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Thrombopathies and Allogeneic Bone Marrow Transplantation: Stakes and Perspectives

Zmouli N[1,2]*, Lamia Ait Ouali[1], Houari Toumi[1] and Mohamed Hammadi[1]

1University Hospital Establishment of Oran (EHUO), Algeria
2Faculty of Medecine,University of Oran, Algeria

Abstract

Thrombopathies are hemorrhagic pathologies involving diverse anomalies and of which the clinical and biological expression are variables. The constitutional thrombopathies are rarer than the acquired forms. However, they are rather frequent in our country because of the strong endogamy. They brought an essential information about the molecular bases of the platelet function. Treatment of thrombopathy requires, first of all symptomatic measures: haemostatic glues, desmopressin and the blood transfusion which must be only reserved for the difficult gestures or for the high hemorrhagic risk. The Allogeneic bone-marrow transplantation represents the only curative treatment and requires a compatible donor HLA.

Keywords: Thrombopathy; Allogeneic bone marrow transplantation; Blood transfusion

Introduction

Bone marrow is the place for the production of the hematopoietic cells which differentiate in to three groups: red blood cells, white blood cells and platelets. It is located in the hollow bones. Bone marrow aspiration is carried out by a puncture on the level of the sternum or the posterior iliac peaks under local anesthesia by the doctor. Hematopoietic stem cells (HSCs) are very rare cells, representing approximately one in 100,000 bone marrow (BM) cells in the adult. HSCs are characterized by their unique ability to self-renew and give rise to the entirety of the blood and immune system throughout the lifetime of an individual. The concept of the existence of an HSC that is capable of reconstituting hematopoiesis *in vivo* was first introduced more than 60 years ago, when Jacobson et al. demonstrated that lead shielding of the spleen protected mice from otherwise lethal γ-irradiation [1]. Subsequently, Jacobson and colleagues demonstrated that similar radioprotection of mice could be achieved via shielding of one femur. Shortly thereafter, it was demonstrated that intravenous injection of BM cells also provided radioprotection of lethally irradiated mice. Interestingly, investigators initially hypothesized that the radioprotected spleen or BM provided soluble factors that mediated radiation protection. Since then, allogeneic hematopoietic stem cell transplantation (HSCT) has evolved to become a frequently used and effective therapy for many hematologic malignancies.

Changes in both HSCT and non-HSCT therapy have modified the indications and applicability of HSCT over time. In chronic myeloid leukemia (CML), HSCT which is once the mainstay for cure is now largely supplemented by molecularly targeted therapy. In recent years, especially after the advent of reduced intensity conditioning in the late 1990s, allogeneic HSCT is increasingly used in older patients and as an effective salvage strategy for patients with lymphoma or myeloma not responding to chemotherapy or autologous HSCT. Transplant-related mortality (TRM), although steadily declining, still remains a challenge [2].

Gift of Bone Marrow

Allogeneic bone marrow transplantation, as we understood it, allows saving lives, but cannot take place without donors. We initially search a potential donor within the siblings of the patient by determining HLA type, true genetic identity card of the cells. If one of the brothers and sisters is compatible, we speak about geno-identical allogeneic transplantation having the advantage of reducing the complications post-transplantation. Statistically, two people born of same parents have 25% of chance to be compatible. If the geno-identical transplantation is impossible, we will direct ourselves towards the national and international register donors of bone marrow. In this case we will speak about pheno-identical allogeneic transplantation. The gift is anonymous and free. The donor must be between 18 and 50 years at the time of the registration which takes place after a medical interview and a blood sample to determine its typing HLA. Once registered, the donor commits himself to remain available and reachable. Clinical and serologic assessments complementary will be necessary, as well as the second medical interview to confirm the gift. Statistically, compatibility between two foreign individuals is with a frequency from approximately 1 out of 1 million; from where importance to increase the number of the voluntary donors. Let us note that a donor has freedom to withdraw from the register instantly.

Methods to Collect Stem Cells

There exist two ways of collecting the stem cells:

Extraction of bone marrow (BM)

Requiring a 48 hours hospitalization; it is carried out under general anesthesia by multiple punctures on the level of the posterior iliac peaks. BM is reconstituted quickly and extracted volume is administered according to the weight of the donor and the patient.

