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Effect of Tandem Autologous Stem Cell Transplant vs Single Transplant on Event-Free Survival in Patients With High-Risk Neuroblastoma
A Randomized Clinical Trial

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IMPORTANCE Induction chemotherapy followed by high-dose therapy with autologous stem cell transplant and subsequent antidisialoganglioside antibody immunotherapy is standard of care for patients with high-risk neuroblastoma, but survival rate among these patients remains low.

OBJECTIVE To determine if tandem autologous transplant improves event-free survival (EFS) compared with single transplant.

DESIGN, SETTING, AND PARTICIPANTS Patients were enrolled in this randomized clinical trial from November 2007 to February 2012 at 142 Children's Oncology Group centers in the United States, Canada, Switzerland, Australia, and New Zealand. A total of 652 eligible patients aged 30 years or younger with protocol-defined high-risk neuroblastoma were enrolled and 355 were randomized. The final date of follow-up was June 29, 2017, and the data analyses cut-off date was June 30, 2017.

INTERVENTIONS Patients were randomized to receive tandem transplant with thiotepa/cyclophosphamide followed by dose-reduced carboplatin/etoposide/melphalan (n = 176) or single transplant with carboplatin/etoposide/melphalan (n = 179).

MAIN OUTCOMES AND MEASURES The primary outcome was EFS from randomization to the occurrence of the first event (relapse, progression, secondary malignancy, or death from any cause). The study was designed to test the 1-sided hypothesis of superiority of tandem transplant compared with single transplant.

RESULTS Among the 652 eligible patients enrolled, 297 did not undergo randomization because they were nonrandomly assigned (n = 27), ineligible for randomization (n = 62), had no therapy (n = 1), or because of physician/parent preference (n = 207). Among 355 patients randomized (median diagnosis age, 36.1 months; 152 [42.8%] female), 297 patients (83.7%) completed the study and 21 (5.9%) were lost to follow-up after completing protocol therapy. Three-year EFS from the time of randomization was 61.6% (95% CI, 54.3%-68.9%) in the tandem transplant group and 48.4% (95% CI, 41.0%-55.7%) in the single transplant group (1-sided log-rank *P*=.006). The median (range) duration of follow-up after randomization for 181 patients without an event was 5.6 (0.6-8.9) years. The most common significant toxicities following tandem vs single transplant were mucosal (11.7% vs 15.4%) and infectious (17.9% vs 18.3%).

CONCLUSIONS AND RELEVANCE Among patients aged 30 years or younger with high-risk neuroblastoma, tandem transplant resulted in a significantly better EFS than single transplant. However, because of the low randomization rate, the findings may not be representative of all patients with high-risk neuroblastoma.

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Visual Abstract

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Supplemental content

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Neuroblastoma is a pediatric cancer of the developing sympathetic nervous system that accounts for 10% to 12% of deaths from malignancy in childhood.[1] It arises in sympathetic ganglia or the adrenal glands with propensity to metastasize to lymph nodes, bone, bone marrow, liver, and, rarely, to lungs and the central nervous system. Forty-three percent of children diagnosed with neuroblastoma and enrolled in Children's Oncology Group trials present with high-risk disease, characterized by widespread metastasis in patients older than 18 months and/or amplification of the *MYCN* oncogene.[1] Standard of care for patients with high-risk neuroblastoma includes multiagent chemotherapy induction and surgical tumor resection, consolidative high-dose chemotherapy with autologous stem cell transplant, posttransplant radiotherapy, and postconsolidation treatment with biological agents and immunotherapy.[2] This approach has resulted in improved overall survival (OS), but relapses occur in 50% to 60% of patients,[3-5] and more than 90% of patients who relapse die of the disease.[6-9]

Results of nonrandomized clinical trials suggested that intensification of consolidation therapy using sequential or "tandem" autologous transplant after induction therapy was feasible and may improve outcome in patients with high-risk neuroblastoma.[10-12] Children's Oncology Group trials demonstrated collection of sufficient numbers of autologous peripheral blood stem cells (PBSC) to support tandem transplant using a topotecan-containing induction regimen[13] and described the toxicity profile and feasibility of a tandem high-dose chemotherapy regimen.[12] These pilot trials provided the rationale for the current multicenter randomized clinical trial, which included a uniform induction regimen followed by randomization to receive high-dose chemotherapy and single or tandem autologous transplant for patients without a defined contraindication to transplant. The primary objective of this randomized clinical trial was to determine whether intensifying consolidation treatment with tandem transplant can improve event-free survival (EFS) compared with single transplant.

Key Points

Question Does intensification of consolidation therapy using tandem autologous transplant improve event-free survival for patients with high-risk neuroblastoma?

Findings In this randomized clinical trial that included 652 eligible patients with high-risk neuroblastoma, tandem autologous stem cell transplant vs single transplant resulted in 3-year event-free survival of 61.6% vs 48.4%, a difference that was statistically significant.

Meaning Tandem autologous transplant after induction chemotherapy resulted in better event-free survival than single transplant, but, because of the low randomization rate, the findings may not be representative of all patients with high-risk neuroblastoma.

