PERIODICUM BIOLOGORUM
VOL. 114, No 4, 519–525, 2012

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

overview

Stem cell transplantation in University Hospital Center, Zagreb, Croatia

BORIS LABAR

University Hospital Center Zagreb,
Schoolof Medicine University of Zagreb
Hegedušić street 6,
10000 Zagreb, Croatia
E-mail: boris.labar@inet.hr

Received November 27, 2011.

INTRODUCTION

Stem cell transplantation (SCT) is nowadays a routine therapy for many malignant and non-malignant hematological disorders *(1–5)*. Two main antitumor mechanisms have been recognized in SCT. First is based on aggressive myeloablative chemotherapy with or without total body irradiation *(6–7)* while the second one is based on immune antitumor mechanism mediated by donor immunocompentent T-cells (the graft-versus tumor reaction (GvT) and/or graft-versus leukemia reaction (GvL) *(8–10)*. However, still the main problem of SCT is high treatment-related toxicity (TRT) and/or treatment-related mortality (TRM) accompanied by the mortality rate related to transplant between 25–40% *(11, 12)*. Recently more efficient supportive care, better control of infections and main complication graft-versus-host disease (GvHD) significantly reduced the mortality rate due to transplant *(13)*. In this respect reduced intensity conditioning (RIC) substantially decreased early toxicity and mortality complications of standard myeloablative conditioning *(14–16)*. Therefore RIC as immunosuppressive conditioning allow the engraftment of donor cells which than can mediate GvL. Consequently in many centers much older patients are undergoing transplantation. Instead of basic malignant disease, the indication for SCT mainly depends on patient's performance and co-morbidity score (so-called biological age) *(17–18)*. SCT from matched unrelated donor (MUD) become eligible for many patients *(19–20)*. With new high resolution technique for HLA-typing, combined with constantly increasing number of the volunteer donors in the world--wide Registries a chance to find e compatible donor is generally more realistic. Thus results of transplantation with an unrelated donor compatible in 10 out of 10 antigens practically correspond to those with related identical donor *(21)*. Furthemore stem cells from cord blood *(22)* and new data from allografting with haploidentical donor cells are also very encouraging *(23)*. All these new developments suggests that in the future there will be no problem to find appropriate donor for high risk patients.

THE HISTORY OF SCT IN UNIVERSITY HOSPITAL CENTER, ZAGREB

Main SCT events

At University Hospital Center Zagreb first allogeneic SCT had been performed on February, 8th, 1983. Five years later, in 1988 autologous

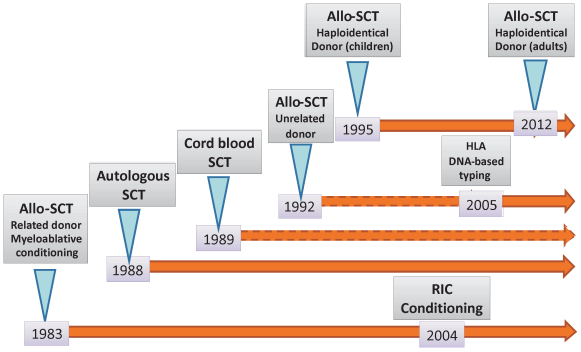

Figure 1. *Main transplantation events at University Hospital Center, Zagreb.*

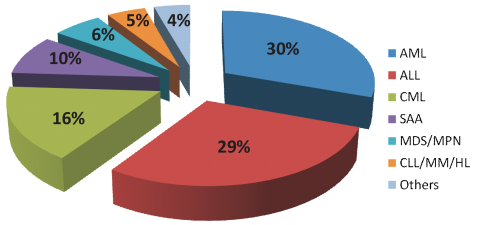

Figure 2. *Indication for SCT. Acute leukemia, myeloproliferative neoplasms and severe aplastic anemia (SAA) are the most frequent indications for SCT.*

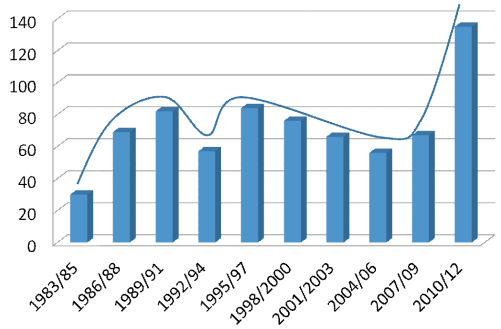

Figure 3. *Incidence of SCT per three year period. The number of transplants have been singificantly increased in the recent years.*

SCT program have been started, mostly in myeloma, lymphoma and acute myeloid leukemia but until 2005 transplantaiton program has been performed only sporadically. From 2005 onward we have been using transplant with stem cells obtained from cord blood of unrelated donor. For the first time in 2006 an adult patients received two unrelated cord blood. In 2012 transplant with stem cells from haploidentical donor was given in adult patient with aggressive lymphoma.

During the 30 years period 659 patients underwent allogeneic transplantation in our institution. Figure 1. summarizes the main transplant events wheras indications for transplants are given in Figure 2.

The number of transplants performed per three year period is given in Figure 3.

From 2011 we have been treated more than 50 patients per year which is twice more than before 2009.

This is mostly because from 2010 we are routinely performed SCT from unrelated donor and transplant with reduced intensity conditioning in older patients.

Early phase of SCT in Zagreb

During the 1970-ies SCT had been recognized as new and effective therapy mainly for leukemia. At the beginning SCT had been performed at the end stage of hematological malignancies *(24)*. First results clearly proved that SCT treatment was feasible and effective *(25–26)* but still at that time being only experimental treatment. The main complication GvHD and the beneficial antiimmune tumor effect were recognized clinically, but still without scientific explanation. Nevertheles SCT in many countries had become an increasing treatment options for many hematological disorders.

