Clinical Research: Alternative Donors

Robust Vaccine Responses in Adult and Pediatric Cord Blood Transplantation Recipients Treated for Hematologic Malignancies

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Abstract

Because cord blood (CB) lacks memory T and B cells and recent decreases in herd immunity to vaccine-preventable diseases in many developed countries have been documented, vaccine responses in CB transplantation (CBT) survivors are of great interest. We analyzed vaccine responses in double-unit CBT recipients transplanted for hematologic malignancies. In 103 vaccine-eligible patients, graft-versus-host disease (GVHD) most commonly precluded vaccination. Sixty-five patients (63%; engrafting units median HLA-allele match 5/8; range, 2 to 7/8) received protein conjugated vaccines, and 63 patients (median age, 34 years; range, .9 to 64) were evaluated for responses. Median vaccination time was 17 months (range, 7 to 45) post-CBT. GVHD (n = 42) and prior rituximab (n = 13) delayed vaccination. Responses to Prevnar 7 and/or 13 vaccines (serotypes 14, 19F, 23F) were seen in children and adults (60% versus 49%, P = .555). Responses to tetanus, diphtheria, pertussis, Haemophilus influenzae, and polio were observed in children (86% to 100%) and adults (53% to 89%) even if patients had prior GVHD or rituximab. CD4þCD45RAþ and CD19þ cell recovery significantly influenced tetanus and polio responses. In a smaller cohort responses were seen to measles (65%), mumps (50%), and rubella (100%) vaccines. No vaccine side effects were identified, and all vaccinated patients survived (median follow-up, 57 months). Although GVHD and rituximab can delay vaccination, CBT recipients (including adults and those with prior GVHD) have similar vaccine response rates to adult donor allograft recipients supporting vaccination in CBT recipients.

INTRODUCTION

Disease-free survival after cord blood transplantation (CBT) is comparable with that of adult donor allografts in many series [1–8]. With increasing survivorship and the loss of pretransplant immunity, vaccine responses in CBT recipients are of great clinical relevance. Moreover, vaccine responses may differ from those observed after adult donor unmodified hematopoietic stem cell transplantation because of the lack of transfer of memory T and B cells capable of peripheral expansion. As in all allograft recipients, responses could be altered by the development of graft-versus-host disease (GVHD). Vaccine responses are also of scientific interest in CBT survivors because they are an excellent test of immune competence. Although several groups have evaluated the kinetics of immune recovery after single- and double-unit CBT [9–16], no data exist examining vaccine responses in CBT recipients. Many centers vaccinate at fixed
time points without formal evaluation of responses [17,18], precluding evaluation of vaccine efficacy. Documentation of vaccine efficacy is especially important in older patients, those with clinically significant GVHD, and patients who have received peri- or post-CBT rituximab who are at particular risk of negligible or inadequate responses.

Memorial Sloan Kettering Cancer Center practice has increasingly been to initiate vaccines once patients have achieved immunological milestones with measurement of pre- and post-titters to evaluate responses. This is appropriate in CBT recipients given the lack of data concerning vaccine responses. We examined the incidence and time to vaccination, the incidence of severe vaccine side effects, responses to protein conjugated vaccines, and survival after vaccination in double-unit CBT recipients transplanted for hematological malignancies at our center. In a smaller cohort of patients, we also evaluated responses to live vaccines. Our hypothesis was that although GVHD and/or the administration of rituximab could prevent or delay vaccination, CBT recipients could otherwise respond to nonlive vaccines similar to adult donor allograft recipients.

METHODS

Patients
All consecutive CBT recipients treated for hematological malignancies at Memorial Sloan Kettering Cancer Center from October 2005 to February 2012 were reviewed for study inclusion. Patients eligible for this retrospective analysis included recipients of a first allograft for the treatment of high-risk or advanced hematological malignancies who were engrafted and disease-free at 6 months post-CBT (the earliest time point that vaccines were considered) and had pre- and post-vaccine titers. All patients received double-unit grafts that were 4-6/6 HLA-A, -B antigen, -DRB1 allele matched to the recipient as previously published [19]. High-resolution typing for class I HLA alleles was also performed. Patients predominantly received fludarabine and total body irradiation-based conditioning, although a small cohort received chemotherapy-only preparative regimens [5,20,21].

