for possible late side-effects in splenectomized ITP patients must be conducted. Further research, including clinical trials that incorporate clinically relevant end points (the severity of bleeding), quality of life assessment and economic considerations, is needed to improve management.

The results obtained emphasize the multiple therapeutic uses of rituximab as well as the urgent need for research to extend and optimize the use of this drug in the yet little explored world of autoimmune diseases.

Martino Introna, Josée Golay,* Tiziano Barbui°*
**Molecular Immunohaematology Laboratory, Istituto di Ricerche Farmacologiche "Mario Negri", Milan; °Division of Hematology, Ospedali Riuniti di Bergamo, Italy*

References

1. Harrington WJ, Minnich V, Ollingsworth JW, Moore CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. J Lab Clin Med 1951;38:1-10.
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002;346:995-1007.
3. Berchtold P, Muller D, Beardsley D, Fujisawa K, Kaplan C, Kekomaki R, et al. International study to compare antigen-specific methods used for the measurement of antiplatelet autoantibodies. Br J Haematol 1997;96:477-83.
4. Zaja F, Vianelli N, Sperotto A, De Vita S, Iacona I, Zaccaria A, et al. The B-cell compartment as the selective target for the treatment of immune thrombocytopenias. Haematologica 2003;88:538-46.
5. Maloney DG, Smith B, Rose A. Rituximab: mechanism of action and resistance. Semin Oncol 2002;29 Suppl 2:2-9.
6. Golay J, Lazzari M, Facchinetti V, Bernasconi S, Borleri G, Barbui T, et al. CD20 levels determine the in vitro susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: further regulation by CD55 and CD59. Blood 2001;98:3383-9.
7. Golay J, Zaffaroni L, Vaccari T, Lazzari M, Borleri GM, Bernasconi S, et al. Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood 2000; 95:3900-8.
8. Golay J, Gramigna R, Facchinetti V, Capello D, Gaidano G, Introna M. Acquired immunodeficiency syndrome-associated lymphomas are efficiently lysed through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity by rituximab. Br J Haematol 2002;119:923-9.
9. Introna M, Cittera E, Nota R, et al. Complement activation determines the therapeutic activity of rituximab in vivo. Blood 2002;100 Suppl 1:161a[abstract].
10. Hedge UP, Wilson WH, White T, Cheson BD. Rituximab treatment of refractory fludarabine associated immune thrombocytopenia in chronic lymphocytic leukemia. Blood 2002; 100:2260-2.
11. Van der Kolk LE, Grillo-Lopez AJ, Baars JW, Hack CE, van Oers MH. Complement activation plays a key role in the side-effects of rituximab treatment. Br J Haematol 2001;115: 807-11.
12. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune disease. N Engl J Med 1999; 340:227-8.

Non-myeloablative conditioning before allogeneic stem cell transplantation in adult acute lymphoblastic leukemia

In adult acute lymphoblastic leukemia (ALL) complete remission (CR) rates of 80-85% and leukemia-free survival (LFS) rates of 30-40% were achieved in recent studies.[1] It seems, however, that the options for further improvement are limited. This is particularly true for the high proportion of elderly ALL patients who are not covered in most trials. Nowadays many study groups refer ALL patients with high risk or very high risk (Ph/BCR-ABL positive) to allogeneic stem cell transplantation (SCT) from sibling donors in first CR with LFS rates of 30-40% in prospective studies and high risk patients.[2] This procedure is associated with nearly equally high rates of transplant-related mortality (TRM) and relapse (RR) of around 30%. The outcome of matched unrelated (MUD) SCT is approaching these results, with a somewhat higher TRM but lower RR. Results of allogeneic SCT are probably improving further by better donor selection, supportive care, etc. The complications, such as graft-versus-host disease (GvHD), organ toxicities and infections, are nevertheless considerable and the risk increases with age, comorbidities such as fungal infections, decreasing performance status or use of mismatched (MM) transplants. Alternative SCT regimens — excluding intensified conditioning — are urgently required for these patients with a high risk of TRM.