At that time, in Croatia, a group of immunologists at Institute Rugjer Boskovic studied experimental bone marrow transplantation in mice and they were the first in the world who demonstrated that transplanted lymphoid cells can mediate both anti-leukemia effect *(27)* and the antileukemia effect of graft-versus-host reaction *(28)*. They organized in 1979. a workshop on the necessities and possibilities for clinical SCT in Croatia *(29–30)* and proposed that clinical SCT project should be organized

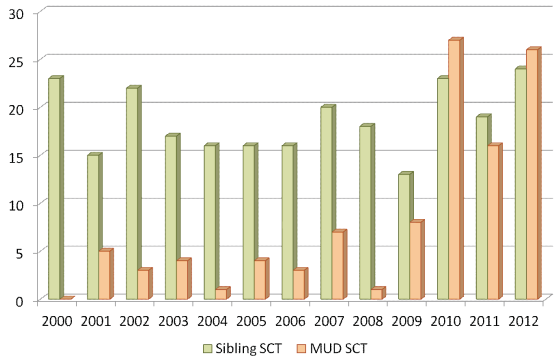

Figure 4. *Incidence of SCT according to the donor. The number of SCT from compatibile unrelated donor in the last 3 years reach the number of SCT from sibling donor.*

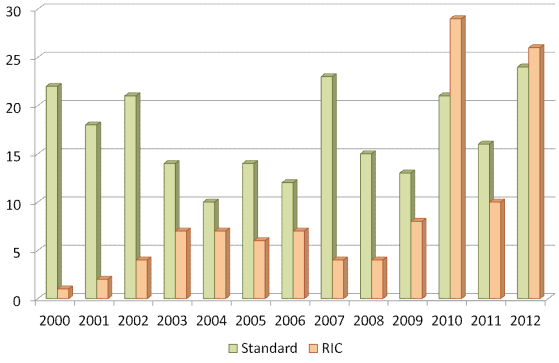

Figure 5. *Incidence of SCT according to the conditioning regimen. From 2010 reduced intensity conditioning have been performed as standard conditioning for patients older than 50 years of age.*

and located at University Hospital Center Zagreb. Before clinical SCT was started, Interdisciplinary transplant team (TT) was formed including experts from different clinical and laboratory fields, which proposed the Protocol of therapy for SCT and produced manual with defined indications and priorities for SCT.

First clinical allogeneic transplantation had been performed on 8th of February 1983, in patients with severe aplastic anemia. The source of stem cells was marrow from HLA-identical sibling donor *(31)*.

"Is the transplant rational and priority in the country with relatively low income?" This question was raised at that time by many physicians. Many of them had been against the high tech medicine, primarily because of financial problems. They were asking us: "What is more important transplantation or vaccination? There is no money for the basic medical needs such as vaccination, and you are doing SCT?!" they said. The only possible answer was: "Of course, vaccination is more important, but we need vaccination and transplantation". We tried to elaborate this problem in Sounding Board article: Transplanted technology: Third world options and first world science (37).

Let me cited some of the relevant part of this article to explain the needs for transplant at that time:

"*In the end, only two options were feasible: continue sending patients abroad or do bone marrow transplantation at home. The latter was in all ways preferable….. Economically, a domestic transplantation program was far cheaper, since salaries and hospital costs are low and paid in dinars….. Overall five transplantations could be done at home for the price of single one abroad.*

In addition Transplant project really was speed-up "engine" for the development of clinical medicine in Zagreb. Namely the prerequisite for SCT was organization on much higher level of quality of many clinical wards and clinical laboratories such as immunology and HLA-typing, transfusion medicine, pathology, microbiology especially diagnostics of viral and fungal infections, biochemistry and last but not least molecular biology which are not only important for routine work of SCT program.

SCT AT UNIVERSITY HOSPITAL CENTER ZAGREB – STANDARD THERAPY FOR MANY HEMATOLOGICAL MALIGNANT TUMORS

After first clinical experience with severe aplastic anemia, the program has been expanded, and SCT was offered to patients with acute leukemia and chronic myeloproliferative neoplasms. For CML before the era of tyrosine kinase inhibitors, SCT was the treatment of choice. During that period our first professional and scientific interest was to reach the therapeutical outcome similar to the most European Blood and Marrow Transplant (EBMT) Centers. So we decided to optimize diagnostic and treatment approach of SCT by standardizing diagnosis and therapy for skin GvHD (38–39), proposed criteria for selection of donor for allografting *(40),* by introducing new methods for monitoring the chimerism after transplantation by measuring isoenzymatic polymorphism of erythrocyte phosphoglucomutase-1 *(41–42),* by successful elimination of antibodies by plasma exchange in ABO incompatible SCT *(43)* and the monitoring of immunologic recovery after transplant *(44)*. In addition, original modification of total body irradiation (TBI) created by our physicist *(45)* have been still using for the standard myeloablative conditioning *(50)*.

In the mid-1990-ies we have enough clinical data to publish our early results of survival and disease-free survival for AML and ALL patients. For AML patients allografted in 1st complete remission leukemia-free survival at 5 year period was 68%. The relapse rate for this group of patients was pretty low, 12% at 5 years *(41)*. For ALL patients in 1st complete remission leukemia free survival and probability of leukemia relapse at 3 years was 52% and 20% respectively *(42)*. Our prospective clinical study on GvDH prophylaxis clearly showed that cyclophoshamide in combination with short methotrexate is most effective prophylactic regimen *(43)*.

