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Bexxar®: novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma

By Julie M. Vose, MD

Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska
Chair, ABMTR Advisory Committee

Recent developments in the use of monoclonal antibodies (Mabs) to target malignant B cells have produced promising new therapies for low-grade or indolent non-Hodgkin's lymphoma (NHL). Investigators have targeted well-defined surface antigens on differentiated B cells, including CD20,[1] CD19,[2] CD22,[3] CD52[4] and human leukocyte antigen-DR,[5,6] with a variety of Mabs. CD20 is an excellent target for immunotherapy because it is not shed from the cell surface or internalized when bound by antibody, and it is expressed by nearly all B-cell tumors. When anti-CD20 antibodies bind to surface antigens, they induce apoptosis, antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cellular cytotoxicity (CDCC) of lymphoma cells.[7–10] Early studies with the chimeric anti-CD20 Mab rituximab produced favorable results in patients with relapsed, low-grade NHL. In the pivotal rituximab trial involving 166 patients, rituximab induced a 48% objective response (OR) rate, including a 6% complete response (CR) rate, and the median time to progression for responders was 13 months.[1] Although this study established the efficacy of Mab therapy in relapsed patients, the low CR rate indicated a need for other therapeutic advances. Therefore, studies combining chemotherapy with rituximab or utilizing radioimmunotherapy (RIT) with radionuclide-conjugated Mabs were pursued. The combination of rituximab with conventional CHOP chemotherapy demonstrated both safety and efficacy in patients with untreated or relapsed low-grade NHL.[11] Recent studies with RIT demonstrated higher response rates than those achieved with unconjugated antibodies.[1,12–15]

Radioimmunoconjugates investigated in patients with low-grade lymphoma,[16] include tositumomab, iodine-131 (^{131}I)-tositumomab (Bexxar®, GSK, Corixa Corp., Seattle, WA) and ^{90}Y-labeled Y2B8 (ibritumomab tiuxetan, Zevalin®, IDEC). This article reviews the efficacy and safety of Bexxar in patients with low-grade and transformed low-grade NHL, based on the cumulative clinical experience of the past 10 years.

Mechanism of action

RIT is a particularly attractive approach for treating NHL for several reasons: (i) lymphomas are among the most radiosensitive of all malignancies;[17,18] (ii) unlike total body irradiation, RIT deposits the greatest energy within the tumor, thereby limiting damage to normal tissues; (iii) radiolabeled anti-CD20 antibodies have multiple mechanisms of action. In addition to inducing apoptosis and mediating ADCC and CDCC, radiolabeled antibodies deliver cytotoxic ionizing radiation. Therefore, unlike unconjugated antibodies, radioimmunoconjugates can be effective when the host immune system is not fully functional, can destroy antigen-negative cells within tumors, and can overcome poor penetration of antibody into tumors. The high-energy beta particles emitted by ^{131}I are cytotoxic over distances of approximately 1–2 mm (average path length, 0.8 mm; maximum path length, 2.4 mm),[19,20] thus permitting eradication of antigen-negative tumor cells by crossfire from neighboring antibody-coated cells.[20]

Clinical pharmacology

The clinical pharmacology of ^{131}I is well suited to RIT. ^{131}I, which has a long track record and an excellent safety profile in the treatment of thyroid conditions, was the first radioisotope used for RIT because it is readily available and is easily conjugated to antibodies. Additionally, ^{131}I can be used for both imaging and treatment since it has dual emissions (both beta and gamma particles). Utilizing the gamma emissions, relatively simple dosimetry can be performed and used to calculate the clearance rate of the radionuclide in an individual patient, thus determining the patient-specific therapeutic dose. The half-life of ^{131}I (~ 8 days) is also well suited for RIT,[21] because it is similar to the half-life of murine antibodies in humans – when ^{131}I-labeled tositumomab is bound to CD20, the tumor receives high doses of radiation for several days. Another advantage of ^{131}I is the relatively short average path length of the beta emissions, which minimizes collateral damage to healthy tissue. As ^{131}I-conjugated antibody is metabolized, free ^{131}I metabolites are released into the bloodstream and rapidly excreted in the urine.[22–24] Free ^{131}I in the blood may be taken up by the thyroid; however, thyroid accumulation can be blocked by administering supersaturated potassium iodine (SSKI) solution before and during treatment. Nevertheless, thyroid dysfunction is observed in approximately 5% of patients receiving Bexxar therapy.

^{90}Y-labeled anti-CD20 antibodies are also used to treat lymphoma. Compared with ^{131}I, ^{90}Y has a shorter half-life and emits higher energy beta particles with a longer average path length. Other beta-emitting isotopes such as copper-67 (^{67}Cu) appear promising,[25] but their availability is limited. Therefore, in terms of half-life, path length, imaging capabilities and clinical utility, ^{131}I may have some advantages over other isotopes.

Detailed dosimetry studies conducted at the University of Michigan show that ^{131}I-tositumomab has a favorable tumor-to-normal-organ ratio. The dose-limiting toxicity (DLT) of Bexxar therapy, as for all RIT, is hematologic; therefore, the ratio of the absorbed radiation dose to bone marrow versus tumor is critical for determining therapeutic index. In several phase I and II studies of Bexxar, the absorbed radiation dose to bone marrow was approximately 10-fold lower than the dose to tumor. A phase I dose-escalation study determined the maximum tolerated total-body dose to be 75 cGy in patients with a platelet count ≥ 150,000/mm^3.[26] At this dose level, the absorbed dose to bone marrow was approximately 100 cGy. Most patients treated with 75 cGy had only mild-to-moderate myelosuppression 4–6 weeks after treatment, whereas 2 of 3 patients treated with a whole-body dose (WBD) of 85 cGy experienced grade 3/4 leukopenia and thrombocytopenia.[26]

Efficacy in the treatment of low-grade NHL

Three multicenter trials[12,27,28] demonstrated the efficacy of Bexxar in patients with relapsed or refractory low-grade or transformed low-grade NHL, and a single-institution study demonstrated efficacy in newly diagnosed patients.[13] In all of these trials, Bexxar produced high OR and CR rates;[16] many responses were of long duration.

In one multicenter phase II trial, 47 patients with histologically confirmed, CD20-positive, low-grade (79%) or transformed low-grade (21%) NHL were treated with Bexxar.[27] Median time from diagnosis to study entry was 41 months; median patient age was 49 years. All patients had previously received at least 1 chemotherapy regimen containing an anthracycline or anthracenedione, and all had failed to respond to or had relapsed within 1 year of their last chemotherapy. Most patients were heavily pretreated, with a median of 4 (range, 1–8) prior chemotherapy regimens. Administered therapeutic activity ranged from 45 to 177 mCi, to deliver a total body dose of 65 or 75 cGy. More than half (57%) of patients had a response to treatment, with a median response duration of 9.9 months; 32% had a CR with a median duration of 19.9 months.[27] Six patients remained in CR after a median of 50.8 months.[29]

A multicenter open-label trial was conducted in 60 patients with refractory low-grade or transformed low-grade NHL.[12] The patients were again heavily pretreated, with a median of 4 (range, 2–13) prior chemotherapy regimens, and a median time from diagnosis of 53 months. Thirty-eight percent had transformed low-grade NHL. All had failed to respond to or had relapsed within 6 months of their last qualifying chemotherapy (LQC). Following Bexxar therapy, the OR rate was 65% (intent-to-treat), with a median duration of 6.5 months; 20% achieved a CR. The OR rate and response duration achieved with Bexxar therapy were significantly greater than those achieved with the LQC (Table 1). Bexxar therapy was also associated with significant improvement in patient-assessed quality of life.[30] Histology, extent of prior therapy, prior radiotherapy, bone marrow involvement and tumor burden were all significantly associated with response.[12] Eighty-one per cent of patients with refractory low-grade NHL had an OR compared with 39% of patients with transformed low-grade NHL. The OR rate was 90% in patients who had received 2–3 prior therapies versus 53% in patients who had received 4 or more (p = 0.01).

