

REVIEW

Haploidentical haematopoietic stem cell transplantation for acute leukaemia in adults: experience in Europe and the United States

F Aversa

Haematopoietic Stem Cell Transplant Unit, Section of Haematology and Immunology, IBIT Foundation, University of Perugia, Perugia, Italy

Work on one haplotype-mismatched transplants has been proceeding for over 20 years all over the world and novel transplant techniques have been developed. Some centres have focused on the conditioning regimens and post transplant immune suppression; others have concentrated on manipulating the graft. Haploidentical transplant modalities are based mainly on high-intensity conditioning regimen, but reduced intensity regimens have recently been introduced. The graft may be a megadose of extensively T cell-depleted or unmanipulated progenitor cells. Excellent engraftment rates are associated with a very low incidence of GVHD- and regimen-related mortality even in patients who are over 50 years old. Overall, event-free survival and transplant-related mortality compare favourably with reports on transplants from sources of stem cells other than the matched sibling. Improvements will come with successful implementation of strategies to accelerate and strengthen post transplant immune reconstitution as well as transplantation of patients in early stage disease.

Bone Marrow Transplantation (2008) **41**, 473–481; doi:10.1038/sj.bmt.1705966; published online 7 January 2008

Keywords: myeloablative conditioning regimens; RIC; *ex vivo* positive and negative selection in T-cell depletion; unmanipulated stem cell transplant; outcomes

Introduction

Interest in BMT from haploidentical donors arises from the immediate availability of a one haplotype-mismatched donor for virtually all patients, particularly those who urgently need transplantation. Most adults with ALL or AML relapse especially when they have unfavourable cytogenetics at diagnosis, when they do not achieve

CR after the first induction cycle and when they are in second or later remission.^{1–4} Under these circumstances, an allogeneic haematopoietic stem cell transplantation (HSCT) is preferred as post-remission therapy but the ideal donor, an HLA-identical sibling, is available for 30% of patients.

The only option is transplantation from an alternative donor. In the international registries the probability of finding a matched unrelated donor (MUD) ranges from 10% in poorly represented ethnic groups to 60% in Caucasians.⁵ Many patients relapse while the HLA typing is in progress or while waiting to start transplant procedures. Unrelated cord blood (UCB) offers the advantages of easy procurement and immediate availability.^{6,7} For adults, the great divergency between body weight and the number of haematopoietic cells in a cord blood unit, particularly if associated with a two antigen mismatch, increases the risk of graft failure and delays haematopoietic reconstitution. Even though transplantation of two cord blood units is providing promising results,⁸ the only feasible option for many adults is transplantation from a haploidentical donor.

Besides immediate donor availability, mismatched family donors offer several other advantages: (1) ability to select the best of many relatives on the basis of age, infectious disease status and natural killer (NK) cell alloreactivity;⁹ (2) optimal graft composition and (3) immediate access to donor-derived cellular therapies. Furthermore, for nearly all patients who reject the graft, the haploidentical transplant offers the advantages of another family member as donor or a second graft from the original donor.

Basic and clinical research on haploidentical transplantation has been proceeding for over 20 years and has spread to centres worldwide. Some centres focused on manipulating the conditioning regimens and post transplant immune suppression; others, such as our centre in Perugia, Italy, concentrated on manipulating the graft. There is consensus that rejection and GVHD, which were inevitably linked to transplantation across the HLA barrier, have been resolved. Best survival rates were around 55% for AML and 28% for ALL in adults transplanted in CR; best rates in children were 47% for acute leukaemia and 87% for non-malignant diseases.¹⁰ Poor post transplant immune reconstitution and infection-related mortality remain open problems which are discussed in depth below.

Correspondence: Professor Dr F Aversa, Haematopoietic Stem Cell Transplant Unit, Section of Haematology and Immunology, IBIT Foundation, University of Perugia, Ospedale SM della Misericordia, 06156 Perugia, Italy.

E-mail: aversa@unipg.it

Received 31 May 2007; revised 29 August 2007; accepted 29 October 2007; published online 7 January 2008

Engraftment and GVHD

Despite proof that a haploidentical graft could be successfully transplanted without causing GVHD in SCID patients receiving a lectin-separated BMT from haploidentical parents,¹¹ unmanageable T-cell alloreaactions across the HLA barrier caused a high incidence of severe GVHD and rejection of extensively T cell-depleted BMT in leukaemia patients.^{12,13} Enhancing immunosuppression and myeloablation did not ensure engraftment.^{14–19} Removing under two log T cells from donor marrow improved the engraftment rate but required post transplant immunosuppression to prevent GVHD. A series of clinical trials administered TBI-based myeloablative conditioning, a graft with partial *ex vivo* T-cell depletion by T10B9 monoclonal antibody in 143 patients or by OKT3 in 58 patients. GVHD prophylaxis also included antithymocyte globulin (ATG), cyclosporine and steroids. Engraftment was successful in 98% of patients; grades II–IV acute GVHD and chronic GVHD were 13 and 15%, respectively.¹⁴

In 1993, we were the first to produce a megadose of human haematopoietic stem cells by adding G-CSF-mobilized PBPCs to bone marrow cells,²⁰ using a lectin-based technique to ensure over three log T-cell depletion. Primary engraftment was achieved in 16/17 patients with end-stage leukaemia. Without post transplant immunosuppressive treatment, severe acute GVHD occurred in only one patient and there were no cases of chronic GVHD.

