Immunity of patients surviving 20 to 30 years after allogeneic or syngeneic bone marrow transplantation


The duration of immunodeficiency following marrow transplantation is not known. Questionnaires were used to study the infection rates in 72 patients surviving 20 to 30 years after marrow grafting. Furthermore, in 33 of the 72 patients and in 16 donors (siblings who originally donated the marrow) leukocyte subsets were assessed by flow cytometry. T-cell receptor excision circles (TRECs), markers of T cells generated de novo, were quantitated by real-time polymerase chain reaction. Immunoglobulin G2 (IgG2) and antigen-specific IgG levels were determined by enzyme-linked immunosorbent assay. Infections diagnosed 15 years after transplantation occurred rarely. The average rate was 0.07 infections per patient-year (one infection every 14 years), excluding respiratory tract infections, gastroenteritis, lip sores, and hepatitis C. The counts of circulating monocytes, natural killer cells, B cells, CD4 T cells, and CD8 T cells in the patients were not lower than in the donors. The counts of TRECs \(^*\) CD4 T cells in transplant recipients younger than age 18 years (at the time of transplantation) were not different from the counts in their donors. In contrast, the counts of TRECs \(^*\) CD4 T cells were lower in transplant recipients age 18 years or older, even in those with no history of clinical extensive chronic graft-versus-host disease, compared with their donors. The levels of total IgG2 and specific IgG against Haemophilus influenzae and Streptococcus pneumoniae were similar in patients and donors. Overall, the immunity of patients surviving 20 to 30 years after transplantation is normal or near normal.

Patients who received transplants in adulthood have a clinically insignificant deficiency of de novo-generated CD4 T cells, suggesting that in these patients the post-transplantation thymic insufficiency may not be fully reversible. (Blood. 2001;98: 3505-3512)

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Introduction

More than 125,000 allogeneic and syngeneic hematopoietic cell transplantsations (HCTs) have been performed worldwide for hematologic malignancies, aplastic anemia, and inborn errors of hematolymphopoietic cells. Immunodeficiency follows HCT and lasts for more than 1 year. Because HCT only came into general practice in the 1980s, there has been, up until now, no opportunity to observe the immunity of very long-term survivors. There are conflicting views about what might happen to the immunity of these patients. On the one hand, infection rates as well as laboratory parameters of immunity like CD4 T-cell counts gradually improve in the first 5 years after transplantation (reviewed in Parkman and Weinberg and Storek and Witherspoon). Thus, by 20 years, one might expect relatively complete recovery. On the other hand, there is the possibility that the replicative potential of the transplanted immune cells and/or their precursors might be limited. This possibility could result in late onset immune deficiency. We have undertaken a study of a unique cohort of patients, the first group surviving 20 to 30 years after transplantation. We have asked the following questions: (1) What are the counts of immune cells in this group of patients? CD4 T cells were of particular interest because low CD4 T-cell counts have been associated with high rates of postengraftment infections and because the duration of CD4 T lymphocytopenia in adult marrow transplant recipients is not known (CD4 T-cell counts remain low for at least 5 years after transplantation). (2) What are the counts of T cells generated de novo (from hematolymphopoietic cells)? This question is important because concerns have been raised that the grafted hematolymphopoietic cells or the host thymus cannot sustain de novo T lymphopoiesis for more than 14 years after transplantation. (3) What are the levels of immunoglobulin (Ig)G2 and IgG against the capsular polysaccharides of commonly encountered encapsulated bacteria? Low levels have been associated with infections in HCT recipients, and the duration of this selective immunoglobulin deficiency is not known (levels remain low for at least 2 to 5 years after transplantation). (4) How frequently do the very late survivors develop infections? Infections, the incidence of which is the most clinically relevant measure of immunity, have been described to cause significant morbidity and mortality even between 2 and 16 years after transplantation.
20 or more years (range, 20-30 years). All 72 patients were evaluable for infections through questionnaires (see “Enumeration of infections” that follows). Thirty-three patients and 16 of their 33 marrow donors also agreed to have blood drawn for the determination of lymphocyte subset counts and antibody levels. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board. Demographic and clinical characteristics of the patients are given in Table 1. Patients received no immunosuppressive drugs, prophylactic antibiotics, or intravenous immunoglobulin beyond year 15 after transplantation, except for one lung transplant recipient (Table 1, footnote). Except for a higher incidence of hepatitis C, the 33 patients who gave blood were generally representative of the whole cohort of the 72 patients (Table 1).