Bexxar has demonstrated efficacy in patients failing rituximab or relapsing after initial response to rituximab. Among 40 patients with low-grade or transformed low-grade lymphoma, including 24 patients who failed to respond to rituximab, Bexxar therapy produced an OR in 68% (including 30% with a CR), with a median response duration of 14.7 months.[31]

Table 1. Response to Bexxar versus last qualifying chemotherapy (LQC) in the pivotal trial (n = 60)

	Bexxar	LQC	p value[a]
Overall response (%)	65	28	< 0.001
Median duration (months)	6.5	3.4	< 0.001
Complete response (%)	20	3	< 0.001
Median duration (months)	NR[b]	6.1	–

[a]McNemar's test for response, log-rank test for durations.
[b]NR = not reached after 47 months.
Data from Kaminski MS *et al*.[12]

The efficacy of Bexxar therapy was further supported by an expanded-access study involving 65 sites and 475 patients with relapsed or refractory NHL. A recent interim efficacy analysis of 394 patients evaluable for response showed a 59% OR rate and a 26% CR rate.[28] Median time to progression for responders was 18 months.

Transformation of low-grade lymphoma to more aggressive histology is associated with poor prognosis.[32] Data are available for 71 evaluable patients with transformed low-grade NHL who were treated with Bexxar in five trials.[33] Median time from diagnosis was 74 months (range, 8–334 months); median time from transformation was 21 months (range, 0–123 months). Median number of prior therapies was 4 (range, 1–11). Twenty-eight per cent of patients had bulky disease and 57% had elevated lactate dehydrogenase (LDH) levels. Treatment with Bexxar resulted in an OR rate of 39%, with a median response duration of 20 months; 25% had a CR with a median duration of 36.5 months.[33]

In a retrospective analysis of patients with poor prognostic features, data were collected from 70 patients aged > 60 years (median, 69 years; range, 61–82 years) with low-grade (66%) or transformed low-grade (34%) NHL treated in phase I–III trials from 1990 to 1999.[34] Thirty-one percent of patients had bulky disease (> 500 g). Treatment with Bexxar therapy resulted in an OR in 60% of patients, with a median duration of 9 months. Twenty percent of patients had a CR, with the median duration not reached after a median of 15 months' follow-up. A similar analysis of phase I–III clinical trials showed efficacy with Bexxar therapy in patients with poor prognostic factors, such as age > 60 years, bulky disease, elevated LDH or ≥ 4 prior chemotherapies (Table 2).[35]

Seventy-six patients with newly diagnosed advanced-stage follicular lymphoma were treated with Bexxar therapy in a phase II study at the University of Michigan. The OR rate was 95%; the CR rate was 74%.[36] Among 56 patients with a CR, 45 remained in CR from 30 to 66 months. Median duration of response and median progression-free survival had not been reached at a median follow-up of 43 months. At 5 years, 62% of patients remained free of progression. Bexxar is also currently being investigated as first-line therapy in combination with fludarabine in newly diagnosed patients with NHL.[37] Of 35 patients treated, all achieved an investigator-assessed response, and 27 (77%) achieved a CR. Median duration of response was not reached after a median follow-up of 23 months.

An analysis of the duration of responses to Bexxar demonstrated excellent durability of CRs in 269 evaluable patients with low-grade or transformed low-grade NHL treated from 1990 to 1999 and followed for a median of 1.5 years.[38] Within this population, 88 patients (33%) had a CR and 74 patients (28%) had a

Table 2. Rate and duration of objective response (OR) and complete response (CR) to Bexxar therapy in patients with poor prognostic features

Prognostic factor	OR rate (%)	OR duration (months)	CR rate (%)	CR duration (months)
Age > 60 years	62	9	21	NR
Bulky disease (> 500 g)	60	8	23	20
≥ 4 prior chemotherapies	60	7	24	19
Elevated LDH	62	6	20	36

NR = not reached; LDH = lactate dehydrogenase.
Data from Rohatiner A *et al.*[35]

confirmed CR (i.e. ≥ 2 assessments 4 weeks apart). Median CR duration was 3.25 years; median confirmed CR duration was 5 years. The median response duration was not reached in newly diagnosed patients, and previously treated patients had median CR durations ranging from 20 to 40 months.

Safety of Bexxar

RIT with Bexxar in patients with low-grade and transformed low-grade NHL was shown to be safe and effective in five separate clinical trials and in a multicenter expanded-access study.[14,27,28,39–44] All of these trials used dosimetry to determine the patient-specific therapeutic dose required to administer the maximum tolerated total body dose (75 cGy). Administration of a patient-specific therapeutic dose allows for greater uniformity of tumor dose with more predictable hematologic toxicity. This is critically important because total body residence times for the radiolabeled antibody can vary depending on tumor burden, bone marrow involvement and the presence of splenomegaly. In all of these trials, Bexxar therapy was well tolerated and hematologic toxicity was acceptable.

Bexxar treatment can be associated with infusion-related adverse events. The most common nonhematologic adverse events associated with Bexxar are shown in Table 3[43] and are typically mild-to-moderate in severity. In the multicenter phase II trial, Bexxar therapy infusions were well tolerated: 83% of patients had no infusion reactions and there were no grade 3 infusion reactions.[27] Only 4% of infusions required a rate adjustment.

The DLT of Bexxar treatment is bone marrow suppression.[27,39] Patients often develop mild-to-moderate transient neutropenia, thrombocytopenia or anemia; the incidence of grade 3/4 hematologic toxicity is generally 30–40%.[45] Nadirs typically occur at weeks 4–6, with recovery of neutrophil and platelet counts to grade 2 by week 8–9. Among 677 patients with low-grade or transformed low-grade NHL there was a fairly low incidence of grade 4 neutropenia (16%), thrombocytopenia (3%) and anemia (2%).[45] Median nadirs and time to nadir are shown in Table 4.[45] Twenty-three percent of patients required transfusions. Growth factor support, including filgrastim and erythropoietin, was required by 15% of patients. Hematologic toxicity was proportional to the extent of prior therapy. No previously untreated patients experienced grade 4 thrombocytopenia or anemia in this study, and only 5% had grade 4 neutropenia. Hematologic toxicity associated with Bexxar therapy has not been shown to correlate with the extent of bone marrow involvement.[46] Among patients with 20–25% bone marrow involvement, 50% had grade 4 neutropenia, and there was no grade 4 thrombocytopenia or anemia.

