EDITORIAL

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Regeneration of the immune system to fight leukemia at relapse post alloHSCT

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Introduction: Leukemia is a common malignancy in children and adults that occurs in bone marrow when alterations in normal cell regulatory processes induce uncontrolled proliferation of hematopoietic stem cells. The incidence of leukemia in both whites and males is typically higher, and rises with age. Around one in seventy people grow leukemia during their lifetime. The four subtypes of leukemia that primary care doctors most commonly experience are acute lymphoblastic, acute myelogenous, chronic lymphocytic and chronic myelogenic. Family physicians should be able to identify the typical leukemia presentations, conduct the initial diagnostic assessment and understand how to care for survivors of leukemia.

Allogeneic stem cell transplantation requires moving the stem cells from a healthy person (the donor) to the patient's body following high-intensity chemotherapy or radiation. The donated stem cells may come from either a related or an unrelated donor.

When a transplant is successful, the donor stem cells can replace stem cells in the bone marrow. It can also have the only long-term treatment to the patient's condition. Some of the advantages of allogeneic stem cell transplantation are that once the donor cells engraft in the recipient, they establish a new immune system. The donated cells generate white blood cells that kill any residual cancer cells in the patient's body. That is called the “graft-versus-tumor effect.” and it could be much more important than the very rigorous treatment protocol that is performed to kill the cancer cells. Such gain will only arise through allogeneic stem cell transplantation.

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is well-established and manifest therapy for several patients suffering from malignant diseases such as leukaemia and lymphoma. AlloHSCT has also successfully treated patients suffering from inherited diseases, such as haematological, metabolic and primary immunodeficiency disorders.

The hypothesis that the immune system plays a prominent role in the regulation of leukemic disease in allogeneic hematopoietic stem cell transplantation (alloHSCT) is reinforced by the clinical finding that pathways for the immunological effector lead to the suppression of leukemic blasts. The inability to induce sustained remission following alloHSCT led to a resurgent interest in complementing concepts

The use of allogeneic hematopoietic stem cell transplantation in AML patients suffering from intermediate and high risk disease was the real breakthrough in improvement of treatment results. AlloHSCT offers rebuilding of the normal hematopoiesis ruined by leukemia and chemotherapy as well as regeneration of the immune system which after transplantation has the immune system potential of healthy donor what also means that if exposed to leukemic blasts may identify them as alien. Therefore, allogeneic hematopoietic stem cell transplantation makes the immune response against the transplanted patient cells including the blasts possible. If the immune response is not effective enough the donor lymphocytes may be infused (DLI). This approach proved to be effective especially in chronic myelogenous leukemia and in some indolent lymphomas but not good enough in AML. Unfortunately, DLI associates with a considerably toxicity with acceleration of the graft vs host process as a main cause.

Aim

The aim of the project was to evaluate the feasibility of the use of intra bone route and also to identify the cells which boosted in their potential by IB-DLI might be involved in anti-leukemic effect in other words in graft vs leukemia.

Having under our observation an ALL patient who relapsed after alloHSCT with leukemic infiltrations of the bones but not the marrow we injected the donor cells directly to the bone lesions with a positive effect. To exploit this approach further we started a project on the use of intra-bone route for injection of donor lymphocytes directly to the marrow cavity at relapse - thus providing the direct contact between the leukemic cells and the fresh lymphocytes from which those seeing blasts may be recruited. Nine patients they relapsed after alloHSCT entered the experimental group having as counter-partners the patients they received at relapse standard therapy.

Conclusion

The observation led to the following conclusions:

1. The intra-bone route proved to be convenient and free from unwanted effects.
2. The lymphocyte used for infusion were taken from the primary transplant material (stimulated) or obtained *de novo* from the blood with the use of leukophoresis (unstimulated), both cell populations except of the content of CD34+ cells did not differ especially the proportion of CD3+ cells was very similar.

3. Local anesthesia and low molecular heparin secured that infusion procedure was undisturbed
4. The patients which received IB-DLI enjoyed better 12- and 18-months survival as compared to those on standard therapy (77% vs 11%, p=0.006, and 55% vs 11%, p=0.035, respectively).
5. The positive effect was seen rather in the patients having the leukemic cells invaded by CD8+ lymphocytes which proportion in the marrow cell population declined as leukemia vanished (3053±1036 vs 937±47 × 10E6 cells/L, p<0.070). The same was with the proportions of CD8+cells co-expressing PD-1 (1238±476 vs 255±73 × 10E6 cells/L, p<0.060).
6. The key observation was associated with the analysis of the clonotype profiles (next generation sequencing) which showed that: (i) dominant clones identified in the recipients of IB-DLI were different from those seen in the lymphocytes prior to infusion (ii) the dominant clones rather persisted along the observation time even when the leukemia cells disappeared from the marrow, (iii) the profile of clonotypes in the marrow and in the blood was very similar in 32 out of 50 immunodominant clones what shows on the similarity between the immune system potential of the blood and marrow lymphocytes, however, the marrow lymphocyte had their local environment dependent distinctiveness.

The Conclusion IB-DLI (i) is feasibly, (ii) results with the improvement of the patients survival, (iii) is effective rather in those they have already responded to the leukemic cells with CD8+ cells but they had to be regenerated (PD-1 positivity of CD8+ cells) by providing fresh cells to achieve reversal of T-cell exhaustionand, finally, to exert clinically relevant activity.

Keywords: Stem cells, leukemia, lymphocyte, and Allogeneic stem cell transplantation.