Enumeration of mononuclear cell subsets

Blood specimens were drawn at a median of 20 years after transplantation (range, 20-27 years). Enumeration of mononuclear cell subsets (Table 2) was done by 3-color flow cytometry as described.11,23,24

Quantitation of T-cell receptor excision circle (TREC) levels (number of TREC copies per 100 000 CD3+CD4+ or CD3+CD8+ cells sorted by flow-activated cell sorter) was performed by real-time quantitative polymerase chain reaction (PCR) as described.25 Briefly, sorted cells were lysed in 100 µg/mL protease K at 10°C cells/mL. The 5’-nuclease (Taqman) assay was performed on 5 µL cell lysate (equivalent to 50 000 cells) with the primers CAACCTCACTACTACAGCT and GCCAGTGCAGGGT- TAGG and the probe FAM-ACACCTCGTTTTGTAAAGTGCC-CAC-TAMRA (Megabases, Chicago, IL). PCR reactions contained 0.5 U Taq polymerase, 3.5 mM MgCl2, 0.2 mM dNTPs, 500 nM of each primer, 150 nM probe, and Blue-636 reference (Megabases). The reactions were run at 95°C for 5 minutes, then 95°C for 5 minutes and 60°C for 1 minute for 40 cycles, using ABI7700 system (PE Biosystems, Norwalk, CT). Samples were analyzed in duplicates. A standard curve was plotted, and TREC levels (the number of TREC copies per 100 000 CD4 or CD8 T cells) were calculated by the ABI7700 software. The TREC levels reflect not only the de novo generation of T cells but also the postrearrangement expansion of thymocytes or T cells. For example, the TREC levels drop when peripheral T cells proliferate as a result of an infection. In contrast, the

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 72)</th>
<th>Patients who gave blood (n = 33)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sex, male/female (no. of patients)</td>
<td>38/34</td>
<td>16/17</td>
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<tr>
<td>Patient age at transplantation, y, median (range)</td>
<td>17 (3-40)</td>
<td>17 (5-36)</td>
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<tr>
<td>Donor age at transplantation, y, median (range)</td>
<td>19 (4-45)</td>
<td>20 (4-42)</td>
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<tr>
<td>Patient age at blood draw, y, median (range)</td>
<td>NA</td>
<td>39 (28-62)</td>
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<tr>
<td>Donor age at blood draw, y, median (range)</td>
<td>NA</td>
<td>42 (26-53)</td>
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<td>Donor type, HLA-matched sibling/identical twin (no. of patients)</td>
<td>66/6</td>
<td>30/3</td>
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<tr>
<td>Reason for transplantation, leukemia/aplastic anemia (no. of patients)</td>
<td>29/13</td>
<td>10/23</td>
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<td>Cytomegalovirus serostatus before transplantation (patient), positive/negative/unknown (no. of patients)</td>
<td>6/13/53</td>
<td>3/6/24</td>
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<tr>
<td>History of splenectomy, yes/no (no. of patients)</td>
<td>1/71</td>
<td>0/33</td>
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<td>Conditioning, TBI + Cy/Cy only/other (no. of patients)</td>
<td>24/36/12</td>
<td>7/19/7</td>
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<td>T-cell depletion, yes/no (no. of patients)</td>
<td>0/72</td>
<td>0/33</td>
</tr>
<tr>
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<td>9/57</td>
<td>7/23</td>
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<td>Chronic GVHD (clinical),§ extensive/none or limited/unknown (no. of patients)</td>
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<td>6/4/0</td>
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<td>Karnofsky performance score at 20 years after transplantation, 90% or greater/under 90%/unknown (no. of patients)</td>
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<td>29/2/2</td>
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<td>Posttransplantation conditions potentially impairing immunity (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse of original disease, yes/no</td>
<td>26/70</td>
<td>26/31</td>
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<tr>
<td>Secondary malignancy, yes/no</td>
<td>14/58</td>
<td>5/28</td>
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<td>Treatment with interferon and/or ribavirin, yes/no</td>
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<td>6/27</td>
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<td>Diabetes mellitus,†† yes/no</td>
<td>7/65</td>
<td>2/31</td>
</tr>
<tr>
<td>Obstructive lung disease, yes/no</td>
<td>32±69</td>
<td>1±32</td>
</tr>
</tbody>
</table>

NA indicates not applicable; TBI, total body irradiation; Cy, cyclophosphamide.

