Graft Failure Following Bone Marrow Transplantation for Severe Aplastic Anemia: Risk Factors and Treatment Results

By Richard E. Champlin, Mary M. Horowitz, Dirk W. van Bekkum, Bruce M. Camitta, Gerald E. Elfenbein, Robert Peter Gale, Eliane Gluckman, Robert A. Good, Alfred A. Rimm, Ciril Rozman, Bruno Speck, and Mortimer M. Bortin

Graft failure was analyzed in 625 patients receiving allogeneic bone marrow transplants from HLA-identical sibling donors as treatment for severe aplastic anemia. Sixty-eight (11%) had no or only transient engraftment. Second bone marrow transplants were successful in achieving extended survival in 16 of 27 patients with transient initial engraftment but in none of ten patients with no sign of engraftment after the first transplant. The major factors associated with a reduced risk of graft failure were use of radiation for pretransplant immunosuppression and use of cyclosporine rather than methotrexate or T-cell depletion of the donor bone marrow for prophylaxis against graft-versus-host disease (GVHD). Among 266 patients prepared for transplantation with cyclophosphamide alone, the risk of graft failure was increased in patients who received previous transusions and reduced in those who received corticosteroids for previous therapy. Neither cell dose nor administration of donoruffy coat cells affected the probability of engraftment. Although use of radiation in conditioning reduced graft failure, survival was not improved. Posttransplant treatment with cyclosporine and avoidance of pretransplant blood transfusions were associated with improved survival.

Bone marrow transplantation is an effective therapy for severe aplastic anemia and is generally considered the preferable treatment for young patients who have an HLA-identical sibling donor. Recent studies report 55% to 80% extended survival. Factors associated with graft failure and the efficacy of various immunosuppressive regimens in preventing this complication were investigated in this study.

Materials and Methods

Results of allogeneic bone marrow transplantation were analyzed in patients with severe aplastic anemia receiving bone marrow transplants at 98 centers worldwide from January 1978 through December 1986 and reported to the International Bone Marrow Transplant Registry. Six hundred twenty-five of 657 consecutive patients who received transplants from HLA-identical sibling donors and who survived ≥21 days were considered evaluable for engraftment. An additional 19 patients who received transplants from identical twins were analyzed separately. Criteria for the diagnosis of severe aplastic anemia have been previously described.

Graft failure was defined as either (a) primary graft failure, ie, absence of hematologic recovery in patients surviving ≥21 days posttransplant; or (b) transient engraftment, ie, complete or partial recovery of hematopoiesis of donor origin followed by recurrent pancytopenia with a markedly hypocellular bone marrow in the absence of moderate to severe acute graft-versus-host disease (GVHD).

Statistical analysis. Actuarial probability of graft failure was calculated using standard life-table methods. Life-table curves were terminated when fewer than three patients were at risk of graft failure. Univariate analyses were used to test associations between patient and treatment variables and the probability of graft failure using the Lee-Desu statistic. Factors associated with the risk of graft failure in these univariate analyses with a P value ≤.10 were entered into a multivariate Cox proportional-hazards model using a forward stepwise approach. Variables significantly associated with the probability of graft failure in multivariate analysis were examined for their association with survival using a Cox proportional-hazards model adjusted for patient age. Because of the multiple comparisons made, only variables which improved the model with P < .01 were considered statistically significant. P values between .01 and .05 were considered marginally significant and are presented to show trends. Relative risks of graft failure and mortality for patients with unfavorable as compared to those with favorable risk factors are derived from the multivariate models and are adjusted for the effect of all other significant variables. Relative risks for mortality are also adjusted for patient age. Because of the very low incidence of graft failure observed in irradiated patients, separate univariate and multivariate analyses were performed on the 266 patients who received cyclophosphamide alone for conditioning.
Unless otherwise specified, all $P$ values are based on the results of the multivariate analyses.

All multivariate analyses were examined for a possible center effect, i.e., differences among centers not explained by identifiable patient and treatment differences using the following methods: entering transplant team into the regression model as a categorical covariate; stratifying the regression model by transplant center; repeating the analysis after exclusion of each of the seven largest centers; and dividing patients according to whether they were transplanted in centers reporting <20 and those reporting >20 patients. The relative risks and $P$ values associated with each of the prognostic variables were similar with and without these adjustments.

