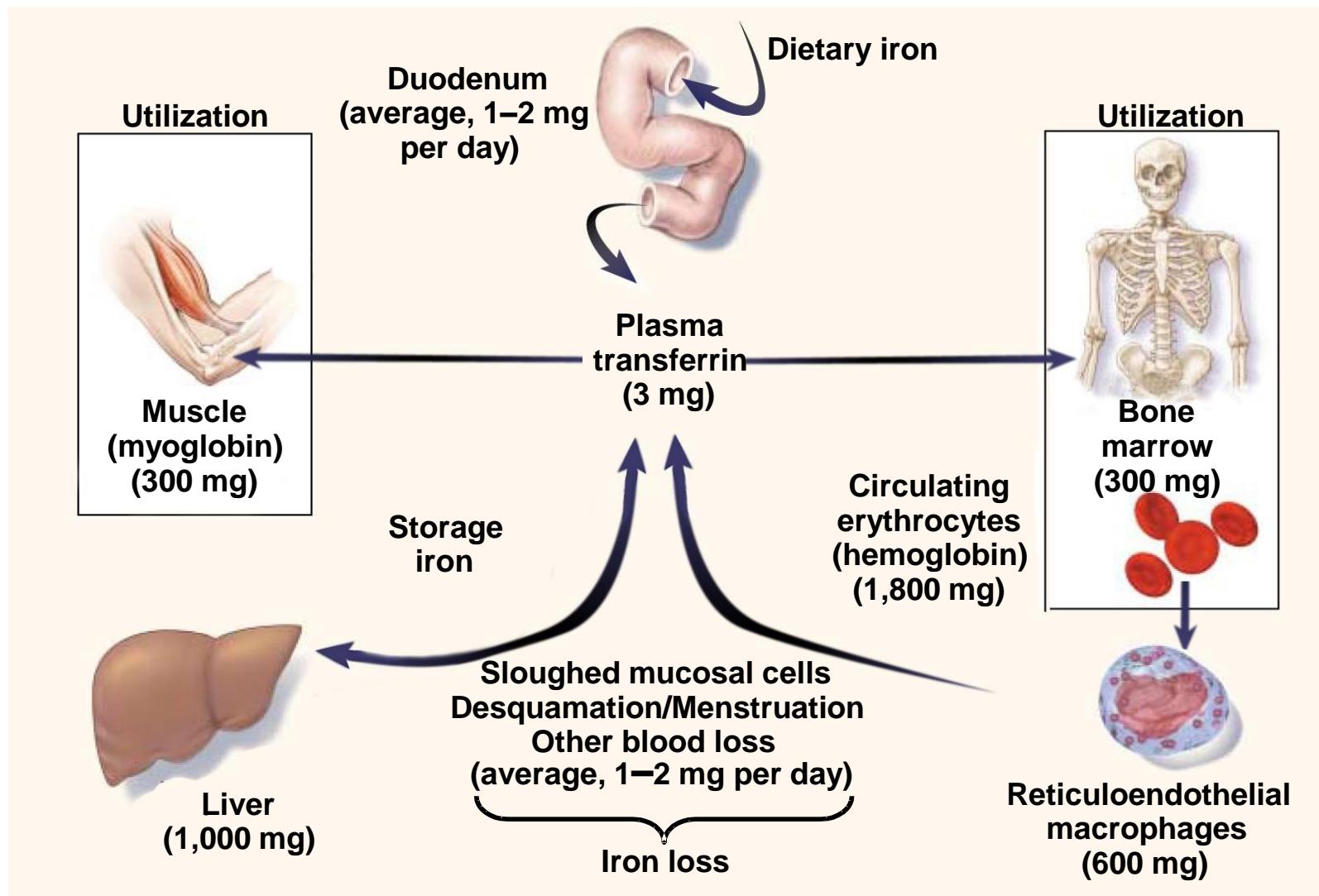


Grundlagen, Diagnostik und Therapie der sekundären Eisenüberladung bei angeborenen Anämien

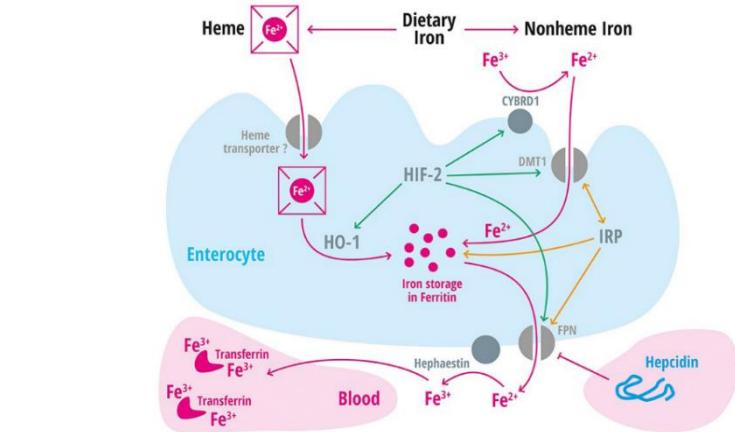
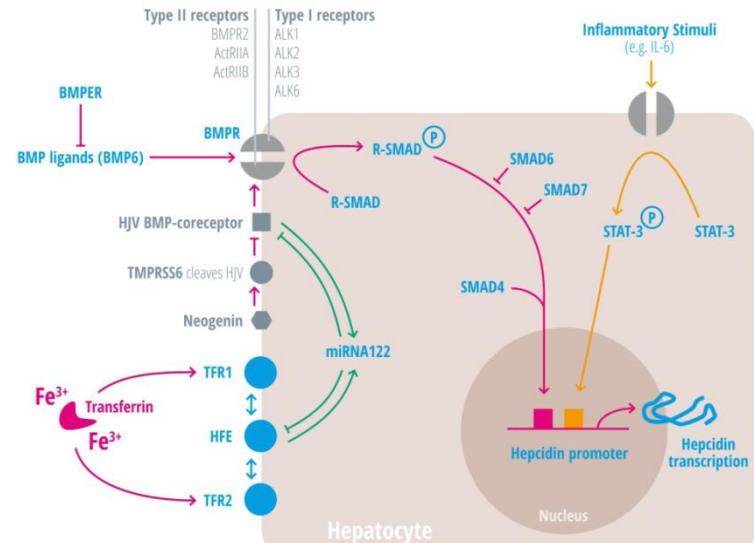
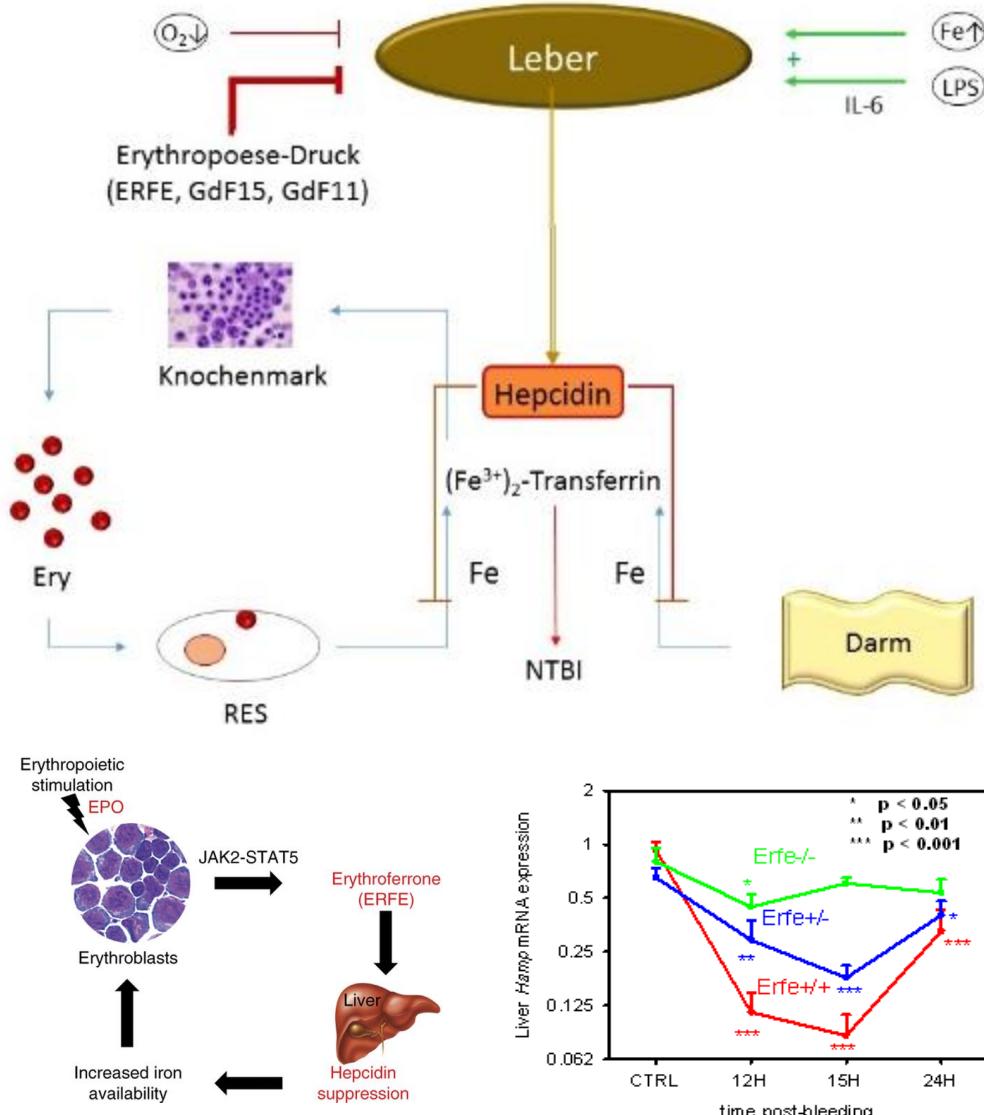
Holger Cario

Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Ulm
Zentrum für Seltene Störungen der Hämatopoese und für Immundefekte (ZSHI)
im Zentrum für Seltene Erkrankungen Ulm (ZSE Ulm)

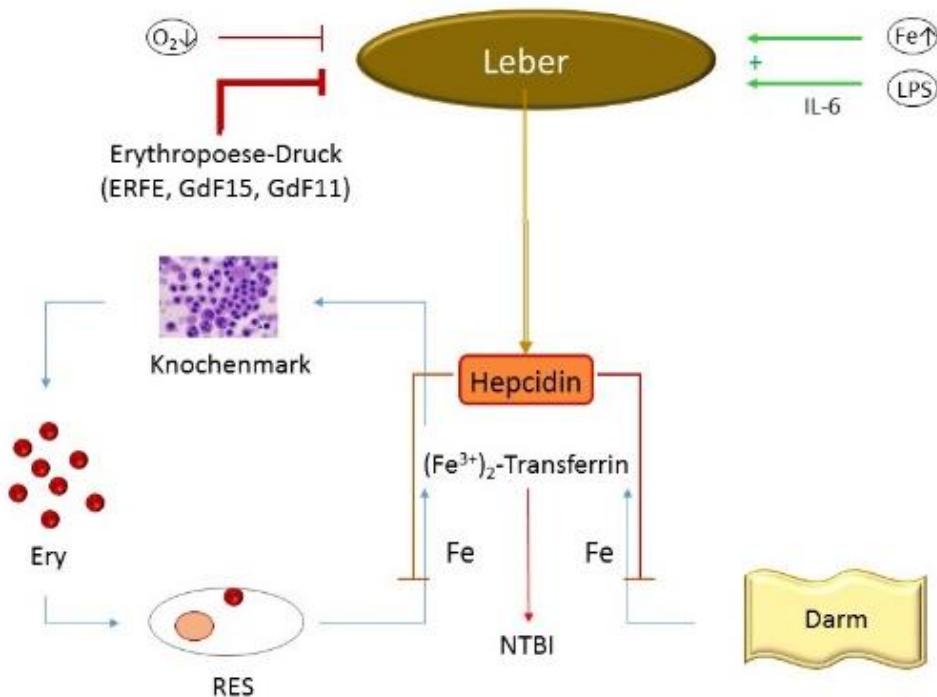
Eisenhomeostase des menschlichen Organismus



Eisenhomeostase des menschlichen Organismus



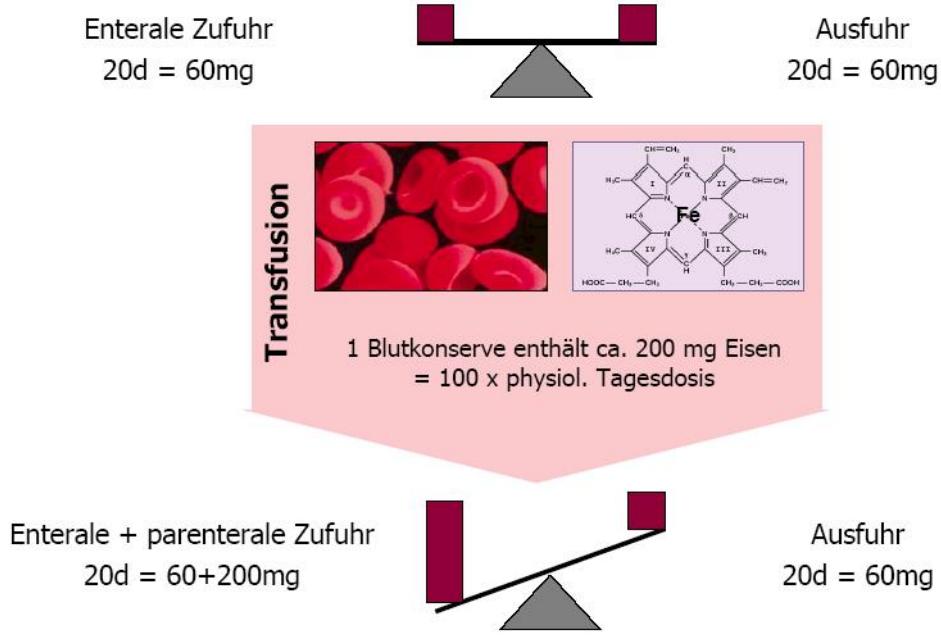
Resorptions-bedingte Eisenüberladung



- Thalassaemia intermedia
- Kongenitale dyserythropoet. A. (CDA I, II, III)
- Pyruvakinase-Mangel
- Patienten mit anderen Anämien (z.B. Sichelzellkrankheit, Sphärozytose) ohne Transfusionsabhängigkeit

