Bone marrow biopsy in uremic patients with erythropoietin therapy January 2009 – July 2012

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Abstract

The aimed of this study is identified the BM changes that associated with (CRF), especially in those patients, treated with the recombinant erythropoietin and secondly how was the hematological response to erythropoietin itself. We followed 75 uremic patients whom were on (RDP) and were treated with a recombinant erythropoietin and supplemented by a parenteral iron because of symptomatic anemia, by bone marrow biopsy through anterior superior an iliac crest approach. All the specimens had been submitted to a histopathological examination by the same well certified pathologist. We found that 50 patients (66.66%) were males and 25 patients (33.33%) were females. Regarding the BM biopsy results 35 patients (46.66%) got (EH) 30 patients (40%) got normal cellular BM 10 patients (13.33%) got hypoplastic BM. There was no evidence of granuloma, carcinoma, sclerosis osteomalacia or osteoporosis in any of our patients. Regarding the response to erythropoietin, we found that most of our patients got a frequently symptomatic anemia and needed a blood transfusion irrespective of the regular (HD) that was supplemented by erythropoietin with a parenteral iron. We concluded that there was no specific BM changes that can be attributed to CRF. As far as the matter of erythrpoietin therapy was concerned, we found that most of our patients were still in a real need for a blood transfusion because of the symptomatic anemia irrespective of the erythropoietin administration in addition to parenteral iron. So we think that we must search for other modalities of therapy for the anemia in CRF in addition or an alternative to erythropoietin which had not reduced remarkably the need for the blood transfusion in our patients.

Keywords: Bone marrow (BM); Chronic renal failure (CRF); Hemodialysis (HD); Regular dialysis program (RDP); Erythroid hyperplasia (EH)

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Introduction

Secondary hyperparathyroidism (HPTH) develops relatively early in chronic kidney disease as a consequence of impaired phosphate, calcium, and vitamin D homeostasis. The disease state in chronic kidney disease, which included the histological features of bone disease, defined as renal osteod-ystrophy, and the hormonal and biochemical disturbances, have recently been redefined as a disease syndrome and is referred to as "chronic kidney disease–mineral and bone disorder. As disease progresses, specific histological disturbances in the bone develop, which may or may not be predictable from the biochemical and hormonal changes that are associated with chronic kidney disease. In addition, patients may have had underlying bone disease before developing kidney failure or may have been treated with agents that will alter the classical pathologic findings of the bones in chronic kidney disease and their relation to parathyroid hormone. Thus, in stage 5 chronic kidney disease, bone biopsy with quantitative histomorphometric analysis is considered the gold standard in the diagnosis of renal osteodystrophy. In contrast to stage 5 chronic kidney disease, there are very few data on the histological changes in bone in earlier stages of chronic kidney disease. There also is no adequate information on the etiopathogenesis of bone disease in stages 3 and 4 chronic kidney disease. Thus, because biochemical data cannot predict bone pathology in stages 3 and 4 chronic kidney disease, bone biopsy should be used to define these bone changes and to allow appropriate therapeutic approach [1].

Most observed changes associated with compensatory hyperparathyroidism are that involve the skeletal system. Although it is a life-saving therapy, and hemodialysis unfortunately fails to perform vital metabolic or endocrine functions and does not correct the crucial calcium-phosphate imbalance. In some cases, renal osteodystrophy becomes worse during hemodialysis. Some of the changes that are accelerated are bone remodeling, osteomalacia, osteitis fibrosa cystica (a rarefying osteitis with fibrous degeneration and cystic spaces that result from hyper-function of the parathyroid glands), and osteosclerosis. In children, the predominant lesion is osteomalacia (a deficiency or absence of osteoid mineralization), which is associated with bone softening that leads to deformities of the ribs, pelvis, and femoral neck (renal rickets). Early stages of renal osteo-dystrophy detected histological or biochemically without the presence of definitive radiographic changes. Most recently, a new form of renal bone disease termed a dynamic bone disease has emerged as the most frequent finding in biopsy of patients who are on dialysis. The etiology of this new condition is not fully understood, but relatively low levels of intact serum parathyroid hormone are often associated with this disorder and may play a role in its pathogenesis [2].

