

**Review Article** 

# The Current Role of Bone Marrow Transplantation in the Treatment of Hemophilia A

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#### Abstract

Bone marrow transplantation (BMT) is nowadays used in various hematological disorders including leukemias. Hemophilia A is sex linked bleeding disorder in which there are various genetic abnormalities in factor VIII gene. Among various hematological disorders, bleeding disorders mainly hemophilia in now widely treated using plasma derived and recombinant factor VIII concentrates. Day to day transfusion of coagulation factor VIII in current lifelong disorder is a burden for the patients and decreases their quality of life. Although infection of coagulation products with blood-borne viruses that was major concern in treatment of hemophilia has been eliminated nearly complete at the present time, but appearance of factor VIII inhibitor is huge burden in treatment of hemophilia for both clinicians and patients. In this day and age BMT has gathered new insight and acceptable treatment for many hematological and non-hematological disorders. If BMT will be successful in treatment of hemophilia, it will improve quality of life (by nearly permanent treatment without necessary of daily treatment) and decrease mortality rate (by providing continuous coagulation factor level in blood system).

The aim of current review was to determine current role of BMT in treatment of hemophilia and to evaluate current usage of BMT for treatment of hemophilia. The review of literatures showed that although BMT has been used in a rare cases with hemophilia (mainly hemophilia with another blood disorder), it does not use commonly in treatment of patients with hemophilia A at present time. Literature review showed that scientists now focused on bone marrow transplantation in animal model of hemophilia.

Keywords: Hemophilia A; Treatment; Bone marrow transplantation

#### Introduction

Hemophilia A is X-linked bleeding disorder that mainly affects men. It affects 1 in 5000 males [1]. The current hemostasis defect originated from a deficiency or functional defect in factor VIII protein in circulation that terminated to inability to form blood clot and finally hemorrhage [2]. Occurrence of vast genetic abnormalities from single point mutation to complete deletion of factor VIII gene have been reported in hemophilia A [3]. These genetic abnormalities reflect in plasma level of factor VIII in affected patients. The severity of hemophilia correlates with plasma level of factor VIII (severe form <1%, moderate 1-5% and mild form 5-30%) [4]. The spectrum of clinical manifestation varies from mild ecchymosis to fatal spontaneous intracranial hemorrhagic episodes [5]. The hallmark of severe type of hemophilia is occurrence of massive bleeding that happen spontaneously or after minor trauma [6].

The main stone of treatment is replacement therapy using various factor VIII containing products including cryoprecipitate, plasma derived factor VIII concentrate, recombinant factor VIII and other products such as recombinant activated factor VII (rFVIIa), prothrombin complex concentrate, anti-fibrinolytic agents (Desmopressin and  $\varepsilon$ -aminocaproic acid) and activated prothrombin complex concentrates [7,8]. Nowadays the common treatment option comprises infusion of plasma derived and recombinant factor VIII

concentrates in many countries. The burden resulted of current treatment is the appearance of factor VIII inhibitor in plasma of the patients that makes the control process of hemorrhagic episodes unfruitful and challenging [2]. The life-expectancy in patients with hemophilia who have complete access to modern treatments has been improved and they now encounter age related diseases such as cancers [9].

Bone marrow transplantation (BMT) is an ideal cure for some cancers, inborn errors of metabolism or immune system [10]. New insights and attractions have been absorbed to novel therapeutic options including gene therapy and BMT to overcoming current problem using manipulation of hematopoietic stem cells [11]. The accessibility and capacity of ex vivo manipulation of hematopoietic stem cells have made them as an attractive target for treatment of hemophilia [12] while a multidisciplinary team work needs to manage the condition [10].

Here we will review contributions on efforts of bone marrow transplantation in treatment of hemophilia and will pay attention to role of BMT in treatment of hemophilia at present time.

### **Common Treatment Options**

#### Cryoprecipitate

The first preparation was described widely and introduced by Dr. Pool in 1965. It was prepared using precipitation method from plasma

[13]. Each bag of cryoprecipitate contain about 100 units of factor VIII proteins, so for example in treating hemarthrosis in adult patients with hemophilia there is to about 10-20 units of it. The other negative remarks of current preparation are existence of huge amount of other human proteins and its preparation method lacks any process for inactivation of blood-borne viruses [14]. Nowadays it has been replaced with factor VIII concentrates in developed countries while at least in part of developing countries it is use [15].

#### Desmopressin

It is synthetic analogue of vasopressin that is used in mild and moderate hemophilia A and some subtypes of von Willebrand disease (vWD) and can increase plasma level of factor VIII between 2-15 fold of baseline in patients with mild and moderate hemophilia A [16,17].

Desmopressin is treatment of choice for part of patients with mild and moderate hemophilia A and it is dependent to type of factor VIII mutation, but not useful in treatment of severe hemophilia A, severe hemophilia B and severe forms of vWD [18].