Methods

Study Design

Patients were enrolled in the Children's Oncology Group Study ANBL0532 at 142 participating Children's Oncology Group institutions (see the protocol in Supplement 1). The protocol and amendments (Supplement 1 and Supplement 2) were reviewed and approved by the institutional review boards at each enrolling center. Written informed consent was obtained from the patient or guardian prior to enrollment and randomization. The study was open to accrual from November 2007 to February 2012. The final date of follow-up was June 29, 2017, and the data cut-off date for analyses was June 30, 2017.

Participants

Eligible patients had newly diagnosed high-risk neuroblastoma, as defined by Children's Oncology Group criteria,[14] including patients with International Neuroblastoma Staging System (INSS) stage 4 neuroblastoma who were older than 18 months; INSS stage 3 neuroblastoma who were older than 18 months with International Neuroblastoma Pathology Classification (INPC) of unfavorable histology[15]; INSS stage 2, 3, 4, or 4S neuroblastoma with *MYCN* amplification; and INSS stage 4 neuroblastoma diagnosed from age 12 to 18 months whose tumors showed any unfavorable features (*MYCN* amplification, unfavorable histology, diploidy, or data indeterminate). Patients initially diagnosed with non–high-risk neuroblastoma (including stage 1) who had not received chemotherapy and progressed to high-risk neuroblastoma were eligible. Permitted prior therapy included emergency radiotherapy to manage a life-threatening or organ function–threatening tumor or 1 cycle of alternative chemotherapy before the determination of high-risk status. Enrollment criteria included registration in a companion biology study (Children's Oncology Group Study ANBL00B1); age 30 years or younger; adequate kidney, cardiac, and liver function; and anticipated ability to tolerate PBSC collection, based the on treating facility's guidelines for collection.

Randomization

Patients eligible for inclusion were randomized in a 1:1 ratio prior to the start of consolidation therapy to receive single transplant or tandem transplant. Randomization was balanced for the following prognostic factors, resulting in 15 possible strata: tumor *MYCN* amplification, INSS stage at diagnosis, and response to induction therapy.[5,16] Missing *MYCN* data were considered "*MYCN* not amplified" for the purposes of randomization. Randomization was conducted in block sizes of 2 to these strata; block size was not available in the protocol or disclosed to study personnel, sites investigators, research associates, or participants. Computer-generated randomization occurred at the Children's Oncology Group statistical office and institutions were informed of the unmasked treatment assignment.

Interventions

The protocol therapy included 3 phases: induction,[13] consolidation,[4,12] and postconsolidation[16-18] (eFigure S1 in Supplement 3). Induction therapy began with 2 cycles of

topotecan/cyclophosphamide, after which patients underwent PBSC collection followed by 4 alternating cycles of cisplatin/etoposide and doxorubicin/cyclophosphamide/vincristine.[13] Surgical resection of the primary tumor (if not performed at diagnosis) occurred after cycle 4 or 5. Disease response was evaluated after cycle 2 and after completion of induction chemotherapy.

Eligibility for consolidation therapy included no disease progression; no uncontrolled infection; recovery from induction therapy toxicity; sufficient PBSC level (≥4×10^6 CD34+ cells/kg); and adequate kidney, cardiac, and liver function. Patients with a more favorable prognosis[19-21] (patients aged 12-18 months with INSS stage 4 neuroblastoma with a favorable histology, hyperdiploid DNA content, and no *MYCN* amplification or patients aged >18 months with INSS stage 3 neuroblastoma with no *MYCN* amplification and an unfavorable histology) were nonrandomly assigned to receive a single transplant. Their data do not contribute to the analyses presented. Patients randomized to the single transplant group received carboplatin, etoposide, and melphalan using a previously published regimen,[4,13] with dosing adjusted for patients with low glomerular filtration rate and for patients who weighed less than 12 kg. Patients in the tandem transplant group received cyclophosphamide/thiotepa followed by dose-reduced carboplatin, etoposide, and melphalan 6 to 10 weeks later[12] (eTable S1 in Supplement 3). Criteria for receiving a second transplant included no clinical evidence of neuroblastoma progression; available PBSC product; resolution of acute toxicity from the first transplant; adequate cardiac, kidney, hematopoietic, and hepatic function; no uncontrolled infection; and no history of moderate or severe sinusoidal obstruction syndrome during the first transplant. Participants received PBSC infusion (at least 1×10^6 CD34+ cells/kg) following completion of each high-dose chemotherapy regimen. After recovery from the single or tandem transplant, patients received radiotherapy to the primary site and sites of residual or metaiodobenzylguanidine-positive metastatic sites detected at the end of the induction therapy.

Patients without disease progression following consolidation therapy received twice-daily oral isotretinoin for 14 days of each month for 6 months.[16] Per protocol, patients were strongly encouraged to enroll in 1 of 2 Children's Oncology Group trials (ANBL0032 or ANBL0931), which evaluated antidisialoganglioside (GD2) chimeric antibody and cytokines immunotherapy[17,18] in addition to isotretinoin. Outcome data were captured for patients enrolled in these trials.

