BANTAO Journal 2013; 11(2): 65-69

BJ
BANTAO Journal

Original Article

Iron Status, Iron and Epoetin Therapy in Chronic Hemodialysis Patients-A Single Center Experience

Karmen Romozi and Jadranka Buturovic-Ponikvar

Department of Nephrology, University Medical Center Ljubljana, Ljubljana, Slovenia

Abstract

Introduction. Recent KDIGO anemia treatment guidelines encourage the use of iron in treating renal anemia in chronic hemodialysis patients. However, a recent study by Rostoker, *et al*. has demonstrated, by using magnetic resonance imaging, hepatic iron overload in significant proportion of chronic hemodialysis patients. The aim of our retrospective cross-sectional clinical study was to evaluate iron status, levels of iron and epoetin therapy in chronic hemodialysis patients from our center.
Methods. All patients treated by chronic hemodialysis in the Dialysis center for acute and complicated hemodialysis at the University Medical Center in Ljubljana during the month of March 2013 were screened (N=181). Median age was 66 (inter-quartile range 57-80) years, 58.6% were male. The data for the study were obtained from the hospital's laboratory database. Iron and epoetin therapy during that time were recorded from our dialysis charts.
Results. A total of 174 adult chronic hemodialysis patients participated in this study. 150/174 (86.2 %) of the patients have been receiving epoetin therapy, all intravenously, while a lower percentage (100 patients, 57,4%) have received intravenous iron therapy. Out of the patients being treated with epoetins, 36/150 (24%) have received darbabopetin, and the rest of them either epoetin-alfa or epoetin-beta. Average laboratory results were: hemoglobin 11.7±1.1 g/dl, serum iron 10.1±3.9 µmol/l, ferritin 681±440 µg/l, TIBC 40.2±5.8 µmol/l, TSAT 25.7 ±10.4% iPTH 341±314 ng/l, 78.7% of the patients used arteriovenous fistulas as vascular access, 52/174 (29.9%) had elevated CRP levels.
Conclusions. Weekly iron and epoetin dose in our patients were not high. Average serum ferritin level was rather high. Caution on possible iron accumulation should be in focus of renal anemia treatment during the next period.

Keywords: anemia, chronic kidney disease, epoetin, hemodialysis, hemosiderosis, parental iron

Introduction

Anemia is a common complication among patients with chronic kidney disease (CKD). It is present in the vast majority of patients on dialysis, leading to considerable morbidity, mortality and reduced quality of life [1-10]. It reflects a combination of erythropoietin deficiency and iron deficiency, as well as bone marrow resistance to erythropoietin [11]. Diet restrictions, poor absorption of iron, frequent blood tests, or removal of iron and vitamins by hemodialysis also contribute to anemia in a chronic dialysis patient.
As defined by the Kidney Disease: Improving Global Outcome (KDIGO) anemia treatment guidelines, anemia is a hemoglobin (Hb) concentration <12 g/dl for women and <13 g/dl for men [3]. The European Best Practices (ERBP) Guidelines for the Management of Anemia in Patients with Chronic Renal Failure define anemia according to age and sex. Anemia is defined as an Hb concentration of <12 g/dl in women, <13.5 g/dl in men ≤70 years of age, and <13,2 g/dl (in men >70 years of age [1]. Iron deficiency was defined using the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines criteria: ferritin level <100 ng/ml or the percentage of transferrin saturation (TSAT) <20% when ferritin is <800 ng/ml [2].
Erythropoiesis-stimulating agents (ESAs) are frequently used to treat anemia of chronic kidney disease in the dialysis setting. ERBP guidelines recommend to initiate ESA maintenance therapy when the Hb values are between 9 and 10 g/dl. For patients, who are already receiving ESA therapy, the recommended Hb target value should be kept between 10 and 11.5 g/dl and should not be allowed to routinely fall below 10 g/dl. Individualization of therapy is reasonable as in some low-risk patients (i.e. in younger patients with very few comorbidities), those with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia, or in those in whom a clear benefit on quality of life can be foreseen, ESA therapy may be started at higher Hb values but not exceeding 12.0 g/dl [1].

