 6 to +24 months. Responders had a recent diagnosis, normal karyotype, no excess of marrow blasts and were younger than non-responders. Thalidomide may be effective for treating anemia in selected MDS patients.

haematologica 2002; 87:884-886
(http://www.haematologica.ws/2002_08/884.htm)

Pellegrino Musto, Antonietta Falcone, Grazia Sanpaolo, Michele Bisceglia,° Rosella Matera,# Angelo Michele Carella

**Unit of Hematology and Stem Cell Transplantation; °Unit of Pathologic Anatomy, IRCCS "Casa Sollievo della Sofferenza "S. Giovanni Rotondo; #Unit of Hematology and Oncology, CROB, Rionero in Vulture Italy*

MDS-004: first randomised placebo-controlled study of lenalidomide in patients with del(5q) MDS

Aim: to compare the efficacy and safety of two lenalidomide doses and schedules with placebo

Patient characteristics (n=139)*

- RBC-TD, %: 100
- IPSS risk category, %
  - low: 49
  - int-1: 51
- Karyotype, %
  - del(5q): 76
  - del(5q) + ≥1: 24
- Blood counts, %
  - ANC 500–1000 cells/μL: 12
  - Platelets ≥150,000/μL: 81

Stratification (IPSS score and cytogenetics)

Randomisation

Double-blind phase

- LEN, orally 10mg/day for 21 days of each 28-day cycle
- LEN, orally 5mg/day for 28 days of each 28-day cycle
- Placebo, for 28 days of each 28-day cycle

At week 16

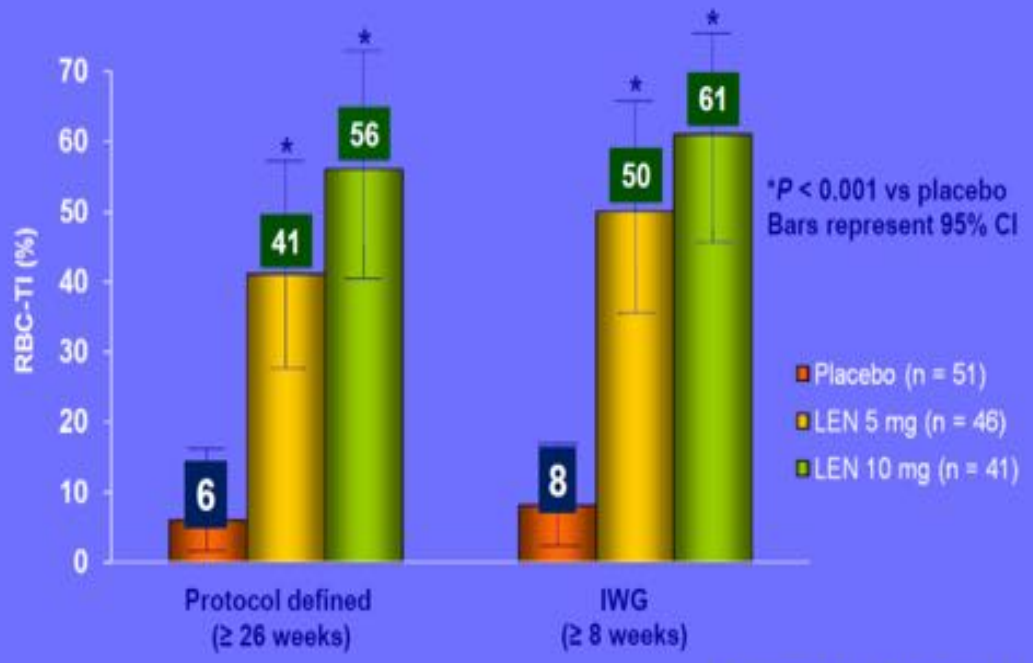
- Responders continued double-blind treatment for up to 52 weeks
- Non-responders entered open-label treatment or withdrew

- Primary endpoint: RBC-TI for ≥26 weeks (absence of transfusions during 26 consecutive weeks on treatment and haemoglobin increased >1g/dL from baseline)
- Secondary endpoints: erythroid response, duration of RBC-TI, BM and cytogenetic response, time to AML progression, QoL and AEs

*Patients in modified intent-to-treat (mITT) population, defined as patients with centrally confirmed MDS who received ≥1 dose
QoL = Quality of life

Fenaux P, et al. Blood 2011;118:3765–76

Randomized double-blind controlled phase III trial of lenalidomide in del 5q Low/Int-1 MDS (MDS-04): RBC-TI



Fenaux et al, Blood 2011

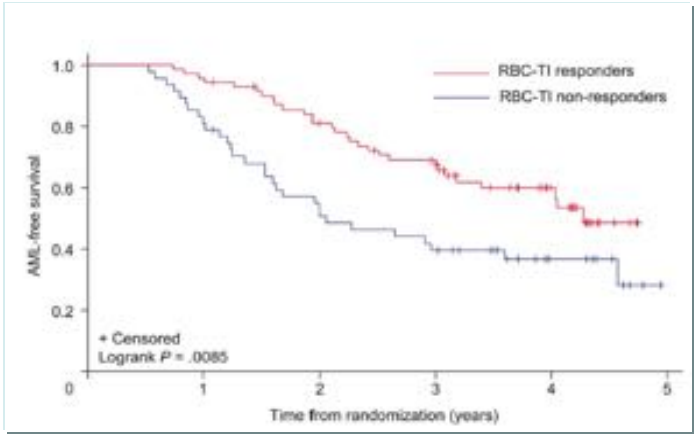
MDS-004: cytogenetic response and progression*

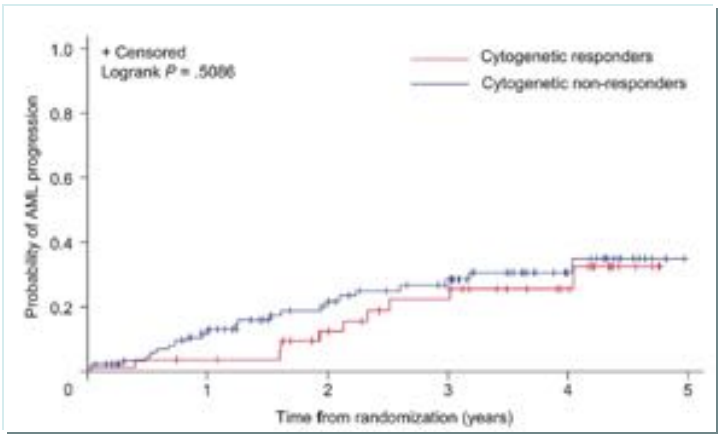
	Placebo (n=51)	LEN 5mg (n=46)	LEN 10mg (n=41)
Response (%)			
CR	0	15.6	29.4
PR	0	9.4	20.6
CR + PR	0	25.0†	50.0†
Cytogenetic progression			
New clones/additional aberrations in existing clones	14.3	31.3	23.5

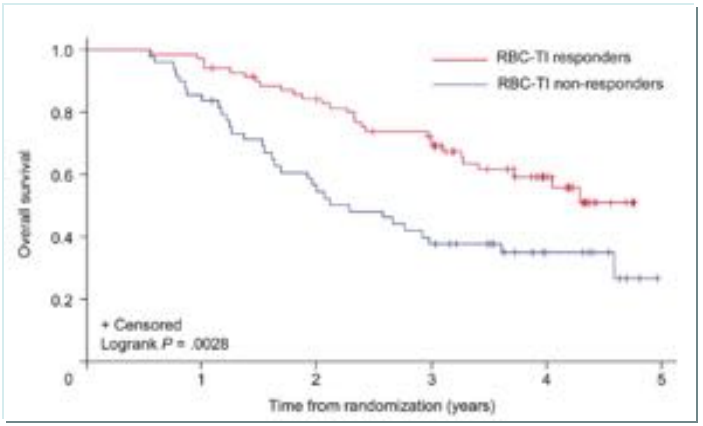
*mITT population
†p<0.001 versus placebo

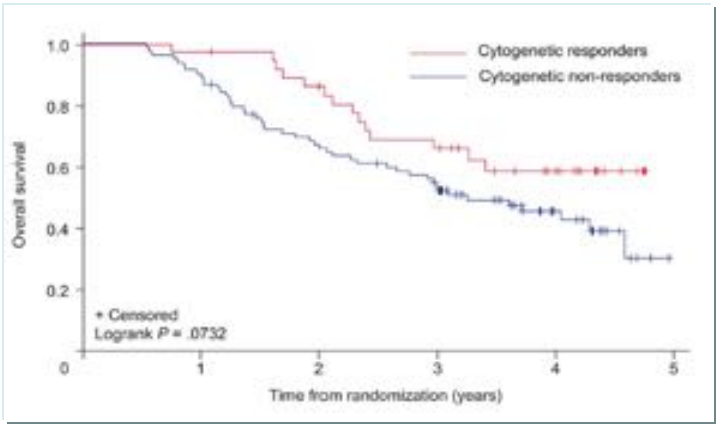
Fenaux P, et al. Blood 2011;118:3765–76

MDS-004 study: LENALIDOMIDE 25 vs 10 vs placebo in del5q, transfusion-dependent, low/int-1 MDS









Achievement of RBC-TI for ≥ 26 weeks (but not cytogenetic response) with lenalidomide was associated with a 41% reduction in the relative risk of AML progression or death (*P* = .046) and a 47% reduction in the relative risk of death (*P* = .019)

Fenaux et al, Blood 2011

REGULAR ARTICLE

blood advances

The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort

Maximilian Stahl,[1] Michelle DeVeaux,[2] Theo de Witte,[3] Judith Neukirchen,[4] Mikkael A. Sekeres,[5] Andrew M. Brunner,[6] Gail J. Roboz,[7] David P. Steensma,[8] Vijaya R. Bhatt,[9] Uwe Platzbecker,[10,11] Thomas Cluzeau,[12] Pedro H. Prata,[13] Raphaël Itzykson,[13] Pierre Fenaux,[13] Amir T. Fathi,[6] Alexandra Smith,[14] Ulrich Germing,[4] Ellen K. Ritchie,[7] Vivek Verma,[9] Aziz Nazha,[5] Jaroslaw P. Maciejewski,[5] Nikolai A. Podoltsev,[1] Thomas Prebet,[1] Valeria Santini,[15] Steven D. Gore,[1] Rami S. Komrokji,[16,*] and Amer M. Zeidan[1,*]

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Key Points

- IST leads to a response in nearly half, and to RBC transfusion independence in about a third, of selected lower-risk MDS patients.
- Hypocellularity of bone marrow and the use of horse ATG plus cyclosporine are associated with increased rates of transfusion independence.

Most studies of immunosuppressive therapy (IST) in myelodysplastic syndromes (MDS) are limited by small numbers and their single-center nature, and report conflicting data regarding predictors for response to IST. We examined outcomes associated with IST and predictors of benefit in a large international cohort of patients with MDS. Data were collected from 15 centers in the United States and Europe. Responses, including red blood cell (RBC) transfusion independence (TI), were assessed based on the 2006 MDS International Working Group criteria, and overall survival (OS) was estimated by Kaplan-Meier methods. Logistic regression models estimated odds for response and TI, and Cox Proportional Hazard models estimated hazards ratios for OS. We identified 207 patients with MDS receiving IST, excluding steroid monotherapy. The most common IST regimen was anti-thymocyte globulin (ATG) plus prednisone (43%). Overall response rate (ORR) was 48.8%, including 11.2% (95% confidence interval [CI], 6.5%-18.4%) who achieved a complete remission and 30% (95% CI, 22.3%-39.5%) who achieved RBC TI. Median OS was 47.4 months (95% CI, 37-72.3 months) and was longer for patients who achieved a response or TI. Achievement of RBC TI was associated with a hypocellular bone marrow (cellularity < 20%); horse ATG plus cyclosporine was more effective than rabbit ATG or ATG without cyclosporine. Age, transfusion dependence, presence of paroxysmal nocturnal hemoglobinuria or large granular lymphocyte clones, and HLA DR15 positivity did not predict

Table 2. Response to IST

Response	Percentage	95% CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR (CR+PR+HI)	48.8	39.8-57.9
TI	30	22.3-39.5

CR, complete response; HI, hematologic improvement; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TI, RBC transfusion independence.

