Adoptive Immunotherapy in Chimeras with Donor Lymphocytes

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Key Words
Stem cell transplantation · Chimerism · Transplantation tolerance · Adoptive immunotherapy · Donor lymphocyte transfusion

Abstract
Allogeneic stem cell transplantation has a well-defined indication in the treatment of hematological malignancies. The beneficial immune effect of allogeneic marrow transplantation has long been known, but only recently have methods been developed to separate the graft-versus-leukemia (GVL) effect from graft-versus-host disease (GVHD). Animal experiments have shown that lymphocytes from the marrow donor can be transfused without causing severe GVHD if stable chimerism and tolerance is established. First clinical studies have been performed in patients with recurrent chronic myelogenous leukemia. In these patients complete molecular remissions were induced that persist without further maintenance treatment. These results have been confirmed in larger multicenter studies in Europe and the USA. The best results were obtained in chronic myelogenous leukemia (CML); repeated successes have been reported in relapsing acute myeloid leukemia (AML), myelodysplastic syndromes and multiple myeloma (MMY), and rare responses were reported for acute lymphoid leukemia. Contrary to animal experiments GVHD has been observed in human patients although to a lesser extent than expected in transplants not given immunosuppression. Secondy myelosuppression has been observed in patients treated with relapsing CML. In CML the incidence of GVHD could be reduced by depleting CD8+ T cells from the donor lymphocyte concentrate. Alternatively only small numbers of T lymphocytes can be transfused and in the case of failing responses, the numbers of donor lymphocytes may be increased. Results in recurrent AML have been improved by the use of low-dose cytosine arabinoside, granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor mobilized blood cells as compared to lymphocytes only. In MMY the response rate is higher than in AML, but the remissions are of limited duration in most patients. Several protocols have been designed to include preemptive donor lymphocyte transfusion in patients with a high relapse risk after transplantation. Problems remain to avoid chronic GVHD and to circumvent the immune escape mechanisms of leukemia.

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0001–5792/03/1103–0110$19.50/0
Adoptive Immunotherapy in Chimeras with Donor Lymphocytes

The success of donor lymphocytes in the treatment of recurrent leukemia has changed the perspectives of hematopoietic stem cell transplantation [1]. The antileukemic effects of myeloablative conditioning have been substituted by adoptive immunotherapy using cells of the marrow donor (fig. 1). Formerly the treatment of leukemia and other neoplastic diseases of the hematopoietic system focused on the maximal tolerated dose of radiation and chemotherapy to destroy the leukemia as much as possible and to rescue the patient from hematopoietic failure by transplanting bone marrow. Today the limitations and risks of high-dose chemotherapy and radiotherapy are well known and the conditioning treatment is designed to allow the establishment of chimerism and the development of transplantation tolerance as a platform for immunotherapy. The conditioning does not need to be myeloablative. There is a therapeutic dilemma in bone marrow transplantation for malignant diseases. Acute graft-versus-host disease (GVHD) and its sequelae are the major complications of allogeneic stem cell transplantation. The most effective method to prevent GVHD is the depletion of T lymphocytes from the transplant [2, 3]. However, the depletion of T cells from the graft ablated most of the antileukemic effect of allogeneic transplantation [4]. Adding back small amounts of T cells to the depleted graft was not successful in reducing the risk of relapse without inducing GVHD. However, transfusion of donor lymphocytes into stable canine chimeras did not produce GVHD [5]. Therefore in the 1980s we studied donor lymphocyte transfusions (DLTs) in canine chimeras with the aim of influencing chimerism and transfer immunity from the donor to the host [6].

The animal experiments encouraged us to use donor lymphocytes for the treatment of relapse of chronic myelogenous leukemia (CML) in 3 patients [7]. The results were confirmed by several single centers [8–14], and the spectrum of graft-versus-leukemia (GVL) activity was assessed in multicenter analyses [15, 16]. Native donor lymphocytes and sensitized T cells, T-cell lines and clones were successful in the treatment of viral infections [17–19]. Similar strategies have been explored using minor histocompatibility antigens with restricted tissue expression in the treatment of leukemia [20–22]. Here we review the current status of adoptive immunotherapy with donor cells and we try to give a perspective to the future of immunotherapy.

