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Low Dose Total Body Irradiation Followed by Allogeneic Lymphocyte Infusion for Refractory Hematologic Malignancy—an Updated Review

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Abstract

Allogeneic stem cell transplantation is curative for certain cancers, but the high doses of chemotherapy and radiotherapy used in conventional myeloablative conditioning regimens may lead to severe toxicity. In our initial study, we treated 25 patients with refractory cancers with 100 cGy total body irradiation (TBI) followed by allogeneic, non mobilized peripheral blood cells. Eighteen patients received sibling and 7 patients received unrelated cord blood stem cells. None of the 13 patients with solid tumors achieved donor chimerism or had a sustained response. Twelve patients with hematologic malignancies were treated, 1 received a cord blood transplant and 11 received sibling donor cells. Nine of these 11 patients achieved donor chimerism, ranging from 5% to 100%. Four patients had sustained complete remission of their cancers, and 2 are long-term survivors. The development of chimerism correlated with total previous myelotoxic chemotherapy ($p < 0.001$). This technique is now being extended into the haploidentical setting.

Keywords

Transplantation; Cellular immune therapy; Leukemia

SCIENTIFIC BACKGROUND

These clinical studies were based on a mouse transplant model. The development of the cellular immune therapy approach followed from studies showing that syngeneic murine marrow could be transplanted into untreated or minimally treated (100 cGy) mice with establishment of long-term multi-lineage chimerism [1,2]. The level of this chimerism was based on stem cell competition. The nontoxic reduction of host stem cells secondary to 100 cGy total body irradiation resulted in very high levels of donor cell chimerism [2]. These studies led to studies of B6 SJL to BALB/C H-2 mismatched transplants using 100 cGy total body irradiation, and

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CD-40 ligand costimulator blockade, showing stable long-term multi-lineage chimerism in the allogeneic setting [3]. These initial studies led to the design of the initial cellular immune therapy clinical trials.

Engraftment in Nonmyeloablated Mice

Previously, several groups transplanted marrow into nonmyeloablated mice [4–6]. These studies were variously interpreted, but established that some level of engraftment could occur in this setting. Brecher *et al.* [5] carried out several studies showing high levels of syngeneic engraftment out to 13 weeks when female BALB/C mice were infused with 40 million male cells daily for 5 days—a total of 200 million cells. Subsequently, Stewart *et al.*, employing the Brecher model, showed sustained multi-lineage chimerism for over 2 years [1]. In these studies, engraftment was quantified by determining the presence of male DNA in female marrow, spleen, or thymus, using either southern blot or fluorescence-*in-situ* hybridization. There was a linear relationship between cell dose infused and engraftment.

Further studies detailed the total cellularity in a BALB/C mouse showing a mean of 530 million total marrow cells. In a large series of experiments, 58 female mice were infused with 40 million male cells and engraftment analyzed at 8 weeks. We calculated a theoretical engraftment based on the following assumptions: (1) differentiated cell numbers correlate directly with new stem cell numbers, (2) all marrow stem cells home to marrow and the infused marrow population replaced the marrow population. This last assumption is, in turn, based on observations of mice infused with up to 800 million cells over time [7]. In these animals, total marrow cell and progenitor numbers were not increased, suggesting a replacement rather than an augmentation model. Given these assumptions, the theoretical engraftment rate in untreated mice given 40 million cells would be $40/530 = 7.5\%$, the observed engraftment was 7.7%. This suggested that stem cell competition determined engraftment.

Subsequently, we found that reducing host stem cells by exposure to 100 cGy, resulted in marked increases in donor chimerism, also consistent with the stem cell competition model [2]. This approach was tested in a murine H-2 mismatched allogeneic transplant model. Long-term multi-lineage chimerism with tolerance could be obtained by adding anti-CD-40 ligand antibody treatment to a regimen consisting of 100 cGy to BALB/C hosts and 40 million B6 SJL infused marrow cells. The engrafted BALB/C mice were tolerant to B6 SJL skin grafts, but not to third party skin grafts.