In a retrospective analysis of patients aged > 60 years, safety data were collected on 70 patients with low-grade (60%) or transformed low-grade (34%) NHL treated in phase I–III trials from 1990 to 1999.[34] Median age was 69 years (range, 61–82 years). Safety in this subgroup of patients was comparable to that in patients aged < 60 years. Subsequently, safety data were assessed for 269 patients aged > 60 years with low-grade (72%) or transformed low-grade (28%) NHL enrolled in multiple clinical trials, including the expanded-access study, from 1990 to 2000.[44] This analysis in a larger patient population demonstrated that Bexxar therapy is generally well tolerated in elderly patients and suggested that specific age-related dose adjustments are not required.

Table 3. Summary of most common nonhematologic toxicities in patients with low-grade or transformed low-grade non-Hodgkin's lymphoma treated with Bexxar in the expanded-access study (n = 359)[a]

	Grade (%)	
Adverse experience	1/2	3/4
Asthenia	20	3
Nausea	17	1
Fever	11	2
Pain	9	2
Rash	9	0
Chills	8	< 1
Headache	7	< 1
Arthralgia	6	1
Vomiting	6	1
Diarrhea	6	1
Myalgia	6	< 1
Pruritus	6	0
Increased cough	6	0

[a]Events occurring in > 5% of patients; all reported events.
Data from Schenkein DP *et al.*[43]

Potential long-term safety concerns include damage to the thyroid, development of human antimouse antibodies (HAMA) and secondary malignancies. All patients are treated with a thyroid-blocking agent to prevent the development of hypothyroidism. Elevated thyroid stimulating hormone (TSH) was observed in 5 (8.5%) patients in the phase I study, and 2 of these patients were placed on thyroid hormone supplementation.[27] In the multicenter expanded-access study, TSH elevation occurred in 3% of patients treated with Bexxar therapy.[28] The percent of patients who develop HAMA is related to the extent of prior therapy and has ranged from 0% to 8% in previously treated patients,[27,28] whereas 63% of previously untreated patients developed a HAMA response.[36] Although patients treated with Bexxar may develop HAMA, the immune response to tositumomab does not appear to have marked clinical consequences.

Hematologic and nonhematologic secondary malignancies are of concern with any radiation-based therapy. To date, at a median

Table 4. Summary of hematologic toxicity in patients with low-grade or transformed low-grade non-Hodgkin's lymphoma treated with Bexxar

Platelets	
Median nadir (cells/mm^3)	66,000
Median time to nadir (days)	33
Nadir < 10,000/mm^3 (%)	3
Neutrophils	
Median nadir (cells/mm^3)	1,200
Median time to nadir (days)	42
Nadir < 500 cells/mm^3 (%)	17
Hemoglobin	
Median nadir (g/dL)	11
Median time to nadir (days)	43
Nadir < 6.5 g/dL (%)	2

Data from Kaminski MS *et al.*[45]

follow-up of 1.5 years (range, 0–8.2 years) from the dosimetric dose, secondary myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) has been reported in 19 (3.1%) of 620 patients receiving Bexxar therapy.[47] These patients had received a median of 3 prior therapies, and median time from diagnosis to study entry was 45 months. This observed incidence of secondary MDS/AML following Bexxar therapy is consistent with the reported cumulative incidence in lymphoma patients 5–6 years after initial cytotoxic therapy.[48] A retrospective review of baseline bone marrow biopsies showed that five of these patients had evidence of MDS/AML at study entry, and chromosomal analysis at clinical diagnosis of MDS/AML revealed changes in chromosomes 5 and/or 7 consistent with alkylator-induced chromosomal damage in 11 of 12 patients tested. Moreover, none of the 76 newly diagnosed patients who have been treated with Bexxar therapy have developed MDS/AML at a median follow-up of 4.1 years (range, 0.7–6.3 years).[47] While longer follow-up is needed to determine the potential contribution of Bexxar therapy to the development of MDS/AML, none of the available data from multiple studies indicates that Bexxar therapy substantially increases the risk above what would be expected in a group of heavily pretreated lymphoma patients.

Dosing and administration of Bexxar

The complete course of therapy with Bexxar is carried out in two phases. First, patients receive a trace-labeled dosimetric dose, and dosimetry studies are conducted to establish the patient-specific therapeutic dose. Second, a single therapeutic dose is administered. With appropriate instructions, the patient can generally be treated on an outpatient basis.

The dose of Bexxar administered is calculated based on patient-specific variables. The delivered therapeutic dose is determined based on the clearance rate of the radiolabeled antibody from each individual patient (i.e. patient-specific residence time), which is affected primarily by the patient's lean body mass and tumor burden.[49] The therapeutic dose is then calculated to ensure that the patient receives a dose estimated to deliver a 75-cGy WBD (for patients with a baseline platelet count ≥ 150,000/mm^3). Patients with platelet counts of 100,000–149,999/mm^3 receive a WBD of 65 cGy. Bexxar is not recommended for patients with platelet counts < 100,000/mm^3. The actual amount of radioactivity administered to each patient is variable (ranging from 45 to 239 mCi), with a median of 81.8 mCi.[45]

Oral iodine supplements to block ^{131}I uptake by the thyroid gland are administered beginning 1 day before administering the dosimetric infusion and continuing for 2 weeks after the therapeutic dose. Patients are also pretreated with oral acetaminophen (650 mg) and either diphenhydramine (50 mg) or chlorpheniramine (4 mg) 1 h before each infusion of tositumomab to reduce infusion reactions to the antibody. A 60-min infusion of 450 mg unlabeled (i.e. cold) tositumomab is administered before administering the dosimetric dose on day 0 to improve biodistribution of the radiolabeled antibody. The dosimetric dose of ^{131}I-labeled tositumomab (5 mCi) is then administered via a 20-min infusion followed by a 10-min flush. The patient then undergoes three whole-body gamma camera counts (immediately postinfusion on day 0; on day 2, 3 or 4; and on day 6 or 7). Based on the calculated residence time of the antibody, a patient-specific therapeutic dose is calculated. Between day 7 and day 14, the patient will receive a 60-min infusion of 450 mg cold tositumomab followed by the therapeutic dose of ^{131}I-tositumomab via 20-min infusion plus a 10-min flush. Dosage adjustments are made for patients with low platelet counts (100,000–149,999/mm^3) and for obese patients (> 135% of ideal body weight).

Bexxar can safely be administered in an outpatient oncology clinic, although patients must have access to a nuclear medicine facility equipped to perform standard whole-body gamma camera counts. The radiation safety precautions followed during Bexxar administration are similar to those followed during standard radioiodine therapy; however, because the ^{131}I is conjugated to an antibody, the problems associated with the volatility of sodium iodide are minimized. It is recommended that the infusion equipment be dedicated exclusively for Bexxar use; however, under normal operating conditions, infusion pumps should not become contaminated. During the infusion, the ^{131}I-tositumomab is shielded and patients are usually isolated in a specially prepared room, access to which is restricted.