Symptomatic anemia is a common complication of chronic renal failure and the treatment is now possible with the availability of the recombinant human erythropoietin (Epoetin alfa). Previous experimental studies have suggested that correcting the anemia of chronic renal failure may be harmful in that renal failure may be accelerated. Although experience with this drug has been primarily restricted to its use in patients with end-stage renal

disease, several recent trials have been reported in patients with varying degrees of chronic renal failure. We review these studies with particular reference to the progression of renal failure and the drug's reported side effects. We conclude that the use of epoetin is beneficial and well tolerated and that there is no compelling evidence for the acceleration of renal failure associated with its use in patients [3].

Erythropoietin (EPO) is one of the main cytokines involved in the regulation of erythropoiesis. The main site of EPO production is the kidneys. An altered EPO production leads to pathological conditions such as anemia and polycythaemia. Due to the progressive loss of renal peritubular cells, patients with chronic kidney disease (CKD) have low EPO plasma levels. This decreases erythron stimulation with the direct consequence of developing anemia. In the late 1980s, before the introduction in the clinical practice of recombinant human erythropoietin, the only solution for treating this type of anemia were blood transfusions and anabolic steroids. Even recombinant human erythropoietin has proven to be safe and effective for treatment of anemia, there are some concerns about its cost, the need for frequent parenteral administration, and development of anti-EPO antibodies. These inconveniences prompted the search for novel erythropoiesis stimulating agents. Different strategies lead to isolation or chemical synthesis of such agents as darbepoetin alfa and EPO mimetic [4].

When erythropoietin (epoetins or darbepoetin) is used to treat the anemias of chronic renal failure, cancer chemotherapy, inflammatory bowel diseases, HIV infection and rheumatoid arthritis, functional iron deficiency rapidly ensues unless individuals are iron-overloaded from prior transfusions. Therefore, iron therapy is essential when using erythropoietin to maximize erythropoiesis by avoiding absolute and functional iron deficiency [5].

The partial correction of ESRD anemia by recombinant human erythropoietin (EPO) has resulted both in generalized improvement in quality of life and physical activity and in reduced mortality and hospitalization rate. The question remains as to whether normalizing hemoglobin (Hgb) is desirable in patients with chronic kidney disease (CKD). In dialysis patients, normalization of Hgb is associated with improved quality of life and exercise capacity but not with reduced mortality and hospitalization rate. Moreover, no significant changes in the degree of left ventricular hypertrophy have been demonstrated. By contrast, an increased mortality rate has been reported for hemodialysis patients with overt cardiovascular disease (CVD) when randomly assigned to normal hematocrit by EPO. The conclusion that can be drawn from the available studies is that Hgb >11 g/dl is the minimum required to achieve improved quality of life in patients with CKD, whereas values >12 g/dl are not recommended for patients with overt CVD [6].

Methods

A cross–sectional study was conducted at Samawa renal dialysis unit we followed our 75 uremic patients, whom were on a regular HD program by performing an iliac crest a bone marrow biopsy through superior anterior an iliac crest approach. All the specimens had been examined by a well certified pathologist. Those patients were on

a recombinant erythropoietin (Epirex) 50 i.u/kg subcutaneously 2-3 times weekly and supplemented by a parenteral iron. We were doing a frequent hematological and clinical assessment for all those patients so as to observe the benefits or side effects of Epirex and if the anemia were symptomatic irrespective of our regimens.

Results

We found that 50 patients (66.66%) were males and 25 patients (33.33%) were females regarding the age groups the results as in table -1, BM biopsy results as in table (2) & regarding the sex incidence as in table -3.

