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REVIEW

ACUTE LEUKEMIA AND STEM CELL TRANSPLANTATION

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Abstract

Acute leukemias are a type of clonal proliferative malignancies that affect all ages with a predominance of ALL in children and AML in adults. Left untreated they are lethal and require rapid medical management. Not only it imposes high health risks through complications such as infections, but the treatment itself is also a source of potential risks. Acute leukemias require intense medical observation and care. Current treatment consists of a combination of chemotherapeutic agents, stem cell transplantation and supportive care. Recent research offers a better understanding of the pathogenesis of these diseases and provide an advancement in the field of targeted therapeutic agents.

Keywords: *acute leukemia, stem cell transplantation*

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Introduction

Acute leukemia represents a heterogeneous group of malignancies that primarily affect the ability of differentiation, maturation and proliferation of pluripotent stem cells or their precursors. It is characterized by clonal expansion of immature cells (blasts) that invade the bone marrow and disrupt normal hematopoiesis, thus installing bone marrow failure which is clinically translated into three syndromes: anemia, infection and bleeding. Leukemic blasts are also capable of invading extramedullary territories such as: lymph nodes, liver, spleen, skin, central nervous system and testes (1) (2).

Acute leukemias can be divided into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), according to the origin of the malignant clone.

- ALL is the most common malignancy in children, accounting for approximately 25% of pediatric cancers. In pediatric population, ALL is 4 times more common than AML with two incidence peaks between 2-7 years and adolescents and young adults (3, 4).
- AML can occur at any age, with a high frequency in adults and an incidence that increases with age (median age at diagnosis being 70 years) (5).

Although acute leukemia is a potentially lethal disease with a rapidly progressive

course, there are multiple chemotherapeutic regimens designed to induce complete remission (CR), partial remission or even cure.

Over the years, a multitude of therapeutic strategies have been engaged and researched in disease management. Until recently, these diseases have been considered fatal. New advances offered improvement in survival rates, starting from administering chemotherapy alone with no significant results to administering a combination of cytotoxic chemotherapy with much higher response rates and much longer survival rates. Unfortunately, the disease is often very aggressive at the time of diagnosis, without response to high-dose chemotherapy or with multiple relapses after obtaining a brief partial remission (PR) or CR.

Patients that are unresponsive to standard therapy are candidates for allogeneic stem cell transplantation (ALLO). Recent studies focused on targeted therapies in acute leukemia have demonstrated favorable results after stem cell transplantation. It is indicated in the first- comlete remission in patients with intermediate or high risk ALL (6, 7).

Stem cell transplantation, also called hematopoietic stem-cell transplantation (HSCT) or hematopoietic cell transplantation involves restoration of normal hematopoiesis by transferring stem cells from a donor or from the patient himself (rarely used in acute leukemia) (8).

There are two types of stem cell transplantation depending on the origin of the stem cell:

Allogeneic transplant: also called ALLO- transplant, offers the possibility of replacing abnormal hematopoiesis with stem cells from a donor who is genetically matched. The donor is most commonly a family member. If there is no match with a parent or a sibling available, stem cells can be obtained from an unrelated matched donor (Figure 1 A).

Autologous transplant: also called AUTO- transplant, a type of transplant that uses the patient's own stem cells collected before the administration of high-dose chemotherapy or radiation, and then frozen for storage and later use. After chemotherapy or radiation, the harvested and processed cells are reinfused back to the patient (Figure 1 B) (9).

The type of stem cell transplant (ALLO or AUTO) is selected based on the type and stage of the disease, patient’s age and general health (10).