Further work with murine models has continued. Multi-lineage chimerism could be obtained in an H-2 mismatched B6 SJL to BALB/C model without any irradiation, but with anti-CD-40 ligand antibody and with “scheduling of the marrow infusions” [8]. In these more recent studies, multi-lineage chimerism was obtained with no irradiation but with administration of anti-CD40 ligand when 40 million marrow cells were infused at time 0 and at 4, 5, 6, and 7 weeks for a total of 200 million cells. Interestingly, when 200 million cells were infused at time 0, there was essentially no engraftment, so that scheduling was a critical component of engraftment. Most recently, we have shown that with lesser degrees of H-2 histoincompatibility there are higher levels of engraftment [9].

CLINICAL STUDIES USING MATCHED, RELATED DONORS

Over the last few years, many investigators have used minimally ablative doses of chemotherapy or chemoradiotherapy (“mini-transplants”) to treat older patients with hematologic malignancies. These studies were based on data which indicated that donor lymphocyte infusions could induce remissions in patients who have a relapse after allogeneic transplantation, illustrating a graft-vs.-leukemia effect [10–12].

Slavin *et al.*, Khouri *et al.*, Spitzer *et al.*, McSweeney *et al.*, Dey *et al.* and others have shown that engraftment and disease response can be achieved using reduced intensity conditioning regimens that are well tolerated [13–17]. Nonmyeloablative allogeneic transplants have been used successfully in patients who have relapsed after autologous stem cell transplantation [18,19]. Dey and colleagues, at Massachusetts General Hospital, treated 13 patients with hematologic malignancies that had relapsed after autologous SCT, with nonmyeloablative allogeneic transplant [18]. The conditioning regimen was cyclophosphamide, anti-thymocyte globulin, and thymic irradiation. The graft vs. host disease prophylaxis was a short course of cyclosporine alone. All patient achieved initial mixed chimerism. Seven patients achieved a complete response. The 2 year disease-free survival probability was 38%.

Porter *et al.* treated 18 patients at Brigham and Women's Hospital and at the University of Pennsylvania with donor lymphocyte infusion as primary therapy without conditioning [20]. Four of these 18 patients had relapsed disease after a prior autologous stem cell transplant (Hodgkin's disease, $n = 3$, myeloma, $n = 1$). Sustained mixed chimerism (1 – 5% donor chimerism) was seen in all 4 of these patients but not in the less heavily pre-treated patients. Three of the 4 patients with mixed chimerism had an antitumor response including one patient with relapsed Hodgkin's disease who experienced a complete remission for over 30 months. Treatment related mortality was limited to one patient who developed marrow aplasia and grade IV GVHD. Two other patients with sustained engraftment developed grade II and III acute GVHD. Therefore, this initial study demonstrated that donor lymphocyte infusion could be given as primary therapy with acceptable toxicity, sustained mixed chimerism could be achieved in some patients, and that primary DLI without prior conditioning therapy could result in clinically significant graft versus tumor effect. Engraftment and tumor response was limited to the most heavily pre-treated patients.

A subsequent report from this group was limited to 14 patients who received either donor lymphocyte infusions or stem cell transplantation and no conditioning regimen ($n = 4$) or after low dose immunosuppressive conditioning ($n = 10$) [17]. All but one patient had evidence of donor chimerism by day 30 after cell infusion, and 8 patients had greater than 80% donor chimerism at some time after treatment. Ten of the 14 patients (71%) responded including 6 patients who experienced a complete response (5 patients with lymphoma and one with myeloma). These data confirmed that sustained engraftment was frequent in heavily pre-treated patients with the use of no, or minimal, conditioning, and that sustained graft vs. tumor responses, even in patients who had failed high dose therapy, could be generated.

A Phase I cellular immune therapy trial was conducted at U Mass Memorial Health Care [21]. Twenty-five patients, with a median age of 47 years, were enrolled. Patients were required to have cancer refractory to all standard therapy. Thirteen patients had solid tumors; the diagnoses were lung cancer ($n = 3$), melanoma ($n = 2$), esophageal cancer ($n = 2$), and one patient each with hepatocellular carcinoma, neuroendocrine cancer, adrenocortical cancer, pancreatic cancer, renal cell carcinoma, and sarcoma. Twelve patients with hematologic malignancies were treated; they include 7 patients with lymphoma, 2 patients with myeloma, and 3 patients with leukemia. Seventeen patients received a sibling graft, and 7 patients received a cord blood transplant. The cord blood transplants are discussed in the section on alternative donors.