Animal models had shown that transplantation of high doses of T-depleted marrow cells engrafted without causing GVHD as they reduced the frequencies of anti-donor CTL precursors (p.) *in vivo*, probably through deletion mediated by tumour necrosis factor- α .^{21–24} Cells within the CD34⁺ cell population exhibited 'veto' activity, that is, in bulk-mixed lymphocyte reactions they neutralized specific CTL-p, directed against their antigens but not against a third party.^{22,23}

In 1995, fludarabine was substituted for cyclophosphamide to minimize extra-haematological toxicity of the TBI-based conditioning regimen,^{25,26} and CD34⁺ cells were positively selected from leukapheresis products to reduce T cells to one log less than in the previous series. The final inocula contained a median of 10×10^6 per kg CD34⁺ cells and 2×10^4 T cell per kg. The engraftment rate was 95% with no GVHD.²⁶ The threshold dose of 2×10^4 CD3⁺ cells per kg prevented severe GVHD as long as it was associated with ATG in the conditioning because ATG has a plasma half-life of several days and could exert *in vivo* T-cell depletion.^{27–29}

In 1999, we started using the automated Clinimacs device (Miltenyi Biotech, Bergisch Gladbach, Germany) which, besides providing a good yield of CD34⁺ cells, ensured a median of 4.5 log T-cell depletion and 3.2 log B-cell depletion,³⁰ which helps prevent EBV-related lymphoproliferative disorders in recipients of an extensively T cell-depleted HSCT after a conditioning regimen with ATG.^{31,32} This automated graft processing system, which provides reliable and reproducible yields, has contributed to make extensively T cell-depleted haploidentical transplantation feasible in any transplant centre.

In 255 adults with acute leukaemia treated under fludarabine-based protocols we achieved 95% primary

engraftment rate, which rose to 98% when we included the few recipients of a second haplo-transplant. Severe acute and extensive chronic GVHD were largely prevented. At the San Raffaele Hospital, Milan (Italy), the same transplant protocol was associated with similar results in a cohort of patients with advanced stage haematological malignancies.³³

At the University of Tuebingen (Germany), positive selection of CD34⁺ cells and a myeloablative conditioning regimen were associated with high transplant-related mortality (TRM) in pilot studies.³⁴ Consequently, negative selection of G-CSF-mobilized PBPCs (CD3/CD19 depletion with anti-CD3- and -CD19-coated microbeads on a Clinimacs device) was used so as to infuse large numbers of CD34⁺ and CD34⁻ cells, CD8⁺ T cells, NK cells and other accessory cells.³⁵ Their current HSCT protocol includes reduced intensity conditioning (RIC)—melphalan, thiotepea and fludarabine—followed by CD3/CD19-depleted PBSCs. OKT3 is used instead of ATG.^{36,37} Mycophenolate mofetil was needed in patients who received more than 2.5×10^4 CD3⁺ cells per kg. In 27 adults (median age 41 years) with high-risk leukaemia, they confirmed 100% full-donor engraftment. Patients (13/27; 48%) developed acute GVHD (nine grade II, two grade III and two grade IV).³⁷ Shifting from positive to negative PBPC selection re-introduces GVHD, which requires immunosuppressive therapy, thus counteracting the advantage of early post transplant immunological recovery and compromising the quality of life of long-term survivors. Furthermore, RIC does not guarantee leukaemia burden debulking and, as follow-ups are very short, no definitive conclusions can be drawn about relapse.

At the Dana Farber Cancer Institute, Boston (USA), costimulatory blockade was used to induce tolerance in haploidentical transplantation.³⁸ Engraftment was successful in 11/12 evaluable patients, 3 with acute GVHD. When results were updated to include another 12 patients,³⁹ graft failure occurred in 4.2%, aGVHD grade II–III in 35% and cGVHD in 4.2%. This approach appears to support engraftment but does not eliminate GVHD.

Other researchers focussed on haploidentical transplants without T-cell depletion.^{40,41} At Peking University (China), Huang *et al.*⁴⁰ combined G-CSF-primed BM and unmanipulated PBSCs after myeloablative conditioning and post transplant immune suppression with mycophenolate and cyclosporine (CYA). All 171 patients (86/171 at high-risk) achieved full-donor chimaerism. At 100 days after transplantation, grades II–IV and III–IV acute GVHD developed in 55 and 23%, respectively. Acute GVHD grades II–IV occurred in 52/66 patients (78%) and grades III–IV in 9 (13%) who were three-loci mismatched with donors. Despite ATG in the conditioning and intense post transplant immunosuppression, the incidence of chronic GVHD was 73.6%, suggesting patients enjoy a poor quality of life and may be at risk of late TRM due to opportunistic infections and toxicity related to long-term immunosuppression.

At Durham University, NC (USA), Rizzieri *et al.*⁴² used unmanipulated PBSCs after a new RIC: alemtuzumab, fludarabine and cyclophosphamide (CY). Additional GVHD prophylaxis included mycophenolate and CYA.

Of the 49 patients, 94% engrafted; 8% had secondary graft failure. Acute GVHD (grades III–IV) occurred in 8%. This immunosuppressive RIC was associated with a high engraftment rate and a relatively low incidence of GVHD. Long-term outcomes remain to be ascertained.

After successful canine experiments, high-dose post transplant CY was tested in a phase I trial to determine the minimal conditioning that ensured engraftment of an HLA-1 to -3 antigen-mismatched BMT.⁴³ A total of 13 patients with haematological malignancies were conditioned with low-dose TBI, fludarabine ± CY and received CY again on day +3 post transplant. Altogether 9 of 13 patients engrafted; 6 developed acute GVHD. Attempts to compensate low-intensity conditioning with post transplant immune suppression were once again associated with low engraftment rates and GVHD.

Several groups exploited the principle of tolerance induction resulting from *in utero* exposure to maternal antigens in haploidentical stem cell transplantation. Due to transplacental trafficking of maternal and foetal cells during pregnancy, maternal antigens induce mutual hyporesponsiveness and long-lasting feto-maternal microchimerism.⁴⁴ Non-T cell-depleted haploidentical HSCT from tolerized donors (typically mothers or non-inherited maternal antigen (NIMA) mismatched siblings) was successful but most patients developed acute and/or chronic GVHD.^{45,46} In several Japanese transplant centres, myeloablative or non-myeloablative conditioning followed by unmanipulated transplants from microchimeric NIMA-mismatched donors resulted in a 56% incidence of acute GVHD grades II–IV in 34 evaluable patients. The risk of GVHD was significantly lower when the donor was NIMA mismatched in the GVHD direction.^{46–48} A large International Bone Marrow Transplant Registry (IBMTR) analysis showed that after unmanipulated haploidentical HSCT, the incidence of grades II–IV acute GVHD was related to haplotype inheritance; acute GVHD was significantly less frequent after transplants from NIMA-mismatched siblings, but TRM was significantly higher in transplants from a parent.⁴⁹

