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Mild chronic anemia following heart transplantation: a syndrome with prognostic relevance?

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Abstract The clinical relevance of mild chronic anemia in patients after heart transplantation (HTX) has not yet been demonstrated. Forty-five outpatients who had undergone HTX 2–99 months prior to investigation and who had not received blood transfusions or erythropoietin (EPO) before data acquisition were observed over a period of 37 months. Anemia was found in 36 of the 45 patients and was normocytic, normochromic, and slightly anisocytotic (coefficient of variation = 16 ± 2, normal 11.5–14.5). Anemic patients showed elevated EPO levels, whereas in nonanemic patients EPO levels were normal. Survival after HTX differed significantly in anemic and nonanemic patients ($P < 0.02$), with 100 % survival in the nonanemic and 85 % in the anemic group. Chronic anemia in patients after HTX shows a typical pattern. Even when mild, anemia in patients after HTX seems to be of prognostic value and thus might be an indicator of chronic disorders.

Key words Chronic anemia, heart transplantation, prognosis · Heart transplantation, chronic anemia

Introduction

Chronic anemia is reported to be frequent after solid organ transplantation and to be of multifactorial etiology [4, 6, 9, 11, 15, 18, 24]. The typical pattern of post-transplant anemia seems to depend entirely on the type of organ transplanted. In lung and heart-lung recipients [6, 15], erythropoietin (EPO) levels below normal have been observed. This may be due to cyclosporin A (CyA) nephrotoxicity [9] and has been regarded as a major cause of anemia in these patients. Several studies [24, 28] have indicated a relative EPO deficiency in renal transplant recipients who show elevated EPO levels. These findings suggest a kind of "EPO resistance" [24, 28] with a poor bone marrow (BM) response to elevated EPO levels and a disruption of the feedback

mechanism that is associated with an inadequate release of EPO, all of which are probably symptoms of chronic disorder [6, 15, 19, 26].

Iron deficiency has been reported to be an additional factor that contributes to the development of anemia in lung and kidney recipients [6, 18]. Other mechanisms in the pathogenesis of anemia after solid organ transplantation are thought to be azathioprine (Aza)-related [1, 11], caused by antibodies that lead to hemolysis [4, 15, 23], or due to parvovirus B_{19} infection [2, 25, 27].

In adult heart transplant recipients, chronic anemia has been described as less severe and less frequent than in kidney or lung transplant recipients [15], but its etiology and clinical relevance have not yet been established. We present a long-term follow-up study of 45 outpatients after HTX. The aim of the study was to report laboratory findings of anemic and nonanemic patients after HTX and to evaluate differences between the two patient groups with respect to morbidity and mortality in order to reveal a possible clinical relevance of mild chronic anemia in patients after HTX.

Materials and methods

Patient population

All of our outpatients (48 patients, 7 female, 41 male) who had undergone HTX at least 2 months prior to the beginning of the study (November 1994) were evaluated. Median age was 54 years (range 16–66 years), and the median time after HTX was 33 months (range 2–98 months) at the beginning of the study. Thirty of the patients had undergone transplantation for dilated cardiomyopathy, 14 for coronary artery disease, 2 for heart failure following valve replacement, 1 for fibroelastosis of the endocardium, and 1 for toxic heart failure after chemotherapy for a non-Hodgkin's lymphoma.

Surgery of evidence of other blood loss within the sampling period, known malignoma, and a known disease of the hematopoietic system were taken as exclusion criteria, and three patients were consequently excluded from the statistical analysis, the first because β thalassemia, the second due to pernicious anemia, and the third due to chronic blood loss with severe iron deficiency due to hypermenorrhea. The remaining 45 patients were analyzed. Two of these patients were known to have cold agglutinins, but there was no sign of any clinical relevance. During the time of probe sampling and in the last 3 weeks before that period, neither blood cell transfusions (BT) nor EPO was given to any of the patients.