Non-myeloablative conditioning stem cell transplantation

Chimerism & Tolerance

Adoptive immunotherapy with specific T-cells ± dendritic cells

Principles Derived from Animal Studies

There have been many studies on murine leukemia which differs in several aspects from human leukemia. Bacteria-free mice with spontaneous AKR leukemia have been treated with some success using marrow and low-dose lymphocytes from major histocompatibility complex (MHC) mismatched donors [23].

The concept that leukemia expresses minor histocompatibility antigens on the hematopoietic cells of the host was the starting point for the production of mixed DLA-identical chimeras in dogs. Conversion of mixed chimerism into complete chimerism served as a model for a GVL reaction. Mixed chimeras were produced by transplantation of low numbers of marrow cells depleted of T cells by the treatment with absorbed antithymocyte globulin (ATG) to prevent GVHD. These animals were stable mixed chimeras. Transfusion of donor lymphocytes on days 1 and 2, or days 21 and 22 after marrow transplantation induced fatal GVHD. However, transfusion on days 61 and 62 did not produce GVHD and the animals survived. These animals were mixed lymphoid and myeloid chimeras prior to transfusion and they became complete chimeras thereafter [6]. The donors were immunized against tetanus toxoid and the recipients developed antibody titers after DLT that persisted for more than 3 years after booster injections. Transfused and nontransfused animals were immunized against diphtheria toxoid as a new antigen. Transfused dogs developed significantly higher antibody titers than nontransfused dogs.
In mice a delay of 3 weeks for the transfusion of donor lymphocytes was enough to prevent GVHD [24].

The importance of the delay of DLT is obvious, but the cause of GVHD is not clear. One possibility is the ‘cytokine storm’ set free by the conditioning treatment with radiation and chemotherapy [25] that may have settled after 3 weeks and 2 months, respectively. Another possibility is the establishment of peripheral tolerance maintained by donor T cells in collaboration with host dendritic cells. The latter mechanism is supported by the finding that depletion of donor lymphocytes in the chimera prior to DLT predisposes the recipient to vigorous GVHD (Menzel H, 1996, unpublished) [26]. In man the necessary delay is not known. It may vary with age and previous chemo- and radiotherapy.

**Results of DLTs in CML**

Three patients with recurrent CML after allogeneic marrow transplantation were treated with DLT in 1988 and 1989 [27], they are still in hematologic and molecular remission of CML. Acute GVHD developed in 2 patients requiring immunosuppressive treatment, and chronic GVHD in 1. Immunosuppressive treatment could be discontinued in both. Severe myelosuppression was observed in a 4th patient treated 1991. Pancytopenia occurred 2 months after DLT and it did not respond to treatment with granulocyte colony-stimulating factor, but to the transfusion of donor marrow (fig. 2).

The analysis of the results of centers of the European Cooperative Group of Blood and Marrow Transplantation (EBMT) showed best results in cytogenetic and hematologic relapses of CML, intermediate results in transformed phase CML, acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), and poor results in acute lymphoblastic leukemia (ALL) [15]. Single patients with chronic myeloproliferative diseases as polycythemia vera and myeloid fibrosis [28] also responded to DLT. Both the absence of chimerism [29] and the presence of GVHD at the time of DLT were adverse factors for a response. In CML the GVL effect correlated with the severity of GVHD, but responses were also seen in patients without GVHD. However GVL was limited to patients with an allogeneic donor, it failed in patients with a monozygotic twin donor. The time until molecular remission was between 4 and 6 months after a single transfusion in most patients; in some patients molecular remissions were reached after more than a year (fig. 3).

Antigen presentation could be improved by treatment with cytokines. In particular the combination of interferon-α (IFN-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) improved the expression of class-I and II human lymphocyte antigens (HLAs), CD40 and CD80 [30]. Preliminary results confirm the beneficial effect of GM-CSF and IFN-α in patients with recurrent CML refractory to donor lymphocytes.