At the end of the last century SCT program in our Center has become routine and standard therapy for malignant as well as for non-malignant hematological disorders. The problem of transplant at that time was in general the availability of the donors. In order to expand the program we started with unrelated marrow transplant program in the early 90-ies. In our HLA- typing Center, serology due to its inability to identify all specific products of the HLA alleles has been widely replaced with DNA-based typing methods. It has been shown that in order to improve the clinical outcome of SCT from an unrelated donor, it is essential to identify and match patient and donor's HLA genes at the allele level *(44, 45)*. The MUD program during the last two year have been expanded and now more than 50% of patients receive stem cell from unrelated donor (Figure. 4.). Organization of Croatian Registry known under name "*Ana Rukavina*" with more than 30.000 volunteer donors is the second very important event that significantly influenced MUD program in Croatia and our Center *(45, 46)*.

As stated before stem cells from cord blood as source for transplantation have been used sporadically. At the beginning transplant with cord blood was reserved for patients with non-hematological disease i.e. aplasia and Fanconi anemia. In 1991 we have been able to perform transplant in a very young child with Philadelphia positive CML with stem cells obtained from cord blood of her sister. That was the first report of cord blood transplantation for patients with Philadelphia positive CML *(47, 48)*. SCT has the potentiality to cure primary immune deficiency syndromes, predominantly severe combined immune deficiency (SCID). which can be corrected by partial reconstitution of normal immune cells. In other words full donor chimerism of the affected cell subset may not be required.

SCT have been also applied for lymphoma treatment, not as the treatment of choice, but mostly for patients in advantage stage of disease *(49)*. In the recent years SCT with RIC conditioning as a second line therapy significantly improved the outcome for patients with SLL/CLL *(50)*.

SCT and International collaboration

By using SCT as a standard therapy we have been able to join several international cooperative groups, and to participate in many clinical studies. More than 20 years, Zagreb center is an active member of Leukemia and Lymphoma Group of EORTC. EORTC leukemia group was the first one which in prospective clinical trial analyzed the outcome of SCT as a postremission therapy for patients with AML *(51)*. Patients with HLA-identical sibling achieving complete remission after induction therapy were assigned to undergo allogeneic bone marrow transplantation; the others were randomly assigned to undergo autologous bone marrow transplantation or a second course of intensive chemotherapy.

In AML patients who achieved first complete remission allogeneic as well as autologous SCT results in better disease free survival than intensive consolidation chemotherapy *(52)*. In the subsequent studies, according to intention to treat *(53)*. AML patients younger than 46 years with an HLA-identical sibling donor were assigned to undergo allogeneic (allo) stem cell transplantation (SCT), and patients without such a donor were planned for autologous (auto) SCT.

The DFS rates in patients with and without a sibling donor were similar in patients with good/intermediate risk. Contrary to that in patients with bad/very bad risk cytogenetics DFS for those with donor and without donor were 43.4% and 18.4%, respectively. In younger patients (15–35 years), the difference was more pronounced. The strategy to perform early allo-SCT led to better overall results than auto-SCT, especially for younger patients or those with bad/very bad risk cytogenetics. This data were also proved in AML-12 study *(54)*.

The similar clinical trials have been investigated in high-risk myelodysplastic syndrome (MDS) and secondary AML. The first large EORTC leukemia group prospective study showed the feasibility of both alloSCT and ASCT. This treatment approach leads to a relatively high remission rate, and the majority of patients in remission received the SCT in first complete remission *(69)*. The subsequent studies investigate whether this approach is better than treatment with chemotherapy only. The data was pooled with the other European studies with the intention to investigate the outcome of patients with and without an HLA-identical sibling donor. After a common remission-induction and consolidation course, patients with an HLA-identical sibling donor were scheduled for allogeneic transplantation and patients lacking a donor for autologous transplantation. This analysis showed that patients with high-risk MDS and secondary AML may benefit from both allogeneic and autologous transplantation. We were unable to demonstrate a survival advantage for patients with a donor compared to patients without a donor *(56)*.

Evaluation of older patients, i.e. patients an older 60 years with newly diagnosed MDS/AML and impairments in activities of daily living, Karnofsky Index of $<80\%$, quality of life/fatigue$=50$ are likely to have poor outcomes, and they are not the candidate for SCT. (57). In two EORTC studies ALL-3 and ALL-4, for acute lymphoblastic leukemia SCT was proved as the best antileukemia treatment. Because of high TRM there was no advantage in survival for SCT group compared to chemotherapy *(58, 59)*.

As the member of EBMT we have been participating in many retrospective studies. For many years we have been chairing EBMT group for outreach program. This gave us the opportunity to collect the data from Central and Eastern European countries and to compare the outcome with EBMT data from well developed countries. The published data of transplant in these countries clearly showed that SCT is very effective therapy for patients with acute leukemia, especially for patients transplanted in first CR *(60, 61)*. But transplant rates were substantially lower in eastern European countries for autologous, allogeneic, and unrelated HSCT than in Western Europe. There was a clear correlation between economic factors, measured as gross national income per capita, and transplant rates for low-income countries. There was also a clear correlation between team density (number of teams per 10 million population) and transplant rates. These data document that economic factors can only partly explain the differences in transplant rates between eastern and western European countries *(76)*. Another important factor seems to be the access to the therapeutic procedure(s). These data provide a basis for adequate health care planning.