„iron-loading anemias“

Transfusions-bedingte Eisenüberladung



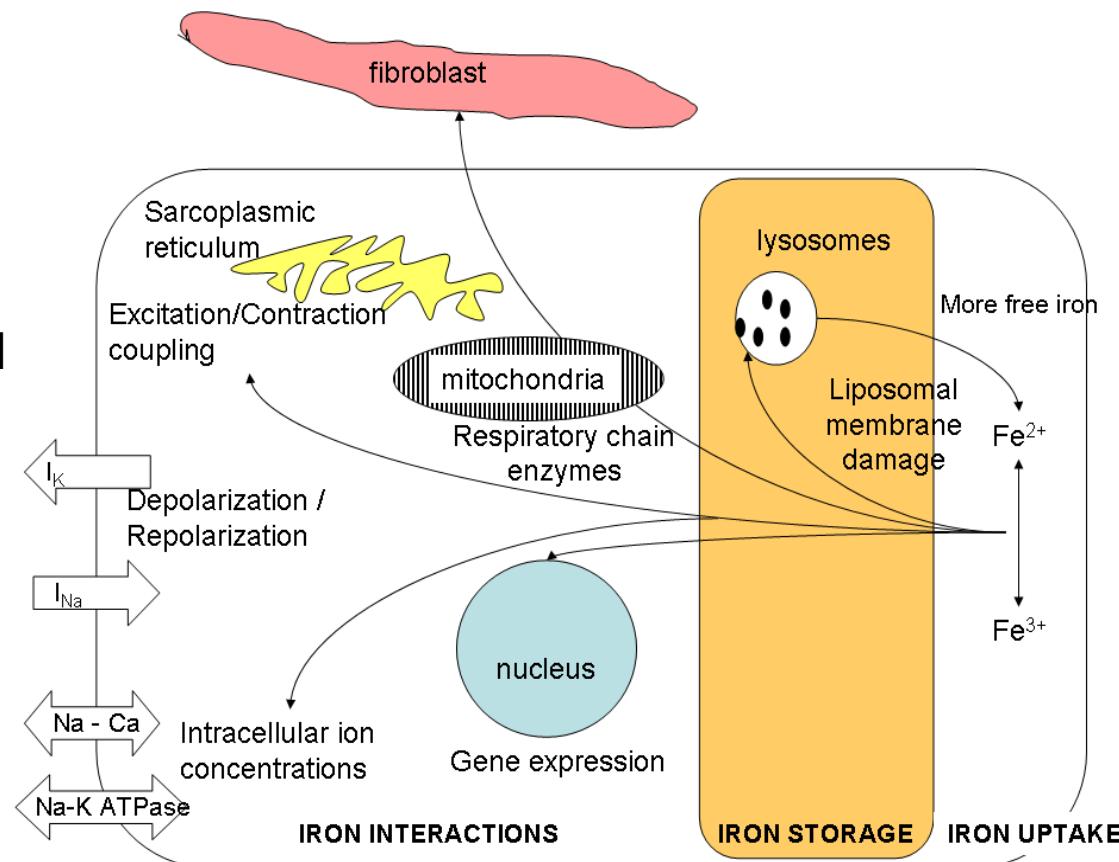
- Thalassaemia major
- Diamond-Blackfan-Anämie
- Sichelzellkrankheit
- Transfundierte Patienten mit kongenitaler dyserythropoet. A. (CDA)
- Pyruvakinase-Mangel
- Sphärozytose
- sideroblastischer Anämie etc.

Siderose-bedingte Organschäden - Pathogenese

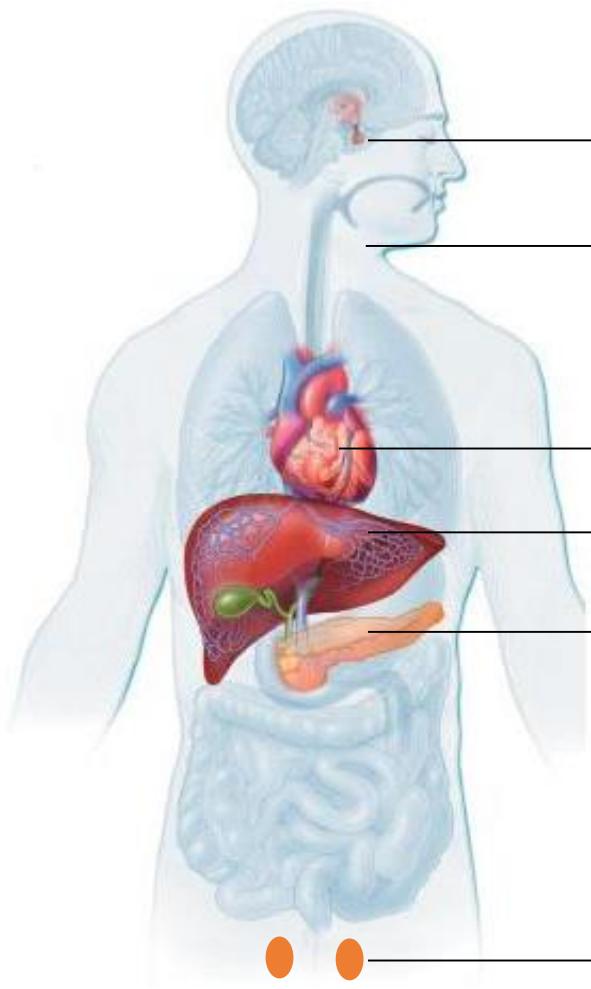


Hauptquelle der reaktiven Sauerstoffspezies (*reactive oxygen species, ROS*) in der Zelle

- Membrane damage
 - lysosomal hydrolase release – cell death
 - Ca^{++} release → decoupling
- Disturbance of the mitochondrial respiratory chain
- Blockade of ion channels (Na, K -ATPase)
- DNA damage
- Modulation of gene expression
- Fibroblast stimulation → extracellular matrix → fibrosis



Siderose-bedingte Organschäden - Übersicht



- Hypophyse** → Wachstumsretardierung, Hypogonadismus
- Schilddrüse** → Hypothyreose
Nebenschilddrüse → Hypoparathyreoidismus
- Herz** → Kardiomyopathie, Herzinsuffizienz, Arrhythmie
- Leber** → Hepatopathie, Insulinresistenz, Leberfibrose, -zirrhose, HCC
- Pankreas** → Diabetes mellitus, exokrine Dysfunktion
- Gonaden** → Hypogonadismus und Infertilität

Sekundäre Eisenüberladung - Monitoring

Gesamtkörpereisen,
Lebereisen



Ferritin, MRT, SQUID

Herzeisen



Kardio-MRT (T2*)

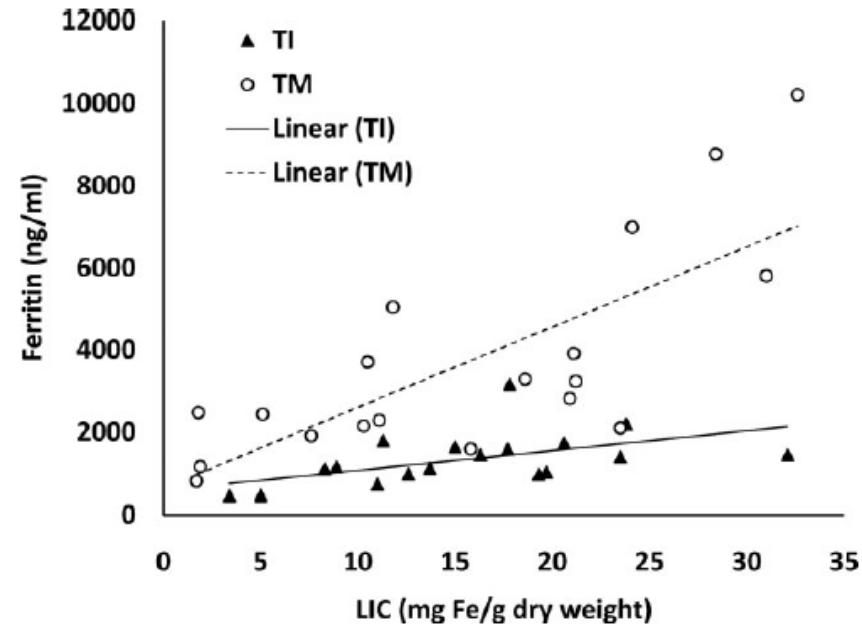
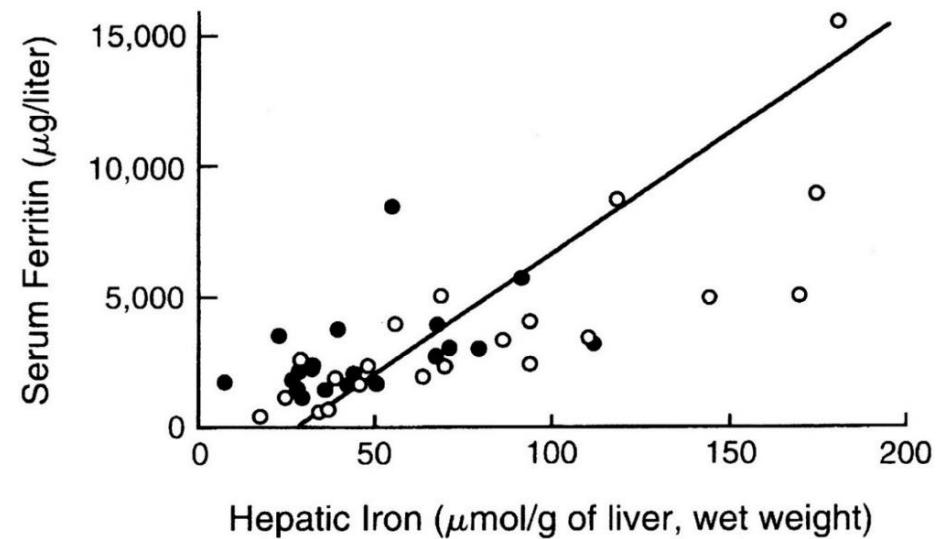
Eisenüberladung
endokrine Organe



Laboruntersuchungen,
(MRT: Pankreas, Hypophyse)

Sekundäre Eisenüberladung - Monitoring

Serumferritin

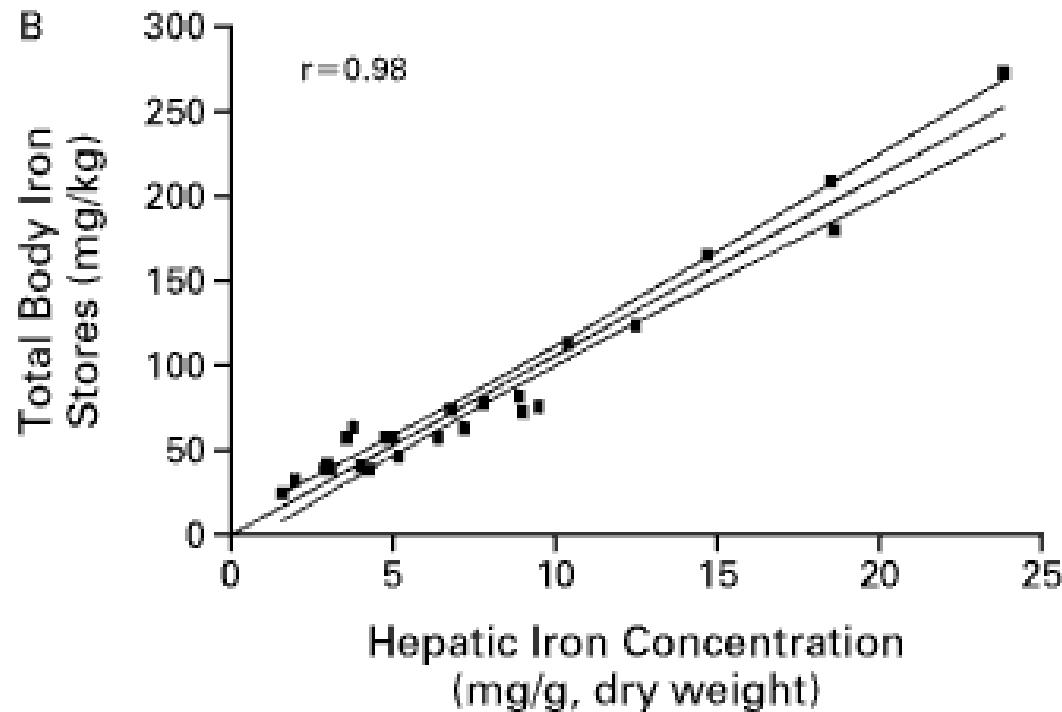


Parameter	Thalassemia intermedia, <i>n</i> = 19	Thalassemia major, <i>n</i> = 19
Mean SF ± SD, ng/ml (range)	1316.8 ± 652.3 (460–3,157)	3723.8 ± 2568.8 (827–10,214)
Mean LIC ± SD, mg Fe/g dw (range)	15.0 ± 7.4 (3.4–32.1)	15.7 ± 9.9 (1.7–32.6)
Mean cardiac T2* ± SD, msec (range)	47.3 ± 7.1 (35.0–66.9)	21.5 ± 15.2 (5.1–50.7)

Sekundäre Eisenüberladung - Monitoring

Lebereisenkonzentration (LIC)

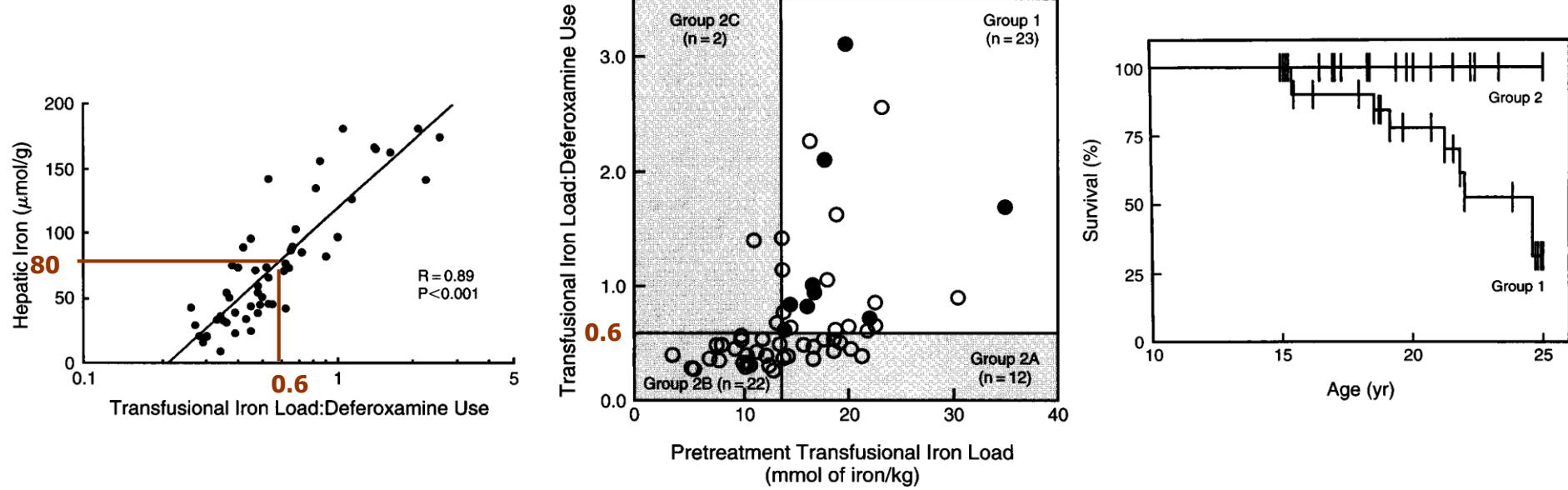
Proportional zum Gesamtkörpereisen



Sekundäre Eisenüberladung - Monitoring

Lebereisenkonzentration (LIC)