Leukaemia relapse

Extensive T-cell depletion might be expected to result in a weak or no GVHD–GVL effect which is conventionally achieved through T cell-mediated alloreactions directed against histocompatibility antigens displayed on recipient leukaemic cells.^{50,51} Under the Perugia protocol, despite the lack of GVHD–GVL effect and unfavourable prognostic features at transplant, relapse rates were very low. Relapse occurred in respectively 18 and 30% of AML and ALL patients transplanted in any CR. In AML the cumulative incidence of relapse was significantly lower after transplantation from NK alloreactive donors (3 versus 47%; $P < 0.003$).⁵² Relapse rates rose to 34 and 58%, respectively for AML and ALL patients who were in relapse at transplant and there was no difference whether the donor was NK alloreactive or not (32 versus 37%; $P = \text{NS}$).⁵²

Factors which may have contributed to control post transplant relapse include: a highly myeloablative conditioning regimen, which successfully debulked the leukaemia

burden; no post transplant immunosuppression which may have allowed the few T cells in the graft to exert a sub-clinical GVHD–GVL effect; donor-versus-recipient NK cell alloreactivity which exerts a specific Graft-versus-AML effect in susceptible patients^{9,52–54} and in T, but not B, phenotype ALL.⁵³ Engineering NK cells to express anti-CD19 chimeric and activating receptors was reported to provide cytotoxicity against NK cell-resistant ALL.⁵⁵ Furthermore, Leung *et al.*⁵⁶ showed that ALL cells are susceptible to NK-cell lysis when donor NK cells expressed natural killer cell immunoglobulin-like receptor (KIRs) in the absence of cognate ligand in the recipient. In addition when NK-cell alloreactivity is combined with donor-activating KIR genetics, which protect against infection, a significant survival advantage is obtained.^{52,54} Therefore, as donor-versus-recipient NK-cell alloreactivity contributes to prevent graft rejection, GVHD- and infection-related mortality such donors are preferred for all haploidentical transplants.

In the German series, 6/27 adults and 8/21 children relapsed after receiving negatively selected haploidentical grafts.³⁷ The Dana Farber approach was associated with a 12.5% relapse rate.³⁹ Unfortunately no definitive conclusions can be drawn because of the small patient cohorts and brief follow-ups. As far as regards unmanipulated haploidentical transplantation Peking University reported relapse rates ranging from 12% in standard-risk patients to 39% in high-risk patients.^{40,41} In the Durham report, relapse was the main cause of death, occurring in 24/49 patients.⁴² Therefore, relapse rates, despite the incidence of GVHD, were the main reasons for transplant failure.

Other studies have suggested a $\gamma\delta$ T cell-mediated anti-leukaemic effect.^{57–59} A retrospective analysis on 201 patients with acute leukaemia who received partially mismatched HSCT from 1993 to 1999 at the South Carolina Cancer Center⁵⁹ showed 77 ALL and 76 AML survivors on day +59. Eighteen patients with high $\gamma\delta$ T-cell counts post transplant had better 5-year survival than those with normal or low counts (70.8 versus 19.6%; $P = 0.0001$). Like macrophages and NK cells, $\gamma\delta$ T cells exhibit biological characteristics of innate immunity and recognize malignant cells through mechanisms that require no prior antigen exposure or priming. Since few reports have investigated $\gamma\delta$ T-cell recovery during post transplant immune reconstitution, it remains to establish whether these observations are related to graft processing procedures or donor-related factors.

TRM and post transplant immune re-building

After all forms of transplantation from alternative donors TRM, post transplant immune re-building and infectious mortality remain outstanding issues for several reasons: (1) conditioning-induced tissue damage prevents T-cell homing to peripheral lymphoid tissues, where T-cell memory is generated and maintained; (2) for months after transplant, immune recovery in adults with their decayed thymic function stems from expansion of mature T cells in the graft, and afterwards, from *de novo* production of naive T cells; (3) delays in immune construction are due to (1) GVHD and its immunosuppressive treatment in unmanipulated transplants and (2) T-cell depletion and ATG in the

conditioning, which creates a deficit in T-cell immunity.^{60–63} Administering G-CSF after T cell-depleted haploidentical transplant promotes Th-2 immune deviation which, unlike Th-1 responses, does not protect against fungi, bacteria and viruses.⁶⁴ Patients who did not receive G-CSF after transplant recovered CD4⁺ cells count faster and most post transplant CD4⁺ cell clones exhibited Th1-Th0 features.⁶⁴

The Perugia group reported 40% of patients died of non-relapse causes. Most deaths were caused by infections, mainly CMV and *aspergillus*.^{26,30} TRM depended on disease stage at transplant and was significantly higher in patients transplanted in relapse (58 versus 36%; $P=0.02$). Due to the absence of chronic GVHD and its treatment the risk of life-threatening episodes plateaued after about 1 year, confirming that immune competence was completely recovered at this stage.

Under the Tuebingen protocol, 7/27 adult patients and 2/21 children died (infections in six; GVHD in one).³⁷ The two children died of non-specified causes, presumably transplant-related toxicity. The Dana Farber group reported early death in 50% of their 24 patients, the most common cause being bacterial or fungal infections.³⁹ Peking University reports a TRM of 9.1 and 12.7% at day 100, respectively in standard- and high-risk groups. TRM rises to 19.5 and 31.1% at 2 years.⁴⁰ Of the 39 non-relapse deaths 21 (54%) were due to opportunistic infections.

The Durham group achieved 10.2% TRM at 100 days after transplantation, projecting to 40% at 2 years.⁴² Causes include infections, lymphoma, haemolytic anaemia and neurotoxicity. Quantitative lymphocyte recovery through expansion of transplanted T cells and immunoscope analysis of the $\gamma\beta$ family of T cells were noted by 3–6 months only in patients who did not develop GVHD. Although RIC followed by unmanipulated PBSCs seems appealing because of the low TRM at 100 days post transplant, the 2-year probability of relapse mortality approaches 50% (24/49 patients).