Another important analysis was done for the Eastern Mediterranean (EM) region *(63)*. In comparison to Europe and North America, differences in patterns of diseases and pre-SCT general status, particularly for patients with BM failure, are described. Other differences including high sero-positivity for CMV, hepatitis B and C infection, and specific observations about GVHD and its relation to genetically homogeneous communities are also evident. A total of 7617 SCTs have been performed by these programs including 5701 allogeneic SCTs. The observed area has low-SCT team density (1.56 teams per 10 million inhabitants vs 14.43 in Europe) and very low-SCT team distribution (0.27 teams per 10 000 sq km area vs <1–6 teams in Europe) while gross national income per capita had no clear association with low--SCT activity.

The only way to substantially improve leukemia therapy is by cooperative research. To optimize research, the European LeukemiaNet *(64)* integrates 105 national leukemia trial groups and networks, 105 interdisciplinary partner groups and about 1,000 leukemia specialists from 175 institutions. Their ultimate goal is to take care for

tens of thousands of leukemia patients in 33 countries across Europe.. Since its inception in 2002, the European LeukemiaNet has steadily expanded and has unified leukemia research and management across Europe. Achievements of described concept has led to funding by the European Commission as a network of excellence. Problems recognized in transitional countries especially in the area of high tech medicine and SCT could be summarized as follows: Transplant rates were substantially lower for all type of SCT, the important diagnostic and clinical facilities for SCT are not optimal or some of them are missing, mostly because of low national income. To make a progress in our countries in October 2009 we founded Central and Eastern European Leukemia Group (CELG). The main goal of the group is to speed-up implementation of standard diagnostic and treatment approach for acute leukemia in the member countries. When someone is asking what is the main impact of SCT until now, the answer is very simple: SCT increased the cure rate for at least 20% to 30% for many malignant hematological tumors.

FUTURE AND CONCLUSIONS

During the 30 years period SCT has been established as a standard and routine therapy at University Hospital Center Zagreb for many malignant and non-malignant hematological disorders. Transplant has significant influence on the quality level and the development of many clinical diagnostic and treatment facilities. In the future by *in vitro* manipulation and selection of stem cells one might expect further development of SCT in terms of its safety and efficacy. In our hospital we are able to isolate and cultivate bone marrow derived mesenchymal stem cells (MSCs), multipotent nonhematopoietic cells or bone marrow stromal cells *(65)*.

Clinical interest for MSCs was initiated by the observation that MSCs are immuno-privileged cells that display immuno-modulatory properties in vitro. Ex vivo expanded MSCs have therefore become a new type of cellular therapy in development with a wide range of potential clinical applications. Infused MSCs suppress graft versus host disease, support engraftment of transplanted allogeneic hematopoietic stem cells and stimulate growth in patients with osteogenesis imperfecta. Although underlying immuno-modulatory mechanisms of action are not completely understood, potential benefit of MSC therapy justifies its clinical use in a broad range of disorders. They have capacity for self-renewal in a number of non-hematopoietic tissues. Moreover MSCs display a significant capacity of decreasing inflammation, modulating immune responses and protecting tissue from injury, including stroke and anoxic damage, stemmed from the assumption that stem cells differentiate and replace dead cells representing the basis for a new discipline, *regenerative medicine*. This new multidisciplinary field intended to repair, replace and regenerate cells tissue as well as organs for restoring or establishing normal function. The basic idea behind regenerative medicine is to cure human ailments by replacing failed body organs and damaged tissues with laboratory-grown cells and organs. Regenerative medicine employs small molecule drugs, medical devices, cell-based therapies and biologics. In a broader sense, the term includes advanced cell-based therapies, tissue engineering, stem cells and developmental biology, cellular therapeutics, biomaterials and gene therapy.

REFERENCES

1. GRATWOHL A, BALDOMERO H, FRAUENDORFER K, URBANO-ISPIZUA A; Joint Accreditation Committee, International Society for Cellular Therapy; European Group for Blood and Marrow Transplantation 2006 EBMT activity survey 2004 and changes in disease indication over the past 15 years. *Bone Marrow Transplant 37:* 1069–85
2. BACIGALUPO A 2008 Treatment strategies for patients with severe aplastic anemia. *Bone Marrow Transplant 42 (Suppl 1):* S42–S44
3. GRATWOHL A, BALDOMERO H, SCHWENDENER A, ROCHA V, APPERLEY J, FRAUENDORFER K, NIEDERWIESER D; Joint Accreditation Committee of the International Society for Cellular Therapy; European Group for Blood and Marrow Transplantation 2009 The EBMT activity survey 2007 with focus on allogeneic HSCT for AML and novel cellular therapies. *Bone Marrow Transplant 43:* 275–91
4. JANTUNEN E, SUREDA A 2012 The evolving role of stem cell transplants in lymphomas. *Biol Blood Marrow Transplant 18:* 660–73
5. SNOWDEN J A, SACCARDI R, ALLEZ M, ARDIZZONE S, ARNOLD R, CERVERA R, DENTON C, HAWKEY C, LABOPIN M, MANCARDI G, MARTIN R, MOORE JJ, PASSWEG J, PETERS C, RABUSIN M, ROVIRA M, VAN LAAR J M, FARGE D; EBMT Autoimmune Disease Working Party (ADWP); Paediatric Diseases Working Party (PDWP) 2012 Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant 47:* 770–90
6. LINK H, KOLB H J, EBELL W, HOSSFELD D K, ZANDER A, NIETHAMMER D, WANDT H, GROSSE-WILDE H, SCHAEFER U W 1997 Transplantation of hematopoietic stem cells. II: Indications for transplantation of hematopoietic stem cells after myeloablative therapy. *Med Klin 92:* 534–45
7. GREINIX H T, LOIDOLT H, RABITSCH W, SCHULENBURG A, KEIL F, MITTERBAUER M, LACZIKA K, LECHNER K, DIECKMANN K, FISCHER G, JÄGER U, ROSENMAYR A, KNÖBL P, SCHWARZINGER I, HÖCKER P, MANNHALTER C, HINTERBERGER W, HAAS O A, FONATSCH C, KALHS P 2000 Excellent disease eradication by myeloablative therapy and stem-cell transplantation in patients with acute myelogenous leukemia. *Ann Hematol 79:* 206–13
8. HOROWITZ M M, GALE R P, SONDEL P M, GOLDMAN J M, KERSEY J, KOLB H J, RIMM A A, RINGDÉN O, ROZMAN C, SPECK B, TRUITT R L, ZWAAN F E, BORTIN M M 1990 Graft-versus-leukemia reactions after bone marrow transplantation. *Blood 75:* 555–62
9. BRENNER M K, HESLOP H E 1991 Graft versus leukaemia effects after marrow transplantation in man. *Baillieres Clin Haematol 4:* 727–49
10. ZEIS M, UHAREK L, HARTUNG G, GLASS B, STEINMANN J, SCHMITZ N 2001 Graft-vs-leukemia activity and graft-vs-host disease induced by allogeneic Th1- and Th2-type CD4+ T cells in mice. *Hematol J 2:* 136–44
11. SAVANI B N, MONTERO A, WU C, NLONDA N, READ E, DUNBAR C, CHILDS R, SOLOMON S, BARRETT A J 2005 Prediction and prevention of transplant-related mortality from pulmonary causes after total body irradiation and allogeneic stem cell transplantation. *Biol Blood Marrow Transplant 11:* 223–30
12. DITSCHKOWSKI M, ELMAAGACLI A H, TRENSCHEL R, STECKEL N K, KOLDEHOFF M, BEELEN D W 2006 Myeloablative allogeneic hematopoietic stem cell transplantation in elderly patients. *Clin Transplant 20:* 127–31
13. GRATWOHL A, BRAND R, FRASSONI F, ROCHA V, NIEDERWIESER D, REUSSER P, EINSELE H, CORDONNIER C; Acute and Chronic Leukemia Working Parties; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation 2005 Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analy-