Total: 207 patients

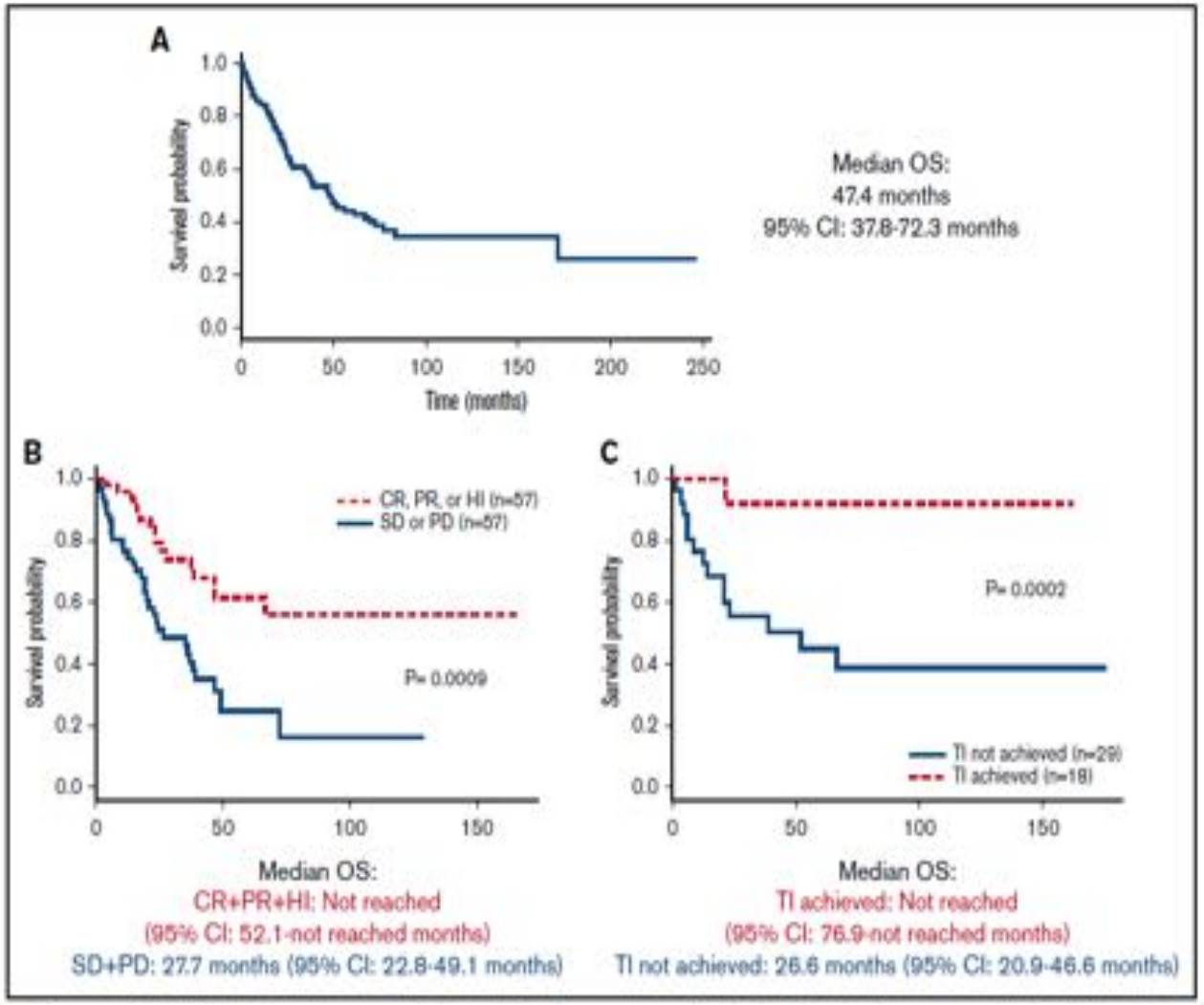

Figure 2. OS from onset of IST. (A) For all patients treated with IST. (B) According to response (CR+PR+HI) achieved vs no response achieved. (C) According to TI achieved vs TI not achieved.

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Leukemia (2019) 33:2495–2505
https://doi.org/10.1038/s41375-019-0457-1

ARTICLE

Myelodysplastic syndrome

Clinical, histopathological and molecular characterization of hypoplastic myelodysplastic syndrome

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Abstract

Diagnostic criteria for hypoplastic myelodysplasic syndrome (h-MDS) have not been clearly established, making the differential diagnosis from other bone marrow failure syndromes (BMF) challenging. In this study, we aimed to delineate clinical, histopathological, and molecular features of h-MDS, based on a large and well-annotated cohort of patients with bone marrow (BM) hypocellularity. The study included 534 consecutive adult patients with hypocellular BM (278 h-MDS and 136 aplastic anemia), and 727 with normo- or hypercellular MDS (n-MDS). Comparison of clinical features of patients with h-MDS as defined by BM cellularity ≤25% ($n = 204$) or reduced age-adjusted cellularity ($n = 74$) did not reveal significant differences. We developed a diagnostic score to discriminate h-MDS from non-malignant BMF based on histological and cytological variables with the highest specificity for MDS (h-score). The information from chromosomal abnormalities and somatic mutation patterns was then integrated into a cyto-histological/genetic score (hg-score). This score was able to segregate two groups of h-MDS with a significantly different risk of blast progression ($P < 0.001$). The integration of cyto-histological and genetic features in adult patients with hypocellular BM facilitated segregation into two distinct groups, one with clinical and genetic features highly consistent with myeloid neoplasm, and one with features more consistent with non-malignant BMF.

Stanf et al, Haematologica 2019

Blood Reviews 32 (2018) 368–377

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

Review

To chelate or not to chelate in MDS: That is the question!

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ARTICLE INFO

Keywords:
Myelodysplastic syndromes
Transfusion
Iron chelation
Deferasirox
Deferoxamine
Deferiprone

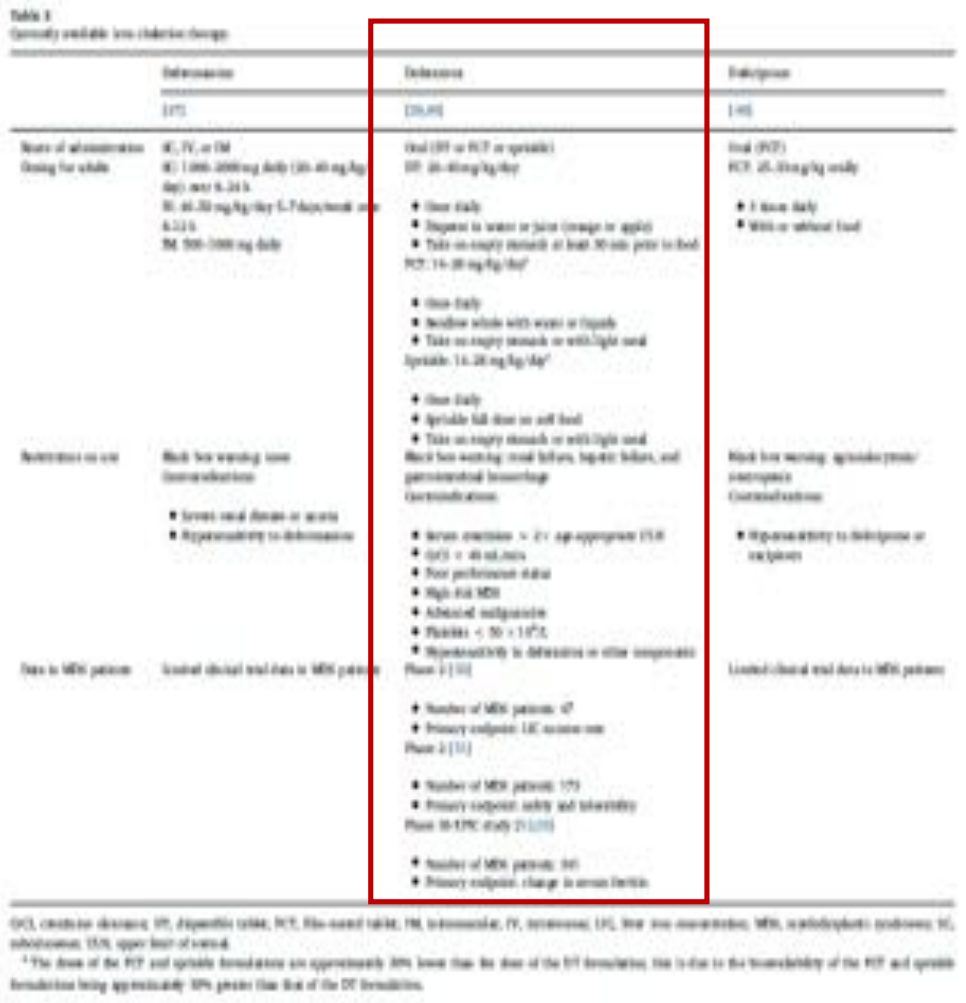
ABSTRACT

Myelodysplastic syndromes (MDS) are a heterogeneous group of hemopathies that exhibit physical manifestations with clinical consequences of bone marrow failure and inherent risk of progression to acute myeloid leukemia. Iron overload (IO) is common in MDS due to chronic transfusion support and disease-related alterations in iron metabolism. IO has been conclusively associated with inferior outcomes among MDS patients. Despite lack of randomized trials showing a survival impact of iron chelation therapy (ICT), ICT is recommended by experts and guidelines for select MDS patients with IO and is often used. The availability of effective oral ICT agents has reignited the controversy regarding ICT use in patients with MDS and IO. Here we summarize the studies evaluating the value of ICT in MDS and suggest a practical approach for use of these therapies. We also highlight controversies regarding use of ICT in MDS and discuss some ongoing efforts to answer these questions.

Guidelines and drugs for iron chelation therapies in MDS

Table 1
Guidelines on iron chelation therapy in patients with MDS [22–32].

