

# IBMTR/ABMTR newsletter

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## CONTENTS

Report from the second iwNST meeting ..... 1

Filipovich, Vose assume Registry chairs; Ringdén, Champlin named as chairs-elect ..... 1

Perspectives:  
– Julie M. Vose  
– Armand Keating ... 2

Tandem BMT meetings – in appreciation ..... 3

Forbeck Forum discusses recommendations for clinical trials in hematopoietic stem cell transplantation ..... 9

Recent peer-reviewed publications from the IBMTR/ABMTR ..... 10

Foundation and corporate support of the IBMTR/ABMTR . 11

IBMTR/ABMTR Executive Committees and Statistical Center personnel ..... 12

## Report from the 2<sup>nd</sup> International Workshop on NST

January 25–28, 2001, St Martin, West Indies



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The inaugural meeting of the International Working Group on Non-myeloablative Stem-cell Transplantation (iwNST) was held in St Lucia in 2000. The meeting brought together a small group of international transplantation experts with an interest in the development of non-myeloablative or reduced-intensity preparative regimens for blood and marrow transplantation (BMT). Following the success of this meeting, a second iwNST meeting was held with the support of Schering AG in St Martin from January 25–28, 2001. The aims of the second meeting were twofold. First to discuss progress made in NST in hematologic malignancies, solid tumors and a range of other therapeutic settings, including autoimmune diseases, and second to determine areas of consensus suitable for establishing multicenter prospective clinical trials in non-myeloablative stem cell transplantation (NST). The meeting was divided into three sections:

*continued on page 4*

## Filipovich, Vose assume Registry chairs; Ringdén, Champlin named as chairs-elect

At the February 2001 Annual Meeting, Dr. Alexandra Filipovich of Children's Hospital Medical Center in Cincinnati assumed the Chair of the IBMTR Advisory Committee. Dr. John Goldman (Imperial College of Medicine, London) will continue to serve on the Executive Committee for a three-year term as Immediate Past-Chair. Dr. Olle Ringdén of Huddinge University Hospital, Stockholm, Sweden was chosen as IBMTR Chair-Elect in the pre-meeting balloting. Dr. Julie Vose of the University of Nebraska, Omaha assumed the Chair of the ABMTR Advisory Committee; Dr. Armand Keating (University of Toronto) will continue to serve on the Executive Committee as Immediate Past-Chair. Dr. Richard Champlin from M.D. Anderson Cancer Center was chosen as ABMTR Chair-Elect.

Dr. Gérard Socié from Hôpital St. Louis in Paris, France (Secretary-Treasurer) and Drs. Sergio Giralt from M.D. Anderson Cancer Center in Houston, Texas and Axel Zander from University Hospital Eppendorf in Hamburg, Germany (Members-at-Large).

For the ABMTR, Dr. Michael Bishop from the US National Cancer Institute has been elected Nominating Committee Chair, and Dr. Koen van Besien from the University of Chicago Medical Center has been named Secretary-Treasurer. New ABMTR Executive Committee Members-at-Large are Drs. Elizabeth Reed from the University of Nebraska, Omaha and Patrick Stiff from Loyola University Medical Center in Maywood, Illinois.

In other IBMTR election results, Dr. Daniel Weisdorf of the University of Minnesota, Minneapolis was selected as Nominating Committee Chair. Newly elected IBMTR Executive Committee members are

We thank Drs. A. John Barrett, Robert Peter Gale, Hans-Jochem Kolb and John Wingard for their past service on the IBMTR Executive Committee and Drs. James Armitage, Bruce Camitta, Carole Miller and

*continued on page 4*

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## Perspectives



### Julie M. Vose, MD

*ABMTR Advisory Committee Chair*

*Professor of Medicine, University of Nebraska Medical Center, Omaha, NE, USA*

It is my distinct pleasure to assume the chair of the ABMTR from Armand Keating. Over the past three years Dr. Keating, along with Dr. Mary Horowitz and the entire Statistical Center, has led the ABMTR to the forefront of autologous transplantation research.

From the inception of the ABMTR in the late 1980s, the activity of the organization has continued to grow and prosper. Accomplishments include the collection of data on more than 63,000 patients receiving autologous transplantation for various malignancies or conditions since 1989. Collaborations on research papers with multiple investigators and other

research groups have ultimately led to many excellent papers in peer-reviewed journals. In addition to research contributions, the Registry is an invaluable source of information for patients, physicians, and healthcare agencies interested in transplantation.

The future of this outstanding organization must include the planning, organization, and conduct of prospective clinical trials in transplantation. This can be accomplished through a large network of transplant centers which collaborate on transplant clinical trials that have been specifically developed to answer important questions regarding transplantation and disease-

specific issues. Our organization is in an excellent situation to be able to assist in the statistical planning, development, and implementation of such studies. With such efforts, scientific questions can be definitely answered in appropriately designed clinical trials.

Developments in transplantation over the next several years will shape the future of transplantation clinical care and research and will affect countless patients with malignancies and other conditions. It is exciting to be able to assist in the next phase of the ABMTR's development and to be a part of the future of blood and marrow transplantation.



### Armand Keating, MD

*ABMTR Immediate Past-Chair*

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It is indeed gratifying that both the ABMTR and IBMTR continue to thrive. This is true for registration activity as well as for active contributions to the field of blood and marrow transplantation. For example, over 63,000 cases have been registered with the ABMTR, including the approximately 19,000 detailed research reports since 1989 when the Registry began. Perhaps most impressively, during the 2000–2001 year there have been 17 papers published, with 10 in press and 6 under review from the IBMTR and ABMTR. Many have, and will appear in first rate international peer-reviewed journals. These accomplishments attest to the vigor and leadership of the Working Committees and of Mary Horowitz and the Statistical Center. The merging of the IBMTR and ABMTR roles in the Working Committees has been an important and creative force in this productivity.