Immunosuppression therapy was given as previously described with a calcineurin inhibitor and mycophenolate mofetil without antithymocyte globulin [5,14]. Permission to use clinical and laboratory information was obtained from the Institutional Review/Privacy Board.

Vaccines and Definitions of Response

The primary series included protein conjugated vaccines as follows: pneumococcal vaccine (Prevnar 7, which was replaced by Prevnar 13 in 2010); tetanus, diphtheria, and pertussis (Tdap; usually given as Boostrix B μg/dose); Haemophilus influenzae type b (HiB); and inactivated polio vaccine. Patients were also offered hepatitis B vaccine given as Twinrix (hepatitis A and B combination), hepatitis B recombinant vaccine, or Pediarix (which also contains tetanus, diphtheria, and polio). Most clinicians vaccinated patients after 6 months (usually after 1 year in adults) and achievement of basic immune milestones (CD4+ count > 200 cells/μL and IgG level > 500 mg/dL independent of intravenous immunoglobulin replacement) who were on no or minimal immune suppression. Some clinicians also considered phytohemagglutinin responses [14], and, more recently, a CD19+ count > 50 cells/μL has also been included in the guidelines for vaccine initiation.

Prevaccine titers were measured by ELISA and were drawn before vaccine initiation. Three doses of Prevnar 7 or 13, Tdap, and HiB (≥ hepatitis B vaccines) were recommended at time 0 and at +1 month and +2 months, but only 2 doses of polio vaccine (time 0 and +1 month) with titers were given 1 to 3 months later. A response was defined as seroconversion in a seronegative individual, a 3-fold geometric mean fold rise of the IgG geometric mean concentration, or 2-fold for pertussis. The Architect i2000R instrument (Abbott, Abbott Park, IL, USA) was used for hepatitis B titers with the manufacturer cut-off <3.0 μIU/mL for negative and ≥12.0 μIU/mL for positive. For the purposes of analysis, patients were categorized as having a pneumococcal vaccine response if they had a >3-fold rise in titers against the clinically significant serotypes 14, 19F, and 23F found in both Prevnar 7 and Prevnar 13 because these serotypes can cause resistant invasive infection after hematopoietic cell transplantation [22,23]. Polio response was defined as response to all 3 serotypes. Boosters were recommended in patients without a response to the primary series, although subsequent assessment of vaccine efficacy was influenced by frequency of patient follow-up.

Patients off immune suppression, without active GVHD, and with documented responses to at least 2 primary series vaccines who were seronegative were offered live vaccines (measles, mumps, and rubella [MMR]). Patients received 1 to 2 doses of the MMR vaccine. Response was defined as seroconversion in a seronegative individual or a 3-fold geometric mean fold rise of the IgG geometric mean concentration.

Statistical Analysis

Children were defined as aged <16 years of age. Acute and chronic GVHD were graded according to Center for International Blood and Marrow Transplant Research [24] and National Institutes of Health [25] criteria, respectively. Clinically significant GVHD was defined as grades II to IV acute GVHD and/or moderate to severe chronic GVHD. Low-dose immunosuppression therapy was defined as calcineurin inhibitor level lower than half of the lower limit of therapeutic range, ≤0.2 mg/kg per day of prednisone, and/or other immunosuppressive agent prescribed at less than half the therapeutic dose. Comparisons of time to vaccination used the Mann-Whitney U test, whereas the assessment of factors associated with vaccine responses used the Fisher’s exact test (2-sided). A P < 0.05 was considered statistically significant.

