The Well-Transplant Visit: Management of Post Transplant Anemia

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Conflict of Interest

Advisor/consultant for:

Amgen, Affymax, AMAG, Astellas, Fibrogen, Fresenius, Sandoz/Hexal

Clinical Encounter

- Ms. K.T. is a 38-y/o Asian patient with ESRD due to IgAN, received preemptive kidney transplant from sister 2006
- Routine visit, no complaints other than recent onset of fatigue
- Removal of basal cell carcinoma from forehead 6 months ago
- Maintenance IS: steroid, sirolimus, MMF
- Physical: unremarkable; BP: 115/75 mmHg; HR: 80/min.
- Laboratory Results:
  - Creatinine: 1.4 mg/dL (CKD-EPI eGFR: 48 mL/min/1.73m^2; stable)
  - Hemoglobin: 10.8 mg/dL (was 12.3 mg/dL 4 months ago)
  - Sirolimus concentration: 9 ng/mL

Agenda

- Definition of anemia
- Epidemiology of anemia in KTR
- Pathogenesis of anemia in KTR
- Prognostic significance of anemia in KTR
- Treatment of anemia in KTR
- Does correction of anemia reduce risk in KTR?

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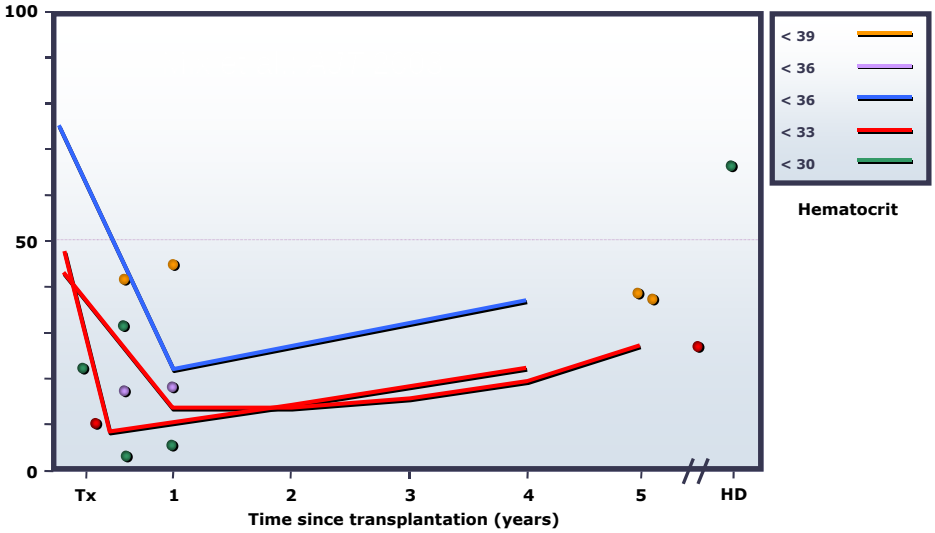
Definition of Anemia

	Hemoglobin
Women	< 12 g/dL
Men	< 13 g/dL

Unfortunately, no consistently-used definition in the KT literature…

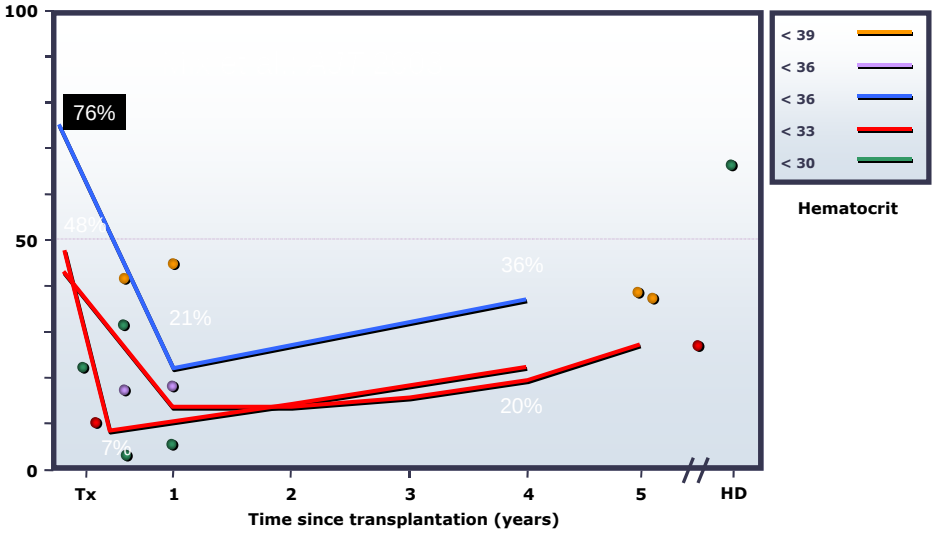
World Health Organization 1968
American Society of Transplantation 2000