Proportional zur Eisen : Chelator Ratio = von prognostischer Relevanz

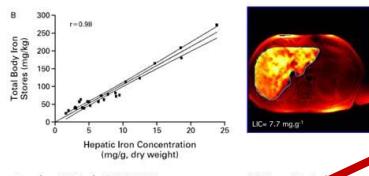


Sekundäre Eisenüberladung - Monitoring

Lebereisenkonzentration (LIC)

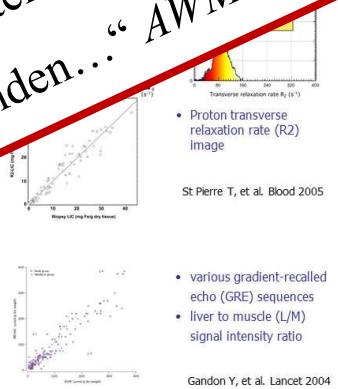
Liver biopsy

- + Direct measurement of LIC
- + Quantitative, specific, sensitive
- + LIC accurately reflects TBI
- + Allows parallel histopathology (hepatitis, fibrosis, cirrhosis)
 - Previous reference method
- Uneven iron distribution in liver possible – Risk of sampling
- Invasive, painful, risk of infection potentially serious



Magnetic Resonance Imaging (MRI)

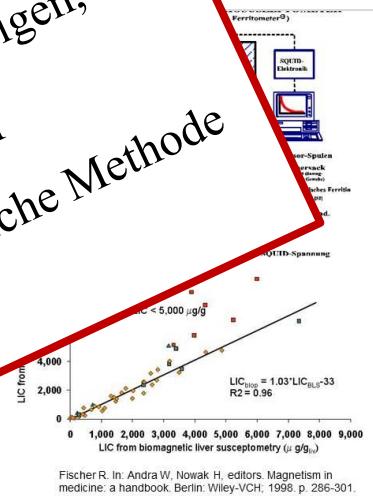
- + Non-invasive
- + LIC measured "non-invasively" without sample
- + Potential for widespread application
- Up to date limited availability
- Costs (?)
- (indirect measurement)



„... vergleichende Untersuchungen ... zur Lebereisenmessung zeigen, dass die Ergebnisse differieren können, so dass zu empfehlen ist, bei wiederholten Messungen bei einem Patienten jeweils die gleiche Methode anzuwenden...“ AWMF-Leitlinie S2k 025/029 (2015)

Biomagnetic Liver Susceptometry

Supra



Magnetic Resonance Imaging (MRI)

LIC Rennes (Gandon et al.)

- Gradient-recalled echo sequences
- three ROI à 1cm² (100 Pixel)
- Mean per ROI
- Published patients:
Not well defined (HFE?) n=174

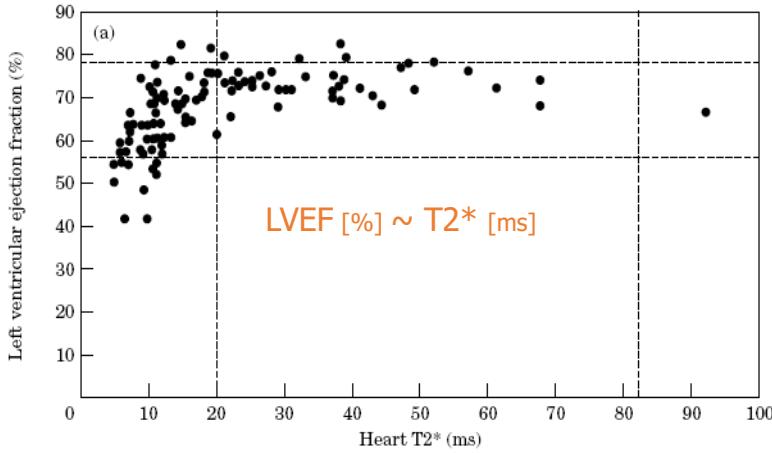
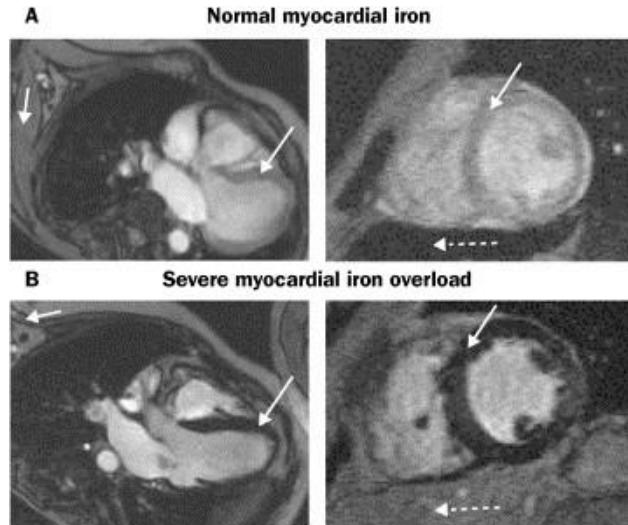
- Algorithm free of costs (WWW)
- Scanner specificity not considered
- No control of accuracy

LIC Ferriscan (St. Pierre et al.)

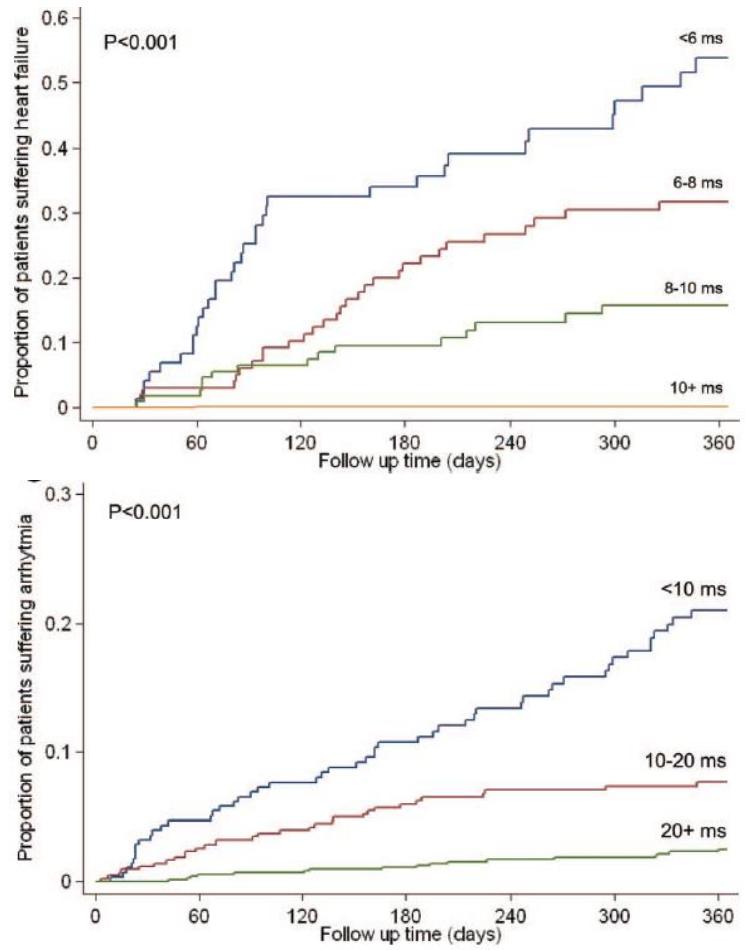
- Spin echo sequences
- Total area of slice
- Calculation per voxel
- Published patients:
HFE n=23, TM n=9, TI n=41
- Algorithm commercially available
- Scanner specificity considered
- Phantom scans, quality management (FDA approved)

Sekundäre Eisenüberladung - Monitoring

Herzeisenbestimmung - Kardio-MRT T2* Relaxationszeit



Anderson LJ et al., Lancet 2002



Kirk P et al., Circulation 2009

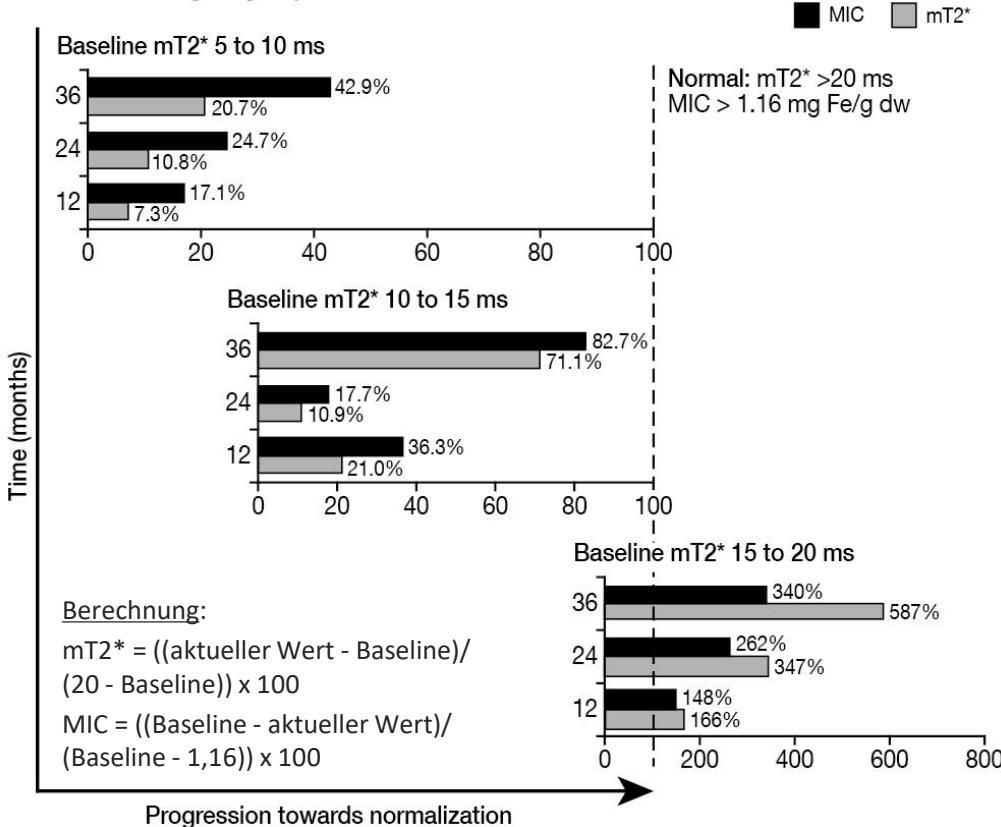
Sekundäre Eisenüberladung - Monitoring

Herzeisenbestimmung - Kardio-MRT T2* Relaxationszeit

Carpenter et al 2013:

$$\text{MIC lt. mT2*}: [\text{Fe}] = 45,0 \times (\text{mT2*})^{-1,22}$$

Figure. Progression towards normalization of mT2* and MIC over time by baseline mT2* category (illustrated as percentage progression towards mT2* >20 ms and MIC >1.16 mg Fe/g dw)



Gesamtgruppe	Base-line	Mo. 12	Mo. 24	Mo. 36
mT2* (ms)	12,0	13,9	15,6	17,1
MIC (mg Fe/g dw)	2,43	2,10	1,94	1,80

schwere myokardiale Eisenbelastung:
prozentuale Veränderung in Richtung Normalisierung zu Mo12, Mo24 und Mo36 geringer für mT2* als für MIC

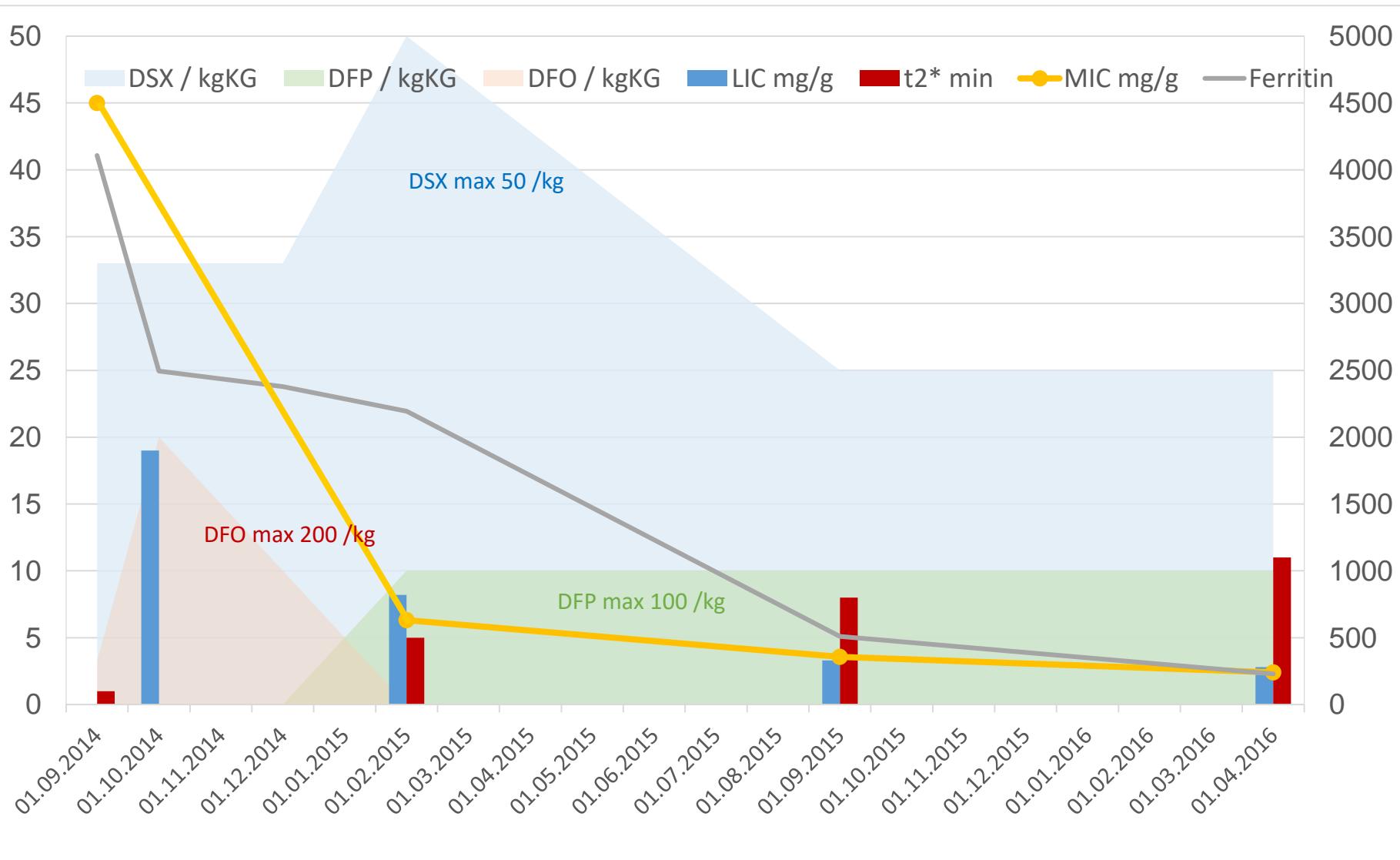
Porter JB et al. ASH 2014

Anmerkung: Werte >100 % bei Überschreiten der Schwellen für Normalwerte (=100 %)