**RESULTS**

*Characteristics of patients, donors, and treatments.* Data from 384 males and 241 females surviving ≥21 days after transplant were analyzed for factors associated with graft failure. Pretransplant patient characteristics are summarized in Table 1. Median age was 19 years (range 1 to 56 years) for recipients and 20 years (range 1 to 59 years) for their HLA-identical sibling donors. Donor and recipient age were highly correlated ($r = .82$). The median duration of aplasia was 2 months (range 1 to 158 months) at the time of transplantation. The etiology of aplastic anemia was idiopathic in 464 (74%) patients, drug/toxin related in 74 (12%), hepatitis related in 63 (10%), and associated with other causes in 22 (4%). Two hundred seventy patients were maintained in laminar airflow isolation, and 349 were maintained in conventional protective isolation.

All patients received pretransplant immunosuppressive treatment with cyclophosphamide, usually 50 mg/kg for four days; 266 patients received no additional pretransplant therapy, and 25 received additional chemotherapy such as procarbazine and/or antithymocyte globulin. Three hundred thirty-four patients received cyclophosphamide plus radiation, including 121 who received total body irradiation (TBI) 3.0 to 12.0 Gy (median 3.0 Gy), and 213 who received limited-field (total lymphoid or thoracoabdominal) radiation, 1.5 to 18.0 Gy (median 6 Gy).

Posttransplant immune suppression to prevent or modify GVHD consisted of methotrexate in 288 patients, cyclosporine in 206, cyclosporine and methotrexate in 24, methotrexate and other drugs in 50, cyclosporine and other drugs in 35, T-cell depletion in ten, corticosteroids alone in three, and no prophylaxis in nine patients. Among recipients of T-replete transplants, the median dose of bone marrow cells was 3.3 (range 0.4 to 13.0) $\times 10^8$/kg recipient body weight.

**Graft failure.** Graft failure occurred in 68 (11%) of the 625 patients with an actuarial probability of 13% ± 3% (95% confidence interval) at 5 years. Nineteen of 68 (28%) patients had primary graft failure (failed to show any sign of engraftment), and 49 (72%) patients had transient engraftment with loss of the graft 3 weeks to 3 years (median 11 weeks) posttransplant. Outcome differed for patients with no engraftment and those with transient engraftment (Table 2).

Seven of the 68 patients survived with full or partial recovery of host hematopoiesis. All seven cases occurred in the group of 49 patients who had transient engraftment after

### Table 1. Characteristics of Patients, Donors, and Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (yr)</td>
<td>19</td>
<td>1-56</td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>20</td>
<td>1-59</td>
</tr>
<tr>
<td>Interval diagnosis-transplant (mo)</td>
<td>2</td>
<td>1-158</td>
</tr>
<tr>
<td>No. of pretransplant transfusions</td>
<td>22</td>
<td>0-163</td>
</tr>
<tr>
<td>Performance rating pretransplant (%)</td>
<td>80</td>
<td>10-100</td>
</tr>
<tr>
<td>Unmanipulated cell dose ($\times 10^8$/kg body wt)</td>
<td>3.3</td>
<td>0.4-13.0</td>
</tr>
</tbody>
</table>

*Includes 24 patients who received androgens + corticosteroids + antithymocyte globulin.
†Includes ten patients who received androgens + antithymocyte globulin.
‡Includes 12 patients who received corticosteroids + antithymocyte globulin.
§Includes 14 patients who received antithymocyte globulin.
[]Median.
†Range.
#Includes total lymphoid, total nodal, and thoracoabdominal radiation.
Thirty-four patients and 27 patients with transient engraftment received a subsequent transplant. The median interval between the first and second transplant was 2.6 months (range 0.9 to 31 months). Ten patients with primary graft failure (no engraftment) after the first transplant; none of the 19 patients with primary graft failure died with aplasia as the primary or contributing cause of death for a case-fatality rate of 54%. The mortality rate owing to graft failure was 6% for the 625 patients studied.

