Essential Role of the Thymus to Reconstitute Naive (CD45RA⁺) T-Helper Cells After Human Allogeneic Bone Marrow Transplantation

By Andreas Heitger, Nikolaus Neu, Hannelore Kern, Eva-Renate Panzer-Grümmayer, Hildegard Greinix, David Nachbaur, Dietger Niederwieser, and Franz Martin Fink

To contribute to the understanding of the role of the thymus in humans in the reconstitution of naive (CD45RA⁺) T cells after bone marrow transplantation (BMT), we compared T-cell regeneration in a unique situation, namely a thymectomized cancer patient (15 years old), with that of thymus-bearing patients after allogeneic BMT. These cases shared features of transplantation (total body irradiation, HLA-matched donors, and graft-versus-host disease prophylaxis with cyclosporine A) and all had an uncomplicated post-transplantation course. As shown by fluorescence-activated cell sorting analyses, the thymectomized host failed to reconstitute CD45RA⁺ T-helper cells even 24 months after BMT (11% CD45RA⁺ of CD4⁺ cells). In this patient, preferentially CD45RO⁺ cells contributed to the recovery of CD4⁺ cells (206 of 261/μL at 6 months and 463 of 598/μL at 24 months after BMT, CD45RA⁺ of CD4⁺ cells), whereas CD45RA⁺ cells remained low (<60/μL). In contrast, nine thymus-bearing hosts (5 children and 4 adults) examined between 6 and 24 months after BMT effectively reconstituted CD4⁺/CD45RA⁺ cells according to their normal age-related range (≥28% in adults and ≥50% in children). Five of these were analyzed sequentially at 6 and 9 months after BMT. Within this period, CD45RA⁺ cells increasingly contributed to the recovery of CD4⁺ cells (median, +21%), even when total CD4⁺ cells decreased. With respect to T-cytotoxic/suppressor cells, the thymectomized host retained the capacity to recover CD45RA⁺ T-cytotoxic/suppressor cells, but residual thymus is essential to reconstitute naive (CD45RA⁺) T-helper cells after BMT in humans.

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The biologic basis of this phenomenon is a matter of controversy. Two models of explanation have been proposed. One is based on a murine study that showed that thymectomized mice lethally irradiated and reconstituted with syngeneic bone marrow and mature T cells were able to recruit T cells with a CD45RO⁺ phenotype but failed to recover CD4⁺/CD45RB⁺ cells (CD45RB characterizing naive T cells in rodents¹). From this finding it was concluded that the recovery of naive T cells is thymus-dependent. The second model is based on the observation that the conversion of a T-cell from a CD45RA⁺ phenotype to a CD45RO⁺ phenotype is not irreversible and that T cells may bidirectionally switch between these two phenotypes. Therefore, it was proposed that the initial predominance of CD45RO⁺ T cells after BMT reflects a state of activation in the allogeneic environment and that the reappearance of CD45RA⁺ cells occurs when individual T cells revert their phenotype from CD45RO⁺ to CD45RA⁺.

To contribute to the understanding of the role of the thymus in the reconstitution of CD45RA⁺ T cells after BMT in humans, we studied T-cell regeneration in an extremely rare situation, namely in a pediatric cancer patient who underwent thymectomy before allogeneic BMT. The T-cell reconstitution with respect to CD45 isotype expression of this patient was compared with that of thymus-bearing recipients of allogeneic bone marrow. The results showed a difference in the regeneration of CD4⁺/CD45RA⁺ cells, whereas CD8⁺/CD45RA⁺ cells regenerated similarly, suggesting that the thymus is essential to the reconstitution of naive T-helper but not of naive T-cytotoxic/suppressor cells.

PATIENTS AND METHODS

Patients. The thymectomized patient, a previously healthy 15-year-old boy, was initially diagnosed with granulocytic sarcoma of the mediastinum involving the thymus. He was treated with conventional intensive polychemotherapy according to a German/Austrian protocol for acute myelogenous leukemia. Because after 4 months of treatment he still had considerable residual tumor, he was assigned to surgery. The tumor including the thymus was completely removed.