Fallbeispiel

w., geb. 5/1980, TM

Stand 5/2016

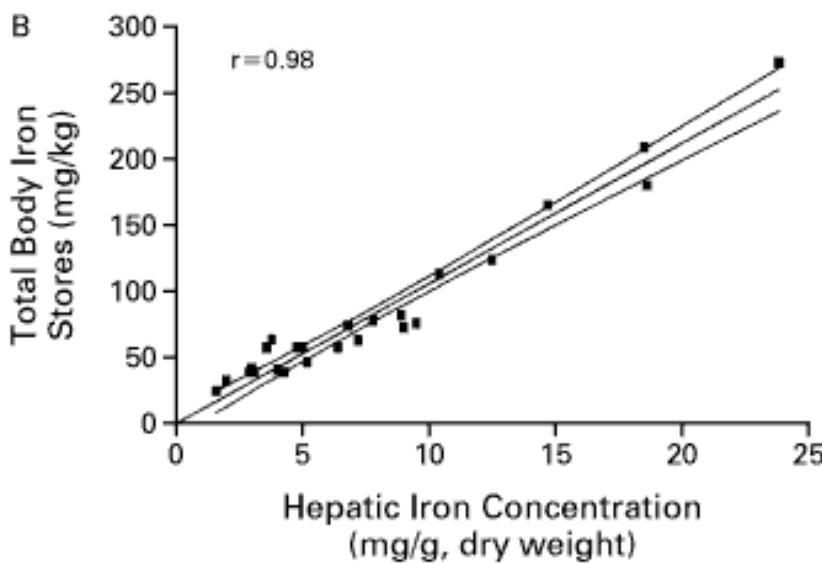


Eisenelimination durch Aderlasstherapie

Phlebotomie

Dauer: 26±16 Mo. (9-66)

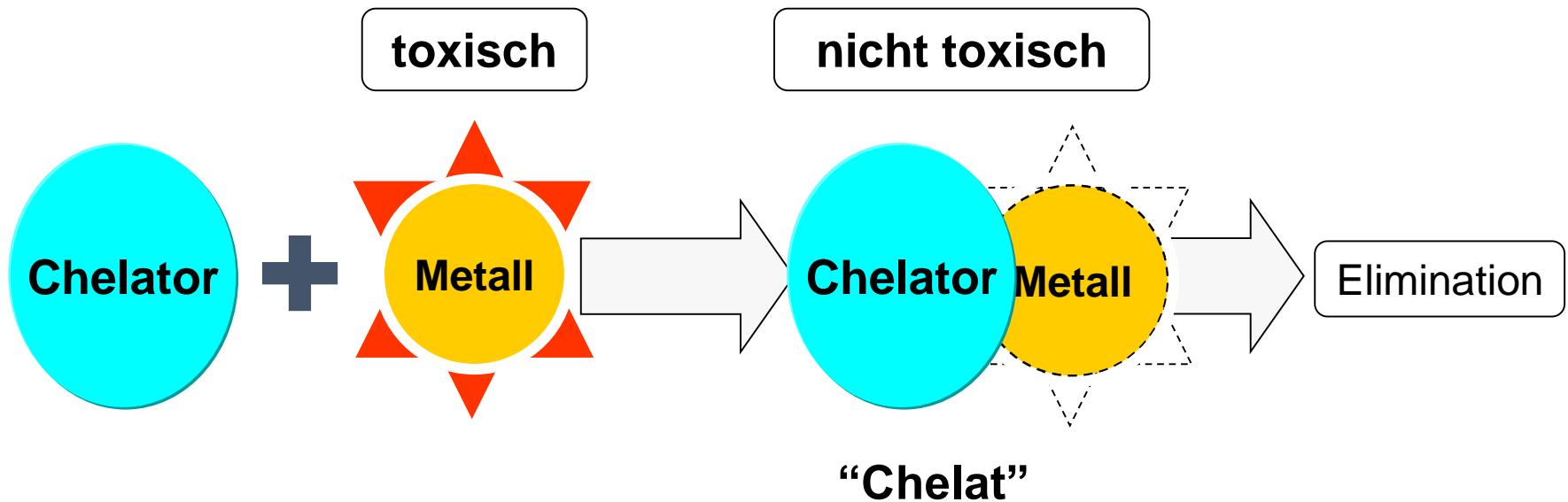
Intensität: 6ml/kgKG 14-tägig



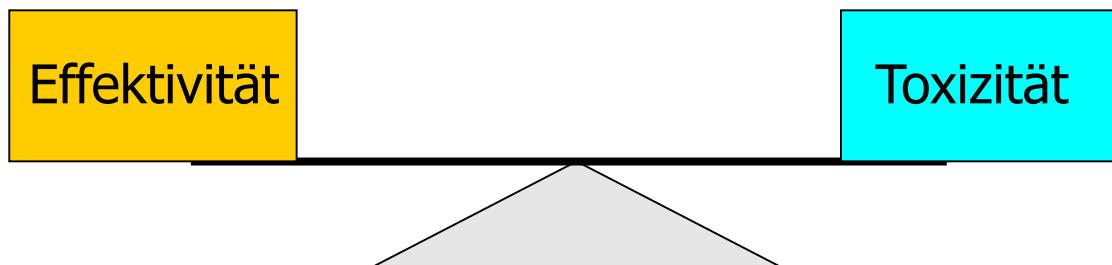
VARIABLE	TOTAL (N=48)
Age (yr)	17±4
Female sex (no. of patients)	17
Spleen present (no. of patients)	37
Hepatic iron (mg/g, dry weight)†	
Before phlebotomy	10.8±6.3
After phlebotomy	1.1±0.4
Serum ferritin (ng/ml)‡	
Before phlebotomy	1498
Median	842–2344
Interquartile range	
After phlebotomy	110
Median	59–147
Interquartile range	

Medikamentöse Eiseneliminationstherapie

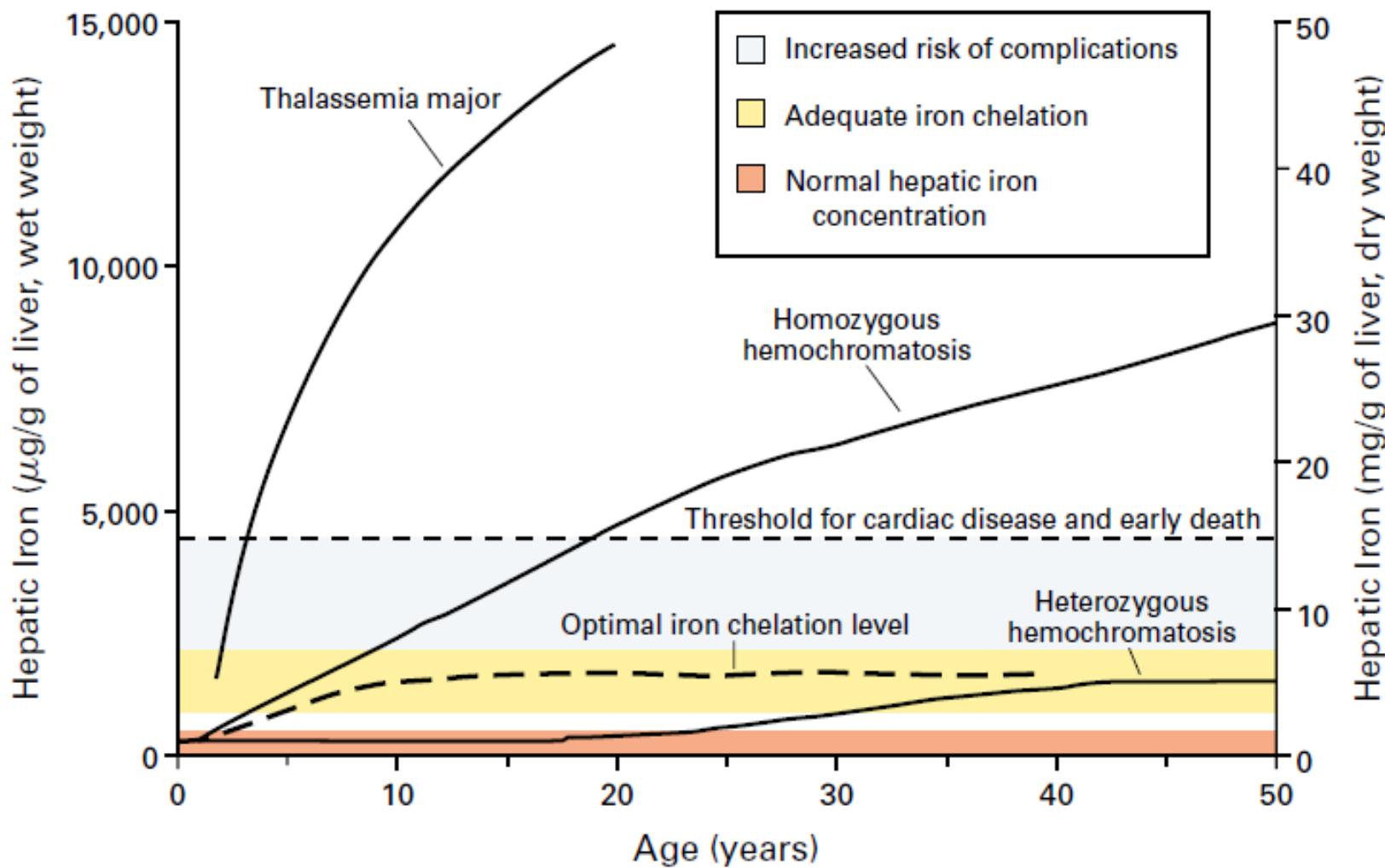
Prinzip



Toxizität – eine Frage der Balance



Eiseneliminationstherapie – Indikation, Beginn, Ziel



Eiseneliminationstherapie – Indikation und Beginn

Anämien mit regelmäßigen Transfusionsbedarf

AWMF-Leitlinie 025/029

- Ferritin > 1000ng/ml
- Zahl der Transfusionen > 10-15 (ca. 200ml/kg)
- Lebereisenkonzentration > 4.5 (3.2) mg/g d.w.

- Beginn der Eiseneliminationstherapie bei Patienten mit angeborenen Anämien mit regelmäßigem Transfusionsbedarf i.d.R. im Alter von 2-4 Jahren
- Immer dauerhafte (lebenslange) Therapie

Eiseneliminationstherapie – Ziel

Anämien mit regelmäßigen Transfusionsbedarf

AWMF-Leitlinie 025/029 **alt**

I. Zu Kapitel 2

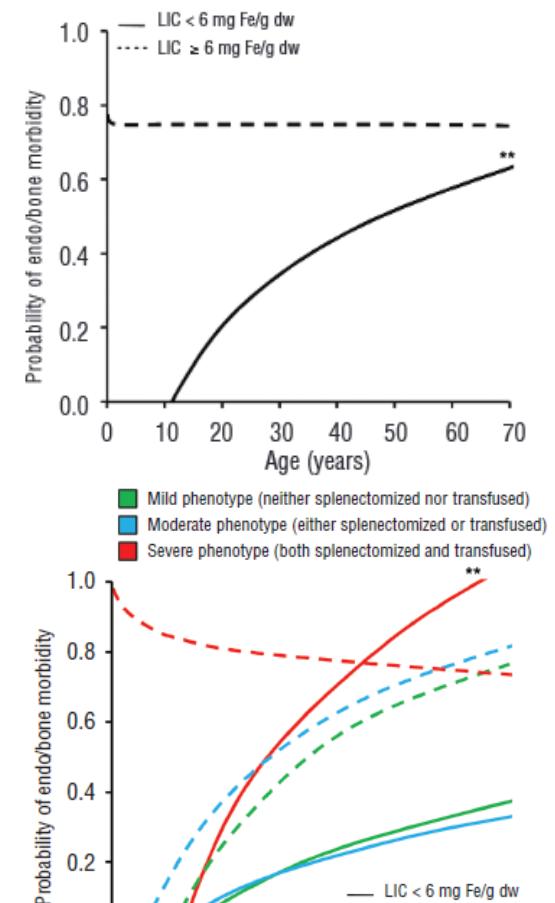
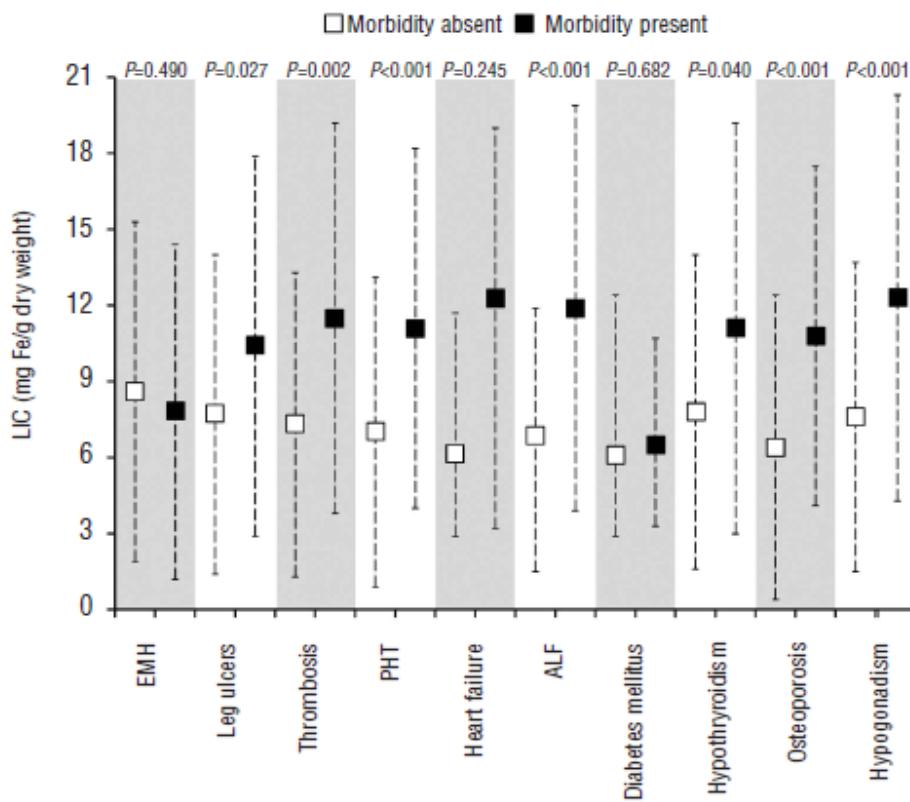
FerriScan Gandon et al.