Three patients who did not meet the study criteria for graft failure also received a second transplant. All had partial hematopoiesis in the setting of GVHD. Two died of acute GVHD and interstitial pneumonitis; one is alive with full recovery of hematopoiesis, extensive chronic GVHD, and a Karnofsky performance score of 80% ten months after the second transplant.

Risk factors for graft failure. Variables significantly associated with graft failure in multivariate analysis of the 625 patients surviving ≥21 days are shown in Table 3. It was not possible to distinguish factors associated with primary graft failure v transient engraftment. The most important risk factor was whether or not the preparative regimen included radiation (Fig 1A). The 290 patients who were not given radiation had an increased risk of graft failure in comparison with the 334 patients who received radiation.

Table 3. Variables Analyzed for Their Association With Graft Failure and Shown to be Significantly Associated With Graft Failure in Analysis of All Patients Transplanted for Severe Aplastic Anemia or Patients Transplanted After Conditioning With Cyclophosphamide Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Relative Risk of Graft Failure (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning regimen</td>
<td>Radiation</td>
<td>No radiation</td>
<td>3.2 (1.8-5.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Drug to prevent GVHD</td>
<td>CsA ± other*</td>
<td>MTX ± other</td>
<td>2.1 (1.2-3.4)</td>
<td>&lt;.008</td>
</tr>
<tr>
<td>T-cell depletion</td>
<td>No T-cell depletion</td>
<td>T-cell depletion</td>
<td>10.8 (3.5-34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients prepared with cyclophosphamide alone</td>
<td>Pretransplantation therapy of aplasia</td>
<td>Corticosteroids ± other drugs</td>
<td>2.5 (1.2-5.2)</td>
<td>&lt;.007</td>
</tr>
<tr>
<td></td>
<td>&lt;40</td>
<td>≥40</td>
<td>2.9 (1.5-5.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>&lt;40</td>
<td>≥40</td>
<td>2.9 (1.5-5.8)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Includes regimens containing both MTX and CsA; Cl, confidence interval; CsA, cyclosporine; MTX, methotrexate.
Risk factors for graft failure in patients receiving cyclophosphamide alone. Because the markedly reduced incidence of graft failure in association with preparative regimens that included radiation may have obscured findings that would help our understanding of other mechanisms of graft failure, data for the 266 patients prepared with cyclophosphamide alone were analyzed separately. Variables associated with the risk of graft failure in this group are shown in Table 3.

Two pretransplant variables were significantly associated with the risk of graft failure. Patients whose aplastic anemia was not treated with corticosteroids prior to referral for transplantation had an increased risk of graft failure as compared with those who had received corticosteroids (relative risk 2.5, \( P < .007 \), Fig 2A). Increasing numbers of pretransplant transfusions were associated with an increased risk of graft failure, with risk increasing continuously (relative risk 1.01\( ^n \), where \( n \) = number of units transfused, \( P < .007 \)) and with patients who received the largest number of transfusions having the highest risk (Fig 2B). Posttransplant immunosuppressive therapy also was significantly associated with the risk of graft failure. Patients receiving methotrexate had a higher risk than those receiving cyclophosphamide (relative risk 2.3, \( P < .008 \), Table 3). Because only one patient in this subgroup of 266 patients received T-cell--depleted bone marrow, the effect of T-cell depletion could not be evaluated.

Among patients receiving cyclophosphamide alone for pretransplant immune suppression, the probability of graft failure decreased significantly over the course of the study. For the patients transplanted in the years 1978 through 1980, the 3-year probability of graft failure was 31\% \pm 12\% for patients transplanted after 1980 it was 16\% \pm 6\% (univariate \( P < .005 \)). This change coincided with a significant decrease in the use of methotrexate and a corresponding increase in the use of cyclophosphorine to prevent GVHD (univariate \( P < .0001 \)). There was no significant change in the median number of transfusions received or the type of drugs used to treat severe aplastic anemia over this time period. After adjustment was made for the difference in drugs used as prophylaxis against GVHD, the probability of graft failure was not significantly different in the earlier and later years of the study.