None of the patients was on hemodialysis at that time. Acute rejection (ISHLT grade above 2) did not occur in our group during the period of data acquisition. A screening for parvovirus B_{19} IgM antibodies was negative in all patients. By the end of December 1997, 39 (86.6%) of the 45 patients included in the analysis and all 3 of the patients excluded were alive and well.

Data acquisition, definition of anemia

The laboratory data were obtained over a period of 3–5 months. During this time, four to six blood samples were taken of every patient. In one patient who died 3 months after the beginning of the study, only three samples could be obtained.

Normal hemoglobin values in our laboratory range from 14 to 18 g/dl in men and from 12 to 16 g/dl in women. Thus, anemia was defined as hemoglobin below 14 g/dl whole blood in men and below 12 g/dl in women, which is in accordance with Harrison's Principles of Internal Medicine [12]. Blood samples were generally taken between 8 : 00 and 9 : 00 a.m. [22].

Therapeutic regimen

Patients were on immunosuppressive triple-drug therapy with CyA (Sandimmun Neoral, Sandoz), Aza (Imurek, Wellcome), and prednisolone (Pred; Aprednislon, Merck). The CyA dosage was adjusted monthly after measuring whole blood trough levels with a target value of 200–250 ng/ml during the first 6 months, 180–220 ng/ml during the following 6 months, and 100–180 ng/ml after the 1st postoperative year. The dosage of Aza was adjusted in order to keep the white blood cell (WBC) counts between 4000 and 6000 per mm^3; in patients with persistent WBC counts below 4000, Aza was discontinued. Pred was given at a dosage of 15 mg daily during the first 6 months after HTX and was reduced to 7.5 mg daily within 1 year.

Acute rejection grade 1 A was not treated; in the case of acute rejection ISHLT grade 1 B or 2, 1 g of methylprednisolone (Solumedrol, Pharmacia & Upjohn) was given daily for 3 days as rejection therapy. Mean CyA trough levels and mean daily Aza of the patients are presented in Table 1.

As an additional therapy, all patients had an H_2-blocker (ranitidin or famotidin) and most were on diuretics (furosemide, 20–80 mg daily), antihypertensive drugs (alpha blockers and/or calcium antagonists or alpha/beta blocker), a thrombocyte aggregation inhibitor (acetylsalicylic acid in combination with dipyridamole) and allopurinol or benzbromaron as therapy for elevated uric acid. No ACE inhibitors were used in this patient group [11].

Laboratory investigations

Red and white blood cell counts and hemoglobin concentrations were measured with an automatic cell counter (Coulter-Counter, Coulter). Serum electrolytes, serum iron, and creatinine levels were obtained with the routinely used nonselective analyzer (SMAC-3, Technicon). Ferritin, vitamin B_{12}, and folate serum levels were measured with immunoassay methods on a standard analyzer (Stratus II, Baxter) and transferrin levels by immunonephelometry (Nephelometer, Behring).

Serum concentrations of EPO were analyzed with a radioimmunoassay (Incstar, Stillwater) using a goat anti-EPO polyclonal antibody. In our laboratory the sensitivity of the assay is 4 mU/ml. The levels of the immunoreactive EPO correlate with the levels of biologically active EPO measured with the polycythemic mouse bioassay. EPO concentrations of 50 healthy volunteers between 21 and 60 years of age served as normal controls.

CyA trough levels were measured from whole blood taken exactly 12 h after evening administration and immediately before morning administration (trough levels) by the HPLC method. The normal ranges of parameters are presented in Table 1.