*Data on late hematopoiesis in 17 patients have been reported.35 In 15 of 16 patients studied more than 97% of donor-derived hematopoiesis was documented, whereas 1 patient had indeterminate chimerism.

††One patient had paroxysmal nocturnal hemoglobinuria with hypoplastic marrow.

§Allogeneic patients only.

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Determination of antibody levels

Serum levels of total IgG2 and IgG specific for tetanus toxoid, for Haemophilus influenzae capular polysaccharide, or for a mixture of 23 common pneumococcal polysaccharide serotypes were determined by enzyme-linked immunosorbent assay (ELISA), using kits purchased from The Binding Site (Birmingham, United Kingdom). Questionnaires asking whether the patients and the donors had been vaccinated against tetanus, H influenzae, or Streptococcus pneumoniae since transplantation were sent to them at the time of the blood draw. Specific IgG levels of only the unvaccinated patients/donors are presented.

Enumeration of infections

Questionnaires were sent annually (at the end of each posttransplantation year) to the patients and their primary physicians, asking about events (including infections and vaccinations) occurring since the time of the last returned questionnaire and about current medications. We counted infections occurring in the 16th year after transplantation through the last year covered by the questionnaire (data not shown). TREC levels were matched to a 3-year older or younger control, and one patient was matched to a 2-year older or younger control, 3 patients were matched to a 3-year older or younger control, and one patient was matched to a 4-year older control. Whenever 2 controls of equal age difference from the patient were available, the control was chosen randomly (by a coin toss). Two-tailed P values are given.

Results

Mononuclear cell subset counts

As shown in Figure 1, the counts of monocytes, natural killer (NK) cells, total B cells, IgG T cells, total CD4 T cells, CD28+ CD4 T cells, CD28+ CD4 T cells, CD45RAlow/CD4 T cells, CD45RAhigh CD4 T cells, CD8 T cells, CD8 T cells, CD11ahigh CD8 T cells, CD11ahigh CD8 T cells, and TREC+ CD8 T-cell counts were lower in the patients compared with their donors. These counts were also not significantly lower in the patients compared with the unrelated controls (data not shown). TREC+ CD4 T-cell counts were lower in the patients compared with the donors (Ppaired = .005, Pnonpaired = .06) as well as compared with the unrelated controls (Ppaired = .007, Pnonpaired = .008).

The reconstitution of TRECs might be influenced by irradiation, graft-versus-host disease (GVHD), or patient age (Douek et al., 25 Chung et al., 26 Weinberg et al., 27 and Storek et al. 28). We observed no significant difference in the counts of TREC+ CD4 or CD8 T cells between patients conditioned with versus without total body irradiation, allogeneic versus syngeneic graft recipients, patients who had versus had not developed grade 2 to 4 acute GVHD, or patients who had versus had not developed clinical extensive chronic GVHD. Also, there was no significant difference between patients with versus without chronic hepatitis C or patients treated...
versus not treated with interferon. However, there were significant differences between patients who received transplants before the age of 18 years (n = 17) and patients who received transplants at the age of 18 years or older (n = 15) (median TREC^* CD4 T-cell counts, 27.5 versus 4.5 × 10^6 /L, P = .004; median TREC^* CD8 T-cell counts, 17.5 versus 3.2 × 10^6 /L, P = .006). Because even in healthy individuals the quantity of TRECs declines with age, we next compared the patients with their sibling donors as well as unrelated age-matched controls (for the size and median age of these subgroups, see the legend to Figure 2). In the younger patients, the counts of TREC^* CD4 T cells and TREC^* CD8 T cells were not significantly different from the counts in their donors or the age-matched unrelated controls. In contrast, the older patients’ TREC^* CD4 T-cell counts (but not TREC^* CD8 T-cell counts) were significantly lower compared with the donors (P paired = .004, P nonpaired = .005) or to the age-matched unrelated controls (P paired = .05, P nonpaired = .04) (Figure 2). In agreement with that finding, the older patients’ (but not the younger patients’) CD45RA^high CD4 T-cell counts were lower compared with the donors (P paired = .004, P nonpaired = .005) or to the age-matched unrelated controls (P nonpaired = .03, P nonpaired = .04) (Figure 2). In agreement with that finding, the older patients’ (but not the younger patients’) CD45RA^high CD4 T-cell counts were lower compared with the donors (P paired = .004, P nonpaired = .005) or to the age-matched unrelated controls (P nonpaired = .03, P nonpaired = .04) (Figure 2).