Vital organizations do not stand still. I believe that the ABMTR (and IBMTR – it is becoming increasingly difficult to separate their functions) will have an increasingly important role in moving the field forward

in North America and internationally. In order to carry this out effectively, it must adapt, change and grow in new ways. I would like to provide three examples of how this is already taking place.

The first is a strong interest in participating in prospective clinical trials. The Registry with its large network of participating transplant centers (including large and small, highly academic as well as service-based programs) is extremely well positioned to evolve as a hub of a prospective trials network. Indeed, a network of transplant programs is already established through the Statistical Center by virtue of the data exchange that takes place between them. Because of its broad constituency of participating transplant programs, the Registry is well placed to facilitate rapid and large accrual to important trials. Another major advantage is that Registry studies are hypothesis-generating, enabling key prospective trials to be quickly developed. Importantly, the feasibility of such trials can be readily tested by analyzing the extensive Registry database.

A second and important area for further development is the ongoing need to collaborate with related organizations. The reasons are obvious: synergy and the avoidance of duplication among many others. An excellent example is the collaboration with the ASBMT that has resulted in the continued success of the Tandem BMT Meetings. Another successful collaboration is with the EBMT, and it is recognized that greater interaction can only help the field. The IBMTR/ABMTR is currently exploring the possibility of collaborating with the Canadian Bone Marrow Transplant Group (CBMTG) to develop a national registry database. This is of some significance because the 24 centers in Canada perform about 1200 transplants per year. The development of such a registry will help facilitate the CBMTG's goal of establishing a cohesive national clinical trials network. They already have the advantage that all the centers are associated with teaching hospitals and their directors are committed to addressing important transplant-related questions.

*continued on page 3*

# Tandem BMT Meetings

## Tandem BMT Meetings 2001— in appreciation

By D'Etta Waldoch, CMP

It is simply time to say thank you – time to acknowledge the many people who contributed to the success of this year's Tandem BMT Meetings.

The 2001 Tandem BMT Meetings were held at the newly expanded Keystone Resort and Conference Center in Colorado. The ASBMT (American Society for Blood and Marrow Transplantation) met from February 15–17, and the IBMTR/ABMTR Annual Participants' Meeting was held February 17–19.

So! Thank you! To the 1300+ attendees who constitute a significant sample of the world's best in BMT: clinicians, scientists, pharmacists, nurses, clinical research associates, administrators, pharmaceutical company representatives, and other allied professionals. Thank you for serving as planners and organizers, session chairs, speakers, facilitators, poster presenters, judges, educators and (not least of all) sponsors, staff and clean-up crew. Great strides have been made in integrating the IBMTR/ABMTR and ASBMT scientific programs into one complete meeting package, and thank you for noting your appreciation of these efforts on your evaluation forms.

For its initial effort, the Tandem BMT Meetings' online registration and housing program worked well. Many thanks to those a little less electronically-inclined, who struggled a bit with the new program and provided insights into improving our

efficiency next year. Online registration proved itself worthy with 60% fewer on-site registrations at Keystone, resulting in fewer on-site surprises and much less congestion at the registration desk. Thanks also to a delightful set-up and registration staff, led by Patty Vespalec, Marmie Kiva and Debbie Schaubel, who kept a smile at all times.

It takes an incredible amount of diligence to keep the lively banter of the Working Committee meetings humming while the alternative for the afternoon could be skiing or basking in the Colorado sunshine with a good book. Thanks to those who took the initiative to download materials from the IBMTR/ABMTR web site, in advance preparation for more stimulating interaction at the committee meetings. Thanks also to a dedicated statistical staff, whose workload increases exponentially each year just keeping up with the number of studies proposed and approved, tempering ambitious plans with reality.

Thanks to 30+ pharmacists and Orphan Medical, Inc. for pioneering the first BMT pharmacists conference into an unqualified success and to Kathy Kovatovic from the Medical College of Wisconsin and Harry Hopkins from the Ottawa Hospital for organizing the event. Plans are to continue this as a regular part of the annual Tandem BMT Meetings.

BMT clinical research associates and research nurses worldwide are to be

heralded for gathering and nurturing the quality data without which not one valid scientific study or presentation could exist. The highly-interactive and well-attended data management sessions were primarily orchestrated by Diane Knutson and other dedicated members of the Statistical Center staff. A special thanks goes out to transplant centers for support of these training efforts.

Let it not be said that we aren't also thankful for the exceptional service, hearty smiles and professionalism of the Keystone Resort staff. Large meetings can produce some very tense moments despite the best planning. Always courteous and willing to go the extra mile, Keystone's Conference Services Department works proactively to keep the most trying times invisible to meeting attendees. Thank you for more than doubling the size of your state-of-the-art Conference Center, which will allow the Tandem BMT Meetings to return in 2003, 2005 and beyond. And, oh yeah! the food was spectacular! Now ... about building a few more condos ...

A special thanks to Gérard Socié and Donna Reece for serving as IBMTR/ABMTR program chairs at this year's Annual Participants' Meeting, and to Julie Vose for her service as program chair for ASBMT. Finally, thanks to the many scientists and clinicians who have brought the IBMTR/ABMTR to the forefront of clinical research in this exciting field.

*continued from page 2*

The third area of growth in a new direction involves the exploration by the ABMTR (and IBMTR) of a Working Committee on gene therapy / gene marking. The timing for this endeavor is important because of the current uncertainty surrounding the entire field of gene therapy, especially from the standpoint of government regulatory agencies. There have been over 30 RAC-approved protocols for cell marking and gene therapy involving more than 200 patients, using predominantly autotransplants to deliver a variety of gene-modified cells. There does not

appear to be any existing mechanism to monitor, review and report outcomes on all these patients. A relevant and particularly unfortunate aspect, given the current relatively negative climate towards gene therapy, is the prevailing publication bias in which negative studies are unlikely to be reported. The expertise of the Registry and the enthusiasm of a cadre of transplant physicians responsible for many of these gene marking/therapy protocols could help to provide much needed data that will better inform scientific and public policy in this important area of medicine. These are only some of the developments

that are likely to vouchsafe the continuing contributions of the Registry to blood and marrow transplantation. In looking back over the last few years, I realize that I have been very fortunate in witnessing from within, the dynamism, growth and maturation of the ABMTR. I have been truly honored and privileged to be the Chair and I thank all my colleagues and friends for their good natured, rigorous and unstinting efforts to move the field forward. In the challenging times ahead we will be very ably served by the leadership, already evident, of Julie Vose, the new ABMTR Chair.