Non-myeloablative SCT or reduced intensity conditioning regimens (NMSCT) are new approaches which deserve evaluation in ALL and may lead to an extension of indications for allogeneic SCT. In contrast to conventional SCT, which mainly relies on killing cells by high-dose chemotherapy and total body irradiation (TBI), NMSCT aims to exploit graft-versus-leukemia (GvL) effects. Immunosuppression, for example, with purine analogs, other cytostatic drugs and/or low dose TBI, is followed by the infusion of donor stem cells from siblings or MUD with adapted immunosuppression to establish host tolerance.[3]

Consequently this approach can only be effective in diseases with a relevant GvL effect. NMSCT yielded quite impressive results in indolent leukemias such as chronic myeloid leukemia but also in acute myeloid leukemia.[4] There is, however, the general opinion that GvL effects are less pronounced in ALL than in other malignancies. Nevertheless these effects are present as indicated by the lower RR in patients with acute and/or chronic GvHD,[5-7] the lower RR after MUD SCT, and the induction of remissions by withdrawal of GvHD prophylaxis or donor lymphocyte infusions (DLI) in single patients with relapsed ALL.

Until recently, published results of NMSCT in ALL were limited to 1-9 patients, who were included in larger cohorts of patients with different hematologic malignancies.[3,8-13] Only four groups have reported on 10 or more patients.[14-17]

The largest, fully published cohort so far is included in the study by Martino *et al.*[18] in this issue of Haematologica which summarizes the features of patients from four prospective studies. As in the beginnings of conventional SCT, NMSCT studies mainly include patients with advanced disease. Thus Martino *et al.*[18] report only 4 patients treated in first CR. Again, as in other NMSCT studies, the cohort of patients represents an unfavorable selection since it included those with a very high risk of relapse (41% Ph/BCR-ABL$^+$) and all patients were considered ineligible for conventional transplantation because of age or comorbidities. This is also indicated by the high median age of 50 years which is comparable to that of other NMSCT studies with a median age of 46-56 years[3,8-17] and 1-2 decades higher than in conventional SCT studies. Furthermore, the study covers patients with relapse after autologous SCT (30%). Other NMSCT studies in ALL even included a considerable proportion of patients with relapse after conventional allogeneic SCT.[8,12,16]

The majority of NMSCT studies in ALL relied on sibling donors[3,9-10,12-15,17] and only few studies included a significant proportion of unrelated donors.[8,11,16] Martino *et al.*[18] report that 30% of the donors were MUD and 15% MM related. All these unfavorable features increase the likelihood of high TRM in this study.

Despite this expectation the results are quite favorable. As in most other NMSCT studies no graft failure was observed. The overall survival (OS) is 31%, with a RR of 49% and a TRM of 23%. The OS is better than that in other larger cohorts of NMSCT in ALL patients with OS rates of 15%,[14] 21%[15] and 18%.[16] In other studies considerably higher TRM rates were observed: in an EBMT report the TRM was 72% in ALL compared to 47% in AML.[14] The relatively low TRM rate is also suprising since MUD and MM donors accounted for 45% of the donors and the rate of GvHD was considerable with 38% extensive chronic GvHD. Since the therapeutic activity of NMSCT is mainly based on GvL effects, as anticipated, the lack of GvHD was associated with a higher progression rate. This is of interest since a significant correlation has not been shown in other studies with NMSCT in ALL. It remains open however, whether patients with GvHD also achieved a higher OS. Furthermore — as in most SCT studies — the quality of life of the patients is not considered.