Correspondence to: Karmen Romozi, Department of Nephrology, University Medical Center Ljubljana, "Zaloska cesta" 7, 1000 Ljubljana, Slovenia; Phone: +386 1 522 3328; Fax: +386 1 522 2292; E-mail: karmen.romozi@kclj.si

Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD and also improve the erythropoietic response to ESA treatment. Due to having a readily available vascular access, intravenous (IV) administration of supplemental iron is preferred among hemodialysis patients. Treatment with IV iron is recommended when transferrin saturation (TSAT) falls below 30% and ferritin is <500 mg/l [1-3,8-10]. According to ERBP guidelines, in adult CKD patients on ESA therapy who are not receiving iron supplementation, a trial of IV iron should be initiated if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is below 30% and ferritin is <300 ng/ml. In hemodialysis patients with higher serum ferritin levels a course of IV iron therapy can be considered in the presence of hyporesponsiveness to ESA or a risk/benefit ratio going against ESA use [1].

The aim of our retrospective cross-sectional clinical study was to evaluate iron status, levels of iron and epoetin therapy in chronic hemodialysis patients treated in our center.

Materials and methods

For this retrospective cross-sectional clinical study we have used the laboratory database of the University Medical Center Ljubljana, Dialysis center for acute and complicated hemodialysis, for the three month period between January and March 2013. During that time 181 chronic hemodialysis patients were treated at our center, 174 of whom were included in this study. Seven patients were not recruited because they were either absent from our center or have passed away during the observation period. Patients' dialysis charts were retrospectively examined to obtain data regarding the iron and epoetin therapy in the observed time period.

The study population consisted of 102 men and 72 women, with median age of 66 (inter-quartile range 57-80) years. The patients' complete blood count (CBC), serum iron, ferritin, C-reactive protein (CRP) levels, albumin levels (Alb), total iron binding capacity (TIBC) and TSAT were monitored on a monthly basis, prior to the first mid-week hemodialysis session of the second half-month. Intact parathyroid hormone (iPTH) levels were monitored on a 3-month basis.

In accordance with European Best Practice and KDIGO guidelines [1,3], anemia treatment in our hemodialysis center comprised of intravenous administrations of either darbepoetin alfa (Aranesp®, Amgen, Thousand Oaks, USA), epoetin alfa (Eprex®, Janssen-Cilag, Buckinghamshire, UK) or epoetin beta (NeoRecormon®, Roche, Basel, Switzerland) and, if required, iron sucrose (Venofer®, Lek, Ljubljana, Slovenia), with the following targets: hemoglobin 10-11,5 g/dl; TSAT: lower limit 20%, target range 30%-50%; and serum ferritin: lower limit 100 µg/l, target range 200-500 µg/l.

Levels of hemoglobin, serum iron, ferritin, TSAT and TIBC, along with the iron and epoetin therapy doses measured during the month of March 2013 were compared between groups with normal and elevated C-reactive protein (i.e. CRP≥10 mg/l [8]), low serum albumin levels and high iPTH values. We also evaluated the angiotensin-converting enzyme inhibitors (ACEI) use and the choice of dialysis procedure. To evaluate the dose-response effect of erythropoetin therapy, we used the erythropoietin resistance index (ERI), calculated as the weekly weight-adjusted dose of ESA divided by the hemoglobin level. Finally, we also compared the before mentioned laboratory parameters between patients who recevied ESA and iron replacement therapy and those who did not require it.

Results

A total of 174 adult chronic hemodialysis patients participated in this study. 86.2% of the patients have been receiving epoetin therapy, all intravenously, while a lower percentage (57.5%) have received intravenous iron therapy in the last month. Out of the patients receiving epoetins, 27.8% have received darbabopetin alfa, and the rest of them either epoetin-alfa or epoetin-beta.

Table 1. Patients' main treatment and laboratory data

Parameters	All (n=174)	Range
Age (yrs)	66±15	26-92
Male (%)	58.6	
AVF[a] (%)	78.7	
HDF[b] (%)	24.7	
ACEI[c] (%)	25.3	
Hb (g/dl)	11.7±1.1	8.7-16.1
Ht (%)	0.352±0.03	0.271-0.485
ESA[d] (IU/week)[h]	5268±4562	0-24000
Iron Sucrose (mg/month)[h]	136±116	0-533
Ferritin (µg/l)	681±440	13.7-2758
Serum Fe (µmol/l)	10.1±3.9	4.25-23.4
TIBC[e] (µmol/l)	40.2±5.8	22.3-64.3
TSAT[f] (%)	25.7±10.4	8.43-65.5
iPTH (ng/l)	341±314	3-1843
Alb (g/l)	37.6±3.2	26-45.3
ERI[g] (IU/kg/week/g per dl)[i]	7.7±0.5	0.4-24.8