Extraction of peripheral stem cells (CSP)

Immature hematopoietic cells not differentiated from bone marrow. It is carried out by cytapheresis after stimulation of marrow

***Corresponding author:** Zmouli N, Assistant Professor, University Hospital Establishment of Oran (EHUO), Algeria and Faculty of Medecine, University of Oran, Oran 31000, Algeria, Tel : 0021341533331, 00213770773234; E-mail: noudjoum@yahoo.fr

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by growth factors during several days preceding the extraction. This process consists of extracting the CSP from the donor by blood test, by selecting them via a device. It lasts one half-day in external care. This presents an advantage for the donor. BM and CSP are then conditioned in the form of packet of transfusion by the cellular service of therapy. The choice of one or the other will be done according to the pathology treated and of the effectiveness of stimulation by growth factors.

65% of transplantations are peripheral stem cells transplantation, 35% are of BM transplantation [3].

Stem Cell Transplantation at the Receiver

The stem cells of the donor are injected into the receiver like a blood transfusion. The cells directly will nest in the BM of the patient. 14 to 24 days' time is necessary to note a resumption of the graft, that is to say the production of new blood cells by the grafted stem cells. During this time, the patient remains particularly vulnerable to the infections and there must remain isolated from the other patients [4].

Thrombopathies

Thrombopathies or functional anomalies of platelets can either be constitutional or acquired. They can be accompanied by thrombopenia to a variable extent. The constitutional thrombopathies are rare: their knowledge, each day refined, allowed however formidable progress in the comprehension of platelet physiology and consequently of the hemorrhagic or thrombotic phenomena. Each stage of platelet physiology can be reached and we will describe these thrombopathies while insisting on the description of the structural anomalies which underlie the functional anomalies. The acquired thrombopathies are much more frequent but also more heterogeneous; often multifactorial, their physiopathogenic mechanism in general is less understood [5].

The constitutional platelet anomalies are at the origin of relatively rare pathologies causes of clinical bleedings of variable intensity. These hereditary pathologies of the megakaryocytic lineage, which affect sometimes other cellular lineages, are located by not specific clinical signs (bleeding) coming along with anomalies of the platelet functions. These platelet defects affect the processes of adhesion and platelet aggregation, the genesis or the secretion of granules, the procoagulant activity of platelets or still cell surface receptors and/or the intraplatelet signalling.

The characterization of some constitutional thrombopathies allowed to understand the mechanisms of production and activation of blood platelets better and was a source of inspiration for the development of few current antithrombotic strategies [6]. Their discovery is done at the time of a cutaneous-mucosal hemorrhagic syndrome associated with a lengthening of the bleeding time with a normal rate of platelets or slightly decreased [5]. Abnormalities of platelet function all lead to signs and symptoms characteristic of defects of primary haemostasis like bleeding into the mucous membranes, epistaxis, menorrhagia and skin ecchymosis. The patient may also suffer from abnormal intraoperative or postoperative bleeding and oozing from small cuts or wounds [7].

The quality of the interrogation and the confirmation of the platelet functional defects *in vitro* are fundamental for a precise diagnosis [5]. The peripheral blood platelet count, the bleeding time and, for some laboratories, Platelet function analyser tests, PFA-100 or PFA-200 are first-line tests of platelet function. However, some disorders of platelet function are not detected by these tests. Additional information may be obtained by inspecting a peripheral blood smear, which may show abnormalities of platelet size or morphology that may be of diagnostic importance. If the screening procedures or clinical history suggest a disorder of primary haemostasis and Von Willebrand factor function is normal, further tests should be organized.

Drugs (Aspirin, non-steroidal anti-inflammatory drugs, corticosteroids, alpha-antagonists, beta blockers, clopidogrel, penicillin etc.) may affect platelet function tests and the patient must be asked to refrain from taking such substances for at least 7 days before the test. Platelet aggregation tests like turbidometric technique using ADP, collagen, ristocetin, adrenaline, thrombin, arachidonic acid, endoperoxide analogues, and calcium ionophore should be performed. Expression of platelet glycoproteins can be assessed by flow cytometry, although this does not necessarily correlate with functional activity and electron microscopy investigate granules content and release [7].

Management

At present, the treatment of the constitutional thrombopathies calls on symptomatic measurements initially. Personal hygiene is advised and sporting activities with strong traumatic risk, prescription of the drugs which interfere with the platelet function and the intramuscular injections must be avoided. Prior to hemorrhagic demonstrations, local compressions, the haemostatic adhesives must be applied in first intention if possible, before the decision of platelet transfusion which must be avoided to the maximum. In the same way the arterial embolisation can be effective in the event of severe and repeated epistaxis, and can make it possible to postpone the platelet transfusions concentrates.