RESULTS

Eligibility for Vaccination

Of 143 patients transplanted during the study period, 103 (72%) were disease-free at 6 months post-CBT and potentially eligible for vaccines. Of the 103 patients, 65 (63%) were vaccinated with the primary series protein conjugated vaccines. Sixty-three of these patients were assessable for vaccine responses because they had long-term follow-up with both pre- and post-vaccine titers, whereas 2 patients left the New York area and did not have post-vaccine titers and were excluded. The remaining 38 patients (37%) were not vaccinated at the time of analysis primarily because of GVHD or administration of rituximab (n = 28, including 12 rituximab). Other reasons for lack of vaccination included relapse (n = 6), corticosteroids for pulmonary disease (n = 2), or loss to follow-up (n = 2).

Characteristics of Patients Evaluated for Vaccine Responses

The patient and graft demographics of the 63 assessable vaccinated patients are listed in Table 1. Patients (median age, 34 years) predominately had acute leukemia (67%) and received high-dose (51%) or intermediate-intensity but functionally myeloablative (32%) conditioning. Engrafting units had a high degree of donor—recipient HLA mismatch. Thirteen patients (21%) received rituximab as part of the preparative regimen (n = 6), as treatment for CD20+ relapse (n = 1), as part of both the conditioning and treatment of relapse (n = 1), and as treatment for Epstein-Barr viremia (n = 3), of RBC aplasia (n = 1), or of autoimmune hemolyis (n = 1). The last dose of rituximab was given a median of 15 months (range, 3.0 to 35) before the commencement of vaccination.

Most vaccinated patients (n = 38, 60%) had grades II to IV acute GVHD before day 180 post-CBT. Ten patients had previously had chronic GVHD (6 with prior acute GVHD and 4 with de novo disease). Thus, 42 of 63 patients (67%) had acute and/or chronic GVHD before vaccination. Eighteen of 63 patients (29%) were vaccinated while on low-dose immune suppression, whereas immunosuppression had been stopped in the remainder. CD4+ and CD19+ cell counts and IgG levels were adequate in most patients, although there was a wide range of immune recovery immediately before vaccine initiation.

Time to Vaccination Initiation

The 63 assessable patients were vaccinated at a median of 17 months post-CBT (range, 7 to 45). Within this group vaccination was delayed in the rituximab recipients (19
months; range, 12 to 45) compared with patients who did not receive anti-B cell therapy (15 months; range, 7 to 41; \( P = .034 \)). Vaccination was also delayed in 42 patients with prior grades II to IV acute and/or moderate to severe chronic GVHD with a median onset of 17 months (range, 9 to 45) post-CBT as compared with 14 months (range, 7 to 33) in those without clinically significant prior GVHD (\( P = .029 \)). The median time from GVHD onset to vaccination was 15.7 months (range, 6 to 44).

**Responses to Pneumococcal Vaccines**

Response to 3 doses of the pneumococcal vaccine was assessable in 58 patients. Of the 5 other patients, 3 received only 2 vaccines, 1 with prior pneumococcal infection was not vaccinated, and 1 did not have postvaccine pneumococcal titers. The 58 assessable patients received Prevnar 7 (n = 24), Prevnar 13 (n = 33), or both (n = 1). Thirty (53%) responded to all 3 clinically critical pneumococcal serotypes (14, 19F, and 23F). Response rates by clinically significant serotype (Figure 1) did not differ between children (9/15, 60%) and adults (21/43, 49%) (\( P = .555 \)). Among the 28 nonresponders, 19 patients (33%) responded to 1 to 2 critical serotypes and 9 patients (16%) did not respond to any.

There were no significant differences between pneumococcal vaccine responses and exposure to prior rituximab, prior clinically significant GVHD, or vaccination while on low-dose immunosuppression therapy. There was also no association between vaccine response and basic measures of immune recovery (CD4\(^+\), CD4\(^+\)CD45RA\(^-\), CD19\(^+\) cell counts, IgG levels, and phytohemagglutinin responses [14] above versus below the median or in tertiles; data not shown).

