Cognitive Outcome After Pediatric Stem-Cell Transplantation: Impact of Age and Total-Body Irradiation

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose

To examine the influence of age and conditioning with total-body irradiation (TBI) on the trajectory of cognitive functioning after treatment with pediatric hematopoietic stem-cell transplantation (SCT).

Patients and Methods

Pediatric patients who were scheduled to undergo a SCT were eligible for the study, with 315 patients completing a baseline assessment. Of these, 183 patients (58.1%) were alive at 1 year after SCT and completed additional assessments at 1, 3, and 5 years after SCT. Half of the long-term sample (52.1%) received TBI during conditioning. Cognitive functioning was assessed via age-appropriate standardized measures.

Results

At baseline, there were no differences in intelligence quotient (IQ) based on age. At 5 years after SCT, the youngest patients (< 3 years old at baseline) who received TBI demonstrated a significantly lower IQ than those who did not receive TBI ($P = .05$). Longitudinal analyses (piecewise linear mixed-effects models with a knot at 1 year after SCT) revealed a significant impact of age and TBI over time. The youngest patients evidenced declines in cognitive functioning during the first year; however, patients who did not receive TBI largely recovered their functioning in subsequent years. In contrast, young patients who received TBI failed to recover the losses experienced during the first year after SCT, demonstrating stability in their functioning, but at a lower level.

Conclusion

Our findings clarify the relationship between TBI and age on cognitive outcomes in pediatric SCT survivors. Young patients who receive TBI may benefit from early intervention efforts to minimize cognitive losses during the first year after SCT and to maximize potential recovery.

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INTRODUCTION

Research on survivors of hematopoietic stem-cell transplantation (SCT) has been conducted with the assumption that patients are at risk for neurocognitive late effects. This assumption was based on the prevalence of late effects observed in survivors of leukemia and brain tumors who receive similar, although more intense, rates of CNS-directed therapies.^{1,2} However, research to date has generally shown minimal evidence of cognitive decline over time in the SCT population at large,³⁻⁸ although there are some studies that contradict these findings.^{9,10} Questions have remained regarding the impact of younger age at SCT and treatment with total-body irradiation (TBI) on the development of neurocognitive late effects, with studies both confirming¹⁰⁻¹² and discounting^{6,13} these risk fac-

tors. As such, the objective of the current study was to attempt to resolve these discrepancies by prospectively following a large group of patients who have undergone SCT, with the sample being diverse with regard to age and TBI status.

Previous research has been limited by small sample sizes^{8,10,12,13} and cross-sectional outcomes with little longitudinal follow-up.¹¹⁻¹³ However, multiple studies have reliably demonstrated that, despite the inherent medical risks associated with SCT, survivors are doing well from a quality-of-life standpoint.¹⁴ Indeed, a series of longitudinal studies from our institution⁵⁻⁷ has confirmed these findings. Specifically, our data, which were strengthened by large sample sizes and long-term, prospective follow-up, demonstrated relative stability in cognitive functioning over time.^{6,7} There were some statistically, but not clinically, significant declines

Fig 1. The two-step recruitment process (initial sample and the additional sample of patients < 6 years old). The number of patients who contributed data for each time point is provided, both as a total sample and by age at baseline. Number of patients who received total-body irradiation (TBI) is also provided in the boxes on the right.

observed based on a variety of factors, including younger age at transplantation,⁶ use of TBI,⁷ and presence of graft-versus-host disease.⁷ Perhaps the most striking finding, however, was the influence of socioeconomic status (SES), which was significantly predictive of outcome, with differences of at least one standard deviation observed, overshadowing the effects of SCT treatment-related variables.⁷ The discrepancies in the literature regarding the effects of age and TBI are mirrored by inconsistencies in findings from our own cohort, such that, in our earlier analysis,⁶ younger age at transplantation (< 3 years old) emerged as a significant predictor of cognitive decline, whereas TBI did not. In contrast, in our subsequent analysis, with a larger cohort and longer follow-up, we no longer found a significant age effect, whereas TBI had a small, but significant, impact.⁷