sis of lethal infectious complications and changes over calendar time. *Bone Marrow Transplant 36:* 757–69

14. HORAN J T, LOGAN B R, AGOVI-JOHNSON M A, LAZARUS H M, BACIGALUPO A A, BALLEN K K, BREDESON C N, CARABASI M H, GUPTA V, HALE G A, KHOURY H J, JUCKETT M B, LITZOW M R, MARTINO R, MCCARTHY P L, SMITH F O, RIZZO J D, PASQUINI M C 2011 Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? *J Clin Oncol 29:* 805–13
15. DREGER P, BRAND R, MILLIGAN D, CORRADINI P, FINKE J, LAMBERTENGHI DELILIERS G, MARTINO R, RUSSELL N, VAN BIEZEN A, MICHALLET M, NIEDERWIESER D; Chronic leukemia working party of the ebmt 2005 Reduced-intensity conditioning lowers treatment-related moratlity of allogeneic stem cell transplantation for chronic lymphocytic leukemia: a population--matched analysis. *Leukemia 19:* 1029–33
16. AOUDJHANE M, LABOPIN M, GORIN N C, SHIMONI A, RUUTU T, KOLB H J, FRASSONI F, BOIRON J M, YIN JL, FINKE J, SHOUTEN H, BLAISE D, FALDA M, FAUSER A A, ESTEVE J, POLGE E, SLAVIN S, NIEDERWIESER D, NAGLER A, ROCHA V; Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT) 2005 Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia 19:* 2304–12
17. BLAISE D, FARNAULT L, FAUCHER C, MARCHETTI N, FÜRST S, EL CHEIKH J, LADAIQUE P, VEY N, BOUABDALLAH R, STOPPA A M, LEMARIE C, CALMELS B, PREBET T, CASTAGNA L, CHABANNON C, MOHTY M, ESTERNI B 2010 Reduced-intensity conditioning with Fludarabin, oral Busulfan, and thymoglobulin allows long-term disease control and low transplant-related mortality in patients with hematological malignancies. *Exp Hematol 38:* 1241–50
18. SORROR M, STORER B, SANDMAIER B M, MALONEY D G, CHAUNCEY T R, LANGSTON A, MAZIARZ R T, PULSIPHER M, MCSWEENEY P A, STORB R 2008 Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer 112:* 1992–2001
19. GREINIX H T, REITER E, SCHULENBURG A, KEIL F, LECHNER K, FISCHER G, ROSENMAYR A, LEITNER G, KALHS P 1998 Matched unrelated donor marrow transplantation in patients with advanced acute leukemia. *Bone Marrow Transplant 22 (Suppl 4):* S53–6
20. AVERSA F, REISNER Y, MARTELLI M F 2004 Hematopoietic stem cell transplantation from alternative sources in adults with high-risk acute leukemia. *Blood Cells Mol Dis 33:* 294–302
21. ERLICH H 2012 HLA DNA typing : past, present, and future. *Tissue Antigens 80:* 1–11
22. VAN BESIEN K, LIU H, JAIN N, STOCK W, ARTZ A 2012 Umbilical Cord Blood Transplantation Supported by Third Party Donor Cells: Rationale, Results and Applications. *Biol Blood Marrow Transplant* (in press)
23. LUZNIK L, O'DONNELL P V, SYMONS H J, CHEN A R, LEFFELL M S, ZAHURAK M, GOOLEY T A, PIANTADOSI S, KAUP M, AMBINDER R F, HUFF C A, MATSUI W, BOLAÑOS-MEADE J, BORRELLO I, POWELL J D, HARRINGTON E, WARNOCK S, FLOWERS M, BRODSKY R A, SANDMAIER B M, STORB R F, JONES R J, FUCHS E J 2008 HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant 14:* 641–50
24. THOMAS E D, STORB R, CLIFT R A, FEFER A, JOHNSON L, NEIMAN P E, LERNER K G, GLUCKSBERG H, BUCKNER C D 1975 Bone-marrow transplantation (second of two parts). *N Engl J Med 292:* 895–902
25. STORB R, THOMAS E D 1976 Marrow transplantation for the treatment of aplastic anemia and acute leukemia. *Transplant Proc 8 (2 Suppl 1):* 159–63
26. THOMAS E D, FEFER A, BUCKNER C D, STORB R 1977 Current status of bone marrow transplantation for aplastic anemia and acute leukemia. *Blood 49:* 671–81
27. BORANIĆ M 1968 Delayed mortality in sublethally irradiated mice treated with allogeneic lymphoid and myeloid cells. *J Natl Cancer Inst 41:* 439–50
28. BORANIĆ M, TONKOVIĆ I 1971 Time pattern of the antileukemic effect of graft-versus-host reaction in mice. *Cancer Res 31:* 1140–7
29. BORANIĆ M 1978 Conference on the needs and possibilities of clinical bone marrow transplantation. introduction. *Lijec Vjesn 100:* 373