Complications of the treatment were GVHD and myelosuppression. Myelosuppression was more frequent in hematological relapse than in cytogenetic relapse. The
use of mobilized blood cells containing stem cells instead of lymphocytes did not prevent myelosuppression [31]. Prevention of GVHD could be achieved by two methods without ablating the GVL effect: depletion of CD8+ T cells from the transfusion [32, 33], and using escalating doses of DLT [34] starting at $2 \times 10^6$ lymphocytes/kg. The escalating dose schedule has significantly lowered the risk of GVHD [35]. Patients should be surveyed by regular quantitative reverse transcriptase polymerase chain reaction for bcr/abl, and in case of persisting or recurrent positivity the proposed schedule is started at a dose of $2 \times 10^6$ lymphocytes/kg from unrelated donors and $1 \times 10^7$ lymphocytes/kg from an HLA-identical sibling donor. Doses are escalated if there is no GVHD within 30 days or no response within 60 days.

### Results of DLTs in AML and MDS

The EBMT results indicated inferior responses in patients with recurrent AML after DLT. In patients without chemotherapy-induced remission the response rate was 25% with very few patients surviving more than 4 years. In a second analysis of 120 patients with AML and MDS reported to the EBMT, complete remissions could be induced in 45 (41.6%) of 108 evaluable patients including patients treated with chemotherapy and DLT [36]. The median duration of remission was 304 days, in 18 patients remissions lasted more than a year, and in single patients more than 5 years. Overall survival was greater in responding patients. Three risk factors could be identified as being associated with a poor response to DLT: a short remission after allogeneic transplantation of less than the median of 194 days ($p = 0.02$); withholding chemotherapy prior to DLT ($p = 0.001$), and the absence of acute GVHD of grade II or higher after DLT ($p < 0.0001$). Of patients without GVHD only 18% responded as compared to 66% of patients with GVHD > grade I. Patients with late relapse after transplantation responded more frequently (48%) than those with early relapse (28%). After DLT the complete remission rate was independent of gender and age of the patient and donor, their relationship, the number of cells transfused and whether or not T-cell depletion was used for prophylaxis of GVHD after transplantation. Survival of patients without complete remission was poor, but once a complete remission was achieved survival was different whether or not the remission was induced by chemotherapy. This finding supports the hypothesis that DLT maintains the remission and favors the use of chemotherapy for remission induction.

Only limited data were available on the FAB subtype and cytogenetic analyses in these patients. With these limitations neither the FAB subtype nor the karyotype influenced the response.

Poor antigen presentation and the rapid progression of the disease were considered as the major obstacles for adoptive immunotherapy in recurrent AML. Improvement of antigen presentation and production of cytotoxic T cells against autologous blasts was studied in vitro (fig. 4). The combination of GM-CSF, IL-4, TNF-$\cdot$ and FLT3-L was particularly effective in inducing dendritic cells from AML blasts [37]. The culture was effective in 77% of patients and included patients with unfavorable karyotypes. Specific cytotoxic T cells against autologous blasts could be produced in more than 60% of these patients.

In a recent study we have used low-dose cytosine arabinoside as mild chemotherapy for halting progression of the disease and GM-CSF for improving antigen presentation. Mobilized blood (MDBC) was transfused as a preparation of stem cell-enriched donor lymphocytes and GM-CSF was applied for 14–28 days after transfusion. This way antigen presentation was optimized by induction of dendritic cells from AML blasts and substitution of dendritic cells derived from CD34+ cells of the graft. The response rate was improved from 25 to 67% and the actuarial probability of survival is 25% at 4 years [38].
Fig. 4. Pathophysiology of GVHD. There is mutual activation of donor CD4+ T cells and host dendritic cells which may be accelerated by pre-activation of dendritic cells by radiation, chemotherapy, endotoxin from intestinal flora, viral infections and by pre-immunization on the side of the T cells against minor histocompatibility antigens, viral antigens and others. Activated dendritic cells activate CD8+ T cells and present HLA class-I-restricted peptides to CD8 T cells which become activated and react against normal cells of the host.

In patients with progressive disease after MDBC, low-dose cytosine arabinoside and the transfusion of donor T cells has been used with success, but GVHD was mostly severe.