Factors not associated with the risk of graft failure. Factors which were not significantly associated with graft failure are presented in Table 4. Within the range available for testing, higher bone marrow cell doses were not associated with better engraftment; however, >95\% of patients received \( \geq 2.0 \times 10^8 \) cells/kg body weight. Whether cell doses lower than these would be associated with graft failure is unknown. Use of laminar airflow isolation, infusion
of donor buffy coat cells, and donor-recipient sex-match did not significantly affect the probability of stable engraftment in the entire series or in the subgroup prepared with cyclophosphamide alone. Prior treatment with antithymocyte globulin was not associated with the probability of graft failure.

Relationship between risk factors for engraftment and mortality. Each of the factors significantly associated with an increased risk of graft failure was studied for its association with GVHD, interstitial pneumonia, and survival. Overall, patients treated with methotrexate rather than cyclophosphamide to prevent GVHD had a significantly higher incidence of interstitial pneumonia (21% vs 10%, univariate $P < .0009$), and a higher risk of mortality posttransplant (relative risk 1.6, $P < .0009$). The incidence of moderate-to-severe acute GVHD and chronic GVHD was similar whether methotrexate or cyclosporine was used. Only one of six patients who engrafted after transplantation with T-cell–depleted marrow developed acute GVHD; none developed chronic GVHD; two developed interstitial pneumonia. The relative risk of dying was increased after T-depleted as compared with T-replete transplants, but this was not statistically significant (relative risk 1.5, $P > .10$). In comparison with irradiated patients, patients conditioned with cyclophosphamide alone had a lower incidence of moderate-to-severe acute GVHD (36% vs 45%, univariate $P < .03$), a similar incidence of chronic GVHD, and a lower incidence of interstitial pneumonia (12% vs 21%, univariate $P < .004$). The risk of mortality was not higher for nonirradiated as compared with irradiated patients (relative risk 0.99, $P > .10$).

Among the 266 patients prepared for transplantation with cyclophosphamide alone, patients receiving methotrexate to prevent GVHD had an incidence of acute GVHD, chronic GVHD, and interstitial pneumonia similar to that of patients receiving cyclosporine. Patients receiving methotrexate had a higher risk of mortality posttransplant that was marginally significant (relative risk 1.6, $P < .03$). Greater numbers of pretransplant transfusions were not associated with the incidence of acute GVHD, chronic GVHD, or interstitial pneumonia. Patients who received $\geq 40$ transfusions pretransplant had a higher risk of dying than those who received $<40$ (relative risk 1.2, $P < .01$). Pretransplant treatment with corticosteroids was not associated with GVHD, interstitial pneumonia, or survival.

Although not associated with the probability of engraftment, use of buffy coat transfusions posttransplant was associated with an increased incidence of moderate-to-severe acute GVHD (48% vs 38%, univariate $P < .05$), and chronic GVHD (45% vs 36%, $P < .07$), and an increased risk of mortality (relative risk 1.4, $P < .05$).

Identical twin transplants. Nineteen patients received transplants from identical twin donors. Six received pretransplant immune suppression with cyclophosphamide
alone (four patients) or cyclophosphamide plus TBI (two patients). All six are alive and well with sustained engraftment 12 to 92 months after transplantation. Thirteen of the 19 patients initially received bone marrow infusion without pretransplant or postransplant immune suppression. Four of 13 had full hematopoietic recovery and are alive 11 to 50 months after transplantation. Nine of 13 had either no (two patients) or transient (seven patients) engraftment and received a second transplant; one of the nine received a third transplant. Prior to the second transplant, all patients received immune suppression. Six received cyclophosphamide alone, two received cyclophosphamide plus radiation, and one received nitrogen mustard. Twelve of the 13 multiple transplant recipients are alive with full recovery of hematopoiesis five to 79 months after transplantation. One patient died of Aspergillus pneumonia 3 weeks after the second transplant; she had full erythroid and granulocytic recovery but still had severe thrombocytopenia at the time of death.