[a]Arterio-venous fistula, [b]Hemodiafiltration, [c]Angiotensin-Converting-Enzyme Inhibitor, [d]Erythropoiesis-stimulating agent, [e]Total Iron-binding Capacity, [f]Transferrin saturation, [g]Erytropoetin Resistance Index, [h]All patients included, [i]n=157

The main patients' treatment and laboratory data are presented in Table 1. Laboratory values, calculated as the mean of the last three values, of serum hemoglobin, iron, ferritin, TIBC and TSAT were 11.7 g/l, 10.2 µmol/l, 662 µg/l, 40.1 µmol/l and 25.7%, respectively. Mean ERI was 7.7 IU/kg/week per 100 ml. 78.7% of the patients had arteriovenous (AV) fistulas as vascular access, postdilutional hemodiafiltration (HDF) was prescribed in 24.7% and standard bicarbonate dialysis (BHD) for in the rest of the patients. 25.4% of patients were treated

with ACE inhibitors. Mean ESA and iron sucrose doses were calculated from the data collected from all patients who participated in the study (N=174). If these doses are calculated by only including patients who were recieving ESA and iron sucroce during the observed period, the results are 6534±4631 IU/week and 239±250 mg/month (Table 2 and Table 3). 29.9% of the patients had elevated CRP levels, 17.8% of the patients had hypoalbuminemia and 41.9% iPTH levels >300 ng/l. Their mean age was higher and a larger proportion of patients used central venous catheters instead of arterio-venous fistulas as a form of vascular access.

Table 2. Comparison of characteristics between patients without and with ESA (erythropoesis-stimulating agent) replacement therapy

Parameter	Without therapy (n=24)	ESA (n=150)	p-value
Age (yrs)	62.7±13.3 (34-88)	66.5±15.6 (26-92)	0,814
Hb (g/dl)	12.9±1.7 (8.4-15.5)	11.5±1.3 (7.9-17.5)	<0.001
ESA (IU/week)[d]	0	6534±4631 (1000-24000)	
Iron Sucrose (mg/month)	121±206 (0-1000)	140±227 (0-1200)	0.7
Ferritin (µg/l)	555±435 (34-1587)	724±500 (15-3334)	0.12
Serum Fe (µmol/l)	9.5±4.3 (3.1-23.2)	10.2±4.6 (3.1-25.7)	0.486
TIBC (µmol/l)[b]	42.4±7.4 (28.2-57.1)	39.9±6.3 (15.1-58.6)	0.08
TSAT (%)[b]	22.9±11.1 (7.2-61.7)	25.4±11.4 (6.7-64.3)	0,612

Data are presented as mean ± standard deviation
[a]Erythropoiesis-stimulating agent, [b]Total Iron-binding Capacity, [c]Transferrin saturation

Table 3. Comparison of characteristics between patients without intravenous iron replacement therapy

Parameter	Without therapy (n=74)	Iron Sucrose (n=100)	p-value
Age (yrs)	64.5±16.7 (28-88)	67±14.8 (26-92)	0.505
Hb (g/dl)	11.7±1.4 (7.9-14.4)	11.6±1.4 (8.4-17.5)	0.642
ESA (IU/week)[d]	4990±4194 (0-20000)	6109±5262 (0-24000)	0.133
Iron Sucrose (mg/month)	0	239±250 (100-1200)	
Ferritin (µg/l)	675±375 (42-2338)	719±568 (15-3334)	0.563
Serum Fe (µmol/l)	10.6±4.3 (3.6-23.2)	9.8±4.7 (3.1-25.7)	0.252
TIBC (µmol/l)[e]	39.5±4.6 (28.2-49.9)	40.8±7.5 (15.1-58.6)	0,189
TSAT (%)[f]	27±10.9 (9.7-61.7)	23.6±11.5 (6.7-64.3)	0,05

Data are presented as mean ± standard deviation
[a]Erythropoiesis-stimulating agent, [b]Total Iron-binding Capacity, [c]Transferrin saturation

Patients with elevated CRP (>10 mg/l) had significantly lower hemoglobin level (11.3±1.3 versus 11.8±1.4, p=0.03) and serum iron (8.3±4.2 versus 10.9±4,4, p<0.001), higher ferritin (764±527 versus 673±475, p=NS), ERI (8.9±7 versus 6.9±5.9, p=0.05) and epoetin doses (6154±4884 versus 5411±4846, p=NS) and a lower iron sucrose dose (113.5±201 versus 142±240, p=NS).

