Eculizumab before and after allogeneic hematopoietic stem cell transplantation in a patient with paroxysmal nocturnal hemoglobinuria

Paroksismal noktürnal hemoglobinürili bir hastada allojeneik hematopoetik kök hücre nakli öncesi ve sonrasında Ekulizumab kullanımı

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by the triad of intravascular hemolysis, venous thrombosis, and cytopenia. Treatment of PNH is generally supportive. Bone marrow transplantation is the only curative therapy for PNH, but is associated with significant morbidity and mortality. Herein, we present a patient with PNH that received eculizumab, a humanized monoclonal antibody that blocks activation of the terminal complement at C5, before and immediately following allogeneic peripheral stem cell transplantation. Prior to hematopoietic stem cell transplantation eculizumab treatment markedly reduced hemolysis and transfusion requirement; however, 1 d post transplantation a hemolytic episode occured, which was successfully stopped with eculizumab re-treatment. Afterwards the patient did not require additional transfusions. The results of this study indicate that early administration of eculizumab may be a safe and effective therapy for hemolytic episodes associated with allogeneic peripheral stem cell transplantation in patients with PNH. *(Turk J Hematol 2011; 28: 223-7)*

Key words: Paroxysmal nocturnal hemoglobinuria, eculizumab, complement, hemolytic episode

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Özet

Paroksismal noktürnal hemoglobinüri (PNH) intravasküler hemoliz, venöz trombozlar ve sitopenilerden oluşan bir triadla kendini gösterir. Hastalığın tedavisi genellikle destekleyici türdedir. Kök hücre nakli tek şifa sağlayıcı tedavi yolu olmakla birlikte, anlamlı oranda morbidite ve mortaliteyle birliktedir. Burada ekulizumab (C5 düzeyinde terminal kompleman aktivitesini inhibe eden monoklonal insan kaynaklı antikor) tedavisinin işlem öncesi ve hemen sonrasında kullanıldığı bir allojeneik çevresel kök hücre transplantasyonu olgusunu sunmak istedik. Ekulizumab, allojeneik nakil öncesinde kullanıldığında hastanın hemoliz ataklarında ve transfüzyon ihtiyacında belirgin bir azalma gözlendi. Bununla birlikte, naklin ilk gününde meydana gelen hemolitik atak nedeniyle ekulizumab uygulaması tekrarlandı.

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Hemolitik atak başarıyla tedavi edilirken, sonrasında hastanın transfüzyon ihtiyacı olmadı. Bu olgu sunumu bize, PNH'lı ve allojeneik periferik kök hücre nakli uygulaması yapılan hastalarda meydana gelebilecek hemolitik atakların tedavisinde ekulizumabın güvenli ve etkili bir şekilde uygulanabileceğini düşündürmektedir. *(Turk J Hematol 2011; 28: 223-7)*
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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal hematopoietic stem cell disorder, which is caused by a somatic mutation in the phosphatidylinositol glycan-complementation class A gene, with an estimated prevalence of 1-2 cases per million people in the United States [1-2]. The disorder causes partial or complete deficiency of the complement inhibitors CD55 and CD59, which results in red blood cell susceptibility to terminal complement-mediated lysis. CD55 inhibits complement at the C3 level, whereas CD59 prevents terminal complements from forming a hemolytic membrane pore (C5b9) [3-5]. Subsequent chronic intravascular hemolysis is the hallmark of the disease, and causes morbidity and mortality [6].

The clinical course of PNH varies and is affected by hemolytic episodes and/or thrombotic events. Fifteen percent of patients with PNH may experience spontaneous remission and long-term survival [7]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapeutic intervention that can result in eradication of the PNH clone [7]. Eradication of the PNH clone has been achieved with both myeloablative and reduced-intensity conditioning regimens [8-12]. Transplant-related mortality in a recent study was 42% (26% and 63% for transplant patients following myeloablative and reduced intensity conditioning, respectively) [13].