Outcomes

The primary outcome was EFS from the time of randomization to the occurrence of the first event (ie, relapse, progressive disease, second malignancy, or death), calculated within the subgroup of randomized patients with high-risk neuroblastoma. Patients without an event were censored on the date of last contact. Two additional primary outcomes were response assessed at the end of the induction therapy and local recurrence, which will be reported separately to allow for full presentation of the interventions, clinical data, and outcomes with comparisons to historical data (Supplement 1). There were 10 secondary outcomes (see the study protocol in Supplement 1) that will be reported separately.

The post hoc outcomes were (1) OS time, defined as the time from randomization until the time of death from any cause (patients who were last reported alive were censored on date of last contact); (2) EFS time from enrollment (or the beginning of treatment for patients who underwent emergency treatment before enrollment), calculated from the earliest date of enrollment (or the beginning of treatment), until occurrence of the first event for the overall cohort; and (3) EFS and OS time from the start of postconsolidation immunotherapy within the subgroup of patients assigned to receive postconsolidation immunotherapy in Children's Oncology Group Study ANBL0032 or ANBL0931.

Statistical Methods

Power Analysis and Sample Size Calculation

The study was powered to address the primary objective by enrolling 664 patients, with an expected randomization rate at the end of induction therapy of at least 50%, to yield 332 randomized patients and 80% power to detect a 12% difference in 3-year EFS from time of randomization using a 1-sided log-rank test at a significance level of .05. A 12% difference in EFS was deemed of clinical benefit and chosen based on contemporary clinical trial designs for high-risk neuroblastoma.[4,5] Accrual to the study was halted once the planned accrual goal was met.

Statistical Analyses

The primary analysis was an intention-to-treat comparison of EFS from randomization between single vs tandem transplant groups using a 1-sided log-rank test. Patients were analyzed according to their assigned treatment group, and all randomized patients were included in the comparison. Interim monitoring of EFS for futility or superiority of the tandem transplant group using Fleming-Harrington-O'Brien boundaries was performed yearly starting after 20% of the expected events had occurred. EFS curves were generated using the Kaplan-Meier method,[22] with point estimates reported at 3 years and 95% CI with standard errors calculated per the methods of Peto et al.[23]

Post hoc analyses included (1) a comparison of OS rates for the tandem transplant vs single transplant group using a 2-sided log-rank test; (2) a comparison of EFS and OS rates for the tandem transplant vs single transplant group, using a 2-sided log-rank test, among the subgroup of patients who received postconsolidation immunotherapy (EFS and OS curves were generated as noted per methods described above); and (3) identification of features independently prognostic of EFS (within the context of the standard treatment for high-risk neuroblastoma) among previously validated neuroblastoma prognostic features,[24] including response after induction therapy using International Neuroblastoma Response Criteria,[25] INSS stage (non–stage 4 vs stage 4), age (<18 months vs ≥18 months), *MYCN* status (nonamplified vs amplified), and INPC histology (favorable vs unfavorable). Multivariable Cox proportional hazards models were fit using the Efron method of handling-tied event times, and the assumption of proportionality

Table 1. Characteristics of Eligible Patients With High-Risk Neuroblastoma in a Study of the Effect of Tandem Transplant vs Single Transplant on Event-Free Survival

Characteristic	No. (%)[a]		
	Tandem Transplant Group (n = 176)	Single Transplant Group (n = 179)	All Patients (n = 652)
Age at diagnosis, median (q1-q3), mo	34.1 (22.4-52.1)	37.3 (23.0-51.8)	37.2 (23.0-53.6)
Sex			
Female	78 (44.3)	74 (41.3)	286 (43.9)
Male	98 (55.7)	105 (58.7)	366 (56.1)
MYCN oncogene			
Amplified	83 (47.2)	81 (45.3)	249 (38.2)
Not amplified	74 (42.0)	76 (42.5)	327 (50.2)
Unknown	19 (10.8)	22 (12.3)	76 (11.7)
Histology			
Favorable	4 (2.3)	5 (2.8)	23 (3.4)
Unfavorable	155 (88.1)	151 (84.4)	588 (86.2)
Unknown	17 (9.7)	23 (12.8)	71 (10.4)
INSS stage[b]			
1 or 2	2 (1.1)	2 (1.1)	7 (1.1)
3	16 (9.1)	16 (8.9)	68 (10.4)
4s	1 (0.6)	0	3 (0.5)
4	157 (89.2)	161 (89.9)	574 (88.0)
Primary site			
Adrenal	87 (49.4)	72 (40.2)	277 (42.5)
Abdominal, other	68 (38.6)	82 (45.8)	281 (43.1)
Paraspinal, other	1 (0.6)	2 (1.1)	8 (1.2)
Thorax	11 (6.3)	8 (4.5)	40 (6.1)
Other	9 (5.1)	15 (8.4)	46 (7.1)
Response after cycle 2 induction chemotherapy			
At least partial response	80 (45.5)	83 (46.4)	255 (39.1)
No/mixed response	71 (40.3)	63 (35.2)	262 (40.2)
Progressive disease	2 (1.1)	4 (2.2)	28 (4.3)
Not evaluated or missing	23 (13.1)	29 (16.2)	107 (16.4)
Response after induction therapy			
Complete/very good partial response	85 (48.3)	91 (50.8)	277 (42.5)
Partial response	73 (41.5)	72 (40.2)	213 (32.7)
No/mixed response	17 (9.7)	13 (7.3)	79 (12.1)
Progressive disease	1[c] (0.6)	3[c] (1.7)	46 (7.1)
Not evaluated/missing	0	0	37 (5.7)
Immunotherapy[d]	121 (68.8)	129 (72.1)	373 (57.2)

Abbreviations: INSS, International Neuroblastoma Staging System; q1, first quartile; q3, third quartile.