No. of cases	Age groups
15 patients (20%)	10-20 years)
10 patients (13.33%)	(20-30 years)
10 patients (13.33%)	(40-50 years)
19 patients (25.33%)	(50-60 years)
11 patients (14.66%)	(60-70 years)
10 patients (13.33%)	(70-80 years)

Table 1.
Cases studied according age group

No. of patients	Bone Marrow biopsy results
35 patients (46.66%)	Erythroid hyperplasia
30 patients (40%)	Normocellular B.M
10 patients (13.33%)	Hypoplastic B.M

Table 2.
Bone biopsy results.

sex	No. of patients	Rate
Male	50	66.66%
Female	25	33.33%

Table 3.
Sex of predominance in our patients.

Discussion

Since a long time we were thinking about whether there might be specific BM changes, accompanying CRF patients especially those on a regular HD program, then we extended our idea so that we wanted to see if erythropoietin can affect the BM in uremic patient. We had performed BM biopsy to 75 patients in Samawa dialysis unit and followed them carefully. We found an evidence of erythroid hyperplasia in 35 (46.66%) of our samples, 30 (40%) showed a normocellular BM while in 10 (13.33%) we got hypoplastic changes. We reviewed the literatures for comparison and we found no such study which had been done to verify the bone marrow changes that were associated with advanced renal failure. All our patients were dealt with by a regular HD program in addition to Epirex S.C 2-3 times weekly supplemented by a parenteral iron. We found that most of our patients got frequent episodes of symptomatic anemia so we were obliged to do a blood transfusion in addition to the a above regimens, so as to avoid the complications of anemia in an already incapacitated uremic patients. The targets of treatment are Hb 11-12 g/dl, HCT: 33-36%, TSAT (transferring saturation) ≥ 20% and serum ferritin level of ≥ 100 ng/ml [7].

Anemia is associated with bad outcomes and is nearly universal in advanced renal disease. Mortality increases with treatment to higher targets. Recent studies have found an increased risk of death, blood clots, strokes, and myocardial infarction in patients with chronic renal disease who received ESAs (erythropoiesis stimulating agents) at doses that maintained their hemoglobin levels at more than 12 g/dl, and support partial correction, not normalization

of hemoglobin and the target is of 10–12 g/dl [8].

Conclusion

We had not seen specific BM changes in our uremic patients that can be attributed to CRF. Also there was no evidence of osteodystrophy. Our findings were subdivided between erythroid hyperplasia, normochromic and hypoplastic BM. Regarding the recombinant erythropoietin therapy which is used a world widely for the correction of anemia in CRF, it was not an optimal medication in our patients and irrespective of its administration regularly, most of our patients were presenting with a symptomatic anemia necessitating a blood transfusion. So we think that we should search for a new medication that is a supplement or an alternative to the recombinant erythropoietin in the treatment of anemia that is associated with CRF.

Competing interests

The author declare that they have no competing interests.

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References

1. Gal-M, Sprague SM. Role of bone biopsy in stages 3 to 4 chronic kidney disease. Clin J Am Soc Nephrol 2008;3(3):S170-S174.
2. Michele RB. Nick Cannon diagnosed with "lupus-like" autoimmune disorder. Celebrity diagnosis website, 2012.
3. Pinevich J, Petersen J. Erythropoietin therapy in patients with chronic renal failure. West J Med 1992;157(2):154–157.
4. Stoian I, Manolescu B, Atanasiu V, Lupescu O. New alternatives for erythropoietin therapy in chronic renal failure. Central European Journal of Medicine 2007;2:361-378.
5. Joseph WE. Iron requirements in erythropoietin therapy. Best practice and research clinical haematology 2005;18(2): 347–361.
6. Ernesto P, Giuseppe C. Update on erythropoietin treatment. J Am Soc Nephrol 2006;17:S74–S77.
7. Radhakrishnan J, chronic kidney disease definitions and optimal management. Columbia nephrology website, 2008.
8. Hayat A. Erthropoietin friend of foe in chronic kidney disease anemia: An analysis of randomized controlled trials, observational studies and meta-analyses. BJMP 2009: 2(3) 12-20.