Filipovich, Vose assume Registry chairs; Ringdén, Champlin named as chairs-elect – continued from page 1

Donna Reece for their past service on the ABMTR Executive Committee. Also, our gratitude goes to Dr. H. Grant Prentice and Dr. Patrick Stiff, for their service as IBMTR and ABMTR Nominating Committee Chairs, respectively.

We congratulate our new officers and look forward to working with them. We know we speak on behalf of all IBMTR and ABMTR participants when we express our gratitude for the time and effort these individuals have devoted to Registry activities. We also thank all IBMTR/ABMTR centers that gave their input in

determining the leadership of the Registries. We genuinely appreciate your continuing input and suggestions. Please see page 2 for perspectives on the ABMTR given by incoming Advisory Committee Chair, Julie M. Vose, MD and Immediate Past-Chair, Armand Keating, MD. The next Newsletter will feature perspectives on the IBMTR by incoming Chair Alexandra Filipovich, MD and Immediate Past-Chair John M. Goldman, DM. A complete listing of the membership of the IBMTR and ABMTR Executive Committees is shown on page 12, along with a listing of Statistical Center personnel.

Report from the second iwNST meeting – continued from page 1

1. **Update on tolerance and immunotherapy** – This included an entire day of presentations focusing on basic science issues relevant to NST. This session covered topics such as basic immunology of tolerance and transplantation tolerance, induction of immunoregulation and immunotherapy, effector cells of immunotherapy, and induction of self-tolerance in autoimmune diseases.
2. **Update on clinical experience with NST** – The second day included presentations from a dozen clinicians who summarized the NST protocols being studied at their respective hospitals and institutions, with details of the types of patients being treated, treatment outcome and associated toxicities.
3. **Protocol development sessions** – The final day of the meeting was dedicated to protocol development. The goal of the protocol development sessions was to encourage focused discussion among all the participants in the meeting, resulting in consensus on a number of possible trial protocols that could be initiated by them. Separate sessions addressed NST in myeloma, solid tumors, myeloid leukemias, lymphoid malignancies, and pediatrics / non-malignant disorders. The management of graft-versus-host disease (GVHD) in NST was also discussed.

This report summarizes the experience with NST in a variety of settings at both the Hadassah University Hospital and M.D. Anderson Cancer Center (MDACC), as reported at the workshop. Additionally, a summary of the protocol development sessions chaired by ourselves and others is included.

## Update on tolerance and immunotherapy

### Induction of transplantation tolerance by donor bone marrow cells

At the Hadassah Hospital conditioning for transplantation using no post-graft immunosuppression has been studied in mice. The regimen consisted of a short course (6 daily fractions of 200 cGy) of total lymphoid irradiation (TLI), followed by selective elimination of those donor-specific alloreactive cells of the host that have survived the low-dose TLI. Donor-specific alloreactive cells were activated by intravenous inoculation with a high dose ( $3 \times 10^7$ ) of donor bone marrow cells (BMC) 1 day after TLI, and eliminated by a single intraperitoneal dose (200 mg/kg) of cyclophosphamide given 1 day after cell transfer. Infusion of a low number of T-cell-depleted (TCD) BMC ( $3 \times 10^6$  cells) after this approach to tolerance induction converted recipients to stable mixed chimeras free of GVHD. This strategy allowed acceptance and life-long

survival of full-thickness donor skin allografts in mice if they achieved a mixed chimeric state with 20–50% donor cells in the blood. This suggests that, after TLI, additional selective clonal deletion of residual host cells can induce a state of long-lasting specific tolerance to a wide variety of donor-derived tissues.<sup>1</sup>

### Elimination of self-reactive lymphocytes – “graft versus autoimmunity” potential of NST and DLI

No specific therapy exists for autoimmune diseases caused by self-reactive lymphocytes (SRLs). However, as shown in animals and pilot clinical studies, SRLs can be eliminated using high-dose chemoradiotherapy, followed by autologous stem cell transplantation (SCT).<sup>2</sup> These SRLs may also be successfully eliminated using highly immunosuppressive but not necessarily myeloablative conditioning in conjunction with allogeneic SCT. An NST protocol including fludarabine 30 mg/m<sup>2</sup>/day x 6, anti-T-lymphocyte globulin (ATG) 10 mg/kg/day x 4, and busulfan 4 mg/kg/day x 2 resulted in elimination of all signs of autoimmunity (psoriasis and arthritis) in a patient with chronic myelogenous leukemia and severe systemic psoriasis and psoriatic polyarthritis.<sup>3</sup> This response of autoimmune disease manifestations via a “graft versus autoimmunity” (GVA) effect in parallel with the elimination of host-derived hematopoietic cells supports the hypothesis that autoimmune diseases caused by SRLs may be effectively treated by alloreactive elimination of the SRLs following induction of host-versus-graft tolerance. This approach is analogous to the replacement of malignant or genetically abnormal host cells following donor lymphocyte infusion (DLI) in patients having previously received an allogeneic transplant. It is therefore suggested that intentional GVA effects may be inducible by DLI following NST in recipients with life-threatening autoimmune diseases resistant to conventional modalities. Adoptive immunotherapy of autoimmunity may thus involve a two-step procedure: first, inducing host-versus-graft (HVG) and graft-versus-host (GVH) transplantation tolerance through a transient stage of mixed chimerism; second, inducing controlled GVA effects, initially by discontinuation of ciclosporin (CSA) and then, if indicated, by late outpatient DLI to eradicate residual hematopoietic cells of host origin.