Statistical analysis

In order to minimize the effects of daily variations and to obtain representative values over the period of data acquisition, mean

Table 1 Characteristics and laboratory findings of nonanemic and anemic patients after heart transplantation (HTX). Values are presented as medians (25th percentile/75th percentile)

	Normal range	Group 1 Nonanemic	Group 2 Anemic	P-value
No. of patients (females)		9 (4)	36 (3)	
Age (years)		50 (40.5/55.5)	55 (49.7/61.7)	NS
Months after HTX		58 (27/79)	29.5 (7.25/66.5)	NS
Serum hemoglobin (g/dl)	female: 12–16 male: 14–18	14.5 (12.6/15.3)	12.0 (11.3/12.3)	
Mean cellular volume (MCV) $10^{-6} \cdot m^3$	82–101	94.6 (88.1/103.2)	99.1 (93.6/103.4)	NS
MCV: Coefficient of variance	11.5–14.5	15.3 (13.1/17.9)	16.0 (13.8/17.9)	< 0.05
Cellular Hb-concentration (g/dl)	31.5–36	33.4 (32.9/33.6)	33.8 (33.6/34.0)	< 0.01
Reticulocytes (%)	5–15	12.3 (9.8/18)	12.2 (9.5/17.3)	NS
Leukocytes ($10^3/mm^3$)		5.7 (4.7/6.5)	5.6 (5.0/6.2)	NS
Erythropoetin (mU/ml)	8–20	16.3 (12.7/18.9)	28.7 (21.7/41.1)	< 0.001
Serum iron (µg/dl)	60–160	98.7 (82.5/147.4)	98.8 (86.1/128.8)	NS
Ferritine (µg/l)	11–132	122.5 (37.2/221.3)	181.6 (100.0/439.9)	NS
Transferrin-Sat (%)	16–45	23 (20/41)	32 (25/40)	NS
Daily azathioprine (mg)		30 (10.8/45.5)	21.7 (4.7/68.6)	NS
CyA trough level (ng/ml)		175 (138/196)	158 (133/195)	NS
Serum creatinine (mg/dl)		1.6 (1.5/2.4)	2.1 (1.7/2.5)	NS
Daily allopurinol (mg)		200 (50/250)	200 (125/300)	NS

values of the consecutive parameters were calculated in every patient. The intraindividual variations between single values were generally low and tended to show normal distributions. The calculated means of each parameter were used for statistical analysis, so that there is one value for every parameter in each of the patients.

Patients were retrospectively divided into a nonanemic group (group 1) and an anemic group (group 2). Within these groups, normal distributions were not found for most of the parameters. Medians and quartiles were calculated for all variables in both groups. For comparisons between the groups, the Mann-Whitney U-test was used. Survival was analyzed by life-table analysis according to Kaplan-Meier. Survival comparison was done with the log-rank test. P-values below 0.05 were considered significant. Values are presented as medians and 25th percentile/75th percentile.

Results

General findings

Anemia was found in 36 of the 45 patients (3 females, 33 males; 80%). No significant differences between group 1 and group 2 were found with respect to age, time after transplantation, creatinine serum levels, mean CyA trough levels, or daily Aza and allopurinol dosage (Table 1). Vitamin B_{12} and folate serum levels, reticulocyte counts, and C-reactive protein (CRP) as a marker of acute inflammation were within the normal range in all patients. Total lactate dehydrogenase (LDH), which was taken as an indicator for hemolysis since haptoglobin was not available, was in the upper normal range in almost all patients. There was a trend to higher values within the group of nonanemic patients, but this was not statistically significant.

Patients in group 2 had a normocytic, normochromic anemia. Slight anisocytosis was seen in both groups, but the coefficients of variations of the cellular volume were significantly higher in the anemic group (Table 1). Cellular hemoglobin concentration was significantly higher in group 2 but within the normal range in both groups.

Outstanding laboratory findings of both groups are presented in Table 1.

Erythropoietin and parameters of iron metabolism

EPO serum levels were normal in most patients in group 1 and elevated in most patients in group 2, with a highly significant difference between the groups ($P < 0.001$). Generally, there was a significant inverse correlation between hemoglobin and logEPO ($r = -0.272$, $P < 0.05$; Fig. 1).

