A phase I/II single centre study of haploidentical transplantation combined with G-GSF, or GM-CSF, and escalating DLI in high-risk patients with no matched donors

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In 1999, we decided to start a phase I/II study of haploidentical transplantation for high-risk patients. The aim of the work was to implement a strategy to accelerate and strengthen the immune reconstitution by using nonspecific manipulation post-transplant and by developing specific strategies directed against viral antigens. The goal was to increase the graft-versus-leukemia effect without inducing or aggravating the deleterious graft-versus-host disease. The conditioning regimen, adapted to our group of patients, remained the same throughout. Importantly, the first recruited patients were in refractory disease, over time we were referred less advanced patients (complete remission 2 or more). There were 45 patients, all at high-risk, among which 27 were in refractory relapse. We questioned the importance of post-transplant growth factors policy and the influence of donor lymphocyte infusion. Because of the conditioning, transplant-related mortality was low at 3 months, but thereafter changed unfavourably when using granulocyte macrophage-colony stimulating factors in an increased incidence of acute graft-versus-host disease. As a whole the long-term survival of the patients was poor (18%) but improved a lot when transplanted patients were in complete remission (leukaemia-free survival of 39% at five years). Regarding the use of growth factors and donor lymphocyte infusion, granulocyte macrophage-colony stimulating factors with donor lymphocyte infusion induced a very high transplant-related mortality due to a high rate of severe graft-versus-host disease, while the combination of granulocyte colony-stimulating factors and a moderate dose of donor lymphocyte infusion was much safer but didn't overcome the high relapse rate in refractory patients. The combination of granulocyte colony-stimulating factors and donor lymphocyte infusion might nonetheless be sufficient to decrease the infection rate in patients transplanted in complete remission. The use of granulocyte macrophage-colony stimulating factors leads to an unacceptable lethal graft-versus-host disease rate. The 39% at five years leukaemia-free survival in patients in complete remission compares favourably with what can be achieved with matched unrelated donors in complete remission 2 or more.
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Introduction

At the start of this study (in August 1999), we were confronted with, partly for ethnic reasons, and referred a non-negligible number of patients who had to be transplanted because of high-risk acute leukaemia or because they relapsed several times, and for which no matched donor was available. At this time, haploiden-

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tical transplant was practiced by very few centres, the most important being the group from Perugia.[1,2] This group had already demonstrated the importance of natural killer (NK) mismatched alloreactivity in the direction of donor against recipient in acute myeloid leukemia (AML).[5,6] This feasibility study was composed of three groups of patients: granulocyte colony-stimulating factor (G-CSF) post transplant followed by escalating low dose G-CSF-primed donor lymphocyte infusion (DLI); granulocyte-macrophage colony-stimulating factor (GM-CSF) from the start followed by one G-CSF-primed DLI at day 45; and low dose of GM-CSF alone, without DLI, starting later post-transplant in attempt to decrease the acute graft-versus-host disease (aGVHD) rate.

Patients and methods

Forty-five patients were enrolled in the study from August 1999 to December 2008. All donors were true fully haplotype mismatched sibling according to the definition of three or more antigen mismatches in HLA-A, HLA-B, HLA-C, HLA-DRB1 and DQ loci. We set up a slightly different conditioning regimen compared to the standard regimen of Perugia, Melphalan was chosen to spare the heart (most of patients having been heavily treated before) and one drug used by this group (Thiotepa) was not available in Belgium. Finally we had to reduce the irradiation dose to five x two Gy because of the impossibility to have lung shielding in our centre. We also increased the pre-transplant immunosuppression; pre-SCT CSA was added to decrease the risk of graft rejection. Thus the conditioning regimen consisted of melphalan: 60 mg/m2/d (day -9, -8), TBI: 5 x 2 Gy (day -7 to -3), fludarabine: 40 mg/m2/d (day -7 to -3), ATG Fresenius: 5 mg/kg/d (day -6 to -1) and cyclosporine A: 5 mg/kg/d (day -7 to -2). If contra-indicated by previous irradiation, TBI was replaced with busulfan for myeloid disorders, or cyclophosphamide for lymphoid diseases, at standard transplant doses. No post-transplant immune suppression was given. When possible, the donor was chosen with NK reactivity in the GVH direction based on HLA-C high resolution typing.