Hypoalbuminemic patients (compared to patients with albumin level >40 g/l) had significantly lower Hb levels (10.7±1.3 versus 11.9±1.3, p<0.001) and serum iron (8.2±4.2 versus 10.6±4.5, p=0.007), similar ferritin levels (714±451 versus 697±505, p=NS), a higher ERI (10.1±6.8 versus 6.7±6, p=0.006) and epoetin dose (6774±4911 versus 5385±4825, p=NS), with lower dose of iron sucrose (105±119 versus 145±240, p=NS).

Patients with iPTH >300 ng/l (compared to patients with iPTH <300 ng/l) had similar Hb levels (11.7±1.4 versus 11.6±1.4, p=NS), similar serum iron (11.6±4.4 versus 10.1±4.6, p=0.03) and ferritin levels (692±499 versus 706±494, p=NS), however ERI was higher (8.2±7.3 versus 7±5.5, p=NS) in parallel with ESA dose (6310±5868 versus 5144±3297, p=NS), The dose of iron sucrose was lower in this group (116±162 versus 154±259, p=NS).

No significant difference was found between the groups with or without ACE inhibitor therapy as concerns hemoglobin level, serum iron, ferritin, ERI, ESA and iron sucrose dose.

Patients treated by postdilutional HDF had lower ERI (5.6±4.9 versus 8.15±6.6, p=0.02) and lower ESA dose (4360±4233 versus 6051±4987, p=0.03). No significant difference was found in the level of hemoglobin, serum iron, ferritin and iron sucrose dose compared to patients treated with bicarbonate hemodialysis.

Discussion

The major finding of our study was that average hemoglobin level was within the guidelines [1] and that average ferritin levels were rather high, including the subgroup in the group with non-elevated CRP, normal albumin and iPTH levels. Interestingly, ferritin levels were elevated even among patients who did not receive

intravenous iron replacement therapy during the month the screening took place. This can be explained by the fact that a vast majority of patients have received intravenous iron in previous months, with only 26.7% of patients not receiving any iron supplements during the observed period. Also, some of the patients were taking iron supplements by oral route and some received intravenous iron outside our center (for e.g. patients treated for hematological conditions in other clinics). There was a noticeable increase of ESA dosage among patients with hypoalbuminemia and high iPTH levels, while patients treated with HDF procedures needed smaller doses of epoetins compared to those treated with BHD procedures

Renal anemia is a common complication among patients with chronic kidney disease, especially among those requiring hemodialysis and can be corrected by erythropoiesis-stimulating agents (ESA) [12]. Current guidelines recommend initiation of ESA therapy when serum hemoglobin drops below 10 g/dl, but should not be used to intentionally increase Hb concentration above 13 g/dl as higher Hb concentrations raise the risk for stroke, hypertension, vascular access thrombosis and may perhaps also increase risk for death or serious cardiovascular events [1-3.8]. Among our study population, a significant proportion was receiving ESA (86.2%). The mean Hb concentration was 11.7±1.1 g/dl, with 5.2% of the patients having target Hb concentration below 10 g/dl, and 10.3% above 13 g/dl.

Failure to achieve adequate iron stores and availability is the main cause of hyporesponsiveness to ESA therapy. For the optimal management of anemia, use of iron supplements in combination with ESA is required [12]. Iron however, is considered to be somewhat of a double edged sword as it is critical for health, yet highly toxic because of its oxidative properties. As a result, the hepcidine system carefully regulates iron absorption from the diet and the availability of iron from storage tissues. Intravenous injection of iron directly into the circulation bypasses these protective controls, and this raises concerns regarding the safety of intravenous iron [13]. In a MRI-based study from Rostoker, *et al.* of hemodialysis patients receiving both erythropoeisis-stimulating agents and intravenous iron, hepatic iron overload was observed in the majority of cases [14]. Iron overload can also increase the risk of infection as it facilitates bacterial growth and impairs host defense against microbial pathogens [15].