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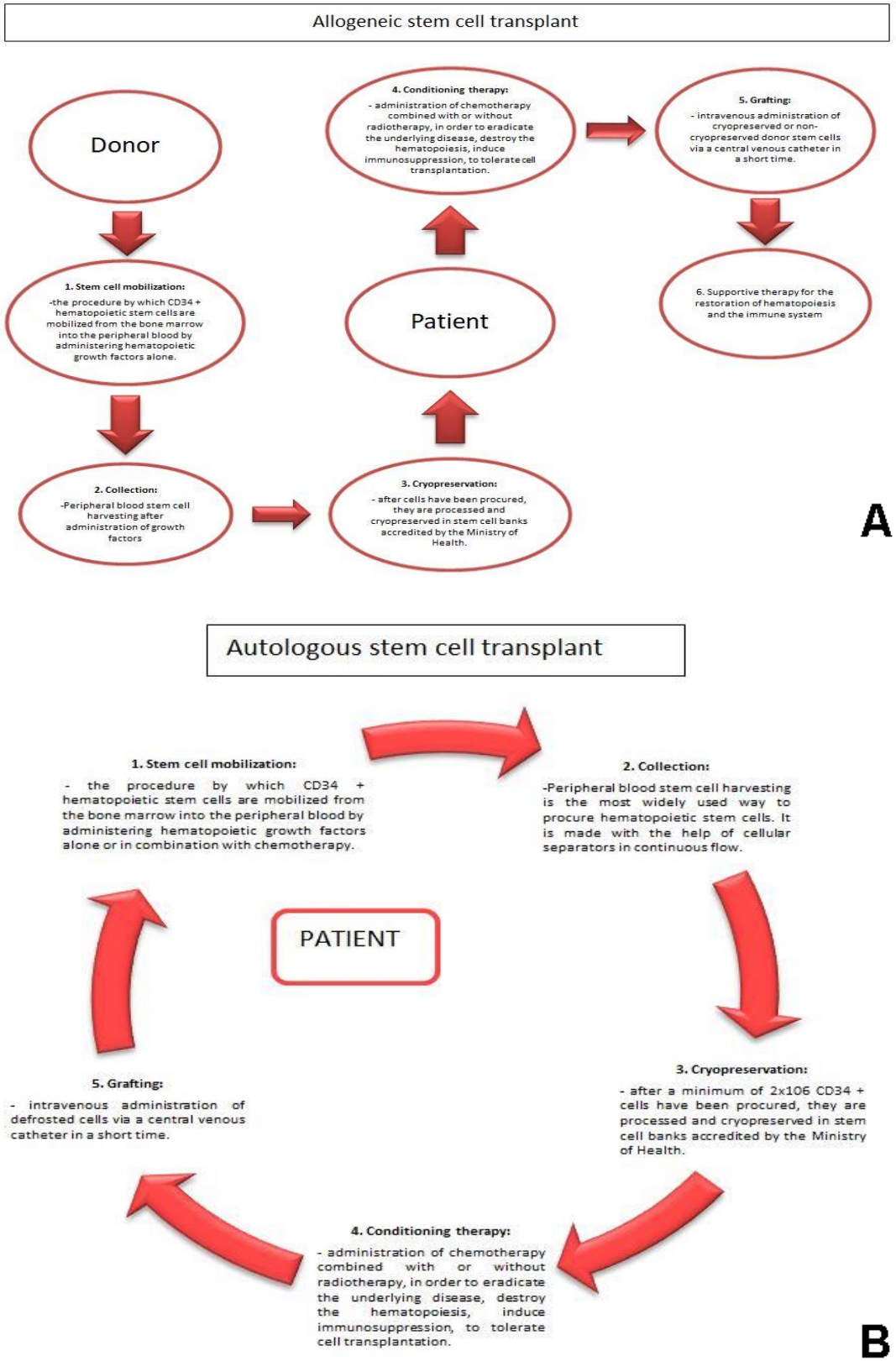

Figure 1 Stem cell transplant precedure. A. Allogeneic stem cell transplant precedure, B. Autologous stem cell transplant procedure

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Stem cell sources

The source of stem cells is represented by:

- bone marrow,
- peripheral blood after administration of granulocyte colony-stimulating factor (G-CSF), and
- umbilical cord blood.

After the allogeneic bone marrow is harvested, the patient undergoes myeloablative therapy, immunosuppressive and antitumor therapy, consisting of high doses of chemotherapy and/or radiotherapy which destroys cancer cells and also suppresses the immune system so that the risk of graft versus host disease (GVHD) is minimized. A disadvantage is the impairment of physiological hematopoiesis.