There were three consecutive cohorts of patients. Their median age was 40, range from 18 to 55 years. The first one consisted of nine patients (5 AML in refractory relapse, 3 ALL, refractory relapses 2 and 1 MRD+ CR1, and 1 HD in third refractory relapse) who received G-CSF and G-CSF primed DLI (negative fraction of the CD34+ hematopoietic stem cell positive selection). The DLI dose was $1x10^4$ CD3/kg at day 28, and then escalated monthly for three months (1, 3 and $5x10^4$ CD3/kg) provided no acute GVHD had occurred at the time of infusion. In the second group (twelve patients: 5 partial response AML (2 PR1, 2 PR2 and 1 PR3), 3 CR AML (2 CR2 and 1 CR3), 2 CML (1 AP2 and 1 CP2) and 2 refractory relapse mantle cell lymphoma) G-CSF was substituted with GM-CSF combined with one G-CSF primed DLI on day 45 at $1X10^4$ CD3/kg. GM-CSF was given at a dose of 100 μγ/day from day five post transplant and discontinued when ANC was greater than 1000/μL. Given the very high incidence of aGVHD, we switched for a third scheme. In the third group (24 patients: 3 refractory relapse AML, 2 partial response AML (2 PR2), 6 CR AML (3 CR1, 2 CR2 and 1 CR3), 7 CML (1 AP1, 2 AP2, 1 AP3 and 3 CP2), 5 ALL (2 refractory relapse and 3 CR2) and 1 aplasia), we took into account the disease type, status at transplant and the existence or absence of GVH NK alloreactivity. The strategy was to give lower doses of GM-CSF without DLI, only in ALL patients and in AML patients who could not benefit from GVH NK alloreactivity (13/24). AML patients with NK alloreactivity didn't received GM-CSF or DLI (11/24). GM-CSF was given at the same dose (100 μγ/day) for five days from day +5 to day +9, in patients with non-myeloid disorders or with myeloid leukaemia having no GVH NK alloreactivity.

Anti-CMV T lymphocyte generation

23 hematopoietic stem cell donors agreed to undergo mononuclear cell leukapheresis to generate anti-CMV T lymphocytes for their sibling for whom they had already given hematopoietic stem cells. All donors were cytomegalovirus (CMV) seropositive (*Figure 1*). Peripheral blood mononuclear cells (PBMC) were then seeded at $5x10^6$ cells/mL in a dendritic cell (DC) generation bag (Miltenyi Biotec Inc.) using RPMI, 2% autologous serum, 800 U/ml GM-CSF and 1000 U/ml IL-4. DC were purified by counterflow centrifugal elutriation on day six. DC were plated in culture wells pulsed with 1 mg/mL CMV antigen (Dade Behring, Marburg, Germany) for four hours then washed twice and irradiated (15 Gy). PBMC were used as responders in a 1:10 DC/T-cell ratio in a three week primary mixed leukocytes reaction (MLR). On day 21, the cell culture was cryopreserved in appropriate aliquots. The mean T-cell expansion was 2.3 times the initial T-cell population (range, 0.4 - 6.7). T lymphocytes were tested by intracellular INFγ flow cytometry detection to assess their capacity to specifically recognise