Older patients have a higher propensity to develop chronic GVHD than young patients, and chronic GVHD and/or its treatment may inhibit de novo T lymphopoiesis. To evaluate whether the low TREC^* CD4 T-cell counts in our older patients could be attributed to chronic GVHD and/or its treatment, we next analyzed only the patients who received transplants at the age of 18 years or older who had no history of clinical extensive chronic GVHD (n = 11). Their TREC^* CD4 T-cell counts were lower compared with their donors (median 4.6 versus 38.3 × 10^6 /L, P paired = .03, P nonpaired = .04) and tended to be lower compared with their unrelated age-matched controls (median 4.6 versus 31.0 × 10^6 /L, P paired = .12, P nonpaired = .25). Thus, the long-lasting thymic insufficiency in the older patients was not due to a high incidence of clinical extensive chronic GVHD or its treatment. Because of insufficient data, we could not exclude a role of clinical limited or subclinical chronic GVHD.

**Antibody levels**

There were no significant differences between the patients and their donors in the serum concentrations of total IgG, H influenzae polysaccharide-specific IgG (evaluated in only 29 patients and 15 donors not vaccinated since the transplantation), and S pneumoniae polysaccharide-specific IgG (evaluated in only 26 patients and 15 donors not vaccinated since the transplantation) (Figure 3). The following facts constitute further evidence that the IgG and antipolysaccharide IgG levels in our patients were normal:
A total of 41 infections occurred over the 591 patient-years between the 16th and the 30th year after transplantation. Thus, the rate was 0.07 infections per year (one infection every 14 years). In the patients who received transplants at age 18 years or older, the rate was 0.09 per year (one infection every 11 years). Details on the infections are given in Table 3. It should be noted that infections were rare despite the fact that some patients suffered from conditions known to be associated with increased susceptibility to infections, such as diabetes or cancer (Table 1).

The 72 of 389 very late survivors may have been highly selected for those who had normal or near-normal immunity already early after transplantation. To ascertain whether the 72 patients were immunocompromised early after transplantation, we reviewed their records and counted early postengraftment infections, excluding respiratory tract infections, gastroenteritis, and lip sores. Early postengraftment infections were defined as infections diagnosed between day 30 and day 365 (65 of 72 patients reached sustained...
absolute neutrophil count > 500 × 10⁹/L by day 30; the remaining 7 patients engrafted by day 43 and did not have an infection between day 30 and the day of engraftment). A total of 85 early postengraftment infections occurred (rate of 1.29 infections per year). This rate is 18 times higher than the rate around 20 years after transplantation (0.07 infections per year). Thus, these patients were immunocompromised early after transplantation.

Deaths

Five deaths occurred between year 20 and the time of the last contact. One was due to pneumonia in a patient who appeared to have had ongoing chronic GVHD (cachexia and advanced scleroderma with leg ulcers and contractures were reported during the last 4 years of life). Four additional deaths were not attributed to infection; one due to lung graft rejection, one due to poly cystic liver disease, one due to advanced esophageal cancer, and one due to metastatic cancer of uncertain origin.

Discussion

This is the first study on the immunity of transplant recipients surviving 20 years or more. Given the extremely low infection rates, normal counts of monocytes, NK cells, total B cells, total CD4 T cells and total CD8 T cells, and normal levels of antibodies against commonly encountered encapsulated bacteria, we conclude that the immunity has recovered to normal or near normal by 20 years after transplantation.

In theory, a limited replicative potential of the grafted immune cells and/or their precursors or a limited ability of adult patients to generate T cells de novo (Storek et al., Muckall et al., Jenett et al., Weinberg et al., Dumont-Girard et al., and Storek et al. (1996)) could have caused long-lasting immunodeficiency after HCT. Data shown here suggest that the limit of replication extends beyond 20 years after transplantation, as patients surviving 20 years or more did not have low counts of monocytes, NK cells, B cells, CD4 T cells, or CD8 T cells. This finding is in agreement with the recent studies of Rufer et al. (1996) and Mathioudakis et al., showing that immunocyte telomeres are only slightly shorter in patients surviving 10 to 27 years after transplantation than in their donors and that the slope indicating the shortening of telomeres over time is not steeper. In our study, even the counts of the T-cell subsets expected to have the shortest telomeres (memory/effector cells and CD28 cells) were not low. Collectively, these data suggest that the replicative potential is not severely limited. However, patients who received transplants in adulthood appeared to have a mild deficiency of phenotypically naive CD4 T cells and TREC+ CD4 T cells. It is unclear whether this might be due to a limited potential of the grafted adult hematolymphopoietic progenitors to generate T cells (“seed deficiency”) or a limited potential of the adult thymic microenvironment to support the differentiation of the hematolymphopoietic progenitors to T cells (“soil deficiency”). The fact that in the patients who received transplants in adulthood the counts of monocytes, NK cells, and B cells were not lower than in their donors argues against any seed deficiency. It is possible that the thymic histologic defects observed early after transplantation, presumably induced by conditioning or GVHD, may be only partially reversible in patients who received transplants as adults.