The release of patients administered Bexxar must be carried out in the US in compliance with federal and state regulations. In states that have adopted the Nuclear Regulatory Commission (NRC) regulations, patient release is carried out in compliance with NRC regulations specified in the Code of Federal Regulations 10 CFR Part 35 and Regulatory Guide 8.39, Release of Patients Administered Radioactive Materials.[50] These new regulations specify that patients can be released as long as the radiation doses to other individuals (e.g. family members) are not likely to exceed 500 millirem (mrem). Patient-specific release criteria that are consistent with federal regulations have been developed based on the total body residence time of the antibody (determined by serial gamma camera scans after administering the dosimetric dose) and the measured dose rate at 1 m in mrem/h (measured immediately after administering the therapeutic dose). With this information, a simple look-up table is consulted to determine whether the patient can be released. Most patients can be released immediately after administering the therapeutic dose.

NRC regulations state that the patient must be provided with clear, written instructions. These instructions advise patients on how close they can be to others and how they should conduct themselves and dispose of bodily wastes in order to minimize radiation exposure to others.[51] For example, patients are instructed to sleep in a separate bed (≥ 6 feet from others), not to take a long trip (≥ 4 h) during which they will be sitting near others, to maintain a safe distance (≥ 6 feet) from others, and to avoid contact with children and pregnant women. The duration of these restrictions is calculated on individual patients' residence time and dose rate at 1 m. For example, a patient with a residence time of 75 h and a dose rate of 10 mrem/h would be restricted to sleeping in a separate bed for 6 days, not taking long trips for 1 day and maintaining safe distances from children and pregnant women for 9 days. These patient release instructions have been validated by providing radiation-monitoring devices to caregiving family members of 22 patients who were treated with Bexxar and released.[52] Radiation exposure levels were monitored for 2–17 days after therapeutic dose administration, which ranged from 25 to 129 mCi in these patients. The radiation exposure to caregivers ranged from 17 to 409 mrem, with an average exposure of 144 mrem. This was well below the 500-mrem limit set by the NRC. These results indicate that patients treated with Bexxar can be released with confidence, that the instructions they are provided with are adequate and that the exposure of caregivers and family members is not likely to exceed 500 mrem.

A recent study estimated the radiation exposure of family members based on an analysis of 139 patients treated with Bexxar.[53] The mean activity administered to these patients was 84 mCi (range, 33–161 mCi), and the mean observed dose rate at 1 m was 10.9 mrem/h (range, 4–24 mrem/h). The estimated radiation exposure to maximally exposed family members and caregivers

ranged from 195 to 496 mrem. This study suggested that all 139 patients qualified for immediate release after Bexxar therapy.

Conclusions

RIT with Bexxar has been shown to be safe and effective for the treatment of indolent lymphoma. The advantage of Bexxar over conventional radiotherapy, chemotherapy and unconjugated antibodies is the ability to target a patient-specific dose of radiation to the tumor with minimal toxicity to normal organs. Clinical trials have demonstrated that Bexxar induces high OR and CR rates, and durable responses in relapsed and refractory patients, newly diagnosed patients and patients who failed rituximab. In relapsed and refractory patients, Bexxar produced superior response rates and durations when compared with patients' last chemotherapy and improved quality of life, thus providing a viable treatment option for patients who have become refractory to chemotherapy. Hematologic toxicity was generally short-term, predictable and manageable. It has also been demonstrated that Bexxar can be administered safely in the outpatient setting by following established and validated guidelines.

Future directions

Given the proven efficacy of Bexxar therapy in patients with relapsed and refractory low-grade NHL, it may play an important role as second-line therapy in patients who have failed prior chemotherapy, rituximab or both. High response rates and durable responses have also been demonstrated in patients with transformed low-grade NHL, suggesting that Bexxar could potentially be effective in the treatment of aggressive lymphoma. Its role as first-line therapy for indolent lymphoma has yet to be defined. However, several cooperative group trials are investigating Bexxar therapy in combination with chemotherapy in newly diagnosed patients. Based on the encouraging results of SWOG trial S9911, an intergroup trial has been initiated to compare CHOP plus rituximab versus CHOP plus Bexxar therapy for follicular lymphoma. A myeloablative ^{131}I-tositumomab regimen with stem-cell support is also being actively investigated and appears promising. In this setting RIT has advantages over total-body irradiation and is less toxic than many preparative chemotherapy regimens. The role of RIT for the treatment of indolent lymphoma will undoubtedly continue to evolve.

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2004 Tandem BMT Meetings –

the combined annual meetings of the International Bone Marrow Transplant Registry/Autologous Blood & Marrow Transplant Registry (IBMTR/ABMTR) and the American Society for Blood and Marrow Transplantation (ASBMT)

By D'Etta Waldoch, CMP

You are invited to attend the 2004 Tandem BMT Meetings, February 13–17, at the Coronado Springs Resort in Orlando, Florida, USA, where the attire is casual and the science is not.

Each year these comprehensive educational meetings bring together hundreds of BMT clinicians, investigators, laboratory technicians, clinical research associates, data managers, nurses, pharmacists, BMT center directors and administrators and other allied health professionals from around the world. The Chairs for the 2004 Scientific Program are Richard Champlin, MD (Houston), Robert Negrin, MD (Stanford) and Olle Ringdén, MD, PhD (Stockholm).

In addition to 5 days of scientific and clinical meetings there are six related events: BMT Pharmacists Conference, February 12–13; Clinical Research Associates Data Management Conference, February 12–14; FACT Training Workshops, February 12; BMT Center Medical Directors Conference, February 13; BMT Center Administrators Conference, February 14–15; and the Oncology Nursing Society Conference, February 15–17.

The 2004 Tandem BMT Meetings agenda and registration forms, hotel reservations form, and abstract submission program (abstract deadline October 20, 2003) are available online at the IBMTR/ABMTR (www.ibmtr.org) or ASBMT (www.asbmt.org) Websites.

Attendees may also contact Coronado Springs Resort directly for guestroom rates of $138 single or double occupancy, through January 12, 2004 (after which rooms are not guaranteed and can only be reserved if available). Mention the "Tandem BMT Meetings" when you talk to the Group Reservations Department at 407-939-1020, or send an e-mail to wdw.cgr@disney.com.

Advance Registration (through October 20) for MD and/or PhD Members of IBMTR/ABMTR and ASBMT is $450; Standard Registration (after October 20, but before January 30, 2004) is $550. Reduced fees are available for physicians-in-training, and other allied health professionals. Late Registration includes a $100 surcharge, applied to all on-site registrations and those received after January 30, 2004. (More information available online.)

For general information, please e-mail the conference office at: bmtmeetings@cs.com; questions regarding conference registration may be directed to Patty Vespalec, Conference Registration Manager at 414-456-4261 or patty@mcw.edu; questions regarding support opportunities at the 2004 Tandem BMT Meetings may be directed to Jane Rebro at 414-456-4254 or janer@mcw.edu.