Donors received no filgrastim or chemotherapy priming. The target dose was initially set at 1×10^7 CD 3 + cells/kg and was then increased to 1×10^8 CD 3 + cells/kg. Patients were treated with 100 cGy of total body irradiation (TBI). The pheresis product was given 4 – 6 h after the TBI. The primary endpoint of the study was percent donor chimerism measured by polymerase chain reaction-short tandem repeats at weeks 1, 2, 3, 4, and 8 post transplant.

Thirteen patients were treated for refractory solid tumors; 6 patients received a cord blood transplant and 7 a sibling transplant. Two of the sibling patients received the lower cell dose of 1×10^7 CD 3 + cells/kg. Neither of these two patients showed engraftment or had any tumor response. Five patients received the higher cell dose of 1×10^8 CD 3 + cells/kg. None of these patients developed any donor chimerism. One patient, a woman with adrenocortical cancer, had a transient nodal response.

Twelve patients with hematologic malignancies were treated; 11 of these patients received a sibling graft with a cell dose of 1×10^8 CD 3 + cells/kg. The chimerism values and responses are outlined in Table I. Nine of these 11 patients achieved some degree of donor chimerism. Three patients achieved 100% donor chimerism, 2 patients achieved 67% donor chimerism, 2 patients had 10% donor chimerism, and 2 patients 5% donor chimerism.

Four patients achieved a complete remission (CR) of their cancers. One patient, a 51-year-old woman with large cell lymphoma that had relapsed after autologous transplantation, achieved a CR by CT scan although she only had transient 5% donor chimerism. Restaging CT scans at 36 months post transplant showed no evidence of disease and the patient's blood showed all recipient cells. The patient is alive and well, 52 months after transplantation.

Three other patients achieved a complete remission of their cancers. These three patients had 100% donor chimerism. A 56-year-old woman with lymphoblastic lymphoma who had relapsed after autologous transplantation was in CR by 8 weeks post transplant. She was 100% chimeric by 4 weeks after transplant. She relapsed 5 months after infusion and died of recurrent disease.

A 55-year-old woman with multiple myeloma recurred after autologous transplantation and multiple other therapies, resulting in pancytopenia at the time of treatment. She developed complete donor chimerism by 4 weeks after transplant; CR was documented by bone marrow aspirate and biopsy. Her course was complicated by skin graft-versus-host-disease (GVHD), pancytopenia, and *Pseudomonas* sepsis. Therefore, she received a second infusion of G-CSF primed stem cells from the same donor. She continued to have 100% donor chimerism. She died of liver GVHD, 3.5 months after infusion. There was no evidence of myeloma at autopsy.

The fourth patient who achieved CR was a 24-year-old woman with acute myelogenous leukemia, who had failed 3 induction regimens and was in frank relapse. She developed CR, based on bone marrow morphology and flow cytometry, and 100% donor chimerism. She remains in complete remission, 30 months after transplant.

There was one treatment-related death as described above. Acute GVHD occurred in 6 patients. Two patients survive in CR, at 52 and 30 months post therapy.

We evaluated whether there were associations between donor chimerism and tumor response. The following variables were studied: disease (hematologic malignancy vs. solid tumor), development of GVHD, T cell dose (1×10^8 CD 3 + cells/kg vs. other), and number of prior chemotherapy drugs. We developed a myelotoxicity index to evaluate the number of chemotherapy regimens. Patients who received a chemotherapy regimen with one drug were given a score of 1, two drugs a score of 2, etc. A prior bone marrow transplant was given a score of 5. A patient who had been treated with CHOP chemotherapy followed by autologous stem cell transplant, for example, would have a score of 4 + 5 or 9. The average myelotoxicity index in the patients with hematologic malignancies was 9, compared to 2, for the patients with solid tumors. This lack of prior treatment and prior immunosuppression may explain why patients with solid tumors did not have donor engraftment in this study. Prior chemotherapy was correlated with chimerism ($P < 0.001$). Other variables associated with donor chimerism were diagnosis of hematologic malignancy ($P < 0.001$), higher T cell dose ($P = 0.03$), and

GVHD ($P = 0.01$). Donor chimerism was also shown to be associated with tumor response ($P = 0.01$).