**Responses to Tdap, HiB, and Polio Vaccines**

Responses to Tdap, HiB, and polio were evaluated in all 63 patients. However, only patients who received \( \geq 2 \) primary series vaccines were included in the response evaluation (from 53 to 60 patients; Figure 2, Table 2). Overall response rates ranged from 86% to 100% in children and from 53% to 89% in adults. Children had better responses to tetanus (93% versus 53%, \( P = .005 \)) and pertussis (100% versus 54%, \( P = .002 \)) vaccines. There were no differences in response rates according to prior rituximab (\( P = .256 \) to 1.00) or prior clinically significant GVHD (\( P = .155 \) to 1.00), and no adverse effects of low-dose immunosuppression therapy were identified.

There was a significant association between tetanus and polio responses and measurements of immune recovery. Patients with CD4\(^+\)CD45RA\(^-\) counts above the median had better response rates to tetanus vaccine (79% versus 50%, \( P = .032 \)), and patients with CD19\(^+\) cells above the median had higher responses to tetanus (86% versus 44%, \( P = .001 \)) and polio (92% versus 62%, \( P = .023 \)) vaccines. Other parameters

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**Table 1**

Patient and Graft Demographics of 63 Vaccinated Double-Unit CBT Recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (range)</td>
<td>34 (9-64)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>AML (CR1-3)</td>
<td>31 (49%)</td>
</tr>
<tr>
<td>ALL (CR1-4)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>MDS/CML</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Conditioning</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Cy/Flu/TBI1320-1375</td>
<td>26</td>
</tr>
<tr>
<td>Thio/Flu/TBI1320</td>
<td>1</td>
</tr>
<tr>
<td>Clo/Mel/Thio</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Cy/Flu/Thio/TBI 400</td>
<td>17</td>
</tr>
<tr>
<td>Reduced intensity</td>
<td></td>
</tr>
<tr>
<td>Mel/Flu</td>
<td>3</td>
</tr>
<tr>
<td>Nonmyeloablative</td>
<td></td>
</tr>
<tr>
<td>Cy/Flu/TBI 200</td>
<td>11</td>
</tr>
<tr>
<td>Median engrafting units (range)</td>
<td>8 HLA-allele match</td>
</tr>
<tr>
<td></td>
<td>5/8 (2-7)</td>
</tr>
<tr>
<td>Infused TNC ( \times 10^9/)</td>
<td>2.1 (1.2-11.3)</td>
</tr>
<tr>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>Infused CD34 ( \times 10^9/)</td>
<td>.8 (.1-4.1)</td>
</tr>
<tr>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>Prevaccination rituximab</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>GVHD</td>
<td></td>
</tr>
<tr>
<td>Grades II-IV acute (grade)</td>
<td>38 (60%)</td>
</tr>
<tr>
<td>Chronic</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Vaccinated on immunosuppression</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45 (71%)</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Median prevaccine immune recovery (range)</td>
<td></td>
</tr>
<tr>
<td>CD4(^+)</td>
<td>577/µL (190-2296)</td>
</tr>
<tr>
<td>CD4(^+)CD45RA(^-)</td>
<td>127/µL (14-1856)</td>
</tr>
<tr>
<td>CD19(^+)</td>
<td>793/µL (0-5533)</td>
</tr>
<tr>
<td>IgG</td>
<td>786 mg/dL (502-2965)</td>
</tr>
</tbody>
</table>

AML indicates acute myeloid leukemia; CR, complete response; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; Thio, thiotepa; Clo, clofarabine; Mel, melphalan; TNC, total nucleated cell count.

* Donor—recipient HLA match.

† Twenty-seven grade II, 10 grade III, 1 grade IV.

‡ Nine mild, 1 severe (prior acute: 6 yes, 4 no).
of immune reconstitution, including CD4⁺ cell count, phytohemagglutinin responses [14], and IgG levels, were not significantly associated with response.

**Hepatitis B Vaccine Responses**

Forty-two patients were assessable for hepatitis B response (2 to 3 vaccines administered). However, 10 of these patients had positive prevaccine titers, so their responses were considered indeterminate. Of 32 remaining patients with negative pretransplant titers, 1 of 4 (25%) responded to 2 vaccines and 12 of 28 (43%) to 3 vaccines. Two nonresponders received a second series and responded.