Given the discrepancies in the literature, as well as those observed in our own cohort, the objective of the current study was to attempt to disentangle the impact of age and TBI on the trajectory of cognitive functioning after SCT. We first characterized the cognitive functioning of our sample at 5 years after SCT, based on age at baseline and history of TBI. We then used longitudinal analyses to evaluate the impact of age at baseline and history of TBI over time. As such, we expanded our previous cohort of patients by recruiting an additional sample of patients who were younger than 6 years old at the time of SCT. It was hypothesized that although our cohort as a whole would demonstrate relatively intact cognitive functioning over time, declines would be observed in patients who were younger than 6 years old at

the time of transplantation and who received TBI as part of their conditioning regimen.

PATIENTS AND METHODS

Patients and Procedures

Patients who were scheduled to undergo an SCT (allogeneic or autologous) at St Jude Children's Research Hospital (Memphis, TN) were eligible for the study. Exclusion criteria included diagnosis of a brain tumor and non-English speakers. Patients were scheduled for assessments before SCT and 1, 3, and 5 years after SCT. Two cohorts of patients were enrolled (Fig 1). The first cohort included 268 patients of all ages who enrolled onto study and completed a neurocognitive assessment before SCT. Findings from this cohort were previously reported.⁷ Of these, 158 patients (58.9%) were alive at 1 year after SCT and completed at least one additional assessment. The second cohort included 47 patients younger than 6 years old who were scheduled to undergo transplantation; 25 of these patients (53.2%) survived and completed multiple assessments.

The combined cohort included 315 patients who completed a baseline evaluation before SCT and 183 patients (58.1%) who completed additional assessments. Table 1 lists the demographics and medical characteristics of the baseline and 1-year survivor cohorts, and Figure 1 shows the recruitment process. Multiple SCT treatment protocols are represented among our sample; however, a limited number of conditioning regimens were used and have been previously described.⁷ Approximately half of the sample who survived for 1 year after transplantation (52.1%) received TBI. Depending on the donor type (matched sibling or unrelated), TBI was administered to a total dose of either

Table 1. Demographics and Medical Characteristics of the Study Sample

Characteristic	Baseline Cohort (N = 315)		1-Year Survivors (n = 183)	
	No.	%	No.	%
Age, years				
Mean	9.58		8.95	
Median	8.71		6.92	
Standard deviation	6.36		6.34	
Range	0.25-24.50		0.33-23.75	
Sex				
Male	174	55.3	101	55.1
Female	141	44.7	82	44.9
Socioeconomic status				
I and II (high)	95	30.1	61	33.5
III (middle)	104	33.1	57	31.3
IV and V (low)	116	36.7	65	35.2
Diagnosis				
ALL	57	18.2	22	12.0
AML	101	32.1	52	28.5
Other leukemia	53	16.8	38	20.9
Solid tumor	64	20.2	41	22.7
Nonmalignancy	40	12.7	30	16.5
Transplantation type				
Allogeneic	212	67.5	113	62.0
Autologous	100	31.8	70	38.0
Other	2	0.7	—	—
Conditioning with TBI				
Yes			95	52.1
No			88	47.9
Acute GVHD				
None			121	66.0
Mild			46	25.0
Severe			16	9.0
Chronic GVHD				
None			156	85.1
Limited			18	9.6
Extensive			9	5.3

NOTE. There were no demographic differences (age at baseline, sex, or SES) between patients who did and did not survive to the 1 year post-transplantation assessment. Patients who had an autologous transplantation were more likely to survive to the 1-year evaluation ($P < .01$).
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GVHD, graft-versus-host disease; TBI, total-body irradiation.

12 or 14 Gy, respectively, in eight fractions over 4 days. For the purpose of analyses, patients were dichotomized into those who received TBI and those who did not. Patients who received TBI were older at baseline ($P < .01$), more likely to have received an allogeneic transplantation ($P < .001$), and more likely to have experienced graft-versus-host disease ($P < .001$).