Any further reduction in TRM after haploidentical transplantation will only be achieved by hastening post transplant immune recovery. However alloreactivity is attenuated, T cell-based adoptive therapy is problematic in the adult haploidentical transplant setting as infusion of grafts containing only a few more T cells than the threshold dose of 10⁴ per kg may cause lethal GVHD. Obstacles to the transfer of donor immunity are (1) the HLA barrier; (2) the need to transfer donor T cells early when patients are most vulnerable to GVHD; (3) lack of post transplantation GVHD prophylaxis because immune suppression would protect against the GVHD potential of infused T cells and (4) the increased susceptibility of adults to GVHD.

Despite this, several strategies are under investigation. The Perugia group has recently transferred donor pathogen-specific immune responses safely across the HLA barrier.⁶⁵ Donor T-cell clones raised against *aspergillus fumigatus* and CMV antigens were screened for cross-reactivity to host alloantigens by MLR. Nonhost-reactive clones, presumably devoid of GVHD potential, were pooled and infused into recipients soon after transplant. This study demonstrating the maximum tolerated dose of

1 million CD3⁺ cells per kg recipient body weight was clinically effective as CMV reactivation and *aspergillus* galactomannan antigenemia tended to disappear over time. In patients who were infused, the frequencies of anti-*aspergillus* and -CMV-specific T-cell clones increased rapidly unlike the control group, where they developed *in vitro* more than 9 months post transplant.⁶⁵ In other transplant centres similar results were achieved when *ex vivo*-expanded EBV-specific allogeneic CTL clones were used to prevent or manage EBV-associated diseases, including post transplant lymphoproliferative disorders.^{66,67} The main drawbacks of both approaches are that they are time-consuming, labour intensive and, at present, unsuitable for routine clinical use as cloning and screening procedures do not always satisfy quality controls.

Genetic manipulation of donor lymphocytes with a suicide gene is a promising strategy that was developed in Milan.^{68,69} Should GVHD develop, after genetic engineering of donor lymphocytes with the herpes simplex virus-thymidine kinase (TK) suicide gene, transduced cells can be eliminated by ganciclovir treatment. In 17 patients, TK cells provided protection against CMV reactivation and disease. Overall, the cumulative infectious mortality at 6 months post transplant was 12.5% with only 6% CMV-related mortality. This strategy may find a place in preventing relapse, selectively controlling GVHD and/or enhancing wide-spectrum immunological reconstitution after transplantation.⁷⁰

Results of *ex vivo*-expanded immunomodulatory cells (T-regs, NK/T-regs, MSCs and donor-derived NK),^{71–74} adoptive transfer of allogeneic T cells that are specific for viral^{65,67,75–78} or tumour antigens⁷⁹ appear promising. All these diverse approaches show that cell therapy is feasible after haploidentical transplantation and may help re-build immunity to infections.

Survival

Event-free survival (EFS) after haploidentical transplantation is closely related to disease and disease status at transplant and compares favourably with survival after MUD transplant in the same risk category.^{80,81} In Perugia, EFS in 83 AML patients transplanted in CR, ranges from 35% for those in second or later CR to 50% for CR1, while 62 patients with ALL who were transplanted in CR have about 25% probability of surviving event-free. With no chronic GVHD, all these long-term survivors enjoy an excellent quality of life.

Patients in chemoresistant relapse had no option other than transplantation from a mismatched family donor. The 14% 10-year EFS for 64 end-stage AML patients is more than encouraging, but as only 5% of 46 ALL patients survive event free, we do not recommend haploidentical transplant in advanced stage ALL.

In a multivariate analysis, donor-versus-recipient NK-cell alloreactivity impacted favourably upon survival in AML patients.⁵² A total of 30 patients in any CR who received a transplant from an NK-cell alloreactive donor enjoy 67% EFS versus 18% in 31 patients transplanted from non-NK alloreactive donors ($P=0.02$). In 21 AML patients who were in relapse at transplantation, NK-cell

Table 1 T cell-depleted and unmanipulated haploidentical stem cell transplantation

Centre	Disease	Patients (n)	Conditioning	GVHD prophylaxis	Rejection	Acute GVHD II–IV	Chronic GVHD Ext	TRM	Relapse	DFS	Reference
<i>T-cell depleted</i>											
University of Perugia (Italy)	AML/ALL/CML	17	TBI/TT/CY/ATG	Extensive TCD	1/17	1/16	0/9	9/17	2/17	6/17	Aversa <i>et al.</i> ²⁰
University of Perugia (Italy)	AML/ALL	43	TBI/TT/F/ATG	Extensive TCD	5%	0	0	40%	13% AML 63% ALL	36% AML 17% ALL	Aversa <i>et al.</i> ²⁶
University of Perugia (Italy)	AML/ALL	104	TBI/TT/F/ATG	Extensive TCD	6%	8/100	3/70	38/104	16/67 AML 10/37 ALL	47% in CR 4% in relapse	Aversa <i>et al.</i> ³⁰
University of Tuebingen (Germany)	AML/ALL/others	27	TBI or BU/CY/TT ± F	CD3/CD19 depletion	0	48%	NA	7/27	6/27	14/27 (52%)	Bethge <i>et al.</i> ³⁷
Dana Farber Cancer Centre, Boston (USA)	ALL/AML/NHL/others	24	TBI/Ara-C/CY/steroids	CTLA4-Ig CSA + MTX short	4.2%	35%	4%	NA	NA	8/24	Guinan <i>et al.</i> ³⁸
University of South Carolina (USA)	AL/MM/NHL/CML	49	TBI/VP16/Ara-C/ATG	Partial TCD, ATG, PDN, MMF	7/49	16%	15%	15/49	24/49	31% @ 1 year	Rizzieri <i>et al.</i> ⁴²
<i>Unmanipulated</i>											
People's Hospital (China)	ALL/AML/CML/MDS	171	BU/Ara-C/CY/Me-CCNU/ATG	CSA/MMF/MTX short	0	55% 73/171	47% 35/150	19% SR @ 2 years 31% HR @ 2 years	12% SR 39% HR	68% SR @ 2 years 42% HR @ 2 years	Huang <i>et al.</i> ⁴⁰
China (multicentre)	CML/AML/ALL/MDS	135	BU/Ara-C/CY/Me-CCNU/ATG	CSA/MMF/MTX short	0	40%	55%	22% @ 2 years	18% @ 2 years	64% @ 2 years	Lu <i>et al.</i> ⁴¹