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such that the patient achieved complete remission. One month later, he underwent allogeneic BMT, receiving a fully HLA-matched graft from his brother. Nine nontymphectomized patients (termed thymus-bearing hosts) having undergone allogeneic BMT were used as controls (Table 1). Five of them (hosts no. 1 through 5) had at least two sequential examinations of T-cell regeneration at 6 and 9 months after BMT and four (hosts no. 6 through 9) had a single examination between 6 and 24 months after BMT. These thymus-bearing hosts comprised a wide age-range at transplantation (1.5 to 35 years). Common features of these cases were (1) transplantation from an HLA-matched donor (host no. 1 had one mismatch in DB1 and DQ, and host no. 3 had one mismatch in DRB3), (2) rapid engraftment, and (3) an uncomplicated posttransplant course (no severe infection, no evidence of graft-versus-host disease [GVHD] while being investigated for T-cell regeneration). However, the cases were heterogeneous with respect to some features of transplantation with potential relevance to T-cell regeneration such as differences in the underlying disease, preparative regimen (with or without total body irradiation [TBI]), the type of transplant (syngeneic, HLA-matched sibling, or HLA-matched unrelated donor), and GVHD prophylaxis (with or without cyclosporine A [CSA]). All patients were alive and well except the thymus-bearing host no. 2, who had a further relapse of acute lymphoblastic leukemia 10 months after BMT and died of progressive disease. Sampling of blood was timed together with routine laboratory examinations. Informed consent to perform the research studies was obtained from the patients and, in cases of pediatric patients, from their parents.

Analysis of T-cell regeneration. The pattern of T-cell regeneration was assessed by the quantification of total T cells and T-cell subsets by fluorescence-activated cell sorting (FACS). The initial investigation was performed 6 months after BMT. The thymectomized host was observed for 24 months and the thymus-bearing hosts for a minimum of 9 months. This observation period was sufficient for the detection of differences in the pattern of T-cell regeneration.

Peripheral blood mononuclear cells (PBMC) were isolated from whole blood by Lymphoprep (Nycomed, Oslo, Norway) density centrifugation and washed twice. Cells were either stained immediately or frozen in liquid nitrogen. The procedure of freezing and thawing did not alter the detectability of even small T-cell subsets. The following fluorochrome-labeled monoclonal antibodies (MoAbs), all purchased from Becton Dickinson (BD; Mountain View, CA), were used: negative controls, Simultest control (IgG, fluorescein isothiocyanate [FITC], and IgG2a phycoerythrin [PE]), IgG1 (peridinin chlorophyll protein [PerCP]), anti-CD3 (PerCP), anti-CD4 (PerCP or FITC), anti-CD8 (PerCP or PE), anti-CD45RA (FITC), and anti-CD45RO (PE). To quantify contamination with red blood cells, one portion of each sample was also stained with anti-glycophorin A (PE). The isolated PBMC population usually contained less than 2% glycophorin A-positive cells. Aliquots of 300,000 cells were first incubated with MOPC 21 (mouse IgG1; Sigma, St Louis, MO) on ice for 20 minutes to block nonspecific binding. The cells were then stained with MoAbs by incubation on ice for 30 minutes, washed twice, and immediately analyzed on a FACScan flow cytometer (BD). Lymphocytes were identified by forward scatter (FSC) versus side scatter (SSC) and gated electronically.

Aquisition and analysis of two- and three-color studies were performed on a FACScan research software 2.1 (BD). Three-color analysis was performed to examine T-cell subsets within a preselected T-cell population. To quantify CD4+ and CD8+ cells, CD3+ cells were identified by quadrant analysis of FL3 (PerCP) versus SSC, gated, and then examined for dual cell surface antigen expression by quadrant graphs (set to exclude background activity) of FL1 (anti-CD4, FITC) versus FL2 (anti-CD8, PE). To quantify CD45RA+ and CD45RO+ cells within the T-helper and T-cytotoxic/suppressor subset, CD4+ or CD8+ cells were identified by quadrant analysis of FL3 (PerCP) versus SSC, gated, and then examined by quadrant graphs of FL1 (anti-CD45RA, FITC) versus FL2 (anti-CD45RO, PE). The absolute number (expressed as cells per microliter) of each T-cell subpopulation was calculated by multiplying the fraction of cells staining positive by the absolute lymphocyte count, which was derived from the differential count of the white blood count.

