

Comparing sources of stem cells for transfusion in acute myeloid leukemia

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Abstract

Stem cell transfusion have undeniable benefits for patients with Acute Myeloid Leukemia (AML) especially for augmenting the mostly suppressed normal precursor stem cell necessary for fighting infections. While many patients use own stem cells, other patients that might benefit from this treatment are unable to use own stem cells and may lack Human Leucocyte Antigen (HLA) identical donor because of HLA polymorphism. Stem cells collected from the bone marrow, umbilical cord blood and peripheral blood stem cells may be from own or HLA partially mismatched unrelated or related donors. The data obtained show that hematologic recovery is highest in peripheral blood and lower in cord blood than in bone marrow, graft versus host disease is higher in peripheral blood than in bone marrow and lowest in cord blood, incidence of relapse and survival were comparable across sources, mortality is higher in cord blood than in peripheral blood and bone marrow and is mostly as a result of infection due to poor engraftment. This comparison is aimed at improving the quality of decision taking on source of stem cells for transfusion in cases of AML as it compares cord blood, peripheral blood and bone marrow in a single study.

Keywords: Acute Myeloid leukemia (AML), Stem cell transfusion, Hematopoietic stem cells, cord blood, peripheral blood, bone marrow, graft versus host disease, relapse, mortality, survival.



This article can also be found as part of the book

"New therapies for Acute Myeloid Leukaemia" that can be purchased in **Amazon**.

Introduction

Acute Myeloid Leukemia (AML) is the prevalent form of acute leukemia in adults with about 13,000 new cases diagnosed each year in America with children accounting for less than 10 percent(1). The subtypes of AML are diagnosed by examining blood and bone marrow samples for leukemic cells and the cytogenetic changes in the cells (2). This diagnosis is necessary for treatment decision because in AML, the precursor stem cells that are formed are abnormal and so cannot differentiate into normal white blood cells that fights infection(3). A typical treatment plan in AML include chemotherapy, stem cell transfusion, all-trans retinoic acid (ATRA) and other newer treatments approved or in clinical trials(4). Stem cell transfusion is increasingly playing a critical role in AML treatment because the myeloid blast are not functional and needs to be augmented to fight infections(5). However it is still not

clear which of the treatment option is best for consolidation, treatment decisions for patients with AML should be made on a case by case basis taking into consideration age, health and other factors.

In AML, chemotherapy is the first-line of treatment, it is aimed at inducing a remission which may be followed by another chemotherapy or stem cell transfusion to restore the bone marrow function in the patients. These cells may be harvested from the patient (autologous) or from a donor (allogeneic). Depending on the site of harvest, the sources of stem cell for AML therapy may include bone marrow(BM), peripheral blood(PB) or cord blood(CB) (6).

Complications may arise from stem cell transfusion which could affect the outcome of the treatment with the early ones being associated with the effects of the preparative

regimen used and may include mucositis, hemorrhagic cystitis and hepatic veno-occlusive disease(7).Others are acute and chronic GVHD caused by the donors mature T- lymphocytes, infections mainly caused by prolonged pancytopenia, relapse and mortality.(8,9)

Despite this shortcomings, stem cell transfusion is increasingly being used for patients with more aggressive forms of AML, those who have had a relapse following remission, and those who do not achieve remission after initial induction therapy(5).

Technological advances have resulted in improved HLA typing and good GHVD management, these advances together with the establishment of more cord blood banks and recent data showing comparable result of cord blood to other sources of stem cell have left a fair options for selection. This study is one of the few that aim to compare bone marrow, peripheral and cord blood stem cells specifically for AML patients.

Bone Marrow

Majority of hematopoietic stem cells(HSC) are resident in the bone marrow which has made HSC synonymous to bone marrow(10). Stem cells from bone marrow can be transfused as autologous or allogeneic (11) . Allogeneic transfusion is indicated in patients in second remission and in untreated first relapse but patients transfused in first remission achieve better outcome(7). Autologous transfusion are offered to older patients and in patients in first remission and as a therapeutic option in second remission (12). Results from randomized studies in patients that were transfused with bone marrow and those that received chemotherapy alone have been mixed with some showing promise while others show no superior advantage in the outcome(13-17).

Peripheral Blood

The subcutaneous injections of Granulocyte-colony stimulating factor to mobilize stem cells from the patient or donor's bone marrow into the peripheral circulation has made peripheral blood the most common source of stem cell for transfusion (18). Mobilized peripheral blood is now replacing bone marrow, as harvesting peripheral blood stem cells (PBSCs) is easier than harvesting bone marrow stem cells (19). A randomized study show a relapse advantage and comparable survival rate of PBSC over chemotherapy as post remission therapy(20)

Cord Blood

Cord blood is increasingly becoming an important source of hematopoietic stem cells. The increase in number of cord

blood banks have opened options for cord stem cells to be stored for individual, family or for public use after it is harvested(21).The advantages of cord blood stem cells are the availability, ease of harvest, and the reduced risk of graft-versus-host-disease (GVHD). It use however , have been limited by the less number of cells that can be harvested and the delayed immune reconstitution, which leaves patients vulnerable to infections for a longer period of time(22-23). Large number of children with AML have benefitted from CB transfusion and they are increasingly being used in adults when matched unrelated donor or a haploidentical donor are not available with some promising result (24-27).