## Update on clinical experience with NST

### The Hadassah experience in myeloid leukemias

The Hadassah Hospital uses an NST preparative regimen that consists of fludarabine 30 mg/m<sup>2</sup>/day x 6, busulfan 4 mg/kg/day x 2 and ATG 5–10 mg/kg/day x 4. Peripheral blood stem cells are

collected from related donors. Posttransplant immunosuppression of the host is with CSA from day -1 until neutrophil engraftment, when it is rapidly withdrawn. This approach has been used in over 120 patients with hematologic malignancies. In his presentation, Reuven Or focused on patients with acute myeloid leukemia (AML). To date, 23 patients with a median age of 33 years have been treated. Seventeen patients were in first CR, and 6 were in second CR. Twenty-one patients had an HLA-identical sibling donor, and the remainder a related donor who was a single-locus mismatch. Acute GVHD was a common problem with an incidence of 52% while patients were taking CSA and increasing to 78% once CSA was withdrawn after engraftment. The overall survival (OS) at one year was 48% and the disease-free survival (DFS) at one year was 46%.

Results in patients with CML were also presented. Twenty-one patients with CML in first chronic phase, median age of 35 years, received NST - 16 from HLA-matched siblings and 5 from matched unrelated donors. The interval between diagnosis and NST was a median of 9 months. The median time posttransplant to full hematopoietic engraftment was 21 days. Acute GVHD was again common in this patient population, 57% while taking CSA rising to 87% after CSA was discontinued following engraftment. The overall incidence of chronic GVHD was 60% after 15 months of follow-up. The addition of posttransplant methotrexate had no effect on the incidence of acute or chronic GVHD.

These data indicate that consistent and durable engraftment of donor hematopoietic stem cells and immunocompetent lymphocytes can be achieved following NST, with rapid replacement of host with donor cells. This initial experience supports the potential for NST to replace conventional BMT in some settings, potentially by reducing transplantation-related toxicity and mortality. Although associated with a low treatment related mortality, acute and chronic GVHD remain common complications that need to be addressed in future studies. Larger cohorts of patients and longer follow-up are required to assess the overall potential benefits of NST, which may be further improved by more effective and selective immunotherapy with specific immune donor lymphocytes. In time, randomized controlled trials will be required to definitively determine the place of NST in the management of these diseases.

**The M.D. Anderson Cancer Center experience in myeloid leukemia**

Sergio Giralt reviewed the MDACC experience with two NST regimens, FLAG-Ida and fludarabine + melphalan, in myeloid malignancies. In one study AML and MDS patients were treated if they were ineligible for a conventional allogeneic transplant due to age or comorbid disease. In all, 32 patients with a median age of 62 years (range 28-75) were treated. Twenty-six patients had AML and 6 a myelodysplastic syndrome (MDS). The median time from primary diagnosis to treatment was 10 months (range 1-49). Patients received the FLAG-Ida (fludarabine, high-dose cytarabine, idarubicin, G-CSF) preparative regimen pretransplant as previously reported.<sup>4</sup> At the time of transplant 9 patients were in first CR, 3 were in untreated first relapse, 4 were in second CR, and 16 had more advanced relapsed or refractory disease. As summarized in Table 1, the degree and rate of engraftment were similar to that seen with conventional allogeneic transplants. There were 4 cases of primary graft failure and 2 of late graft failure, all resulting in autologous reconstitution.

Toxicity was limited, with 1 treatment-related death and 2 acute GVHD-related deaths. The major problem was relapse, the rate of

Table 1. Engraftment after NST with Flag-Ida conditioning in AML/MDS patients

Count	recovery	n	median days (range)
ANC > 500 / $\mu$ L		28	14.5 (10-38)
platelets > 20,000/ $\mu$ L		25	18 (10-78)
platelets > 100,000/ $\mu$ L		17	27 (18-90)
Chimerism*		median % (range)	
Day +30		27	95 (0-100)
Day +90		23	83 (0-100)
Day +360		7	100 (0-100)

\*Chimerism assessment was performed on bone marrow aspirates

which was directly related to the status of disease at the time of transplant. For patients in first or second remission at the time of transplant the OS was 64% with a median follow up of over 18 months. For patients not in remission the OS was approximately 30% (Figure 1). Many of the patients who relapsed were successfully salvaged using a reduced-intensity regimen such as fludarabine + melphalan. DLI were not routinely given. These results are considered encouraging enough to warrant a randomized trial comparing this approach with conventional BMT.

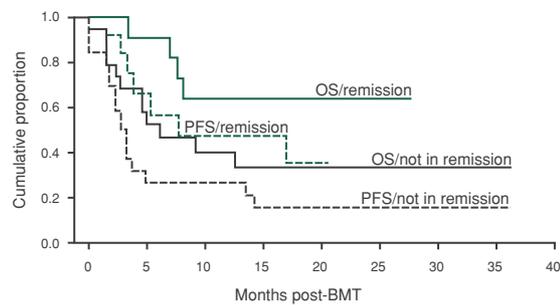


Figure 1. Survival, according to remission status at BMT, of AML/MDS patients treated with FLAG-Ida-based NST: OS, overall survival; PFS, progression-free survival

Flag-Ida was also used as the preparative regimen pre-NST for 13 patients with CML. The patients had a median age of 56 years (range 42-72 years) and the median time from diagnosis to transplant was 30 months. At the time of transplant 7 patients were in first chronic phase and 6 had more advanced disease. Of the 7 chronic phase patients, 4 achieved 100% donor cell engraftment, 2 patients reached 15% donor cell engraftment with subsequent autologous reconstitution and 1 patient did not have any evidence of donor engraftment. Thus, although in the setting of chronic phase CML it is possible to achieve donor cell engraftment with FLAG-Ida in some patients with a low incidence of non-relapse mortality, this approach is not sufficiently immunosuppressive to facilitate unrelated donor cell engraftment. The approximately 20% incidence of secondary autologous reconstitution in the related setting using FLAG-Ida also suggests that other non-ablative or reduced intensity conditioning regimens should be explored.