An interesting finding of the study was the evidence of engraftment with a low CD 34 + cell dose. Patients received a non-mobilized peripheral blood cell pheresis product with a target dose of 1×10^8 CD 3 + cells/kg. There was no target dose of CD 34 + cells; the CD 34 + dose ranged from 1.5×10^4 to 2.8×10^5 cells/kg with a median dose of 5.2×10^4 CD 34 + cells/kg in the infused product. This dose of CD 34 + cells is about two logs lower than what is used in traditional transplantation. Chimerism did occur with a low CD 34 + cell dose. Thus, non-mobilized blood has CD 34 + cells and can give at least short-term 100% donor chimerism.

The results of this study with low dose TBI and donor lymphocyte infusion from matched, related donors in patients with refractory cancers are as follows:

1. Engraftment can occur in humans with a radiation dose as low as 100 cGy.
2. Chimerism and tumor responses were associated with intensity of prior therapy.
3. Complete remission can occur with the development of only transient, partial chimerism.
4. Engraftment can occur with a CD 34 + dose as low as 10 (4) cells/kg.
5. Stem cell competition, with recipient cells depleted by prior therapy, may facilitate engraftment.

RESULTS IN PATIENTS WITHOUT MATCHED, RELATED DONORS

Only about 30% of patients have a matched, sibling donor [22]. Therefore, we extended this approach to patients without a 5/6 or 6/6 HLA allele match in their family with the use of umbilical cord blood. Banks of cryopreserved umbilical cord blood units have been established worldwide and provide an alternative stem cell source for patients without matched related or unrelated donors [23–25]. Umbilical cord blood has been shown to engraft after ablative conditioning regimens, and lead to successful transplants, especially in pediatric patients [26–28]. However, cord blood had not been studied after low dose total body irradiation.

In the initial cellular immune therapy study, we treated 7 patients without sibling donors with 100 cGy TBI followed by the infusion of one cord blood unit [21]. Cord blood units were obtained from the American Red Cross Cord Blood Program and were matched at 4/6 or more HLA loci. The median number of cells infused was 3.1×10^4 CD 34 + cells/kg and 1.7×10^6 CD 3 + cells/kg. Seven patients were treated with this approach. None of these 7 patients achieved a tumor response or evidence of donor chimerism. Three additional patients were treated with cord blood units and also did not show evidence of engraftment. The poor results seen with cord blood may be related to the low CD 3 + dose infused; the dose of T cells is two logs lower than used in the sibling transplants.

Haploidentical transplants may be another option for patients without sibling donors. These transplants employ family members who are mismatched at 2 or more loci and have been utilized after both ablative and nonmyelo-ablative conditioning regimens [29–31]. Investigators at Roger Williams Hospital in Providence has extended the low dose radiotherapy approach to patients with haploidentical donors [32]. Donors can include the patient's parent, children, siblings, or more distant relatives.

In a Phase I study, patients with refractory hematologic malignancies received 100 cGy TBI, followed by infusion of escalating doses of CD 3 + mobilized peripheral blood stem cells (1

$\times 10^6 - 2 \times 10^8$ cells/kg infused) [33]. Thirteen patients with hematologic malignancies have been treated; 5 patients with acute myeloid leukemia, 5 patients with lymphoma, 2 patients with multiple myeloma, and one with chronic myeloid leukemia. There was one treatment-related death from graft versus host disease. There was no response in the myeloma patients; three patients with AML achieved a complete response and one patient with lymphoma achieved a partial response. All of the responses occurred in the absence of measurable donor chimerism. There was one long-term survivor.

Twelve of the 13 patients experienced a “haplo-immunostorm”, a syndrome of fever, rash, and capillary leak within 12 h of infusion. The symptoms resolved promptly after initiation of steroid therapy, which was routinely administered if fever persisted 48 h after cell infusion.

