The Possible Role of Cord Blood in the Management of Radiation Damage.

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These comments are presented in the hope that they describe the possible roles of cord blood transplantation in the aftermath of Chernobyl-type accidents and other situations involving the release of large amounts of radiation. The consequent exposure of large numbers of people to radiation damage is a dreaded catastrophe, 20 years after Chernobyl.
I will focus specifically on the currently known functions of cord blood stem cells and their potential application to the treatment of victims of such catastrophes.

Introduction

It has long been known that ionizing radiation produces deleterious effects on organisms and cells. These effects have been well characterized and there has been considerable study of the clinical effects of chronic and acute exposure. Clearly, the type and dose of radiation and the rate at which it is absorbed by cells and tissues, are major variables. In acute exposures of the Chernobyl type, that also produce radioactive materials that continue to produce ionizing radiation in a more chronic way, the consequences have been characterized as either rapidly developing, called deterministic or stochastic, which develop slowly over many years. Additional damage was produced by the context: the explosion of the reactor and the fire that ensued produced thermal burns on many of the victims who died in the first weeks after the explosion, which, together with burns due to high dose beta radiation complicated greatly the treatment of victims enduring acute radiation syndrome. A large body of experimental data in animal models demonstrates that it is possible to rescue individuals exposed to lethal doses of radiation by restoring their bone marrow function with hematopoietic (blood-forming) stem cells.
Until recently, the only source of stem cells for bone marrow restoration was bone marrow from related or unrelated, HLA-matched donors. Grafts could be obtained directly from the bone cavities where bone marrow grows or from peripheral blood by first “mobilizing” the stem cells with growth factors. More recently, cord blood has proven to be a very good stem cell source for the restoration of bone marrow in the treatment of leukemia and other diseases and legislation has been signed into law for the support of a National Cord Blood Program with a substantial inventory.

The Role of Hematopoietic Stem Cell Transplantation in Nuclear Emergencies

Bone marrow aplasia, as a lethal consequence of exposure to large doses of radiation, originally prompted interest in bone marrow transplants more than fifty years ago. However, the role of hematopoietic stem cell transplantation in the care of victims has been questioned, although it is, still, the only hope for individuals whose own stem cells have been destroyed in nuclear attacks or accidents. The reason for questioning the efficacy of these transplants is the low yield of transplanted survivors in previous accidents, including Chernobyl, a result largely determined by logistic difficulties: finding bone marrow donors opportunely, measuring accurately the quality and quantity of the radiation received to determine the amount and type of radiation damage, and overcoming the burns and other direct damage, in the field. A group of 13 patients exposed to ≥ 4

Gy, received bone marrow transplants to combat the radiation-induced bone marrow suppression but only two survived. Among engrafted survivors, apparent transplant rejection was encountered in several patients, suggesting that immune cells may have survived the high dose of radiation, despite their much reduced numbers in the blood.

If the radiation dose received is sub-lethal (destroying only some fraction of the hematopoietic stem cells) patients should be recoverable without transplantation, by using growth factors, as in the Brazilian accident (Butturini A, et al., Lancet 2(8609):471-475, 1988). If, however, the amount of radiation received exceeded the maximum tolerated by tissues other than the marrow, such as the skin, gut, lung or nervous system, obviously, hematopoietic stem cell rescue would obviously not overcome other lethal lesions. **The realm of hematopoietic rescue, therefore, lies in a range of radiation doses between these two circumstances.**

The total-body irradiation absorbed by individual victims of nuclear explosions and accidents is not likely to be homogeneous and risk levels based on dose calculations are, therefore, treacherous. An example of the difficulties in estimating the radiation received was described for Patient A after the 1999 accident at Tokai-mura (T. Ishii, et al, J Radiat Res (Tokyo) 42 Suppl:S167-182).