Since 1996, a reduced-intensity regimen consisting of fludarabine (25-30 mg/m<sup>2</sup>/day x 4-5 days) and melphalan (70-90 mg/m<sup>2</sup>/day x 2 days) (FM) has been studied in patients with AML or MDS. The results are summarized in Table 2.

The incidence of graft failure was low with no cases of secondary autologous reconstitution. Non-relapse mortality (NRM) was

Table 2. Outcome of patients with AML/MDS undergoing reduced intensity conditioning with fludarabine and melphalan at MDACC from 2/96 through 9/00

	6/6 HLA-matched sibling n = 31	6/6 HLA-matched unrelated donor n = 34
Median age, years (range)	53 (36-75)	55 (22-64)
Median time to treatment, months (range)	13 (1-38)	12 (2-176)
Reason for NST *		
Advanced age	12	15
Extensive prior Rx	13	11
Poor organ function	10	13
Median days to ANC > 0.5 x 10 <sup>9</sup> /L	14	16
Graft failure primary/secondary	1 / 0	1 / 0
Mean % donor chimerism day 30 / day 100	93.5 (n = 21) / 100 (n = 10)	93.5 (n = 21) / 100 (n = 13)
Acute GVHD II-IV / III-IV	19% / 10%	57% / 33%
Chronic GVHD	44%	64%
Non-relapse mortality @ 100 days / @ 365 days	17% / 23%	41% / 48%
OS / PFS at 18 months	36% / 34%	37% / 33%
OS / PFS at 18 months		All patients
If in remission at BMT		90% / 90%
If not in remission at BMT		26% / 23%

\* Patients may have more than one reason for NST  
ANC, absolute neutrophil count; OS, overall survival; PFS, progression free survival

moderate though reasonable for this older population of patients. NRM was low in patients in remission at the time of transplant. GVHD was the single most important complication in the unrelated-donor group. Grade 3-4 GVHD occurred in 33% of these patients. This degree of GVHD was a relatively rare occurrence in the patients with matched related donors (about 10%). As seen in other disease types the OS and progression-free survival (PFS) were directly related to the disease status at the time of transplant. To further improve results the anti-CD33 monoclonal antibody gemtuzumab ozogamicin (Mylotarg) has been added to the preparative regimen, and rapid immunosuppressive withdrawal followed by DLI has been applied in patients who do not develop GVHD by 90-180 days posttransplant and who were not in remission at the time of transplant.

The FM preparative regimen has also been studied in 39 patients with CML. Most of the patients had transformed disease, and the median age was 51 years. Thirty-six patients engrafted donor cells, 2 had autologous recovery and 1 patient did not recover their counts. Early or late mixed chimerism was a rare event, with most patients being 100% donor at 30 days and 6 months post-transplant. The study is continuing for patients in chronic phase. A phase I study using fludarabine + busulfan in patients with advanced disease is being considered.

These first generation studies have shown that the FLAG-Ida NST approach is feasible in older patients with AML, and in fact these studies do not have an upper age limit as part of the entry criteria. The results have been encouraging in patients who were in remission at the time of transplant, and a phase III study will be

starting shortly. The FLAG-Ida regimen in CML is less successful, with graft failure being a major problem. The fludarabine + melphalan regimen in patients with myeloid leukemias holds more promise, producing good engraftment and disease control in these initial studies. GVHD and relapse remain the main problems associated with this transplantation technique.

### The M.D. Anderson Cancer Center experience in lymphoid leukemias

Issa Khouri presented data on NST studies in patients with lymphoid leukemias at the MDACC. Patients were eligible for NST if they were > 50 years with or without comorbid disease and had disease beyond first remission. For patients with large-cell lymphoma, NST was given if a poor outcome was expected with autologous BMT or if they had failed prior autologous transplant. Different conditioning regimens were used for aggressive and indolent lymphomas. Patients with aggressive NHL were conditioned with cisplatin 25 mg/m<sup>2</sup>/day *ci* x 4 days (Days -6 to -3), fludarabine 30 mg/m<sup>2</sup>/day x 2 days (Days -4 and -3) and cytarabine 1 g/m<sup>2</sup>/day x 2 days (Days -4 and -3). Patients with indolent NHL received fludarabine 30 mg/m<sup>2</sup>/day x 3 days (Days -5 to -3), cyclophosphamide 750 mg/m<sup>2</sup>/day x 3 days (Days -5 to -3) and rituximab 375 mg/m<sup>2</sup> on Day -13 and 1000 mg/m<sup>2</sup> on Days -6, +1, and +8.

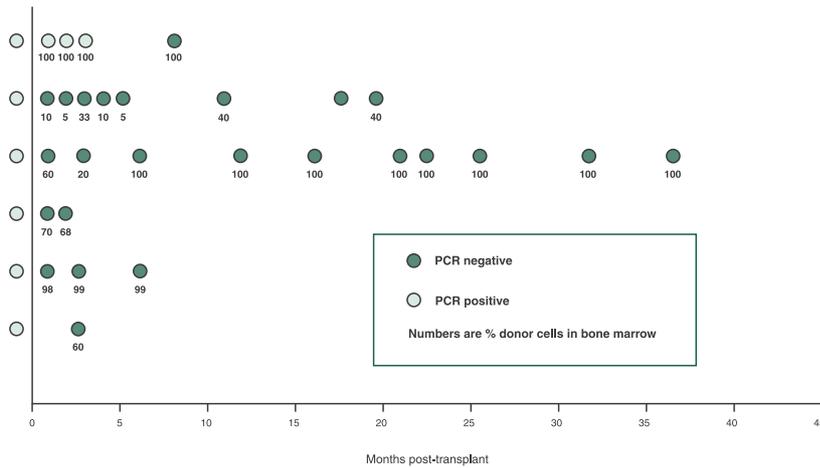
To date 57 patients with a median age of 55 years (range 21-73 years) have been treated including 5 patients who had received a prior autologous transplant. Twenty-five patients with aggressive histologies (13 DLCL, 5 mantle cell, 4 CLL with Richter's transformation and 3 others) and 32 with indolent B-cell disorders (20 FL/SLL and 12 CLL) were transplanted. The chemosensitivity of the patients at the time of transplant is shown in Table 3.