DISCUSSION

This analysis examined the incidence and clinical consequences of graft failure following bone marrow transplantation for aplastic anemia and identified risk factors associated with this complication. Since it is generally not possible to discern the mechanism of graft failure in a given patient, it was operationally defined in this analysis as occurring in patients who survived >21 days but either failed to show any recovery of hematopoiesis or had engraftment manifested by partial or full hematologic recovery followed by recurrent aplasia in the absence of moderate to severe acute GVHD.

Frequently graft failure after HLA-identical sibling transplants is assumed to result from immunologic rejection directed at donor minor histocompatibility antigens. Other mechanisms may be responsible for graft failure as well, such as abnormalities of the recipient microenvironment, inhibition of hematopoiesis by infection, or nonimmune mechanisms. Data from identical twins reported in this article and elsewhere support the concept that host immunologic reactions against histocompatibility alloantigens on the transplanted bone marrow cells are not the sole mechanism for graft failure.

Graft failure occurred in 68 of 625 evaluable recipients of HLA-identical marrow transplants. Of 19 patients with no sign of engraftment, none survived despite attempts at further immunosuppressive preparative treatment and retransplantation in ten of the 19. The clinical condition of patients who fail to engraft is highly precarious. They tolerate further intensive immunosuppressive treatment poorly and often succumb to drug toxicity, infections, or other complications before engraftment can occur. Patients with transient engraftment have a better prognosis with second transplants; 16 of 27 are surviving six to 96 months after the second transplant, and their actuarial survival is 59% ± 20% at 3 years. Second transplants were reported by the International Bone Marrow Transplant Registry in 1976 to be successful in four of 12 (33%) patients and, in a more recent study by Storb et al,22 in six of 16 (38%) patients with graft failure after transplantation for aplastic anemia.

Analysis of the entire group identified no pretransplant patient or donor characteristic that was significantly associated with graft failure. Various therapeutic interventions were associated with a reduced risk of graft failure, although some may lead to an increased likelihood of other complications, as shown in Table 5.5,8,12,14,15,24

Pretransplant immunosuppressive regimens of cyclophosphamide plus radiation resulted in a significantly lower rate of graft failure as compared with cyclophosphamide without radiation. This is particularly notable since many centers reserve radiation therapy for transfusion-sensitized patients believed to be at highest risk for graft failure. Posttransplant immunosuppressive treatment also had an impact on graft failure. Patients receiving cyclosporine-containing regimens had a significantly lower rate of graft failure and a higher rate of survival as compared with patients receiving methotrexate with or without drugs other than cyclosporine. Methotrexate did not adversely affect engraftment when combined with cyclosporine. These data are in accord with preliminary reports suggesting that cyclosporine enhances engraftment,24 although the possibility that methotrexate inhibits engraftment cannot be excluded.

For patients prepared with cyclophosphamide alone (ie, without radiation or other drugs), pretransplant transfusions were important; untransfused patients had a lower risk of graft failure than transfused recipients and the risk increased progressively with large numbers of transfusions. Patients who received >40 U blood or blood products had a risk of graft failure significantly greater than those who received 20 to 40 U and patients who received no transfusions had the lowest risk. This finding is in agreement with the reports by Storb et al14 and Deeg et al15 showing that in patients prepared with cyclophosphamide alone, pretransplant blood transfusions increase the risk of graft failure. In contrast to their findings and data in animals,25 no significant association was found between engraftment and bone marrow cell dose. Storb et al14 reported an increased risk of graft failure in patients receiving low doses of bone marrow cells14; based on their data, most centers have attempted to use high cell doses. The cell doses used in this study were relatively high and may have been above some critical threshold value needed for engraftment. We found no evidence that use of Buffy coat transfusions decreases the risk of graft failure.

### Table 5. Results of Therapeutic Interventions on Transplant Outcome in Patients With Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rejection</th>
<th>Interstitial Pneumonia</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Methotrexate rather than</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>cyclosporine to prevent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>T-cell depletion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple transfusions pre-</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids pretransplant</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffy coat infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Increased (↑), no change (—), decreased (↓).
*Among patients not receiving radiation for conditioning.
A trend toward a higher probability of engraftment in recent years was observed in patients conditioned with cyclophosphamide alone. This can be accounted for by the increasing use of cyclosporine to prevent GVHD. Other treatment and/or patient variables associated with this trend were not identified. Changes in blood transfusion practices or other unidentified factors may also have contributed to the reduced rate of graft failure.

