Adoptive Transfer of Autologous T Cells Improves T-cell Repertoire Diversity and Long-term B-cell Function in Pediatric Patients with Neuroblastoma

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Abstract

Purpose: Children with high-risk neuroblastoma have a poor prognosis with chemotherapy alone, and hematopoietic stem cell transplantation offers improved survival. As a dose-escalation strategy, tandem transplants have been used, but are associated with persistent immunocompromise. This study evaluated the provision of an autologous costimulated, activated T-cell product to support immunologic function. 

Experimental Design: Nineteen subjects with high-risk neuroblastoma were enrolled in a pilot phase and 23 subjects were entered into a randomized study. Immunologic reconstitution was defined by flow cytometric and functional assays. Next-generation sequencing was conducted to identify changes to the T-cell repertoire. Twenty-two patients were vaccinated to define effects on antibody responses.

Results: Subjects who received their autologous costimulated T-cell product on day 2 had significantly superior T-cell counts and T-cell proliferation compared with those who received T cells on day 90. Early administration of autologous T cells suppressed oligoclonality and enhanced repertoire diversity. The subjects who received the day 2 T-cell product also had better responses to the pneumococcal vaccine. 

Conclusions: The infusion of activated T cells can improve immunologic function especially when given early after transplant. This study showed the benefit of providing cell therapies during periods of maximum lymphopenia. 

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Introduction

Neuroblastoma is the most common extracranial solid tumor in childhood (1). It is remarkable for its clinical range, encompassing spontaneous regression to progression and death. Approximately 12% of pediatric deaths from malignancy are due to neuroblastoma. The high-risk phenotype is generally characterized by disseminated disease and increased mortality (2, 3). Additional features associated with the high-risk phenotype include histopathologic features and MYCN amplification (2, 4). In these high-risk patients, more than half of the patients relapse after multimodal therapy. Recently, anti-GD2 immunotherapy to treat minimal residual disease after achieving remission has led to additional improvements in survival; however, stem cell transplantation is considered standard-of-care currently for high-risk patients (5, 6).

Autologous stem cell transplantation for neuroblastoma has been under investigation for more than 20 years, and in 1997, a large retrospective analysis found improved survival in patients treated with stem cell transplant as opposed to conventional chemotherapy (7). The single largest randomized trial of autologous stem cell transplantation was the Children’s Cancer Group 3891 study (8). In this study, all patients received a consolidation regimen and then were randomized to autologous transplantation or additional chemotherapy. The study established autologous transplantation and isotretinoin therapy as the standard-of-care for high-risk patients. Despite this, more than half of the patients relapsed. In recent years, the autologous stem cell transplantation concept has been extended to sequential cycles. A tandem transplant allows for greater dose intensity and has shown promise as a strategy to improve outcomes with the largest study showing a 3-year event-free survival (EFS) rate of 55% (9–11).

One of the significant issues in patients who receive a tandem stem cell transplant is prolonged immunosuppression. Posttransplant lymphoproliferative disease and other
viral morbidities can occur (12, 13). This suggests that there is prolonged, medically significant immunosuppression in this population. To mitigate immunosuppression in other settings, autologous expanded T cells have been used to provide defense against viral infections (14–18). We examined the use of an autologous T-cell infusion to support children who undergo tandem transplants for neuroblastoma. T-cell infusions were showed to increase T-cell counts as expected; however, multiple measures of T-cell function and B-cell function were improved in a group that received their T-cell infusions early after transplant. This study not only shows the promise of autologous T-cell infusion support after transplantation but also shows there is critical time window to maximize the effect.

**Materials and Methods**

**Study design**

This study protocol was approved by the Institutional Review Boards at Children’s Hospital of Philadelphia (Philadelphia, PA) and Boston Children’s Hospital (Boston, MA), and informed consent was obtained from all participants. The trial was preregistered at ClinicalTrials.gov as NCT00017368. The analysis plan was determined before study initiation, and laboratory assays were conducted in a blinded fashion. In an initial (pilot) safety and feasibility phase, patients received autologous expanded T cells on day 2 (early), day 12 (middle), or day 90 (late) after the second stem cell infusion. In a second phase of the study, patients were randomized after enrollment to either the early (day 2) or late (day 90) T-cell infusion group (Fig. 1). The seasonal inactivated influenza vaccine and the conjugated 7-valent pneumococcal vaccine were administered on days 12 and 60 after the second transplant. This protocol did not include immunoglobulin administration. In the analyses, baseline refers to samples obtained after diagnosis, but before chemotherapy. Days 30, 60, 90, 120, and 365 refer to the time after the second transplant.