Table 3. Chemosensitivity of lymphoid malignancy patients at transplant

	Aggressive NHL n (%)	FL/SLL n (%)	CLL n (%)
Refractory	9 (36)	1 (5)	8 (67)
Sensitive	15 (60)	17 (67)	4 (33)
Untested	1 (4)	2 (10)	0 (0)

Of the 57 patients, 2 experienced primary and 2 secondary graft failure. Thirty days posttransplant, the median percentage of donor cells in the bone marrow was 50% (range 30-100%). Grade II-IV acute GVHD was seen in 10 patients (17.5%). Twenty patients (35%) developed chronic GVHD that was extensive in 12 patients (6 post-DLI) and limited in 8 patients. The 100-day mortality was approximately 3.5% (2 patients with follicular lymphoma died: 1 from GVHD and the other from infection at Day 35). After a median follow-up of 6 months (range 1-50 months), the OS was 63% and DFS was 54%.

Predictors of a good response were chemosensitive disease, early stage disease, and age < 55 years and no acute GVHD. All 5 patients who had previously received an autologous transplant were alive in remission 12 to 24 months post-BMT. The presence of the *bcl-2* rearrangement was studied pre- and posttransplant using PCR in 6 patients with follicular lymphoma. The patients were followed periodically, and all are now PCR negative (Figure 2). The transition from PCR positivity to negativity does not necessarily relate to the presence of 100% donor cells, and the response can be gradual, taking up to a year. These results led to the decision to base DLI administration not on mixed chimerism but on disease response. If patients are continuing to



**Figure 2.** PCR status, for *bcl-2* rearrangement, and chimerism in 6 patients who received NST for follicular lymphoma

recipients of MUD grafts and is therefore an attractive option for CML patients with unrelated donors. Further studies to confirm these initial results are required.

Our initial experience with haploidentical NST holds promise that this approach could successfully be applied to high-risk patients who do not have a matched sibling or MUD. As with other types of stem cell transplantation, the outcome is influenced by disease status, type of disease (non-malignant > CML > AML > ALL), age, cell dose, and immune factors. Transplant-related mortality is still high because mismatched transplants are usually reserved exclusively for high-risk cases. We are optimistic that by using such innovative, fludarabine-based transplantation procedures, the success rate may be increased to about 50% in young patients transplanted in good

have disease response they are followed without initiating DLI. It was agreed that for future studies that, as with traditional transplants, results need to be presented grouped by disease, as the response to NST varies between diagnostic groups.

**Hadassah experience with NST in unrelated and mismatched transplants**

Only 20–30% of patients have an HLA-identical sibling. Mismatched family or unrelated donors are a potential alternative although these approaches are currently limited by graft rejection and a high incidence and severity of GVHD. Intensified doses of chemotherapy are generally used in the unrelated setting to facilitate engraftment. The intensified conditioning results in a high frequency of transplant-related complications. It has been previously demonstrated that it is possible to achieve rapid and stable engraftment and low transplant-related organ toxicity with fludarabine + ATG based NST with matched related donors. This approach minimizes the intensity of the conditioning regimen while maximizing short-term immunosuppression and the GVL effect. We have treated 33 patients, median age 24 years with mismatched related or unrelated donors using the same regimen. Diagnoses were CML 11, AML 8, ALL 5, MDS 5, lymphoma 3 and solid tumor 1. Most patients (88%) achieved stable full chimerism. Toxicity was lower than is usually observed in patients receiving conventional transplants from matched related or unrelated donors. Nine patients (27%) experienced Grade III–IV acute GVHD, and 3 developed severe and extensive GVHD. The 42-month estimated OS was 45%, and the DFS was 40% with a median follow-up of 20 months. Fifteen patients died: 5 from relapse, 4 from GVHD, 3 from organ toxicity, 2 from infections and 1 from graft rejection. Engraftment and rates of full chimerism were similar to what is seen with traditional ablative allogeneic transplants from matched unrelated donors.

For CML, the most common indication for matched unrelated donor (MUD) transplant, the course of MUD transplants following fludarabine-based non-myeloablative conditioning does not appear to differ from that of transplants from fully ablative HLA-matched sibling donors. Fludarabine-based NST seems to enable engraftment with low transplant-related toxicity in CML

performance status, but this will need to be demonstrated in subsequent studies. In parallel with better patient selection, a focus of future research should be on developing strategies to improve post-grafting immune reconstitution, as late infectious or immune deficiency-related complications (e.g. second cancers) may become the critical factor for long-term success, after overcoming the rejection barrier and GVHD.

**Protocol development sessions**

The future development of NST relies on the coordination of large multicenter cooperative clinical trials to define the proper role for this approach. It also remains important for pilot studies testing new concepts to be carried out, but studies investigating minor variations in preparative regimens should not be pursued. Strategies to separate the GVH and HVG reactions are important and should focus on non-alloreactive transplants, specific immunotherapy, and enhancement of immune reconstitution. Phase III studies are required to prove the efficacy of NST and should be carried out in larger numbers of patients, have longer follow-up, and provide disease-specific results. Randomized phase II studies should be initiated to test alternative NST strategies while definitive phase III trials of non-ablative approaches versus standard therapy (ablative transplants or non-transplant treatments depending on the disease) should be pursued based on the most promising phase II results. In order to move the field forward as efficiently as possible, all patients receiving NST should do so on well designed clinical trials and all patients should be reported to one of the international blood and bone marrow transplant registries (IBMTR or EBMT). The ultimate aim of NST is to achieve engraftment, immune reconstitution and separation of GVH and graft-versus-malignancy reactions that will enable this novel approach to result in more patients being cured of their disease. This could be achieved by developing cellular immunotherapy specific for antigens of the target malignancy and major infections, and devoid of potential for GVHD. The consensus on useful studies that should be carried out presently is summarized below.

