Tailoring iron chelation by iron intake and serum ferritin: prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias

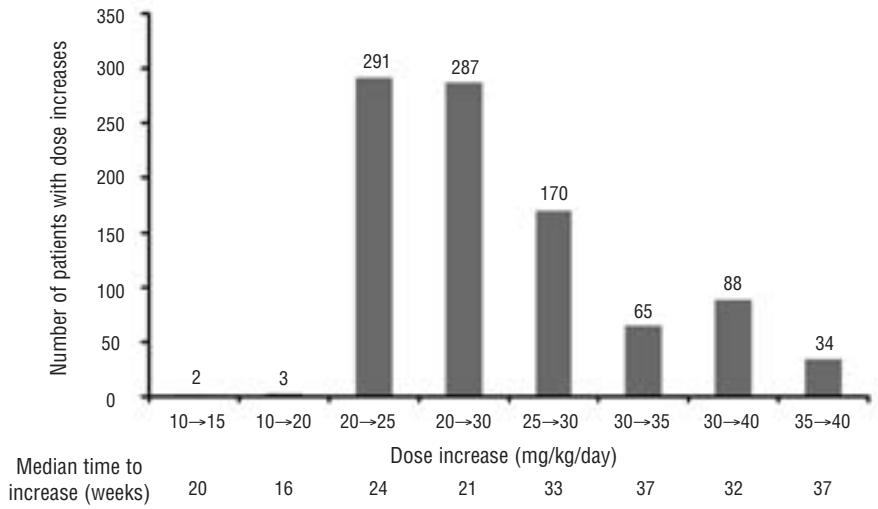
Maria Domenica Cappellini,[1] John Porter,[2] Amal El-Beshlawy,[3] Chi-Kong Li,[4] John F. Seymour,[5] Mohsen Elalfy,[6] Norbert Gattermann,[7] Stéphane Giraudier,[8] Jong-Wook Lee,[9] Lee Lee Chan,[10] Kai-Hsin Lin,[11] Christian Rose,[12] Ali Taher,[13] Swee Lay Thein,[14] Vip Viprakasit,[15] Dany Habr,[16] Gabor Domokos,[17] Bernard Roubert,[17] and Antonis Kattamis[18] on behalf of the EPIC study investigators*

[1]Universitá di Milano, Policlinico Foundation IRCCS, Milan, Italy; [2]University College London, London, UK; [3]Cairo University, Cairo, Egypt; [4]Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]Ain Shams University, Cairo, Egypt; [7]Heinrich-Heine-University, Düsseldorf, Germany; [8]Hôpital Henri Mondor, Créteil, France; [9]The Catholic University of Korea, Seoul, South Korea; [10]University Malaya Medical Centre, Kuala Lumpur, Malaysia; [11]National Taiwan University Hospital, Taipei, Taiwan; [12]Hôpital Saint-Vincent de Paul (Groupe Francophone des Myélodysplasies), Lille, France; [13]American University of Beirut, Beirut, Lebanon; [14]King's College London School of Medicine, King's College Hospital, London, UK; [15]Siriraj Hospital, Mahidol University, Prannok, Bangkoknoi, Bangkok, Thailand; [16]Novartis Pharmaceuticals Corp., East Hanover, NJ, USA; [17]Novartis Pharma AG, Basel, Switzerland, and [18]First Department of Pediatrics, University of Athens, Athens, Greece

Citation: Cappellini MD, Porter J, El-Beshlawy A, Li C-K, Seymour JF, Elalfy M, Gattermann N, Giraudier S, Lee J-W, Chan LL, Lin K-H, Rose C, Taher A, Thein SL, Viprakasit V, Habr D, Domokos G, Roubert B, and Kattamis A on behalf of the EPIC study investigators. Tailoring iron chelation by iron intake and serum ferritin: prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica 2009; XXX. doi:10.3324/haematol.2009.014696

Supplementary Table 1. Exposure to study treatment.