I.1. Empfohlene Grenzwerte zur Steuerung der Eiseneliminationstherapie anhand der Lebereisenkonzentration (LIC) (nach Fischer et al.⁴)

LIC <i>in vivo</i> ^a (mg/g _{lever})	LIC <i>tb</i> ^b (μmol/g _{w.w.})	LIC <i>frisch</i> ^c (mg/g _{d.w.})	LIC <i>paraffin</i> ^d (mg/g _{d.w.})	Kommentar	
1	18	3,33	4,5 ± 0,8	5,5 ± 1,0	Untergrenze des akzeptablen Bereiches
2,1	38	7,0	9,6 ± 1,7	11,7 ± 2,1	Obergrenze des akzeptablen Bereiches
4,5	80	15	20,1 ± 3,6	24,6 ± 4,5	Risikoschwellenwert für schwere Organsiderose [#]

Eiseneliminationstherapie – Ziel

Musallam KM et al. Elevated liver iron concentration is a marker of increased morbidity in patients with β thalassemia intermedia. *Haematologica* 2011



Ziel der Eiseneliminationstherapie:

- Ferritin < 1000ng/ml
- Lebereisenkonzentration ≤ 4.5 (3.2) mg/g d.w.

Sicherheit ?

Eiseneliminationstherapie – Ziel Sicherheit ?

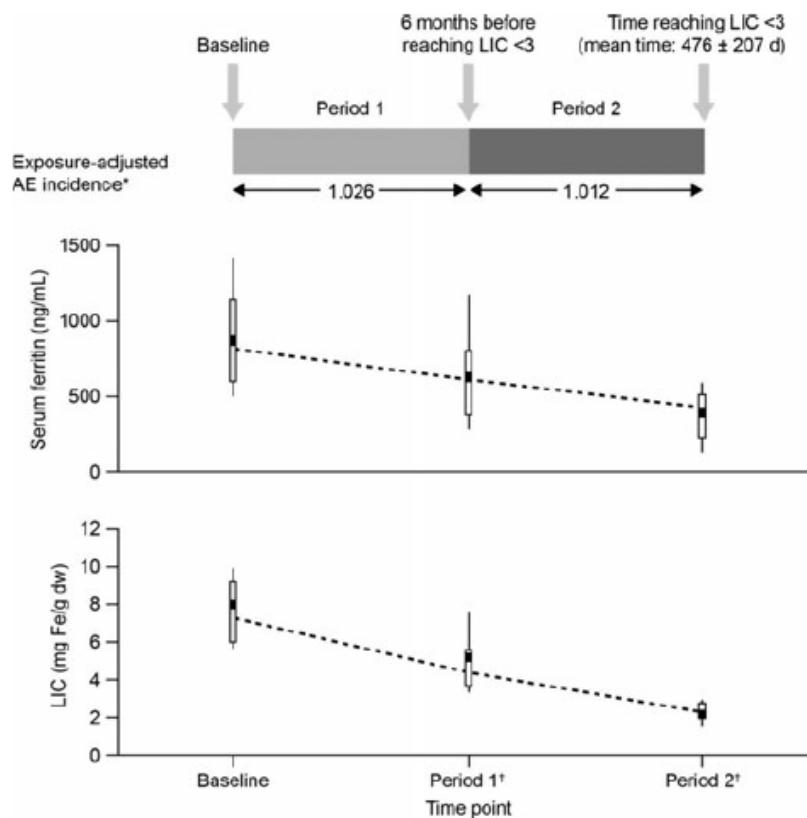
Taher AT et al. Approaching low liver iron burden in chelated patients with non-transfusion-dependent thalassemia: the safety profile of Deferasirox. *Eur J Haematol* 2014

N = 24 / 166

Table 1 Laboratory parameters at baseline and prior to reaching LIC <3

Parameter, mean \pm SD	Baseline	End of period 1 ¹	End of period 2 ¹
Creatinine, $\mu\text{mol/L}$	51.8 \pm 14.6	62.0 \pm 21.9	61.0 \pm 19.9
Creatinine clearance, mL/min	144.8 \pm 42.3	129.8 \pm 53.9	129.5 \pm 52.3
Alanine aminotransferase, U/L	31.4 \pm 20.4	16.9 \pm 7.4	16.4 \pm 6.8
Urinary protein/ creatinine ratio, mg/mg	0.2 \pm 0.1	0.3 \pm 0.2	0.2 \pm 0.1

¹Last available assessment.



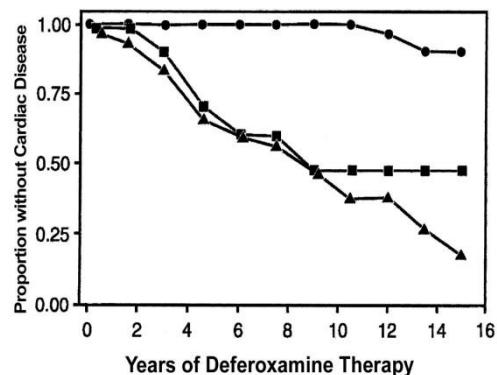
Eiseneliminationstherapie - Medikamente

Eigenschaft	Deferoxamin	Deferipron	Deferasirox
Chelator : Eisen	1:1 (Hexadentat)	3:1 (Bidentat)	2:1 (Tridentat)
Standarddosis (mg/kg/day)	(25–)40-50	75(-100)	20–30(-40) 14-21(-28)
Verabreichung	Subkutan, intravenös (12 h, 7 Tage/Woche)	Oral 3 x täglich	oral 1 x täglich
Halbwertzeit	20–30 Minuten	3–4 Stunden	12 – 16 Stunden
Ausscheidung	Urin, Faeces	Urin	Faeces (<10% Urin)
Nebenwirkungen	lokale Reaktionen, Augen-, Innenohr- und Knochenschäden, pulmonale, allergische und neurologische Reaktionen	gastrointestinale Störungen, Agranulozytose / Neutropenie, Arthralgien, Leberenzymmerhöhung	Gastrointestinale Störungen, Exanthem Kreatinin ↑, renales Fanconi-S., ALT ↑; Katarakt?, Ototoxizität?
Anwendung bei	Thal. major, intermedia, SCA, DBA, CDA, ...	Thal. major	Thal. major, SCA, DBA, CDA*, ..., Thal. Intermedia

Eiseneliminationstherapie - Medikamente

DFO

Olivieri NF et al. *NEJM* 1994



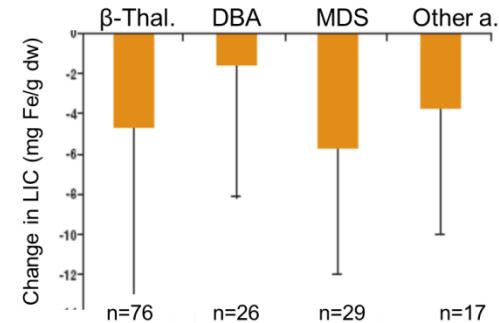
DFP

Maggio A et al. *BCMD* 2002

DFO 50mg/kg ≥ 5d □ Differenz Ende-vs.-Start Therapie DFP 75mg/kg/d; t=1 J.	
	Differenz Ende-vs.-Start Therapie
DFP (n=71)	DFO (n=73)
Ferritin (ng/ml)	-222
LIC (mg/g dw)	-1.02 (n=20)
Leber MRT	-0,06
Kardio-MRT	-0,19
LVEF (%)	0
	1

DSX

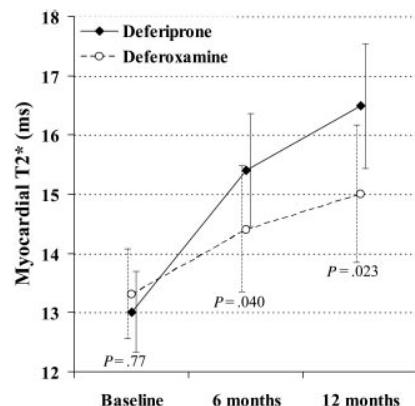
Greenberg P et al. *ASH* 2005



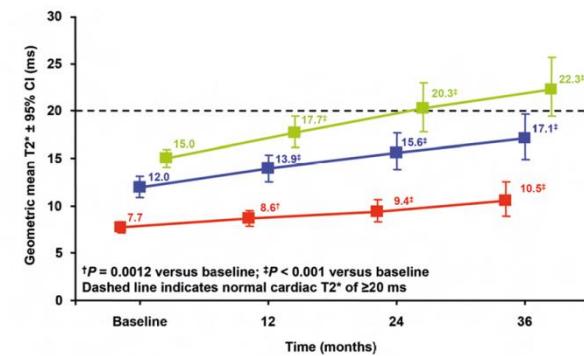
Serielle Ferritinmessungen >2.500µg/l

- < 33%
- 33%-67%
- ▲ > 67%

Pennell D et al. *Blood* 2006

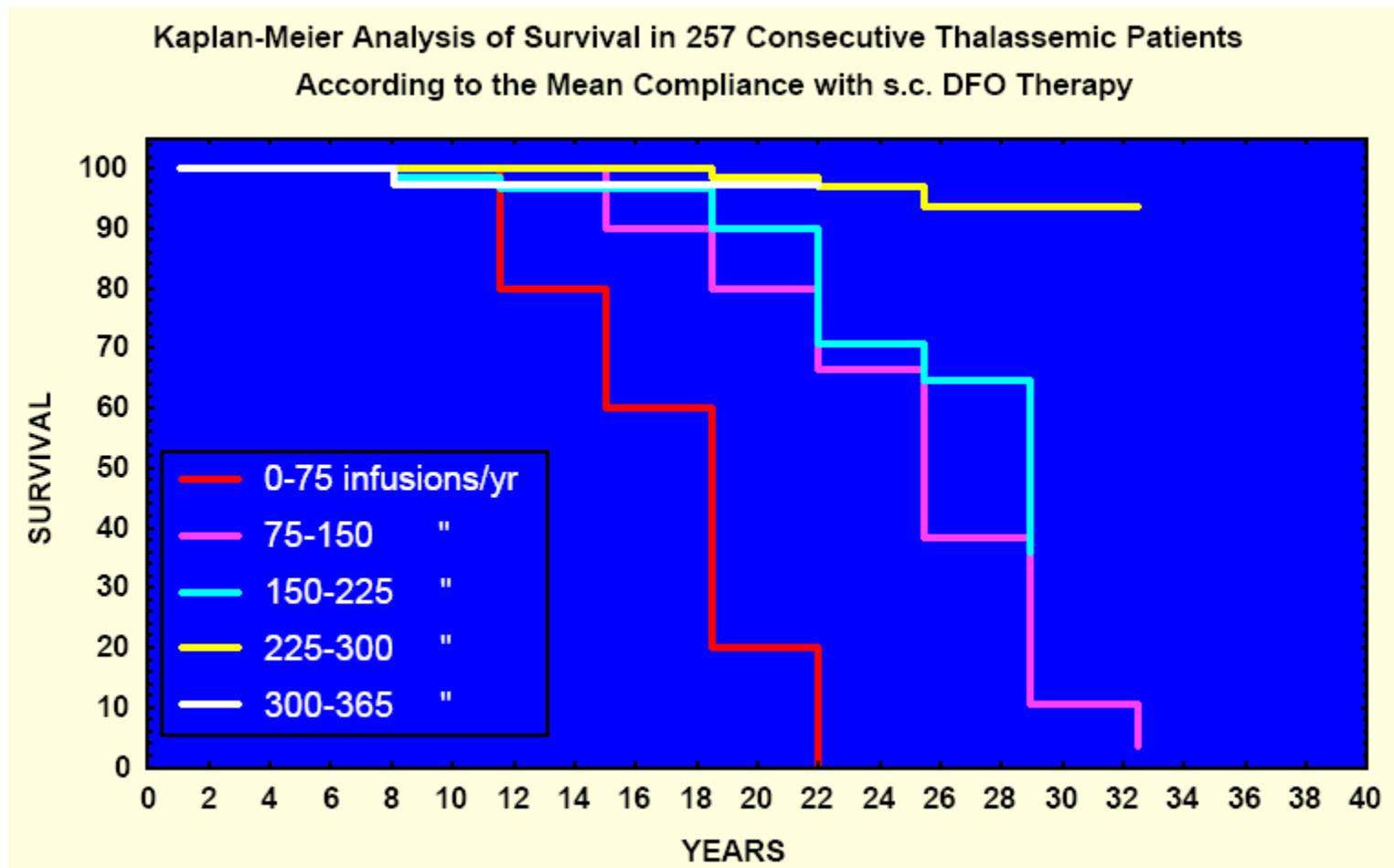


Pennell D et al. *Haematologica* 2012



Eiseneliminationstherapie – Bedeutung der Compliance

Deferoxamine / Desferrioxamine / DFO (DesferalTM)