Prevalence of Anemia in KTR over Time



G. Sunder-Plassmann; GfN Meeting 2005

Prevalence of Anemia in KTR over Time



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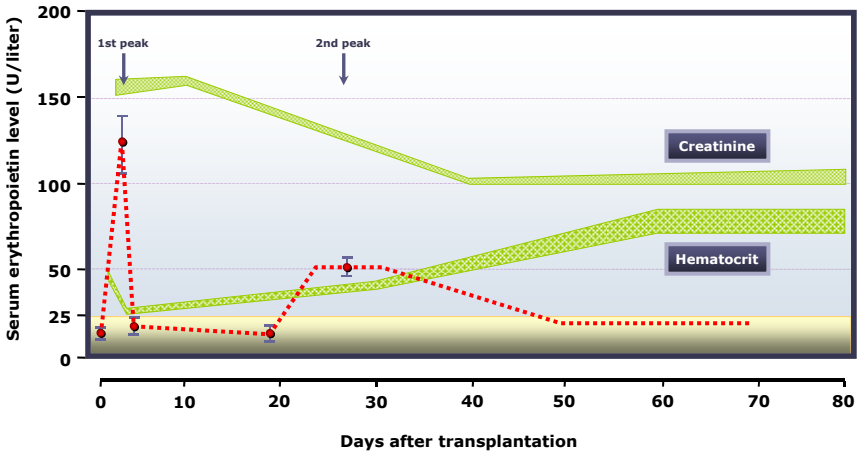
Erythropoietin Production after Kidney Transplantation



Sun et al., NEJM 1989

Anemia, Iron Status, Assessment and Treatment by Stage of CKD

	Stage 2 N=103	Stage 3 N=274	Stage 4 N=66	Stage 5 N=6
Mean Hgb (g/dL)	14.0	13.2	11.8	11.7
Hgb <11 g/dL (%)	3	7	27	33
Hgb <11 g/dL and on EPO (%)	0	22	33	50
TSAT <20% (%)	35	42	32	25
Ferritin <100 ng/mL (%)	19	54	38	50

Karthikeyan et al., AJT 2003

Causes and Correlates of Anemia after Kidney Transplantation

- Age
- Donor age
- Gender
- Graft Dysfunction
  - Acute rejection
  - CAN
- Blood loss
  - Acute
  - Chronic
- Iron deficiency
  - Absolute
  - Functional
- Infection
- Inflammation
- Malignancy
- Medications
  - RAAS inhibitors
  - Immunosuppressants
    - Mycophenolate
    - Azathioprine
    - Tacrolimus
    - Sirolimus
  - Antivirals

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Anemia and Risk of CHF

Retrospective study of 638 KTR w/o cardiac disease at 1 year after transplantation.

Follow-up:	7.2 (1-28) years
De novo CHF:	n=63
De novo CAD:	n=61

Rigatto et al., JASN 2002

Anemia and Risk of CHF in KTR

	Incident CHF RR (95% CI)	Mortality RR (95% CI)
Age (10 yrs increase)	1.43 (1.16-1.77)	1.51 (1.31-1.73)
Diabetes	2.30 (1.43-3.69)	2.10 (1.52-2.92)
SBP (10 mmHg increase)	1.29 (1.10-1.50)	1.14 (1.03-1.27)
Deceased donor	3.18 (1.24-8.18)	2.04 (1.19-3.51)
Hb (1 g/dL decrease)	1.24 (1.10-1.39)	1.16 (1.07-1.26)

Rigatto et al., JASN 2002

Anemia, Iron Deficiency and the Risks of Allograft Loss and All-Cause Mortality

Prospective study of 438 KTR who had received their transplant 4.4 years prior.

Follow-up: 7.8 years
Renal allograft loss: n=208 (47.5%)
All cause mortality: n=129 (29.5%)

Winkelmayer et al., AJT 2004

Anemia, Iron Deficiency and the Risks of Allograft Loss and All-Cause Mortality

	Allograft Loss HR (95% CI)	Mortality HR (95% KI)
Hb (g/dL increase)	**0.94 (0.86-1.02)**	**1.01 (0.90-1.14)**
HRBC >10% (*vs.* <5%)	**1.26 (0.72-2.19)**	**2.06 (1.12-3.79)**
EPO Therapy	**1.55 (0.92-2.62)**	**1.93 (0.87-4.29)**
Iron Supplementation	**0.94 (0.54-1.65)**	**1.29 (0.61-2.69)**

Winkelmayer et al., AJT 2004

Anemia and the Risks of Allograft Loss and All-Cause Mortality

Data merge of two prospective cohort studies yielding 825 KTR overall.