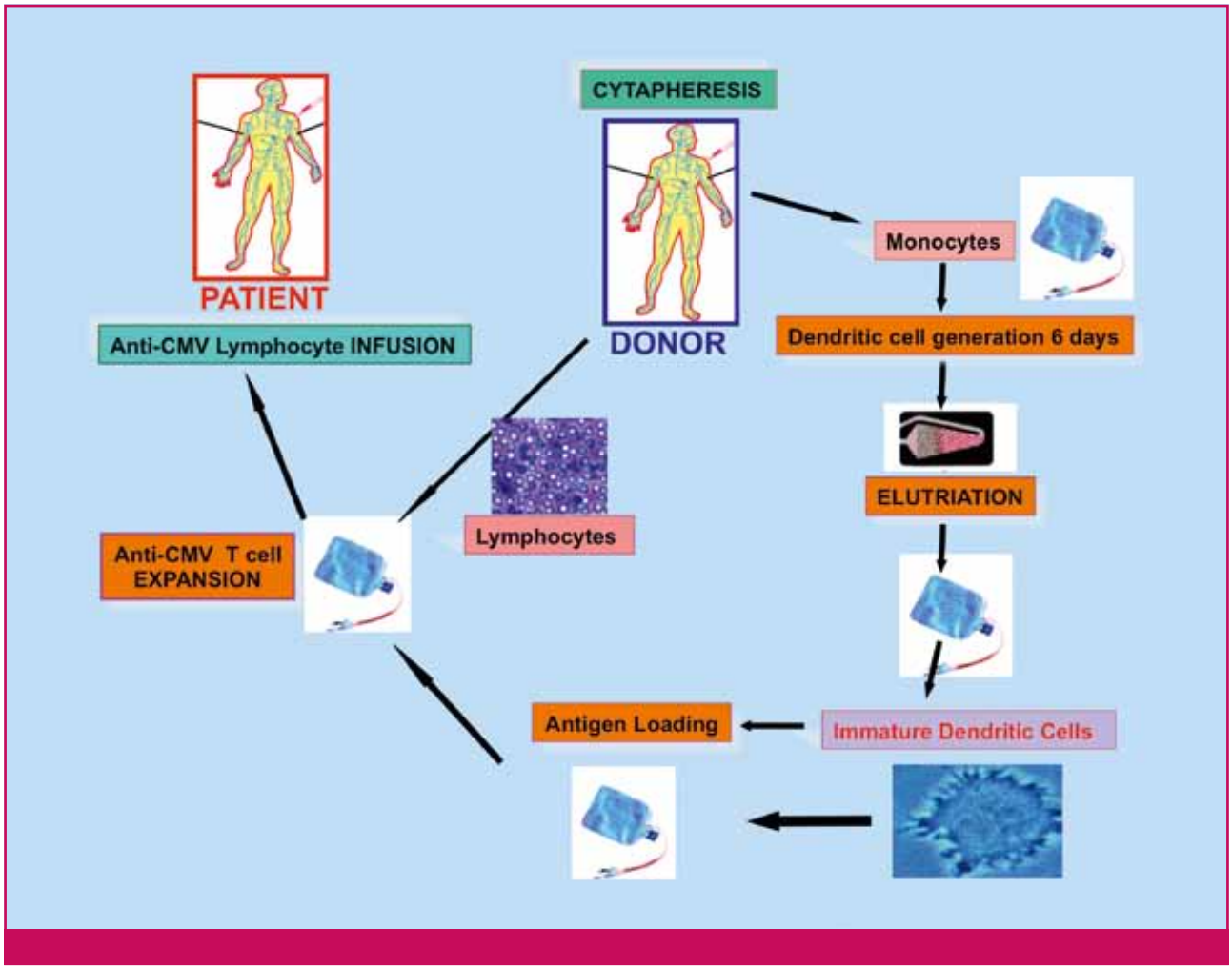

Figure 1. Anti-CMV T lymphocyte generation for adoptive T cell transfer.

CMV protein-loaded DC (*Figure 2*). The average percentage of CD4+ specific anti-CMV T lymphocytes was 34.1% (SD 21%; range, 2 - 70%) and 18.9% for CD8+ T lymphocytes (SD 20%; range, 1- 80%).