Eiseneliminationstherapie - Medikamente

Eigenschaft	Deferoxamin	Deferipron	Deferasirox
Chelator : Eisen	1:1 (Hexadentat)	3:1 (Bidentat)	2:1 (Tridentat)
Standarddosis (mg/kg/day)	(25–)40-50	75(-100)	20–30(-40) 14-21(-28)
Verabreichung	Subkutan, intravenös (12 h, 7 Tage/Woche)	Oral 3 x täglich	oral 1 x täglich
Halbwertzeit	20–30 Minuten	3–4 Stunden	12 – 16 Stunden
Ausscheidung	Urin, Faeces	Urin	Faeces (<10% Urin)
Nebenwirkungen	lokale Reaktionen, Augen-, Innenohr- und Knochenschäden, pulmonale, allergische und neurologische Reaktionen	gastrointestinale Störungen, Agranulozytose / Neutropenie, Arthralgien, Leberenzymverhöhung	Gastrointestinale Störungen, Exanthem Kreatinin ↑, renales Fanconi-S., ALT ↑; Katarakt?, Ototoxizität?
Anwendung bei	Thal. major, intermedia, SCA, DBA, CDA, ...	Thal. major	Thal. major, SCA, DBA, CDA*, ..., Thal. Intermedia

Eiseneliminationstherapie – Monitoring zur Chelatortoxizität

Anämien mit regelmäßigen Transfusionsbedarf

AWMF-Leitlinie 025/029

Konsensusempfehlung 1

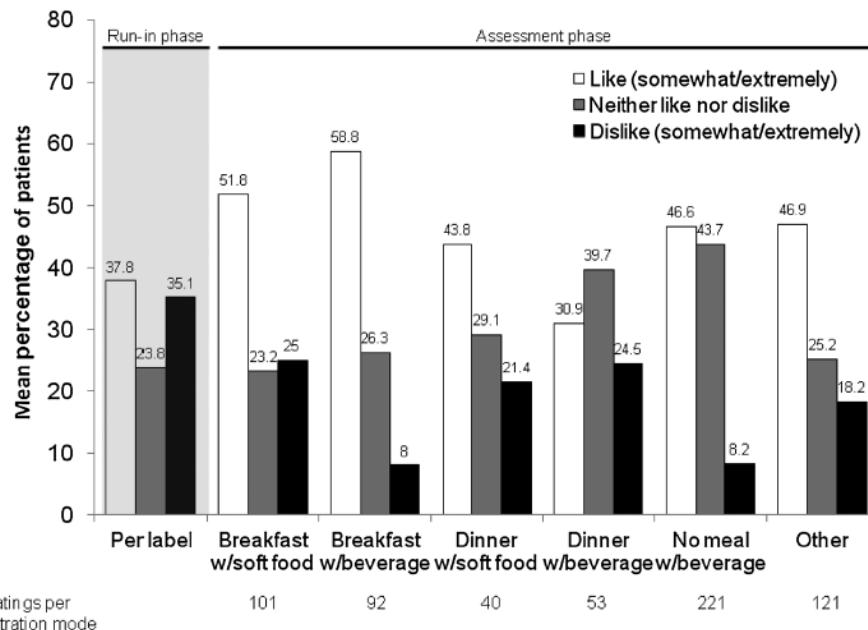
Tabelle 1. Zur Beurteilung der Eisenüberladung, von Organschäden und von Nebenwirkungen der Chelatbildner empfohlene Maßnahmen (N = notwendige Verfahren, E = im Einzelfall nützlich).

<u>Chelatbildnertoxizität</u>						
Deferipron	Diff.-Blutbild wöchentlich*	N	Deferasirox	Krea mtl.		N
	Zink i.S. (nüchtern) jährl.	N		im 1. Monat u. bei Dosissteigerung wöchentl. Kontrolle		
				Cystatin C mtl.		N
Deferoxamin	Ophthalm. Untersuchung jährl.	N		Kreatinin-Clearance jährl. (ab 6 Jahre.)		N
	Audiometrie jährl.	N		ALT, AST, GGT, AP, Bili mtl.		N
	Kreatinin-Clearance jährl. (ab 6 Jahre.)	N		im 1. Monat u. bei Dosissteigerung		
	Cystatin C 3- mtl.	N		2-wöchentl. Kontrolle		
				Kalzium, Phosphat i.S., 3- mtl.		N
				Urin-Stix (Proteinurie?) mtl.		N
				Ophthalm. Untersuchung jährl.		N
				Audiometrie jährl.		N

*Empfehlung des Herstellers

Eiseneliminationstherapie Deferasirox

Goldberg SL et al. The Palatability and Tolerability of Deferasirox Taken With Different Beverages or Foods. *Pediatr Blood Cancer* 2013



Ferritin:

Stabil bei 18 – 60 jährigen
Rückl. Trend in anderen Altersgruppen

Pharmakokinetik:

Dosis 20/kg/d: Anstieg um 84% (41-239)

Dosis 30/kg/d: Anstieg um 19% (-30 - 80)

TABLE II. Gastrointestinal Adverse Events (AEs) During the Run-In and Assessment Phases*

AE system organ class n (%)	Run-in phase n=62	First 4 weeks of	Overall assessment phase n=62
		assessment phase n=62	
Gastrointestinal disorders	23 (37)	12 (19)	20 (32)
Abdominal pain	6 (10)	2 (3)	5 (8)
Upper abdominal pain	2 (3)	3 (5)	6 (10)
Diarrhea	15 (24)	4 (7)	7 (11)
Nausea	9 (15)	3 (5)	7 (11)

Eiseneliminationstherapie Deferasirox

Chang HH et al. Improved Efficacy and Tolerability of Oral Deferasirox by Twice-Daily Dosing for Patients With Transfusion-Dependent β-Thalassemia. *Pediatr. Blood Cancer* 2011

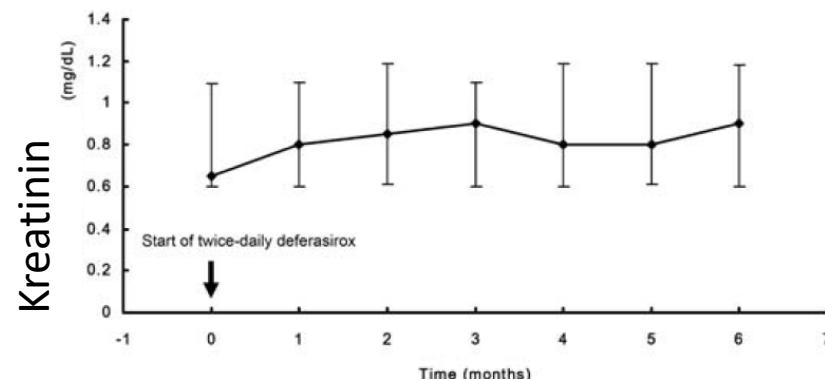
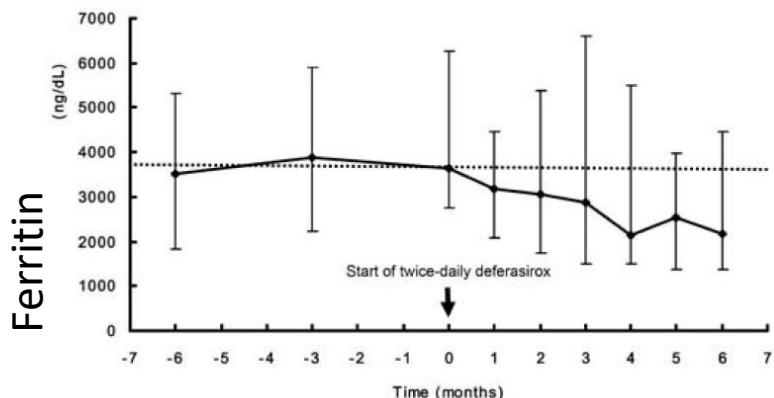
Bessere Verträglichkeit

TABLE II. Demographic Data and Outcomes for the Seven Patients Who Received Twice-Daily Deferasirox Due To Intolerance to Previous Once-Daily Deferasirox

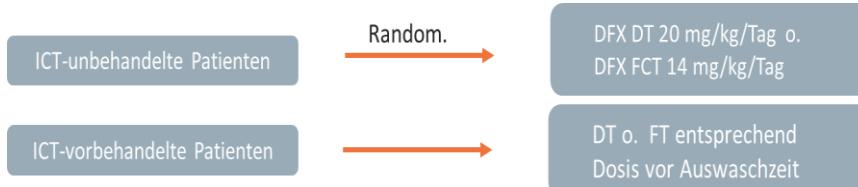
Subject no.	Gender	Age (years)	Hepatitis B	Hepatitis C	DM	Adverse events (AEs)	Severity of AEs	Dosage (mg/kg/day)	Outcomes	Total duration (months) ^a	Serum ferritin levels (ng/dL) ^b
1	Male	24	No	No	No	Arthralgia	Grade 2	15	Disappeared after twice-daily deferasirox for 1 month	8	1,357–1,769
2	Female	28	No	Yes	Yes	Arthralgia	Grade 2	30	Improved to Grade 1 after twice-daily deferasirox for 2 months	3	566–488
3	Male	24	No	No	No	Elevated liver enzyme levels	Grade 1	25	Returned to normal after twice-daily deferasirox for 1 month	3	1,104–575
4	Male	25	No	Yes	No	Elevated liver enzyme levels	Grade 1	40	Returned to normal after twice-daily deferasirox for 3 months	3	6,246–3,988
5	Female	32	No	Yes	No	Gastrointestinal pain (GI upset)	Grade 2	30	Disappeared after twice-daily deferasirox for 1 month	5	5,860–6,016
6	Male	28	Yes	No	No	Elevated liver enzyme levels	Grade 2	40	Not improved	3	4,318–2,766
7	Female	18	No	No	No	Pancreatitis (only elevated serum amylase levels)	Grade 2	20	Not improved	5	864–816

DM, diabetes mellitus. ^aTotal duration of twice-daily deferasirox at the time of analysis; ^bSerum ferritin levels at baseline and the time of analysis.

Bessere Wirksamkeit



Eiseneliminationstherapie Deferasirox



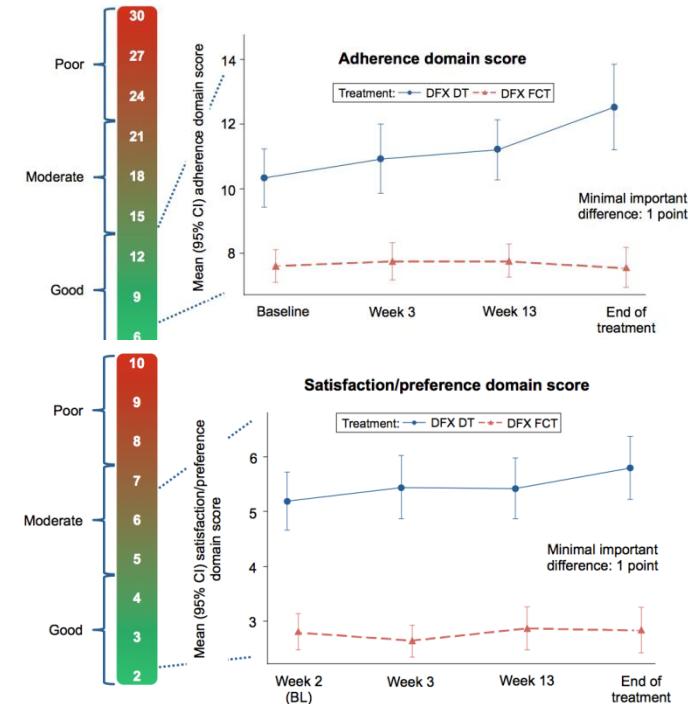
	DFX-DT (n = 86)	DFX – FCT (n = 87)
Serumferritin (SF) bei Start [ng/mL]	2485 (915–8250)	2983 (939–8250)
Absolute ΔSF n. 24 Wo. [ng/mL][Median]	-85,5 (-2146 - 8250)	-350 (-4440 - 3572)
Relative ΔSF n. 24 Wo. [ng/mL]	-4,1%	-14,0%

Table 3. Most Common Adverse Events (>10% in Any Group)

AE	Deferasirox DT (N=86)		Deferasirox FCT (N=87)	
	All AEs n (%)	Severe AEs n (%)	All AEs n (%)	Severe AEs n (%)
Total	77 (90)	22 (26)	78 (90)	17 (20)
Diarrhea	30 (35)	6 (7)	29 (33)	1 (1)
Nausea	23 (27)	2 (2)	24 (28)	1 (1)
Abdominal pain	23 (27)	4 (5)	23 (26)	2 (2)
Increased UPCR	11 (13)	2 (2)	18 (21)	0 (0)
Vomiting	19 (22)	1 (1)	15 (17)	0 (0)
Abdominal pain upper	6 (7)	1 (1)	10 (11)	0 (0)
Constipation	13 (15)	2 (2)	7 (8)	0 (0)
Headache	12 (14)	2 (2)	5 (6)	0 (0)

Taher A, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomized, phase II ECLIPSE study. Am J Hematol 2017; 92(5):420-428.

Adhärenz, Zufriedenheit, Präferenz



AES: $n_{DT} = n_{FCT}$

SAEs: $n_{DT} > n_{FCT}$

GI-SAEs: $n_{DT} > n_{FCT}$

renalAES: $n_{DT} = n_{FCT}$

Eiseneliminationstherapie Deferasirox

- Vergleichbares Sicherheitsprofil für die DFX- FCT und DFX – DT
- Übereinstimmung mit dem bekannten DFX Profil
- Weniger GI-SAEs unter der DFX-FCT
- Patienten mit FCT
 - hatten eine bessere Adhärenz
 - führten die Behandlung länger fort
 - erzielten eine größere SF-Reduktion

☞ Potentiell effektivere Behandlung der Eisenüberladung

Eiseneliminationstherapie Deferipron

Long-term safety of deferiprone treatment in children from the Mediterranean region with beta-thalassemia major: the DEEP-3 multi-center observational safety study

Botzenhart S, et al. Haematologica 2018; 103:e1

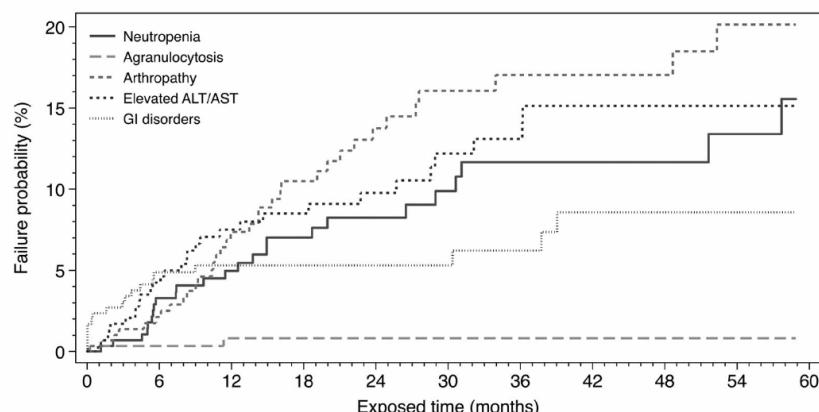
Patients	297 (100.0)
Age (years)	8.5 (4.0-12.2)
< 6 years	112 (37.7)
6-10 years	66 (22.2)
> 10 years	119 (40.1)
at diagnosis of β-TM	0.8 (0.4-1.2)
at start of transfusion therapy	0.7 (0.5-1.2)
at start of chelation therapy	2.8 (2.0-4.5)
Transfusional iron intake	293 (100.0)
Low (< 0.3 mg/kg/day)	46 (15.7)
Intermediate (0.3-0.5 mg/kg/day)	197 (67.2)
High (> 0.5 mg/kg/day)	50 (17.1)
Annual blood requirement (mL pure RBC/kg/year)	125 (117-156)
Spleen status	289 (100.0)
Normal	51 (17.7)
Splenomegaly	168 (58.1)
Splenectomized	70 (24.2)
Serum ferritin	268 (100.0)
< 2,000 ng/mL (n, %)	143 (53.4)
2,000-4,000 ng/mL (n, %)	93 (34.7)
> 4,000 ng/mL (n, %)	32 (11.9)

Median (interquartile range)

Median age at start of DFP 8.5 yrs. (0.6-17.6)

Table 2. Identified adverse drug reactions (ADR) to deferiprone (DFP).