Follow-up: 8.2 years
Anemia (WHO) 41%
Renal allograft loss: n= 401 (48.6%)
All cause mortality: n= 261 (30.4%)

Winkelmayer et al., NDT 2006

Anemia and the Risks of Allograft Loss and All-Cause Mortality

	Allograft Loss HR (95% KI)	Mortality HR (95% KI)
Anemia (multivariate)	**1.27 (1.02-1.59)**	**1.08 (0.80-1.45)**

Winkelmayer et al., NDT 2006

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EPO – Utilization in KTR

Several studies observed that the proportion of patients treated with EPO was low even in those with the greatest need:

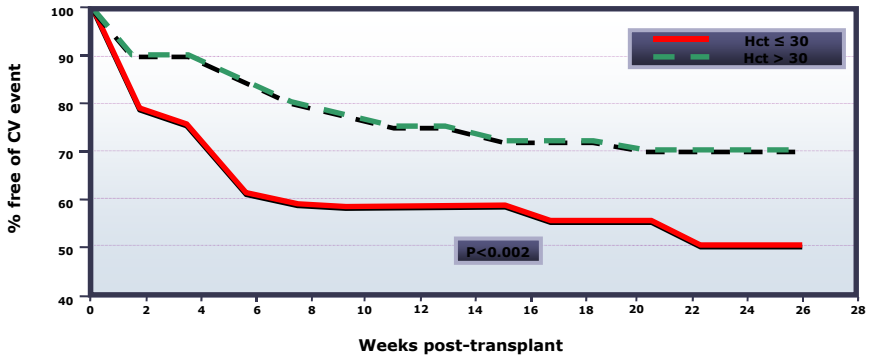
- In KTR with Hgb <11g/dL, 27% received EPO
  (Karthikeyan et al.; AJT 2003)
- In KTR with Hct <33%, ~25% received EPO
- In KTR with Hct <30%, ~40% received EPO
  (Mix et al.; AJT 2003)
- In KTR with Hct <30%, <42% received EPO
  (Winkelmayer et al.; JASN 2004)

Safety and Efficacy of EPO in KTR

- EPO therapy in HD patients immediately prior to kidney transplantation did not impair post transplant graft function
- Conflicting evidence on whether early initiation of EPO therapy yields higher Hct values in the first months after transplantation
- Anemia can be treated with EPO in the late post-transplant period, i.e. in KTR with advanced CAN
- Sample sizes too small to determine safety of EPO in KTR

Anemia, EPO Therapy and Early Cardiovascular Outcomes in KTR

Retrospective study of 404 KTR with type 1 diabetes
Follow-up over 6 months after transplantation



Djamali et al., Transplantation 2003

Anemia, EPO Therapy and Early Cardiovascular Outcomes in KTR

	RR (95% CI)
Hct > 30%	0.56 (0.33-0.91)
Iron deficiency	1.60 (1.21-2.14)
Hx of CVD	3.8 (3.1-5.3)
EPO-Therapy	n.s.

Djamali et al., Transplantation 2003

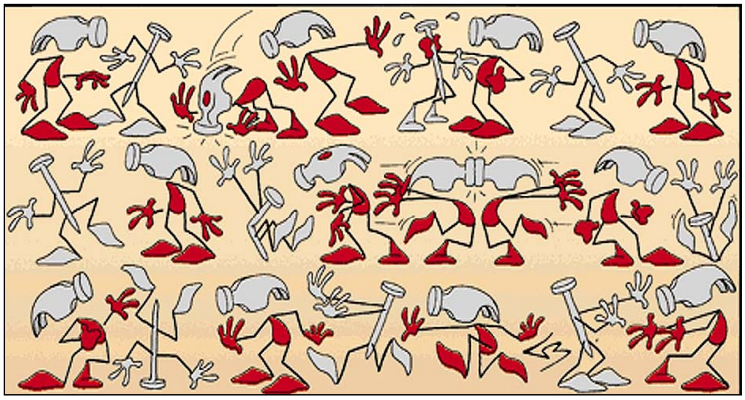
EPO Therapy and Renal Outcomes

- Retrospective study of 166 KTR
- Group 1 (n=109)
  Early EPO therapy (day 18-294) – no association with course of creatinine over time
- Group 2 (n=57)
  Late EPO therapy (from day 294) reduced progression of allograft function loss

Caveat: 22 patients in group 2 lost their allograft during follow-up and were excluded from analyses

Becker et al., NDT 2002

Critical Problem



Evidence from Randomized Trials?

Correction of Anemia
and Progression of Renal Insufficiency
in Transplanted patients
(CAPRIT trial)

Choukron and Martinez, Transplantation 2005

Summary

- Anemia is prevalent in KTR, especially in the late posttransplantation period
- EPO has been shown to be an effective treatment for anemia in KTR
- Anemia – a risk factor for adverse outcomes in KTR?
- Does treatment of anemia with EPO improve outcomes?
- Clearly, more research specifically in KTR is needed.
- For the time being, conservative treatment of anemia is warranted in KTR