Academic clinical trials run by the Transplant Committee of the Belgian Hematological Society

Belgian transplantation clinical trials

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The Transplantation Committee of the Belgian Hematological Society (BHS) is supported by all university centres and nonuniversity centres with significant transplant activity. The committee is involved in the development of transplant guidelines and recommendations, the transplant peer review process, contacts with regulatory authorities, the introduction of expanded access and medical need programs and the initiation of academic studies addressing important questions in the transplant field. Since 2008, eight clinical trials have been initiated after approval by the Ethics Committees and the National Competent Authority (AFMPS/FAGG). So far, one of them has been completed and is being prepared for publication. In this paper, we briefly describe the rationale, objectives, treatment arms, major inclusion criteria and current status of these different trials. In addition and for each trial a link is provided to the BHS website to obtain more details regarding inclusion criteria, participating centres and administrative/contact information.

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Introduction

The allogeneic stem cell transplantation (alloSCT) activity in Europe is continuously increasing. On the one hand, indications become more restricted as molecular techniques enable to identify subsets of patients who are more likely to benefit from the graft-versus-tumor (GVT) effect. On the other hand, the introduction in the mid-nineties of non-myeloablative alloSCT (NM-alloSCT) has allowed to expand the indications to more elderly patients or those with comorbidities. Despite improvements in supportive care, alloSCT remains a potentially dangerous treatment option because of the risk of infections and graft-versus-host disease. Many centers and/or collaborative groups are still initiating studies aiming at improving conditioning regimens and posttransplant immunosuppression as well as the use of donor lymphocyte infusions or other cel-

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lular therapeutic interventions. The Transplantation Committee of the Belgian Hematological Society (BHS) has initiated a number of studies related to these issues.

1. Trials related to the conditioning regimen

1.1. Allogeneic haematopoietic cell transplantation with HLA-matched donors: a phase II randomised study comparing two nonmyeloablative conditionings (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC01.pdf)

Alloreactivity of donor immune cells or the GVT effect plays an important role in eradicating residual malignant cells after alloSCT. This prompted the development of NM-alloSCT in which the burden for engraftment and tumor eradication is shifted from high-dose chemo-radiotherapy towards GVT effects. The Seattle team has developed a regimen of low-dose TBI (2 Gy) and fludarabine (90 mg/m^2), followed by immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP).[1] In this setting, acute GVHD has no impact on the risk of relapse/progression, but is associated with non-relapse mortality and decreased progression-free survival (PFS), while extensive chronic GVHD is associated with a decreased risk of relapse/progression and improved PFS.[2] The Stanford group has developed another nonmyeloablative regimen of total lymphoid irradiation (TLI; 8 Gy) and ATG (Thymoglobulin, 7.5 mg/kg), and postgrafting immunosuppression with MMF and cyclosporine.[3] This regimen favors the presence of NK-T regulatory cells and is associated with a very low incidence of acute GVHD, while preserving GVT effects.

In our study, we aimed at comparing the FLU-TBI and TLI-ATG regimens for the primary endpoint of grade II-IV acute GVHD. The trial started in January 2008 and recruitment was stopped in January 2011 (one year ahead of schedule) after 100 patients had been included. The results of the interim analysis planned after including 60 patients have been presented at the annual meeting of the BHS in 2011. A preliminary analysis of the sub-study investigating immune reconstitution in the two groups of patients (those conditioned with Fluda-TBI versus those receiving TLI-ATG) has also been presented at the same meeting. Final analysis of the trial is being carried out.

1.2. Busulfan dosage in allogeneic stem cell transplant recipients receiving PO Busulfan containing conditioning regimens (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC08.pdf)

High-dose conditioning regimens containing busulfan may be associated with severe organ toxicities, including veno-occlusive disease of the liver. Absorption of oral busulfan is highly variable, leading to unpredictable patient exposure. There are three main reasons for busulfan dosing and dose adjustment. First, one could reduce toxicity by avoiding excessive exposure to the drug, second, one could ensure adequate levels to decrease the incidence of relapse and graft failure, and third, one could aim at obtaining more comparable steady state levels in all patients. Therefore, therapeutic drug monitoring seems important to achieve maximal systemic busulfan exposure while minimising toxicity.

The BHS Transplant Committee decided to run a small non-interventional study, in which the feasibility and validity of the BU dosing method will be examined in patients receiving an oral busulfan-containing conditioning regimen. The Ghent University Hospital has set up the study for twenty patients in Belgium. Busulfan levels are determined in consecutive plasma samples after the first dose administration, so that, based on the area under the curve (AUC), physicians may decide whether to modify BU doses on following days. The study should start in 2012.