**GVHD prophylaxis** – The role for CAMPATH-1H either pre- or post-transplant needs to be elucidated. A pilot study using CAMPATH-1H pre-transplant as a strategy to reduce the incidence of acute GVHD is required.

**Myeloid leukemia** – A study comparing the fludarabine and busulfan regimen to fludarabine, busulfan and CAMPATH-1H (replacing ATG to reduce the incidence of GVHD) was of interest. In addition a comparison of fludarabine and cyclophosphamide (FC) versus fludarabine and busulfan could demonstrate whether there is a difference in effectiveness of these two regimens in the NST setting. There was significant interest in a trial of NST versus standard care in elderly patients with AML. The accrual of CML patients onto transplant studies may be affected for the foreseeable future by the increasing use of imatinib mesylate (STI571, Gleevec) in this indication.

**Lymphoid malignancies** – FC + rituximab should be studied as conditioning prior to transplant in patients with indolent lymphomas or CLL beyond first remission. Large-cell lymphoma is currently a more difficult indication to evaluate. Only pilot data exist, and more phase II data are needed before a consensus on the best approach can be reached. In Hodgkin disease the EBMT is active in investigating a number of preparative regimens. The results from these trials can be compared with historical controls to determine the potential of NST in this disease. Indolent B-cell disorders were also identified as an appropriate setting within which to compare existing different approaches to NST.

**Non-malignant diseases** – There was interest in investigating the use of fludarabine + busulfan for genetic diseases (considering higher doses of busulfan in pediatric patients), FC for severe aplastic anemia, or fludarabine + low-dose cyclophosphamide for Fanconi's anemia. Again, a study ± CAMPATH would provide data on the possibility of reducing GVHD.

**Multiple myeloma** – There was interest in comparing autologous transplantation with the tandem autologous–NST approach. A study comparing high-dose melphalan with high-dose melphalan

followed by NST would be useful. There was no interest in comparing different NST regimens in this setting at this time.

**Solid tumors** – There is a need for a series of phase II studies in a number of malignancies, as the data available to date are still relatively preliminary.

Participants were identified to lead the further development of these ideas with the goal of having two or more accruing multicenter trials in the area of NST by the time of the third iwNST meeting in 2002.

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## Non-myeloablative stem cell transplant trials at the IBMTR

The IBMTR has undertaken the coordination of two multicenter trials in non-myeloablative stem cell transplantation. Dr. Robert Collins of Texas Southwestern University and Dr. Christopher Bredeson of the IBMTR are co-PIs on the two trials, which are being conducted at approximately a dozen centers in the USA and Canada.

The first trial, "A phase II multicenter randomized study of two non-myeloablative stem cell strategies for low-grade lymphoma and chronic lymphocytic leukemia" randomizes patients to either fludarabine 30 mg/m<sup>2</sup>/day x 3 days + 200 cGy TBI with cyclosporine and mycophenolate mofetil (MMF) as posttransplant immunosuppression, or fludarabine 25 mg/m<sup>2</sup>/day x 5 days + cyclophosphamide 1 g/m<sup>2</sup>/day x 2 days with FK506 and methotrexate as posttransplant immunosuppression. DLI in escalating doses is reserved for patients experiencing disease progression posttransplant. The goal of this trial is to identify which regimen to bring into phase III trials against traditional myeloablative allogeneic transplants for this patient population. One hundred patients are to be randomized over the next year at the participating institutions.\* The trial is being supported by Schering AG, Amgen and Roche.

The second trial, "Low dose TBI and fludarabine followed by HLA matched allogeneic stem cell transplantation for hematologic malignancies – a multicenter study", uses the same fludarabine + TBI regimen approach of the randomized phase II trial but has different schedules for the tapering of posttransplant immunosuppression based on the perceived risk of relapse / disease progression of the different eligible disease groups. In low risk disease groups, immunosuppression is tapered by day +180 and DLI is reserved for disease progression as

in the randomized phase II trial above. For patients deemed at higher risk of relapse / disease progression, immunosuppression is tapered by day +90 and DLI can be initiated for failure to achieve a CR. One hundred patients in five disease groups are to be entered by the participating institutions\* over the next year.

Centers interested in referring patients for consideration or learning more about the trials can contact either Dr. Robert Collins ([Robert.Collins@utsouthwestern.edu](mailto:Robert.Collins@utsouthwestern.edu)) or Dr. Christopher Bredeson ([bredeson@mcw.edu](mailto:bredeson@mcw.edu)).

\* The following investigators and sites are participating in one or both of the above trials: Dr. Robert Collins, University of Texas Southwestern Medical Center, Dallas, Texas; Dr. Christopher Bredeson, Medical College of Wisconsin, Milwaukee, Wisconsin; Dr. Steven Goldstein, H. Lee Moffitt Cancer Center, Tampa, Florida; Dr. J.J. Iftikharuddin, Strong Memorial Hospital, Rochester, NY; Dr. Richard Maziarz, Oregon Health Sciences University, Portland, Oregon; Dr. Scott Rowley, Hackensack University, Hackensack, New Jersey; Dr. Mark Juckett, University of Wisconsin, Madison, Wisconsin; Dr. Thomas Kiss, Princess Margaret Hospital, Toronto, Ontario; Dr. Margarida Silverman, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Dr. Madhuri Vusirikala, Vanderbilt University Medical Center, Nashville, Tennessee; Dr. Neal Flomenberg, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; Dr. Robert Rifkin, Rocky Mountain BMT Program, Denver, Colorado; Dr. John Edwards, Walt Disney Memorial Cancer Institute, Orlando, Florida. Dr. Lothar Huebsch, University of Ottawa, Ottawa.