In all, 22 patients received T cells at day 2, 10 patients at day 12, and 12 patients at day 90. Two patients were
excluded for early relapse or treatment-related mortality, and the other 42 patients were included in the pilot study analysis of the impact of a T-cell infusion, and the timing of the infusion, on T-cell recovery. One day 90 patient developed CMV disease after stem cell infusion and received T cells under a compassionate exception to the protocol at day 60 and is included in the analysis of the day 90 group, as assigned. In the analysis of the second randomized phase, 22 patients were randomized and included in the immune response analysis, including vaccine response.

T-cell infusions
Patients underwent a single 2 to 6 blood volume leukapheresis at diagnosis (before receiving chemotherapy) to collect peripheral blood mononuclear cells (PBMC). The cells were depleted of monocytes and cryopreserved. The T cells underwent an established GMP costimulated activation and expansion protocol using CD3- and CD28-linked beads (19). All infused T-cell products were required to meet U.S. Food and Drug Administration (FDA)-specified safety and release criteria before infusion. The target number of T cells for infusion was $2 \times 10^8$ to $8 \times 10^8$ T cells/kg. As this was the first effort at expanding T cells from children, we compared the expanded product from children and adults (Supplementary Data S1).

Immunologic assays
For the primary endpoint of T-cell count after stem cell transplant in the pilot phase, samples were submitted to CLIA-approved clinical laboratories for a complete blood count with differential, as well as CD4 percentage and CD8 percentage according to standard clinical protocols. For the second randomized phase, detailed analyses of lymphocyte subsets were conducted according to research protocols. T-cell subset analyses were conducted after fixation with 1% paraformaldehyde on an LSR II (BD Biosciences) using FlowJo software (TreeStar). CD4-naive cells were defined as CD45RA+/CD27+ and CD4 effector memory T cells were defined as CD45RO+/CD27+/CCR7+. CD4 reverted memory T cells were defined as CD45RA+/CD31+/CCR7+, and regulatory T cells (Treg) were defined as CD4+/CD25+/CTLA4+. CD8-naive cells were defined as CD45RA−/CD31−/CCR7−, CD8 central memory T cells were defined as CD27+/CD45RO−/CCR7−, and CD8 effector memory T cells were defined as CD45RA−/CD31−/CCR7−. For B-cell phenotyping, fresh blood was stained with antibodies (all from BD Pharmingen), as described previously (20) and run on a FACSCalibur (Becton Dickinson) with CellQuest software (Version 5.2.1, Becton Dickenson). CD19+ lymphocytes were analyzed for CD27 and IgM. The absolute B-cell count was obtained by multiplying the absolute lymphocyte count by the CD19+ fraction.

T-cell proliferation, T-cell repertoire, T-cell ELISPOTs, and B-cell ELISPOTs were conducted as previously described (18). The assessment of influenza and pneumococcal vaccine responses used a standard hemagglutination inhibition (HAI) assay optimized for the vaccine administered each year and a commercial laboratory for pneumococcal responses (21). Next-generation sequencing was conducted by Adaptive TCR technologies (www.immunoseq.com) using DNA from PBMCs, TCRβ-specific primers, and a deep level of sequencing on the Illumina platform (22).

Statistical analysis
The linear regression model was used for analyzing repeated measures based on the generalized estimating equation (GEE) method using SAS GENMOD. The regression models included group effects, time effects, and the interaction of group × time. Baseline differences were examined to exclude group differences related to randomization. To define the cumulative differences between the 2 groups, the area under the curve was calculated. The independent t test, Kruskal–Wallis test, or the Mann–Whitney test were used for the comparisons of single time points. The small size of the patients and the severity of their illness occasionally prevented obtaining all study samples. Each analysis indicates the number of subjects included. The studies reported were predefined in the study design. Significance was set at $P \leq 0.05$. Data analysis was conducted by Drs. Sullivan, Grupp, Boyer, Luning Prak, and Jawad. All authors had access to study data.