Measures

Standardized measures of global intelligence were used, with measures selected based on age of the patient at the time of assessment. Given the length of this longitudinal study, new versions of each measure were released and integrated as needed. Efforts were made to evaluate patients with the same instrument throughout their participation. Analyses were conducted to verify that change of instrumentation did not influence overall results (data not shown). Because of the wide age range of the cohort and our interest in longitudinal changes, analyses were limited to global outcomes that could be assessed across all participants at all time points.

Bayley Scales of Infant Development. These scales are designed for infants and toddlers age 1 to 42 months.^{15,16} They provide the following two global scores: the Mental Development Index and the Psychomotor Develop-

ment Index. Standard scores with a mean of 100 and a standard deviation of 15 are derived.

Wechsler Intelligence Scales. The Wechsler scales are the most commonly used measures of intelligence, with well-documented psychometric properties. Versions are available for young children (age 3 to 6 years: Wechsler Preschool and Primary Scales of Intelligence, Revised¹⁷), school-age children (age 6 to 16 years: Wechsler Intelligence Scale for Children^{18,19}), and adults (age ≥ 16 years: Wechsler Adult Intelligence Scale^{20,21}). Standard scores are derived with a mean of 100 and a standard deviation of 15. At baseline, a three-subtest version that yields an estimated intelligence quotient (IQ) score that is highly correlated with the full-scale IQ ($r = 0.92$ to 0.94)^{22,23} was administered. The full battery was administered at subsequent time points. However, to be consistent, the three-subtest prorated IQ score was used for all longitudinal analyses. There was a strong correlation ($r = 0.93$, $P < .001$) between the year 5 prorated and full-scale IQ scores.

Statistical Approach

One-way analyses of variance were conducted to evaluate the impact of age at baseline on prorated IQ at baseline and year 5. Analyses were conducted with patients divided into the following four categorical age ranges: 0 to 2.99, 3 to 5.99, 6 to 15.99, and ≥ 16 years of age. These age ranges correspond to those dictated by the various measures of cognitive functioning (Bayley scales and Wechsler scales). Independent sample t tests were conducted to assess the impact of history of TBI or no TBI at year 5, with analyses completed for each age group separately. Piecewise linear mixed-effects models were then conducted with a knot at 1 year after SCT, which showed the best fitting using either Akaike information criterion or Bayesian information criterion compared with a simple linear model or knots fitted at other time points. This method allowed for separate slopes to be calculated for the time frames of baseline to 1 year and 1 year to 5 years after SCT. In the final fitted model, age was treated as a continuous variable to maximally use the information. Missing data are treated as missing at random rather than missing not at random. A linear mixed-effects model is a likelihood-based procedure and handles missing at random as ignorable.²⁴

RESULTS

Baseline and Year 5 Outcomes

At the pretransplantation baseline evaluation, there were no differences in prorated IQ across the four age groups (0 to 2.99, 3 to 5.99, 6 to 15.99, and ≥ 16 years), with all means within the average range (Table 2). At 5 years after SCT, there was a significant effect of TBI on prorated IQ, but only for the youngest patients. Specifically, the mean prorated IQ for the youngest patients who received TBI was more than 16 points lower than the IQ of those who did not receive TBI (Table 2) and fell below the average range. The same pattern was true when analyses were conducted with the full-scale IQ score at year 5 ($P < .04$).

Preliminary Observations

Prorated IQ scores were plotted to observe changes in IQ values across time by addressing age effect at the same time. Patients were again divided into four age ranges (0 to 2.99, 3 to 5.99, 6 to 15.99, and ≥ 16 years). Examination of preliminary plots revealed potential variability in prorated IQ based on both age at baseline and time (Fig 2A). Specifically, a pronounced decline in prorated IQ was seen in the younger patients from baseline to year 1, with additional changes in functioning observed after year 1 (eg, either increases in IQ or stability depending on age). The same method was used to observe the effect of TBI over time (Fig 2B) and revealed similar trajectories regardless of TBI, with a decline in prorated IQ from baseline to year 1 and additional variability after year 1.

