Current state of unrelated donor bone marrow transplant treatment for severe aplastic anemia, Fanconi anemia, and Diamond-Blackfan anemia.

Casey Greene, 13 April 2012.

Severe aplastic anemia (SAA) is characterized by the bone marrow's inability to replenish blood cells, and patients have low counts of red and white blood cells, as well as platelets. Its cause is generally unknown, though certain patients have autoimmune disorders or exposure to certain toxins or radiation. There are two main types of therapy: immunosuppressive therapy (IST) and bone marrow transplantation (BMT). IST generally works without recurrence in 10-15% of cases, however, with IST alone, 15-20% of those patients see myelodysplastic leukemia or acute myelogenous leukemia within 10 years[1,2]. Bone marrow transplants offer better results, but carry higher risks such as graft vs host disease (GVHD), graft rejection and infection. Depending on the type of conditioning regimen, 5-year survival rates can be as high as 95%[2].

Fanconi anemia (FA) is characterized by bone marrow failure leading toward myelodysplastic syndrome or acute myelogenous leukemia. Its cause is the result of a genetic defect in several DNA repair proteins, and the only known treatment is bone marrow transplantation. The conditioning regimen generally consists of immunosuppressants, total body or limited field radiation therapy and other drugs after graft transplantation.

Diamond-Blackfan anemia (DBA) is pure red cell aplasia, and 40% of patients also see somatic malformation in the cephalic area, heart, limbs, hands and urogenital region. Its cause is defective or depleted erythroid progenitor cells, and 25% of patients have a mutated allele for the production of ribosome protein synthesis 19 (RPS19)[3]. Another study has found evidence for a non-RPS19 genetic defect that may also contribute to DBA[4]. 80% of patient respond to corticosteroid treatment, but 20% require red cell transfusions and immunosuppressants. These patients very often see complications such as hemochromatosis. BMT is not generally used as a treatment, but many BMT patients see greatly restored heart and cardiovascular function, a reversal of damage done by multiple transfusions[3, 5, 6].

Immunosuppressive therapy for SAA patients as a first course of treatment generally includes antithymocyte globulin and cyclophosphamide. These drugs

target host T cells which are thought to attack SAA patients' blood cells. A small percentage of SAA patients respond to IST the first time (around 11%), but generally multiple courses of IST are given before the thought of BMT is considered[2, 7]. However, patients can build severe allergies to ATG, and cyclophosphamide is very cardiotoxic[1, 5]. A side effect of cyclophosphamide generally seen 3-10 years after initial treatment is the incidence of myelodysplastic leukemia and acute myelogenous leukemia, reported as high as 15-20%[1, 2, 5]. Horse ATG is more effective than rabbit ATG, but production of horse ATG was stopped in 2007 due to manufacturing quality control concerns[2].

Multiple blood transfusions are done to replace missing or damaged blood cells in SAA, FA and DBA patient. This helps patients survive until IST works, or with BMT, until a match is found. However, many complications arise in correlation to the number of transfusions done - hemochromatosis, liver damage, alloantigen sensitization and greater probability of new viral infection[1, 3, 5, 6]. A correlation has also been found with the number of transfusions and the success rate of BMT - the more blood transfusions a patient has had, the less chance of success the patent has of survival after BMT[1, 5, 8, 9]. Another factor adding to this is that patients who have a longer interval between diagnosis and BMT are older, and have generally required more blood transfusions to keep them alive[2, 8-10]. It is unclear whether the patient's age, or time interval between diagnosis and treatment has any direct effect, but the number of blood transfusions certainly does.

Radiation therapy, whether total body (TBI) or limited field (LFR) is a complex component of treatment. Significant improvements in immunosuppression and graft rejection have been shown, but complications can drastically impact the patient's quality of life, and even be fatal. Many changes have been made in TBI levels - in the 1980's and 90's, levels were as high as 14 Gy, in the 2000's levels were between 3-5Gy, and recent treatments have shown success with as little as 2 Gy[1, 2, 8]. However, some patients such as the very young, old or further progressed in their disease are much more susceptible to the side effects of radiation, and non-myeloablative therapy has also been shown to be a satisfactory treatment[2, 6, 10].

Bone marrow transplants are popularly considered to be very risky endeavors, done only when all else has failed. However, much progress has been made in the field, and survival rates for patients even with unrelated donor grafts near those of unaffected persons. In one study, they found 5 year survival rates for SAA patients of 13.3% with IST, and 95% with non-myeloablative BMT[2].

Generally speaking, the bone marrow transplant process has three steps - preconditioning regimen given to the patient which includes drugs and sometimes radiation therapy, T-cell depletion of graft prior to transplantation, and post-transplant care. Measurement of complete engraftment of donor cells, chimerism, is assayed by PCR or FISH of short tandem repeat markers, and usually in evidence by day 30, but can be as long as a year [3, 5, 11, 12]. The Karnofsky activity score is another good indicator of success, measuring general well-being with 90-100% being normal or nearly normal as compared to unaffected people[13]. Some of the greatest concerns with BMT are GVHD, graft rejection, histocompatibility, viral infections, but steps can be taken to ameliorate all of these issues.