RESULTS

Failure of regeneration of CD45RA+ T-helper cells in the thymectomized host. The initial evaluation of CD45 isotype expression within the CD4+ subset (Fig 1, column A) 6 months after BMT as performed in the thymectomized host and the thymus-bearing hosts no. 1 through 5 showed a predominance of CD45RO+ cells in all cases except for host no. 3. The CD45RA:RO ratio was 0.21 in the thymectomized host and 0.3, 0.24, 0.74, and 0.27 in the thymus-bearing hosts no. 1, 2, 4, and 5, respectively, and 1.36 in host no. 3. This finding is consistent with previous studies.13 However, the subsequent analysis after an interval of 3 months

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Table 1. Features of Transplantation Relevant to T-Cell Regeneration

<table>
<thead>
<tr>
<th>Patient, Age, Sex, Diagnosis</th>
<th>Conditioning Regimen</th>
<th>Donor</th>
<th>Engraftment (WBC &gt; 1.0 G/L)</th>
<th>GVHD Prophylaxis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymectomized host</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 yr, M, GS</td>
<td>Cy, Eto, TBI (12 Gy)</td>
<td>Sibling, 17 yr</td>
<td>Day 18</td>
<td>CSA (12 mo)</td>
<td>Alive, well 24 mo after BMT</td>
</tr>
<tr>
<td>Thymus-bearing hosts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) 8 yr, M, ALL relapse</td>
<td>Cy, ATG, TBI (12 Gy)</td>
<td>MUD, 33 yr</td>
<td>Day 20</td>
<td>CSA (12 mo)</td>
<td>Alive, well 18 mo after BMT</td>
</tr>
<tr>
<td>(2) 4 yr, F, ALL relapse</td>
<td>Eto, TBI (12 Gy)</td>
<td>Sibling, 16 yr</td>
<td>Day 17</td>
<td>MTX (3 mo)</td>
<td>Dead of disease 12 mo after BMT</td>
</tr>
<tr>
<td>(3) 2 yr, M, ALL relapse</td>
<td>ATG, Bu, Cy, Eto</td>
<td>MUD, 28 yr</td>
<td>Day 17</td>
<td>CSA (6 mo)</td>
<td>Alive, well 18 mo after BMT</td>
</tr>
<tr>
<td>(4) 35 yr, F, AML</td>
<td>Cy, TBI (12 Gy)</td>
<td>Sibling, 33 yr</td>
<td>Day 15</td>
<td>CSA (9 mo)</td>
<td>Alive, well 9 mo after BMT</td>
</tr>
<tr>
<td>(5) 2 hr, M, SAA</td>
<td>ATG, Cy</td>
<td>Sibling, 30 yr</td>
<td>Day 17</td>
<td>CSA (5 mo)</td>
<td>Alive, well 9 mo after BMT</td>
</tr>
<tr>
<td>(6) 1.5 yr, FLH</td>
<td>ATG, Bu, Cy, Eto</td>
<td>MUD, 33 yr</td>
<td>Day 13</td>
<td>CSA (6 mo)</td>
<td>Alive, well 15 mo after BMT</td>
</tr>
<tr>
<td>(7) 5 yr, F, ALL relapse</td>
<td>Eto, TBI (12 Gy)</td>
<td>Syngeneic, 5 yr</td>
<td>Day 19</td>
<td>CSA (6 mo)</td>
<td>Alive, well 9 mo after BMT</td>
</tr>
<tr>
<td>(8) 24 yr, M, SAA</td>
<td>ATG, Cy</td>
<td>Sibling, 14 yr</td>
<td>Day 17</td>
<td>CSA (18 mo)</td>
<td>Alive 24 mo after BMT</td>
</tr>
<tr>
<td>(9) 35 yr, F, CML</td>
<td>Cy, TBI (12 Gy)</td>
<td>Sibling, 30 yr</td>
<td>Day 23</td>
<td>CSA (12 mo)</td>
<td>Alive, well 14 mo after BMT</td>
</tr>
</tbody>
</table>