Results

Results of all 45 patients are summarised in *Table 1*. The use of DLI after GM-CSF showed a significant increase in the CD4 and CD8 recovery with no impact on CD56 (*Figure 3*). Nevertheless because of the high incidence of GVHD, a majority of the cohort was treated by high dose steroids, which has significant effect on the occurrence of viral and fungal infection and, jeopardizes the potential benefit of the treatment by GM-CSF combined with DLI with a TRM of 8/12 patients. There was no impact on the lymphocyte count after G-CSF and DLI or after GM-CSF alone. The use of GM-CSF alone was nevertheless also associated with a high TRM 8/13. Although there was an improvement after DLI on the viral infection rate in the G-CSF +DLI cohort, the use of G-CSF combined with prophylactic DLI didn't impact on the LFS because of the still very high relapse rate in such bad prognosis patients (6/9).

Results for CMV lymphocyte infusions

Twelve patients received anti-CMV-enriched T lymphocytes. Nine patients received anti-CMV T lymphocytes (104 total cultured cells/kg) as pre-emptive treatment, from which six were combined with antiviral therapy and three with no concomitant antiviral therapy. Conventional antiviral drugs were administered according to institutional guidelines (ganciclovir 5 mg/kg intravenously twice daily or Foscavir 120 mg/kg intravenously daily for ganciclovir-resistant CMV). Three patients received anti-CMV-enriched T-cells as prophylaxis of CMV reactivation on day 45 post transplant; these three patients had no GVHD and no immunosuppressive therapy at the time of the T-cell infusion. No infusion toxicities (pyrexia, hyper/hypotension, tachy/bradycar-

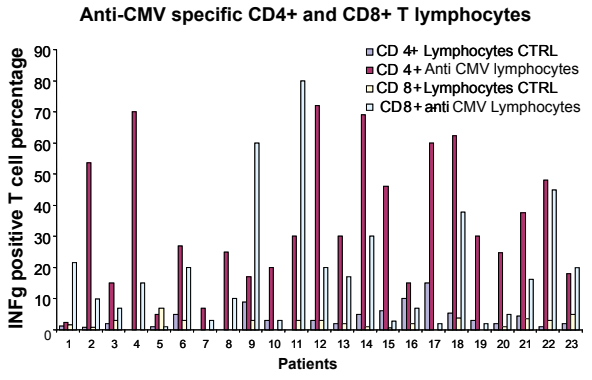

Figure 2. Day 21, T lymphocytes (CD4-positive and CD8-positive) assessed for intracytoplasmic INFg by flow cytometry in order to analyze the capacity of the DC to prime CMV-specific type-1 T cell response. The controls consisted of T cells with control lysate loaded DC. Data represent individual percentage of anti-CMV specific INFg-secreting T cells for 23 patients.

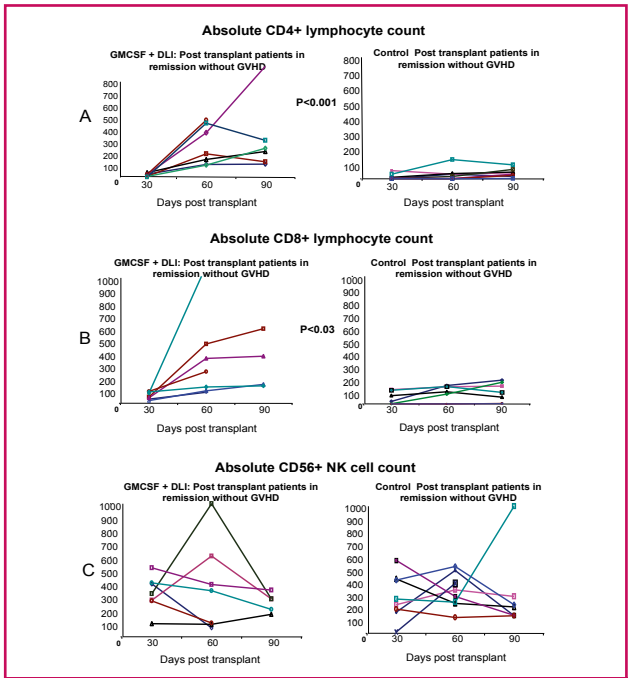

Figure 3. Immune reconstitution (CD4+ (A), CD8+ (B), CD56+ (C) absolute lymphocyte count) measured by Flow cytometry, comparison between the control cohort and the GMCSF + DLI cohort.