The dDAVP or desmopressin is effective for few hours to prevent or attenuate a moderate hemorrhagic syndrome. A shortening of bleeding time was thus shown among patients of thrombopathy by membrane anomaly (other than the Type I Glanzmann thrombasthenia) or by defect of secretion. The mechanism of action brings a release of the Von Willebrand factor of the endothelial vascular cell and a platelet activation thus favoring adhesion and aggregation. After administration of desmopressin, in rule in intravenous perfusion with the amount from 0.3-0.4 μg/kg, there exists one refractory period from 48-72 hours. However, this molecule even made it possible in certain cases to carry out small interventions (dental extractions, cutaneous biopsie etc.) there by avoiding the platelet transfusion concentrates. Thus, those must be held with the cases where the hemorrhagic demonstrations are alarming, or for the preparation with heavy surgical operations, even possibly with the childbirth. The use of the concentrated leukocyte-depleted blood, by apheresis of single donor, in order to avoid to the maximum the anti-HLA allo-immunization is recommended. In the event of thrombopenia by membrane glycoproteinic anomaly, the risk of allo-immunization against the missing glycoprotein is added again to that of the anti-HLA allo-immunization, making the patient refactory with any later platelet transfusion.

It is in these conditions that the bone marrow transplant was able to be envisaged [5], for example during Glanzmann thrombasthenia (TGZ) and syndrome of Bernard Soulier (BSS) which are most frequent in Algeria (20 families of BSS and 80 families of TGZ at the level of the CTS of Algiers center over a period of 2 years) [8]. When this one was made during certain immunizing deficits (syndrome of Wiscott-Aldrich and syndrome of Chediak-Higashi) we noted a correction of the thrombopathy.

Stakes

The Allogeneic bone marrow transplantation remains the only

curative treatment of the severe constitutional thrombopathies and thus avoiding the blood transfusion [5].

Only 30% of patients who require an allogeneic HSCT will have an HLA matched sibling donor. A search for an unrelated donor will be undertaken for patients without a matched family donor. However, for many patients, particularly patients of diverse racial and ethnic backgrounds, it may not be possible to rapidly identify a suitably matched unrelated donor.

The rate of complications is higher in the case of allogeneic transplantation than of the autogenic transplantation. One of the most important risks is the reaction of the graft against host (GVH). The GVH occurs when the grafted stem cells have an immune reaction against the cells of the donor. The grafted cells see the cells of the receiver like the foreign ones and then they start to destroy them [9]. GVH is of two types namely acute GVH arising in 3 months following the transplant and would be more frequent when the transplant is of medullary origin, chronic GVH arising after the 100th day would be more frequent with the transplants of stem cells stemming from some circulating blood. It would be due to lymphocytes TH2. In spite of numerous existing treatments, it can become to it alone the real disease.

Delayed or poor graft function can exaggerate and prolong the risks of infection and can increase the risk for peritransplant mortality. Failure to engraft can occur if insufficient hematopoietic progenitors are infused. Most investigators recommend infusion of a minimum of at least 2×10^8 mononuclear cells per kilogram to ensure establishment of an allogeneic graft. Umbilical cord blood (UCB)-derived hematopoietic grafts can engraft with a lower number of cells.

Infections are among the foremost causes of non-relapse mortality in HSCT recipients and can cause significant morbidity, both in the early and late transplant period. Immune defects occurring in the post-transplant period can be divided into predictable phases based on time from engraftment (sustained absolute neutrophil count >500/μL), with characteristic infections in each phase. Antimicrobial prophylaxis regimens tailored to address the risk for specific infections during these time periods are effective in decreasing the incidence of post-transplant opportunistic infections. Evidence-based guidelines for preventing infectious complications among HSCT recipients have been published and can be used as a reference for determining infection risk and assigning antimicrobial prophylaxis for an individual patient. Engraftment generally occurs within 14 to 28 days in allogeneic HSCT recipients. Recipients of grafts from unrelated donors (URDs) or umbilical cord blood (UCB) tend to engraft later compared to sibling donors; more importantly 5-10% of unrelated-donor and 5-20% of UCB grafts may fail to engraft, leading to prolonged neutropenia and extended transfusion dependence. The main risk factors for infection during this pre-engraftment phase are disruption of mucocutaneous barriers and indwelling venous catheters. Bacterial infections can occur in up to 30% of transplant recipients during this initial period and usually arise from normal flora of the skin (coagulase-negative *Staphylococcus*), oropharynx, and gastro-intestinal tract (Viridans streptococci, *Enterococcus* spp., and enteric gram-negative bacilli). Colonizing yeasts or molds also invade because of neutropenia and disruption of normal host flora and can lead to systemic mycotic infections (most often *Candida* spp. or *Aspergillus* spp.) in 10-15% of patients. Reactivation of herpes viruses can occur in the absence of prophylaxis.