30. BORANIĆ M, GRGICEVIĆ D, GRGIĆ Z, KASTELAN A, KOSUTIĆ Z 1978 Conference on the needs and possibilities of clinical bone marrow-transplantation. Conclusion. *Lijec Vjesn 100:* 395–6
31. LABAR B, BOGDANIĆ V, KASTELAN A, GRGICEVIĆ D, VRTAR M, KRAJINA Z, KAMAUF-BALABANIĆ B, KERHIN-BRKLJACIĆ V, FRANCETIĆ I, ZIMONJA-KRISKOVIć J 1984 Transplantation of bone marrow in the treatment of severe aplastic anemia. *Lijec Vjesn 106:* 219–23
32. WOOLHANDLER S, HIMMELSTEIN D U, LABAR B, LANG S 1987 Transplanted technology: Third World options and First World science. *N Engl J Med 317:* 504–6
33. DOBRIĆ I, VUJASINOVIĆ S, KASTELAN A, BARICEVIĆ B, LABAR B, BOGDANIĆ V, NEMET D 1988 [Changes in the skin due to the graft-versus-host reaction. 1. Pathogenesis and diagnosis]. *Lijec Vjes 110(12):* 436–8, Croatian. No abstract available.
34. DOBRIĆ I, VUJASINOVIĆ S, LABAR B, BOGDANIĆ V, NEMET D, KASTELAN A, BARICEVIĆ B, VRANESIĆ D, SKRINJAR L 1989 Changes in the skin in transplantation versus host reaction. 2. Our clinical findings from observations using light microscopy and electron microscopyĆ. *Lijec Vjesn 111:* 76–80
35. ZUPANCIĆ-SALEK S, AURER I, BOGDANIĆ V, NEMET D, MRSIĆ M, LABAR B 1989 Donor characteristics in allogeneic bone marrow transplantation.*Bone Marrow Transplant 4 (Suppl 3):* 107
36. GRAHOVAC B, LABAR B, STAVLJENIĆ A 1988 Subtyping of erythrocyte phosphoglucomutase-1 as a genetic marker for bone--marrow engraftment and hematopoietic chimerism after allogeneic bone-marrow transplantation in a patient with acute lymphoblastic leukemia. *Clin Chem 34:* 2586–8
37. GRAHOVAC B, LABAR B, STAVLJENIĆ A 1988 Phenotyping of phosphoglucomutase (PGM1) isoenzymes – a new method for the follow-up of chimerism after bone marrow transplantation. Follow-up of chimerism after bone marrow transplantation by phenotyping of phosphoglucomutase (PGM1) isoenzymes. *Enzyme 40:* 37–9
38. GASPAROVIĆ V, LABAR B, PULJEVIĆ D, SKODLAR J, BOGDANIĆ V, IVANOVIĆ D, GJURASIN M 1989 Elimination of antibodies by plasma exchange in ABO incompatible bone marrow transplantation. *Bone Marrow Transplant 4 (Suppl 3):* 109
39. PAVLETIĆ Z, PETROVECKI M, BOGDANIĆ V, NEMET D, UZAREVIĆ B, MATEK Z, MARKOVIĆ J, MARUSIĆ M, LABAR B 1989 The significance of immunological monitoring after allogeneic bone marrow transplantation. *Bone Marrow Transplant 4 (Suppl 3):* 111
40. LABAR B, BOGDANIĆ V, NEMET D, MRSIć M, VRTAR M, GRGIĆ-MARKULIN L, KALENIĆ S, VUJASINOVIĆ S, PRESECKI V, JAKIĆ-RAZUMOVIĆ J, MARUSIC M 1992 Total body irradiation with or without lung shielding for allogeneic bone marrow transplantation. *Bone Marrow Transplant 9(5):* 343–7
41. LABAR B, NEMET D, MRSIĆ M, BOGDANIĆ V, KAŠTELAN A, BOBAN D, KALENIĆ S, RADMAN I, BATINIĆ D, VRTAR M, GRGIĆ-MARKULIN L J, MARAVIĆ N 1998 Autologous versus Allogeneic Marrow Transplantation for Parients with Acute Myeloid Leukemia in 1st Remission. *Cancer Res Ther Control 5:* 143–149
42. MRSIĆ M, NEMET D, LABAR B, BOGDANIĆ V, RADMAN I, ZUPANCIĆ-SALEK S, KOVACEVIĆ-METELKO J, AURER I, MARAVIĆ N 1993 Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia. *Transplant Proc 25:* 1268–70.
43. MRSIĆ M, LABAR B, BOGDANIĆ V, NEMET D, PAVLETIĆ Z, PLAVSIĆ F, DOBRIĆ I, MARUSIĆ M, FRANCETIĆ I, KASTELAN A, KALENIĆ S, VRTAR M, MARKULIN-GRGIĆ L J, AURER I 1990 Combination of cyclosporin and methotrexate for prophylaxis of acute graft-versus-host disease after allogeneic bone marrow transplantation for leukemia. *Bone Marrow Transplant 6:* 137–41
44. BRKLJAČIĆ-KERHIN V, ČEČUK-JELIČIĆ E, GRUBIĆ Z, STINGL K, LABAR B. 2007 Registry of cell and tissue donors. *Acta Med Croatica. 61:* 463–6.
45. ČEČUK-JELIČIĆ E, KERHIN-BRKLJACIĆ V, GRUBIĆ Z, LABAR B 2009 World's registry of bone marrow donors. *Acta Med Croatica 63:* 251–3