In addition, damage to different tissues and organs may be additive to some extent and radiation in these cases is often accompanied by thermal burns and traumatisms that increase overall morbidity and mortality. There is consensus, however, in that the blood and immune system are the tissues most easily damaged beyond possible spontaneous repair because of the high radio-sensitivity of the hematopoietic stem cells. Hence, stem cell rescue will be necessary and will succeed in some patients. In others, stem cell transplants may be performed although conceivably, they might have recovered with just hematopoietic growth factors. Thus, for example, in the 1988 Brazilian accident, eight patients developed marrow aplasia after a cesium-137 exposure and were treated with recombinant GM-CSF. Four of seven evaluable cases survived. It is an open question whether the other three would have had a chance if cord blood had been available and all had been transplanted.

The use of both, allogeneic cells and growth factors, in the same patient is an obvious possibility of bypassing uncertainty as to the marrow lethality of the dose. This approach was tried on one of the three victims of the Tokai-maru accident in October, 2000, who lacked matched bone marrow donors either related or unrelated and was transplanted with DRB1-mismatched cord blood (Nagayama H, et al., Bone Marrow Transplant 29:197-204, 2002). Donor neutrophils and platelets appeared rapidly in the blood (engraftment) and the patient did not experience GvHD, but autologous recovery followed promptly the termination of GvHD prophylaxis with steroids plus cyclosporine. The patient lived for 210 days and succumbed to infection, attributed to severe immunologic impairment despite, or perhaps because of, autologous recovery with the progeny of heavily irradiated lymphocytes. The other two patients that suffered acute radiation syndrome, died shortly thereafter, one despite a bone marrow transplant.

Advantages of Cord Blood as a Stem Cell Source

These advantages include:

<u>Logistics</u>:

a) Cord blood grafts reduce very substantially the waiting time between the start of a search and the availability of a graft, an important issue for acute leukemia and some inherited diseases and an even more important one in the response to a terrorist action or accident. Cord blood can be routinely released for transplantation within 1-2 weeks, within 24 hours in an emergency.

b) Banked cord blood is free of attrition, in contrast to volunteer donors who sometimes cannot be located or may be unwilling or unable to donate when needed.

Infectious Disease Risk:

Cord blood grafts reduce exposure of recipients to latent common viral infections in the donor that can have severe consequences for immuno-suppressed patients, as is the case of transplant recipients. These infections are, principally, CMV and EBV. CMV has a prevalence among neonatal donors well below 0.5%, compared with 50-60% in US adults, while EBV is almost always negative in newborns and its prevalence in US adults is also above 50%.

Immunological:

For reasons still not completely understood, immune cells in cord blood are much less likely to produce the severe forms of acute Graft vs. Host Disease, a potentially lethal complication of stem cell transplantation. As a consequence, the recipients of cord blood grafts may receive partially mismatched grafts without a remarkable increase in the incidence of this complication of adult-donor transplants. Freedom from severe Graft vs. Host Disease allows us to provide partly mismatched grafts to a much larger fraction of potential recipients. This advantage is particularly important for members of ethnic minorities, whose spectrum of HLA types is different from that of Caucasoid donors, and whose frequency among potential donors is, per force, lower (minority).

Cord Blood Stem Cell Use in Transplantation.

Because of the lower post-transplant morbidity and mortality from GvHD, clinicians can perform transplants with HLA-mismatched cord blood units that would be undoable with similarly mismatched grafts of bone marrow or mobilized peripheral blood stem cells. Cord blood, therefore, is becoming more widely accepted as a source of hematopoietic stem cells for transplantation. Worldwide some 7,000 to 8,000 cord blood transplants have been accomplished. For the past 2-3 years, about half of transplants in U.S. children have used cord blood. Acceptance for adult patients is also becoming more widespread, especially with the success of double unit transplant protocols. Last year 45% of CBUs provided by the New York Blood Center's National Cord Blood Program went to teenagers and adults. Ethnic minority patients have especially benefited from cord blood: while 12% of the US population, for example, is African-American, 19% of US patients given New York Blood Center NCBP cord blood units have been African-American, comparing to only 6% of patients who succeeded in finding an unrelated donor through the National Marrow Donor Program (NMDP) (Source: GAO Report, October, 2002).