Abbreviations: ATG = anti-thymocyte globulin; AML = acute myeloid leukaemia; ALL = acute lymphoid leukaemia; BU = busulfan; CML = chronic myeloid leukaemia; CR = complete remission; CSA = cyclosporine A; CY = cyclophosphamide; DFS = disease-free survival; F = fludarabine; GVHD = graft-versus-host disease; HR = high risk; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MTX = methotrexate; NA = not applicable; NHL = non-Hodgkin lymphoma; PDN = prednisolone; SR = standard risk; TBI = total body irradiation; TCD = T-cell depletion; TRM = transplant related mortality; TT = thiotepa.

alloreactivity was associated with better survival (30 versus 6%; $P=0.04$). In fact, we recommend transplantation for AML patients in relapse only if an NK alloreactive donor is available.

A preliminary report from the Tuebingen group that 14/27 patients (52%) survive at a median follow-up of 8 months³⁷ needs to be confirmed in a much larger series of patients with a longer follow-up.

Guinan *et al.* reported 5 of the original 12 patients were alive and in remission 4.5–29 months after transplantation which was updated to 8/24 long-term survivors (33.3%) at a median follow-up of 3.3 years.^{38,39} All eight had an excellent performance score with good immune function; none was on chronic medication.

The Chinese study reported a 2-year probability of leukaemia-free survival as 68% for standard-risk patients and 42% for high-risk patients. When patients were stratified for age, survival was worse in patients over 35 ($P=0.033$), probably because of a higher incidence of GVHD-related mortality.^{40,41}

In the Durham study, 75% of evaluable patients achieved CR after transplantation and 1-year survival was 31% (95% CI, 18–44%).⁴² Better results were obtained in a small group of 19 patients with standard risk that is remission or aplasia. Overall 1-year survival was 63% (95% CI, 38–80%) with a 2.9-year median overall survival (95% CI, 6.2–48 months).

In the small series of 13 patients who received CY after transplantation, O'Donnell *et al.*⁴³ reported 6/13 patients were alive, 5 in CR at a median of 191 days post transplant. The most recent trials on haplotransplant are reported in Table 1.

Conclusions

The past few years have seen growing interest in haploidentical transplantation, with several groups modifying conditioning regimens, graft processing and post transplant cellular immunotherapies in attempts to improve outcomes and provide convincing clinical evidence in favour of this transplant modality. The choice of the best alternative source of stem cells for individual patients without matched sibling donors is hampered by lack of randomized studies supplying data on outcomes after MUD, UCB and haploidentical transplants. Designing such a study is difficult because, at present, allocation of a patient to one of these three options could reflect a transplant centre's preferential use of a particular transplant modality rather than selection of the best donor for each individual patient.⁸² However, retrospective data analyses show survival rates overlap after haploidentical transplants for high-risk acute leukaemia and transplants from other alternative sources.^{80–82} It is worth noting that the probability of EFS after matched unrelated transplants is confounded by the gap between the number of activated searches and *de facto* transplants and many patients relapse and die while searching for an appropriate donor. Furthermore, independently of matching, many UCB transplants for adults were not performed because units

did not contain the recommended threshold cell dose for engraftment.

Neither time lapse nor insufficient stem cell dose is an issue in the haploidentical transplant. Donors are found within the family for virtually all patients with no undue delay between decision-making and transplantation, which is a crucial factor in urgent cases. If the selected donor is a poor mobilizer, another mismatched family member is available as replacement. Although current data in most series refer to small, diverse patient populations, the main complications are GVHD in unmanipulated haploidentical SCT and delayed immune recovery in the T cell-depleted modality because rejection, GVHD and leukaemia relapse are no longer major issues in patients who are not transplanted in end-stage disease. In the absence of alloreactive T cells, the NK cell impacts beneficially upon outcomes. Donor-versus-recipient NK-cell alloreactivity strengthened the Gv-AML effect, improved engraftment and helped prevent GVHD independently of disease.^{52,54}

As disease status at transplantation seems to be the main determinant of treatment failure, one is left with the question of whether transplant timing has become a determining factor in outcomes. It is to be hoped that transplant physicians will be less hesitant to treat patients in better condition and earlier disease stage, and that the mismatched transplant will be offered, not as a last resort, but as a routine option to high-risk acute leukaemia patients.

Acknowledgements

I thank all the laboratory and technical staff, the attending physicians and nurses of the HSCT Unit at the University of Perugia, Italy, for their dedication and professional skills. Special thanks to Professor Massimo F Martelli for pioneering the mismatched transplant, Professor Yair Reisner for his expertise in transplant biology and Dr Geraldine Boyd for his help in writing this paper.

References

- Byrd JC, Mrózek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC *et al.* Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with *de novo* acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood* 2002; **100**: 4325–4336.
- Burnett AK, Wheatley K, Goldstone AH, Stevens RF, Hann IM, Rees JH *et al.* Medical Research Council Adult and Paediatric Working Parties. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. *Br J Haematol* 2002; **118**: 385–400.
- Biggs JC, Horowitz MM, Gale RP, Ash RC, Atkinson K, Helbig W *et al.* Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. *Blood* 1992; **80**: 1090–1093.
- Forman SJ, Schmidt GM, Nademanee AP, Amylon MD, Chao NJ, Fahey JL *et al.* Allogeneic bone marrow transplantation as therapy for primary induction failure for patients with acute leukemia. *J Clin Oncol* 1991; **9**: 1570–1574.