[a] Percentages were calculated on the basis of patients with data available for the given characteristic.

[b] INSS[24] stage 1 and 2 includes localized tumor with complete resection or incomplete resection with ipsilateral nonadherent node involvement; stage 3 includes unresectable locoregional tumor infiltrating across midline or with direct extension into normal structures or with contralateral node involvement; stage 4s is localized primary tumor with special metastatic dissemination limited to liver, skin and bone marrow; stage 4 is any primary tumor with dissemination to distant sites (except as defined for stage 4s).

[c] Response was revised after initial complete response, partial response, and progressive disease.

[d] Participants underwent immunotherapy in Children's Oncology Group Study ANBL0032 or ANBL0931,[17,18] which were clinical trials investigating the use of postconsolidation immunotherapy.

was tested by visual inspection of survival curves. INSS stage and age were known for all patients, but patients with missing end-induction response, *MYCN* status, or INPC were excluded from the Cox model.

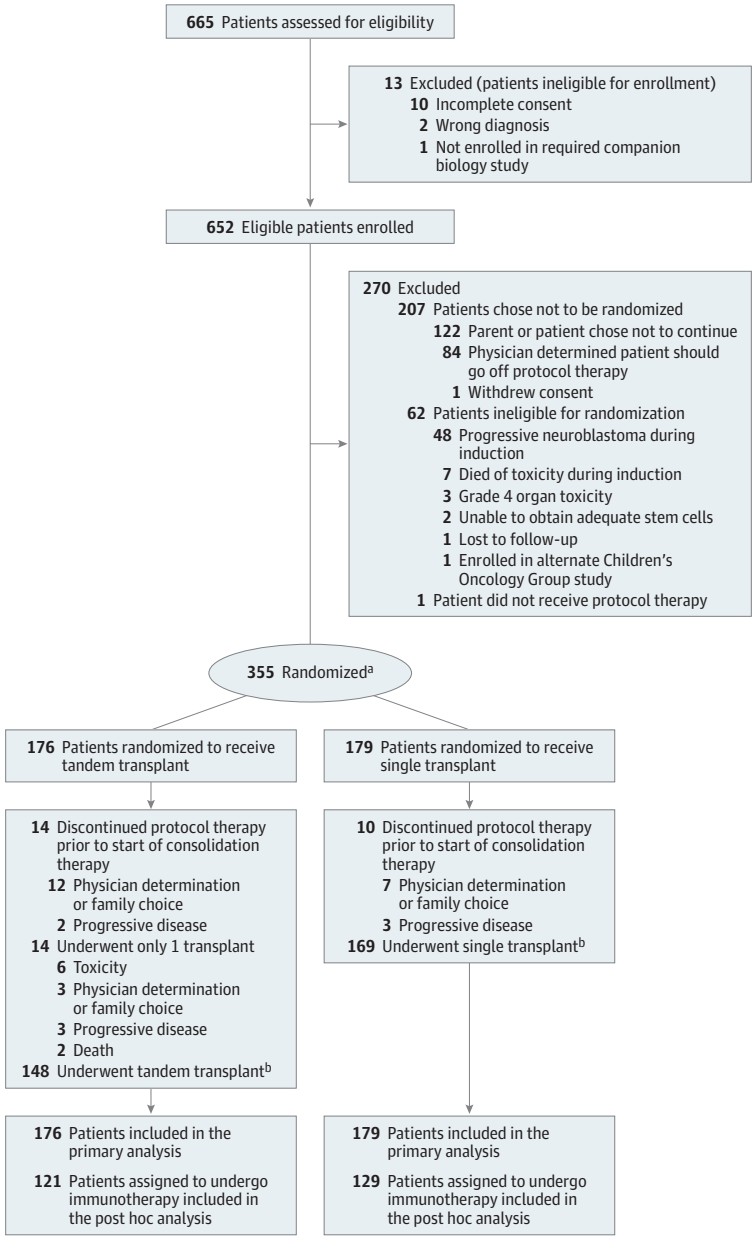
For primary analyses, 1-sided *P* values less than .05 were considered statistically significant and for post hoc analyses, 2-sided *P* values less than .05 were considered statistically significant. Analyses were performed using SAS version 9.4 and survival curves were generated using R software. Patients were followed up for up to 10 years after study enrollment for occurrence of an event. Because of the possibility of type I error, findings from analyses other than the primary analysis should be considered exploratory.