This study of cellular immune therapy using haplo-identical donors is now being extended to a multicenter, Phase II study for patients with refractory leukemia. Patients receive low dose total body irradiation, followed by infusion of haploidentical CD 3 + cells, with the option for later donor lymphocyte infusion. This study is currently accruing patients.

FUTURE DIRECTIONS FOR CELLULAR IMMUNE THERAPY

A possible application of cellular immune therapy is for patients with solid tumors. These patients did not do well in the initial study, perhaps due to their lack of prior immunosuppressive therapy [21]. Patients with tumors that respond to other types of immuno-therapy—for example, cancers such as renal cell carcinoma or melanoma, may be more likely to benefit from this approach. Several trials have shown that nonmyeloablative allogeneic stem cell transplantation may induce responses in patients with renal cell carcinoma, breast cancer, and even ovarian cancer [34–36]. The University of Pennsylvania is currently studying nonmyeloablative allogeneic stem cell transplant followed by *ex-vivo* activated donor leukocyte infusions (described below) in an effort to induce a graft-versus-tumor response for a variety of solid tumors, including ovarian cancer. The preliminary results suggest that this approach is feasible, engraftment is achieved, and regimen-related toxicity is acceptable. Whether allogeneic cell therapy, with or without *ex-vivo* activated donor leukocyte infusion, will induce a meaningful tumor response in patients with advanced ovarian cancer remains to be determined.

One approach to enhance the activity of donor lymphocyte infusion is to administer *ex-vivo* activated and expanded donor lymphocytes. The hypothesis is that *ex-vivo* activation and expansion may reverse T cell tolerance, bypass possible *in-vivo* T cell suppressive mechanisms, and improve the graft-versus-tumor activity [37]. This idea has been piloted as a Phase I study at the University of Pennsylvania [38,39]. The donor T cells are exposed to beads linked to anti-CD 28 and anti-CD 3 antibodies, which results in approximately a 16-fold T cell expansion. In one current trial, patients with hematologic malignancies who relapse after allogeneic stem cell transplantation receive unstimulated donor lymphocyte infusion with or without standard induction chemotherapy, followed by infusion of activated donor lymphocytes on approximately day + 12 after standard donor lymphocyte infusion. Fourteen patients have been treated; 4 have achieved a complete remission, lasting 2 – 22 + months [38]. GVHD has been limited to the skin, except in two patients with stage 3 liver and gut GVHD. When completed, results from these studies may determine if *ex-vivo* activated donor lymphocyte infusion will improve outcomes for relapsed patients when compared to conventional donor lymphocytes alone.

What can be done to improve the results for patients with hematologic malignancies and matched related donors? The use of G-CSF mobilized stem cells may decrease the risk of pancytopenia post transplant, and improve the safety of this approach. Increased immunosuppression, such as with cyclophosphamide or antithymocyte globulin may increase

the chance of donor chimerism for those patients who have not been heavily pretreated. These ideas and others form the basis for future work in this exciting field.

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TABLE I

Chimerism and tumor response in patients with hematologic malignancies treated with a sibling graft

[[Patient number]]	[[Disease]]	[[Maximal donor chimerism]]	Disease state at 8 weeks	[[Survival (days)]]
[[1]]	[[Lymphoma]]	[[5%]]	[[CR]]	[[1585]] *
[[2]]	[[Lymphoma]]	[[10%]]	[[Died of disease]]	[[28]]
[[6]]	[[Myeloma]]	[[100%]]	[[CR]]	[[116]]
[[8]]	[[Myeloma]]	[[10%]]	[[Stable]]	[[229]]
[[9]]	[[CML]]	[[67%]]	[[No response]]	[[129]]
[[11]]	[[Lymphoma]]	[[5%]]	[[Died of disease]]	[[29]]
[[12]]	[[Lymphoma]]	[[100%]]	[[CR]]	[[222]]
[[20]]	[[Lymphoma]]	[[67%]]	[[Died of disease]]	[[37]]
[[23]]	[[CLL]]	[[0]]	[[PR]]	[[179]]
[[24]]	[[Lymphoma]]	[[0]]	[[Died of disease]]	[[40]]
[[25]]	[[AML]]	[[100%]]	[[CR]]	[[930]] *

* Patients currently alive and disease-free