- 5 Hansen JA, Petersdorf E, Martin PJ, Anasetti C. Hematopoietic stem cell transplants from unrelated donors. *Immunol Rev* 1997; **157**: 141–151.
- 6 Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A *et al.* Transplants of umbilical cord blood or bone marrow from unrelated donors in adult with leukemia. *N Engl J Med* 2004; **351**: 2276–2285.
- 7 Sanz MA, Sanz GF. Unrelated donor umbelical cord blood transplantation in adults. *Leukemia* 2002; **16**: 1984–1991.
- 8 Brunstein CG, Setubal DC, Wagner JE. Expanding the role of umbilical cord blood transplantation. *Br J Haematol* 2007; **137**: 20–35.
- 9 Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A *et al.* Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* 2002; **295**: 2097–2100.
- 10 Aversa F, Berneman ZN, Locatelli F, Martelli MF, Reisner Y, Tabilio A *et al.* Fourth International Workshop on Haploidentical Transplants, Naples, Italy, 8–10 July, 2004. *Blood Cells Mol Dis* 2004; **33**: 159–175.
- 11 Reisner Y, Kapoor N, Kirkpatrick D, Pollack MS, Cunningham-Rundles S, Dupont B *et al.* Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood* 1983; **61**: 341–348.
- 12 Anasetti C, Beatty PG, Storb R, Martin PJ, Mori M, Sanders JE *et al.* Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. *Hum Immunol* 1990; **29**: 79–91.
- 13 Kernan NA, Flomemberg N, Dupont B, O'Reilly RJ. Graft rejection in recipients of T cell depleted HLA-nonidentical marrow transplants for leukemia: identification of host derived anti-donor alloctyotoxic T lymphocytes. *Transplantation* 1987; **43**: 482–487.
- 14 Henslee-Downey PJ, Abhyankar SH, Parrish RS, Pati AR, Godder KT, Neglia WJ *et al.* Use of partially mismatched related donors extends access to allogeneic marrow transplant. *Blood* 1997; **89**: 3864–3872.
- 15 Schwartz E, Lapidot T, Gozes D, Singer TS, Reisner Y. Abrogation of bone marrow allograft resistance in mice by increased total body irradiation correlates with eradication of host clonable T cells and alloreactive cytotoxic precursors. *J Immunol* 1987; **138**: 460–465.
- 16 Lapidot T, Singer TS, Salomon O, Terenzi A, Schwartz E, Reisner Y. Booster irradiation to the spleen following total body irradiation: a new immunosuppressive approach for allogeneic bone marrow transplantation. *J Immunol* 1988; **141**: 2619–2624.
- 17 Cobbold SP, Martin G, Quin S, Waldman H. Monoclonal antibodies to promote marrow engraftment and tissue graft tolerance. *Nature* 1986; **323**: 164–166.
- 18 Lapidot T, Terenzi A, Singer TS, Salomon O, Reisner Y. Enhancement by dimethyl myleran of donor type chimerism in murine recipients of bone marrow allografts. *Blood* 1989; **73**: 2025–2032.
- 19 Terenzi A, Lubin I, Lapidot T, Salomon O, Faktorowich Y, Rabi I *et al.* Enhancement of T cell-depleted bone marrow allografts in mice by thiotepa. *Transplantation* 1990; **50**: 717–720.
- 20 Aversa F, Tabilio A, Terenzi A, Velardi A, Falzetti F, Giannoni C *et al.* Successful engraftment of T cell-depleted haploidentical 'three-loci' incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum. *Blood* 1994; **84**: 3948–3955.
- 21 Bachar-Lustig E, Rachamim N, Li HW, Lan F, Reisner Y. Megadose of T cell-depleted bone marrow overcomes MHC barriers in sublethally irradiated mice. *Nat Med* 1995; **1**: 1268–1273.
- 22 Rachamim N, Gan J, Segall H, Krauthgamer R, Marcus H, Berrebi A *et al.* Tolerance induction by 'megadose' hematopoietic transplants: donor-type human CD34 stem cells induce potent specific reduction of host anti-donor cytotoxic T lymphocyte precursors in mixed lymphocyte culture. *Transplantation* 1998; **65**: 1386–1393.
- 23 Gur H, Krauthgamer R, Berrebi A, Klein T, Nagler A, Tabilio A *et al.* Tolerance induction by megadose hematopoietic progenitor cells: expansion of veto cells by short-term culture of purified human CD34(+) cells. *Blood* 2002; **99**: 4174–4181.
- 24 Gur H, Krauthgamer R, Bachar-Lustig E, Katchman H, Arbel-Goren R, Berrebi A *et al.* Immune regulatory activity of CD34+ progenitor cells: evidence for a deletion-based mechanism mediated by TNF-alpha. *Blood* 2005; **105**: 2585–2593.
- 25 Terenzi A, Aristei C, Aversa F, Perruccio K, Chionne F, Raymondi C *et al.* Efficacy of fludarabine as an immunosuppressor for bone marrow transplantation conditioning: preliminary results. *Transplant Proc* 1996; **28**: 3101.
- 26 Aversa F, Tabilio A, Velardi A, Cunningham I, Terenzi A, Falzetti F *et al.* Treatment of high risk acute leukemia with T cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med* 1998; **339**: 1186–1193.
- 27 Muller S, Schulz A, Reiss U, Schwarz K, Schreiner T, Wiesneth M *et al.* Definition of a critical T cell threshold for prevention of GVHD after HLA non-identical PBPC transplantation in children. *Bone Marrow Transplant* 1999; **24**: 575–581.
- 28 Russell JA, Turner AR, Larratt L, Chaudhry A, Morris D, Brown C *et al.* Adult recipients of matched related donor blood cell transplants given myeloablative regimens including pretransplant antithymocyte globulin have lower mortality related to graft-versus-host disease: a matched pair analysis. *Biol Blood Marrow Transplant* 2007; **13**: 299–306.
- 29 Waller EK, Langston AA, Lonial S, Cherry J, Somani J, Allen AJ *et al.* Pharmacokinetics and pharmacodynamics of antithymocyte globulin in recipients of partially HLA-matched blood hematopoietic progenitor cell transplantation. *Biol Blood Marrow Transplant* 2003; **9**: 460–471.
- 30 Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S *et al.* Full-haplotype mismatched hematopoietic stem cell transplantation: a phase II study in patients with acute leukemia at high risk or relapse. *J Clin Oncol* 2005; **23**: 3447–3454.
- 31 Meijer E, Slaper-Cortenbach IC, Thijsen SF, Dekker AW, Verdonck LF. Increased incidence of EBV-associated lymphoproliferative disorders after allogeneic stem cell transplantation from matched unrelated donors due to a change of T cell depletion technique. *Bone Marrow Transplant* 2002; **29**: 335–339.
- 32 Liu D, Tammik C, Zou JZ, Ernberg I, Masucci MG, Ringden O *et al.* Effect of combined T- and B-cell depletion of allogeneic HLA-mismatched bone marrow graft on the magnitude and kinetics of Epstein-Barr virus load in the peripheral blood of bone marrow transplant recipients. *Clin Transplant* 2004; **18**: 518–524.
- 33 Bonini C, Ciceri F, Lupo-Stanghellini MT, Bondanza A, Magnani Z, Penna SK *et al.* Rapid and effective immune reconstitution with HSV-TK engineered donor lymphocyte add-backs after haplo-HSCT. *Bone Marrow Transplant* 2006; **37** (Suppl 1): S23 (abstract O168).