2. Trials involving the use of mesenchymal cell infusions

2.1 Infusion of mesenchymal stem cells as treatment for steroid resistant grade II to IV acute GVHD or poor graft function: a multicentre phase II study (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC02.pdf)

Mesenchymal stem cells (MSC) are stem cells that normally give rise to bone, cartilage and fat, but also have immunosuppressive properties.[4] MSC can be cultured from the bone marrow of normal volunteers, do not need to be HLA-matched with the pa-

tient and can be injected intravenously without significant side effects. Acute GVHD is a redoubtable complication of alloSCT. Its treatment consists in high-dose steroids that produce sustained responses in only 25-50% of patients. In patients not responding to steroids, outcome is dismal whatever second line therapy is used. Le Blanc et al. have recently demonstrated that infusion of third party MSC could be successfully used as treatment of grade III-IV, steroid-refractory, acute GVHD.[5] We aimed at investigating this in a Belgian multicentre setting.

Poor graft function occurs in 5-25% of patients after alloSCT and is associated with consequent morbidity and mortality due to infections and hemorrhagic complications. G-CSF may be considered for neutropenia and erythropoietin for anemia, second alloSCT is associated with high mortality, and a boost of CD34-selected PBSC can be proposed to selected patients. Small studies have suggested that MSC might help improving hematopoiesis in this setting.[6] We aimed at investigating this in a larger number of patients.

Low donor T-cell chimerism is associated with a high risk of graft rejection after nonmyeloablative alloSCT and donor lymphocyte infusions (DLI) are not very efficient in this setting. Animal studies have shown that MSC could help sustain engraftment.[7] We postulated that MSC given before DLI might be able to prevent graft rejection by decreasing/inhibiting host-versus-graft reactions.

The trial started in January 2008 with the aim of including 100 patients (40 for steroid-refractory GVHD, 40 for poor graft function and 20 for poor chimerism) and 72 patients have been included so far. The results in the first 20 patients with refractory acute GVHD were disappointing, so a second cohort was opened at a higher dose level. The results in patients with poor graft function will be analysed before the end of 2012 and recruitment is continuing in the low chimerism setting.

2.2. Co-transplantation of mesenchymal stem cells and HLA-mismatched allogeneic haematopoietic cells after nonmyeloablative conditioning: a phase II randomised double-blind study (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC03.pdf)

Mismatched unrelated donor alloSCT is associated with increased GVHD-related mortality and decreased survival. In an attempt to decrease this risk, we conducted a pilot study investigating the potential of third-party MSC to better prevent GVHD when co-infused into 20 patients undergoing NM-alloSCT from mismatched unrelated donors.[8] Projected 1-yr OS and PFS were 80% and 60%, respectively. These results compared favorably with those of a historical group of patients not given MSC for OS (44%, P=0.02) as well as PFS (38%, P=0.2).

We initiated a prospective, multicentre, randomised, double-blind, placebo-controlled clinical study aiming at evaluating whether an intravenous injection of MSC could improve one-year overall survival in patients receiving MSC compared to patients receiving placebo at the time of NM-alloSCT from a partially compatible donor. The aim is to include 120 patients.

2.3 A pilot study to assess the feasibility of unrelated umbilical cord blood transplantation with coinfusion of third-party mesenchymal stem cells after myeloablative or nonmyeloablative conditioning in adult patients with haematological malignancies (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC04.pdf)

Cord blood (CB) transplantation is increasingly used in patients who lack a suitable family or unrelated donor, both after myeloablative or nonmyeloablative conditioning.[9,10] Whereas CB transplantation is generally associated with lower risks of severe GVHD that transplantation from adult donors, the risk of poor engraftment or graft rejection is increased. In small series of patients, MSC have been suggested to decrease the risk of graft failure after haplo-identical transplantation and have been safely infused in recipients of cord blood transplants.[11,12]

We designed a single arm study to investigate the safety and feasibility of MSC co-infusion at the time of CB infusion in adults undergoing myeloablative or NM-alloSCT. The aim is to include 20 patients in this small pilot study but recruitment has been slow so far.

2.4 Randomized double-blind study of mesenchymal stem cells (MSC) in patients undergoing matched unrelated allogeneic bone marrow or peripheral blood stem cell transplantation - A European multicentre study (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC05.pdf)

Myeloablative alloSCT from unrelated donor peripheral blood stem cell transplantation is associated with a high risk of acute and chronic GVHD. Lazarus reported rapid hematopoietic recovery and a low incidence of GVHD in 46 patients cotransplanted with culture-expanded MSC and HSC from HLA-identical sibling donors after myeloablative conditioning, but this has not been studied in alloSCT with unrelated donors.[13]

Within the Stem Cell Subcommittee of the European Group for Blood and Marrow Transplantation (EBMT), K LeBlanc initiated a prospective, randomised, double-blind, placebo-controlled study comparing alloSCT from unrelated donors, with or without a co-infusion of third party MSC. The aim is to include 172 patients. The primary outcome measures are the cumulative incidences of grade II-IV acute GVHD and of extensive chronic GVHD. The CHU of Liège started the study in 2010 and other Belgian centres joined in 2011.