Results

Characteristics of Study Patients

A total of 665 patients were enrolled between November 2007 and February 2012 and 13 were deemed ineligible for enrollment. The analytic cohort was composed of 652 eligible patients with a median age of 37.2 months at diagnosis (**Table 1**), including 6 patients who had progressed from non–high-risk disease to high-risk disease without intervening chemotherapy. One patient did not receive any therapy and 27 patients were nonrandomly assigned to the single transplant group. Of the remaining patients, 62 were ineligible for

Figure 1. Enrollment and Randomization of Patients in a Study of the Effect of Tandem Transplant vs Single Transplant on Event-Free Survival in Patients With Neuroblastoma



[a] Twenty-seven patients with favorable characteristics were nonrandomly assigned to receive single transplant. Outcome for patients nonrandomly assigned to receive single transplant will be reportedly separately.

[b] Thirty patients (14 in the single transplant and 16 in the tandem transplant group) discontinued protocol therapy after receiving the allocated intervention.

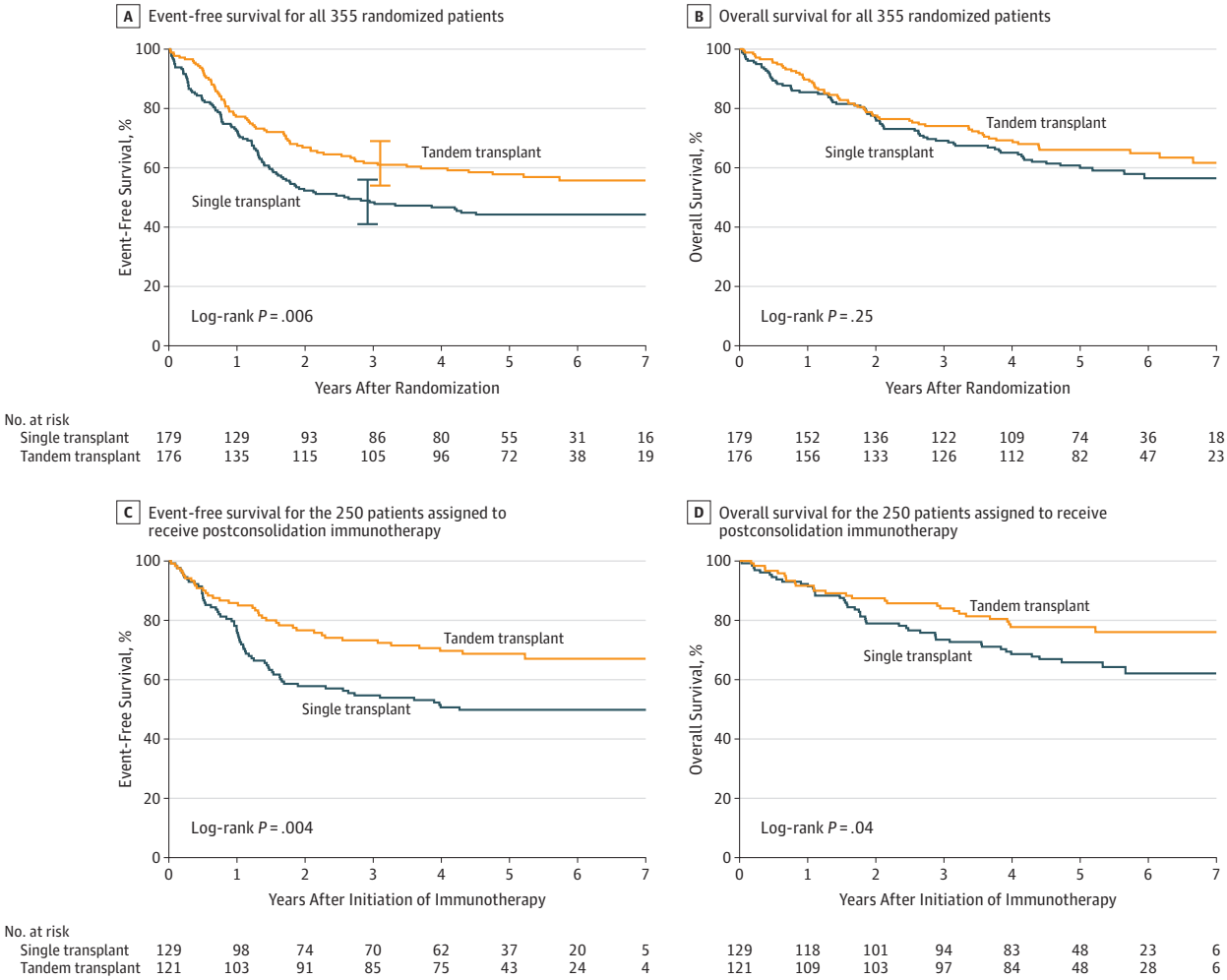
randomization and 207 did not undergo randomization because of physician or family preference (**Figure 1**). The randomization rate (355 of 652 patients [54.4%]) was slightly higher than planned per protocol, yielding 355 eligible randomized patients (176 in the tandem transplant group and 179 in the single transplant group). At the end of the induction therapy, 5 randomized patients initially achieved complete response (n = 4) or partial response (n = 1) but developed disease progression prior to start of consolidation therapy (Figure 1).