- 34 Handgretinger R, Klingebiel T, Lang P, Schumm M, Neu S, Geiselhart A *et al.* Megadose transplantation of purified peripheral blood CD34(+) progenitor cells from HLA-mismatched parental donors in children. *Bone Marrow Transplant* 2001; **27**: 777–783.
- 35 Barfield RC, Otto M, Houston J, Holladay M, Geiger T, Martin J *et al.* A one-step large-scale method for T and B-cell depletion of mobilized PBSC for allogeneic transplantation. *Cytotherapy* 2004; **6**: 1–6.
- 36 Chen X, Hale GA, Barfield R, Benaim E, Leung WH, Knowles J *et al.* Rapid immune reconstitution after a reduced-intensity conditioning regimen and a CD3-depleted haploidentical stem cell graft for paediatric refractory haematological malignancies. *Br J Haematol* 2006; **135**: 524–532.
- 37 Bethge WA, Faul C, Bornhauser M, Stuhler G, Lang P, Stelljes M *et al.* Haplo-identical allogeneic haematopoietic cell transplantation in adults after reduced-intensity conditioning with CD3/CD19-depleted graft. *Bone Marrow Transplant* 2007; **39** (Suppl 1): S178 (abstract P745).
- 38 Guinan EC, Boussiotis VA, Neuberg D, Neuberg D, LaVita Brennan L, Hirano N *et al.* Transplantation of anergic histoincompatible bone marrow allografts. *N Engl J Med* 1999; **340**: 1704–1714.
- 39 Guinan EC. Costimulatory blockade *ex vivo*: results of 2 pilot clinical trials. *Blood Cell Mol Dis* 2004; **33**: 204–205.
- 40 Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W *et al.* Haploidentical hematopoietic stem cell transplantation without *in vitro* T cell depletion for the treatment of hematological malignancies. *Bone Marrow Transplant* 2006; **38**: 291–297.
- 41 Lu DP, Dong L, Wu T, Huang XJ, Zhang MJ, Han W *et al.* Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. *Blood* 2006; **107**: 3065–3073.
- 42 Rizzieri DA, Koh LP, Long GD, Gasparetto C, Sullivan KM, Horwitz M *et al.* Partially matched, nonmyeloablative allogeneic transplantation: clinical outcomes and immune reconstitution. *J Clin Oncol* 2007; **25**: 690–697.
- 43 O'Donnell PV, Luznik L, Jones RJ, Vogelsang GB, Leffell MS, Phelps M *et al.* Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant* 2002; **8**: 377–386.
- 44 Molitor ML, Burlingham WJ. Immunobiology of exposure to non-inherited maternal antigens. *Front Biosci* 2007; **12**: 3302–3311.
- 45 van den Boogaardt DE, van Rood JJ, Roelen DL, Claas FH. The influence of inherited and noninherited parental antigens on outcome after transplantation. *Transpl Int* 2006; **19**: 360–371.
- 46 Ichinohe T, Teshima T, Matsuoka K, Maruya E, Saji H. Fetal-maternal microchimerism: impact on hematopoietic stem cell transplantation. *Curr Opin Immunol* 2005; **17**: 546–552.
- 47 van Rood JJ, Loberiza Jr FR, Zhang MJ, Oudshoorn M, Claas F, Cairo MS *et al.* Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA-haploidentical sibling. *Blood* 2002; **99**: 1572–1577.
- 48 Narimatsu H, Morishita Y, Saito S, Shimada K, Ozeki K, Kohno A *et al.* Conditioning regimen of melphalan, fludarabine and total body irradiation in unmanipulated HLA haploidentical stem cell transplantation based on fetomaternal tolerance. *Intern Med* 2004; **43**: 1063–1067.
- 49 Obama K, Utsunomiya A, Takatsuka Y, Takemoto Y. Reduced-intensity non-T cell depleted HLA-haploidentical stem cell transplantation for older patients based on the concept of fetomaternal tolerance. *Bone Marrow Transplant* 2004; **34**: 897–899.
- 50 Marmont AM, Horowitz MM, Gale RP, Sobocinski K, Ash RC, van Bekkum DW *et al.* T cell depletion of HLA-identical transplants in leukemia. *Blood* 1991; **78**: 2120–2130.
- 51 Holler E. Risk assessment in haematopoietic stem cell transplantation: GvHD prevention and treatment. *Best Pract Res Clin Haematol* 2007; **20**: 281–294.
- 52 Ruggeri L, Mancusi A, Capanni M, Urbani E, Carotti A, Aloisi T *et al.* Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value. *Blood* 2007; **110**: 433–440.
- 53 Ruggeri L, Capanni M, Casucci M, Volpi I, Tosti A, Perruccio K *et al.* Role of natural killer cell alloreactivity in HLA-mismatched hematopoietic stem cell transplantation. *Blood* 1999; **94**: 333–339.
- 54 Ruggeri L, Mancusi A, Burchielli E, Aversa F, Martelli MF, Velardi A. Natural killer cell alloreactivity in allogeneic hematopoietic transplantation. *Curr Opin Oncol* 2007; **19**: 142–147.
- 55 Imai C, Iwamoto S, Campana D. Genetic modification of primary natural killer cells overcomes inhibitory signals and induces specific killing of leukemic cells. *Blood* 2005; **106**: 376–383.
- 56 Leung W, Iyengar R, Turner V, Lang P, Bader P, Conn P *et al.* Determinants of antileukemia effects of allogeneic NK cells. *J Immunol* 2004; **172**: 644–650.
- 57 Boismenu R, Havran WL. An innate view of gamma delta T cells. *Curr Opin Immunol* 1997; **9**: 57–63.
- 58 Wilhelm M, Kunzmann V, Eckstein S, Reimer P, Weissinger F, Ruediger T *et al.* Gammadelta T cells for immune therapy of patients with lymphoid malignancies. *Blood* 2003; **102**: 200–206.
- 59 Godder KT, Henslee-Downey PJ, Mehta J, Park BS, Chiang KY, Abhyankar S *et al.* Long term disease-free survival in acute leukemia patients recovering with increased gammadelta T cells after partially mismatched related donor bone marrow transplantation. *Bone Marrow Transplant* 2007; **39**: 751–757.
- 60 Ochs L, Shu XO, Miller J, Enright H, Wagner J, Filipovich A *et al.* Late infections after allogeneic bone marrow transplantation: comparison of incidence in related and unrelated donor transplant recipients. *Blood* 1995; **86**: 3979–3986.
- 61 Dumont-Girard F, Roux E, van Lier RA, Hale G, Helg C, Chapuis B *et al.* Reconstitution of the T cell compartment after bone marrow transplantation: restoration of the repertoire by thymic emigrants. *Blood* 1998; **92**: 4464–4471.
- 62 Heitger A, Greinix H, Mannhalter C, Mayerl D, Kern H, Eder J *et al.* Requirement of residual thymus to restore normal T cell subsets after human allogeneic bone marrow transplantation. *Transplantation* 2000; **69**: 2366–2373.
- 63 Fujimaki K, Maruta A, Yoshida M, Kodama F, Matsuzaki M, Fujisawa S *et al.* Immune reconstitution assessed during five years after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001; **27**: 1275–1281.
- 64 Volpi I, Perruccio K, Tosti A, Capanni M, Ruggeri L, Posati S *et al.* Post-grafting granulocyte colony-stimulating factor administration impairs functional immune recovery in recipients of HLA haplotype-mismatched hematopoietic transplants. *Blood* 2001; **97**: 2514–2521.
- 65 Perruccio K, Tosti A, Burchielli E, Topini F, Ruggeri L, Carotti A *et al.* Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. *Blood* 2005; **106**: 4397–4406.
- 66 Lucas KG, Small TN, Heller G, Dupont B, O'Reilly RJ. The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation. *Blood* 1996; **87**: 2594–2603.