46. GOLUBIĆ CEPULIĆ B, BOJANIĆ I, BATINIĆ D, NEMET D, LABAR B 2007 Hematopoetic stem cell bank at Zagreb University Hospital Center, Zagreb, Croatia. *Acta Med Croatica 61:* 505–9
47. BOGDANIĆ V, NEMET D, KAŠTELAN A, LATIN V, PETROVEČKI M, BRKLJAČIĆ-ŠURLAKOVIĆ LJ, KERHIN-BRKLJAČIĆ LJ, AURER I, KONJA J, MRSIĆ M, KALENIĆ S, LABAR B 1993 Umbilical Cord Blood Transplantation ina Patient with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia. *Transplantation 56:* 477–479
48. BOGDANIĆ V, AURER I, HITREC V, BOBAN D, NEMET D, ZUPANČIĆ-SALEK S, LABAR B 1995 Donor buffy-coat infusion and chemotherapy for leukemia in relapse after marrow transplantation. *Haematologica 80:* 338–40
49. LABAR B, BOGDANIĆ V, NEMET D, MRSIĆ M, SERVENTI-SEIWERTH R, SERTIĆ D, GOLUBIĆ-CEPULIĆ B, VRTAR M, SANTEK F, BATINIĆ D, MIKULIć M, PULANIĆ D 2002 Allogeneic stem cell transplantation in treatment of aggressive lymphomas: case series. *Croat Med J 43:* 565–8
50. MAURO F R, BANDINI G, BAROSI G, BILLIO A, BRUGIATELLI M, CUNEO A, LAURIA F, LISO V, MARCHETTI M, MELONI G, MONTILLO M, ZINZANI P, TURA S; Italian Society of Hematology; Società Italiana di Ematologia Sperimentale; Gruppo Italiano Trapianto di Midollo Osseo 2012 SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia. *Leuk Res 36:* 459–66
51. ZITTOUN RA, MANDELLI F, WILLEMZE R, DE WITTE T, LABAR B, RESEGOTTI L, LEONI F, DAMASIO E, VISANI G, PAPA G, CARONIA F, HAYAT M, STRYCKMANS P, ROTOLI B, LEONI P, PEETERMANS M E, DARDENNE M, VEGNA M L, PETTI M C, SOLBU G, SUCIU S, for the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) 1995 Leukemia Cooperative Groups Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med 332:* 217–23
52. KEATING S, DE WITTE T, SUCIU S, WILLEMZE R, HAYAT M, LABAR B, RESEGOTTI L, FERRINI P R, CARONIA F, DARDENNE M, SOLBU G, PETTI M C, VEGNA M L, MANDELLI F, ZITTOUN R A The influence of HLA-matched sibling donor availability on treatment outcome for patients with AML: an analysis of the AML 8A study of the EORTC Leukaemia Cooperative Group and GIMEMA. European Organization for Research and Treatment of Cancer. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. Br 0
53. SUCIU S, MANDELLI F, DE WITTE T, ZITTOUN R, GALLO E, LABAR B, DE ROSA G, BELHABRI A, GIUSTOLISI R, DELARUE R, LISO V, MIRTO S, LEONE G, BOURHIS JH, FIORITONI G, JEHN U, AMADORI S, FAZI P, HAGEMEIJER A, WILLEMZE R; EORTC and GIMEMA Leukemia Groups 2003 Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMA AML-10 trial. *Blood 102:* 1232–40
54. WILLEMZE R, SUCIU S, MANDELLI F, HALKES S J M, MARIE J P, LABAR B,VENDITTI A, MUUS P, MISTRIK M, CAMERA A, MAGRO D, MELILLO L, BRON D, MAGRIN S, SELLESLAG D, PASTORE D, TRISOLINI S, FAZI P, KARRASCH M, VIGNETTI M, AMADORI S, DE WITTE T M, MELONI G 2011 High Dose (HD-AraC) Vs Standard Dose Cytosine Arabinoside (SD-AraC) During Induction and IL-2 Vs Observation After Consolidation/Autologous Stem Cell Transplantation in Patients with Acute Myelogenous Leukemia (AML): Final Report of the AML-12 Trial of EORTC and GIMEMA Leukemia Groups on the Value of Low Dose IL-2 Maintenance. *Blood (ASH Annual Meeting Abstracts) 118:* 3612
55. DE WITTE T, SUCIU S, VERHOEF G, LABAR B, ARCHIMBAUD E, AUL C, SELLESLAG D, FERRANT A, WIJERMANS P, MANDELLI F, AMADORI S, JEHN U, MUUS P, BOOGAERTS M, ZITTOUN R, GRATWOHL A, ZWIERZINA H, HAGEMEIJER A, WILLEMZE R 2001 Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. *Blood 98:* 2326–31