Countries	Transfusion status	Serum ferritin (ng/Ml)	Patient profile	Target serum ferritin level
Italian (Ref. [22])	≥50 RBC units	NR	• Life expectancy > 6 months	NR
UK (Ref. [23])	~25 RBC units (5 g iron)	NR	• Pure sideroblastic anaemia • del 5q	<1000
US (Ref. [24])	20–30 RBC units (≥5–10 g iron)	>2500	• IPSS low or Int-1 • Potential transplant patients	For pts with SF > 2500, aim to decrease to<1000
International (Ref. [25])	Transfusion-dependent	>1000–2000	• RA, RARS, del 5q • IPSS low or Int-1	NR
Japanese (Ref. [26])	>40 Japanese units	>1000	• Life expectancy > 1 year	500–1000
Canadian (Ref. [27])	Transfusion-dependent	>1000	• RA, RARS, del 5q • IPSS low or Int-1 • IPSS Int-2 or high (if SF > 1000 and • SCT candidates/life expectancy > 1 year)	NR; reduce dose when < 2000; discontinue chelator when <1000
Spanish (Ref. [28])	Transfusion-dependent	>1000	• IPSS low or Int-1 • WPSS very low, Low, or Int • Spanish prognostic index low risk	NR
Austrian (Ref. [29])	Transfusion-dependent	>2000	• Life expectancy > 2 years	NR
Israeli (Ref. [30])	20–25 RBC units	>1000	• Low or Int-1 (IPSS) • Candidates for SCT	<500 – <1000
MDS Foundation (Ref. [31])	2 RBC units/month for ≥1 year	>1000	• Life expectancy > 1 year	NR
Italian update (Ref. [32])	≥20 RBC units (4 g iron)	NR	• Low or Int-1 (IPSS) • Int-2, high when responding to disease-modifying agent or candidates for SCT	NR



Deferasirox reduces biomarkers of iron overload

EPIC study, MDS cohort

FERRITIN

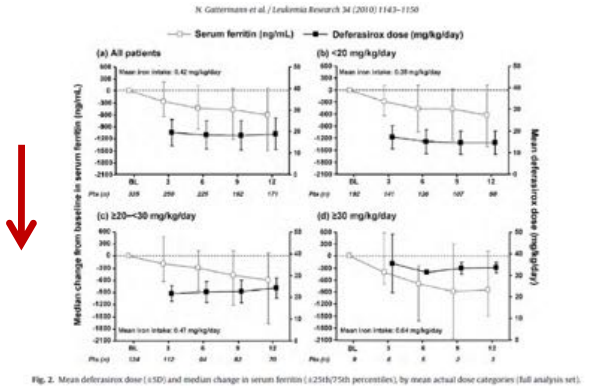
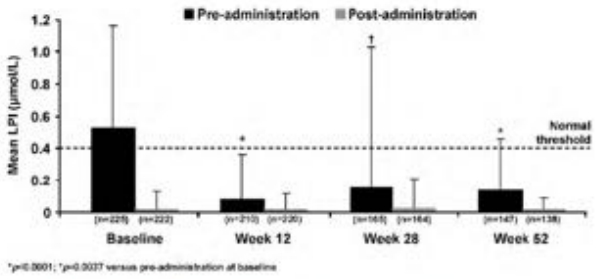


Fig. 2. Mean deferasirox dose (±SD) and median change in serum ferritin (±25th/75th percentiles), by mean actual dose categories (full analysis set).



*p<0.0001; †p=0.0037 versus pre-administration at baseline

Fig. 3. Mean LPI (+SD), pre- and post-deferasirox administration at baseline and after repeat doses.

1. Data from List AF, et al. J Clin Oncol. [Epub ahead of print 2012 Apr 30]
2. Data from Gattermann N, et al. Leuk Res 2010;34:1143-50.

US03 study

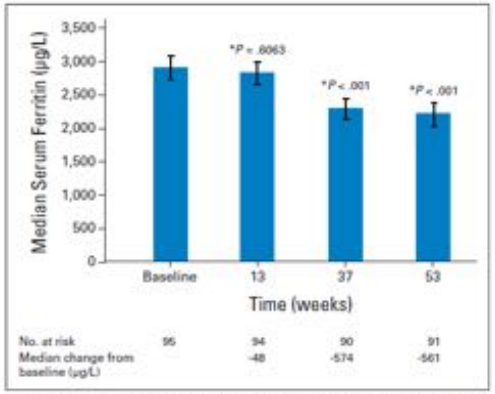


Fig 1. Median serum ferritin (± SEM) in patients who completed 12 months of deferasirox. (*) Versus baseline.

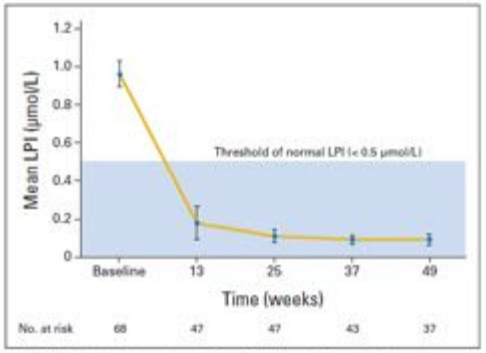


Fig 2. Mean labile plasma iron (LPI; ± SEM) over 12 months in patients with abnormal LPI (> 0.5 µmol/L) at baseline.

LPI

Switching from DT (Dispersible tablets) to FCT (Film-coated tablets) of deferasirox

CURRENT MEDICAL RESEARCH AND OPINION
2018, VOL. 34, NO. 11, 1959–1966
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ORIGINAL ARTICLE

Adherence to iron chelation therapy in patients who switched from deferasirox dispersible tablets to deferasirox film-coated tablets

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ABSTRACT

Objective: To compare real-world adherence to and persistence with deferasirox film-coated tablets (DFX-FCT) and deferasirox dispersible tablets (DFX-DT) among patients who switched from DFX-DT to DFX-FCT, overall and by disease type (sickle cell disease [SCD], thalassemia, and myelodysplastic syndrome [MDS]).

Methods: Patients were ≥2 years old and had ≥2 DFX-FCT claims over the study period and ≥2 DFX-DT claims before the index date (first DFX-FCT claim). The DFX-DT period was defined from the first DFX-DT claim to the index date; the DFX-FCT period was defined from the index date to the end of the study period. Adherence was measured as medication possession ratio (MPR) and proportion of days covered (PDC). Persistence was defined as continuous medication use without a gap ≥30 or 60 days between refills. Comparisons were conducted using paired-sample Wilcoxon sign-rank and McNemar's tests.

Results: In total, 606 patients were selected (SCD: 348; thalassemia: 107; MDS: 106; other: 45). Adherence and persistence in the DFX-FCT vs DFX-DT period was significantly higher across all measures: mean MPR was 0.80 vs 0.76 ($p < .001$); 60.9% vs 54.3% of patients had MPR ≥ 0.8 ($p = .009$); mean 3-month PDC was 0.83 vs 0.71 ($p < .001$); 64.2% vs 45.4% of patients had 3-month PDC ≥ 0.8 ($p < .001$); 87.2% vs 63.4% of patients had 3-month persistence with no gap ≥30 days and 96.1% vs 79.9% with no gap ≥60 days ($p < .001$). Adherence and persistence improved after switching across all diseases, particularly MDS.

Conclusions: Adherence and persistence improved significantly after switching from DFX-DT to DFX-FCT for all diseases, but especially MDS.

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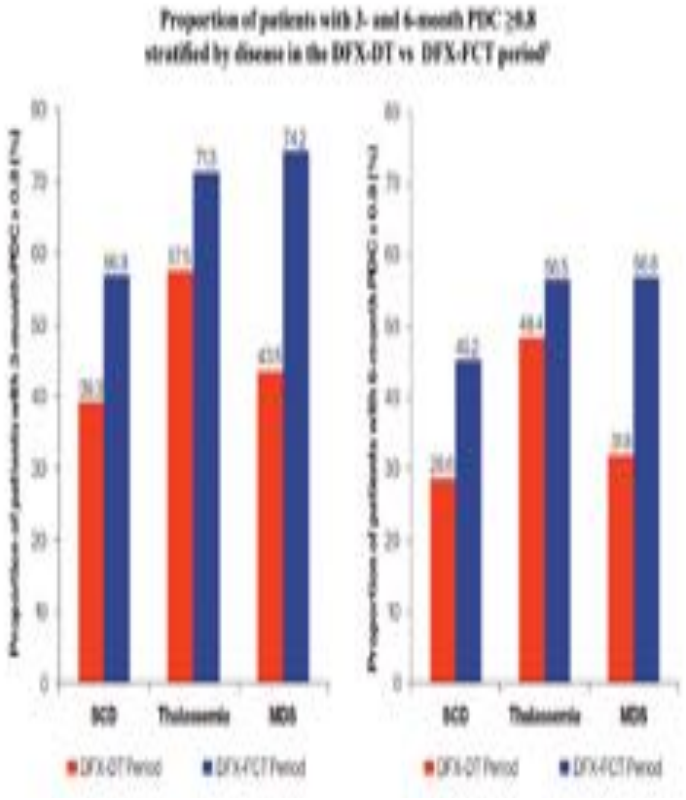
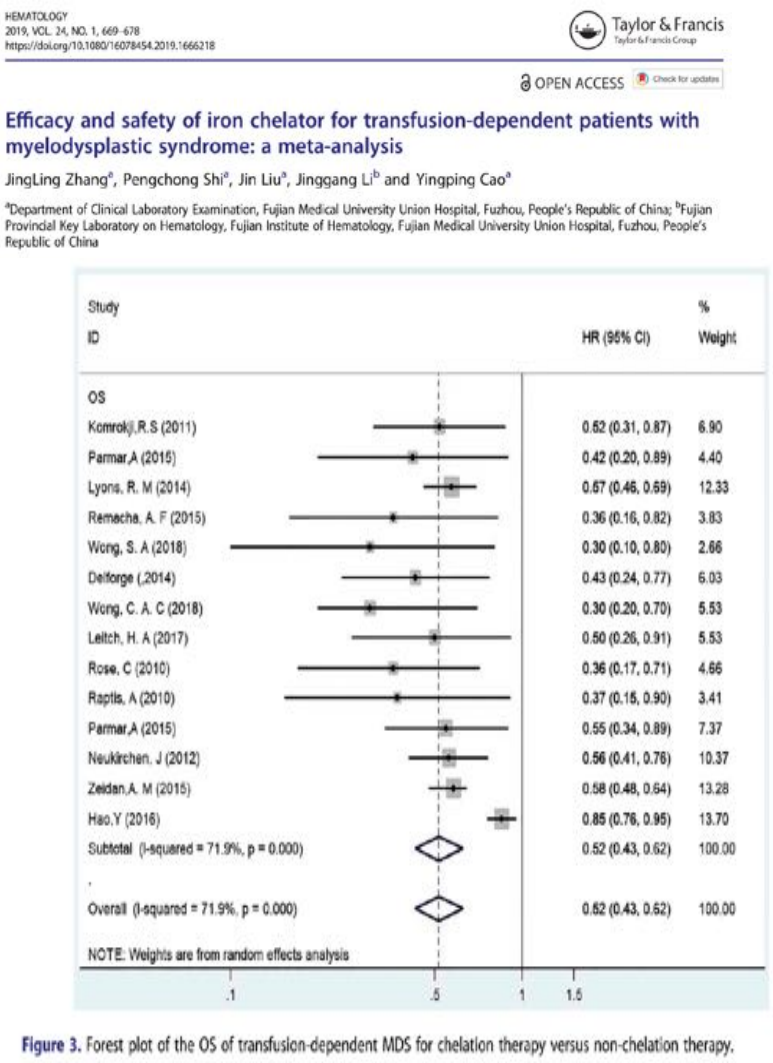
KEYWORDS
Iron chelation therapy; Deferasirox; Adherence; Persistence



Several studies suggest iron chelation therapy improves survival in TD-MDS patients

Study	N	Design	Survival	Non-chelated patients	Chelated patients	*P* value
Leitch 2008	36	Retrospective	Median overall OS	40 mo	Not reached	0.003
			4-year survival rate	43%	64%	0.003
Rose 2010	97	Prospective follow-up	Median OS from diagnosis	53 mo	124 mo	<0.0003
			Median OS with adequate vs weak chelation	NA	124 vs 85 mo	<0.001
Neukirchen 2012[a]	188	Matched pair analysis	Median OS	49 mo	75 mo	0.002
Neukirchen 2012[b]	417	Retrospective, registry	Median time to death in transfusion-dependent patients	30 mo	67 mo	NR
Komrokji 2011	97	Retrospective	Median OS	34 mo	59 mo	0.013
Delforge 2012	186	Retrospective	Median OS in Low/Int-1	37 mo	126 mo	<0.001
Zeidan 2012	4226	Retrospective, registry	Median survival	47 wk	110 wk	0.003
			HR for 27–52 wks on deferasirox	1	0.77	NR
			HR for ≥53 wks on deferasirox	1	0.34	NR
de Witte 2012	1000	Prospective, registry	Adjusted HR	1	0.51 (0.19–1.32)	NS
Remacha 2015	263	Retrospective	Median OS	Not reached	153 mo	<0.001
Lyons 2017	599	Prospective, registry	Median OS from diagnosis	47.8 mo	All 86.3 mo ICT >6 mo 98.7 mo	<0.0001