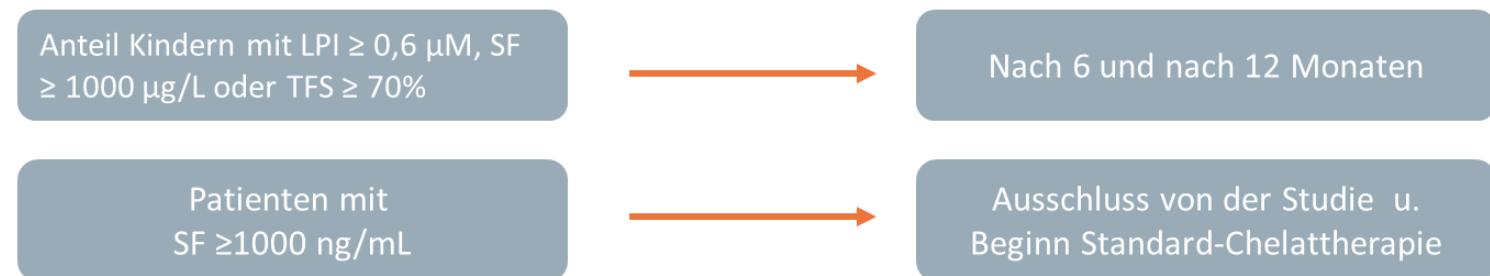
MedDRA SOC / Preferred Term	ADRs / Patients	Severity mild / moderate / severe	Seriousness non-serious / serious	Incidence ^a (95% CI)
Blood and lymphatic system disorders				
Agranulocytosis	2/2	0/2/0	0/2	0.7 (0.1-2.4)
Leukopenia	3/2	3/0/0	3/0	0.7 (0.1-2.4)
Neutropenia	38/25	26/12/0	0/38	8.4 (5.5-12.2)
Thrombocytopenia	1/1	1/0/0	0/1	0.3 (0.0-1.9)
Gastrointestinal disorders				
Abdominal pain	9/8	6/3/0	9/0	2.7 (1.2-5.2)
Diarrhea	1/1	1/0/0	1/0	0.3 (0.0-1.9)
Dyspepsia	4/4	4/0/0	4/0	1.3 (0.4-3.4)
Nausea	3/3	1/2/0	3/0	1.0 (0.2-2.9)
Salivary hypersecretion	1/1	1/0/0	1/0	0.3 (0.0-1.9)
Vomiting	14/10	3/11/0	14/0	3.4 (1.6-6.1)
Musculoskeletal and connective tissue disorders				
Arthropathy	43/35	10/30/3	41/2	11.8 (8.3-16.0)
Bone pain	5/5	2/3/0	5/0	1.7 (0.5-3.9)



Eiseneliminationstherapie Deferipron

Elalfy MS, et al. A Randomized Trial on the Safety and Efficacy of Early Start of Iron Chelation Therapy with Deferiprone in Newly Diagnosed Children with Transfusion Dependent Thalassemia. ASH 2016, #1286

- 64 Kinder mit Thal. major
- 3-4 –wöchl. Bluttransfusionen, Rekrutierung nach ~ 2-3 Transfusionen
- Start Transfusionen i.A. von 8.1 ± 1.7 Mo.
- Serumferritin (SF ≤ 400 µg/L) o. Transferrin-Sättigung (TFS) $\leq 70\%$ o. LPI ≤ 0.2 µM)
- 1:1 Randomisierung in Deferipron (DFP)-Behandlung von 50 mg/kg/Tag vs. keine Chelierung (NC)



Nebenwirkungen	DFP	NC
Durchfall	19%	13%
Erbrechen	13%	13%
Koliken	13%	13%
Erhöhte Leberwerte	6%	3%
Neutropenie (GNZ 1,000-1,500/µL)	6%	6%

Eiseneliminationstherapie Deferipron

Elalfy MS, et al. A Randomized Trial on the Safety and Efficacy of Early Start of Iron Chelation Therapy with Deferiprone in Newly Diagnosed Children with Transfusion Dependent Thalassemia. ASH 2016, #1286

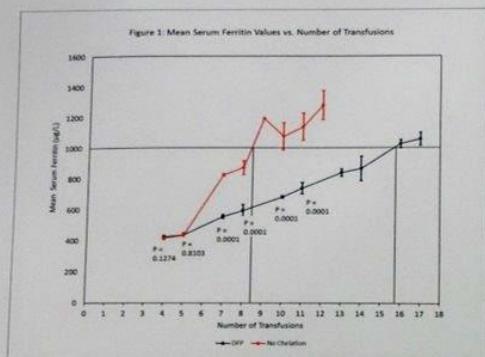


Figure 1: Mean serum ferritin values vs. number of transfusions for patients on sub-therapeutic doses of DFP therapy vs NC

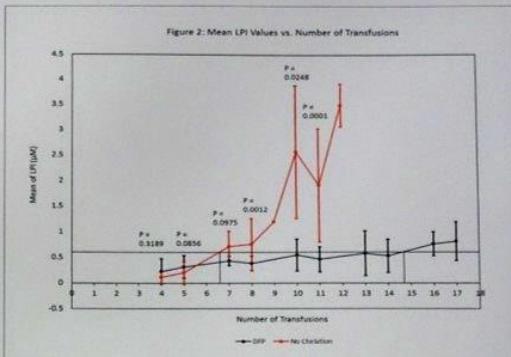


Figure 2: Mean LPI values vs number of transfusions for patients on sub-therapeutic doses of DFP therapy vs NC

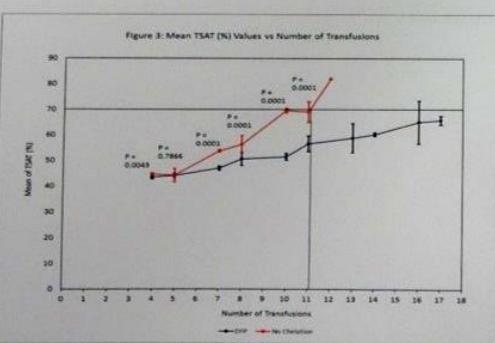


Figure 3: Mean TSAT (%) values vs. number of transfusions for patients on sub-therapeutic doses of DFP therapy vs NC

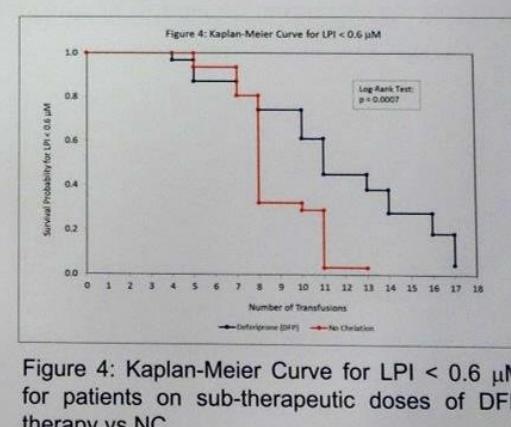


Figure 4: Kaplan-Meier Curve for LPI < 0.6 μ M for patients on sub-therapeutic doses of DFP therapy vs NC

	DFP-Pat.	NC-Pat.
LPI $\geq 0,6 \mu$ M	n. ≥ 10 Tx	n. ≥ 5 Tx
TFS $\geq 70\%$	n. ≥ 17 Tx	n. ≥ 10 Tx
SF ≥ 1000 ng/l	n. ≥ 16 Tx	n. ≥ 8.5 Tx

↳ DFP in subtherapeutic Dosis über durchschnittlich 10 Monate

- bei Kindern mit einer TM und leichten Eisenüberladung gut verträglich
- führen zu einer signifikanten Reduktion der Eisenbeladung

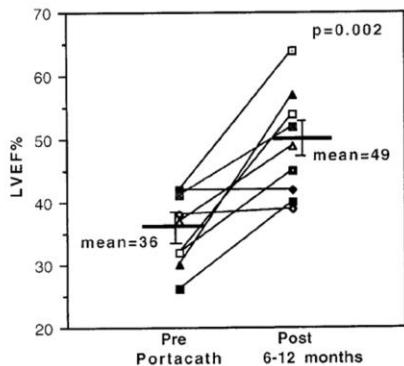
Intensivierte Chelattherapie

iv.± HD - DFO & Kombi-Therapie

Davis B and Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk β -thalassemia. Blood 2000; 95: 1229-1236

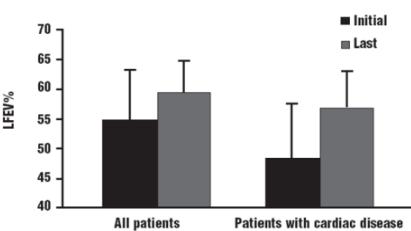
24h DFO iv.
Standard dose:
25-60(80)mg/kg/d

→ Improvement of cardiac function



Origa R, et al. Combined therapy with deferiprone and desferrioxamine in thalassemia major. Haematologica 2005; 90: 1309-14

→ Improvement of cardiac function

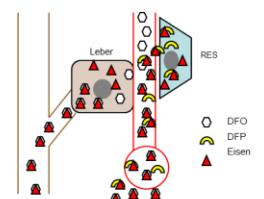


n=64; age: 12-35 J.

DFO 40mg/kg 10-24h 2-6d/wk. + DFP 70-80mg/kg/d
for 12-57 mo. (mean 31±11) (64 pts. 1 Jahr, 45 pts. 2 yrs.)



Grady RW, et al. Optimizing chelation therapy: combining deferiprone and desferrioxamine. Blood 1999; 96: 604a



The „Shuttle“- Effekt !?

→ Combination of deferoxamine und deferiprone

Simultaneous treatment



Sequential treatment



Alternating treatment



Farmaki K, et al. Effect of enhanced iron chelation therapy on glucose metabolism in patients with beta-thalassaemia major. Br J Haematol 2006; 134: 438-44

→ Improvement of glucose tolerance

	OGTT	Before treatment	After treatment
normal		21	28
IGT		15	9
Diabetes mellitus		6	4
total		42	41
normal → pathol.			2
pathol. → normal			12

n= 42; age: 8-42 J.

DFP 75-90mg/kg/d 7d + DFO 20-40mg/kg/d 8-12h 2-6d/wk.



Intensivierte Chelattherapie

Kombinationstherapien

Vlachodimitropoulou E, et al. *BJH* 2015

Synergistic intracellular iron chelation combinations: mechanisms and conditions for optimizing iron mobilization.

(HuH-7 cells)

Chelator	(%) Eisen-entfernung	Chelator	(%) Eisen-entfernung	Chelator	(%) Eisen-entfernung
DFO 10µM	30,7	DFX 10µM	25,6	DFP 10µM	27,5
DFO 10µM+ DFX 5µM	38,2	DFX 10µM+ DFO 5µM	36,9	DFP 10µM+ DFO 5µM	38,3
DFO 10µM+ DFP 5µM	39,3	DFX 10 µM+ DFP 5µM	41,7	DFP 10µM+ DFX 5µM	43,2

Eisenentfernung in % nach 8 Stunden.

bei Kombi DFP/DFO 49% des Effekts = Synergie, 51% additiv

bei Kombi DFP/DFX 59% des Effekts = Synergie, 41% additiv

Intensivierte Chelattherapie

Grady RW et al. Toward optimizing the use of deferasirox: potential benefits of combined use with deferoxamine. *Haematologica* 2013

Kombinationstherapien

1 Wo. DSX 30 mg/kg/d p.o. Mono

1 Wo. DFO 40 mg/kg/d s.c. Mono.

1 Wo. DSX + DFO Kombi

- Fixe low-iron Diät (11-15mg/d)
- Je 1 EK d 1, 11,21,31
- Quantitative Eisenbestimmung (AAS) in
 - Nahrung
 - Stuhl
 - Urin

Table 5. Iron balance (%) related to the frequency of drug administration.

DFO	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	125	107	89	71	53
Patient 2	219	188	157	125	94
Patient 3	143	122	102	82	61
Patient 4	125	107	89	71	54
Patient 5	221	189	158	126	95
Patient 6	171	147	122	98	73

DFX	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	61	53	44	35	26
Patient 2	129	111	92	74	55
Patient 3	45	39	32	26	19
Patient 4	29	24	20	16	12
Patient 5	66	56	47	38	28
Patient 6	102	87	73	58	44

SUM ¹	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	186	160	133	106	79
Patient 2	348	299	249	199	149
Patient 3	188	161	134	108	80
Patient 4	154	131	109	87	66
Patient 5	287	245	205	164	123
Patient 6	273	234	195	156	117

COM ²	7 Days	6 Days	5 Days	4 Days	3 Days	COM/ SUM ¹
Patient 1	251	215	180	144	108	135
Patient 2	268	229	191	153	115	77
Patient 3	206	177	147	118	88	110
Patient 4	241	207	172	138	103	156
Patient 5	270	232	193	154	116	94
Patient 6	267	229	191	153	115	98

Intensivierte Chelattherapie

Kombinationstherapien

Vlachodimitropoulou E, et al. *BJH* 2015

Synergistic intracellular iron chelation combinations: mechanisms and conditions for optimizing iron mobilization.