The Medical College of Wisconsin (MCW) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. MCW designates this educational activity for a maximum of 43.75 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Report on state of the art in blood and marrow transplantation –

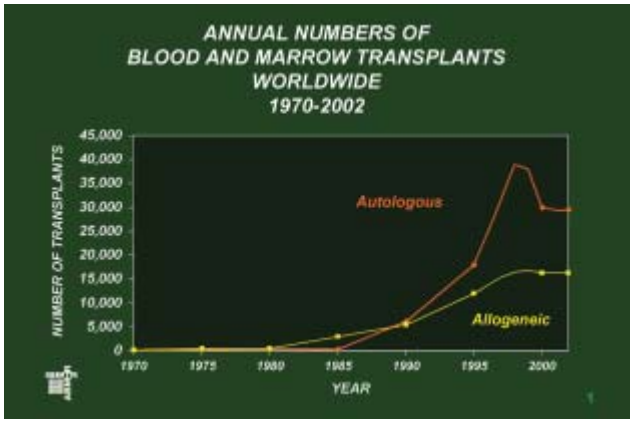
Part I of the IBMTR/ABMTR summary slides with guide

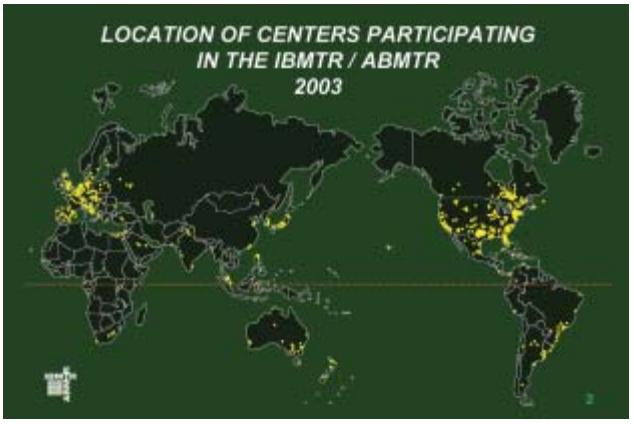
This issue of the IBMTR/ABMTR Newsletter brings you Part I of our annual report on the "State of the Art" in hematopoietic stem cell transplantation (HSCT). Using data submitted by our participating centers, this report summarizes current use and outcomes in HSCT. The report is written by Dr. Fausto Loberiza who joined the Statistical Center in 1998 from the University of Iowa, where, in additional to his clinical training, he received an MS in Biometry and Preventive Medicine. Dr. Loberiza's research interests focus on issues of access to healthcare and the impact of sociodemographic factors on treatment outcomes. He was recently awarded a grant from the U.S. Agency for Healthcare Research and Quality to study center effects in HSCT.

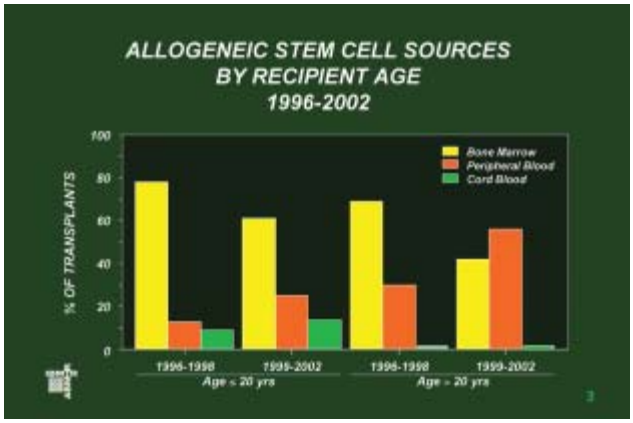
Part I of this report focuses on trends in the use of HSCT – indications, recipient age, graft sources and transplant regimens. Part II, which will appear in the next issue of the newsletter, will summarize outcomes of transplants focusing on survival and disease-free survival. The annual report, distributed widely though our Website (www.ibmtr.org), this newsletter and a compact disc provided free of charge to participating centers, represent a part of the Statistical Center's effort to made the data contributed by IBMTR/ABMTR centers accessible to the transplant community. We hope you find it useful, and welcome suggestions to make future editions even better.

Summary slides 2003

By Fausto Loberiza, Jr, MD, MS



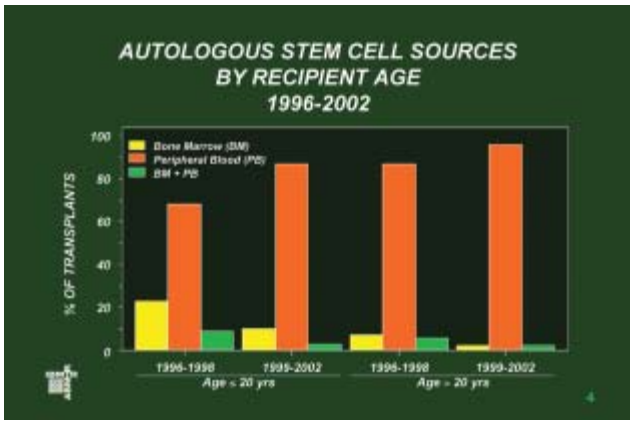


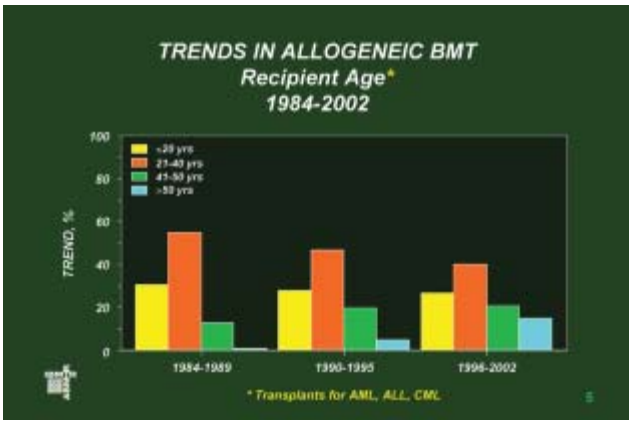


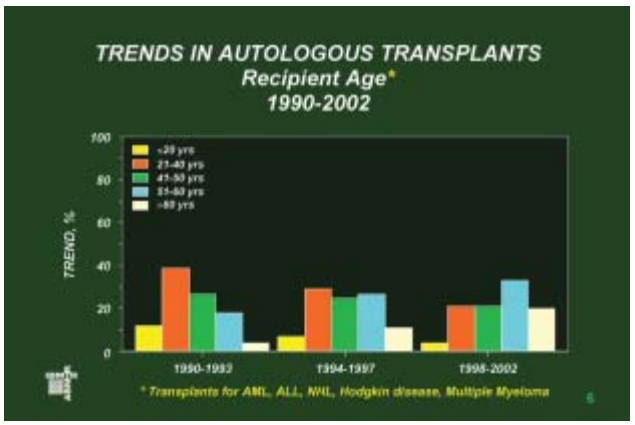
Slide 1: Estimates of the annual numbers of blood and marrow transplants worldwide extrapolated from data compiled by the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), independent market surveys, U.S. hospital discharge data and data reported to the IBMTR. The past few years has seen a slowing in the growth of both autologous and allogeneic transplants. The drop in autotransplants was due to a decrease in their use for breast cancer. The flattening in growth for allotransplants results from a decrease in their use for chronic myelogenous leukemia. Use of allotransplants for other indications continues to increase.