As our understanding of the pathogenesis and clinical course of PNH increases, more specific therapies become available for clinical use. Prior to the advent of eculizumab, treatment options for patients with PNH were generally supportive and directed towards palliation of clinical symptoms rather than treatment of the underlying disease process [14]. While the optimal timing of transplantation may be changing in the era of eculizumab, the most effective conditioning regimen (myeloablative or reduced-intensity) is yet to be determined. The use of HSCT in the treatment of PNH has become less frequent now that there is an effective targeted therapy [13]. Eculizumab is a humanized monoclonal antibody that specifically binds to the C5 complement protein, preventing its cleavage to C5a and C5b, and therefore preventing formation of the membrane attack complex. It is the first approved drug that specifically targets complement activation [15]. Herein we present a case with recurrent hemolytic episodes due to PNH. Administration of eculizumab during hemolytic episodes, both before and after allogeneic HSCT, are discussed.

Case Report

A 45-year-old male patient was diagnosed with PNH in March 2008. Flow-cytometric analysis of peripheral blood stem cells revealed CD55 expression of 7% and CD59 expression of 9% in granulocytes, and 7% and 13% in erythrocytes, respectively. The initial bone marrow biopsy specimen was normocellular and showed significant dysplasia in erythroid progenitor cells. The patient was treated with cyclosporin 100 mg/d (p.o.) and danazol 200 mg/d (p.o.). One month later the drugs were discontinued due to hepatotoxicity and renal toxicity. The patient has been transfusion-dependent since April 2008, requiring about 3-4 units of packed RBCs each month. Prior to the use of eculizumab he was transfused with a total of 22 units of packed RBCs. Due to this transfusion history and frequent hemoglobinuria episodes, eculizumab treatment was used.

The patient was vaccinated against Neisseria meningitides 2 weeks prior to the initiation of eculizumab treatment. Eculizumab (Soliris, Alexion Pharmaceuticals®) therapy began in November 2008 with an induction dose of 600 mg QWK for 4 weeks, and then 900 mg (single dose) 7 days later, followed by a maintenance dose of 900 mg (single dose) after 1 month. The drug was administered via intravenous infusion over a period of 30 min. The patient's hematological parameters before treatment were as follows: Hb: 9.7 g/L (normal range: 13.6-17.2 g/L); WBC:

6.2×10^9/L (normal range: 4.3-10.3 10^9/L); Plt: 56×10^9/L (normal range: 156-373$\times10^9$/L).

The patient had 2 hemolytic episodes during eculizumab therapy that were confirmed via peripheral blood smear and hemolytic parameters, including reticulocyte 3.94% (normal range: 0.60%-2.60%), haptoglobin <5.83 mg/dL (normal range: 36-195 mg/dL), lactate dehydrogenase 1388 U/L (normal range: 240-480 U/L); the 1st episode occurred 2 d after the 2nd dose and the 2nd episode occurred 4 d after the 4th dose. Hemoglobin levels ranged from 7.8 to 10.7 g/L during these two hemolytic episodes. After the sixth dose of eculizumab was administered the patient's Hb level was successfully stabilized and his platelet count was in the normal range without transfusion. Only 3 units of packed RBCs were transfused during the course of eculizumab treatment, and no adverse effects were observed due to its use.

The patient did not require transfusion for 3 months after receiving the last dose of eculizumab. He then underwent allogeneic HSCT from an identical sibling female donor. ABO incompatibility was not noted between the patient and the donor. Prior to transplantation the patient's blood count was as follows: Hb: 8.9 g/L (normal range: 13.6-17.2/L); WBC: 6.5×10^9/L (normal range: 4.3-10.3/L); Plt: 154×10^9/L (normal range: 156-373$\times10^9$/L). His conditioning regimen consisted of intravenous (IV) melphalan (140 mg m^2), IV fludarabine (25 mg m^2), and IV anti-thymocyte globulin (300 mg/d for 2 d). Allogeneic HCST with a reduced intensity regimen was used due to the patients' poor clinical condition. Peripheric stem cells (932 cc [5×10^8 mononuclear cells/kg and 7.44×10^6 $CD34^+$ allogeneic hematopoietic stem cells/kg]) were transplanted. Unfortunately, 1 d post transplantation a hemolytic episode occurred and the patient's Hb level decreased from 8.9 to 5.1 g/L; the same day 900 mg single dose of eculizumab was administered to the patient without any side effects. The patient was given 6 units of packed RBCs over the course of 6 d. Afterwards his Hb level (14.5 g/L) and platelet count were normal. The patient was transfusion-independent with a stable Hb level for 21 months following allogeneic HSCT. For graft-versus-host disease (GVHD) prophylaxis the patient received cyclosporin (175 mg/d) and methotrexate (20, 15, 15, and 15 mg 1, 3, 6, and 11 d post transplantation). Myeloid cell chimerism analysis performed 6 months post transplantation showed 99% donor chimerism, according to 6 alleles (ABI 310 genetic analyzer). As of the time this paper was written the patient had mild chronic GVHD and resumed normal activity.

