Resolution of epoetin-induced pure red cell aplasia 2 years later, successful re-challenge with continuous erythropoiesis receptor stimulator

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Abstract. Epoetin-induced pure red cell aplasia (PRCA) is most commonly associated with epoetin-α; nevertheless, its occurrence has been reported in epoetin-β and darbepoetin-α. We report a young hemodialysis patient who developed PRCA 2 years after receiving intravenous epoetin-β. Epoetin-induced PRCA was confirmed by bone marrow aspiration, associated with markedly elevated anti-erythropoietin antibody. He was treated with prednisolone and cyclophosphamide for 3 months but continued to be transfusion-dependent. 17 months after the development of PRCA, he was started on intravenous continuous erythropoiesis receptor stimulator (CERA) in view of frequent transfusions. He tolerated the CERA injection well and the hemoglobin level stabilized 7 months later. Repeat bone marrow aspiration confirmed complete resolution of PRCA with disappearance of anti-erythropoietin antibody. To date, he maintained a stable hemoglobin level and has been transfusion-independent for the past 1 year. This is the first in the literature that reported the utilization of CERA in epoetin-induced PRCA. Very low or undetectable level of anti-erythropoietin antibody might be the key to the success of re-challenge strategy in cases of epoetin-induced PRCA. Thus, routine checking of anti-erythropoietin antibody before the re-challenge with an alternative erythropoietin product is highly recommended.

Introduction

Pure red cell aplasia (PRCA) is characterized by severe resistant anemia with absence of erythroid precursors in the bone marrow. The acquired form is often idiopathic but many causes have been identified. Epoetin-induced PRCA is extremely rare given the widespread use of erythropoiesis stimulating agents (ESAs). The incidence reached a peak in 2002 and the majority of reported cases was associated with subcutaneous administration of epoetin-α with estimated exposure-adjusted incidence of 18 cases per 100,000 patient-years [1]. Interventions implemented to ensure proper storage, handling and administration of erythropoietin products have resulted in a marked reduction in the incidence of PRCA after 2004. We report the resolution of epoetin-induced PRCA in a hemodialysis patient treated with immunosuppressant followed by treatment with continuous erythropoiesis receptor stimulator (CERA).

Case history

A 26-year-old man with renal failure secondary to small kidneys has been on dialysis since 2006. He was switched to hemodialysis after 18 months of continuous ambulatory peritoneal dialysis (CAPD) due to unresolved CAPD peritonitis. He was well till July 2008 when the hemoglobin level started to drop as low as 4.5 g/dl. All the while he was treated with intravenous epoetin-β (Recormon) 2,000U, 2 times per week.

In view of the recurrent anemia, he was investigated extensively for the cause of anemia. He had normocytic normochromic anemia with very low reticulocyte count despite erythropoietin therapy. He did not have a clinically apparent bleeding source and there was no evidence of active hemolysis. Upper and lower gastrointestinal endoscopy was normal. The dialysis was adequate and he
Lim, Bee, Keng and Chong did not have significant mineral bone disorders. The ferritin level was more than 2,000 µg/l with transferrin saturation of 92% due to frequent transfusions and the folate level was normal. At the peak of the condition, he needed packed-cell transfusions almost every 2 – 3 weeks. (Figure 1)

Bone marrow examination and trephine biopsy confirmed severe erythroid hypoplasia with entirely normal white cell and platelet precursors. Further tests showed that there was no thymoma and parvovirus infection had been excluded. He was then treated for epoetin-induced PRCA, confirmed by presence of anti-erythropoietin (anti-EPO) antibody (14,383 ng/ml). The option of renal transplantation has been explored but unfortunately, he did not have a suitable kidney donor. He was given a trial of prednisolone and cyclophosphamide but continued to require a blood transfusion every month from July 2008 till August 2010. The oral cyclophosphamide was continued for 3 months with a cumulative dose of 9 grams. Though suboptimal initial hematological response, the anti-EPO antibody level had dropped to a very low level (6.9 ng/ml) when it was repeated in August 2009.