The Quantity of Stem Cells in Cord Blood Collections.

One of the characteristics of cord blood collections is the lower total cell content than in typical bone marrow collections, which is balanced in part by a more rapid proliferation of hematopoietic precursors (colony-forming cells). We have defined the cell doses (numbers of total nucleated cells (TNC) per kilogram of patient's weight required to support reasonably fast engraftment as 2.5×10^7/Kg or more. Since the cellular content of individual cord blood units is fixed at the time of collection, the cell dose is part of the criteria for cord blood matching, as well as the HLA match. Consequently, fewer cord blood units are dose-matched to adult patients than to children, explaining the relatively small number of adults given cord blood transplants to date. Double unit transplants, and possibly protocols to expand the number of cells, seem to be overcoming this limitation for adults.

Cord Blood Use in Adults

Because of the reduced cell doses for heavier patients, fewer transplants have been performed in adults and these data are less abundant than for children. Cord blood grafts from the New York Blood Center's NCBP have been given to more than 800 teenagers and adults, however. In Japan, cord blood is being used in more than half of all hematopoietic stem cell transplants in adults. While survival post-transplant is generally lower for adults than for children, it is similar to that of unrelated bone marrow transplants to adults with comparable risk factors. A recent series of papers in the New England Journal of Medicine (November 25, 2004) reported achieving comparable survivals for recipients of cord blood or bone marrow from unrelated donors. Moreover, the use of several grafts simultaneously provides aggregate cell doses in the effective range for adults.

Obviously, transplantation data on patients previously treated with various drugs for leukemia and other diseases cannot be freely extrapolated to the situation of victims, who, although probably healthy at the time of the exposure, might have sustained additional injury in the form of trauma and thermal burns and would be transplanted in very abnormal conditions. Some patients may also have received very high radiation doses, lethal for other tissues and organs and will die for that reason despite the transplant. On the other hand, cord blood grafts may rescue some of the victims and provide temporary support for some patients to survive the period of acute marrow aplasia without incurring much risk from graft-vs-host disease. This could give the patient's own remaining stem cells time to recover and replace the graft with the additional help of growth factors, as in patients whose conditioning regimens may have been insufficient.

Victims and Grafts

To conclude, the actual number of victims of depends on the type and magnitude of the radioactive release and the population density at the site of the explosion and its environs. It is estimated that a "small" nuclear bomb (≈1kiloton) exploding in a city like New York, Boston or Washington would produce some 30,000 victims. The number of irradiated persons, the level of their exposure and additional damage by the mechanical and thermal effects of the explosion would determine the number of grafts that would need to be available in order to provide appropriately matched cord blood stem cells for the victims that may benefit. In the case of accidents or attacks on power plants, the numbers are probably much smaller but potentially could challenge the nation's ability to treat victims appropriately. As opposed to surgically extracted bone marrow, cord blood units are donated without incurring risk and can be transplanted in a few days despite the presence of mismatches.

Because many victims are likely to be adults, current NCBP criteria require higher minimal cell doses for retention, to increase the range of recipient weights who can effectively use these transplants. Furthermore, new strategies for transplant management, including the use of multiple grafts in one transplant, raise confidence that cord blood could soon be at least as effective as bone marrow grafts for patients of all ages and sizes. Thus, a potentially large number of victims could be given access to a life-saving cord blood transplant and have a significant chance of survival.

In the event of an attack or accident, no other form of bone marrow rescue could possibly be mobilized opportunely enough to save many of the victims of radiation induced bone marrow failure: cord blood is especially, if not uniquely, suited to be used in the emergency treatment of subjects exposed to lethal doses of radiation (or to chemical agents that can similarly destroy the marrow's cells).

A fundamentally important aspect of any stem-cell including radiation preparedness plan is that, since cord blood transplants are being used increasingly to treat people with malignant and hereditary diseases, expansion of the existing inventory not only enhances preparedness, but the expansion would serve current and future medical needs as well. Thus the public investment needed for strengthening the National repositories will benefit the public whether or not the emergency materializes.