Table 2. Prorated IQ at Baseline and Year 5, Differentiated by Age at Baseline and History of TBI (year 5 only)

Baseline and Victory IQ TBI (years 0 only)							
Factor	Baseline Prorated IQ Score, All Patients (n = 170)		Year 5 Prorated IQ Score				P ^a
	Mean	SD	No TBI (n = 33)		TBI (n = 49)		
			Mean	SD	Mean	SD	
Age at baseline, years							
0-2.99	99.97	16.40	98.40	14.57	81.82	20.7	.05
3-5.99	96.46	11.87	91.33	12.18	94.00	19.82	.77
6-15.99	94.50	16.82	94.29	15.57	87.91	19.3	.31
≥ 16	92.75	15.84	102.00	8.72	99.71	15.38	.82
P	.27†		.24‡		.66‡		

Abbreviations: IQ, intelligence quotient; SD, standard deviation; TBI, total-body irradiation.

*P value for independent sample *t* tests to compare the difference in prorated IQ for TBI versus no TBI by age at baseline.

†P value for a one-way analysis of variance to determine whether there are differences in baseline prorated IQ by age at baseline.

‡P value for a one-way analysis of variance to determine whether there are differences in year 5 prorated IQ by age at baseline; analyses were completed separately for the TBI and no TBI groups.

Longitudinal Trajectories

Given the significant change in functioning observed in the youngest patients (as demonstrated in Fig 2A and by our year 5 analyses), as well as the extant literature regarding the potential impact of TBI on young patients, a piecewise mixed model was conducted to investigate the effects of age and TBI simultaneously (Table 3 and Fig 3). Separate slopes were fitted for the periods before and after 1 year after SCT. Results demonstrated no differences in baseline IQ based on age or scheduled treatment with TBI, confirming relatively equal groups before initiation of SCT. Furthermore, baseline IQ scores for all patients were comparable to normative means (Table 2).

Results of the piecewise mixed model are listed in Table 3. During the first year after transplantation, there was a significant effect of age. Specifically, there was an overall decline in IQ regardless of whether patients were conditioned with TBI, and there was no difference between patients who did and did not receive TBI ($P = .48$). The significant age effect ($P < .001$) indicates that the decline is greater in younger patients and gets smaller with increasing age. After year 1, there was no further change in those conditioned with TBI, and cognitive function remained relatively stable (slope = 0.13, $P = .84$). However, there was a significant improvement in cognitive functioning for patients conditioned without TBI (slope = 1.28, $P = .04$), who began to recover year 1 losses and return toward baseline levels of functioning. There was a nonsignificant trend for this difference in slopes based on conditioning with or without TBI ($P = .06$). This effect does not significantly differ by age.

In Figure 3, example fitted trajectories were plotted for patients who were of theoretical ages of interest at baseline (age 3 and age 12 years). These ages were chosen to illustrate the different trajectories observed for younger and older children, who underwent transplantation with and without TBI. As seen in Figure 3, the greatest declines were observed in the youngest patients, regardless of whether they were conditioned with TBI. After the first year, patients who did not receive TBI demonstrated a significant increase in IQ over time, with a

Fig 2. Data plots to observe change in intelligence quotient (IQ) over time. Data were plotted separately for (A) age at baseline and (B) receipt of total-body irradiation (TBI). No analyses were completed here, but rather prorated IQ scores were plotted to allow for observation of trends based on either age at baseline or TBI. (A) The data suggested that the youngest patients demonstrated a decrease in functioning from baseline to year 1 and then either stabilized (age 0 to 2.99 years) or recovered (age 3 to 5.99 years). (B) With regard to TBI, the data suggested that all patients demonstrated a decrease from baseline to year 1, and then patients who did not receive TBI showed improvements in prorated IQ over time. This decline in functioning observed from baseline to year 1 for all patients, regardless of age at baseline or conditioning with TBI, suggested the use of a piecewise linear mixed-effects model with a knot at 1 year to allow for the calculation of different slopes before and after 1 year after transplantation.

steeper slope observed for younger patients. In contrast, the young patients who did receive TBI demonstrated a generally flat trajectory, indicating stability in IQ after 1 year, with a failure to recover any of the year 1 losses.

