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Mini Review

Cell-Based Therapy for Schizophrenia: Can Mesenchymal Stem Cells do the Needful?

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Abstract

We present an analysis of three patients from literature with a malignancy treated with high-dose chemotherapy and hematopoietic stem cell transplantation. It is evident that schizophrenia can be transferred during the cell graft from a schizophrenic donor, cured by the graft from a healthy donor, or cured by high-dose therapy and an autologous graft. We suggest that the use of allogeneic MSCs from healthy donors (including MSCs soluble and insoluble paracrine factors) in schizophrenia patients may be an exciting therapeutic option for further exploration.

Keywords: Autoimmune; BMT; Inflammation; MSCs; Schizophrenia; Stem cells; Transplant

Introduction

The term schizophrenia describes a broad group of endogenous psychoses. Our aim is not to detail the best characterization of the disease that the reader can find in the psychiatry textbooks. Briefly, schizophrenia, as an endogenous psychosis, is characterized by the negative and positive symptoms. Negative symptoms include flattened affect, loss of a sense of pleasure, will or drive, and social withdrawal. Positive symptoms include voices that converse with or about the patient, hallucinations, and often paranoid delusions [1,2].

Schizophrenia, with more than 20 million people affected worldwide, is currently the third-most disabling condition [3].

Prenatal and Childhood Infection and Inflammation in the Development of Schizophrenia

There is a huge amount of literature describing the role of infection (and inflammation) in the development of schizophrenia in the prenatal life and childhood. For an interested reader, we strongly recommend the Textbook of Immunopsychiatry for further studies [4].

Role of Anti-Inflammatory and Immunosuppressive Treatment in Schizophrenia

We advise the reader to study Textbook of Immunopsychiatry, Chapter-6 "Effectiveness of Immunotherapies for Psychotic Disorders" written by Rachel Upthegrove and Bill Deakin for more information [4].

The Anecdotal Reports Analysis

In their Letter to the Editor, Sommer and colleagues [5] analyzed the data from a 68-year old man who received allogeneic peripheral blood Stem Cell Transplantation (SCT) from his brother for chronic lymphocytic leukemia/aplastic anemia [5]. The patient was on a standard chemotherapeutic regimen (fludarabine and cyclophosphamide) followed by an infusion of $5.0x10^6$ CD34+cells/kg body weight. Four weeks after SCT, the patient reached complete hematologic recovery and full hematopoietic chimerism. Approximately four months after the transplantation, the patient (in complete remission of the malignancy) developed acute psychotic syndromology that was finally diagnosed as schizophrenia. It is pertinent to mention that the patient had a blank psychiatric history. However, his donor brother had schizophrenia since early adulthood. The patient was unsuccessfully treated with several antipsychotic drugs including risperidone, citalopram, and haloperidol. He died two years later from an unknown cause.

In a subsequent study, Miyaoka and colleagues [6] presented the case of a 24-year old male who was treated with quetiapine, risperidone, and olanzapine for resistant schizophrenia [6]. The patient developed schizophrenia at the age of 23 years with a sudden onset. At the age of 24, acute myeloid leukemia was diagnosed. The patient received allogeneic Bone Marrow Transplantation (BMT). The authors did not specify the conditioning regimen, and CD34+ cells/kg body weight counts. Four weeks after BMT, the psychotic symptoms of this patient almost completely disappeared (assessed by the Positive and Negative Psychiatric Scale). After eight years, the patient was doing very well, and there were no residual symptoms of schizophrenia.

In a more recent article published by González-Llano and colleagues [7], the authors presented a case of a 21-year old male patient with schizophrenia diagnosed at the age of 15 years [7]. The patient had a long treatment history with a poor response to olanzapine and risperidone. The patient referred to the auditory hallucinations about himself. He was somewhat suspicious and socially withdrawn; finally, he dropped out of high school and

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was unable to leave his home. He was diagnosed with Hodgkin's lymphoma. After one year of standard chemotherapy with different chemotherapeutic schemes, he underwent three BMT. The first two BMTs used autologous cells whereas the third BMT was allogeneic. Between the second (autologous) and the third (allogeneic) BMT (January 2014 - July 2014), the patient received quetiapine. In eight months, after the second (autologous) BMT, PANSS of the patient dropped 60 points, his hallucinations significantly decreased (up to 90%). His negative cognitive and social symptoms improved, which allowed him to incorporate them into his previous academic and social life. In case report (iii), the improvement started after the second, autologous BMT. The third, allogeneic BMT only "puts a seal upon" the effect achieved after the second autologous BMT.

Discussion

We have presented three cases from the literature about the potential of stem cell-based therapy for schizophrenia besides the likelihood of horizontal disease transfer from the diseased to a normal person. It is evident that schizophrenia is a spectrum of disorders that share symptoms. Nevertheless, the detailed analysis is striking. In the first case [5], the disease was probably transferred by the graft (peripheral blood stem cells) from his brother, the donor. The authors excluded several disease conditions (mainly infectious) of the donor as the possible underlying cause of schizophrenia in the recipient. The standard screening of infectious diseases performed before the stem cell collection was negative.