Abbreviations: GS, granulocytic sarcoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; SAA, severe aplastic anemia; HLH, hemophagocytic lymphohistiocytosis; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; Eto, etoposide; TBI, total body irradiation; MTX, methotrexate; ATG, antithymocyte globulin; Bu, busulphane; MUD, matched unrelated donor.
Fig 1. Failure to reconstitute naive (CD45RA⁺) T-helper cells in the thymectomized host. CD45 isotype expression was examined on gated CD4⁺ cells identified by PerCP. The dot plots depict CD45RA⁺ (FITC, FL1) cells versus CD45RO⁻ (PE, FL2) cells. Columns A and B show the distribution of CD45 isoform expression at 6 and 9 months, respectively, after allogeneic BMT.
To examine the numbers of CD45RA− expression of FL1 (anti-CD45RA, FITC) and FL2 (anti-CD45RO, PE); to determine total CD4 cells were CD45RA− and CD45RO− represent percentages of CD4− and CD8− cells. Absolute counts of CD4− cells (expressed as cells per microliter) were 858/μL in host (6), 693/μL in host (7), 746/μL in host (8), and 123/μL in host (9). Absolute counts of CD8− cells (expressed as cells per microliter) were 396/μL in host (6), 110/μL in host (7), 395/μL in host (8), and 32/μL in host (9).

T-cell subsets were quantified by FACS. To determine CD4− cells, CD4− cells, CD3− cells were first identified by PerCP (FL3), gated, and then examined for expression of the CD4 and CD8 antigen by quadrant graphs of FL1 (anti-CD4, FITC) and FL2 (anti-CD8, PE). To determine CD45 isoform expression, CD4− and CD8− cells were first identified by PerCP (FL3), gated, and then examined by quadrant graphs for expression of FL1 (anti-CD45RA, FITC) and FL2 (anti-CD45RO, PE); numbers of CD45RA− and CD45RO− represent percentages of CD4− and CD8− cells. Absolute counts of CD4− cells (expressed as cells per microliter) were 858/μL in host (6), 693/μL in host (7), 746/μL in host (8), and 123/μL in host (9). Absolute counts of CD8− cells (expressed as cells per microliter) were 396/μL in host (6), 110/μL in host (7), 395/μL in host (8), and 32/μL in host (9).

Table 2. CD45 Isoform Subsets in Thymus-Bearing Hosts

| Thymus- | Time After | CD4+ | CD45RA+ | CD45RO+ | CD45RA− | CD45RO− |
| Bear- | BMT | | | | | |
| ing Host | | CD45RA+ | CD45RO+ | CD45RA− | CD45RO− |
| (6) | 12 mo | 65 | 28 | 83 | 7 |
| (7) | 12 mo | 66 | 31 | 82 | 5 |
| (8) | 12 mo | 28 | 61 | 72 | 12 |
| (9) | 12 mo | 28 | 65 | 78 | 13 |