NMSCT, as an immunotherapeutic approach, is probably most appropriate in patients with low level disease.[14] Nevertheless it was mainly investigated in patients with overt relapse and large tumor mass. In the study by Martino *et al.*[18] 44% of the patients were even refractory to chemotherapy i.e. had more than 30% blasts in bone marrow at the time of the NMSCT. As in other studies[11,16] there was a surprisingly high CR rate, although often followed by relapse at short notice. Martino *et al.*[18] report a RR of 33% in patients transplanted in CR compared to 60% in those with overt disease. Other authors also achieved poor results in patients with measurable disease[8,11] at the time of NMSCT. In a similarly large cohort only patients with CR at the time of NMSCT survived.[16] This is not surprising since the effects of NMSCT occur more slowly than those of chemotherapy and probably too slowly to inhibit rapidly progressive, resistant ALL.

Martino *et al.*[18] did not include patients with relapse after conventional allogeneic SCT. This may have contributed to the better outcome of their cohort, since results of NMSCT appear to be particularly poor in these patients.[12,16]

It is of particular interest that Martino *et al.*[18] performed minimal residual disease (MRD) monitoring after NMSCT and demonstrated a correlation between positive MRD status and relapse. Single cases of molecular remissions after NSMCT in ALL have also been reported by others.[10] It has already been demonstrated that MRD before and after conventional SCT is correlated with prognosis.[7] MRD evaluation is an ideal method to follow the course of disease and probably also to decide on additional therapeutic interventions such as reduction or termination of GvHD prophylaxis or administration of DLI. Even patients with overt relapse after NMSCT reached CR after administration of DLI.[16]

Overall it can be stated that the initial expectation that NMSCT and GvL effects have no role in ALL has been disproven. Although patients with extremely unfavorable characteristics have been treated so far, there has been a low rate of graft failure, remissions have been achieved in overt relapse and long-term survival has been reported in some cases. However, published results indicate that NMSCT probably has no role in advanced, active ALL with large tumor mass and probably not in relapse after allogeneic SCT. The latter may, however, depend on donor selection.

The optimal preparative regimens and procedures for GvHD prophylaxis remain open.[4,19] The study by Martino *et al.* also included several different approaches and a comparative analysis within this small cohort is probably not possible. Therefore well-defined prospective trials are urgently required. In the future the effectiveness of NMSCT may be measured by MRD evaluation and increased by additional treatment interventions such as STI571 in Ph/BCR-ABL positive ALL or antibody therapy.

Prognostic factors are apparently quite similar for conventional SCT and NMSCT.[15] Several studies demonstrated that older age and poor performance

status are also unfavorable for NMSCT.[8,15,20] It remains open whether better results would be achievable in younger patients with earlier stage of disease. We, therefore, support the final statement by Martino *et al.* that, at present, NMSCT should only be offered in patients with a high risk of TRM and within the context of clinical trials. It is still no alternative to conventional SCT in younger patients with ALL.

Nicola Gökbuget , Dieter Hoelzer
Department for Hematology and Oncology
University Hospital, Theodor Stern Kai 7
60590 Frankfurt, Germany