Graft vs Host disease occurs at two times: acute, within the first 100 days after transplant, and chronic, after the first 100 days after transplant. Many things can be done to combat this, including drugs in the preconditioning regimen for the patient, in the graft before transplantation, and during post-transplant care. On the patient's side, fludarabine has been found to be so wildly successful in combating acute GVHD that it's difficult to find current studies that do not use it[2, 3, 5, 12]. It acts by disrupting DNA synthesis in dividing and resting cells, has immunosuppressive qualities, and improves neutrophil and platelet recovery[9]. cyclophosphamide slows or stops cell growth, and decreases immune response to certain diseases and drugs. At low doses it can be immunostimulatory and antiangiogenic, but with the high doses given to patients prior to BMT, it acts as an immunosuppressant. cyclophosphamide also selectively depletes CD4 and other T regulatory cells, and when used in a preconditioning regimen, by reducing patient T cells, provides niches for graft T cells to proliferate[1, 14]. One of its side effects several years after treatment is myelodysplastic leukemia or acute myelogenous leukemia - this drug may be may be linked to the higher incidence these diseases in SAA patients not treated with BMT[1, 2, 5]. T-cell depletion of the graft prior to transplantation has also been shown to have a massive effect on acute and chronic GVHD incidence, although it isn't always done, for reasons not apparent to the author. One of the major drugs that is used to treat the graft in this manner is alemtuzumab, and it acts by attacking CD52 and depleting mature lymphocytes[2, 8]. Combined with T-cell depletion of the graft pre-transplant, fludarabine lowered the incidence of acute GVHD from 21% to 16%. Without either, GVHD was present in 70% of patients post-transplant[9]. Post-transplant care includes cyclosporine, which is an immunosuppressant that binds to lymphocyte cyclophilin, leading to inhibited lymphokine production and interleukin release and thus reduced function and activity of effector T-cells[1]. It is generally well-tolerated by

patients with few side effects, and has a wide variety of non-BMT applications. This and/or related drugs are given as a matter of course to prevent acute GVHD, and later if chronic GVHD presents itself. TBI has been shown to increase the incidence of GVHD, and that will be discussed in further detail shortly.

Graft rejection, known as host-vs-graft disease in organ transplant papers, is when the patient's immune system attacks the transplanted marrow cells. Drugs such as alemtuzumab that deplete the T-cells from the graft prior to transplantation significantly reduce the incidence of graft rejection, and the use of fludarabine in the preconditioning regimen has been shown to have a very beneficial effect on graft rejection and long-term chimerism[2, 8, 9, 15-19]. Total body irradiation (TBI) or limited field radiation (LFR) is a controversial component of treatment. Even very low levels can reduce graft rejection to under 5%[1], however, the side effects include infection, higher incidence of GVHD, impaired or destroyed fertility, growth and cognitive retardation, and other malignancy including late solid tumors[1, 2, 8, 12]. Higher incidence of both acute (48-77%) and chronic GVHD (29-57%) has been shown in several studies[1, 2, 9, 10, 20, 21], and lowering doses of TBI to 2Gy showed no change in graft failure rates, but did improve overall survival rates in patients 20 years old and under, to those comparable to patients with matched-sibling transplantation[3, 22-25]. Recent papers suggest that radiation therapy not be considered a standard for treatment, and rely on drug therapy to stop graft failure[2, 26-29]. Reducing the number of blood transfusions the patient has prior to transplant reduces alloantigen sensitization which contributes to graft rejection[1, 5]. This underscores once more the need to reduce the time between diagnosis and bone marrow transplantation.

Histocompatibility is very important for the success of bone marrow transplants. Possible donors can be tested on 6-10 alleles, and full matches are always preferred. Donors are categorized as matched sibling donors (MSD), mismatched sibling donors (mmSD), mismatched nonsibling related donors (mmRD) and matched unrelated donors (URD). Studies have shown mmSD and mmRD to be statistically identical, and are usually grouped simply as mmRD[30]. Donors are ranked as one might expect, with MSD having the best outcomes, mmRD having the next best, and URD generally having the least amount of success[10, 30], but recent studies have shown URD survival rates to be comparable to mmRD[26, 31]. Greater histocompatibiity between donor and patient leads to less GVHD and graft rejection, and fewer immunosuppressants are needed leading to lower rates of infection. Currently testable alleles are HLA-A, -B and -C, as well as DRB1 and DQB. Historical reviews of treatments have consistently

noticed a lack of data on HLA-C, and consider it a topic requiring further study[10, 30]. Greater success rates have also been shown in areas where high-resolution allele typing is available, showing differences in success rates for unrelated donor bone marrow transplants from 30-49% in Europe, US and Canada to 56% in Japan[8, 10, 32-36]. However, other factors offer much better statistical predictors of outcome, and complexities in treatment as well as sequencing resolution may be obfuscating a true comparison between mmRD and URD[10]. One hypothesis in favor of URD grafts was the idea that having more mismatch would prompt greater host-vs-disease response to future complications such as leukemia or solid tumor cancers, However, this has not shown to be a significant factor in the patient's response to future cancers[37].

With immunosuppression and blood transfusions comes the risk of infection, and primary infection or revival of typically minor viruses such as CMV or HSV can become life threatening. CMV seropositivity from latent infection or blood transfusion was shown to be a significant indicator of patient survival, and in the early 90's, screening for CMV in donors, and providing gancyclovir or acyclovir for prophylaxis in seropositive patients was instituted as part of standard treatment[8, 9, 38, 39]. Reducing GVHD and graft rejection beginning in the preconditioning regimen allows for lower levels of immunosuppressants to be given and for shorter time periods post-transplant, which helps reduce the incidence of opportunistic infections. Low levels of TBI or non-myeloablative therapy have also been shown to reduce levels of other infection[1, 2, 6, 8, 10].

An unexpected side effect of bone marrow transplantation in SAA, DBA and FA patients is the nearly complete restoration of cardiac functionality post transplant[3, 5, 6].

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