Effective recovery of CD8+/CD45RA+ T cells in the thymectomized host. The CD8+ subset was analyzed in the same manner as the CD4+ subset (Fig 3), but did not show a difference in the reconstitution of CD45 isoform expressing subpopulations between the thymectomized and the thymus-bearing hosts. In all cases, single-positive CD45RA+ or CD45RO+ cells could not be as distinctly identified as in the CD4+ subset. The proportion of CD8+ cells with a double-positive phenotype (CD45RA+/CD45RO+) was 18% ± 8% (mean ± SD) in the thymectomized host and 18% ± 7% in the thymus-bearing hosts. Six months after BMT (Fig 3, column A), the thymectomized and the thymus-bearing hosts no. 1 and 5 showed a slight predominance of CD8+/CD45RO− cells (CD45RA:RO ratio of 0.8, 0.8, and 0.7, respectively), whereas a CD45RA− phenotype was predominant in the thymus-bearing hosts no. 2 through 4 (CD45RA:RO ratio of 2.1, 1.8, and 11, respectively). At the subsequent evaluation 9 months after BMT (Fig 3, column B), all cases, the thymectomized and thymus-bearing hosts, showed a predominance of CD8+ cells with a CD45RA− phenotype (CD45RA:RO ratio of 1.2 in the thymectomized host 1.5, 1.9, 5.6, 11, and 1.5 in the thymus-bearing hosts no. 1 through 5, respectively). In addition, all patients with a single T-cell analysis showed a normal proportion of CD45RA− T-cytotoxic/suppressor cells (Table 2). In the thymectomized host, CD45RA− cells continued to represent the majority of CD8+ T cells throughout the observation period (CD45RA:RO ratio of 1.2 and 2.3 at 12 and 24 months after BMT).
months after BMT), indicating effective recovery of CD45RA⁺ T-cytotoxic/suppressor cells even in the absence of thymus. The analysis of absolute numbers showed that, in the thymectomized host, differently from the T-helper subset, CD8⁺/CD45RA⁻ cells were able to expand and contributed to the full reconstitution of total CD8⁺ cells to a similar extent as CD45RO⁺ cells (eg, 137/μL RA⁺, 160/μL RO⁻ at 6 months; 462/μL RA⁺, 375/μL RO⁻ at 12 months; and 596/μL RA⁺, 267/μL RO⁻ at 24 months of observation). The increase of CD8⁺/CD45RA⁺ cells was similar to that of the thymus-bearing hosts no. 1 through 5 (median fold increase, 1.4-fold; range, 0.5- to 2.8-fold). This absence of a difference between the thymectomized and the thymus-bearing hosts suggests that the reconstitution of CD45RA⁺ cells of the T-cytotoxic/suppressor subset is not thymus-dependent.

Together, the findings indicate that residual thymus is a critical factor for the regeneration of naive T-helper cells, giving rise to an expansion of naive rather than of memory T-helper cells, but is not essentially required to reconstitute naive (CD45RA⁺) T-cytotoxic/suppressor cells.

**DISCUSSION**

The understanding of the pathway of the regeneration of naive (CD45RA⁺) T cells after myeloablative therapy is mainly based on animal studies and has yielded conflicting results as yet. Indirect evidence that the recovery of CD45RA⁺ T-helper cells is thymus-dependent has been generated by the finding of an inverse correlation between the patients’ age and the regeneration of naive T-helper cells after myeloablative treatment. Studying T-cell regeneration in a previously healthy cancer patient who was thymectomized before allogeneic BMT offered a unique chance to directly explore the role of the thymus in the human regeneration of
Fig 3. Normal reconstitution of CD45RA- T cells of the CD8+ subset in the thymectomized and the thymus-bearing hosts. CD45 isotype expression was examined on gated CD8+ cells identified by PerCP. The dot plots depict CD45RA- (FITC, FL1) cells versus CD45RO+ (PE, FL2) cells. Columns A and B show the distribution of CD45 isoform expression at 6 and 9 months, respectively, after allogeneic BMT. Absolute counts of CD8+ cells at 6 and 9 months were 333/µL and 587/µL in the thymectomized host, 31/µL and 54/µL in the thymus-bearing host no. 1, 185/µL and 371/µL in host no. 2, 122/µL and 165/µL in host no. 3, 287/µL and 218/µL in host no. 4, and 50/µL and 41/µL in host no. 5.
CD45RA+ T cells. Notably, neither the thymectomized nor
the thymus-bearing hosts had a complicated posttransplantation
course, eg, no GVHD and no infection, because these
factors may interfere with the regeneration of T-cell subsets
(own unpublished observation).