Results

Patient characteristics
All patients had high-risk neuroblastoma and were older than 1 year. All but 2 patients had stage IV disease. Consistent with the known epidemiology of the disease, the children were ages 1 to 5 years. The subjects were roughly half female and the majority of patients were Caucasian. For the pilot study of T-cell infusions, 8 patients received the infusion on day 2 (8 were stage IV and the median age was 2.4 years), 8 patients received the infusion on day 12 (8 were stage IV and the median age was 3.4 years), and 3 patients received the infusion on day 90 (3 were stage IV and the median age was 5.1 years). The randomized groups consisted of 12 subjects in the early group (day 2 infusion, 11 of 12 stage IV; median age, 1.9 years) and 10 subjects in the late group (day 90 infusion, 9 of 10 stage IV; median age, 2.7 years).

This study was not designed or powered to look at the impact of T-cell infusion on survival. However, we conducted a descriptive analysis of EFS in the cohort and among patients assigned to days 12, 2, and 90 T-cell infusion. Five-year EFS rate in the cohort was 55%, which was similar to our prior report of 47% (12). No differences between T-cell infusion subgroups were apparent, with 5-year EFS rates in the days 2, 12, and 90 subgroups being 55%, 50%, and 58%, respectively. One subject in each group experienced a post-transplant opportunistic infection. There was one case of CMV in the late group at day 30 and one case of EBV lymphoproliferative disease in the early group on day 21. Both of these infections were fatal.
Pilot study of T-cell reconstitution, comparing three time points

We hypothesized that autologous, costimulated expanded T cells would alter the composition of the T-cell compartment significantly. This CD3/CD28 bead–stimulated GMP cell therapy product has been previously shown to produce CD4:CD8 ratios of approximately 1:1 and to maintain the T-cell receptor repertoire of the input T cells (14, 15, 23). For analysis of the initial pilot phase, clinical measurements of ALC, CD3, CD4, and CD8 counts were used. These data are shown in Fig. 2 and show a profound impact of T-cell infusion on the T-cell count. The group receiving T cells at day 2 had improved CD4 and CD8 T-cell counts compared with the day 90 group in the day 2 to 90 interval. Interestingly, the day 2 group also had improved T-cell recovery compared with the day 12 group, suggesting that very early T-cell infusion might result in even more robust CD4 cell recovery. A similar effect across the groups was seen in terms of CD8 T-cell recovery.

T-cell recovery after early or late T-cell infusions

During the randomized phase of the study, we expanded the immunologic reconstitution assessments. We first characterized the T cells in the expanded autologous T-cell product because there have been no previous studies of pediatric specimens. We identified the frequency of stem-like T cells (24), follicular helper T cells, Tregs, and other subsets of biological relevance. Surprisingly, there were almost no differences between the cell populations in the expanded products from children and adults, although naive CD4 T cells were increased in the expanded product.
from the children compared with adults (Supplementary Data S1).

We characterized T-cell subsets using flow cytometry and compared the day 2 early group \((n = 12)\) and the day 90 late group \((n = 7; \text{Fig. 3})\). Absolute counts of both CD4 and CD8 T cells were higher in the early group than in the late group in the early posttransplant interval (Fig. 3). We measured the area under the curve to compare the advantage of the early T-cell product over the late T-cell product between days 0 and 90. The improvement in peripheral blood T-cell counts was significant with \(P = 0.0023\) for CD4 T cells and \(P = 0.0010\) for the CD8 T cells. To determine whether the excess cells in the early group were of a specific subset, we analyzed CD4 and CD8 T-cell naïve and memory subsets (Fig. 3). Examples of the naïve and memory flow cytometric gating are given in Supplementary Data S2. Naïve CD4 and CD8 T-cell counts were higher in the early group than in the late group at the 60-day time point \((P = 0.0380\) and 0.0344, respectively). The CD4 central memory T-cell count was higher in the early group than in the late group with \(P = 0.0311\). Tregs were somewhat higher in the early group. After the T-cell infusion in the late group at day 90, the advantage of the early infusion was lost. The T-cell reconstitution was variable in both groups. We examined age, number of T cells infused, level of stem-like cells in the expanded product, and Tregs in the expanded product for associations with naïve CD4 T-cell reconstitution. We did not identify any associations.