KDIGO anemia treatment guidelines recommend that serum ferritin as a measure of iron storage in the body should be quantified every 3 months in patients who are receiving ESA treatment and intravenous iron supplementation. This is required to establish whether an iron deficiency exists or too much iron supplementation is being administered. It must be noted, that high serum ferritin levels in patients with end-stage renal disease (ESRD) may be a result of inflammation, infection, malnutrition, or malignancy and not necessarily the result of iron overload [3]. In our center, we monitor serum ferritin levels of our patients on a monthly basis. The mean ferritin level in our patients was rather high (681±440 µg/l), with only 23.6% of the patients achieving target ferritin values, which raises concerns about possible iron accumulation.

Fluctuation of Hb levels or "Hb variability" during treatment with ESAs is a well-documented phenomenon. Evidence suggests that inflammation is an important factor associated with Hb variability and that high C-reactive protein levels (a widely used surrogate marker of inflammatory activity) are a predictor for less stable Hb control in CKD patients [16]. 29.9% of our patients had elevated CRP levels. Among this group, a higher ESA and a lower dose of supplemental iron was used to maintain target Hb concentration. As expected, despite using lower doses of iron sucrose, ferritin concentration remained higher than in patients with normal CRP levels.

Several possible strategies exist to enhance the response to ESAs and iron in dialysis patients with persistent low-grade inflammation. Occult infections, when found, should be treated with antibiotics. Also, occult infection of old, non-functioning, arteriovenous grafts may be a cause of ESA resistance and a chronic inflammatory state in HD patients. Resection of old non-functioning arteriovenous grafts with occult infection was associated with the resolution of markers of a chronic inflammatory state and improvement in responsiveness to ESA treatment [16]. Chronic heart failure with fluid overload, a common feature in dialysis patients, may be an important cause of inflammation. Thus, rigorous measures should be taken to avoid or treat fluid overload in these patients [16].

Angiotensin-converting enzyme inhibitors are widely used in renal failure patients in the treatment of hypertension, left ventricular dysfunction, and diabetic nephropathy [17]. Much controversy has been generated over whether these drugs can suppress erythropoiesis, and thereby exacerbate anemia, with several studies suggesting that they do [18,19], while others finding no such effect [20]. Among our study population, 25.4% were treated with ACEI. In our experience, ACEI treatment does not seem to have negative effects on hemoglobin levels and erythropoetin-resistance index. When compared to those not treated with these drugs, the epoetin dose was slightly higher in this group, however, the difference was negligible. While ACEI may evoke a degree of epoetin resistance particularly at high doses, this should be able to be counteracted by a corresponding increase in the dose of epoetin [21].

Hemodiafiltration is associated with a lower incidence of neuropathy, carpal tunnel syndrome, joint pain, and partial correction of anemia [21]. Our results show that patients treated with HDF received a lower dose of ESA and had lower ERI, however, selection bias has to be taken into account.

Hyperparathyroidism is usually listed among the possible reasons for impaired response to recombinant human erythropoietin in patients with renal disease. Possible pathogenic links between anemia and parathyroid hormone (PTH) include reduced erythropoiesis due to calcitrol deficiency, and direct or indirect effects of PTH on erythropoietin release, red blood cell production, survival, and loss [22]. Our study shows that increased iPTH levels are present in 41.9% of our patients and are associated with a decreased erythropoietic response in this group.
A large proportion of CKD patients have also protein energy malnutrition and wasting, low serum levels of albumin and other more specific nutritional markers which are predictors of the response to EPO. It is therefore possible that a diminished nutritional status could be a feature of patients who are resistant to ESA treatment [23-25]. In our study, hypoalbuminemic patients had lower Hb levels despite using significantly higher doses of epoetins.

Limitations of the study

The main limitation of this study is that it is from a single center and it is retrospective and cross sectional. Even so we feel that some findings may be important for further focus on renal anemia treatment, since the number of patients included in the study was rather high for a single center study.

Conclusions

In conclusion, ferritin levels in our maintenance hemodialysis patients were relatively high, even after excluding those with elevated CRP levels. Hemoglobin level was in the target range for the majority of patients, with moderate ESA dose. Possible iron accumulation should be a focus of further studies on renal anemia treatment in the next period.

Conflict of interest statement. None declared.