Exploratory Analysis: Impact of SES

Given prior research^{6,7} highlighting the impact of SES on cognitive functioning, exploratory analyses added SES to the piecewise model. Results suggested that SES had a significant impact on baseline functioning, with children from low SES families demonstrating significantly lower IQs than those from middle or high SES families ($P < .01$). However, SES did not impact slope. This suggests that the impact of age and TBI on slope is stronger than that of SES, whereas the effect of SES is seen only on intercept.

Table 3. Piecewise Linear Mixed-Effects Model of Prorated IQ by Age at Baseline and History of TBI

Effect	Estimate	SE	P
Intercept*†			
TBI_No*	97.05	2.34	.21
TBI_Yes*	95.98	2.71	.14
Δ TBI_No–TBI_Yes†	1.07	2.49	.67
Age at baseline†	–0.16	0.20	.42
Slope before 1 year‡			
TBI_No	–8.52	2.11	< .001
TBI_Yes	–9.96	2.26	< .001
Δ TBI_No–TBI_Yes	1.44	2.06	.48
Age at baseline	0.67	0.16	< .001
Slope after 1 year‡			
TBI_No	1.28	0.63	.04
TBI_Yes	0.13	0.64	.84
Δ TBI_No–TBI_Yes	1.16	0.62	.06
Age at baseline	–0.04	0.05	.48

NOTE. In the fitted model, rather than using a single changing rate over time (slope), we used two slopes with one knot at 1 year by designing two time variables representing baseline to 1 year and 1 year to 5 years. The SEs indicate the variability of estimated parameters in this model setting. Age indicates the parameter estimates for age (to calculate estimate for a specific age, multiply estimate by age).

Abbreviations: TBI, total-body irradiation; TBI_No = patients who did not receive TBI; TBI_Yes, patients who did receive TBI; Δ TBI_No–TBI_Yes, the difference in estimates between patients who did and did not receive TBI.

*P value represents univariable analysis to determine whether intercept is different from an expected (normative) mean of 100.

†P value represents analysis to determine whether intercept is different than an expected intercept of 0.

‡P value represents analysis to determine whether slope is different than an expected slope of 0. Slope of 0 would indicate no change in scores over time (either before or after 1 year).

Fig 3. Piecewise linear mixed-effects model to illustrate the effect of age at baseline and conditioning with total-body irradiation (TBI) over time. Two ages of theoretical interest (age 3 and 12 years at baseline) were chosen to demonstrate predicted pathways. Findings suggest that patients, regardless of age at baseline, evidence a decline in cognitive functioning from baseline to 1 year after stem-cell transplantation (SCT). Then, the majority of patients demonstrate a return to baseline levels (if not higher for older patients) over the next years (through 5 years after SCT). However, young patients who receive TBI do not recover their losses and instead stabilize. Information regarding how these predictions were calculated is available in Table 3. IQ, intelligence quotient.

DISCUSSION

The current study examined the influence of young age and conditioning with TBI on cognitive outcomes after pediatric SCT. Results revealed that both younger age and use of TBI have adverse effects on global cognitive functioning after SCT, but at different time points, with age effects seen primarily in the first year after SCT and TBI effects occurring only after the first year. Although young patients who did not receive TBI evidenced a decline in functioning during the first year after SCT, they demonstrated significant gains in subsequent years and largely recovered year 1 losses. Overall, significant cognitive declines are observed only in patients who were both less than 3 years of age at SCT and received TBI. Exploratory analyses suggest that SES impacted IQ at baseline but did not affect change in IQ after that point.

Our findings are surprising given what would be expected based on research with other populations who receive CNS-directed therapies. Specifically, survivors of leukemia and brain tumors often experience a gradual decline in neurocognitive functioning over time, with significant deficits typically observed several years after completion of treatment.^{25,26} It may be that the significant decline observed in the first year reflects the intensity of the transplantation process, which results in a greater disruption in development in younger children. Then, for patients who do not receive TBI, learning is accelerated once the patient physically recovers, resulting in a return to baseline functioning. The CNS impact of TBI may result in an inability to accelerate learning and a failure to catch up in younger patients. Such hypotheses are admittedly speculative and require further study.