dia) occurred. Two of four patients treated pre-emptively developed grade II acute GVHD following the T-cell infusion, which required steroid therapy. Five out of the nine patients were already on immunosuppressive drugs but not high dose steroids (<0.5mg/kg) and without active GVHD at the time of the T-cell infusion. There was a worsening of the GVHD in three patients requesting an increase of the immunosuppressive treatment. The initial infusion of anti-CMV-specific T-cell occurred between 60 and 330 (median 150) days following transplantation. In our series we could not establish the efficacy of anti-CMV T-cell infusions. As far as our policy of specific anti-CMV T-cell infusions to treat patients pre-emptively is concerned, it seems to have controlled and prevented further reactivations in two patients who received the T-cells without antiviral therapy. Three patients who received the T-cell infusions combined with antiviral therapy didn't develop further reactivations. Four patients, who were on immunosuppressive drugs, developed at least one further reactivation that needed anti-viral therapy. These results remain anecdotal and no clear conclusion could be made on the adoptive cell transfer efficacy.

Discussion

The high relapse incidence in human cancers demonstrates the frequent inefficacy of the immune system to eradicate the residual leukemic burden persisting after chemo-radiotherapy. In this context, allogeneic stem cell transplantation has been proven to be the most effective way to reinforce the immune reaction against leukaemia by achieving a definitive eradication of the residual disease in a significant proportion of patients.[5] Indeed, the whole concept of hematopoietic stem cell transplantation (HSCT) evolved from a defective ill organ replacement to the concept of creating an extraordinary immunotherapeutic platform in which the donor immune system contributes to the eradication of the persisting leukemic cells.[6,7] Nevertheless, the persistent high relapse rate observed in leukaemia patients after HSCT remains the most important cause of death. Thus the issues remain those of finding the best immunomodulatory modalities to achieve a full engraftment, a powerful graft-versus-leukaemia effect and no or moderate graft-versus-host disease.[8-12] Moreover since, depending on the ethnic context, only about 40 to 70% of patients with high-risk haematological malignancies, eligible for allogeneic HSCT, have a fully HLA-matched sibling or unrelated donor, a great deal of effort has been invested to make the use of an alternative haploidentical sibling donor feasible.[13-19] The advantage of this procedure is the immediate availability of a donor for nearly all patients but the slow immune reconstitution in haploidentical transplant procedure is still chiefly responsible for the-

Table 1. Summary of the clinical results of 45 haploidentical transplants performed between 1999 and 2008, at Jules Bordet Institute

	G-CSF + DLI (n=9)	GM-CSF + DLI (n=12)	GM-CSF No NK mismatched (n= 13)	No growth factor No DLI NK mismatched (n= 11)
aGVH II-IV (n)	1	6	8	8
Infections (n)				
CMV reactivation:	2	7	7	4
Aspergillosis:	2	8	7	5
TRM at 3y (n)	2	8	8	5
Relapses (n)	6	2	1	1
LFS (n)				
CR or CML-CP at transplant	1/1	2/4	2/7	2/6
Progressive or Refractory at transplant	0/8	0/8	0/6	0/5

DLI: donor lymphocyte infusion, aGVHD: acute graft versus host disease, TRM: treatment related mortality, DFS: disease free survival

high incidence of early lethal infections, and most probably for early relapses.