On the basis of data from non-human primates, it is estimated that a typical 2- to 3-year-old child has a total body content of approximately \(2 \times 10^{11}\) T cells (25). Therefore, the increase in T-cell count in the peripheral blood was unlikely to be directly due to the addition of \(2 \times 10^8\) to \(8 \times 10^8\) costimulated, activated T cells/kg.
(approximately $3 \times 10^8$ to $12 \times 10^9$ cells total). The lymphocyte count was significantly higher in the early group at day 30 than in the late group ($P = 0.007$). To determine whether T cells expanded in vivo, as has been seen in other settings (26, 27), we identified dividing CD3-positive T cells in the absence of stimulation by carboxyfluorescein succinimidyl ester (CFSE; Fig. 4A). We reasoned that T cells undergoing homeostatic expansion in vivo would complete the response to that signal in vitro. Cells were incubated 5 days after staining with CFSE. There was enormous variability in the early group, whereas the late group consistently showed low cell division in this assay. Nevertheless, the early group exhibited significantly more spontaneous proliferation than the late group, consistent with homeostatic expansion (Wilcoxon: $n = 12$, late group: $n = 7$). To further examine the mechanism of expansion, serum interleukin (IL)-7 was measured in both groups. A slow increase in IL-7 was seen in the late group (Fig. 4B). Chemotherapy-driven release of cytokines may mediate early expansion, whereas IL-7 might be responsible for the late expansion seen before the day 90 infusion (28).

To examine proliferative responses after stimulation, we incubated PBMCs with phytohemagglutinin (PHA). CFSE dilution was defined using flow cytometry and the proliferation index (a measure of average number of cell divisions a responding cell has undergone) and the percentage divided (a measure of the fraction of cells competent to divide) were calculated. The proliferation index was higher in the early group, but this difference did not reach statistical significance ($P = 0.0522$); however, the percentage divided after PHA was significantly higher in the early group than in the late group at day 60 with $P = 0.0232$ (Fig. 4C). Therefore, provision of an autologous T-cell product at an early time point after the second transplantation provided superior quantitative and qualitative reconstitution of the T-cell compartment early posttransplant.

Expansion of T cells could be associated with contraction of the T-cell repertoire. We initially analyzed the diversity of the repertoire by spectratyping (29). Unexpectedly, the diversity was impressively restricted in the patients before any chemotherapy with more than half of the VB families missing or having oligoclonal peaks (Fig. 5). A previous study of adults, using this technology, found approximately 10% abnormal VB families (30). There was a modest increase in the frequency of abnormal VB families at days 30 and 60 in the late group, suggesting expansion of a small number of founder clones. To better explore the contribution of the infusion to the T-cell repertoire, 5 patients in the early group and 4 patients in the late group were examined using next-generation sequencing to better identify alterations to the repertoire. We hypothesized that baseline repertoire contraction could be due to expansion of a tumor-specific clone; however, at baseline, there were no T-cell receptor (TCR) sequences shared by all patients. For all 4 patients who had baseline samples available, the number of unique reads was higher in the infusion sample than in the baseline sample, supporting the previous finding that in vitro expansion using this method preserves polyclonality (15). There were relatively few clones from the infusion that appeared in later time points, $\leq 5.5\%$ in all cases. This is consistent with the small contribution expected from the infusion. Unexpectedly, provision of this small number of cells led to increased repertoire diversity (diminished oligoclonality; Fig. 5). For this analysis, we enumerated the number of clones comprising more than 5% of the total reads as a marker of oligoclonality. There were no oligoclonal sequences at baseline, but at day 30, the late group had an average of 4 oligoclonal sequences, whereas the early group had an average of 0.25 oligoclonal TCR sequences ($P = $ nonsignificant). Similarly, when the frequencies of the most common clones were analyzed, the early group had a mean frequency of 3.5%, whereas the late group had a mean frequency of 13.5% ($P = $ nonsignificant).
As a final measure of diversity, we enumerated the number of distinct Vβ-J combinations at each time point. The early group had significantly more diversity at day 30 than the late group (P = 0.008; Fig. 5).