It is not clear why the patients who received transplants in adulthood had a deficiency of de novo-generated CD4 but not CD8 T cells. In mice, extrathymic CD8 but not CD4 T lymphopoiesis de novo has been well documented. Perhaps, in the patients the putative extrathymic T-lymphopoietic organ was not damaged or has fully recovered by 20 years after transplantation, leading to the normalization of the counts of phenotypically naive and TREC+ CD8 T cells, whereas the thymus has not fully recovered by 20 years after transplantation in the older patients, leading to extremely long-lasting deficiency of phenotypically naive and TREC+ CD4 T cells.

The deficiency of de novo-generated CD4 T cells in the patients 18 years or older was mild (Figure 2) and clinically insignificant (not associated with frequent infections). However, we studied only transplant recipients younger than 40 years of age, because none of the 29 recipients in Seattle who were older than 40 years of age before January 1, 1978, survived 20 years or more. We have not excluded the possibility that, in transplant recipients older than 40 years of age, the deficiency of de novo-generated T cells might be greater. Because de novo generation results in diverse repertoires, transplant recipients older than 40 years of age might have limited T-cell repertoire. Theoretically, this could result in old HCT recipients’ ability to mount T-cell responses against only a limited number of pathogens.

The finding of normal counts of phenotypically naive and TREC+ T cells in our patients who received transplants before age 18 years contrasts with the recent report of Patel et al. showing that, after an initial increase of phenotypically naive T cells and TREC levels in the first 2 years after transplantation, there was a decline to values approaching zero by 14 years after transplantation. Our patients received T-cell–replete marrow after myeloablative conditioning for treatment of aplastic anemia or leukemia, whereas most of Patel’s patients received T-cell–depleted marrow without conditioning for treatment of severe combined immunodeficiency. The former transplant type usually leads to full chimerism (both T and myeloid cells of donor origin) with the engraftment of abundant donor hematolymphopoietic progenitors. In contrast, the latter transplant type usually leads to selective T-chimerism (T cells of donor origin and myeloid cells of host origin) with the engraftment of only a limited number of donor hematolymphopoietic progenitors (in 2 cases studied ≤ 2% of marrow CD34 cells were donor type). In the patients described by Patel et al. phenotypically naive T-cell counts and TREC levels increased as the donor hematolymphopoietic progenitors initially differentiated to T cells. The decline of TREC levels to near zero between 2 and 14 years after transplantation suggests that the limited hematolymphopoietic progenitors were not able to sustain T-lymphopoiesis for more than 14 years. In contrast, in our patients, most of whom were full chimeras (Table 1, footnote), the donor stem cells sustained T lymphopoiesis for 20 years or more. Low TREC+ CD4 T-cell counts with normal total CD4 T-cell counts could be caused by a low rate of de novo T lymphopoiesis or by increased peripheral turnover (expansion and death) of de novo–generated T cells. The association between older patient age and lower TREC+ CD4 T-cell counts favors a low rate of de novo T lymphopoiesis as the more likely explanation. In mice given allogeneic T cells, donor T cells (both alloreactive cells and “innocent bystanders”) undergo significant proliferation and activation-induced cell death during the first 2 weeks after transplantation. It is not known whether the high cell turnover can persist long term.

It was not known whether posttransplantation patients recover from the deficiency of total IgG, and IgG specific for the capsular polysaccharides of commonly encountered encapsulated bacteria. Our results show that they can recover as the total IgG level and the levels of S pneumoniae and H influenzae IgG were not low. Because only patients not vaccinated since the transplantation were included in our analysis, it is likely that the normalization of the specific IgG levels resulted from natural exposure to H influenzae and S pneumoniae.