From our phase I/II study, we conclude that the use of growth factors and DLI have considerable restrictions in haploidentical transplant. Mainly, it could not overcome the very bad prognosis of patient in refractory or progressive relapse. In other words, the addition of donor's lymphocytes does not seem to bring any benefits on relapse when associated with G-CSF, and markedly increase one-year transplant related mortality when combined with GM-CSF, due to a major incidence of severe aGVHD and infectious complications related to its treatment. Moreover, the use of GM-CSF alone was also associated with a high incidence of severe acute GVHD. The conditioning is well tolerated, as witnessed by the low mortality at three months. The only group, with a low transplant-related mortality and morbidity, is the one treated by G-CSF combined to a low dose ($1x10^4$ / kg) of G-CSF-primed donor lymphocyte infusion. Unfortunately, in this first group of patients, none was in complete remission, which, together with the low number of patients, prevents drawing any conclusion about efficiency. It is possible that this modality is the best one from the three we have tried consecutively in terms of infection prevention, but this remains pure speculation. The use of GM-CSF is too toxic, mainly due to untreatable aGVHD. Finally, the long term LFS of patient transplanted in any CR (mostly CR2 and CR3) is 38%, which compares favourably with the results for the same patients transplanted with a graft from a HLA-matched unrelated sibling, and despite a high TRM in the groups treated with GM-CSF. In a survey, Ciceri et al. analysed 173 adults with acute myeloid leukaemia (AML) and 93 with acute lymphoblastic leukaemia (ALL) who received a haplo-HSCT following a T-cell-depleted myeloablative conditioning in Europe.[20] Leukaemia-free survival at two years was 48% plus or minus 10%, 21% plus or minus 5%, and 1% for patients with AML undergoing transplantation in CR1, more than or equal to CR2, and non-remission, and 13% plus or minus 7%, 30% plus or minus 8%, and 7% plus or minus 5% in ALL patients, respectively. Although already affording some rationale for separation of GVHD from GVL, the use of recombinant cytokines or cytokine antagonists in human HSCT still needs optimisation. Results of T-cell-repleted haploidentical SCT with G-CSF-primed bone marrow and peripheral blood as graft source, were published by Chang et al.[21] The incidence of grade 3 or 4 aGVHD was 13% and 22% for cGVHD. The three-year probability of disease free survival (DFS) is, in standard and high-risk patients, 70% and 50% in AML, and 60% and 25% in ALL. Given the literature data about the negative effect of G-CSF on T-cell function and the possible favourable impact of GM-CSF when combined with DLI in patients relapsing after conventional HLA-identical transplant, we used GM-CSF and a single

Table 2. Growth factors and adaptive Immunity

WHY G-CSF ?
• G-CSF is a direct and indirect regulator of the adaptive T cell response
• G-CSF enhances the total T cell count from CD45RO+ memory T cell and NKT cell count
• G-CSF directly favors Th2 polarization, inducing production of IL4,TGFb and IL-10 and decreasing Il-12, TNFa and INFg
• G-CSF indirectly promotes functional regulatory T cell population
• G-CSF induces tolerogenic dendritic cells (DC2 or pDC) and downregulates CD28/CD80/CD86 co-stimulatory signals on dendritic cell and impairs IL12p70 release
• The GVL effect may be preserved through the CD8+ T-cell perforin-dependent pathways
WHY GM-CSF ?
• GM-CSF: promotes type 1 proinflammatory response Th1
• GM-CSF increases production of IL-12, INFg and TNFa by T cell and APCs
• IL-12 and Th1 profile has been associated with improved relapse-free survival without increassing GVHD
• GM-CSF preferentially increases DC1
• After TCD transplant : no increase in GVHD, same relapse rate, better OS
• GM-CSF: has been used as cancer vaccine adjuvant

DLI.[22-32] However, the replacing of G-CSF with GM-CSF led to more GVHD and reduces or overcomes the beneficial effect of faster CD4+ T-cells and CD8+ T-cells recovery (*Table 2*).

Manipulating the T-cell-compartment plays also a role in promoting GVL effect and in infection prevention. Different strategies are under investigation to improve DLI. Ex vivo depletion of alloreactive T-cells, suicide-gene insertion into T-cells, selected donor-Treg infusion prior to DLI are the three main approaches currently considered to improve the immune reconstitution after T-cell-depleted haploidentical transplant.[33-37] In the future, adoptive transfer of specific anti-leukemic T-cells and post transplant vaccine could become complementary options. Alternatively to the T-cell depletion approaches followed by immunotherapies strategies, T-cell-repleted haploidentical HSCT has been developed more recently.[38-42] The major challenge of this last approach is to avoid severe acute and chronic GVHD while preserving a strong GVL effect.[43] In most studies the very high immunosuppression requested for GVHD prophylaxis increased the relapse rate.