Iron serum levels and transferrin saturations (TF-Sat) were comparable and within the normal range [iron 98.7 (82.5/147.4) ng/ml vs 98.8 (86.1/128.8) ng/ml, P = NS; TF-Sat 23 (20/41)% vs 32 (25/40)%].

Ferritin levels (FT) were elevated in group 2 without a significant difference between the groups [122.5 (37.2/

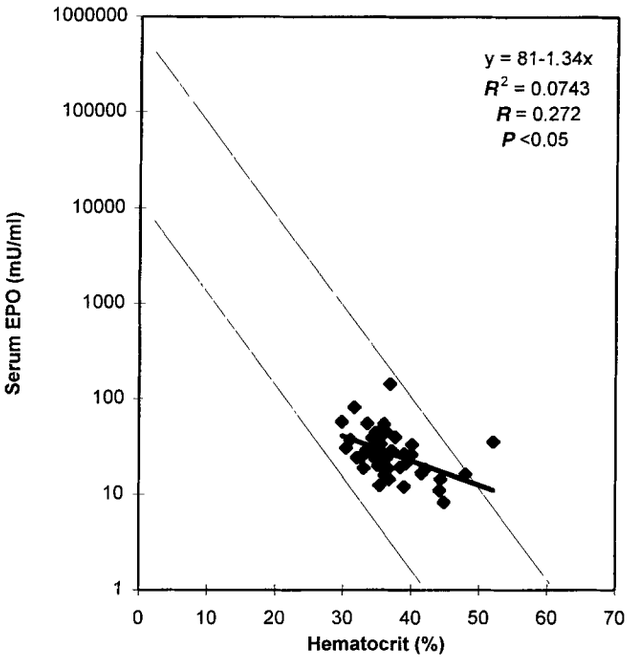

Fig. 1 Hematocrit-to-EPO correlation in comparison to expected EPO levels, as described by Erslev [7]. The area between the thin lines corresponds to 95% confidence intervals of titers of patients with simple anemias

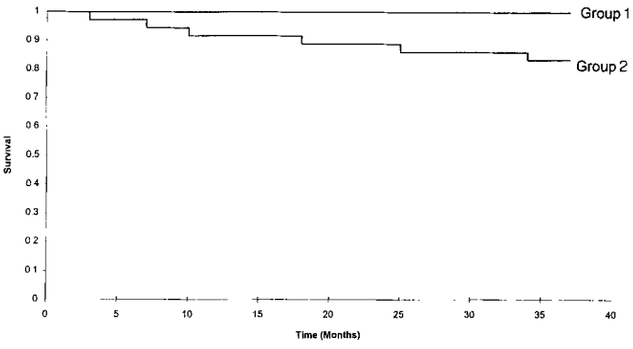

Fig. 2 Patient survival

221.3) μg/l vs 181.6 (100.0/439.9) μg/l, $P = 0.125$] and showed high interindividual variation.

Patient survival and morbidity

Survival after HTX was significantly different in the two groups ($P < 0.02$). In group 1 ($n = 9$), all patients were alive at the end of the study. In group 2 ($n = 36$), six patients died within 2, 7, 10, 18, 25, and 34 months after the beginning of the study. The causes of death were pneumonia ($n = 2$), pneumonia with terminal intracerebral hemorrhage ($n = 1$), and allograft vascular disease ($n = 3$). A Kaplan-Meier curve of patient survival during the study is presented in Fig. 2.

Patient morbidity within the observation period (November 1994–December 1997) was defined as the need for hospitalization due to rejection or infection. The length of time spent in the hospital for other reasons, such as trauma, hypertension, hyperlipemia, and diagnostic purposes, was similar in both groups (data not shown).