# Forbeck Forum discusses recommendations for clinical trials in hematopoietic stem cell transplantation

While laboratory advances have increased fundamental knowledge of transplantation and tumor biology and suggested strategies for improving transplant results, implementing and completing clinical trials that definitively test the efficacy of new transplant approaches has proven difficult. Regulatory and funding agencies, pharmaceutical companies and transplant physicians often have divergent perspectives and objectives that hinder achieving consensus on optimal approaches.

The *Forum on Planning and Conducting Clinical Trials* in Hematopoietic Stem Cell Transplantation held immediately following the recent Tandem BMT Meetings in February attempted to address these issues and provide recommendations for clinical trial design, adverse event reporting and analysis of transplant-specific outcomes. The *Forum* was sponsored by the William Guy Forbeck Research Foundation, which funds opportunities for small groups of leading scientists from a variety of disciplines to participate in an environment where they can freely exchange ideas and build on each other's knowledge, experience and insight, in the hope that they might shorten the cancer research timetable. Invited participants and observers at the February forum included representatives from the academic transplant community, the US Food and Drug Administration, the US National Institutes of Health, the American Society for Blood and Marrow Transplantation, the Foundation for the Accreditation of Hematopoietic Cell Therapy, the International Society of Hematotherapy and Graft Engineering, the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Autologous Blood and Marrow Transplant Registry. It was organized by Dr. James Gajewski (M.D. Anderson Cancer Center, Houston), Dr. Stephen Litwin (FDA, Rockville), Dr. Paul

Martin (Fred Hutchinson Cancer Research Center, Seattle) and Dr. Mary Horowitz (IBMTR/ABMTR Statistical Center, Milwaukee).

The *Forum* was quite successful in achieving its objectives, which included reviewing the current state of clinical trials in hematopoietic stem cell transplantation (HSCT) and the major obstacles to implementing and completing trials in a timely manner. Participants discussed clinical trial designs most likely to be successful in HSCT; streamlined systems for reporting adverse events that ensure patient safety but do not impose an excessive burden on clinical investigators; and strategies for achieving consensus on diagnosis and grading transplant-specific outcomes, particularly engraftment and graft-versus-host disease. These recommendations for clinical trial design, adverse event reporting and analysis of transplant-specific outcomes will be summarized by sub-committees organized to address each topic and submitted for publication. A short summary follows.

Recommendations from the Committee on Designing Clinical Trials in Hematopoietic Stem Cell Transplantation included: (1) enrolling patients as close to start of transplant therapy as possible to avoid high early drop-out rates; (2) striving for relatively homogeneous study populations to avoid unanticipated imbalances; (3) prospective planning for covariate adjustment and judicious use of stratification; (4) appropriate use of non-randomized controls in certain situations; (5) avoiding overly restrictive requirements for supportive care strategies not clearly related to the primary outcome; (6) stratification on center and appropriate strategies for detecting and adjusting for center effects; (7) use of appropriate and, often, multiple statistical techniques and monitoring strategies, that can accommodate competing risks, time-dependent effects and other posttransplant events.

The Committee on Reporting of Adverse Event Data in Transplant proposed a more efficient and effective method for reporting adverse event data in autologous or allogeneic marrow or peripheral blood hematopoietic stem cell transplant clinical trials. The Committee's recommendations included: (1) adoption of a standardized template of organ-specific severity scales, with allowances for ad hoc additions and modifications as needed for specific study drugs; (2) standardized definitions of causality relationships between study drug administration and adverse events; (3) modifications in the criteria for the definition of a severe adverse event; (4) calibrating the level of detail and time window in reporting adverse event data to the severity of the adverse event and its perceived relationship to study drug; (5) encouraging investigators to report adverse events as diseases or syndromes, wherever possible, instead of reporting individual component symptoms, signs, laboratory abnormalities and sequelae; and (6) exempting certain adverse events from mandatory reporting.

The Committee on Reporting Transplant-Specific Outcomes reviewed the current state of the art in diagnosis and grading of major transplant-related outcomes including engraftment, acute graft-versus-host disease (GVHD), chronic GVHD, and relapse. Deficiencies in current systems were discussed and specific studies proposed, particularly in the areas of GVHD. The Committee also recommended proposed changes to existing cell product standards. It was agreed that a series of future meetings, each focused on specific transplant-related outcomes, would be beneficial.

Plans are underway for future forums, the first to focus on diagnosing and grading acute and chronic GVHD.

## Committee on Designing Clinical Trials Addressing Issues in Hematopoietic Stem Cell Transplantation

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 John Wagner, MD, University of Minnesota, Minneapolis, MN

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### nbmtLINK patient care video available

The National Bone Marrow Transplant Link, a non-profit organization committed to reducing the burdens of those challenged by bone marrow / stem cell transplantation through education and support, has created a video to help prepare patients for what they will face when undergoing transplantation. The film, *The New Normal*, comes from the voices of six transplant survivors ranging in age and background, and from 2 to 10 years posttransplant. *The New Normal* hopes to help overcome patients' fears by giving them an idea of what to expect and provides information, inspiration and hope to patients and their caregivers. For more information on this complimentary video, please contact the National Bone Marrow Transplant Link at 20411 W. 12 Mile Road, Suite 108, Southfield, Michigan 48076, USA; telephone: 1-800-LINK-BMT (1-800-546-5268) or 248-932-8483; e-mail: nbmtlink@aol.com.

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For additional information on the Corporate Membership Program, please contact Lisa Schneider, Associate Director of Development, Tel (414) 456-8363, Fax (414) 456-6530.

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