For anti-CMV T-cell infusion, several points can be stressed out from our personal experience. First we treated patients in the context of haploidentical transplant, which increases the risk of GVHD after T-cell infusion even at the lower dose of 10^4 T-cell/kg. This could explain why 5/12 patients in our series worsened or developed GVHD after T-cell infusion. Considering that cross reactions between viral and self peptide-HLA complexes may favour GVHD initiation and that anti-viral T-cells can be responsible for bystander activation of T-cells responsible for GVHD, this could be another reason why we observed more GVHD in our series.[44] Also, the infusions were performed under immunosuppressive therapy in four patients; although no patients were on high dose steroids (>0.5mg/kg), even so, the immunosuppressive therapy may have compromised the ability of the T-cells to expand in these patients. A major limitation of the T-cell adoptive transfer approach will always be its ineffectiveness in patients with intense immunosuppressive therapy, like high dose steroids to treat GVHD and paradoxically those patients are the most likely to present with multiple CMV reactivations.[45] The vicious cycle between GVHD, immunosuppressive therapy and CMV is well known in HSCT. This aspect underlies the problem of T-cell transfer in high-risk GVHD patients.[46,47] The technique is based on three weeks of expansion starting from unselected PBMC that yielded only enriched but not pure cellular products.[48,49] More recently Peggs reported a direct ex-vivo selection of anti-CMV lymphocytes from a donor leukapheresis product.[50] The method involves isolation of INFγ secreting cells by CliniMACS using INFγ capture microbeads (Miltenyi Biotec). This technique allows rapid isolation of an enriched type 1 T-cell product.

Key messages for clinical practice

- **There is a need to increase alternative donor availability.**
  - Matched sibling donor available for 25% of the patients.
  - Matched unrelated for 30%, 10-60% dependent on the ethnic background, of the patients.
  - Haploidentical donor virtually exists for all patients.
- **There is a need to improve allogeneic transplant results for poor and intermediate prognosis patients.**
  - Disease free survival is respectively around 20% and 40%.
- **There is a need to improve immune reconstitution in ex vivo T-cell-depleted haploidentical transplant.**
  - TRM is from 36% in CR1 to 66% for advanced patients mainly related to viral and fungal infections.
  - Adoptive T-cell immunotherapies are strategies currently studied to improve immune reconstitution in ex vivo T-cell-depleted graft transplant.
  - Infusion of unmanipulated graft is studied as alternative strategy to improve immune reconstitution.
- **Growth factors in haploidentical transplant.**
  - G-CSF combined to G-CSF-primed donor lymphocyte Infusion (DLI): feasible and possibly beneficial against infections.
  - GM-CSF with or without DLI: impacts the immune reconstitution but is too toxic.
- **Anti-CMV specific T-cells as adoptive T-cell therapy in haploidentical transplant.**
  - Specific anti-CMV T-cell adoptive transfer can control CMV reactivation.
  - Anti-CMV enriched T-cell lines can initiate or aggravate GVHD.
  - Technical difficulties to obtain high numbers and high purity of non-exhausted specific CD4 and CD8 T-cells.
  - Direct isolation of specific T-cells allows more flexibility but the T-cell dose is low and the purity similar.
  - In haploidentical setting the question of which haplotype presents the immunodominant peptides is important.