Overall disease characteristics were similar between patients randomized and patients who were ineligible for or did not undergo randomization, except for a higher percentage of patients with *MYCN*-amplified neuroblastoma in the randomized cohort (52.2% vs 36.0%; $P < .001$) and a higher percentage of patients with a mixed response or no response at the end of induction therapy in the patients who were not randomized (25.5% vs 8.6%; $P < .001$) (eTable S2 in Supplement 3).

Primary Outcome According to Randomization

Three-year EFS from enrollment or initiation of treatment for all 652 eligible patients was 51.1% (95% CI, 47.1%-55.0%). Forty-two eligible patients were lost to follow-up. For the 355 randomized patients, the 3-year EFS from the time of randomization was 54.9% (95% CI, 49.7%-60.1%). The median (range) duration of follow-up after randomization for 181 patients without an event was 5.6 (0.6-8.9) years. EFS from the time of

Figure 2. Estimates of Survival of Patients in a Study of the Effect of Tandem Transplant vs Single Transplant on Event-Free Survival in Patients With Neuroblastoma



P values were calculated using a 1-sided log-rank test for the primary analysis and a 2-sided log-rank test for the post hoc analyses. A, Median (interquartile range [IQR]) duration of follow-up after randomization for patients without an event was 5.6 (4.9-6.8) years and 3.9 (1.0 to 5.7) years for all patients. The bars represent the 95% CIs for event-free survival at 3 years. B, Median (IQR) duration of follow-up after randomization for patients still alive at the final follow-up was 5.4 (4.9-6.8) years and 4.8 (2.1-6.0) years for all patients. C, Median (IQR) duration of follow-up after initiating immunotherapy for patients without an event was 5.1 (4.6-6.4) years and 4.4 (1.2-5.5) years for all patients. D, Median (IQR) duration of follow-up after initiating immunotherapy for patients still alive was 5.0 years [IQR, 4.6 to 6.4 years] and 4.7 years [IQR, 3.1 to 5.7 years] for all patients.

randomization was significantly higher (1-sided log-rank *P* = .006; **Figure 2**A) for patients in the tandem transplant group. Three years after randomization, the EFS for patients in the tandem transplant group was 61.6% (95% CI, 54.3%-68.9%) and 48.4% (95% CI, 41.0%-55.7%) for patients randomized to the single transplant group. Twenty-one randomized patients were lost to follow-up after completing protocol therapy (9 in the tandem transplant group and 12 in the single transplant group). Thirty-eight patients did not receive treatment according to their randomized group and 30 patients did not complete therapy after undergoing their assigned transplant (Figure 1), but were analyzed according to their randomized group.

Treatment-Related Morbidity and Mortality

The most commonly reported grade 3 or higher toxicities during consolidation therapy, according to version 4 of the National Cancer Institute Common Terminology for Adverse Events,[26] were mucosal (12.9%) and infectious (17.4%), with rare occurrence of sinusoidal obstructive syndrome (3.6%) (**Table 2**).

There were 17 deaths due to toxicity, 7 during induction and 10 during consolidation therapy. Three deaths during induction were due to infectious complications; 2, surgical complications; 1, sinusoidal obstruction syndrome; and 1, cardiac failure. Death during consolidation therapy occurred in 7 patients in the single transplant group and 2 in the tandem transplant group. In the single transplant group, 4 deaths were caused by sinusoidal obstructive syndrome; 2, sepsis; 1, multiorgan failure; and 1, symptoms suggestive of transplant-related microangiopathy (thrombotic thrombocytopenic purpura). In the tandem transplant group, 1 death was caused by symptoms suggestive of transplant-related microangiopathy and 1 by respiratory failure following the initial transplant.

Table 2. Consolidation Nonhematologic Toxicity for Patients With High-Risk Neuroblastoma Who Underwent Single or Tandem Transplant[a]

Grade 3-5 Toxicity	No. (%)	
	Tandem Transplant Group (n = 162)	Single Transplant Group (n = 169)
Infection[b]	29 (17.9)	31 (18.3)
Mucosal[c]	19 (11.7)	26 (15.4)
Kidney[d]	0 (0)	7 (4.1)
Cardiac[e]	2 (1.2)	6 (3.6)
Respiratory[f]	8 (4.9)	15 (8.9)
Bilirubin increased	2 (1.2)	3 (1.8)
Alanine aminotransferase or aspartate aminotransferase increased	9 (5.6)	15 (8.9)
Sinusoidal obstructive syndrome[g]	7 (4.3)	5 (3.0)
Severe sinusoidal obstructive syndrome[h]	2 (1.2)	5 (3.0)
Thrombotic thrombocytopenic purpura related symptoms[i]	5 (3.1)	5 (3.0)
Toxic deaths	2 (1.2)	7 (4.1)

[a] Toxicities reported were based on definitions from version 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events.[26] Grade 3-5 nonhematologic toxicities were reported during consolidation therapy in at least 5% of the patients, plus additional toxicities of interest. Specific toxicities were combined into general categories. Toxicity was analyzed for patients who received any portion of the intended consolidation therapy. Twenty-four patients (10 in the single transplant group and 14 in the tandem transplant group) could not be evaluated for toxic effects (19 chose to stop protocol therapy before starting consolidation therapy and 5 developed progressive disease after randomization but before starting consolidation therapy). Only the worst grade of toxic effect per patient per type is reported.