**Response to Pneumococcal Boosters**

Of 9 patients who did not respond to 1 or more of the pneumococcal serotypes 14, 19F, and 23F after 3 vaccines in the primary series, 6 were revaccinated with 1 to 2 Prevnar boosters. Of these patients, 1 was not evaluated because of disease relapse and 5 patients all responded (3 patients to 1 booster and 2 patients to 2 boosters).

**MMR Vaccine Responses**

To date, 59 patients have had measles titers. Nineteen had positive titers. Twenty-three seronegative patients have been vaccinated with measles vaccine to date with post-vaccine titers and 15 (65%) responded (median age, 16 years; range, 1 to 51). Similarly, of 57 patients with prevaccine mumps titers, 30% were positive; 10 of 20 patients (50%) with negative titers responded to mumps vaccine (median age, 23 years; range, 1 to 51). Finally, of 59 patients, 23 (39%) had positive rubella titers; all 21 patients (100%) with negative titers vaccinated to date have responded to rubella vaccine.

**Vaccine Safety and Survival in Vaccine Recipients**

There were no severe adverse side effects reported or identified after vaccination. With a median follow-up of 57 months (range, 24 to 100), all vaccinated patients survived.

**DISCUSSION**

Similar to the young and the elderly, hematopoietic stem cell transplant recipients rely on herd immunity until they have sufficient immune reconstitution to facilitate successful vaccination [26]. In the community such protection is accomplished through mandatory vaccination in school-aged children [27], but this has been compromised by an increase in nonmedical vaccination exemptions [28,29]. Such exemptions have been linked to outbreaks of vaccine-preventable illnesses [30,31]. Specifically, outbreaks of pneumococcus [32,33], pertussis [34-37], meningococcus [38-40], polio [41-43], measles [44,45], and mumps [46-48] have been documented as detailed by the lay press [49-52] and reviewed by Omer et al. [31] and Orenstein et al. [53]. Moreover, Brazilian allograft recipients succumbed to measles during a national epidemic [54], and a recent measles outbreak in New York involved exposure in medical facilities [50]. Also of concern is the recent measles outbreak at Disneyland [55] because patients often choose such destinations once they can travel post-transplant, and increasingly patients are also traveling internationally. Decreased vaccination rates in underdeveloped countries combined with increased cross-continental travel could further enhance disease transmission such as polio [53,56], and a risk associated with biological warfare has been proposed [57]. These factors make vaccination of both community and allograft recipients of paramount importance.

We investigated vaccine responses in adult and pediatric CBT survivors. Our results have practical clinical importance and are an important addition to the literature concerning immune reconstitution. The quality of immune recovery after CBT is controversial, with some series suggesting delayed immune reconstitution [58] and others showing better recovery especially in those transplanted without antithymocyte globulin [11,12,14-16,59]. We demonstrate that CBT recipients can respond to protein conjugated vaccines similar to adult donor allograft recipients. GVHD and rituximab delayed vaccination but did not preclude responses to primary series vaccines post-CBT in many patients, and responses to live vaccines were also observed. Vaccination of CBT recipients was safe, and vaccinated patients had excellent survival. This is the first major analysis of vaccine responses in CBT especially in a cohort of predominantly (80%) adult patients. It must be acknowledged that only 63% of potentially eligible CBT recipients were vaccinated at the time of analysis, and GVHD was the major contributor to the delay or inability to vaccinate some patients to date. Measures to abrogate GVHD [60-63] could improve GVHD control and thereby potentially enhance the ability to proceed with vaccination provided these interventions did not unduly delay immune reconstitution.