Comparability is limited because of the deaths in group 2. No significant differences were found between the groups when analyzed with the above-mentioned statistical tests. There was a substantial number of patients in both groups who were not hospitalized for either rejection or infection during the follow-up (similar or equal medians). A comparison of the means (± SD) may serve as an indicator of a trend to longer hospitalization in group 2. In group 1, patients were hospitalized for treatment of bacterial infection for a mean time of 2.2 ± 3.1 days vs 14.2 ± 36 days in group 2 ($P = 0.193$). Hospitalization time due to viral infection was 12 ± 14 days in group 1 vs 16 ± 23 days in group 2, and due to rejection 4.4 ± 6.7 days in group 1 vs 5.8 ± 8.1 days in group 2.

Discussion

Although anemia is often seen in solid organ recipients [9], there is little data about anemic heart transplant recipients in the literature. Hunt et al. [15], who analyzed and compared blood films and EPO levels as well as other relevant parameters of heart and heart-lung recipients, concluded that there were "no patients with unexplained anemia" in their group of heart recipients. The difference between Hunt et al.'s results and ours concerning the prevalence of anemia after HTX can be explained by our different definitions of anemia. In their study, anemia was considered significant when hemoglobin was below 10 g/dl. On the basis of our laboratory's normal range, which is in accordance with Harrison's definition [12], a majority of our patients were anemic.

The pattern of anemia in our patients was comparable to that in other reports about anemia after solid organ grafting: a normocytic, slightly anisocytic, normochromic anemia with generally normal reticulocyte counts [3, 6, 9, 10, 12, 14, 15, 18, 24, 26]. Despite these shared characteristics and a similar clinical and immunological situation in allotransplant recipients who receive CyA, Aza, and Pred for standard immunosuppression, a comparison of recipients with different transplanted organs appears to be problematic. In kidney and liver recipients, the transplanted organ is directly involved in endogenous EPO production [5, 8, 9, 17, 24,

28], and in lung and heart-lung recipients a possible influence of a preoperatively impaired oxygen saturation on the EPO feedback mechanism [6, 15] has to be considered. A further argument is that with regard to serum EPO, laboratory findings in the literature are different, indicating that endogenous EPO production may be determined by the type of organ transplanted. End et al. [6] and the Vienna Transplant Group report an absolute EPO deficiency in both anemic and nonanemic patients after lung transplantation, whereas Hunt et al. reported "appropriate" serum EPO levels for the underlying degree of anemia in patients after heart-lung transplantation [15]. Other groups observed a "blunted EPO response" in transplant recipients with a pathological EPO-to-hemoglobin relationship [9] and a reduced ratio of measured-to-expected serum EPO [3, 7, 9, 10, 16, 18, 21, 24, 28].

In our anemic patients, serum EPO levels were elevated as described by Erslev in patients with simple anemias and other diseases complicated with anemia [7] (Fig. 1). It is difficult to state whether the elevation of EPO in our anemic patients can be called "appropriate". On the one hand, the levels measured are within the expected range [7]; on the other hand, a symptomatic therapy with recombinant human EPO [10, 13, 19] proved to be sufficient in anemic heart recipients [29]. Thus, an elevation in endogenous EPO as found in our patients can be characterized as "relatively inappropriate" because it is not able to correct the anemia.

We have not found that EPO production is impaired by CyA [3, 9, 18]. Since CyA is only given when therapeutic immunosuppression is required, it seems likely that immunological reactions [19, 26] cause the reported blunting of EPO response [6, 24], not because of, but regardless of, CyA administration. This would also explain the fact that anemia is not observed in all patients receiving CyA. It seems necessary to analyze post-transplant anemia separately for every type of organ transplanted. We suggest that only patients with the same type of graft be compared.

Aza, which has been described as a possible cause of macrocytic anemia due to its properties as purine-antimetabolite and which is also reported to cause an increase in ineffective iron turnover [1, 14], was given in similar dosages in anemic and nonanemic patients, with a tendency to higher dosages in the nonanemic group. Anemic patients seemed to be less tolerant of Aza, and Aza had to be discontinued more often in that group. Although haptoglobin was not available, chronic hemolysis was a very unlikely additional cause of anemia in our patients. LDH was not elevated and tended to be higher in the nonanemic group.