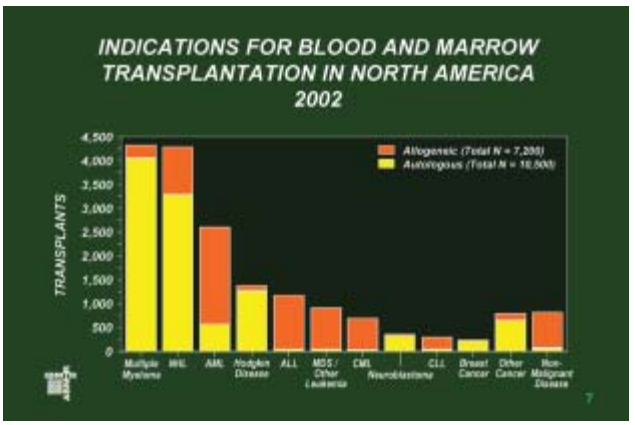
Slide 2: Currently, 458 centers participate in the IBMTR/ABMTR.

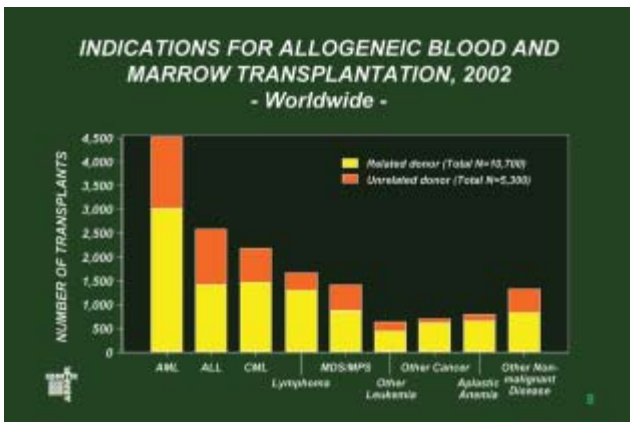
Slide 3: Traditionally, allogeneic transplantation used bone marrow grafts. From 1999 to 2002, there was a steady increase in the use of peripheral blood stem cell grafts; this is now the predominant type of graft used in adults. Among children, use of umbilical cord grafts also increased significantly during this time period, though such grafts still account for < 20% of allotransplants.

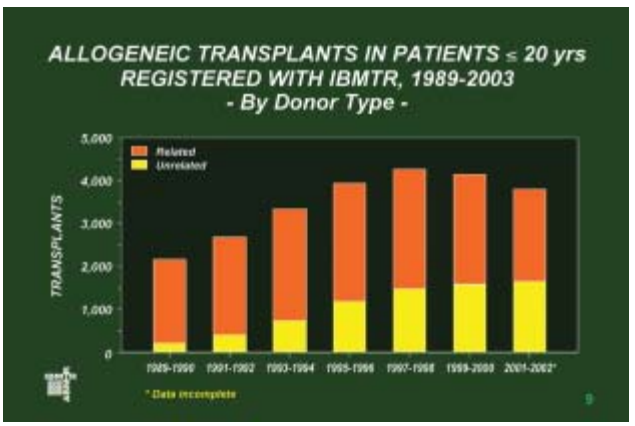












Slide 4: Over 95% of autotransplants in adults and 85% in children use peripheral blood stem cell grafts.

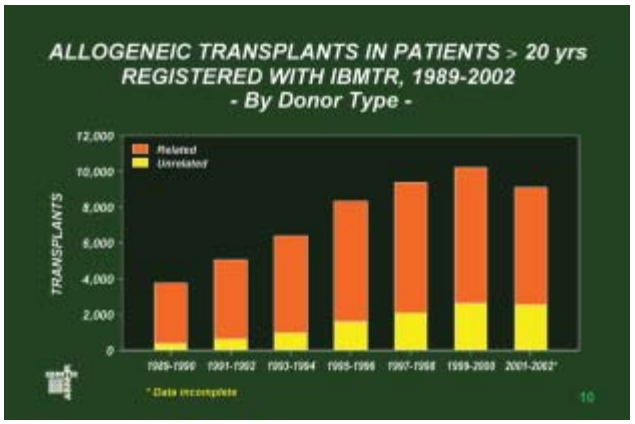
Slides 5 & 6: Both allo- and autotransplants are increasingly used in older patients. Improvements in supportive care and innovations to decrease regimen-related morbidity and mortality may be responsible for this trend. Thirteen percent of allograft recipients and 53% of autograft recipients are older than 50 years. Two percent of allograft recipients and 20% of autograft recipients are older than 60 years.

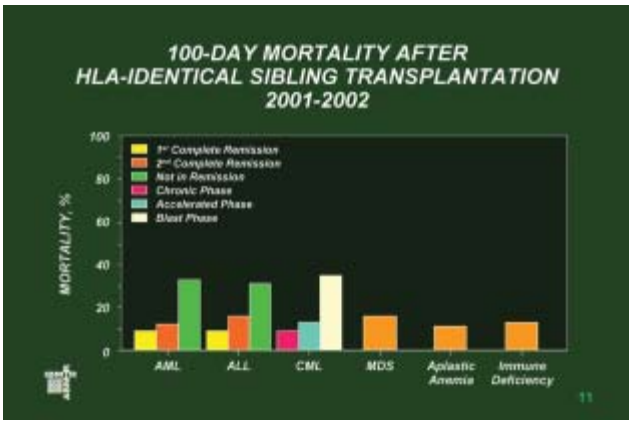
Slide 7: More than 9,000 of the 10,500 autotransplants performed in North America in 2002 were for multiple myeloma or lymphoma. Of the 7,200 allotransplants performed in 2002, more than 5,000 were for leukemia or myeloproliferative diseases.

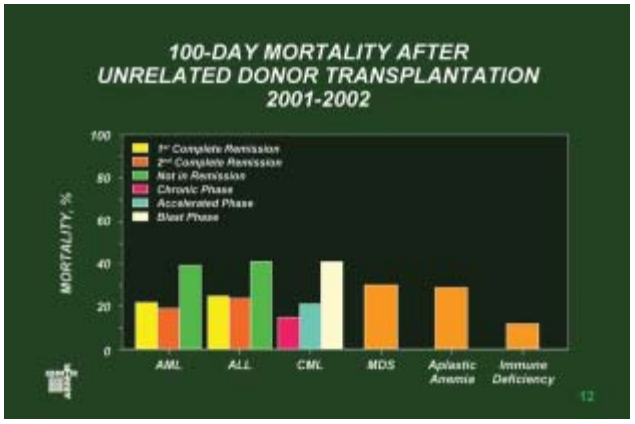
Slide 8: About one-third of allogeneic transplants are from unrelated donors. Indications are similar for related and unrelated donor transplantation.