Discussion

Treatment of PNH is generally supportive and consists of transfusion, folate supplements, and corticosteroid and androgen therapy [16]. Currently, allogeneic bone marrow transplantation (BMT) and eculizumab for complement inhibition are the proven effective therapies for patients with classic PNH [17]. BMT is the only curative therapy for PNH, but is associated with significant morbidity and mortality [17]. Some researchers recommend allogeneic HSCT only for PNH patients with life-threatening cytopenias, or the rare patient with disabling hemolysis or thrombosis that is non-responsive to eculizumab therapy [17]. In fact, use of eculizumab must be considered on a case-specific basis because of the heterogenity of PNH; however, in the era of eculizumab the role of HSCT in the treatment of PNH has changed [13].

Eculizumab has been evaluated in 3 studies, a phase II pilot study and 2 phase III case-parent studies. Results from these studies showed that eculizumab was highly effective in decreasing intravascular hemolysis in patients with classic PNH. It also improved quality of life, reduced or eliminated the need for blood transfusion, and reduced the risk of thrombosis [18-20]. On the other hand, eculizumab treatment does not eradicate the underlying faulty PNH clone and must be given lifelong; therefore, it is best reserved for symptomatic patients with a large percentage (more than 10%) of PNH clones or PNH patients with thrombosis irrespective of the size of the PNH clone [17].

The presented case received eculizumab prior to and immediately following allogeneic HSCT because of hemolytic attacks due to PNH; however, the exact cause of the hemolytic attacks was not determined. The patient was treated successfully with eculizumab, and no drug-related adverse effects were observed. During the course of eculizumab therapy (for 9 weeks) the patient had 2 hemolytic episodes and received 3 units of packed RBCs. After allogeneic HSCT the patient did not have any hemo-

lytic attacks for 3 months and therefore received only 3 units of packed RBCs during a period of 5 months. We think that eculizumab treatment reduced the incidence of hemolysis and reduced the need for transfusion. Each patient treated with eculizumab in a multicenter phase III study had a substantial reduction in hemolysis, according to LDH levels. The number of packed RBC units transfused was also reduced significantly, as compared to pretreatment transfusion requirements. Acute hemolytic exacerbation can occur regularly or unpredictably, and negatively affect quality of life [20].

Mild to moderate thrombocytopenia is common in patients with PNH [21] and the need for transfusion requirement varies widely [20]. Thrombocytopenia in PNH may be related to bone marrow failure or thrombocyte consumption. Data reported by the SHEPHERD trial suggest that patients with a low platelet count (lower than 65×10^9/L) benefit from eculizumab [20]. The presented case had a platelet count of 56×10^9/L before treatment, during eculizumab therapy it ranged from 67×10^9/L to 264×10^9/L, and post treatment it progressively increased to $>300\times10^9$/L.

The effectiveness of eculizumab as a therapeutic agent is based on a small number of short-term clinical trials. The cost of eculizumab and a potential lack of access to the medication in some regions may limit its use. Eculizumab administration did not negatively affect the outcome or engraftment of allogeneic HSCT in the presented case. To the best of our knowledge eculizumab treatment during the course of allogeneic HSCT, i.e. during the conditioning process, has not been previously reported in the English language literature. Additional investigations are needed to definitely demonstrate the effectiveness of eculizumab in patients with PNH and allogeneic HSCT.

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Written informed consent was obtained from the presented case.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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