As in patients with chronic disease [19], anemia in our transplant recipients appeared to be due to an impaired reactivity of the bone marrow to raised EPO serum levels. Unlike anemia in cancer or rheumatoid arthritits patients [19, 20], a functional iron deficiency with low transferrin saturations and low serum iron levels was not observed in our patients and seems generally not to be typical of anemia in transplant recipients [6, 9, 15].

The different survival rates of anemic and nonanemic patients over the observation period of 3 years suggest a clinical relevance of mild anemia in patients after HTX. Latent rejection or episodes of latent infection are probably the cause of both chronic anemia and impaired survival in a majority of the patients. A possible influence of chronic rejection on the effectiveness of EPO in kidney recipients has also been suggested [26].

Our data suggest that chronic anemia after HTX is a sensitive indicator of latent disorders. Anemia in patients after HTX seems to show specific characteristics and should be seen as a separate entity. Separate studies on cytokine levels in anemic and nonanemic patients, especially interleukins-1, -2, and -6 and tumor necrosis factor alpha [19, 20], and on the effects of therapies like enhanced immunosuppression and antiviral treatment in anemic patients are needed to devise a rationale for a causal therapy. Whether a symptomatic elevation in hemoglobin would improve patients survival remains controversial.

References

1. Anastassiades E, Howarth D, Howarth JE, Shanks D, Waters HM, Hyde K, Yin JA, Geary CG, Gokal R (1994) Influence of azathioprine on the ferrokinetics of patients with renal failure before and after treatment with erythropoietin. Nephron 67: 291–296
2. Bertoni E, Rosati A, Zanazzi M, Azzi A, Zakrewska K, Guidi S, Salvadori M (1997) Unusual incidence of aplastic anemia due to B19 parvovirus infection in renal transplant recipients. Transplant Proc 29: 818–819
3. Blackburn MEC, Kendall RG, Gibbs JL, Dickinson DF, Parsons JM, Norfolk DR (1992) Anaemia in children following cardiac transplantation: treatment with low dose human recombinant erythropietin. Int J Cardiol 36: 263–266
4. Cartron J, Blesson S, Celton JL, Bertheleme JP, Broyer M, Niaudet P (1994) Anemie hemolytique apres transplantation renale [Hemolytic anemia after kidney transplantation]. Presse Med 707–709
5. De Paoli Vitali E, Ricci G, Perini L, Malacarne F, Vedovato M, Guerra G, Dapporto M, Gilli P (1996) The determination of plasma transferrin receptor as good index of erythropoietic activity in renal anemia and after renal transplantation. Nephron 72: 552–556
6. End A, Stift A, Wieselthaler G, Griesmacher A, Schlechta B, Koppensteiner R, Schreiner W, Geissler K, Stockenhuber F, Klepetko W (1995) Anemia and erythropoietin levels in lung transplant recipients. Transplantation 60: 1245–1251