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https://doi.org/10.1080/16078454.2019.1666218

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OPEN ACCESS

Efficacy and safety of iron chelator for transfusion-dependent patients with myelodysplastic syndrome: a meta-analysis

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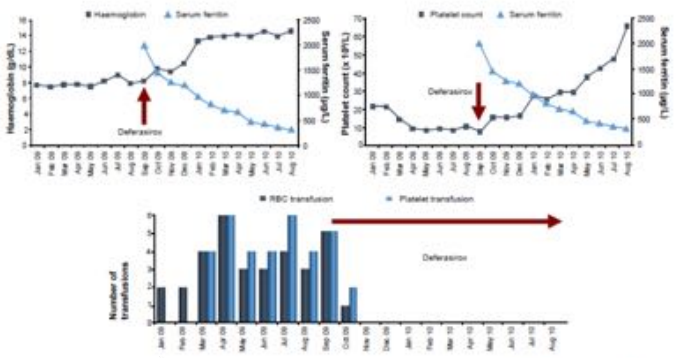
Figure 3. Forest plot of the OS of transfusion-dependent MDS for chelation therapy versus non-chelation therapy.

DFX can improve haemopoiesis in some MDS patients

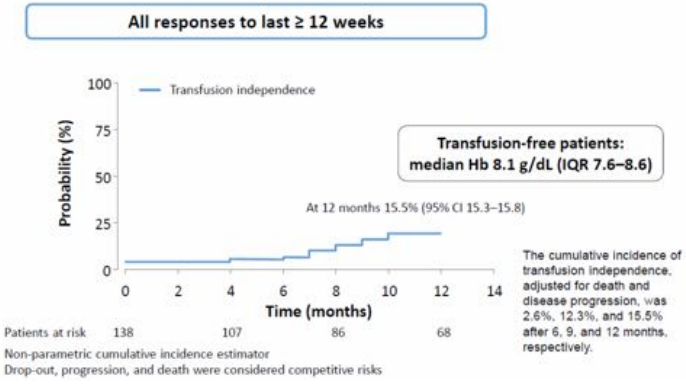
Study	Risk IPSS (N)	Red blood cell response	ANC response	PLT response	Study duration/ starting dose
List A *et al.* 2012	Low/Int-1 (N=173)	15%	15%	22%	3 years 20–40 mg/kg/day
Gattermann N *et al.* 2012	Low/Int-1 (N=247)	21.5% (median 109 days) 11.3% transfusion independent	22%	13%	1 year 20–40 mg/kg/day
Nolte F *et al.* 2013	Low/Int-1 (N=50)	6%*	17%	30%	1 year 6, 20–30 mg/kg/day
Molteni A *et al.* 2013	Low/Int-1 (N=53)	35.1% 9.2% transfusion independent	76.4%	61%	2 years
Angelucci E *et al.* 2014	Low/Int-1 (N=152)	11% transfusion independent	3%	15%	1 year 10–30 mg/kg/day
Maurillo L *et al.* 2015	Low/Int-1 (n=89) Int-2 (n=14)	17.6% 7.1% transfusion independent	7.1%	5.9%	2 years

Transfusion independence following deferasirox in a low-to-high WPSS risk transformed MDS with complete hematologic response



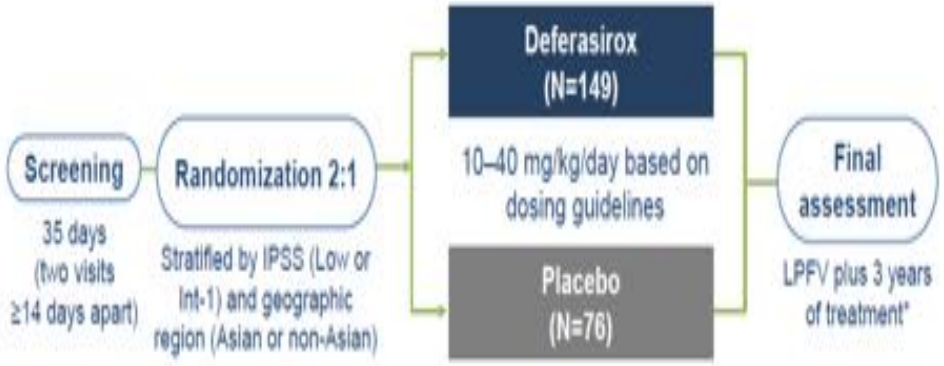
Guariglia R, et al. Leuk Res. 2011;35:566-70.

GIMEMA prospective trial: probability of acquiring transfusion independence



- Angelucci E *et al. Eur J Hematol* 2014;92:527–536;

TELESTO – a Phase II, randomized, double-blind study



*Patients who experienced a non-fatal event were discontinued and followed up for 28 days; patients were then followed up every 3–6 months (for evaluation or survival)

Key inclusion criteria:

- Hematologically stable IPSS Low or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
- Serum ferritin >1000 ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF ≥50% by echocardiography
- ALT or AST ≤3.5×ULN, total bilirubin ≤1.5×ULN, no previous diagnosis of liver cirrhosis; CrCl ≥40 mL/min
- ECOG performance status ≤2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LPFV, last patient first visit; LVEF, left ventricular ejection fraction; pRBC, packed red blood cell; ULN, upper limit of normal

TELESTO – study objectives

Primary

To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an independent adjudication committee, or death, whichever occurred first

Key secondary

To assess:

- Overall survival
- Change in serum ferritin level
- Hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria[1])
- Change in endocrine function (thyroid and glycemic control)
- Safety

1. Cheson BD et al. Blood 2006;108:419–425

Angelucci et al, Blood 2018 132:234

Primary endpoint EFS: Stratified log-rank test and Cox regression model

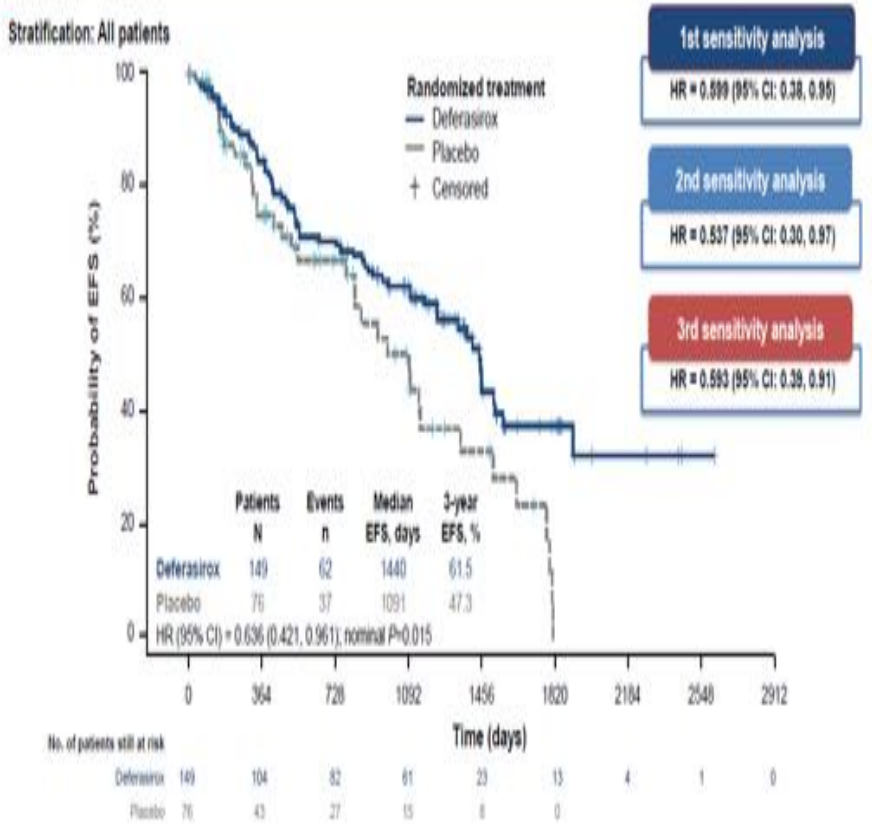
All patients*		Log-rank test		Cox model
	Event/N (%)	Median time to event (95% CI), days†	*P* value‡	HR (95% CI)§
Deferasirox	62/149 (41.6)	1440 (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	37/76 (48.7)	1091 (820, 1348)		

*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

CI, confidence interval; HR, hazard ratio

Kaplan–Meier plot of EFS

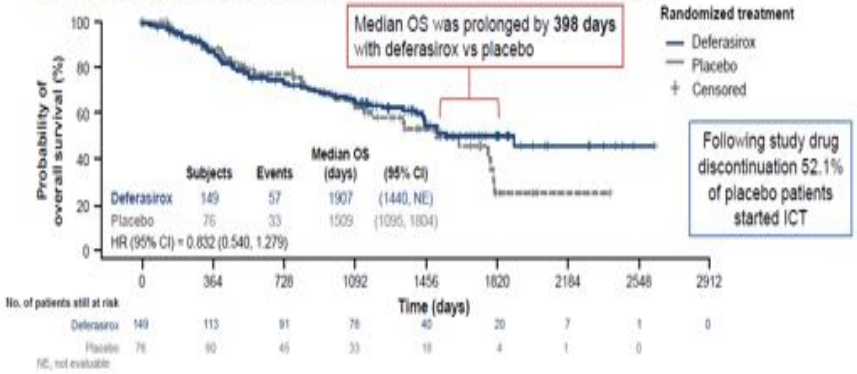


Angelucci et al, Blood 2018 132:234

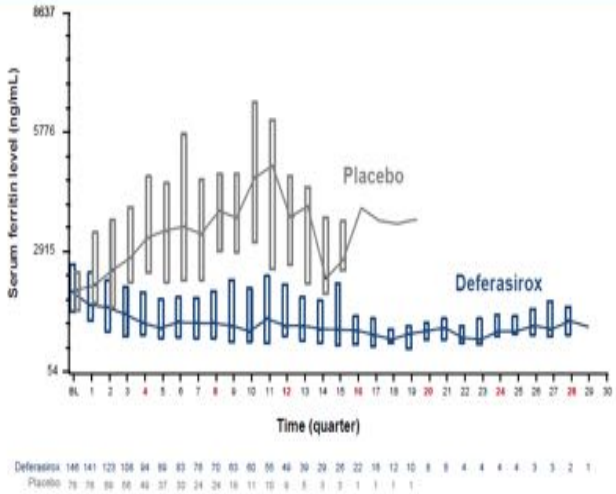
Summary of overall survival

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	1907 (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	1509 (1095, 1804)		

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



Serum ferritin trends



Boxes show lower and upper quartiles, horizontal line shows the median

Hematologic improvement – IWG criteria 2006

All patients	Deferasirox N=149‡		Placebo N=76‡		Difference between treatment groups	
	n* (%)	95% CI†	n* (%)	95% CI†	Difference	95% CI†
Hemoglobin increase of ≥1.5 g/dL in comparison with 8 weeks' pre-treatment values lasting ≥8 weeks	44 (29.5)		14 (18.4)			
Reduction of ≥4.0 RBC transfusions in comparison with 8 weeks' pre-randomization values lasting ≥8 weeks	28 (18.8)		9 (11.8)			
Hematologic improvement (erythroid response)	59 (39.6)	31.4, 47.8	21 (27.6)	16.9, 38.3	12.0	−1.8, 25.7