The suppression of oligoclonality could be due to greater “fitness” of the ex vivo expanded cells or could be due to enhancement of thymic output, such as has been previously suggested (31). Clones that were identified in both baseline and day 150 samples comprised an average of 1.1% of the total day 150 clones and clones that were identified in both the infusion and day 150 samples comprised an average of 0.65% of the total day 150 clones, suggesting that the final composition of the repertoire was modestly derived from the infused cells. Thymic export of new T cells would be consistent with the naïve phenotype identified by flow cytometry (Fig. 3). To explore this, we conducted analyses of T-cell receptor excision circles (TREC). Four of 9 subjects in the early group had increased TRECs at day 30 compared with their baseline, whereas 1 of 7 of the late group did. At day 150, 5 of 7 of the late group and 2 of 6 of the early group had increased TRECs compared with baseline.

Responses to vaccines

Improved T-cell reconstitution could improve B-cell function. To analyze this, we examined the response to the influenza vaccine for each of the 3 serotypes present in the inactivated vaccine. There was wide variability in the early group, whereas the late group exhibited very little variability. There were no significant differences in the mean titer between the 2 groups and overall the responses were extremely low. We also calculated the seroconversion frequency at each time point by defining a 4-fold increase from the baseline titer. Two patients in the early group (n = 14) produced a 4-fold titer increase after vaccination to all 3 serotypes. Three additional patients produced a 4-fold increase in titer to at least one serotype in the early group. In contrast, only one patient in the late group (n = 8) produced a 4-fold response to a single serotype (P = not significant). The low titers at baseline suggest that this population was largely naïve to influenza, which may have compromised their ability to respond to the vaccine. We therefore examined responses to the conjugated pneumococcal vaccine, which the patients should have received as part of their childhood before developing neuroblastoma.

Pneumococcal responses were evaluated as representative of an antigen previously encountered and a typical memory response (Fig. 6). Fourteen serotypes were evaluated: 7 contained in the conjugate vaccine and 7 serotypes not in the vaccine. There were no responses to the serotypes that are not in the vaccine, as expected. For the serotypes in the vaccine, the baseline titers were higher than the non-vaccine serotypes, consistent with prior vaccination. There was a dichotomous response at the 1-year time point with the early group having significantly higher responses than
Fig. 6. Early T-cell reconstitution promotes B-cell memory responses following pneumococcal vaccination. A and B, aggregate pneumococcal mean titers were calculated by summing the antibody responses to the 7 serotypes not in the vaccine (A) and for the vaccine (B) serotypes (early group: n = 9; late group: n = 7). At baseline, the differences between the vaccine serotypes and nonvaccine serotypes were significant for both the early group (Mann–Whitney: P = 0.020) and the late group (P = 0.002), confirming prior vaccination. At 1 year, the difference between the early and the late groups comparing the vaccine serotypes was significant (Kruskal–Wallis: P = 0.002), whereas serologic response to nonvaccine serotypes did not differ. The vertical arrows denote the vaccine administration time points. C, when each serotype was examined separately, the effect at day 365 was consistent across all vaccine serotypes. The vertical arrows denote the vaccine administration time points. Each black line indicates a single vaccine serotype response and each gray line indicates a single nonvaccine serotype response.

Discussion

This study was designed to test the efficacy of an adoptive transfer of a costimulated, activated autologous T-cell product as an approach to regenerate cellular immunity after high-dose cytotoxic therapy. Patients who receive a tandem transplant for high-risk neuroblastoma are rendered severely immunodeficient for a prolonged period of time (5, 9, 13, 32, 12). Consequences of the immunocompromise are viral morbidity and mortality related to infection (13). The provision of an autologous T-cell product can provide support during the vulnerable posttransplant period. In adults, autologous T-cell products have been used with a significant improvement in immunologic function as measured by T-cell counts and vaccine responses (18, 33–36). To our knowledge, no studies have tested the regenerative potential of adoptive T-cell transfer in nonhematologic malignancies. Furthermore, no studies have assessed this in children where the kinetics of immune reconstitution may differ due to increased thymic potential (37).