7. Erslev AJ (1991) Erythropoietin. N Engl J Med 324: 1339
8. Fernandez LM, Marcen R, Villafruela J, Teruel JL, Tato A, Rivera M, Ortuno J (1996) Effect of recombinant human erythropoietin therapy in dialysis patients on endogenous erythropoietin synthesis after renal transplantation. Nephron 73: 54–57
9. Frost AE, Keller CA The Multi-Organ Transplant Group (1993). Anemia and erythropoietin levels in recipients of solid organ transplants. Transplantation 56: 1008–1011
10. Gao SZ, Schroeder JS, Alderman EL, Hunt SA, Silverman JF, Wiederhold V, Stinson EB (1987) Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. Circulation 76: 56
11. Gossmann J, Kachel HG, Schoeppe W, Scheuermann EH (1993) Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin converting enzyme inhibitors. Transplantation 56: 585–589
12. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL (eds) (1998) Harrison's principles of internal medicine, 11th edn. McGraw-Hill, New York St. Louis, Appendix A-2
13. Horina JH, Schmid CR, Roob JM, Winkler HM, Samitz MA, Hammer HF, Pogglitsch H, Krejs GJ (1991) Bone marrow changes following treatment of renal anemia with erythropoietin. Kidney Int 40: 917–922
14. Howarth JE, Waters HM, Shanks D, Hyde K, Yin JA, Geary CG, Anastassides E, Howarth D, Gokal R (1993) Effects of azathioprine on response of renal anaemia to subcutaneous recombinant human erythropoietin. J Clin Pathol 46: 41–44
15. Hunt BJ, Amin S, Halil O, Yacoub M (1992) The prevalence, course and characteristics of chronic anemia after heart and lung transplantation. Transplantation 53: 1251–1256
16. Jelkmann W, Fandrey J, Wiedemann G (1990) Immunoreactive erythropoietin in the anemia of non-renal chronic disease. Biomed Biochem Acta 49: 265
17. Kessler M, Hestin D, Mayeux D, Mertes PM, Renoult E, Nancy F (1996) Factors predisposing to post renal transplant erythrocytosis. A prospective matched-pair control study. Clin Nephrol 45: 83–89
18. Locatelli F, Zecca M, Mamprin F, Gamba A, Giorgani G, De Stefano P (1994) Recombinant human erythropoietin may correct erythropoietin-deficient hyporegenerative anaemia in children given cardiac transplantation. Br J Haematol 88: 623–625
19. Means RT, Krantz SB (1992) Progress in understanding the pathogenesis of the anemia of chronic disease. Blood 80: 1639–1647
20. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL (1990) Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 322: 1689–1692
21. Miller CB, Jones RJ, Zahurak ML, Piantadosi S, Burns WH, Santos GW, Spivak JL (1992) Impaired erythropoietin response to anemia after bone marrow transplantation. Blood 80: 2677–2682
22. Miller ME, Garcia JF, Cohen RA, Cronkite EP, Moccia G, Acevedo J (1981) Diurnal levels of immunoreactive erythropoietin in normal subjects and subjects with chronic lung disease. Br J Haematol 49: 189
23. Mourad G, Cristol JP, Chong G, Lorho R, Argiles A, Seignalet J, Mion C (1992) Disappearence of anti-HLA-antibodies in highly sensitized patients treated with erythropoietin. Transplant Proc 24: 2512–2516
24. Nampoory MRN, Johny KV, A-Hilali N, Seshadri MS, Kanagasabhapathy AS (1996) Erythropoietin deficiency and relative resistance cause anemia in postrenal transplant recipients with normal renal function. Nephrol Dial Transplant 11: 177–181
25. Ndimbie OK, Frezza E, Jordan JA, Koch W, Van Thiel DH (1996) Parvovirus B_{19} in anemic liver transplant recipients. Clin Diagn Lab Immunol 3: 756–760
26. Page B, Zingraff J, Almond MK, Cunningham J (1994) Resistance to recombinant human erythropoietin and kidney graft rejection. Nephrol Dial Transplant 9: 270–273
27. Thio K, Janner D (1996) Aplastic anemia in a cardiac transplant recipient. Pediatr Infet Dis J 15: 1139, 1141–1142
28. Van Loo A, Vanholder R, Bernaert P, De Roose J, Lameire N (1996) Recombinant human erythropoietin corrects anaemia during the first weeks after renal transplantation: A randomized prospective study. Nephrol Dial Transplant 11: 1815–1821
29. Wasler A, Petutschnigg B, Iberer F, Müller H, Allmayer T, Freigassner M, Tscheliessnigg KH (1995) R-HU-EPO zur Behandlung von Anämien nach Herztransplantation – Lecture (Austrotransplant 1995) Acta Chir Austriaca [Suppl] 116: 26