Nevertheless the purity of the product is only slightly-improved and cross-reactivity cannot be avoided. Though the T-cell dose was low, expansion of specific anti-CMV T-cells were detected in vivo in all patient and only 3/18 patients had a further CMV reactivation. Direct isolation of specific T-cells from donor blood allows more flexibility in the plan for their use. We generated CMV-specific T-cells for 23 patients and only twelve actually benefitted from the transfer of the expanded T-cells. If the procedure is started only for the patients with a first episode of CMV reactivation, the time to generate the lymphocytes (four weeks) is too long and the patient could present a new CMV reactivation before the lymphocytes are ready for use. In some cases the patient could develop GVHD, severe infection, relapse or even die before the specific anti-CMV T-cells were generated for the adoptive transfer. The development of a strategy based on direct isolation without culture would make the technique more reproducible and reliable and, in addition, would make it easier to conduct randomised studies to establish the efficacy of the strategy.[51] The optimisation of all these strategies encompasses significant technical difficulties, in particular the reproducibility in drastic alloreactive T-cell depletion required to safely infuse donor lymphocytes to patients, especially after haploidentical transplant. The specificity of the ex vivo generated or sorted T-cells is also a major limitation to this approach in often multi-infected patients. In this regard selective alloreactive T-cell depletion and other donor lymphocyte infusion strategies retaining the anti-viral T-cell pool seems more compelling and could be a more efficient approach.[52,53] The generation of anti-CMV specific lymphocytes opens the door to research on specific anti-leukemic antigen T-cell. Adoptive transfer of anti-tumour T-cell is a new field in rapid development.[54] Several studies are conducted in solid tumour and T-cell engineering (TCR transduction, CARs) have unveiled a total new era of cellular immunothera-

py.[55,56] Leukaemia responses to adoptive immunotherapy are depending not only on T-cell specificity but also on their ability to proliferate and survive after transfer. Adoptive transfer of specific T-cells is a major goal to improve the GVL effect without inducing GVHD. The strategy could be based on some minor histocompatibility antigens after allogeneic transplantation or TAA in allogeneic and autologous transplantation.[57] Currently, for technical and practical reasons, this approach is still the white elephant of the transplant immunologist. Only some very recent scientific and technical advances give us hope that anti-leukemic specific T-cells can be ex-vivo generated and amplified in a reliable and efficient way using large-scale clinical grade methodology in the near future.[58-60] Access to such cellular products will open an era of a totally new concept of treatment centred on immunogenic cell death and anti-leukaemia immune responses rather than chemotherapeutic disease eradication.[61,62] Considering the recently unveiled important Treg role and the difficulties in selectively modulating their activity that is central in inducing post-transplant tolerance, the autologous setting is significant in understanding the mechanisms responsible for the lack of an effective anti-tumour immune response.[63-65] The use of the autologous immune system can be seen as the ultimate goal. If we find a way to restore an efficient autologous immune response to the tumour, the use of an allogeneic immune system with all the immunomodulatory difficulties would no longer be necessary. Cellular immunotherapy will then be sufficient by itself to obtain an optimal cellular immunity against leukaemia without GVHD.

Conclusion

In a near future, haploidentical transplantation will remain a tool of choice especially for treating AML.[66,67] It could even become the first choice in AML patients, if we improve on our current results using post-transplant immune modulation strategies. Although HSCT is a powerful extraordinary cellular immunotherapy treatment, there is still an important need for improvement of immune reconstitution and the response to leukaemia. The concept that the immune system can help to achieve a definitive cure in cancer patients is now clearly established but currently, in most circumstances, manipulations of the autologous immune system are unable to eradicate the residual disease. The high relapse rate observed in leukaemia patients after HSCT remains the most important cause of death along with the slow immune reconstitution that allows for lethal infections to occur and the still unacceptably high incidence of GVHD. So if we compare the success of the transplant procedure with the relapse rate after transplant, it is clear that nowadays the beneficial immune effect of the transplant can only be obtained in less than 50% of the patients and there is still plenty of room for improvement of post-transplant immunotherapy. Today allogeneic HSCT has severely limited effectiveness against high-risk leukaemia and the efficacy of non-specific DLI, prescribed in order to increase the GVL effect, cannot be improved because of the induced GVHD associated with such products.

It is only if we can improve the immune reconstitution by boosting the anti-tumour effect without increasing the GVHD that we will be able to really use HSCT as an immunotherapeutic platform rather than as a sub-optimal organ replacement. The transplantation of a healthy donor immune system in a leukemic recipient offers a unique opportunity to boost anti-leukemic responses but the best way to make the most of it is far from clear.

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