The most striking finding was that, in the thymectomized
host, the regeneration of CD4+CD45RA+ T cells was se-
verely impaired even 24 months after transplantation. In con-
trast, in all thymus-bearing hosts examined within the same
period after BMT, the regeneration of CD4+CD45RA+ T
cells was effective. These thymus-bearing hosts were heter-
ogenous with respect to their underlying diagnoses, their age
(early childhood to adulthood), and their state of remission
before BMT (complete remission in 6 patients, a partial re-
mission in 1 patient, and no remission in 2 patients with
severe aplastic anemia) and were transplanted from several
types of donors. They shared with the thymectomized host
features with potential relevance to T-cell regeneration (eg,
TBI) and treatment with CSA to prevent GVHD. Irrespective
of these factors, in all of them CD4+CD45RA+ T cells
recovered according to their age-related range. Therefore,
the profound difference in the reconstitution of naive
(35RA+) T-helper cells between the thymectomized and
thymus-bearing hosts suggests that the regeneration of naive
T-helper cells in humans after BMT is thymus-dependent.
The age-linked rate of reconstitution of CD4+CD45RA+ T
cells of patients after myeloablative treatment as observed
in this and previous studies13,22 may therefore in fact reflect
age-dependent thymic activity. The findings clearly do not
support the view that the regeneration of CD45RA+ T-helper
cells after myeloablative therapy occurs by reverse switching
from CD45RO+ to CD45RA+ cells.5,19,20

The analysis by absolute cell numbers also yielded a pro-
found difference of T-helper cell regeneration between the
thymectomized and the thymus-bearing hosts. In the thymus-
bearing hosts the relative content of T-helper cells with a
naive (CD45RA+) phenotype, as measured between 6 and
9 months after BMT, increased irrespective of an increase
or decrease of total CD4+ cells. Conversely, in the thymecto-
mized host, the regeneration of T-helper cells was based
preferentially on an expansion of CD45RO+ cells, which
represent mature peripheral memory T cells. These findings
in humans are compatible with a previously described mu-
rine model18 in which the thymus was found to modulate the
pathway of T-helper cell regeneration after BMT. If residual
thymus is present, the reconstitution of T-helper cells is
based on cells that have undergone thymic maturation (as
bearing the CD45RA antigen) and, conversely, the expansion
of peripheral T cells (CD45RO+) is reduced. If residual thym-
us is absent, T-helper cell regeneration may occur via the
expansion of mature peripheral (CD45RO+) cells.23 It is
therefore conceivable that the predominance of CD45RO+
T-helper cells that is consistently observed in the initial
phase after BMT17 reflects a thymus-independent expansion
of peripheral T cells. A potential source of these T cells
could be incula of CD45RO+ T cells present in the alloge-
nic bone marrow or peripheral autologous T cells that have
survived the myeloablative treatment.13,16

In the T-cytotoxic/suppressor subset, the regeneration of
CD45RA+ cells was found not to be impaired by
thymectomy, as shown by the similar regeneration of CD8+/ CD45RA+ cells in the thymectomized host and the thymus-
bearing hosts. This finding suggests that these cells have the
potential to regenerate in a thymus-independent manner, the
mechanism of which remains to be elucidated. One possi-
bility is that, in T-cytotoxic/suppressor cells, reverse switching
from a CD45RO+ phenotype to a CD45RA+ phenotype oc-
curs.24,25 Alternatively, the maturation of CD8+ T cells may
take place in organs other than the thymus, eg, the gut.26,27

Finally, as this single exceptional case suggests, thymec-
tomy before allogeneic BMT may cause a profound alter-
tation of T-cell regeneration, the clinical significance of
which is unknown as yet.28,29 A predominance of circulating
T cells with a memory phenotype has been described in
association with some autoimmune diseases.30-32 Notably,
the patient presented is clinically well. The biologic rele-
ance of his abnormal distribution of peripheral T cells can only
be assessed after a long-term observation.

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