GVHD and extramedullary relapses remain therapeutic problems. In most patients with extramedullary relapse and some patients with systemic relapse, low-dose cytosine arabinoside is not effective in halting disease progression. In these more intensive chemotherapy including anthracyclins is necessary; solitary infiltrates may be radiated prior to transfusion of donor cells [39]. Following more intensive chemotherapy severe GVHD may develop after transfusion of mobilized blood cells and treatment with GM-CSF. In these cases GM-CSF has to be stopped and immunosuppressive treatment with steroids, cyclosporin A and azathioprine or others has to be started. GM-CSF should also be discontinued if blasts are mobilized from the marrow into the blood. Unfortunately leukemia may recur during immunosuppressive treatment and few therapeutic options remain.

Results of DLTs in Myeloma

The best responses next to CML were seen in recurrent multiple myeloma [40–42]. The most sensitive marker for response is the monoclonal paraprotein, next are infiltrates of plasma cells in the marrow and the disappearance of lumps, and the least sensitive are osteolytic lesions. The time to response may be 4–6 months or longer, and unlike in CML hematological remissions are less likely to be complete [43]. In most instances remissions are not as durable as in CML, but durable partial remissions have been observed in single patients (Kolb, unpublished). GVHD is observed in most responding patients, it may even recur after chemotherapy for myeloma [44]. Prevention of GVHD by depletion of CD8+ T cells from DLT was used with some success [33], repeated low doses of unseparated DLT were also effective [45].

Preemptive treatment with DLT may improve the outcome in combination with T-cell depletion, but the optimal strategy has not been found [46]. Immunization of a donor against the idiotype of the myeloma and the transfer of a cellular proliferative response has been reported [47], but the reactive donor T cells were found in the patient with persisting paraprotein.

Results of DLTs in Other Diseases

The response of recurrent ALL to DLT was poor in most cases [5, 48], but there are exceptions with long-lasting remissions [49, 50]. The first case of Slavin et al. [13] was a child with ALL who received donor cells 4 weeks after transplantation for residual leukemia. Remissions have been described in patients with Hodgkin’s disease, non-Hodgkin’s lymphoma [51] and chronic lymphocytic leukemia, but the overall response is controversial.

Neoplastic diseases other than hematological have been treated with allogeneic transplantation and DLT with some success. Metastatic renal cell cancer has shown sustained responses [52], some response was also observed in breast [53] and ovarian cancer (Kolb unpublished).

Non-malignant diseases have benefited from DLT in cases of poor graft function after non-myeloablative conditioning [54]. Allogeneic transplantation and DLT have been advocated for the treatment of autoimmune diseases
Donor Lymphocytes Adoptive Immunotherapy in Chimeras with better understanding of the GVL response.

Infections has shown promising results which may lead to ed and effective [19]. Adoptive immunotherapy of viral response. Pre-immunized T-cell lines were better tolerat-

reactions were associated with an acute inflammatory cases minute numbers of T cells were sufficient and the rus-induced lymphoproliferative disease [18]. In these
tions after transplantation, in particular Epstein-Barr viremia and the GVHD may complicate allogeneic stem cell transplanta-
mice in vivo [62]. However, ex vivo immunized T cells leukemia cells in vitro [21, 61] and in immunodeficient mice in vivo [62]. However, ex vivo immunized T cells have not yet been used widely in human patients. The most convincing example of leukemia treatment with immunized cells is the trial of Falkenburg et al. [63] who selected cytotoxic T cells on the basis of their reactivity to CML cells and infused them repeatedly into a patient with accelerated phase CML. Slavin et al. [64] immunized donor cells with cell lysates of the parents and found a complete response in a patient with accelerated phase CML who had not responded to DLT.

Mechanism of the GVL (Tumor) Effect

The absence of a measurable GVL effect in patients with syngeneic twin donors indicates the importance of an alloimmune response [15]. Minor histocompatibility anti-
gens are expressed on leukemia cells and can serve as targets for a GVL effect without GVHD, if their expression is restricted to hematopoietic tissue [22, 56]. HA-1 and HA-2 are such peptides with restricted expression to the hematopoietic system, but Y-associated minor histocompatibility antigens are also candidates [57, 58]. Tissue-

restricted expression of minor histocompatibility antigens may be operationally limited to the hematopoietic system by presentation of class-II HLAs [59].