Nevertheless, the patient was genetically predisposed to schizophrenia (the donor's brother had this disease). According to the authors who were professional psychiatrists, an acute onset of the disease spectrum at the age of 68 was rare, especially in males. Furthermore, the onset age was strongly correlated among the affected siblings and differences in onset of more than ten years were very rare too. The etiology and the incidence of psychotic disorders, i.e., schizophrenia spectrum, in older people differ from the younger people, with more involvement of secondary causes in the older people. An appraisal of these factors has been provided by Tampi et al. in their recently published narrative review [8]. It seems that the adoptive transfer of schizophrenia in this case is the most appealing etiology. It should be noted that the principle of allogeneic hematopoietic SCT is not only to replace and build up the whole hematopoiesis after myeloablative regimen; it amounts to almost complete transfer and replacement of the "immune system" from the donor to the recipient. Needless to say that after the myeloablative regimen, the recipient's immune system is badly damaged.

On the contrary, in the second case reported by Miyaoka and colleagues [6], the patient had schizophrenia one year before admission to the BMT unit [6]. His treatment was based on myeloablative regimen and allogeneic bone marrow-derived SCT (instead of peripheral blood stem cells) due to Acute Myeloid Leukemia (AML). The improvement of schizophrenia was relatively quick. Thirty days after the BMT, his psychotic syndromes almost wholly disappeared. His Positive and Negative Syndrome Scale (PANSS) dropped to 30 points, and his Global Assessment of Functioning Scale (GAFS) reached nearly 100 during 36 months follow-up. The "cure" of treatment-resistant schizophrenia in this patient is "an inversion" of schizophrenia transfer of the first case. It seems that the replacement of "diseased" recipient's immune system with the donor's "healthy" cells eliminated the "autoimmune" T-cells of the recipient. It is important to note that some reports support the role of immunological phenomena as the critical factor in schizophrenia pathogenesis [9].

The third case described above is somehow more complicated, involving a 22-years old patient diagnosed with schizophrenia at age fifteen, seven years before receiving two autologous SCT for Hodgkin's disease. The improvement of schizophrenia started after the second myeloablative regimen and second autologous SCT. This novel observation can be explained relatively easily. The SCT is an alternative therapy for many chronic autoimmune diseases [10]. In principle, the myeloablative regimen destroys autoreactive immune cells, and the autologous graft contains only "traces" of them, hence the "normal" immunological status can be achieved after autologous SCT. In this case, complete remission of schizophrenia was "sealed" after the third, haploidentical allogeneic SCT.

The observations of the three cases of schizophrenia can be summarized as follows. In the first case schizophrenia was transferred to the recipient by the donor allogeneic stem cell graft. It should be noted that the cell graft contains only 0.1-1% of hematopoietic (CD34+ or CD133+) stem cells while the remaining graft components include platelets, erythrocytes, and white blood cells, i.e., granulocytes and lymphocytes. The granulocytes (if they survive freezing and thawing) have a half-life of approximately 6 hours. Hence, the possible cellular candidates responsible for schizophrenia "transfer" were only B- and T-lymphocytes from the donor cells, which later developed as a new immune system of the recipient from the donor graft.

In the second case, schizophrenia was cured by the donor allogeneic stem cell graft. This seems somewhat plausible because the recipient's bone marrow was destroyed during myeloablation. The allogeneic cell graft established neo-hematopoiesis and re-established the recipient's immune system. In other words the autoreactive immune cells of the recipient were replaced by the immune cells from the healthy donor's cell graft without schizophrenia.

The last case is a rare scenario - wherein the patient has Hodgkin's lymphoma and schizophrenia, which is considered as an autoimmune [11] or inflammatory disorder [12]. The patient received two autologous SCT after each myeloablation. His schizophrenia spectrum started to improve after the second autologous SCT. This is in concert with the concept of the SCT as an alternative therapy for many chronic autoimmune diseases [10]. As mentioned above, the third allogeneic BMT (from a healthy donor) only "put a seal upon" after the second autologous BMT.

The concept of stem cell therapy for schizophrenia is not new [13-15]. However, neither schizophrenia treatment with reprogrammed human adult somatic cells (human induced pluripotent stem cells; hiPSCs) is our aim, nor the translation of data of Mesenchymal Stem Cells (MSCs) from rodent models to patients [16,17]. Led by Prof. Jair Soars at the University of Texas Health Sciences Center, Houston, the use of allogenic MSCs is already entering into Phase-I randomized, double-blinded, placebo controlled clinical trials in 30 patients (18-65 years) having treatment-resistant bipolar depression (ClinicalTrials.gov Identifier: NCT03522545). A similar study was designed to use allogenic MSCs for treating patients with treatment-resistant

depression but unfortunately it was abandoned due to lack of funding (ClinicalTrials.gov Identifier: NCT02675556). Using these studies as initiatives, we suggest this novel approach in treating schizophrenia. As is evident from the three above-mentioned reports that schizophrenia can be either transferred during the cell graft from a schizophrenic donor, cured by the cell graft from a healthy donor, or cured by combinatorial approach of high-dose therapy and an autologous cell graft. The observed cases support the idea of schizophrenia (at least in a subgroup of the patients) as an autoimmune disease resulting from dysfunctional immune system [11]. The co-existence of autoimmune disorders in schizophrenia patients is indicative of an autoimmune component of the spectrum beside genetic predisposition [18,19]. Given that MSCs have well-established potent anti-inflammatory and immunosuppressive properties, it is tempting to exploit MSCs' in treating schizophrenia [20-22]. Given the Good Biological Practice (GBP), the use of freshly prepared allogeneic MSCs from healthy donors in schizophrenia patients may be an exciting therapeutic option. The suggested dose should be relatively high, ranging from 0.5 - 1.0x10^6/kg of body weight, and the cells should be delivered intravenously twice, within a span of 3 months. With the emerging approach of cell-free therapy using soluble and insoluble paracrine factors, their therapeutic use may be assessed to treat schizophrenia [23].

Declaration

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