[b] Includes anorectal infection, catheter-related infection, enterocolitis infectious, febrile neutropenia, infections and infestations, sepsis, skin infection, and small intestine infection.

[c] Includes colitis, esophagitis, gastritis, gastric hemorrhage, lower gastrointestinal hemorrhage, mucositis oral, oral pain, small intestinal mucositis, typhlitis, diarrhea, abdominal pain, enterocolitis infectious, small intestine infection, upper gastrointestinal hemorrhage, gastrointestinal pain, gastrointestinal disorders, and pharyngolaryngeal pain.

[d] Includes increased creatinine and acute kidney injury.

[e] Includes cardiac arrest, heart failure, left ventricular systolic dysfunction, and right ventricular dysfunction.

[f] Includes adult respiratory distress syndrome, bronchopulmonary hemorrhage, dyspnea, hypoxia, pneumonitis, pulmonary hypertension, respiratory failure, and respiratory thoracic and mediastinal disorders.

[g] Includes patients with hyperbilirubinemia ≥2 mg/dL with grade 3 or higher ascites, blood bilirubin increased, hepatic pain, hepatic failure, weight gain in the setting of abnormal liver tests, portal hypertension, or hepatobiliary disorders or patients with at least 2 of the following: ascites, hepatomegaly, or weight gain >5% over baseline.

[h] Defined as an episode of sinusoidal obstructive syndrome accompanied by any of the following: hepatic encephalopathy, grade 4 liver dysfunction/failure, grade 3 or higher hypoxia, grade 3 or higher creatinine, requirement for ventilatory support or dialysis not clearly attributable to another cause.

[i] Includes symptoms of encephalopathy, hypertension, vascular disorders, hemolysis, and blood and lymphatic system disorders.

Post Hoc Analyses

For the 355 randomized patients, 3-year OS from the time of randomization was 71.6% (95% CI, 66.8%-76.3%). Three-year OS was not significantly different for patients in the tandem transplant group (74.1% [95% CI, 67.5%-80.7%]) compared with the single transplant group (69.1% [95% CI, 62.3% to 75.9%]) (P = .25; Figure 2B).

Table 3. Post Hoc Multivariable Analysis of Features Predictive of Event-Free Survival in Patients With High-Risk Neuroblastoma in a Study of the Effect of Tandem Transplant vs Single Transplant on Event-Free Survival[a]

Features	Hazard Ratio (95% CI)	2-Sided *P* Value
From Time of Enrollment (n = 498)[b]		
INSS stage (stage 4 vs non-stage 4[c])	1.96 (1.25-3.06)	.003
Age (≥18 mo vs <18 mo[c])	0.71 (0.46-1.08)	.11
MYCN status (amplified vs nonamplified[c])	1.31 (0.99-1.73)	.06
INPC histology (unfavorable vs favorable[c])	1.59 (0.77-3.27)	.21
End-induction response (other vs ≥ partial response[c])	3.65 (2.76-4.83)	<.001
From Time of Randomization (n = 285)[d]		
Transplant treatment group (tandem vs single[c])	0.67 (0.48-0.94)	.02
INSS stage (stage 4 vs non-stage 4[c])	2.96 (1.42-6.18)	.004
Age (≥18 mo vs <18 mo[c])	0.66 (0.39-1.13)	.13
MYCN status (amplified vs nonamplified[c])	1.10 (0.75-1.63)	.62
INCP histology (unfavorable vs favorable[c])	1.83 (0.56-6.00)	.32
End-induction response (other vs ≥ partial response[c])	2.80 (1.74-4.51)	<.001

Abbreviations: INPC, International Neuroblastoma Pathology Classification; INSS, International Neuroblastoma Staging System.

[a] Results are presented from multivariable Cox models estimating event-free survival in enrolled patients. Patients missing end-induction response, *MYCN* status, or INPC histology were excluded from analyses; INSS stage, age, and randomized treatment group were known for all patients. Of the 652 eligible patients enrolled, 37 (5.7%) were missing end-induction response, 76 (11.7%) were missing *MYCN* status, and 71 (10.4%) were missing INPC histology.

[b] Events/person-year = 0.15.

[c] The reference level for each feature. The hazard ratio is the increased risk of an event compared with the reference level, where a hazard ratio >1 indicates that the non–reference level has an increased risk of event.

[d] Events/person-year = 0.14.