The effector cells of the GVL reaction are not well defined. CD4+ T cells might be candidates, since CD8+ T cells could be depleted without losing the GVL effect [32]. However CD4+ T cells can recruit CD8+ T cells and other cells in vivo [60].

There is good evidence that ex vivo T cells immunized against minor histocompatibility antigens effectively lyse leukemia cells in vitro [21, 61] and in immunodeficient mice in vivo [62]. However, ex vivo immunized T cells have not yet been used widely in human patients. The most convincing example of leukemia treatment with immunized cells is the trial of Falkenburg et al. [63] who selected cytotoxic T cells on the basis of their reactivity to CML cells and infused them repeatedly into a patient with accelerated phase CML. Slavin et al. [64] immunized donor cells with cell lysates of the parents and found a complete response in a patient with accelerated phase CML who had not responded to DLT.

Antigens other than minor histocompatibility antigens that may be candidates for a GVL effect comprise fusion peptides, peptides from proteins encoded by mutated genes and proteins of overexpressed genes. Products of disease-specific rearranged genes as BCR/ABL in CML, PML/RARα in AML, and ALK/ETO and others contain highly specific fusion peptides. Proteins of genes with point mutations as in RAS genes and peptides of overexpressed normal genes such as p53 and proteinase 3 [65] have been studied. The antibody idiotyp of a lymphoma and myeloma could also be seen as an overexpressed normal protein that marks the tumor. T-cell reactivity has been described for all of these, but only BCR/ABL-specific T cells recognize malignant cells in patients, and T cells with that specificity are occasionally found in patients [66]. To date none of these antigens has been used successfully for adoptive immunotherapy in chimeric patients [67].

Our hypothesis that because myeloid leukemia produces dendritic cells of leukemia origin it responds better to DLT than lymphoid leukemia has been supported by the finding that dendritic cells in CML carry the bcr/abl translocation [30, 68, 69], and AML cells differentiated the karyotypic marker to dendritic cells [37, 70] in fluorescent in situ hybridization (FISH).

The production of dendritic cells from leukemia pre-
cursors has been studied in vitro because most cases of AML, as lymphomas and lymphoblastic leukemia, do not express co-stimulatory molecules such as CD80 and CD86. Untreated CML is poorly stimulatory in mixed lymphocyte reactions and fails to induce cytotoxic T cells in many instances [71]. Culture of AML blasts in the presence of GM-CSF, IL-4 with or without TNF-α and FLT3-L induces the expression of co-stimulatory molecules [37] (fig. 5). Similarly culture of CML cells in the presence of IFN-α and GM-CSF stimulates expression of co-stimulatory molecules and the generation of cytotoxic T lymphocytes [72]. The combination of GM-CSF and IFN-α has already been used successfully in patients with relapse of CML not responding to DLT alone and DLT plus IFN-α (unpublished). Other cytokines such as IL-2 have been introduced on the basis of animal experiments [73]. IL-2 may support the T-cell reactivity after immunization. In myeloma and lymphoid neoplasms stimulation of donor T cells is poor and new ways to improve specific T-cell stimulation are being explored. One possibility is the transfer of genes coding for immunostimulatory mole-
cules and proinflammatory cytokines [74]. Other ways are the transfusion of dendritic cells with the DLT or the use of MDBC together with the treatment with GM-CSF.
Immune reconstitution after DLT has been studied with typing for T-cell receptor V-β families [75] and T-cell receptor excision circles [76]. DLT enhanced immune recovery and converted to full donor chimerism. In single patients with GVL reactions clonal T-cell restitution has been observed [75]. T cells of the donor produced similar clones when exposed to the leukemia in vivo as in vitro, but genetic analysis showed that they were different [77].