After a decline in the first several months after transplantation,
levels of specific antibodies to protein antigens frequently encountered after transplantation (eg, cytomegalovirus in patients who were cytomegalovirus-seropositive before transplantation) return to pretransplantation levels within 1 year. In contrast, antibodies to protein antigens that are unlikely encountered after transplantation (eg, tetanus, measles, and polio) continue to decline. However, it was not known whether the decline was faster than the natural decline observed in healthy individuals. Our results document that the decline is faster, because the levels of tetanus IgG were lower in the patients than in their donors (both not vaccinated since transplantation). Surprisingly, the decline may not lead to complete disappearance of the specific IgG even by 20 years after transplantation, as 8 of 8 patients not vaccinated since transplantation had tetanus IgG levels above the sensitivity level of the ELISA (0.009 IU/mL) and 5 of 8 patients had protective levels (> 0.15 IU/mL). It is unlikely that this finding could be due to natural exposure to tetanus toxin. Tetanus antibodies have been detected in unvaccinated individuals living in a developing country under primitive conditions but not in 119 of 119 unvaccinated individuals living in a developed country. The 8 patients we studied lived in developed countries. Therefore, the continued production of tetanus IgG at 20 years or more after transplantation is most likely attributable to the immunization of the donors and/or the patients before transplantation. Given the lower tetanus IgG levels in our patients versus their donors, we support the recommendation of posttransplantation vaccination.

The very low average infection rate (one infection every 14 years) might be attributed to underreporting, because only 361 of 591 (61%) patient-years were covered by patient questionnaires filled out at the end of the posttransplantation year. The remaining 230 patient-years (39%) were covered by patient questionnaires filled out later, usually at the end of the next posttransplantation year. At that time patients may have no longer remembered minor infections from the previous year(s). We believe, however, that any serious infections would have been remembered and recorded by the patients. In addition, physician questionnaires and medical records from the primary physician were used as a further source of information. Thus, we have likely captured a significant majority of serious infections. It would be interesting to directly compare the rates of infections in the patients and their donors or unrelated controls. Unfortunately, we have not been sending the questionnaires to the donors, and a study on infection rates in healthy adult volunteers has not been published to our knowledge.

Because most of the measured laboratory parameters of immunity were normal and because infections occurred rarely in the very long-term survivors, we concluded that their immunity recovered to normal or near normal by 20 years after transplantation. However, there may be an alternative explanation of the results. Instead of gradually improving their immunity over the first 2 decades after transplantation, the patients surviving 20 years or more may have had normal immunity early after transplantation, whereas the patients with poor immunity early died by 20 years after transplantation. Two observations suggest that this situation was not the case. First, among 105 allogeneic marrow recipients we recently studied on day 80 only one had CD4 T-cell count more than 350 × 10⁶/L. Second, in the patients surviving 20 to 30 years after transplantation the rate of significant infections between the time of neutrophil engraftment and day 365 after transplantation was 18-fold higher than the rate of infections around 20 years after transplantation. This finding suggests that the very late survivors were severely immunocompromised in the early period after engraftment and that their immunity subsequently improved. Nevertheless, it is possible that the very late survivors were less immunocompromised early after transplantation than patients who died by 20 years after transplantation, as high infection rates between day 50 and day 730 have been associated with high nonrelapse mortality in the first 5 years after transplantation.

In conclusion, patients surviving 20 years or more after transplantation are no longer significantly immunocompromised. Compared with healthy individuals of similar age, transplant recipients may be more susceptible to rare diseases for which children are commonly vaccinated like tetanus, polio, or measles, unless revaccinated after 14 years. Continued follow-up of patients who received transplants in adulthood is needed to determine whether their counts of de novo–generated T cells will ultimately reach normal levels.

Acknowledgments

We thank the patients who agreed to participate in the study as well as their physicians who kindly provided us with annual updates on the clinical status of the patients and facilitated the blood draw. We also appreciate the hard work of the staff of the Fred Hutchinson Cancer Research Center Long-Term Follow-Up Department, particularly Judy Campbell, Mary-Joy Lopez, Kathy Erne, and Jane Jocom, who diligently gathered clinical information. We also thank Dr Lawrence Corey and Dr Meei-Li Huang for facilitating the TREC assay. Dr German Espino currently works at Complejo Hospitalario Metropolitano CSS, Panama, Republica de Panama. Dr Keith M. Sullivan currently works at the Division of Medical Oncology and Transplantation, Duke University Medical Center, Durham, NC.

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