This study clearly showed a greater effect the earlier the T-cell infusion was administered in the pilot phase, although the improvement was greater than what we could account for by the infusion itself. Patients receiving infusions on day 12 had the least marked T-cell reconstitution, and we hypothesize that this time point fell between inflammatory cytokine-induced expansion and IL-7–induced expansion. We found evidence of homeostatic expansion of the transferred cells at day 30, supporting a role for this process in expansion and reconstitution in the cytokine-rich, lymphopenic environment (28). There was a significant increase in naïve cells. Although strong homeostatic signals drive a naïve to memory conversion, not all homeostatic expansion is associated with conversion to a memory phenotype and we hypothesize that both thymic production and homeostatic expansion contributed to quantitative reconstitution (38–40). The TREC data were not uniform among subjects, but the data were suggestive of the induction of thymopoiesis in some patients after the T-cell infusion. Overall, the early (day 2) T-cell infusions resulted in superior T-cell reconstitution as assessed by quantitative and qualitative measures and we believe this will improve the defense against opportunistic infections.

To probe the breadth of improvement in immunologic function, we vaccinated children after their second transplant. We anticipated that most children would be naïve to influenza because of their young age and that nearly all and various time points after transplantation. Neither total B cells nor any of the subsets differed between the early and late Groups, although B-cell maturation appeared to be modestly accelerated in the early group (Supplementary Data S3). To examine B-cell function, we used B-cell ELISPOTs, measuring both the total IgG and the influenza-specific IgG produced. There were no differences between the early group and the late group, but responses were universally low using this assay (data not shown).

B-cell maturation

To better understand how the early autologous T-cell infusion led to greater antibody production, we examined the B-cell subsets in the peripheral blood at baseline and various time points after transplantation. Neither total B cells nor any of the subsets differed between the early and late Groups, although B-cell maturation appeared to be modestly accelerated in the early group (Supplementary Data S3). To examine B-cell function, we used B-cell ELISPOTs, measuring both the total IgG and the influenza-specific IgG produced. There were no differences between the early group and the late group, but responses were universally low using this assay (data not shown).
children would have had the conjugated pneumococcal vaccine as part of routine childcare. We noted that the baseline aggregate titers to pneumococcal serotypes were significantly different between the vaccine serotypes and the non-vaccine serotypes, confirming that this cohort was previously vaccinated. There was a modest increase in titers at the day 30 time point, but the most remarkable result was the dramatic increase in vaccine-specific pneumococcal titers at the 1-year time point, indicating that long-term B-cell immunity is dependent on antigen-specific T-cell function.

The delayed kinetics were surprising; however, similar studies in adults show that priming before the T-cell harvest markedly improves subsequent vaccine responses (18, 19). In those studies, the conditioning regimen did not deplete memory B cells, and it could not be determined whether the priming of B cells was critical for the vaccine responses. In this study, the conditioning before transplant led to an absence of peripheral blood B cells on day 2, suggesting that the infused primed T cells were largely responsible for the pneumococcal responses in the early group. The early group received the vaccines after infusion of the T cells, whereas the late group received the vaccines before the cell infusion. The presence of primed T cells at the time of vaccination had a salutary if undefined effect on subsequent antibody responses to the vaccine. The delayed kinetics might reflect the recovery kinetics of the B-cell compartment, which achieved normal numbers only at the 1-year time point. The T cells may have had a trophic effect on B-cell development (41).

Harnessing the immune system for an antitumor effect is a long-term goal of immune reconstitution and infusion of genetically modified T cells expanded using CD3- and CD28-linked beads recently show dramatic antitumor responses (34). The most important lesson is that the autologous T-cell product can provide important vaccine responses (34). The most important immunological support but it must be administered early. These results are also the first indication that the kinetics of immune reconstitution in the pediatric immune system has profound effects on long-term humoral immunity. These results may guide future studies to reconstitute immunity after high-dose chemotherapy and perhaps for the induction of antitumor immunity.

Disclosure of Potential Conflicts of Interest

E.L. Prak is a consultant/advisory board member of Genentech. B.L. Levine and C.H. June are inventors on patents related to the T-cell manufacturing process that was used for this protocol. This conflict has been disclosed and was managed in accordance with the policies of the University of Pennsylvania. No potential conflicts of interest were disclosed by the other authors.

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