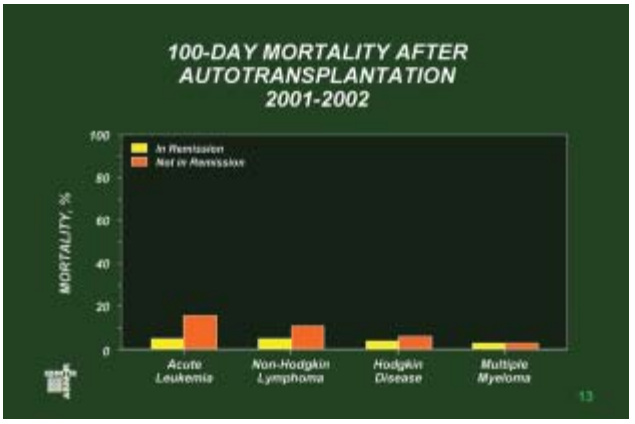
Slides 9 & 10: The proportion of allotransplants from unrelated donors increased steadily over the past decade likely due to the increased availability of donors and the results of studies suggesting that outcomes with unrelated donors are similar to those with HLA-identical sibling donors, especially in younger patients.

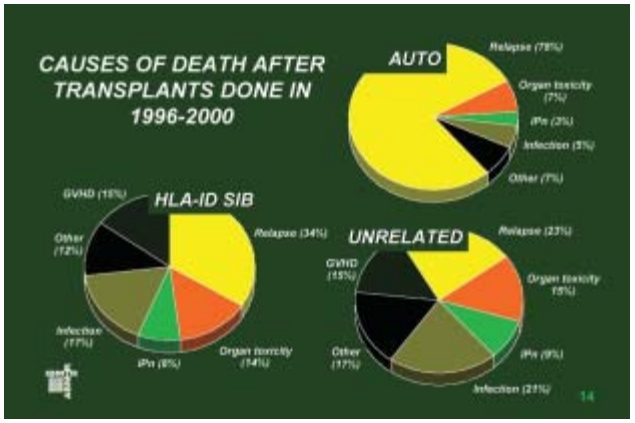
Slides 11 & 12: 100-day mortality rates are often used as a gauge of transplant-related toxicity. Death in the first 100 days following allotransplantation is most commonly due to graft-versus-host disease (GVHD), infections or multi-organ dysfunction. HLA-identical sibling transplants, in general, are associated with lower 100-day mortality rates than are unrelated donor transplants. The











stage of the disease at transplantation also influences 100-day mortality. For instance, the 100-day mortality rate after a HLA-identical sibling transplant for early leukemia is 10–15% compared with about 20–30% following a transplant for advanced leukemia.

Slide 13: Early mortality is lower after autotransplantation than after allotransplantation. As with allotransplants, risk correlates with disease stage at transplantation.

Slide 14: Recurrence of primary disease accounts for the overwhelming majority of deaths after autotransplantation. Infection, interstitial pneumonitis and multi-organ dysfunction account for a relatively larger percentage of deaths after allotransplantation. GVHD is a significant cause of mortality in both the related and unrelated allotransplant settings.

continued on page 10

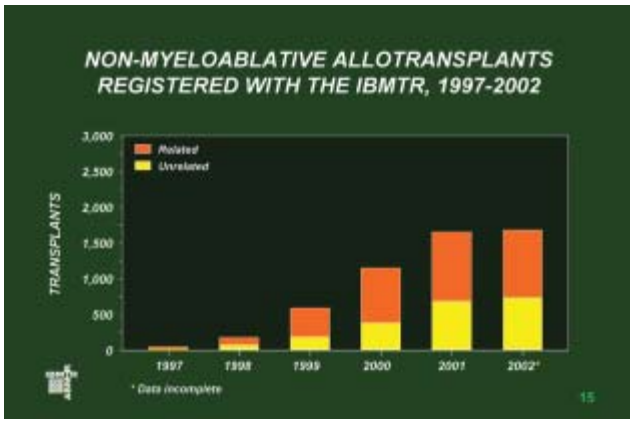
Data Management Conference

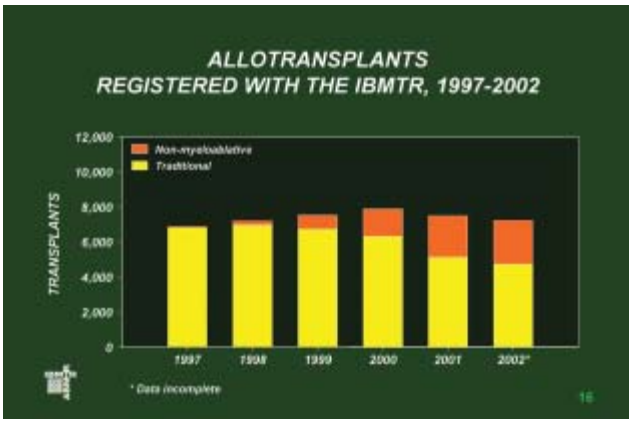
One hundred thirty-three attendees registered for the 2003 Fall Clinical Research Professionals/Data Management (CRP/DM) Conference, September 5–7, at Embassy Suites in Brookfield, WI. This year, members of the BMT Clinical Trials Network were encouraged to attend concurrent training sessions for clinical trials that will soon be enrolling patients.

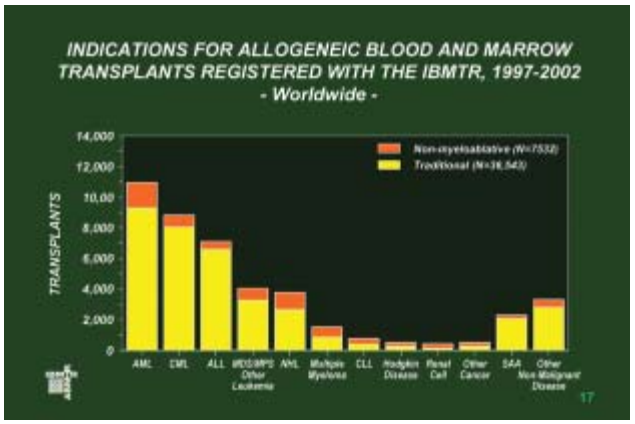
A session on IBMTR/ABMTR data management professionals helping each other was made possible by the CRP/DM Mentoring Committee, who opened the meeting by introducing a new Web-site and online newsletter specifically for CRP/DMs. The Website can be accessed from a link on www.ibmtr.org or directly to the site, www.datamanager.blogspot.com. IBMTR staff presented the sessions on reporting issues. Dr. Dennis Confer from the National Marrow Donor Program (NMDP) explained the complexities of HLA typing, Wendy Kaiser and Terry Zacharias from the Medical College of Wisconsin led sessions on consent issues under HIPAA and BMT insurance reimbursement.

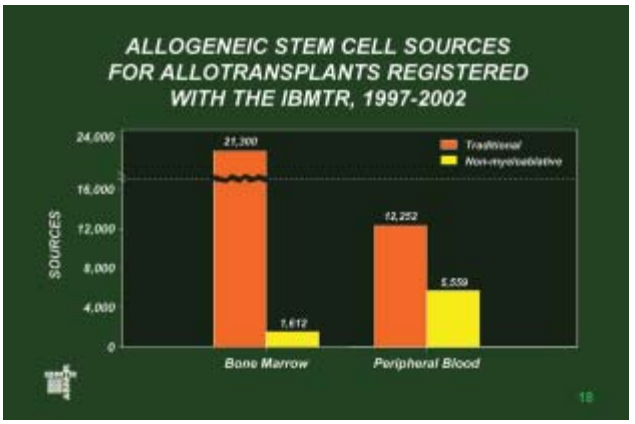
The emphasis for the Fall Conference was on understanding the basics of efficient accurate data collection. The CRP/DM workshop at the Tandem Meetings, February 12–14, 2004, will begin with basics on the first day and expand to more detailed, useful tips and tools for collecting and managing data. It will also focus on specific HSCT topics, clinical trials and Inserts for the Report Forms on days 2 and 3. We look forward to seeing you in Orlando in February!