References

1. Locatelly F, Barany P, Covic A, *et al*. Kidney Disease: Improving Global Outcomes guidelines on anemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013; 28 (6): 1346-1359.
2. KDOQI Clinical Practice Guideline and Clinical Practice Recommondations for Anemia in Chronic Kidney Disease, 2007 Update on Hemoglobin Target. *Am J Kidney Dis* 2007; 49(suppl 2): 51-5179.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; 2(4): 279-335.
4. Tilman BD, Francesco L, Naomi C, *et al*. Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. *N Engl J Med* 2006; 355: 2071-2084.
5. Weiner DE, Tighiouart H, Vlagopoulos PT, *et al*. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol* 2005; 16: 1803-1810.
6. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999; 10: 610-619.
7. Ofsthun N, Labrecque J, Lacson E, *et al*. The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. *Kidney Int* 2003; 63: 1908-1914.
8. KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis* 2005; 45(3): S1-S153 <http://ndt.oxfordjournals.org/content/early/2013/10/27/ndt.gft269.full>
9. Pfeffer MA, Burdmann EA, Chen CY, *et al*. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. *N Engl J Med* 2009; 361: 2019-2032.
10. Locatelli F, Aljama P, Canaud B, *et al*. Anaemia Working Group of European Renal Best Practice (ERBP). Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to reduce cardiovascular events with Aranesp therapy (TREAT) study. *Nephrol Dial Transplant* 2010; 25: 2846-2850.
11. Singh A, Milford E, Fishbane S, *et al*. Managing Anemia in Dialysis Patients: Hemoglobin Cycling and Overshoot. *Kidney Int* 2008; 74(5): 679-683.
12. Horl W. Clinial Aspects of Iron Use in the Anemia of Kidney Disease. *J Am Soc Nephrol* 2007; 18(2): 382-93.
13. Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. *Nephrol Dial Transplant* 2014; 29(2):255-9.
14. Rostoker G, Griuncelli M, Loridon C, *et al*. Hemodialysis-associated Hemosiderosis in the Era of Erythropoiesis-stimulating Agents: A MRI Study. *Am J Med* 2012; (10): 991-999.
15. Hoen B, Kessler M, Hestin D, *et al*. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. *Nephrol Dial Transplant* 1995; 10: 377-381.
16. Dellanna F, Hetzel GR, Backus G, *et al*. Hb-variation in ESRD patients-association between risk factors and ESA dose [abstract SA-PO028]. Presented at American Society of Nephrology Annual Congress, 14-19 November 2006, San Diego, USA.
17. Gavras H, Gavras I. Angiotensin converting enzyme inhibitors: properties and side effects. *Hypertension* 1988; 11 (II): 37-41.
18. Hirakata H, Onoyama K, Iseki K, *et al*. Worsening of anemia induced by long-term use of captopril in hemodialysis patients. *Am J Nephrol* 1984; 4: 355-360.
19. Erturk S, Ates K, Duman N, *et al*. Unresponsiveness to recombinant human erythropoietin in haemodialysis patients: possible implications of angiotensin converting enzyme inhibitors. *Nephrol Dial Transplant* 1996; 11: 396-397.
20. Sanchez JA. ACE inhibitors do not decrease r-HuEPO response in patients with end-stage renal failure. *Nephrol Dial Transplant* 1995; 10: 1476-1477.
21. Bonforte G, Grillo P, Zerbi S, *et al*. Improvement of anemia in hemodialysis patients treated by hemodiafiltration with high-volume on-line-prepared substitution fluid. *Blood Purif* 2002; 20(4): 357-363.
22. Drueke TB, Eckardt KU. Role of secondary hyperparathyroidism in erythropoietin resistance of chronic renal failure patients. *Nephrol Dial Transplant* 2002; 17[Suppl 5]: 28-31.
23. Locatelli F, Andrulli S, Memoli B, *et al.* Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. *Nephrol Dial Transplant* 2006; 21: 991-998.
24. Rocco MV, Paranandi L, Burrowes JD, *et al*. Nutritional status in the HEMO Study cohort at baseline. Hemodialysis. *Am J Kidney Dis* 2002; 39: 245-256.
25. Gaweda AE, Goldsmith LJ, Brier ME, *et al*. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. *Clin J Am Soc Nephrol* 2010; 5(4): 576-581.