*n = number of patients in the corresponding category; †The 95% CIs for the frequency distribution of each variable and for the difference were computed using the Wilson score method; ‡Samples analyzed according to IWG criteria

Angelucci et al, Blood 2018 132:234

Iron chelation in higher risk MDS

bjh research paper

Iron-chelating therapy with deferasirox in transfusion-dependent, higher risk myelodysplastic syndromes: a retrospective, multicentre study

Pellegrino Musto,[1] Luca Maurillo,[2] Vittorio Simeon,[3] Antonella Poloni,[4] Carlo Finelli,[5] Enrico Balleari,[6] Alessandra Ricco,[7] Flavia Rivellini,[8] Agostino Cortelezzi,[9] Giuseppe Tarantini,[10] Oreste Villani,[11] Giovanna Mansueto,[11] Maria R. Milella,[12] Daniele Scapicchio,[13] Gioacchino Marziano,[1] Massimo Breccia,[14] Pasquale Niscola,[15] Alessandro Sanna,[16] Cristina Cilsa,[17] Maria T. Voso,[2] Susanna Fenu,[18] Adriano Venditti,[2] Valeria Santini,[16] Emanuele Angelucci[6] and Alessandro Levis[19]

[1]Scientific Direction, IRCCS-CROB, "Referral Cancer Centre of Basilicata", Rionero In Vulture (Pz), [2]Haematology, Department of Biomedicine and Prevention, "Tor Vergata" University, Rome, [3]Laboratory of Pre-clinical and Translational Research, IRCCS-CROB, "Referral Cancer Centre of Basilicata", Rionero In Vulture (Pz), [4]Haematology Clinic, Department of Clinic and

Summary

Iron chelation is controversial in higher risk myelodysplastic syndromes (HR-MDS), outside the allogeneic transplant setting. We conducted a retrospective, multicentre study in 51 patients with transfusion-dependent, intermediate-to-very high risk MDS, according to the revised international prognostic scoring system, treated with the oral iron chelating agent deferasirox (DFX). Thirty-six patients (71%) received azacitidine concomitantly. DFX was given at a median dose of 1000 mg/day (range 375–2500 mg) for a median of 11 months (range 0·4–75). Eight patients (16%) showed grade 2–3 toxicities (renal or gastrointestinal), 4 of whom (8%) required drug interruption. Median ferritin levels decreased from 1709 μg/l at baseline to 1100 μg/l after 12 months of treatment ($P = 0·02$). Seventeen patients showed abnormal transaminase levels at baseline, which improved or normalized under DFX treatment in eight cases. One patient showed a remarkable haematological improvement. At a median follow up of 35·3 months, median overall survival was 37·5 months. The results of this first survey of DFX in HR-MDS are comparable, in terms of safety and efficacy, with those observed in lower-risk MDS. Though larger, prospective studies are required to demonstrate real clinical benefits, our data suggest that DFX is feasible and might be considered in a selected cohort of HR-MDS patients.

doi: 10.1111/bjh.14621

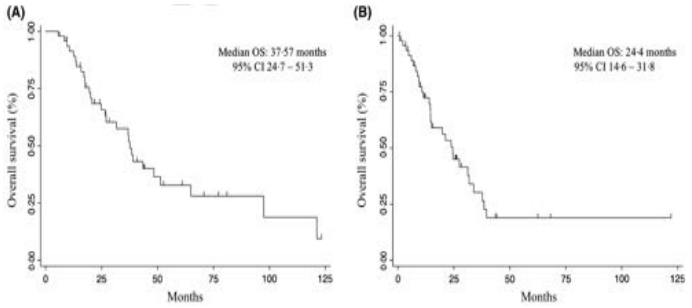


Fig 2. Overall survival curves of 51 higher risk myelodysplastic syndromes patients treated with deferasirox: (A) from diagnosis; (B) from the start of defereasirox. 95% CI, 95% confidence interval; OS, overall survival.

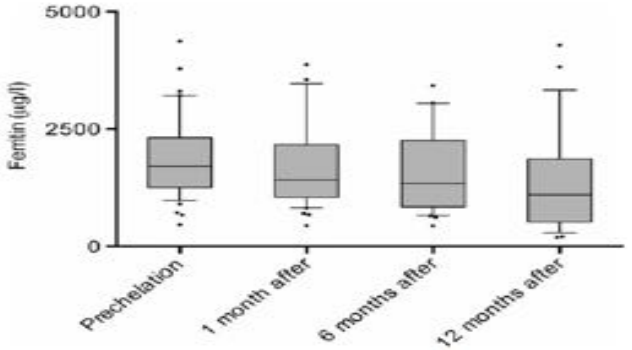


Fig 1. Monitoring of ferritin serum levels (μg/l) during deferasirox therapy in 51 higher risk myelodysplastic syndromes (HR-MDS) patients. Kruskall–Wallis test: $P = 0·0478$; Dunn's multiple comparison test: $P = 0·0205$, in the comparison between pre-chelation and after 12 months of treatment levels.

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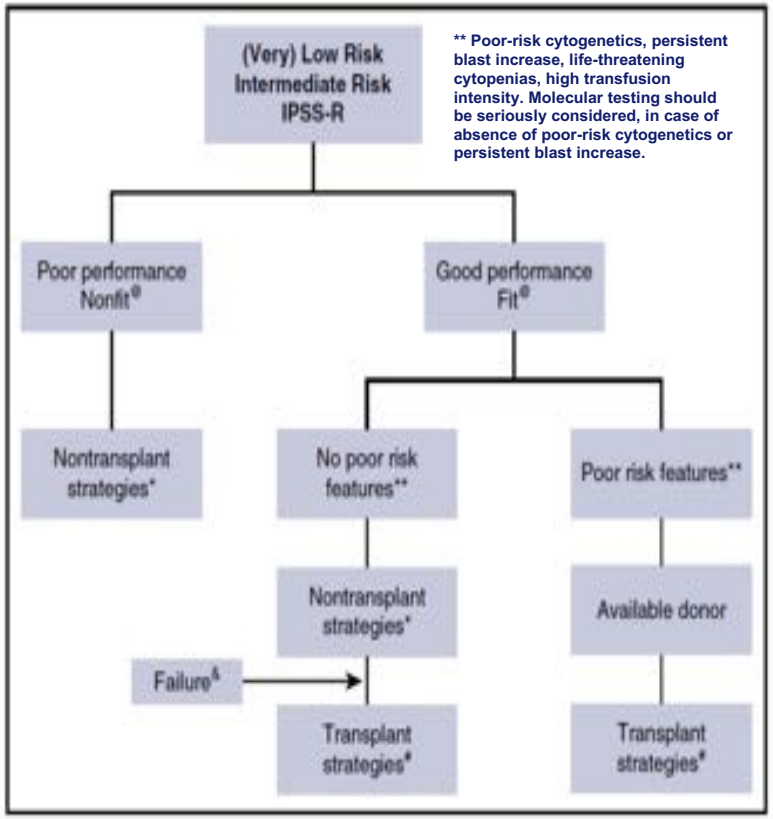
2017 129: 1753-1762
doi:10.1182/blood-2016-06-724500 originally published online January 17, 2017

Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel

Theo de Witte, David Bowen, Marie Robin, Luca Malcovati, Dietger Niederwieser, Ibrahim Yakoub-Agha, Ghulam J. Mufti, Pierre Fenaux, Guillermo Sanz, Rodrigo Martino, Emilio Paolo Alessandrino, Francesco Onida, Argiris Symeonidis, Jakob Passweg, Guido Kobbe, Arnold Ganser, Uwe Platzbecker, Jürgen Finke, Michel van Gelder, Arjan A. van de Loosdrecht, Per Ljungman, Reinhard Stauder, Liisa Volin, H. Joachim Deeg, Corey Cutler, Wael Saber, Richard Champlin, Sergio Giralt, Claudio Anasetti and Nicolaus Kröger



** Poor-risk cytogenetics, persistent blast increase, life-threatening cytopenias, high transfusion intensity. Molecular testing should be seriously considered, in case of absence of poor-risk cytogenetics or persistent blast increase.

ORIGINAL ARTICLE

Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System

MG Della Porta[1,21], CH Jackson[2,21], EP Alessandrino[3], M Rossi[1], A Bacigalupo[4], MT van Lint[5], M Bernardi[6], B Allione[7], A Bosi[8], S Guidi[8], V Santini[8], L Malcovati[3,9], M Ubezio[3], C Milanesi[1], E Todisco[1], MT Voso[10], P Musto[11], F Onida[12], AP Iori[13], R Cerretti[14], G Grillo[15], A Molteni[15], P Pioltelli[16], L Borin[16], E Angelucci[17], E Oldani[18], S Sica[5], C Pascutto[3], V Ferretti[3], A Santoro[1], F Bonifazi[19], M Cazzola[3,9,22] and A Rambaldi[18,20,22] on behalf of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO, www.gitmo.it)

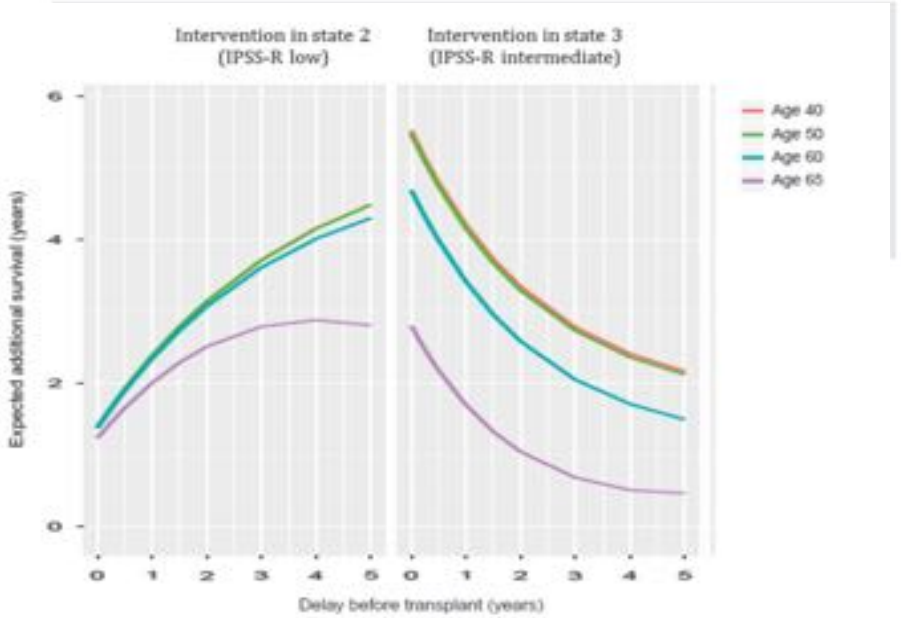


Figure 3. Gain in expected survival under different transplant policies with respect to a non-transplantation policy. We assumed that the MDS patient was classified as very low IPSS-R risk at the time of diagnosis. Each policy was then evaluated for a set of different ages at diagnosis (as shown in the box) and for different waiting times *t* (between 0 and 5 years since entering any disease state).