References

1. Hoelzer D, Gökbuget N. New approaches in acute lymphoblastic leukemia in adults: where do we go? Semin Oncol 2000;27:540-59.
2. Arnold R, Bunjes D, Ehninger G. Allogeneic stem cell transplantation from HLA-identical sibling donor in high risk ALL patients is less effective than transplantation from unrelated donors. Blood 2002;100:77a[abstract 279].
3. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91:756-63.
4. Laport GG. Nonmyeloablative allogeneic stem cell transplantation for acute leukemia. Curr Hematol Rep 2003;2:49-56.
5. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood 1990;75:555-62.
6. Passweg JR, Tiberghien P, Cahn JY, Vowels MR, Camitta BM, Gale RP, et al. Graft-versus-leukemia effects in T lineage and B lineage acute lymphoblastic leukemia. Bone Marrow Transplant 1998;21:153-8.
7. Uzunel M, Mattsson J, Jaksch M, Remberger M, Ringden O. The significance of graft-versus-host disease and pretransplantation minimal residual disease status to outcome after allogeneic stem cell transplantation in patients with acute lymphoblastic leukemia. Blood 2001;98:1982-4.
8. Giralt S, Thall PF, Khouri I, Wang X, Braunschweig I, Ippoliti C, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood 2001;97:631-7.
9. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 2001;97:3390-400.
10. Corradini P, Tarella C, Olivieri A, Gianni AM, Voena C, Zallio F, et al. Reduced-intensity conditioning followed by allografting of hematopoietic cells can produce clinical and molecular remissions in patients with poor-risk hematologic malignancies. Blood 2002;99:75-82.
11. Bornhauser M, Thiede C, Platzbecker U, Jenke A, Helwig A, Plettig R, et al. Dose-reduced conditioning and allogeneic hematopoietic stem cell transplantation from unrelated donors in 42 patients. Clin Cancer Res 2001;7:2254-62.
12. Pawson R, Potter MN, Theocharous P, Lawler M, Garg M, Yin JA, et al. Treatment of relapse after allogeneic bone marrow transplantation with reduced intensity conditioning (FLAG +/- Ida) and second allogeneic stem cell transplant. Br J Haematol 2001;115:622-9.
13. Martino R, Caballero MD, Canals C, Simon JA, Solano C, Urbano-Ispizua A, et al. Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicentre study. ALLOPBSCT Subcommittee of the Spanish Group for Haematopoietic Transplantation (GETH). Group GEL-TAMO. Br J Haematol 2001; 115:653-9.
14. Rezvani K, Lalancette M, Szydlo R. Non-myeloablative stem cell transplant (NMSCT) in AML, ALL, and MDS: disappointing outcome for patients with advanced phase disease. Blood 2000;96:479a[abstract].
15. Michallet M, Bilger K, Garban F, Attal M, Huyn A, Blaise D, et al. Allogeneic hematopoietic stem-cell transplantation after nonmyeloablative preparative regimens: impact of pretransplantation and posttransplantation factors on outcome. J Clin Oncol 2001;19:3340-9.
16. Arnold R, Massenkeil G, Bornhauser M, Ehninger G, Beelen DW, Fauser AA, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. Leukemia 2002;16:2423-8.
17. Ruiz-Arguelles GJ, Gomez-Almaguer D, Ruiz-Arguelles A, Gonzalez-Llano O, Cantu OG, Jaime-Perez JC. Results of an outpatient-based stem cell allotransplant program using nonmyeloablative conditioning regimens. Am J Hematol 2001;66:241-4.
18. Martino R, Giralt S, Dolores Caballero M, Mackinnon S, Corradini P, Fernández-Avilés F, et al. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. Haematologica 2003;88:561-6.
19. Vindelov L. Allogeneic bone marrow transplantation with reduced conditioning (RC- BMT). Eur J Haematol 2001;66: 73-82.
20. Childs R, Baceci E, Eniaffe R. Older patient age remains a risk factor for transplant related mortality following nonmyeloablative allogeneic stem cell transplantation. Blood 2000; 96:520a[abstract].

Economy-class syndrome: media hype or real risk?

Venous thromboembolism (VTE) is a multifactorial disease resulting from the interaction between genetic and environmental risk factors. The former include abnormalities causing inherited thrombophilia, such as deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, protein S, and the gain-of-function mutations in genes encoding coagulation factor V (factor V Leiden) and prothrombin. The environmental, transient risk factors associated with an increased risk of VTE are cancer, recent surgery, pregnancy and puerperium, use of oral contraceptives and prolonged immobilization. For many decades, flights have been considered a risk factor for VTE. Recently, the interest in this topic increased both in the lay and medical press because of the death from pulmonary embolism of a 27-year old woman at the arrival hall in Heathrow airport (London) after a 20-hour flight from Australia.[1]

In 1946, Homans first referred to flights as a possible risk factor for VTE reporting an episode of venous thrombosis in a doctor after a 14-hour flight.[2] The most important pathogenic mechanism for VTE during air travel is stasis in the lower limbs. During the London Blitz in the Second World War it was observed that the incidence of fatal pulmonary