Previous treatment with corticosteroids prior to referral for transplantation was associated with a lower incidence of graft failure. The explanation for this finding is unclear. The interval between diagnosis of aplastic anemia and transplantation was not identified. Changes in blood transfusion practices or increasing use of cyclosporine to prevent transplant-related complications may have facilitated engraftment by this mechanism.26

These data point to several modes of treatment associated with a reduced incidence of graft failure. In conjunction with information regarding some measures that may improve the outcome of bone marrow transplantation for aplastic anemia. Cyclosporine-containing regimens appear to have an advantage over methotrexate. If possible, transfusions should be withheld or minimized prior to initiation of the immunosuppressive preparative regimen, especially if regimens without radiation are to be used.

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APPENDIX 1

This 54th report from the International Bone Marrow Transplant Registry was prepared for the members of the Advisory Committee: Robert F. Gale, MD, PhD, University of California, Los Angeles; Chairman; Kenny Atkinson, MD, St Vincent’s Hospital, Sydney, Australia; Fritz H. Bach, MD, University of Minnesota, Minneapolis; A John Barrett, MD, MRC Path, Westminster Hospital, London; Dirk W. van Bekkum, MD, PhD, Radiobiological Institute TNO, Rijswijk, The Netherlands; James C. Biggs, MD, PhD, St Vincent’s Hospital, Sydney, Australia; Karl G. Blume, MD, City of Hope National Medical Center, Duarte, CA; Mortimer M. Bortin, MD, Medical College of Wisconsin, Milwaukee; Karel A. Dicke, MD, PhD, D. Anderson Hospital and Tumor Institute, Houston; Gosta Gahrton, MD Karolinska Institute, Stockholm; Eliane Gluckman, MD, Hôpital Saint-Louis, Paris; John M. Goldman, MD, Royal Postgraduate Medical School, London; Robert A. Good, MD, PhD, all Children’s Hospital, St Petersburg, FL; Werner Helbig, MD, Karl Marx Universities, Leipzig, GDR; Roger H. Herzog, MD, Cleveland Clinic; Richard Hong, MD, University of Wisconsin, Madison; John H. Kersey, MD, University of Minnesota, Minneapolis; Hans-Jochem Kolb, MD, University of Munich; Alberto M. Marmont, MD, Ospedale San Martino, Genoa, Italy; Tohru Masaoaka, MD, Center for Adult Diseases, Osaka, Japan; Hans A. Messner, MD, PhD, Ontario Cancer Institute, Toronto; Richard J. O’Reilly, MD, Memorial Sloan-Kettering Cancer Center, New York; Ray L. Powles, MD, Royal Marsden Hospital, London; Alfred A. Rimm, PhD, Medical College of Wisconsin, Milwaukee; Olle Ringden, MD, PhD, Huddinge Hospital, Huddinge, Sweden; Jon J. van Rood, MD, PhD, University of Leiden, The Netherlands; Ciril Rozman, MD, University of Barcelona, Spain; Bruno Speck, MD, University of Basel, Switzerland; Roy S. Weiner, MD, University of Florida, Gainesville; and Ferry E. Zwaan, MD, PhD, University of Leiden, The Netherlands.

APPENDIX 2

Institutions contributing data for this report are listed below.