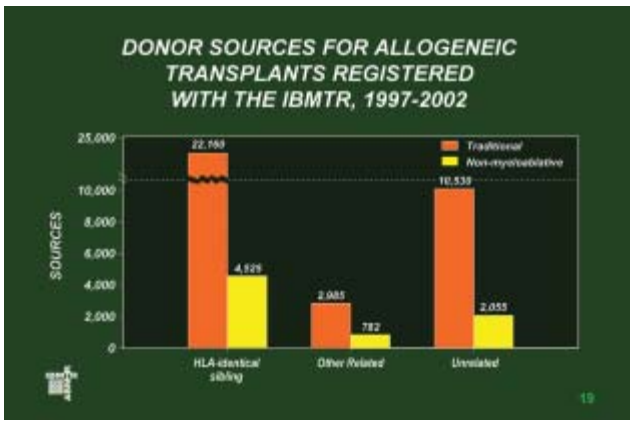
continued from page 9

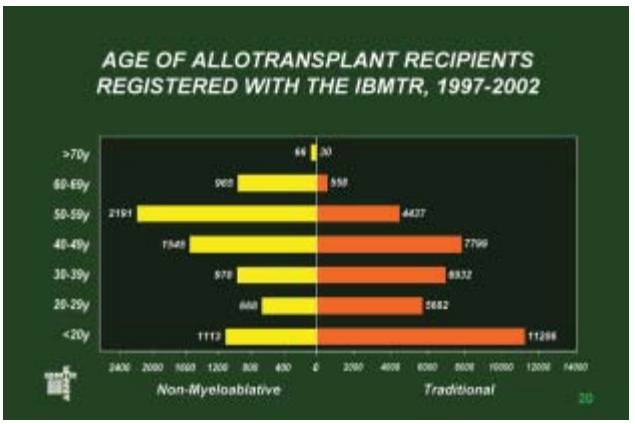












Slides 15–17: Since 1997, a rapidly growing number of allotransplants have been carried out using non-myeloablative or reduced-intensity conditioning regimens. Most non-myeloablative transplants are for acute or chronic leukemias, non-Hodgkin's lymphoma and multiple myeloma.

Slides 18–20: Compared with traditional myeloablative transplants, non-myeloablative transplant strategies are more likely to use peripheral blood stem cell grafts. Most non-myeloablative transplants have used related donors. Recipients of non-myeloablative transplants tend to be older than recipients of traditional transplant regimens; few non-myeloablative transplants have been carried out in children.

Outcomes of transplantation for the most common indications will be illustrated in the next IBMTR/ABMTR newsletter.

Obituary

Robert A. Good, MD, PhD, 1922–2003

Robert A. Good, MD, PhD, a pioneer in bone marrow transplant, considered by many the founder of modern cellular immunology, has died at the age of 81 years.

Dr. Good was a pediatrician, microbiologist and pathologist who gained international recognition in a long and spectacular career that included one of the first successful human bone marrow transplants in 1968. A native of Minnesota, Dr. Good was 6 years old when his father died of cancer. From then on he wanted to become a physician and pursue research that would cure disease. He began teaching at the University of Minnesota in 1944, where he earned his MD and PhD degrees. He drew national recognition in 1962 when he identified the thymus as the primary source of the body's defense mechanisms at the annual meeting of the Federation of American Societies of Experimental Biology (FASEB).

Dr. Good's discoveries helped establish that immunodeficiency diseases are not rare, as once thought, but a frequent and very important basis of serious disease in mankind. His studies led to the recognition and demonstration of the T-cell and B-cell arms of the immune system and the development of useful methods of bone marrow transplantation. In 1965 he reported evidence that tonsils, widely regarded as useless, actually had an important function in developing the immune defense systems in mammals, including young humans, and he advised that they should be removed only if involved in a serious health problem.

Dr. Good was recruited to Memorial Sloan-Kettering Cancer Center in 1973 as President and Director of the Sloan-Kettering Institute and Director of Research at Memorial Hospital. During his tenure Sloan-Kettering became one of the original eight institutions recognized by the National Cancer Institute as a Comprehensive Cancer Center. Since 1983, Dr. Good served as Physician-in-Chief

Dr. Robert A. Good, a founding member of the IBMTR, at a dinner in honor of the late Dr. Mortimer M. Bortin, the IBMTR's first Scientific Director.

at All Children's Hospital in St. Petersburg, Florida, and was at the time of his death Distinguished Research Professor at the University of South Florida in Tampa.

Dr. Good received numerous awards and recognition during his 55 years in medical research. He was a founding member of the National Institutes of Medicine. He was author, co-author or editor of more than 2,000 papers and book chapters, and trained hundreds of students in immunology. At the 2000 Tandem BMT Meetings in Anaheim, he presented the ASBMT's annual E. Donnall Thomas Lecture.

Dr. Good was one of the founding members of the IBMTR and a strong supporter of the IBMTR's research program throughout his life. Dr. Good made many contributions to the IBMTR/ABMTR over the past 30 years, as a contributing team leader, a co-author on numerous IBMTR publications between 1983 and 1996, and a member of the Scientific Advisory Committee. In honor of his significant role in the development of the organization, the IBMTR Scientific Advisory Committee elected him as a Councillor and Charter Member in 1989. He will be remembered with respect, affection and gratitude.

Foundation and corporate support of the IBMTR/ABMTR

Thanks to the many contributors who have joined our international collaboration for research in blood and marrow transplantation. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Allergy and Infectious Disease; the Agency for Healthcare Research and Quality and the generosity of the following supporters:

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Statistical Director

Ruta Bajorunaite, PhD
Biostatistician

Christian Boudreau, PhD
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Biostatistician

J. Douglas Rizzo, MD
Associate Scientific Director

Kathleen A. Sobocinski, MS
Associate Statistical Director

Mei-Jie Zhang, PhD
Associate Professor / Biostatistician

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Please address correspondence to:

IBMTR/ABMTR Statistical Center
Medical College of Wisconsin
8701 Watertown Plank Road
PO Box 26509
Milwaukee WI 53226, USA

Telephone: (414) 456-8325
Fax: (414) 456-6530
E-mail: ibmtr@mcw.edu

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DARWIN GREY COMMUNICATIONS
Sterling House,
Kingston Bagpuize,
Oxfordshire, OX13 5AP, UK

Claudia A. Abel
Sr. Data Coordinator

Sarah C. Anderson
Program Coordinator I

Jessica Attwood
Staff Assistant

Kavita P. Bhavsar
Data Coordinator

Kevin Cao
Sr. Research Associate

Mita K. Desai
Data Coordinator

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Research Assistant

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Hongyu Tian, MS
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D'Etta Waldoch, CMP
Associate Director, International Programs

Wendy Zhang
Data Coordinator

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