Despite the relative stability in global cognitive functioning of most survivors of SCT, there remain questions regarding the potential for neurocognitive late effects in areas such as attention, working memory, processing speed, and executive functioning. Recent research with children treated for acute lymphoblastic leukemia (ALL) without cranial radiation therapy²⁷ suggested the presence of significant attention problems, even in the face of intact intellectual functioning. Other studies have demonstrated similar findings with processing speed²⁸ and working memory.^{29,30} Although continued comprehensive serial assessments may only be beneficial for patients who are most at risk (ie, young patients who receive TBI), future studies are needed to evaluate more specific neurocognitive functions in all patients to ensure relative stability in those domains. Past research with survivors of brain tumors and ALL^{31,32} would support the hypothesis that the minor declines in global functioning observed in older patients who received TBI could be accounted for by larger declines in these key neurocognitive areas.

The significant decline observed in the first year after SCT for young patients treated with TBI and the lack of return of functioning after that year highlight the potential benefit of early intervention for these vulnerable patients. Although many hospitals include rehabilitative and school services during transplantation as part of standard of care, these services may need to be intensified (or implemented) for the youngest patients. Provision of a stimulating environment throughout transplantation (inpatient and outpatient), along with one-on-one enrichment-focused play, could be particularly beneficial.

Questions also remain regarding the long-term outcomes (> 5 years) for patients who undergo SCT. Indeed, although our findings are reassuring regarding the global cognitive functioning of most patients, minor declines were observed in all patients who received TBI, regardless of age, and this seemed to be particularly apparent at

the 5-year time point. It is certainly possible that these declines may have a greater impact on long-term educational and/or vocational attainment. For example, a recent study of French survivors of SCT³³ demonstrated reduced rates of academic attainment, even in patients who did not receive TBI. It has been documented that survivors of pediatric brain tumors experience delays in the attainment of advanced developmental milestones (eg, jobs, living independently, romantic relationships),^{34,35} whereas survivors of ALL are generally commensurate with population norms.³⁶ The long-term outcomes of SCT survivors have not been studied in the same manner and are certainly deserving of attention. Moreover, given the increasing survival rates after SCT, these patients represent a growing population of emerging adults.

Coupled with the need for additional assessment is the need to replicate the findings demonstrated in this study within other institutions. Indeed, a limitation of the current study is its single-institution design, although our sample is well balanced with regard to cultural and socioeconomic backgrounds. However, studies are needed to replicate these findings, particularly given the variability in cognitive functioning after SCT described in the extant literature. In addition, our groups were not randomly assigned to either TBI or no TBI. Although the lack of demographic or treatment differences between groups is reassuring, there is potential bias that we could not account for. Another limitation is the need for patients to change instruments over the course of the study, most notably from the Bayley to the Wechsler scales, a challenge that is inherent to longitudinal work with young participants. However, we completed analyses that verified that there was no difference in trajectory for those patients who changed instruments and those who did not. Finally, our reliance on global IQ as the primary outcome may underestimate adverse cognitive effects,

because effects on specific domains such as processing speed or working memory were not addressed.

In summary, the findings from this study highlight the relative stability of intellectual functioning (IQ) in pediatric patients who undergo SCT, with only the youngest patients conditioned with TBI appearing at significant risk of decline. This study also was able to disentangle the various trajectories observed in patients through the use of advanced statistical methods to evaluate the interaction between age and TBI. Findings highlight the possible benefits of intervening early with young patients who receive TBI to both prevent that decline in functioning and to increase the rate of return to functioning after the first year. Future studies are needed to both replicate and extend the current findings and to design intervention opportunities that could be implemented with our youngest patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Sean Phipps
Provision of study materials or patients: Wing Leung
Collection and assembly of data: Sean Phipps
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

Akaike information criterion: a measure of the goodness of fit of a statistical model that discourages overfitting and is used as a tool for model selection. For a given data set, competing models are ranked according to their Akaike information criterion value. The one with the lowest value is considered the best; however, there is no established value above which a given model is rejected.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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