In January 2010, he was commenced on intravenous CERA 100 µg monthly. In view of the financial constraints, the CERA dosage was maintained throughout 2010. He tolerated CERA injection well with no allergic reactions and received the last blood transfusion in August 2010. Since then, the hemoglobin level stabilized and exceeded 13.0 g/dl in March 2011. The CERA dosage was adjusted to maintain the hemoglobin within the recommended range. A repeat bone marrow examination in May 2011 confirmed the complete resolution of PRCA together with disappearance of anti-EPO antibody. The hemoglobin level at the time of this report was 11.0 g/dl, and the patient continued to receive intravenous CERA of 50 µg every 3 weeks.

Discussion

We report a young hemodialysis patient who had complete resolution of epoetin-induced PRCA 2 years after the development of PRCA. Spontaneous resolution of epoetin-induced PRCA is extremely rare. Most of the patients who recovered were treated with immunosuppressants [2]. Verhelst et al. [3] reported 47 patients with epoetin-induced PRCA, out of which 9 did not receive immunosuppressive treatment. None of these patients recovered, in comparison to 78% recovery (29 out of 37 patients) in those who received immunosuppressive treatment. Many different regimes have been used with varying outcomes. This includes corticosteroids with cyclophosphamide [3], cyclosp-
rine alone [4], corticosteroids with or without intravenous immunoglobulin [3] and Rituximab [5]. From the limited worldwide experience, the combination of prednisolone and cyclophosphamide has been reported to have the highest response rate. Nevertheless kidney transplantation is highly recommended to all eligible patients should there be no favorable response to immunosuppressive strategy, as the resolution of PRCA can be as early as a few weeks post-transplantation [6, 7].

Our patient was treated with prednisolone and cyclophosphamide but with sub-optimal initial response. The cyclophosphamide was stopped after 3 months in view of his young age and potential risk of sterility. Cyclophosphamide was chosen based on literature review which showed encouraging outcome with this agent in combination to prednisolone. The option of kidney transplantation had been explored but unfortunately the patient did not have a suitable kidney donor. The hemoglobin level started to stabilize around 2 years after the initiation of prednisolone and cyclophosphamide. Most patients in a previous report showed response within 3 – 4 months, nevertheless, delayed response up to 18 months after immunosuppressive treatment has been described in few cases [3]. Therefore, the resolution of PRCA in our patient can still be attributed to previous immunosuppressive treatment. Intravenous CERA was initiated in view of frequent transfusions, 17 months after the development of the PRCA. Seven months after the initiation, the hemoglobin stabilized, and patient did not need further blood transfusions.

CERA is a long acting ESA, characterized by addition of 30 kDalton methoxy-polyethylene glycol polymer chain to the original EPO molecule. The greater stimulus for erythropoiesis of CERA results from repeated cycles of receptor binding, stimulation and dissociation. Essentially, all ESAs have the same mechanism of action, i.e. to bind to and activate the erythropoietin receptors resulting in initiation of intracellular signaling pathways which leads to differentiation, proliferation and maturation of red cell precursors. The pathophysiology of epoetin-induced PRCA is well described as immune-mediated and anti-EPO antibodies can cross-react not only with endogenous EPO, but potentially with all recombinant EPO molecules [8]. Therefore, though there have been reports of successful re-challenge with darbepoetin-α especially [9, 10, 11, 12], it is not a routine practice to switch to an alternative EPO product.

Most patients who tolerated the re-challenge had very low or near lower limit level of anti-EPO antibody [13]. This may be the most important prerequisite should re-challenge with other EPO products be considered. Further investigation is needed to give us more clues whether the type of alternative EPO products used for re-challenge is important if the anti-EPO antibody level is very low or undetectable. Our patient was treated with intravenous CERA and tolerated without any allergic skin reactions or anaphylaxis. The anti-EPO antibody level was very low before the initiation of CERA and undetectable when it was repeated later.

This is the first report in the literature that documented the utilization of CERA in epoetin-induced PRCA. The successful re-challenge suggests that CERA might be safe to be used in epoetin-β induced PRCA, should reintroduction of ESA be considered. Nevertheless, one has to be extremely cautious when deciding to re-treat the patients with other ESAs and close monitoring of systemic reactions, reticulocyte response and anti-EPO antibody level is essential to ensure the safety of this practice. Routine checking of anti-EPO antibody is highly recommended to make sure the level is very low or undetectable before the reintroduction of an alternative ESA.

References