56. OOSTERVELD M, SUCIU S, VERHOEF G, LABAR B, BELHABRI A, AUL C, SELLESLAG D, FERRANT A, WIJERMANS P, MANDELLI F, AMADORI S, JEHN U, MUUS P, ZITTOUN R, HESS U, ANAK O, BEELDENS F, WILLEMZE R, DE WITTE T 2003 The presence of an HLA-identical sibling donor has no impact on outcome of patients with high-risk MDS or secondary AML (sAML) treated with intensive chemotherapy followed by transplantation: results of a prospective study of the EORTC, EBMT, SAKK and GIMEMA Leukemia Groups (EORTC study 06921). *Leukemia 7:* 859–68
57. DESCHLER B, IHORST G, PLATZBECKER U, GERMING U, MÄRZ E, DE FIGUERIDO M, FRITZSCHE K, HAAS P, SALIH H, GIAGOUNIDIS A, SELLESLAG D, LABAR B, DE WITTE T, WIJERMANS P, LÜBBERT M 2012 Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. *Haematologica* (in press)
58. LABAR B, SUCIU S, ZITTOUN R, MUUS P, MARIE J P, FILLET G, PEETERMANS M, STRYCKMANS P, WILLEMZE R, FEREMANS W, JAKSIC B, BOURHIS J H, BURGHOUTS J P, DE WITTE T; EORTC Leukemia Group 2004 Allogeneic stem cell transplantation in acute lymphoblastic leukemia and non-Hodgkin's lymphoma for patients <or=50 years old in first complete remission: results of the EORTC ALL-3 trial. *Haematologica 89:* 809–17
59. LABAR B, SUCIU S, WILLEMZE R, MUUS P, MARIE J P, FILLET G, BERNEMAN Z, JAKSIC B, FEREMANS W, BRON D, SINNIGE H, MISTRIK M, VREUGDENHIL G, DE BOCK R, NEMET D, GILOTAY C, AMADORI S, DE WITTE T; EORTC Leukemia Group 2010 Dexamethasone compared to prednisolone for adults with acute lymphoblastic leukemia or lymphoblastic lymphoma: final results of the ALL-4 randomized, phase III trial of the EORTC Leukemia Group. *Haematologica 95:* 1489–95
60. LABAR B, MASSZI T, MORABITO F, MISTRIK M, HOLOWIECKI J, BOGDANIĆ V, NEMET D, MRSIĆ M, KRIEGER O, LUTZ D 1996 Allogeneic bone marrow transplantation for acute leukaemia – IGCI experience. International Group for Chemo--Immunotherapy. *Bone Marrow Transplant 17:* 1009–12
61. GIEBEL S, LABOPIN M, HOLOWIECKI J, LABAR B, KOMARNICKI M, KOZA V, MASSZI T, MISTRIK M, LANGE A, HELLMANN A, VITEK A, PRETNAR J, MAYER J, RZEPECKI P, INDRAK K, WIKTOR-JEDRZEJCZAK W, WOJNAR J, KRAWCZYK-KULIS M, KYRCZ-KRZEMIEN S, ROCHA V 2009 Outcome of HLA-matched related allogeneic hematopoietic stem cell transplantation for patients with acute leukemia in first complete remission treated in Eastern European centers. Better results in recent years. *Ann Hematol 88:* 1005–13
62. GRATWOHL A, BALDOMERO H, LABAR B, APPERLEY J, URBANO-ISPIZUA A 2004 Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Evolution of hematopoietic stem cell transplantation in Eastern and Western Europe from 1990 to 2003. A report from the EBMT activity survey. *Croat Med J 45:* 689–94
63. ALJURF M D, ZAIDI S Z, EL SOLH H, HUSSAIN F, GHAVAMZADEH A, MAHMOUD H K, SHAMSI T, OTHMAN T B, SARHAN M M, DENNISON D, IBRAHIM A, BENCHEKROUN S, CHAUDHRI N, LABAR B, HOROWITZ M, NIEDERWIESER D, GRATWOHL A 2009 Special issues related to hematopoietic SCT in the Eastern Mediterranean region and the first regional activity report. *Bone Marrow Transplant 43:* 1–12
64. HEHLMANN R, GRIMWADE D, SIMONSSON B, APPERLEY J, BACCARANI M, BARBUI T, BAROSI G, BASSAN R, BÉNÉ M C, BERGER U, BÜCHNER T, BURNETT A, CROSS NC, DE WITTE TJ, DÖHNER H, DOMBRET H, EINSELE H, ENGELICH G, FOÀ R, FONATSCH C, GÖKBUGET N, GLUCKMAN E, GRATWOHL A, GUILHOT F, HAFERLACH C, HAFERLACH T, HALLEK M, HASFORD J, HOCHHAUS A, HOELZER D, KILADJIAN J J, LABAR B, LJUNGMAN P, MANSMANN U, NIEDERWIESER D, OSSENKOPPELE G, RIBERA J M, RIEDER H, SERVE H, SCHROTZ-KING P, SANZ M A, SAUSSELE S; European LeukemiaNet 2011 The European LeukemiaNet: achievements and perspectives. *Haematologica 96*: 156–62
65. GOLEMOVIĆ M, SKIFIĆ M, CEPULIĆ-GOLUBIC B 2012 Mesenchymal stem cells: immunomodulatory properties and clinical application. *Lijec Vjesn 134:* 42–9