AUSTRALIA: Alfred Hospital, Prahran; Institute of Medical and Veterinary Science, Adelaide; Prince of Wales Children’s Hospital, Randwick; Royal Perth Hospital; St. Vincent’s Hospital, Sydney; Westmead Centre; AUSTRIA: Med. Universitätsklinik, Vienna. BRAZIL: Hospital de Clínicas, Parana; Instituto Nacional de Cancer, Rio de Janeiro. BELGIUM: Academisch Ziekenhuis St. Raphael, Leuven; Cliniques Universitaires Saint-Luc, Bruxelles. CANADA: McMaster University, Hamilton; Tom Baker Cancer Centre, Calgary. CHINA: Lanzhou General Hospital, Gan Su; Beijing Medical Center, Beijing. DENMARK: Rigshospitalet, Copenhagen. ENGLAND: Charing Cross Hospital, London; Queen Elizabeth Hospital, Birmingham; Royal Marsden Hospital, London; Royal Postgraduate Medical School, London; Westminster Hospital, London. FINLAND: Turku University, Turku; University of Helsinki, Helsinki. FRANCE: Bone Marrow Transplant Unit, Besançon; Centre Hôpitalier et Universitaire, Bordeaux; Centre Hôpitalier Regional, Nancy; Groupe Hôpitalier du Hau Leveque, Pessac; Hôpital Bellevue, Saint Etienne; Hôpital Debrousse, Lyon; Hôpital de Purpan, Toulouse; Hôpital Des Sablons, Grenoble; Hôpital Saint-Antoine, Paris; Hôpital Saint Louis, Paris; Institut J. Paoli I. Calmettes, Marseille. EAST GERMANY: Karl Marx Universität, Leipzig. FRG: Christian Albrechts Universität, Kiel; Med. Universitätssklinik, Tubingen; Universitäts-Kinderklinik, München; Universität Ulm, Ulm/Donaun; Universität Muenchen, Munich. HUNGARY: Semmelweis University, Budapest. INDIA: Tata Memorial Hospital, Bombay. IRELAND: St James’s Hospital, Dublin. ISRAEL: Chaim Sheba Medical Center, Tel-Hashomer. ITALY: Ospedale Riuniti di Pesaro, Pesaro; Ospedale San Martino, Genoa; S. Orsola University Hospital, Bologna; University of Milan; Università-Chieti, Pescara. JAPAN: Center for Adult Diseases, Osaka; Dai Nippon Red Cross Hospital, Tokyo; Fukushima Medical University; Hôpital Universitaire, Isahara; University of Tokyo, Minato-Ku, Tokyo. KOREA: St Mary’s Hospital, Seoul. NEW ZEALAND: Christchurch Hospital, Christchurch. POLAND: Postgraduate Medical Center, Warsaw. SAUDI ARABIA: King Faisal Hospital, Riyadh. SCOTLAND: Glasgow Royal Infirmary, Glasgow; Royal Infirmary, Edinburgh. SOUTH AFRICA: University of Cape Town Medical School, Cape Town. SPAIN: Centro Medico Nacional “Marques de Valdecilla,” Santander; Clínica Puerta de Hierro, Madrid; Hospital de la Princesa, Madrid; Hospital Infantil Vall d’Hebron, Barcelona; Hospital “La Fe,” Valencia; University of Barcelona, Barcelona. SWEDEN: Huddinge Hospital, Huddinge. SWITZERLAND: Kantonsspital Basel, Basel; Kantonsspital Zurich, Zurich. TAIWAN: National Taiwan University Hospital, Taipei; Provincial Taoyuan General Hospital, Taoyuan. THE NETHERLANDS: Academisch Ziekenhuis, Leiden; Dr Daniel Den Hoed Cancer Center, Rotterdam; University Hospital Leiden, Leiden; University of Nijmegen, Nijmegen. UNITED STATES: All Children’s Hospital, St Petersburg, FL; Alta Bates Hospital, Berkeley, CA; Children’s Hospital, Cincinnati; City of Hope National Medical Center, Duarte, CA; Cleveland Clinic; Emory University School of Medicine, Atlanta; Hahnemann University, Philadelphia; Lackland Air Force Base, Texas; Loyola
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University Medical Center, Maywood; Latter Day Saints Hospital, Salt Lake City; Memorial Sloan-Kettering Cancer Center, New York; Medical College of Wisconsin; Oklahoma Teaching Hospitals, Oklahoma City; Roswell Park Memorial Institute, Buffalo; Texas Children’s Hospital, Houston; UCLA-Center for Health Sciences, Los Angeles; University of Alabama, Birmingham; University of Florida, Gainesville; University of Kansas, Kansas City; University of Kentucky, Lexington; University of Minnesota, Minneapolis; University of Oklahoma, Oklahoma City; YUGOSLAVIA: Klinika za Unutrasnje, Bolesti KBC-Rebro, Zagreb.

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