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THE HEALTH OF THE BONE MARROW NICHE FOR HEMATOPOIETIC STEM CELLS DEPENDS ON ITS COMPANY

Health Science

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ABSTRACT

In this paper I study in detail the disease pathogeneses of Aplastic Anemia (AA) and Immune Thrombocytopenia (ITP), and their current treatment practices. Both are autoimmune diseases, hence both are expected to show promising results when they are treated with immunosuppressive drugs. AA show promising result when treated with horse anti-thymocyte globulin (ATG) and cyclosporine A. ITP show promising result with dexamethasone and pednisone. In a certain clinical study the treatment regimens for both AA and ITP are combined with Eltrmobopag, a drug that is supposed to increase the number of healthy platelets in blood. The clinical result show that once the Hematopoietic Stem Cells (HSCs) are impaired the entire machinery of Bone Marrow Niche for Hematopoietic Stem Cells (BMnHSCs) is also impaired. Based on this hypothesis I suggest that the best treatment for AA is horse anti-thymocyte globulin (ATG) and cyclosporine A, Eltrombopag, Filgrastim, Eryhthropoietin.

KEYWORDS

Autoimmune, immune cells, white blood cells, red blood cells, platelets

INTRODUCTION

We study the interaction between the Bone Marrow (BM) niche for Hematopoietic Stem Cells (HSCs) and the HSCs from the study of two disease models: Aplastic Anemia (AA), and Immune Thrombocytopenia (ITP). Both are autoimmune diseases of the blood [1,2]. The autoimmune attack by the T cells on the HSCs and their progenitors residing both in the BM and the peripheral blood (PB) cause AA [2,3]. The result is the total BM failure characterized by the severe reduction in the number of cells in the BM and also in the number of white blood cells, red blood cells and platelets [2]. The autoimmune attack by the autoantibodies that recognizes and attaches to the human platelet antigens (HPAs) cause ITP [1]. These autoantibodies are produced by the B cells which have received the maturation signals from the splenic T follicular helper cells. The result is the severe reduction in the number of platelets characterized by uncontrolled bleeding in many instances. The standard treatment for AA is allogeneic hematopoietic stem cell transplantation (Allo-HSCT) from a matched sibling donor (MSD). The standard treatment for patients who do not qualify for Allo-HSCT is immunosuppression with horse anti-thymocyte globulin (ATG) and cyclosporine A (CyA). More recently clinical trials are underway to combine ATG and CyA with some of the known thrombopoietin receptor agonists (TPO-RAs) like eltrombopag, romiplostin, etc. [2, 4, 5, 6, 7]. The second-line treatment for ITP included splenectomy and rituximab but as far back as in the year 2008 the treatment of the ITP with TPO-RAs received license in the US [7]. In this paper we focus on the treatment responses of these two disease models under different treatment regimens, and in the process derive an important hypothesis concerning the interaction between the BM niche for HSCs and the HSCs.

Immunosuppression Alone In AA

Cyclosporine is a compound that disrupts the immune response by disrupting the priming of T cells, down-regulating/inhibiting the production of cytokines by T cells, and or disrupting the major histocompatibility complex class II (MHC-II)-aided antigen presentation to T cells [8]. Because the cytokines produced by the T cells have effects on the physiological systems other than the immune system also, the cyclosporine may have effects on the physiological responses other than that of the immune also, but there are not much studies focused on this. Because the cytokines produced by the helper T cells (T_h) are also responsible for the activation, proliferation and maturation of B cells, the cyclosporine disrupts the humoral immunity too. CsA inhibits the production of interleukins, including IL-2 from T_h cells [9]. IL-2, through autocrine effect and paracrine effect, enforce the expression of IL-2 receptors on T_h cells and CD8 T cells respectively. The IL-2 mediated signaling is essential for the differentiation of CD8 T cells into the mature cytotoxic T cells (T_c) [10]. It is the T_c cells that directly kill the target cells. Horse-ATGs are the antibodies directed against the human T cells, formed in the blood of the horses when the human thymocytes or the T cells are introduced into it [11].

The patients of the AA who do not qualify for Matched Related Donor Hematopoietic Stem Cell Transplantation (MRDHSCT), are treated with CsA and horse-ATG [Refractory relapsed AA. Pdf-12]. In a certain study [2] conducted on 49 pediatric patients suffering from AA, treated with CsA/horse-ATG, the complete response rate at 4 months was only 12%. In another study [13] conducted on both the adult and the pediatric patients of AA in western India, the complete response rate at 2 years was 23.5% for adults and 39.1% for children.

Let us try to understand these results deeply. If it is so that the Bone Marrows (BMs) of the AA patients have not lost their ability to produce healthy Hematopoietic Stem Cells (HSCs), merely suppressing the immunity (which in the case being discussed here is by the drugs CsA/horse-ATG) should lead to complete response, i.e. should lead to the correction in the number of white blood cells, red blood cells and platelets in a very large number of AA patients . But the observed low values of the complete response rates, as stated in the above paragraph, do not support the above statement. It has been shown by extensive research on Bone Marrow Niche for Hematopoietic Stem Cells (BMnHSCs) that BMnHSCs control the development and the fate of HSCs [14, 15]. We conclude here that in the vast majority of the patients of AA, it is likely that the cellular debris generated because of the dying blood cells and the dying BM cells render the BMnHSCs unhealthy which therefore, thereafter, produce unhealthy HSCs. Hence even if immunity is suppressed in the treatment procedure of AA by CsA and ATG, the BMnHSC continue to produce faulty (unhealthy) HSCs registering non-recovery from the disease. There is a need to restore health to the HSCs exactly at the location where they are being produced in addition to the suppression of immunity in patients of AA.

Immunosuppression with Eltrombopag in AA

Eltrombopag showed improvement in the health of HSCs in refractory AA [4,5]. Hence it is obvious that when in AA immunosuppression is combined with Eltrombopag there is significant improvement in Overall Response Rate vis-a-vis compared to the treatment that involved immunosuppression alone.

Therapy for ITP

The standard therapy for ITP is administration of intravenous globulin followed by high dose of dexamethasone and pednisone [16]. Dexamethasone and pednisone are corticosteroids that suppress immunity by suppressing the activity and the volume of immune cells. In ITP only the platelets are rendered unhealthy where as the rest of the HSCs are healthy. Hence the treatment without Eltrombopag must be high, and also the treatment with Eltrombopag. In a certain study, 76.7% ITP patients without Eltrombopag showed good response to treatment, 86.2% ITP patients with Eltrombopag showed good response to treatment [1].

CONCLUSION

From above analysis it is clear that if the HSCs become unhealthy, they force BMnHSCs to produce more and more unhealthy HSCs. Hence the best treatment in AA would be immunosuppression combined with the treatment that raises the number of healthy platelets, healthy white

blood cells, and healthy red blood cells. The most preferred drug to increase white blood cells is Filgrastim (a Granulocyte-colony stimulating factor), and the most preferred drug to increase red blood cells is Erythropoietin. If AA patients are treated with horse anti-thymocyte globulin (ATG) and cyclosporine A, Eltrombopag, Filgrastim, Eryhthropoietin they are expected to show very-very high overall response rate. The current treatment regimen for ITP as mentioned in this paper is possibly the best for ITP.

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