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet

Luca Malcovati,[1,2] Eva Hellström-Lindberg,[3] David Bowen,[4] Lionel Adès,[5] Jaroslav Cermak,[6] Consuelo del Cañizo,[7] Matteo G. Della Porta,[1] Pierre Fenaux,[5] Norbert Gattermann,[8] Ulrich Germing,[8] Joop H. Jansen,[9] Moshe Mittelman,[10] Ghulam Mufti,[11] Uwe Platzbecker,[12] Guillermo F. Sanz,[13] Dominik Selleslag,[14] Mette Skov-Holm,[15] Reinhard Stauder,[16] Argiris Symeonidis,[17] Arjan A. van de Loosdrecht,[18] Theo de Witte,[9] and Mario Cazzola[1,2]

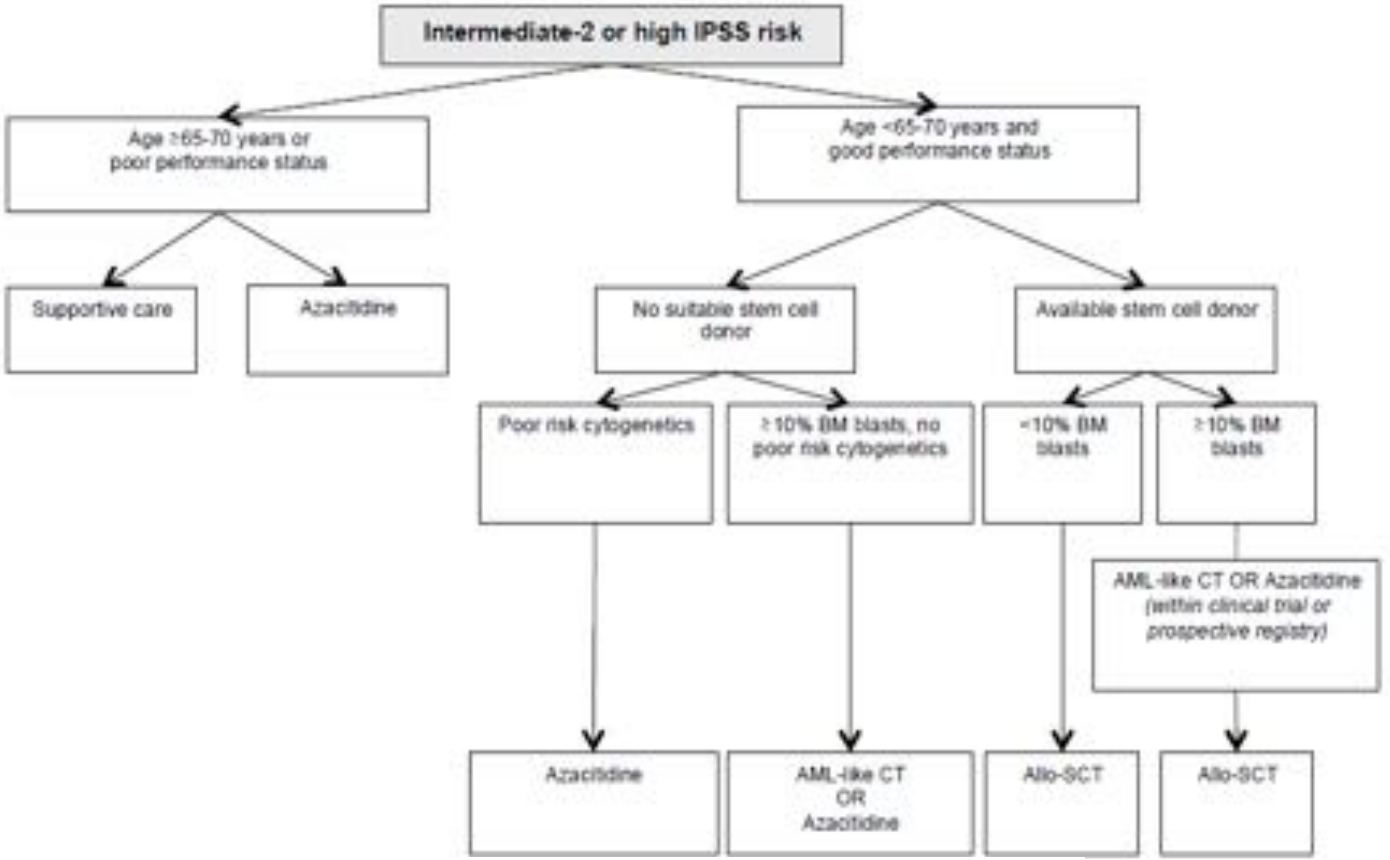
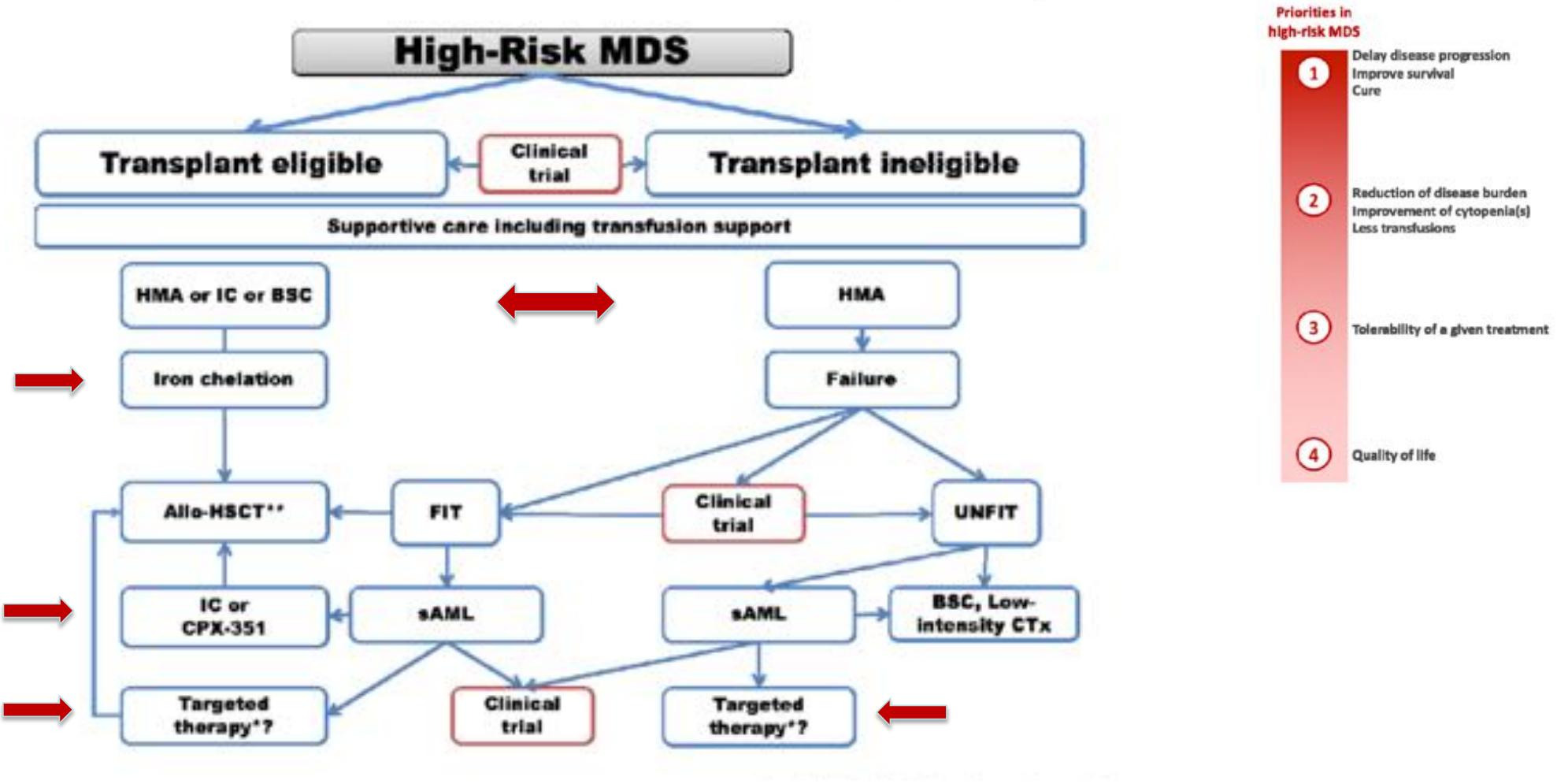


Figure 1: Priorities of therapeutic interventions in patients with MDS according to disease stage



* These could be IDH and FLT3 inhibitors, not presently approved
** Consider post-transplant disease surveillance strategies

Platzbecker U, Blood 2019

AZA-001: Trial Design

Physician choice of 1 of 3 CCRs

1. BSC only
2. LDAC (20 mg/m²/day SC x 14 day q28-42 days)
3. 7 + 3 chemotherapy (induction + 1-2 consolidation cycles)

RANDOMIZE

Azacitidine + BSC (75 mg/m²/day x 7 days SC q28 days) (n = 179)

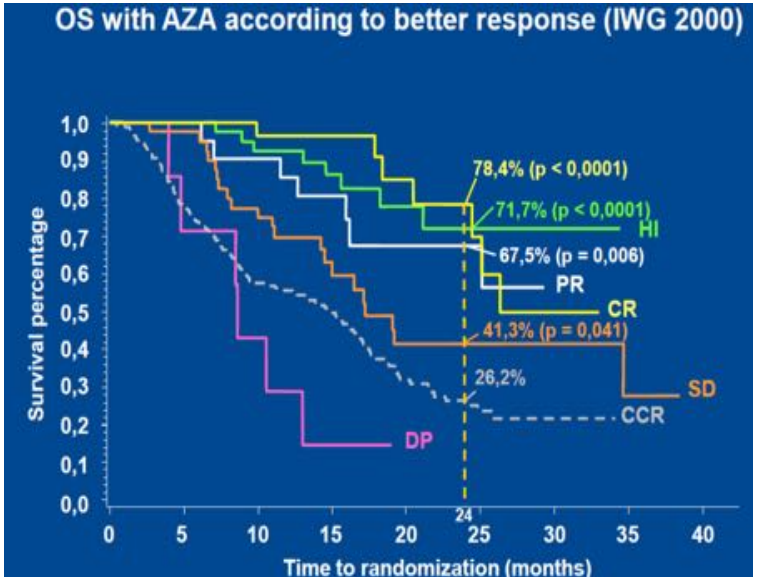
CCR (n = 179)

Stratified by
- FAB: RAEB, RAEB-T
- IPSS: int 2, high

Treatment continued until unacceptable toxicity or AML transformation or disease progression

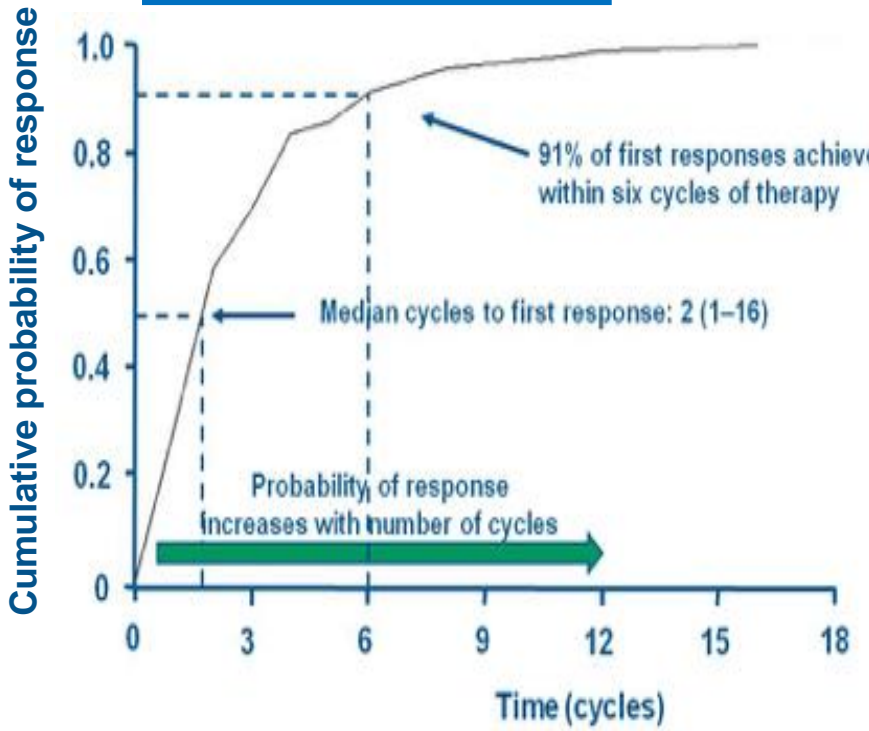
Fenaux P, et al. Lancet Oncol. 2009;10:223-232.