Intercurrent infections with viruses or other intracellular microorganisms may jeopardize the result of DLT. Most patients experiencing viral infections in the first weeks after DLT develop GVHD. A similar observation has been reported in patients given T-cell-depleted transplants and DLT. CMV seropositivity of the patient was the most significant risk factor for survival [78]. It is being discussed whether anti-infectious prophylaxes should be given to patients after DLT.

There are numerous mechanisms how neoplasms and leukemia may escape an immune reaction against themselves (table 1) [79]. Most importantly the expression of antigens on the cell surface may change. Even the loss of the Philadelphia chromosome has been reported [80]. In this context the use of minor histocompatibility antigens is most promising, because in the chimera most hematopoietic cells are substituted by the donor and only leukemia cells are still of host type (fig. 6).

The role of natural killer (NK) cells has always been debated in allogeneic stem cell transplantation. During
post-transplant recovery NK cells are early and trials of substitution early after transplantation have not been successful. In murine models allogeneic NK cells were effective [81], but depletion of CD3+ T cells abrogated the effect [82]. In HLA-mismatched transplantation complete T-cell chimerism is not required for GVL to occur, mixed chimeras can be cured of lymphoma [83]. In mixed chimeras DLT exert a strong effect against lymphoma without causing GVHD [84]. The role of NK cells has recently been investigated in HLA-mismatched transplantation and excellent results were reported in AML, if donor and patient differed in the killer inhibitor receptors [85]. NK cells are inhibited from killing if the target cells share certain HLA antigens. In HLA-mismatched transplantation NK cells of the donor can kill leukemia cells and at the same time suppress rejection of the transplant. In the case of the donor and patient belonging to a different alloreactive group, relapses of AML did not occur.

**Outlook for Adoptive Immunotherapy**

Hematopoietic cell transplantation has come a long way from bone marrow transplantation to adoptive immunotherapy in chimeras. However, the mechanisms of adoptive immunotherapy in chimeras are still far from being understood. The immunobiology of leukemia, other neoplasia and viral infections has to be studied further in human patients. The mechanism of immune tolerance, immune reactivity against normal cells, and transfer of immunity can be studied in animal experiments.

Immunization of donor T cells against minor histocompatibility antigens of the recipient is currently studied in the dog. Sensitized cells convert mixed to complete chimerism much faster than naive T cells. Tests have been developed to demonstrate cellular immunity to hematopoietic progenitor cells in vitro allowing the definition of minor antigens in the dog [86]. The incidence of severe GVHD after transfusion of sensitized donor lymphocytes into stable chimeras may be 30–50% [5]. The percentage is expected to be higher in humans since patients and their donors are exposed to a multiplicity of histocompatibility and viral antigens during their life. Preventive measures against severe GVHD are necessary. Modification of donor lymphocytes with a suicide gene is the most promising way of prevention. T cells of the donor are infected with a replication-deficient retrovirus carrying the herpes simplex thymidine kinase gene (HSV-Tk) which can phosphorylate ganciclovir and the resulting nucleotide leads to the stop of DNA polymerization during cell division [87].

Current problems of the method are altered immune reactivity of transduced T cells, immune reaction against the viral protein and rejection of the transduced cells and altered sensitivity of transduced cells to ganciclovir due to splice variants of the gene. Recently the development of leukemia has been reported in a mouse treated with cells carrying the marker gene (a truncated nerve growth factor receptor) without the suicide gene. We have studied the method in the dog and found a good immune reactivity of transduced canine T cells in vitro. Transfusion of transduced T cells into a canine chimera resulted in a complete chimerism and transfer of immunity to tetanus toxoid [88].

Adoptive immunotherapy in chimeras is a promising way to treat leukemia and possibly solid neoplasia. In particular the immune reactivity against leukemias and neoplasia otherwise refractory to chemotherapy gives new perspectives in hematology and oncology. Several leukemia study groups have included preemptive DLT as prophylaxis in high-risk leukemia according to the schema shown in figure 1. The results are pending.

**Acknowledgments**

This work was supported by the Deutsche Forschungsgemeinschaft, Project Ko 81-1383-2, Wilhelm Sander Stiftung No. 93-018-01-03, and Deutsche José Carreras Leukämie Stiftung e.V.
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