	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
Mean±SD planned dose, mg/kg/day	24.2±5.2	19.4±4.7	18.2±4.6	20.7±3.7	19.0±5.8	18.1±4.6	22.4±5.6
Mean±SD actual daily dose, mg/kg	24.1±5.5	19.2±5.4	17.6±4.8	20.2±3.8	18.6±5.6	17.6±4.6	22.2±5.9
<20, n (%)	238 (21.3)	197 (57.8)	75 (64.7)	41 (51.3)	26 (60.5)	33 (67.3)	610 (35.0)
≥20-<30, n (%)	736 (66.0)	135 (40.0)	41 (35.3)	39 (48.8)	17 (39.5)	16 (32.7)	984 (56.4)
≥30, n (%)	141 (12.6)	9 (2.6)	–	–	–	–	150 (8.6)



Supplementary Figure 1. Number and median time to dose increases in the overall population.

Supplementary Table 2. Drug-related serious adverse events as assessed by the participating investigators.

Patient number	Underlying anemia	Age (years)	Reported drug-related serious adverse events
1	Thalassemia	8	Gastrointestinal hemorrhage*
2	Thalassemia	25	Renal tubular disorder‡
3	Thalassemia	34	Anemia
4	MDS	71	Nausea; vomiting
5	MDS	62	Colitis
6	MDS	75	Upper abdominal pain; diarrhea
7	MDS	82	Dementia
8	Other	83	Rash
9	Thalassemia	9	Rash; fever
10	MDS	71	Increased serum creatinine
11	Thalassemia	37	Angioedema
12	SCD	15	Increased transaminases
13	SCD	9	Increased transaminases
14	MDS	70	Rash
15	MDS	67	1. Rash; 2. Abdominal pain
16	MDS	76	Severe neutropenia
17	MDS	88	Acute renal failure‡
18	MDS	68	Hyperthermia; headache
19	Other (malignant disease)	79	Laryngeal edema
20	MDS	83	Abdominal pain; fever
21	MDS	88	Cardiac failure
22	Thalassemia	21	Cardiac failure
23	MDS	63	Rash
24	Thalassemia	26	Increased transaminases
25	Other (malignant disease)	14	Cholestatic hepatitis
26	MDS	56	Pancytopenia**
27	Thalassemia	12	Rash
28	Thalassemia	30	Post-streptococcal glomerulonephritis leading to acute renal failure, acute tubular necrosis‡‡
29	Thalassemia	10	Rash; pancreatitis
30	Thalassemia	7	Renal tubular disorder‡‡

**Gastrointestinal bleed due to hemorrhagic gastritis; †Serum ferritin fell from 2500 to 1300 ng/mL in 3 months indicative of over-rapid chelation, abnormalities disappeared within 2 weeks of drug interruption, patient permanently discontinued; ‡Patient had various co-morbidities and was taking other medications suspected to be contributory (Bactrim), study drug was interrupted and patient recovered; **Suspected by the investigator to be drug related, although there was no improvement after treatment was withheld; ††Glomerulonephritis was considered not study-drug related but tubular necrosis was, although tubular necrosis often accompanies glomerulonephritis; ‡‡Patient was asymptomatic and serum ferritin was 1100 ng/mL (receiving deferasirox 35 mg/kg/day), findings normalized rapidly following drug interruption.*

Supplementary Table 3. Causes of death in MDS patients after start of treatment (non-study-drug related).

	MDS (n=341)
Sepsis	1
Septic shock	4
Cardiac failure	1
Pneumonia	2
Intestinal infarction	2
Extradural hematoma	2
Respiratory failure	1
Diverticular perforation	1
Gastrointestinal hemorrhage	1
Euthanasia (Patient decision)	1
General health deterioration	1
Aspergillosis	1
Fungal meningitis	1
Rupture of spleen	1
Subdural hematoma	1
Acute myeloid leukemia aggravation	1
Acute pulmonary edema	1
Pulmonary hemorrhage	1
Jaundice acholuric	1
Cerebral hemorrhage	1