Fenaux P, et al. Lancet Oncol. 2009

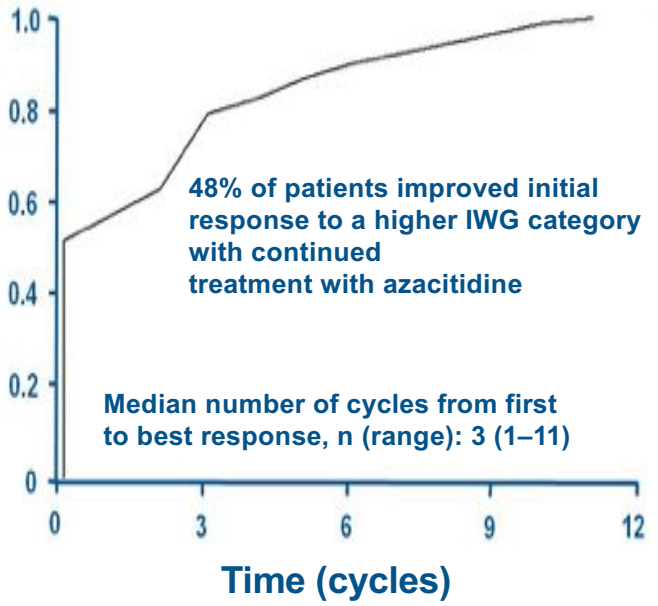


AZA-001: number of cycles of azacitidine to first or best response (CR, PR or HI)

Time to first response



Time from first to best response



The vertical line on the y-axis represents the 52% of patients whose first response was their best response

Silverman LR, et al. Cancer 2011;117:2697–702

Azacitidine in Elderly MDS Patients: current evidences

- CALGB-9221: patients aged ≥ 65 years[1]
  Azacitidine prolonged OS and AML transformation vs BSC in elderly patients with high-risk RAEB and RAEB-T MDS
- AZA-001: patients aged ≥ 75 years[2]
  Azacitidine significantly prolonged OS vs conventional care regimens in elderly patients with higher-risk MDS
- French ATU: patients aged ≥ 80 years[3]
  Azacitidine resulted in clinically meaningful responses and OS rates in elderly patients with higher-risk MDS
  No evidence of increased toxicity vs patients aged < 80 years, except for slightly increased risk of bleeding
- AVIDA Registry: patients < 75 vs ≥ 75 years of age[4]
  Azacitidine in the community setting was effective in patients ≥ 75 years
- Austrian Azacitidine Registry: patients < 80 vs ≥ 80 years of age[5]
  Azacitidine resulted in similar OS for patients < 80 and ≥ 80 years of age
- Italian real-world experience[6]
  Age > 65 should not preclude effective treatment with azacitidine in non-selected patients with MDS.
- Generally, most common AEs with azacitidine treatment were hematologic, gastrointestinal, and infections[1-4]

1. Silverman LR, et al. *Blood.* 2005;106 [poster presentation; abstract 2524].
2. Seymour JF, et al. *Crit Rev Hematol Oncol.* 2010;76:218-227.
3. Itzykson R, et al. *Blood.* 2009;114 [poster presentation; abstract 1773].
4. Komrokji R, et al. *Haematologica.* 2010;95 [oral presentation; abstract 538].
5. Pleyer L, et al. *Leuk Res.* 2011;35 [poster presentation; abstract 101].
6. *Breccia M, et al. Leuk Lymphoma 2012;53:1558–60*

Shapiro and Lazo-Langner BMC Hematology (2018) 18:3
DOI 10.1186/s12878-017-0094-8

BMC Hematology

RESEARCH ARTICLE Open Access

Systematic review of azacitidine regimens in myelodysplastic syndrome and acute myeloid leukemia

Roman M. Shapiro[1] and Alejandro Lazo-Langner[2,3,4*]

Abstract

Background: 5-Azacitidine administered as a 7-day dosing regimen (7–0-0) is approved in high risk IPSS myelodysplastic syndrome (MDS) patients. Alternative regimens such as a 5-day (5–0-0) or 7-day with a weekend break (5–2-2) are commonly used. No randomized controlled trial has been done directly comparing all three dosing regimens. The objective of this study was to compare the efficacies of the 5–0-0, 5–2-2, and 7–0-0 regimens in MDS and AML.

Methods: A systematic review was conducted using MEDLINE, EMBASE and CENTRAL. Eligible studies were randomized controlled trials (RCTs), observational prospective and retrospective studies. The primary clinical outcomes were Objective Response Rate (ORR) defined as the sum of complete response (CR), partial response (PR), and hematological improvement (HI) as defined by the IWG 2006 criteria. A meta-analysis of simple proportions was conducted using a random effects model with weights defined according to Laird and Mosteller. Comparisons between groups were not attempted due to the heterogeneity of study designs.

Results: The only RCT directly comparing alternative azacitidine regimens showed no difference in ORR between the 5–0-0 and 5–2-2 regimens. All other RCTs compared a dosing regimen to conventional care. The pooled proportion of ORR was 44.8% with 95% CI (42.8%, 45.5%) for 7–0-0, 41.2% with 95% CI (39.2%, 41.9%) for 5–0-0, and 45.8% with 95% CI (42.6%, 46.4%) for 5–2-2.

Conclusions: Indirect comparison of alternative azacitidine dosing regimens in MDS and AML shows a benefit for the 7-day regimen in attaining ORR. Additional RCTs are required to definitively address this comparison.

Keywords: Azacitidine, Dosing, Myelodysplastic, Leukemia

blood
2017 129: 1753-1762
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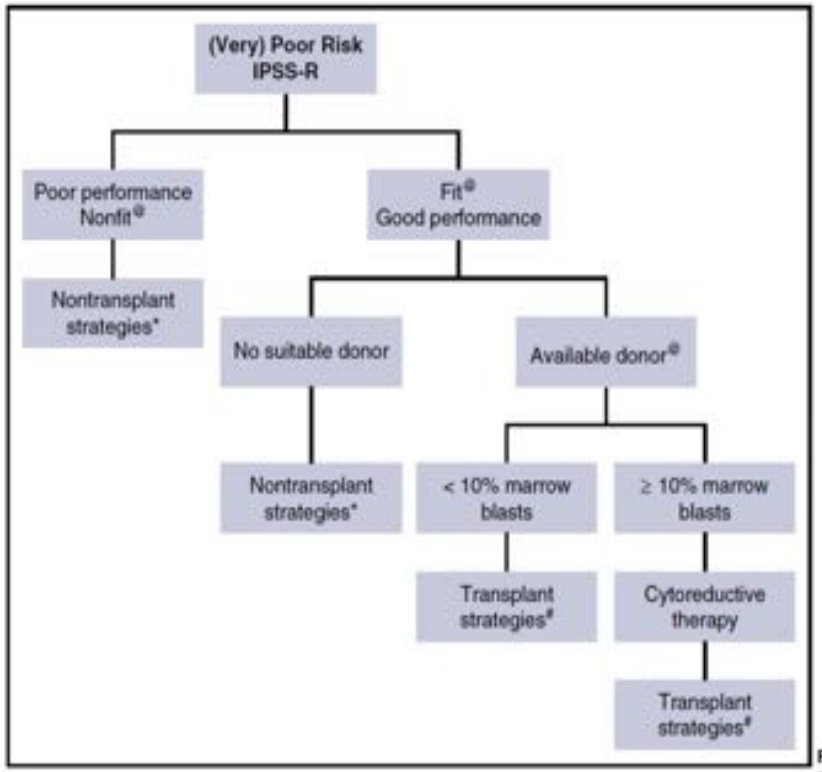
Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel

Theo de Witte, David Bowen, Marie Robin, Luca Malcovati, Dietger Niederwieser, Ibrahim Yakoub-Agha, Ghulam J. Mufti, Pierre Fenaux, Guillermo Sanz, Rodrigo Martino, Emilio Paolo Alessandrino, Francesco Onida, Argiris Symeonidis, Jakob Passweg, Guido Kobbe, Arnold Ganser, Uwe Platzbecker, Jürgen Finke, Michel van Gelder, Arjan A. van de Loosdrecht, Per Ljungman, Reinhard Stauder, Liisa Volin, H. Joachim Deeg, Corey Cutler, Wael Saber, Richard Champlin, Sergio Giralt, Claudio Anasetti and Nicolaus Kröger



ORIGINAL ARTICLE

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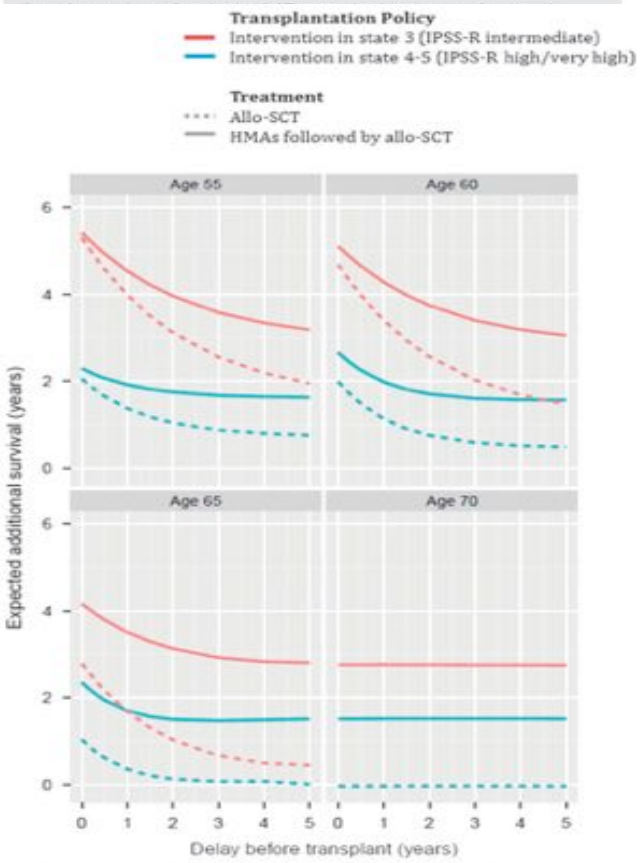

Figure 4. Expected additional survival (compared to no intervention), by transplant policy, age and treatment with HMA.