Invasive disease caused by pneumococcus occurs with increased frequency and higher morbidity and mortality in allograft recipients than in healthy individuals. Implementation of routine childhood pneumococcal vaccination has been associated with a reduction in invasive disease. We focused on the 3 most clinically significant serotypes responsible for pneumococcal infections [64] and showed no differences in response rates between pediatric and adult CBT recipients. Although there was no association between basic measures of immune recovery and vaccine response, this is likely because most patients have achieved at least minimal immune recovery before vaccination. In a small number of nonresponders, pneumococcal boosters were
successful, emphasizing the possibility of achieving a response if one is not initially obtained. The recent Centers for Disease Control and Prevention recommendations for older adults include the addition of a 23-valent pneumococcal polysaccharide vaccine (PPV23) after PCV13 [65,66], and this was recently shown to be safe and able to illicit responses in the transplant recipients upon completion of the Prevnar series [67].

Response rates of 86% to 100% in children and 53% to 89% in adults were also achieved with other protein conjugated vaccines. The responses differed by vaccine type, likely because of their varying immunogenicity, and tetanus and pertussis responses were better in children than adults. An inferior result was demonstrated in patients with low CD4+ CD45RA+ cell counts for tetanus and with a low CD19+ cell count for polio. In a small cohort responses to hepatitis B were observed, although overall this vaccine appeared less effective. From the standpoint of live vaccines, our preliminary data suggest that in patients off immunosuppression therapy in whom responses to protein conjugated vaccines were documented, live vaccines are safe and can be effective. Administration was delayed in adults as compared with children, likely because of differences in clinical practice, especially given the need for revaccination before returning to school. No CBT recipients have been evaluated for varicella-zoster vaccine responses, and further investigation into MMR and varicella vaccine responses in a larger cohort is required [18,68].

Our study has several limitations. The sample size was relatively small, although it did have a significant number of adult patients. Also, although we focused on the pneumococcal serotypes known to be clinically relevant, we acknowledge that the response to other subtypes could be valuable. Finally, adverse events were based on chart review and not recorded prospectively, which may have minimized the identification of minor side effects. Nonetheless, despite these limitations, the vaccine responses after CBT demonstrated in this report are similar to other allogeneic transplant groups for protein conjugated vaccines [69]. For example, the adult CBT response rate to pneumococcal vaccine of 53% is similar to the 44% rate in adult donor allograft recipients reported by Pao et al. [64]. Less information is available for other vaccines, especially in adults, but responses for protein conjugated vaccines have been reported as 36% to 58% for Tdap using 8 μg pertussis toxoid [70,71], 47% to 92% for Hib [72,73], 48% to 95% for polio [73,74], 40% to 64% for hepatitis B [75,76], and 64% to 77% for MMR [77,79]. These rates are similar to those in our series. Only a prospective study with an intention to treat design with concurrent measurements of immune recovery could accurately compare response rates in defined patient populations stratified by hematopoietic stem cell source.

In summary, similar to individuals in the community, CBT recipients can benefit from immunization against vaccine-preventable diseases, and although GVHD is the major cause of vaccination delay, prior GVHD or rituximab and administration of low-dose immunosuppression therapy are not prohibitive in many patients. Our strategy to vaccinate according to immune milestones and document response by pre- and postvaccination titers is in contrast to the Infectious Diseases Society of America and the American Society for Blood and Marrow Transplantation guidelines [17,18,80,81], which recommend vaccination at 6 months to 1 year without testing immune function or titers. The optimal immunization schedule in CBT recipients, however, has not been determined. In this study the median time to vaccination was 17 months. It is possible that patients may benefit from earlier administration of some vaccines. The most appropriate timing may also vary by vaccine. Multicenter studies evaluating pre- and postvaccination titers to determine optimal vaccination schedule and vaccine efficacy are needed. Moreover, although our findings strongly support vaccination in CBT recipients, multiple unanswered questions remain that require future prospective evaluation, including the immunological determinants of response (e.g., the presence of CD19+ CD27+ IgD- memory B cells); the role of boosters to obtain, augment, and maintain responses; the role of vaccination in patients with positive post-transplant serologies; and the responses to live vaccines in a larger patient cohort.

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