There are two types of conditioning therapy:

- Mixed conditioning regimens- using high-dose chemotherapy together with radiotherapy;
- Conditioning regimens without irradiation – only high-dose chemotherapy.

The next step after chemo and/or radiotherapy is infusion of the harvested bone marrow or peripheral blood stem cells through an intravenous (IV) central line. The cells eventually migrate in the bone marrow where they resume the proliferation, differentiation and maturation processes, restoring normal values of peripheral blood cells. When peripheral blood cell counts begin to return to normal (15-20 days), it is considered that the engraftment has occurred. This happens with the help of supportive therapy (antibiotics, platelet transfusion, red blood cell transfusion and drugs which prevent the side effects of chemotherapy and radiotherapy) (10, 11).

Acute myeloid leukemia

Allogeneic transplant is the only current treatment with curative potential in patients with myeloid leukemia, indicated in young patients with high-risk.

There are multiple studies demonstrating sustained complete remissions in patients with acute leukemia treated with allogeneic transplantation from an identical HLA donor (approximately 40% CR). The results depend primarily on the degree of bone marrow dysplasia, the percentage of blasts in the bone marrow, medical comorbidities, cytogenetic abnormalities, international prognostic index (12).

Allogeneic transplant is considered the optimal treatment of acute myeloid leukemia (AML) and it is recommended in high-risk patients in their first complete remission (CR1), and low-risk patients in the second remission (CR2). There is also evidence that patients under 40 years old show a superior outcome compared to those over 40 years, likewise patients with decreased percentage of blasts in the

bone marrow, having low mortality rates and low percentage of relapses.

Besides the outstanding results obtained after stem cell transplantation, the morbidity and mortality associated with the disease remain significant. The decision to initiate hematopoietic stem cell transplantation depends on a number of variables including age, performance status, medical comorbidities, international prognostic index, and many others (1, 13).

Autologous transplantation in acute leukemia is less studied and indicated due to the risk of graft contamination with blasts even in patients with complete remission after chemotherapy (14).

Acute lymphoid leukemia

Allogeneic transplant is recommended promptly to high-risk patients after achieving complete remission, and to those with intermediate risk or in the case of standard risk and relapsed ALL. Minimal residual disease (MRD) also represents an important indication for allotransplant in LAL.

Autologous transplantation can be tried in the absence of a compatible donor. Similar to AML, patients with relapsed ALL and poor prognosis, are treated with stem cell transplantation after achieving first complete remission. It has been shown that patients treated with allogeneic transplantation have significantly better response rates than patients treated with autologous transplantation.

Studies show that patients with a poor prognosis ALL and a matched HLA sibling should undergo stem cell transplantation in complete remission rather than in relapse. CR can be accomplished in 80% of children with ALL after the first relapse. Bone marrow transplantation appears to be at least as effective as conventional therapies in achieving a CR (15-17).

Side effects

Even if there are multiple studies proving the efficiency of stem cell transplantation in acute leukemia, many serious side effects have been reported during the high-dose chemotherapy and body irradiation as conditioning therapies.

The most feared complications are acute and chronic GVHD (13).

Acute GVHD usually occurs after 3 to 4 months post transplant and can affect multiple organs, but only three of them are more often affected. Skin damage is the earliest and most common complication, and the lesions vary from maculopapular rash (on less than 25% of body surface) to extensive exfoliative dermatitis and blisters, ranging from affecting skin palms and soles to the entire upper body. Gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain and hemorrhage may be present. The quantity of fluid loss can range from 500 ml/day to more than 1500 ml/day. Another involved organ is the liver, and its function is evaluated by the serum levels of

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bilirubin (2 mg/dL – 15 mg/dL) or AST 150-750 IU and alkaline phosphatase.

Some of the common side effects are included in Table 1.