ESMO

Annals of Oncology 28: 1547–1553, 2017
doi:10.1093/annonc/mdx154
Published online 30 March 2017

ORIGINAL ARTICLE

Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study

M. T. Voso[1*], G. Leone[2], A. Piciocchi[3], L. Fianchi[2], S. Santarone[4], A. Candoni[5], M. Criscuolo[2], A. Masciulli[6], E. Cerqui[7], A. Molteni[8], C. Finelli[9], M. Parma[10], A. Poloni[11], A. M. Carella[12], F. Spina[13], A. Cortelezzi[14], F. Salvi[15], E. P. Alessandrino[16], A. Rambaldi[8] & S. Sica[2]

[1]Division of Hematology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome; [2]Department of Hematology, Università Cattolica del Sacro Cuore, Rome; [3]Department of Statistical Sciences, La Sapienza University, Rome; [4]Department of Hematology, Centro Trapianti Midollo Osseo, Pescara; [5]Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Ospedaliero-Universitaria di Udine, Udine; [6]Department of Hematology, ASST Papa Giovanni XXIII, Bergamo; [7]Department of Hematology, A.O. Spedali Civili, Brescia; [8]Department of Hematology, Ospedale Niguarda, Milano; [9]Department of Hematology, Ospedale Sant'Orsola Malpighi, University of Bologna, Bologna; [10]Department of Hematology, HSCT Adult Unit, San Gerardo Hospital, Monza; [11]Department of Hematology, Azienda Ospedaliera Universitaria - Ospedali Riuniti di Ancona, Ancona; [12]Department of Hematology, Ospedale Opera Padre Pio, San Giovanni Rotondo; [13]Department of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [14]Department of Hematology Oncology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milano; [15]Department of Hematology, "SS Antonio e Biagio" Hospital, Alessandria; [16]Department of Hematology, Policlinico San Matteo and Pavia University, Pavia, Italy

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Background: Allogeneic stem-cell transplantation (HSCT) is the only curative treatment in myelodysplastic syndromes (MDS). Azacitidine (AZA) is increasingly used prior to HSCT, however in Europe it is only approved for patients who are not eligible for HSCT.

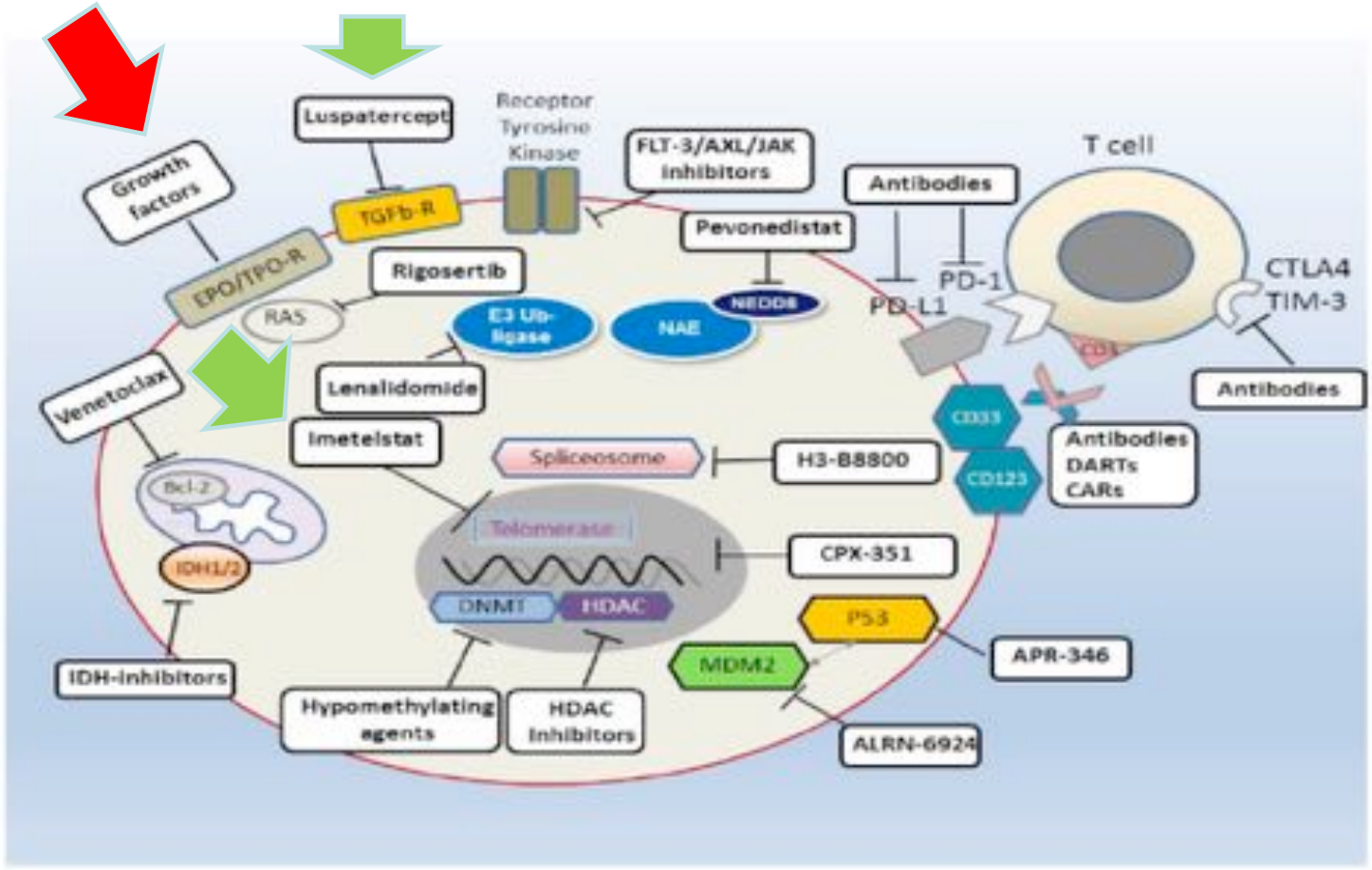
Patients and methods: We conducted a phase II multicenter study to prospectively evaluate the feasibility of HSCT after treatment with AZA in 70 patients with a myelodysplastic syndrome (MDS), 19 with acute myeloid leukemia (AML), and 8 with chronic myelomonocytic leukemia (CMML). After a median of four cycles (range 1–11): 24% of patients achieved complete remission, 14% partial remission, 8% hematologic improvement, 32% had stable and 22% progressive disease. Ten patients discontinued treatment before the planned four cycles, due to an adverse event in nine cases.

Results: A HSC donor was identified in 73 patients, and HSCT was performed in 54 patients (74% of patients with a donor). Main reasons for turning down HSCT were lack of a donor, an adverse event, or progressive disease (9, 12, and 16 patients, respectively). At a median follow-up of 20.5 months from enrolment, response to AZA was the only independent prognostic factor for survival. Compared to baseline assessment, AZA treatment did not affect patients' comorbidities at HSCT: the HCT-CI remained stable in 62% patients, and worsened or improved in 23% and 15% of patients, respectively.

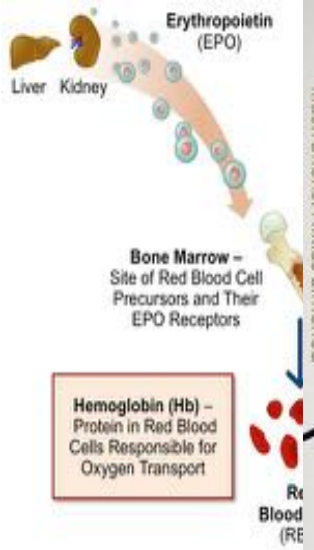
Conclusions: Our study shows that HSCT is feasible in the majority of patients with HR-MDS/AML/CMML-2 after AZA treatment. As matched unrelated donor was the most frequent source of donor cells, the time between diagnosis and HSCT needed for donor search could be 'bridged' using azacitidine. These data show that AZA prior to HSCT could be a better option than intensive chemotherapy in higher-risk MDS.
The trial has been registered with the EudraCT number 2010-019673-1.

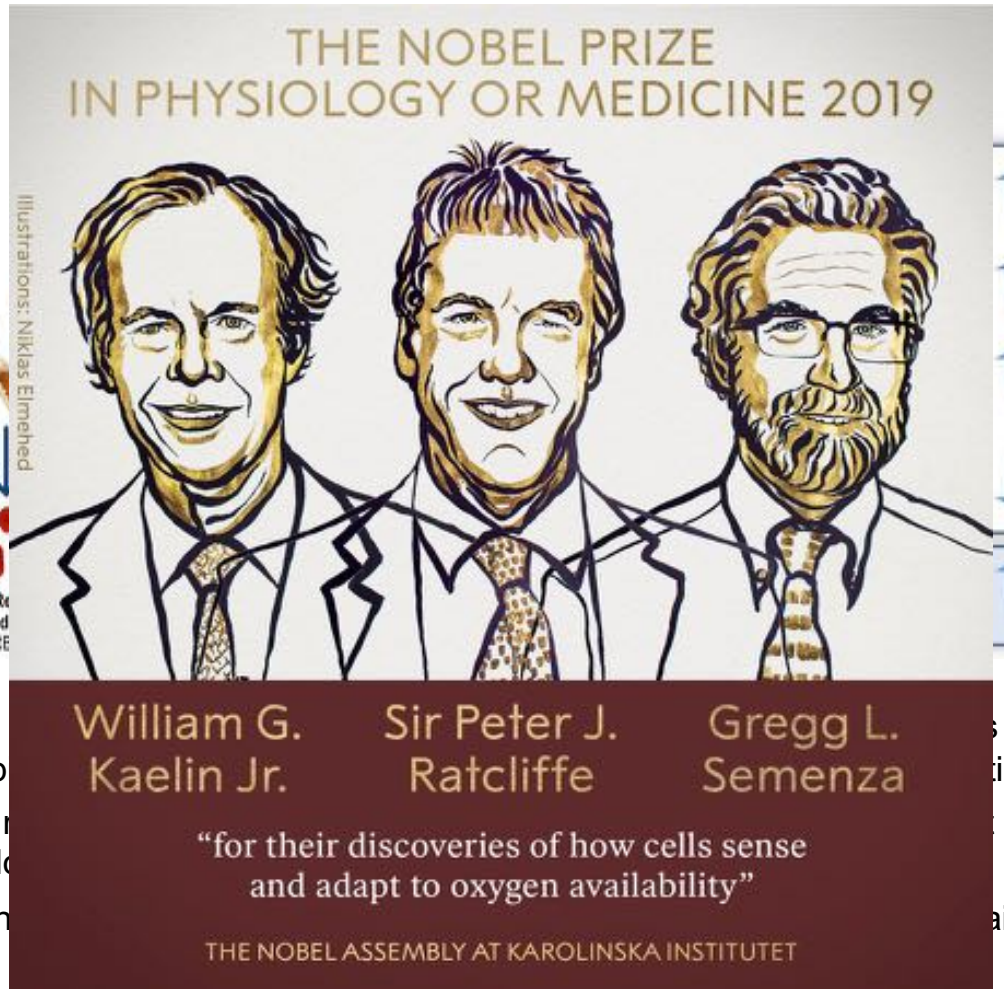
Key words: azacitidine, hypomethylating treatment, high-risk MDS, allogeneic stem-cell transplantation

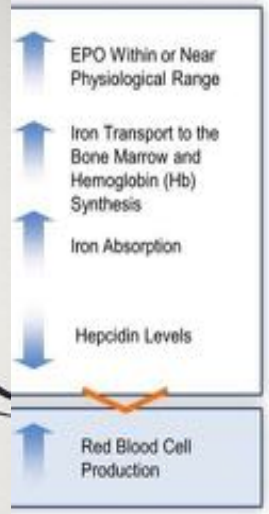
MDS therapy: targets and bullets



Roxadustat: a HIFs (Hypoxia-inducible factors) prolyl-hydroxylase inhibitor







- Roxadustat (also … as a HIF prolyl-hydroxylase inhib… …tin
- Non-inferiority of … dialysis (Chen et al NEJM 2019; gl…
- Two phase 2/3 an… …aive are ongoing.