- 67 Comoli P, Basso S, Zecca M, Pagliara D, Baldanti F, Bernardo ME *et al.* Preemptive therapy of EBV-related lymphoproliferative disease after pediatric haploidentical stem cell transplantation. *Am J Transplant* 2007; **7**: 1648–1655.
- 68 Marktel S, Magnani Z, Ciceri F, Cazzaniga S, Riddell SR, Traversari C *et al.* Immunologic potential of donor lymphocytes expressing a suicide gene for early immune reconstitution after hematopoietic T cell-depleted stem cell transplantation. *Blood* 2003; **101**: 1290–1298.
- 69 Ciceri F, Bonini C, Gallo-Stampino C, Bordignon C. Modulation of GvHD by suicide-gene transduced donor T lymphocytes: clinical applications in mismatched transplantation. *Cytotherapy* 2005; **7**: 144–149.
- 70 Traversari C, Marktel S, Magnani Z, Mangia P, Russo V, Ciceri F *et al.* The potential immunogenicity of the TK suicide gene does not prevent full clinical benefit associated with the use of TK-transduced donor lymphocytes in HSCT for hematologic malignancies. *Blood* 2007; **109**: 4708–4715.
- 71 Dey BR, Spitzer TR. Current status of haploidentical stem cell transplantation. *Br J Haematol* 2006; **135**: 423–437.
- 72 Velardi A, Ruggeri L, Moretta A, Moretta L. NK cells: a lesson from mismatched hematopoietic transplantation. *Trends Immunol* 2002; **23**: 438–444.
- 73 Zorn E. CD4+CD25+ regulatory T cells in human hematopoietic cell transplantation. *Semin Cancer Biol* 2006; **16**: 150–159.
- 74 Le Blanc K, Ringden O. Mesenchymal stem cells: properties and role in clinical bone marrow transplantation. *Curr Opin Immunol* 2006; **18**: 586–591.
- 75 Schattenberg AV, Dolstra H. Cellular adoptive immunotherapy after allogeneic stem cell transplantation. *Curr Opin Oncol* 2005; **17**: 617–621.
- 76 Peggs KS, Verfuether S, Pizzey A, Khan N, Guiver M, Moss PA *et al.* Adoptive cellular therapy for early cytomegalovirus infection after allogeneic stem-cell transplantation with virus-specific T cell lines. *Lancet* 2003; **362**: 1375–1377.
- 77 Einsele H, Hebart H. CMV-specific immunotherapy. *Hum Immunol* 2004; **65**: 558–564.
- 78 Feuchtinger T, Matthes-Martin S, Richard C, Lion T, Fuhrer M, Hamprecht K *et al.* Safe adoptive transfer of virus-specific T cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *Br J Haematol* 2006; **134**: 64–76.
- 79 Thorne SH, Negrin RS, Contag CH. Synergistic antitumor effects of immune cell-viral biotherapy. *Science* 2006; **311**: 1780–1784.
- 80 Ottinger HD, Ferencik S, Beelen DW, Lindemann M, Peceny R, Elmaagacli AH *et al.* Hematopoietic stem cell transplantation: contrasting the outcome of transplantations from HLA-identical siblings, partially HLA-mismatched related donors, and HLA-matched unrelated donors. *Blood* 2003; **102**: 1131–1137.
- 81 Yakoub-Agha I, Mesnil F, Kuentz M, Boiron JM, Ifrah N, Milpied N *et al.* Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. *J Clin Oncol* 2006; **24**: 5695–5702.
- 82 Cesaro S. Role and cost efficacy of unrelated cord blood in adult hematopoietic syem transplantation. *Bone Marrow Transplant* 2005; **36**: 275.