3. Trials related to the posttransplant immunosuppression

3.1 Prevention and treatment of severe GVHD after allogeneic haematopoietic stem cell transplantation, applied as consolidation immunotherapy in patients with haematological malignancies. A prospective randomised phase III trial (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC06.pdf).

After alloSCT, GVT effects significantly reduce the rate of leukaemic relapse. This immunotherapeutic effect is strongly associated with the occurrence of acute and/or chronic GVHD but patients with severe GVHD experience excess mortality. Different immunosuppressive regimens are used in order to prevent GVHD, but the optimal duration of GVHD prevention is not known.

The HOVON group decided to initiate an international collaborative study in HLA-id sibling myeloablative transplantation, in which two preventive regimens combining MMF and cyclosporine are prospectively compared, i.e. a time-restricted immunosuppressive regimen (MMF for 28 days and cyclosporine for 84 days) and a prolonged regimen (MMF for 84 days and cyclosporine for 180 days). In patients with steroid-refractory acute GVHD, anti-thymocyte globulin (ATG) is frequently applied. The study initially proposed to introduce ATG together with steroids in first line therapy for very severe acute GVHD, but this randomisation was closed for lack of accrual.

3.2. Allogeneic haematopoietic cell transplantation from HLA-matched donors after reduced-intensity conditioning : a phase II randomised study comparing two GVHD prophylaxis regimen (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC07.pdf)

Sirolimus (rapamycin) is a naturally occurring macrolide with antineoplastic and immunosuppressive properties, that is active in the prevention and treatment of acute and chronic GVHD, perhaps by preserving regulatory T-cells while inhibiting effector T cell proliferation and activation. The addition of sirolimus to tacrolimus or MMF in patients undergoing unrelated HLA-matched alloSCT after Fludarabine-TBI resulted in a lower incidence of grades II-IV acute GVHD, but not chronic GVHD. In a retrospective analysis of 190 patients undergoing alloSCT for lymphoma, overall survival was significantly superior in patients receiving sirolimus compared to those receiving a calcineurin inhibitor plus methotrexate.[14] Non-relapse mortality was similar, while disease progression and grade II-IV acute GVHD (but not of chronic GVHD) were decreased, but the benefit was restricted to patients undergoing reduced-intensity conditioning.

After completing TC-01, the BHS Transplant Committee thus decided for its next NM-alloSCT protocol in 10/10 matched related or unrelated donor transplantation, to undergo a prospective comparison between two GVHD prevention regimens, i.e. the classical tacrolimus + MMF combination versus a tacrolimus + sirolimus combination. The aim is to include 200 patients and the trial started at the end of 2011.

4. Cell therapy trials

Wilms' tumor (WT1) antigen-targeted dendritic cell vaccination to prevent relapse in patients older than 65 years with acute myeloid leukemia : a multicentre randomised phase II trial (http://www.bhs.be/frontend/files/userfiles/files/Trials/TC09.pdf)

The prognosis of elderly patients with acute myeloid leukaemia (AML) remains dismal, as up to 80% of these patients will eventually relapse, due to a small reservoir of resistant AML stem cells persisting after chemotherapy. For patients ineligible for alloSCT, there is no standard post-remission therapy to avoid relapse. Immunotherapy has come to the fore in recent years. The concept of vaccination is based on the observation that AML cells carry leukaemia-associated antigens (LAA), allowing their recognition and elimination by LAA-specific cytotoxic T lymphocytes (CTLs). Dendritic cells (DC) are the most effective antigen-presenting cells and tumor antigen-loaded DCs are an attractive tool for activating tumor-specific immune response in cancer patients. The Antwerp group has recently reported encouraging results from an open-label phase I/II clinical trial of DC-based vaccination in the AML post-remission setting, using autologous DC loaded with the LAA Wilms' tumor protein 1 (WT1) through mRNA electroporation.[15] WT1 is a tumor-associated antigen that is highly overexpressed in several malignancies, including AML, and is also present in leukemic stem cells. In the first cohort of 17 evaluable patients, they observed a decrease to normal of WT1 transcript levels in eight patients.[16] Median DFS and OS have not been reached for those eight responding patients, whereas in the other nine patients they were only 2.7 months and 5.5 months, respectively. These results support a DC vaccine strategy to eradicate leukaemia and prevent relapse in elderly AML patients.

Upon a study proposal of the Antwerp group, the BHS Transplant Committee agreed to support a randomised study in a larger, multicentre cohort of patients (n=138). The study will be started later in 2012 after approval by the regulatory authorities and securing a grant from the national Cancer Plan.

Conclusion

The Transplantation Committee of the Belgian Hematological Society (BHS) has initiated several academic clinical trials addressing important questions related to the field of allogeneic stem cell transplantation. These efforts have led to a close collaboration between Belgian transplant centres that thus far was unprecedented and benefits progress in science as well as daily care for our transplant patients.

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