Comparison

Hematopoietic recovery

After stem cell transplantation, successful engraftment is determined by performing daily blood cell counts. Neutrophils and platelets are commonly used markers of hematopoietic recovery, an absolute neutrophil count (ANC) of at least 500 for three days in a row and platelet count of 20,000 - 50,000 are required to establish engraftment (28)).Many randomized and meta-analysis studies have shown superior hematopoietic recovery in peripheral blood (PBSC) more than in bone marrow(BM), with days for recovery of neutrophils ranging from 12-35 in PBSC and 13-68 in BM while platelets recover at a median time of 16days for PBSC and 23 days for BM(29-35).Cord blood(CB) hematopoietic recovery is slow compared to BM and PB (36-41).This delayed engraftment in CB has been linked to lower doses of nucleated cell count in single CB donation compared to BM/ PB and have raised concerns about successful engraftment in adults with larger body weight (42).Studies are being done to address this challenge, one being the use of double cord blood units instead of single unit to achieve a human leukocyte antigen (HLA) matching 6/6 and a nucleated cell dose of more than 3×10^6 cells/ kg (43).

Graft versus host disease.

The source of stem cell for AML patients have influence on the risk of GVHD (21).A small increase in the risk of acute GVHD after PBSCT over BM have been reported in cohort studies while randomized studies fail to show any significant increase (34,44,45,46,47,48,49,50).PBSC have been linked to significant increase in risk of chronic GHVD but not acute GVHD(51-54). Concerns about larger concentration of mature, immune-competent T cells that could increase the risk of GVHD have necessitated comparative studies on T- cell depleted sources over non T- cell depleted sources with results showing significant decrease in GVHD in depleted sources

but with high level of graft rejection (55-56). Less graft rejection and better GVL response has been achieved using reduced level of T – cell below 100% (57) but studies involving selective purging of CD 8 T- cell have been most promising(58). CB have low risk of acute and chronic graft versus host disease (GVHD) even with broader HLA disparity than PBSC/ BM(39,59), this may be due to the fewer number and immunological naïve CB-derived T cells thus making it preferable to T- cell depleted sources. There is also a preserved graft versus leukemia (GVL) effect in CB due to higher number and unique properties of NK cells in CB grafts(39).

Relapse

Animal studies showed a lower relapse rate with PBSC than with BM(60) but only few human reports have confirmed this low relapse in PBSC compared to BM (34,61,62). PBSC and BM have been reported in many studies to be comparable in terms of relapse rate (59,63,64) with only one study reporting higher relapse with PBSC than BM (69) but the high relapse rate reported might be due to bias selection with regards to risk profile. No significant difference in the risks of relapse in CB compared to BMT/PBSCT was recorded (65,66).

Mortality

Deaths from stem cell transfusion commonly results from GVHD and infection among other causes. Depending on the cause, the time of death occurred at a median of 3 months with a range of 0 to 200 months(67). Some studies have recorded lower transplantation related mortality in PBSC than BM in Myelodysplastic syndromes (MDS) (68) and in certain subtype of leukemia(69) while a comparable outcome was reported in a meta-analysis study(62). There are attempts to link the increased risk of chronic GVHD in PBSC to the high

mortality in early stage of AML as against the lower mortality rate in the more advanced acute leukemia (70). CB has increase risk of mortality compared to BM/PBSC (40), reduced mortality rate was reported in patients with higher dose of CD34⁺ CB (21). Most of the deaths in CB were caused by infection and may be due to delayed hematopoietic engraftment. Sequential cord blood transplantation, cord blood expansion and combination cord blood and haploidentical stem cell transplants are Strategies being tried to reduce mortality in cord blood with promising results(21,71,72).

Survival

Many studies have reported overall survival and leukemia-free survival to be nearly identical for patients grafted with unrelated donor PBSCs or BM(31,73,74,75,76). Some have showed superior overall survival in PBSC compared to BM in advanced stage of acute leukemia patients in second remission(51,61,77) but fail to establish any significant difference in survival in early stage of the disease with either sources (65). Comparable survival in CB and PBSC/ BM among standard-risk and high-risk groups have also been recorded(41,78 ,79). The comparable survival reported in CB were in double cord blood transplants and young patients which might have contributed to the better rate.

Conclusion

Several factors could influence the outcome of stem cell transfusion for AML treatment, knowing the benefit and risk of the sources of stem cells is critical in taking informed decision.

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