Sinusoidal obstruction syndrome (SOS), also known as hepatic venoocclusive disease (VOD), is a serious liver disorder characterized by jaundice, ascites, fluid retention, and hepatomegaly that complicates up to 5-50% of HSCT.

Alveolar hemorrhage is a clinical syndrome of acute onset of pulmonary infiltrates and hypoxemia with a progressively bloodier Bronchoalveolar lavage (BAL) on bronchoscopy [10].

The level of HLA matching for an optimal HSCT outcome is still a debatable question. The debate concerns the number of authorized HLA mismatches. Some data have suggested that adverse effect on survival is observed with a single HLA-A, B, C, or DRB1 mismatch [11].

Three alternative graft sources, umbilical cord blood (UCB), haploidentical related donor and mismatched unrelated donor (MMUD) are available. UCB is associated with delayed hematologic recovery and immune reconstitution. Haploidentical transplantation is characterized by donor availability for transplantation but may be complicated by a high risk of graft failure and relapse. MMUD transplantation may also be an option, but graft-versus-host disease (GVHD) and immune deficiency may be of greater concern. Phase-2 studies have documented advances in HLA typing, GVHD prophylaxis, and infection prevention, which have improved survival [9]. The same patient evaluated in different transplantation centers may be offered MMUD, UCB, or haploidentical HSCT depending on center preference. However, after both UCB and MMUD transplantations, delayed immune reconstitution and infection risk are of clear clinical concern. Despite advances in antimicrobial therapy, infections remain a major cause of death after alternative donor HSCT, particularly in older patients. UCB contains fewer T cells than other stem cell sources, and UCB lymphocytes have specific immunologic characteristics, such as a different response pattern to cytokines and a greater proportion of naive T cells. In a prospective analysis of immune reconstitution in UCB recipients and HLA-matched unrelated donor (MUD) recipients from the Dana Farber Cancer Institute, Jacobson et al. found that CD3þ T cells recovery was significantly delayed in the UCB group compared with the MUD group for as long as 6 months after HSCT, including naive and memory CD4þ T cells, regulatory T cells, and CD8þ T cells [1]. These unique properties of UCB may contribute to the high risk of infection reported in some studies. However, this study compared UCB to MUD and not to MMUD, the most clinically relevant comparator. So far, no study has compared a cohort of patients who underwent transplantation either from UCB or from MMUD with regard to infectious complications and long-term immune recovery that prompted the report herein.

Patients who underwent transplantation from alternative donors represent a population with very high risk of infection. Detailed phenotypic analysis of immune reconstitution may help to evaluate infection risk and to adjust infection prophylaxes. Physicians not directly involved in the daily care of these patients should be aware of this situation, given the growing numbers of patients who underwent transplantation with alternative donors who survive long term [12].

Perspectives

Researches are in hand with an aim of considering the transplantation with donors having only one genetic half compatibility with the receiver. Haplomismatch transplant (parents, half-brothers and half-sisters etc.) became possible to carry out a allogeneic BM transplantation, without causing rejection, with only a haplotype jointly, takes with an effectiveness which seems also good, if not more, that other compatible transplantation. We thus widen considerably the

field of the potential donors. The two parents and the children of each patient become possible donors. It is currently limited to the treatment of leukemia. It will be extended thereafter to other hematologic pathologies and incontestably will take an increasingly significant part in the activity of the research center in oncology in Marseilles [13].

At present, the transplants of umbilical cord blood are mainly used at the children, but the researches on the expansion of the in vitro stem cells and the use of multiple products of the umbilical cord blood could allow the use more generalized by this type of therapy at the adult [14].

The HLA and KIR genetic systems regulate the transplantation barrier. Clinical outcome after unrelated donor transplantation can be achieved with donor matching for the highly polymorphic HLA loci. When HLA disparity cannot be avoided, judicious selection of a donor with the fewest HLA mismatches and avoidance of certain loci may provide patients with the opportunity for lifesaving transplantation. Disease stage remains a strong predictor of overall transplant outcome, and expediency in timing of transplantation for patients with high-risk disease is paramount. New research avenues include identification of novel MHC resident genetic variation that may contribute to risks of GVHD and transplant-related mortality (TRM) and the precise role of the KIR systems in preventing transplant complications and disease relapse [15].

For the prevention and the treatment of the GVHD, we test at present drips of cells T regulating, the irradiation of the set of lymphoid fabrics as well as of new immunosuppressive drugs [14].

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