After completion of consolidation therapy, 250 of the 355 randomized patients (121 in the tandem transplant group and 129 in the single transplant group) were assigned to receive isotretinoin plus anti-GD2 chimeric antibody and cytokines (immunotherapy) in Children's Oncology Group trials ANBL0032 or ANBL0931.[17,18] Three-year EFS and OS from the time of initiating immunotherapy were higher in the tandem transplant group compared with the single transplant group (EFS: 73.3% [95% CI, 65.2%-81.3%] vs 54.7% [95% CI, 46.1%-63.3%]; P = .004; Figure 2C) (OS: 84.0% [95% CI, 77.3%-90.7%] vs 73.5% [95% CI, 65.8%-81.1%]; P = .04; Figure 2D).

In the multivariable Cox model of the overall enrolled cohort (n = 498 with complete data), EFS was statistically significantly lower in patients with INSS stage 4 neuroblastoma (P = .003) and in patients with poor response to induction therapy (less than partial response; P < .001) (**Table 3**). In the randomized cohort (n = 285 with complete data), the effect of tandem transplant remained statistically significant after adjustment by end-induction response, INSS stage, age, *MYCN*

status, and INPC histology (P = .02; Table 3). The assumption of proportional hazards was upheld.

Discussion

Tandem autologous stem cell transplant resulted in statistically significantly better EFS compared with single transplant in patients with high-risk neuroblastoma. Similar to previous trials of this disease,[4,16] an EFS primary end point was chosen because it permits earlier identification of poor outcome compared with OS and because there is a high likelihood of fatal outcome associated with relapse.[6-9] Results of the current study are consistent with earlier trials demonstrating that induction chemotherapy followed by consolidation with autologous transplant improved EFS compared with less intensive consolidation,[3,16,27] and that further intensification of consolidation benefits some patients.

The use of GD2-directed antibody combined with cytokines and isotretinoin was found to be effective therapy for eliminating minimal residual neuroblastoma that was present after consolidation therapy[18] and became a standard of care for postconsolidation therapy. To provide data relevant to current-day standard of care for high-risk neuroblastoma, a post hoc analysis was performed among the randomized patients who were also treated with postconsolidation immunotherapy. Tandem transplant was associated with improvements in both EFS and OS, suggesting that a second transplant might be effective in reducing the burden of disease at the start of immunotherapy.

Neuroblastoma is one of only a small number of malignancies in which tandem autologous transplant has been shown to be effective. This may be due to dose intensification with multiple chemotherapeutic agents rather than the effect of the transplant of autologous stem cells. It is also possible that the transplanted autologous immune effector cells are capable of tumor recognition and killing following regimen-induced changes, such as novel tumor-specific antigen presentation or elimination of inhibitory tumor-associated macrophages in the microenvironment. Other malignancies in which tandem or multiple consolidations have shown efficacy are relapsed germ cell tumors, multiple myeloma, and high-risk brain tumors in pediatric patients.[28-30] Similar to neuroblastoma, germ cell tumors and pediatric brain tumors are platinum-sensitive tumors in which dose-escalated carboplatin has been used to treat patients who had been previously exposed to cisplatin.[31] As in the management of neuroblastoma, myeloma treatment with sequential dose-intensive cycles of therapy may be enhanced by biologic therapies following transplant.[32]

Quality of life for patients undergoing high-risk neuroblastoma therapy and their families is significantly compromised given the frequent and prolonged hospitalizations. Therapy for high-risk neuroblastoma is expected to be associated with long-term toxicities, including hearing impairment, kidney dysfunction, second cancer risk, infertility, and compromised growth.[33-35] Future studies describing the prevalence of these and other long-term toxicities are necessary, and it will be important to compare long-term outcomes in individuals who received single vs tandem consolidation. In addition, identification of new patient groups whose prognosis is more favorable, based upon newly identified clinical or biologic features, may obviate the need for tandem consolidation for some patients in the future.

Limitations

This study has several limitations. First, a substantial proportion of patients were not randomized, largely due to parent or physician preference, introducing a potential selection bias. Second, while similar cumulative acute toxicity of tandem transplant was observed following single or tandem transplant, tandem transplant is associated with longer hospital stay and therefore potentially greater medical expense.[36] Third, a post hoc analysis was performed to examine OS and found no statistically significant difference in OS rate between patients who underwent single vs tandem transplant. The study was not powered to detect a difference in OS. Moreover, newer therapies for relapsed neuroblastoma have emerged that may prolong survival,[37-40] complicating the use of OS as a primary end point. Fourth, the higher EFS rate associated with tandem transplant is relevant only within the context of the total therapy delivered. It is not known whether tandem transplant will be beneficial when administered after other currently used induction regimens.[3,5,41] Nearly 10% of patients in the current study did not continue beyond induction because of progressive disease or death during induction, an incidence similar to that reported for other induction regimens and highlighting an important need for improvement in induction approaches.[3,5,41] In addition, Ladenstein and colleagues reported superior EFS in patients treated with a single busulfan/melphalan transplant compared with patients treated with carboplatin/etoposide/melphalan after a platinum-intensive induction regimen.[5] It is possible that the benefit of tandem transplant could be obviated or improved with other induction or conditioning regimens.

Conclusions

Among patients aged 30 years or younger with high-risk neuroblastoma, tandem transplant resulted in a significantly better event-free survival than single transplantation. However, because of the low yet anticipated randomization rate, the findings may not be representative of all patients with high-risk neuroblastoma.

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