Liver	Transaminase and bilirubin elevation
Gastrointestinal tract	Diarrhea, nausea, vomiting, mucositis, pancreatitis
Urinary tract/ kidney	Nephrosclerosis, nephrotoxicity
Skin	Rash, hand-foot syndrome
Neurologic	Cerebral atrophy
Pulmonary/ pleural	Pulmonary hemorrhage, pleural effusion
Cardiovascular	Cardiomyopathy, constrictive pericarditis
Risk of infection	Leukopenia
Bleeding risk	Thrombocytopenia
Infertility	
Secondary cancer	

Table 1 Complications or Side effects of Allogeneic Stem Cell Transplant

In order to diagnose the disease, in case of atypical pattern or to make a differential diagnosis, clinical presentation and eventually a tissue biopsy, are needed. Treatment is efficient in only a half of the patients and it may be a risk factor for infections and relapses. It usually consists of glucocorticoids, cyclosporin, tacrolimus, methotrexate and mycophenolate mofetil. In spite of a successful treatment, the patient may develop chronic GVHD that can be fatal in months or years (18-20).

Due to high intensity of conditioning regimens used in preventing graft rejection organ toxicity is one of the main causes of posttransplant mortality and morbidity. Assessing the degree of toxicity of conditioning regimens is important in establishing therapeutic behavior.

Transplantation modalities

Peripheral blood versus bone marrow transplantation

Until recently, peripheral blood was a source of stem cells for allogeneic transplantation. Retrospective studies have compared the outcome of patients receiving allografts with bone marrow versus peripheral blood in related donors. The results were outstanding, all patients who received peripheral blood stem cells achieved more rapidly engraftment and a shorter hospitalization period. In different studies, the incidence of acute GVHD was similar with peripheral blood and bone marrow, but chronic GVHD is more commonly seen in peripheral blood stem cell transplant (21).

Umbilical cord blood transplant (UCBT) advantages

There are two recent publications on stem cells from umbilical cord as unrelated

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transplants in acute leukemia. Because of the delay or inability to engraft, this method is still not used as conditioning treatment in first CR but if the problem could be overcome, it most likely would become the best choice for unrelated transplants (22, 23).

A study by Ooi et al. at the University of Tokyo reported the clinical outcomes of 18 patients with de novo AML. 14 patients were transplanted after their first remission (three relapsed in the first 2 years and 1 died of MODS). All 14 patients were treated with mixed conditioning therapy (ablative total body irradiation + high-dose chemotherapy) + a higher dose of stem cells compared with the other 4 patients with low response. These results confirmed the importance of stem cell dose in obtaining optimal survival rates and engraftment in adults with low rates of acute and chronic GVHD (24).

Differences between allogeneic HSCT, autologous HSCT, and chemotherapy alone

Multiple studies showed that autologous as well as allogeneic bone marrow transplantation offer a better progression-free survival (PFS)/outcome than intensive consolidation therapy.

RA Zittoun and al. in the New England journal of Medicine, report a study on 343 patients with CR of which 144 were assigned to undergo allogeneic bone marrow transplantation, 95 autologous transplantation and 104 intensive chemotherapy.

The results exhibited that PFS at 4 years was:

- 55% for allogeneic transplantation,
- 48% for autologous and
- 30% for intensive chemotherapy.

In conclusion the relapse rate was lower in the autologous and allogeneic transplantation and the mortality rates were lower after chemotherapy alone and the highest after allo/ auto HSCT (9).

New strategy for AML patients

- -low risk- patients in their first CR, chemotherapy and transplant show similar results.
- -intermediate risk- the majority of AML patients. In this case the best option is allo-HSCT with matched sibling donor.
- -high risk- relapsed patients. The only strategy available is early transplant, so it is very important to identify the high-risk patients in order to find a source of hematopoietic stem cell (1, 10).

Conclusions

Allogeneic HSCT is the only treatment with curative potential for AML patients. However, they meet multiple side effects and long/short term complications, but

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treatment led to a better quality of life and a higher PFS, as the main objective.

Most recently, dividing patients into low, intermediate and high-risk groups led to a better assessment of the disease risk and thus optimal treatment and better outcomes.

Conflict of interest

The authors declare no conflict of interest.

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