(HuH-7 cells)

Chelator	(%) Eisen-entfernung	Chelator	(%) Eisen-entfernung	Chelator	(%) Eisen-entfernung
DFO 10µM	30,7	DFX 10µM	25,6	DFP 10µM	27,5
DFO 10µM+ DFX 5µM	38,2	DFX 10µM+ DFO 5µM	36,9	DFP 10µM+ DFO 5µM	38,3
DFO 10µM+ DFP 5µM	39,3	DFX 10 µM+ DFP 5µM	41,7	DFP 10µM+ DFX 5µM	43,2

Eisenentfernung in % nach 8 Stunden.

bei Kombi DFP/DFO 49% des Effekts = Synergie, 51% additiv

bei Kombi DFP/DFX 59% des Effekts = Synergie, 41% additiv

Deferipron (DFP) + Deferasirox (DFX)

vs.

Deferipron (DFP) + Deferoxamin (DFO)

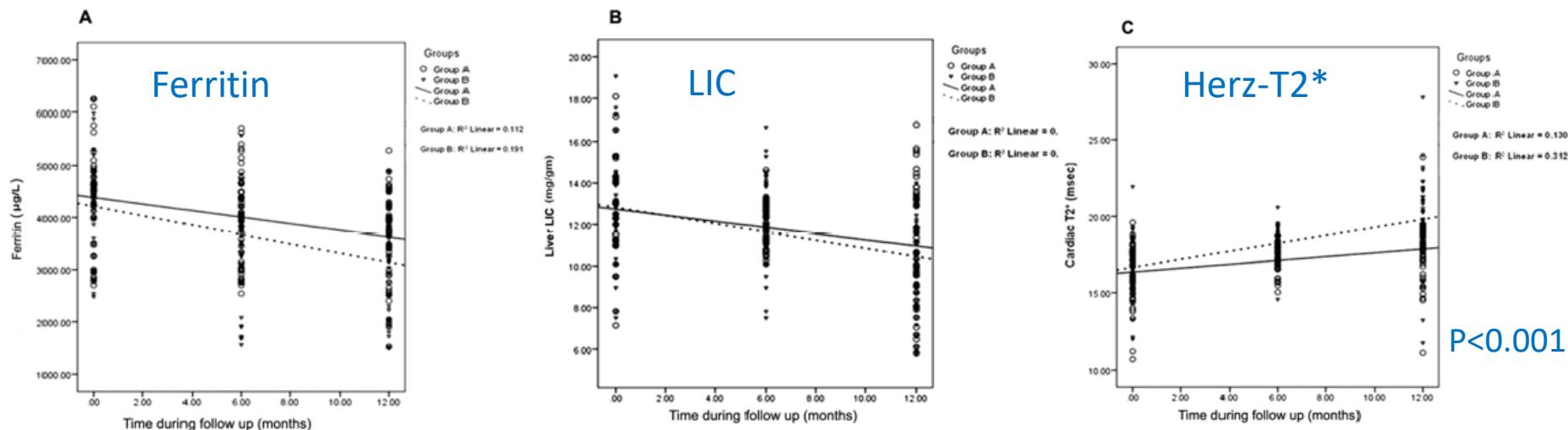
Nebenwirkungen n(%)	DFP + DFO	DFP + DFX
Agranulozytose	-	-
Neutropenie	3 (6,2)	5 (10,4)
Arthralgien	9 (18,7)	8 (16,6)
Gastrointestinale Probleme	10 (20,8)	6 (12,5)
ALT (Anstieg \geq 3 fach)	3 (6,25)	4 (8,33)
S-Kreatinin (\geq 33%) > Bl	1 (2,08)	3 (6,2)
Hautausschlag	-	2 (4,16)

Gruppe A (n=48):
Add. DFO s.c.
40 mg/kg/d Start 22.00h



Gruppe B (n=48):
Add. DSX p.o.
20 mg/kg/d um 22.00h

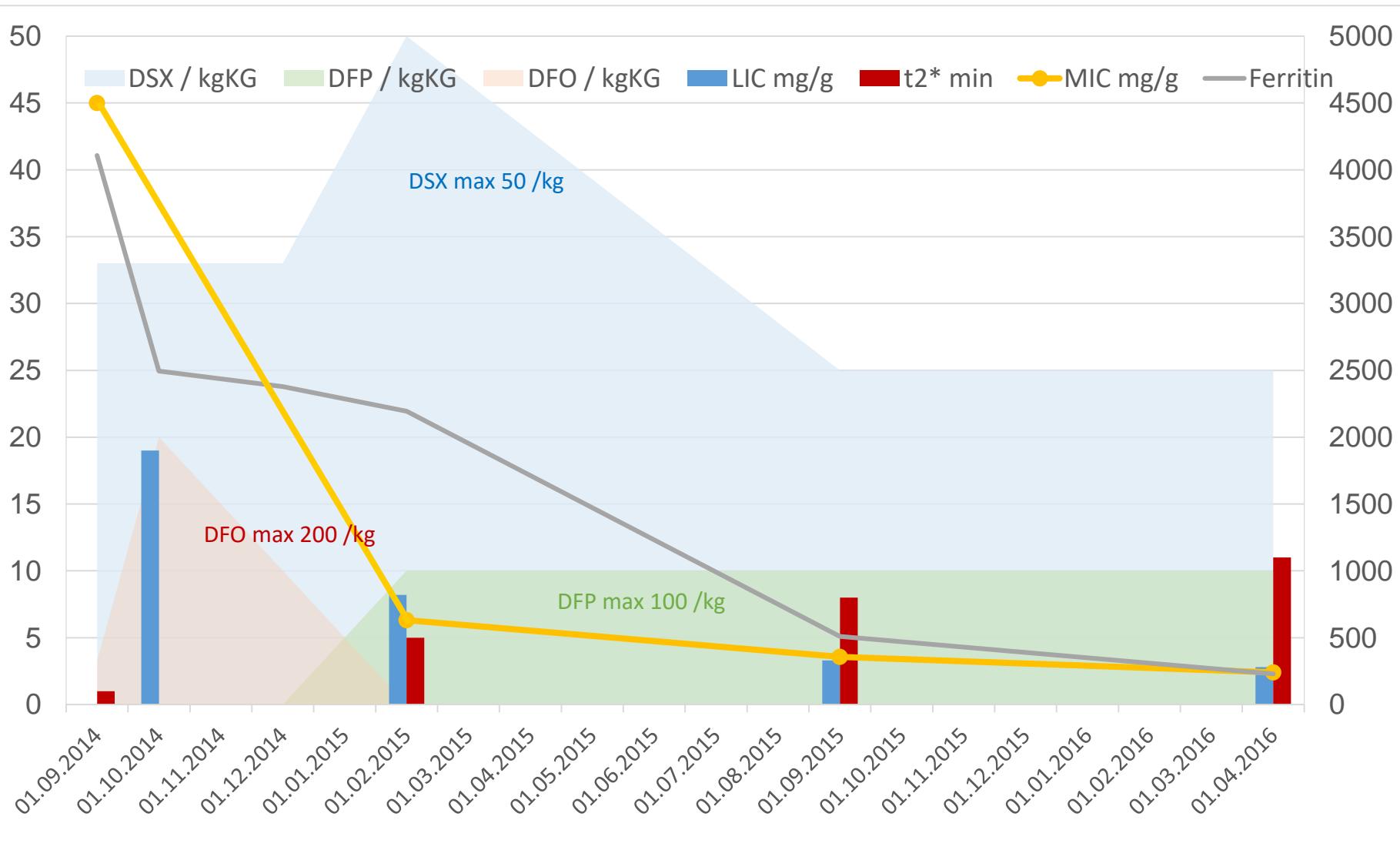
DFP 75 mg/kg/Tag, oral, geteilt in Dosen, Einnahme 8.00 und 15.00



Fallbeispiel

w., geb. 5/1980, TM

Stand 5/2016



Eiseneliminationstherapie + Amlodipin ?

Fernandes JL, et al. A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major. Blood 2016;128(12):1555-1561

Amlodipin (5 mg/d bei KG > 30 kg o. 2.5 mg/d bei KG <30kg) für 12 Monate

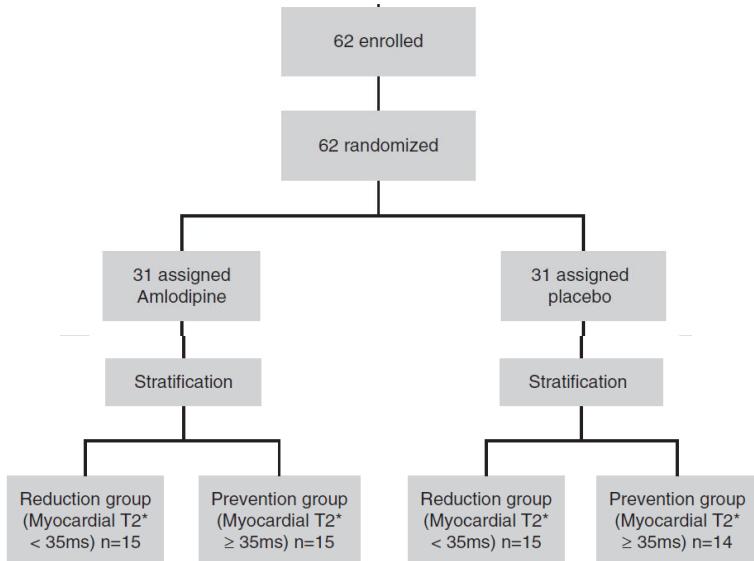


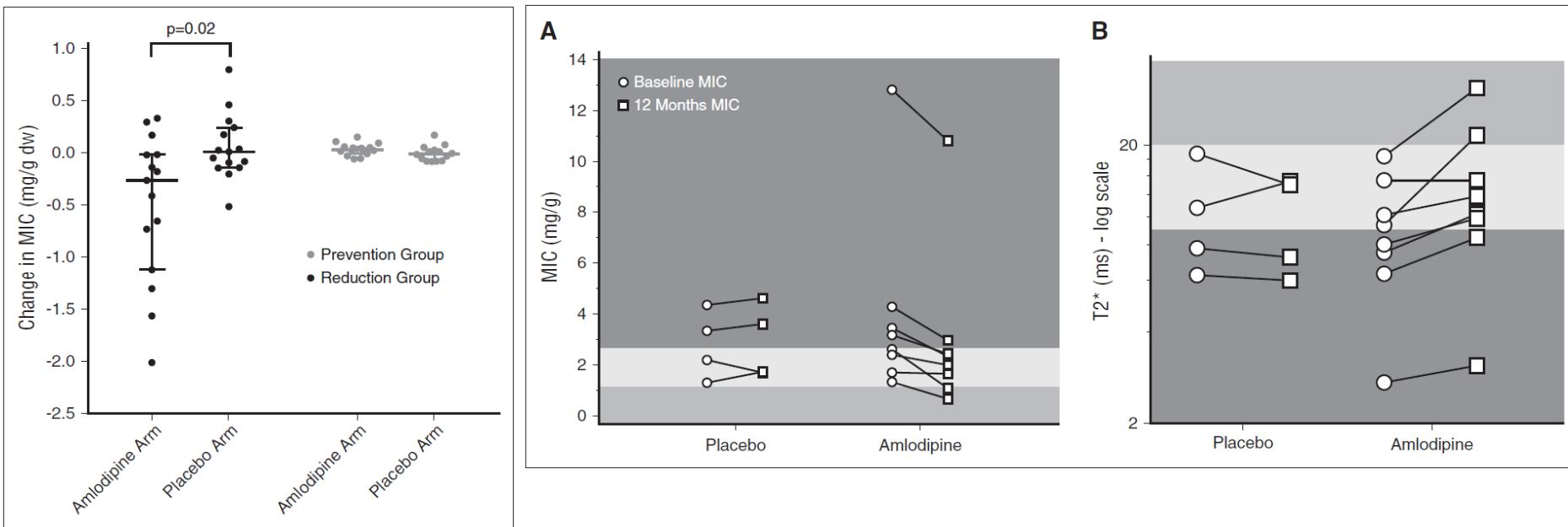
Table 1. Baseline characteristics of patients

Characteristic	Amlodipine (n = 30)	Placebo (n = 29)
Sex, n (%)		
Female	17 (57)	12 (41)
Age, y (range)	23.3 ± 7.7 (12-38)	23.5 ± 10.2 (8-49)
Chelation therapy at baseline, n (%)		
DFO	3 (10)	4 (14)
DFP	5 (16)	6 (21)
DFX	17 (57)	13 (45)
DFO + DFP	5 (16)	5 (17)
DFO + DFX	0	1 (3)
Serum ferritin, ng/mL (median [range])	2638 (478-7282)	1922 (386-13 113)
Myocardial T2*, ms (median [range])	34.1 (2.8-43.8)	34.1 (6.8-42.7)
Myocardial iron concentration, mg/g dry weight (median [range])	0.61 (0.45-12.81)	0.61 (0.46-4.34)
Left ventricular ejection fraction, %	67.7 ± 5.5	67.1 ± 6.6
Myocardial T2* categories, n (%)		
<10 ms	4 (13)	2 (7)
10 to ≤20 ms	4 (13)	2 (7)
20 to <35 ms	7 (23)	11 (38)
≤35 ms	15 (50)	14 (48)
LIC, mg/g, median (range)	11.3 (1.9-40.0)	9.2 (1.5-33.3)
LIC categories, n (%)		
<7 mg/g	10 (33)	12 (42)
7 to ≤15 mg/g	8 (27)	9 (31)
>15 mg/g	12 (40)	8 (28)

Eiseneliminationstherapie + Amlodipin ?

Fernandes JL, et al. A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major. Blood 2016;128(12):1555-1561

Amlodipin (5 mg/d bei KG > 30 kg o. 2.5 mg/d bei KG <30kg) für 12 Monate



- ↳ Keine SAE unter Amlodipine
- ↳ Bei TM-Patienten with kardialer Siderose, führt die Kombination der Chelattherapie mit Amlodipin zu einer effektiveren Reduktion der myokardialen Eisenkonzentration

- solide Basis für Patienten-bezogene, effektive, sichere Chelattherapie
- dennoch Neuerkrankungen durch sekundäre Hämochromatose
 - stetige Überprüfung der Ziele, Indikationen und Strategien
- Fokus auf Compliance- Sicherung
- Strategien zur Vermeidung / Reduktion von Nebenwirkungen
- sorgfältiges Monitoring hinsichtlich Folgen der Eisenüberladung
- sorgfältiges Monitoring hinsichtlich Folgen der Chelattherapie
- sinnvolle Nutzung aller Medikamente einzeln u. kombiniert → Steigerung von Effektivität u./o. Reduktion von Nebenwirkungen
- Anpassung an subjektive (Verträglichkeit, Einfachheit) und objektive (spezifische Situation der Eisenüberladung) Bedürfnisse

Vielen Dank für Ihre Aufmerksamkeit !



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