# Plasma derived factor VIII concentrates (pdFVIIIC)

Several types of pdFVIIIC have been introduced commercially. The intermediated-purity concentrates that are produced of large pools or huge numbers of donors' plasma have 2-5 units of factor VIII per milligram protein. There are noticeable amount of von Willebrand factor (vWF) in them [19]. The high purity concentrates are manufactured using monoclonal antibodies to factor VIII or vWF. These products underwent multiple purification steps including heat treatment to reduce risk of viral transmission [20]. It was revealed in the 1990s, that one lot of pdFVIIIC to be associated with high risk of appearance of factor VIII inhibitor in patients who were extensively under infusion of pdFVIIIC. It was persuaded that it was due to a change in factor VIII molecule during fractionation and purification [21].

# Recombinant factor VIII concentrates (rFVIIIC)

The gene of factor VIII sequenced, cloned and transfected in mammalian cells to produce recombinant FVIII protein in 1984 by Wood et al. [22]. Several types of rFVIIIC have been licensed and introduced commercially. Several clinical trials have showed that halflife in circulation, efficacy and recover of rFVIIIC are similar with those of pdFVIIC [23,24]. The freedom from risk of blood-borne viruses' transmission and independence to collecting numerous bags of plasma is among hallmark advantageous of rFVIIIC. Also surveys demonstrated that there are no immunological differences between rFVIIIC and pdFVIIIC, so predisposing to recombinant concentrate doesn't increase risk of appearance of factor VIII inhibitor in untreated patients with hemophilia [25-27]. A commercially B domain deleted rFVIIIC has been licensed too.

# Recombinant activated factor VII (rFVIIa)

It was demonstrated that rFVIIa can stable hemostasis in patients with high titer of factor VIII inhibitor [28]. Owing to its interaction with tissue factor and platelets, it can activate factor X and cause thrombin burst without needing to factor VIII steps [29]. The disadvantages of current treatment are high cost; needing infusion under supervising of medical center due to higher dose of it can be thrombogenesis.

## BMT in mouse model of hemophilia A

The experiences on BMT in mouse model have been more informative than other struggles. The surveys confirmed while endothelial cells are potent source of factor VIII, transplanted bone marrow does not generate endothelial cells and macrophages, mesenchymal stromal cells and mononuclear derived cell from bone marrow express factor VIII mRNA and make stable hemostasis in mice [30,31].

# BMT in canine model of hemophilia A

The experiments in some animal models have demonstrated that transplantation of wild type hematopoietic stem cells did not accompanying with hemostatic level of factor VIII in plasma with unknown reason [32]. The factor VIII gene expressed in kidney and liver tissue, while only after orthotopic liver transplantation and not kidney transplantation correction of hemophilia appears [33, 34]. Groth et al. [35] showed that transplantation of lymphatic tissue can be effective in hemophilic dog and these cells can produce factor VIII protein after BMT.

The BMT in three dogs terminated to death of one dog due to allograft-related complications or rejection of transplant in 34th day. The factor VIII activity was measured as 5% by one stage method in current dog. In the other dogs, one died due to occurrence of hemorrhage at site of aspiration in 7th day and only one dog survived healthy for about more than 2 years with about 8% factor VIII plasma level [36,37].

# BMT in patients with hemophilia A

At the best of our knowledge, BMT experiences in patients with hemophilia A limited to four cases [10,38-40]. Allogenic BMT has applied for two cases with concurrent diseases; the first one was a hemophilic child with severe aplastic anemia who received HLA-identical from his five year unaffected brother [38]. The second patient was a hemophilia patient infected with HIV and concurrent Burkitt-type acute lymphoblastic leukemia (ALL). He was transplanted using of homozygous twin brother [39]. In none of them hematopoietic stem cell transplant could create hemostatic level of factor VIII [37,39]. The experience on BMT in current patients was done using 3.5x10<sup>8</sup> and 6.8x10<sup>8</sup> bone marrow cells/kg respectively and wasn't informative knowledge [30].

The third case was a patient with hemophilia and high titer of inhibitor who underwent allogenic BMT in hope to induce immune tolerance. He experienced several episodes of hemorrhage and severe arthropathy [40]. The last case was a 12 year old boy with hemophilia and extrosseous Ewing's sarcoma that after treatment using standard protocol and chemotherapy underwent auotologous hematopoietic stem cell transplantation. He developed anaplastic large cell lymphoma (ALCL) and treated using standard protocol and chemotherapy. To strengthen second remission allogenic BMT was done for him. He survived with good clinical outcome for 3 year until reporting and he upgraded from severe hemophilia to moderate hemophilia A [10].

# Conclusion

Until now, most informative surveys on treatment of hemophilia by BMT have been on mice models and canine or human models have not successful. In the body, hepatocytes and endothelial cells are two main source of factor VIII production. As in hemophilia mice, BMT can correct hemophilia in most cases with regard to the other side of the coin that we know bone marrow transplanted cells cannot generate endothelial and hepatocytes cells [30]. We can conclude that mononuclear cells and mesenchymal cells release factor VIII in circulation. These findings offer importance of mesenchymal and mononuclear cells in correction of hemophilia mice and create a penetration to hope. Some researchers showed that bioengineered factor VIII transgenes and B lineage-specific factor VIII gene can correct mouse model of hemophilia [31,41].

It seems there is lingering way to establish BMT as a common treatment option for patients with hemophilia. Now we need to complete our knowledge and strength our ideas with investigation on animal models to find solutions toward setting BMT in hemophilia.

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#### Page 4 of 4

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