Pilot Induction Regimen Incorporating Pharmacokinetically Guided Topotecan for Treatment of Newly Diagnosed High-Risk Neuroblastoma: A Children's Oncology Group Study

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See accompanying editorial on page 4345

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ABSTRACT

Purpose

To assess the feasibility of adding dose-intensive topotecan and cyclophosphamide to induction therapy for newly diagnosed high-risk neuroblastoma (HRNB).

Patients and Methods

Enrolled patients received two cycles of topotecan (approximately 1.2 mg/m²/d) and cyclophosphamide (400 mg/m²/d) for 5 days followed by four cycles of multiagent chemotherapy (Memorial Sloan-Kettering Cancer Center [MSKCC] regimen). Pharmacokinetically guided topotecan dosing (target systemic exposure with area under the curve of 50 to 70 ng/mL/hr) was performed. Peripheral-blood stem cell (PBSC) harvest and surgical resection of residual primary tumor occurred after cycles 2 and 5, respectively. Patients achieving at least a partial response received myeloablative chemotherapy with PBSC rescue and radiation to the presurgical primary tumor volume. Oral 13-*cis*-retinoic acid maintenance therapy was administered twice daily for 14 days in six 28-day cycles.

Results

Thirty-one patients were enrolled onto the study. No deaths related to toxicity or dose-limiting toxicities occurred during induction. Mucositis rarely occurred after topotecan cycles (9.7%) in contrast to 30% after MSKCC cycles. Thirty patients underwent PBSC collection with median 31.1×10^6 CD34+ cells/kg (range, 1.8 to 541.8×10^6 CD34+ cells/kg), all negative for tumor contamination by immunocytochemical analysis. Targeted topotecan systemic exposure was achieved in 26 (84%) of 31 patients. At the end of induction, 26 patients (84%) had tumor response and one patient had progressive disease. In the overall cohort, 3-year event-free and overall survival were $37.8\% \pm 9.4\%$ and $57.1\% \pm 9.4\%$, respectively.

Conclusion

This pilot induction regimen was well tolerated with expected and reversible toxicities. These data support investigation of efficacy in a phase III clinical trial for newly diagnosed HRNB.

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INTRODUCTION

Outcome for patients with advanced-stage neuroblastoma or those whose tumors exhibit unfavorable biologic characteristics such as *MYCN* gene amplification is poor, with survival of only 20% to 35%.¹⁻⁶ Achievement of complete tumor response following induction therapy is associated with improved survival, and escalation in chemotherapy dose intensity improves initial tumor response.⁷⁻¹⁰ However, recent multicenter trials of dose-intensive chemotherapy induction regimens reveal response

rates of only 52% to 75%.¹¹⁻¹⁴ An alternative strategy is to incorporate new agents with non-cross-resistant mechanisms of cytotoxicity into induction therapy. This led to our testing the feasibility of adding cyclophosphamide and topotecan to a backbone dose-intensive induction regimen.¹⁰ Topotecan, an inhibitor of topoisomerase I, has activity against neuroblastoma,¹⁵⁻¹⁸ potentiates the effects of other DNA damaging agents,^{19,20} and demonstrates a non-cross-resistant mechanism of action.^{21,22} Topotecan has a toxicity profile most notable for dose-limiting myelosuppression²³⁻²⁵ and can be safely

Fig 1. Study schema. AUC, area under the curve; CisRA, 13 *cis*-retinoic acid; CrCl, creatinine clearance; GFR, glomerular filtration rate; IV, intravenous; PBSC, peripheral-blood stem cell; PK, pharmacokinetics; XRT, external beam radiation therapy.

combined with cyclophosphamide.²⁶⁻²⁹ A randomized study of topotecan alone versus topotecan-cyclophosphamide in patients with recurrent neuroblastoma demonstrated a trend toward improved response rate (19% v 32%, respectively), decreased rate of grades 3 or 4 infectious complications, and increased time to tumor progression following topotecan-cyclophosphamide therapy.³⁰

Early clinical trials estimated a topotecan maximum-tolerated dose of 0.75 mg/m²/d daily for 5 days when combined with cyclophosphamide.²⁶ Xenograft models predict that a higher topotecan systemic exposure (52 to 88 ng/mL/hr), achieved by topotecan dosages of 1.0 to 1.6 mg/m²/d will improve antineuroblastoma tumor activity^{31,32} and support further topotecan dose intensification. We report the feasibility of incorporating dose-intensive topotecan plus cyclophosphamide (TopoCy) into a conventional chemotherapy backbone as a novel induction regimen for newly diagnosed patients with high-risk neuroblastoma. Pharmacokinetically guided topotecan dosing^{33,34} was used to achieve the optimal topotecan systemic exposure suggested by preclinical models.^{31,32} The feasibility of peripheral-blood stem cell (PBSC) mobilization, in vivo PBSC tumor purging following TopoCy, tumor response, and survival rates were determined.

PATIENTS AND METHODS

Patient Selection

Patients had a diagnosis of neuroblastoma or ganglioneuroblastoma verified by histology or demonstration of clumps of tumor cells in bone marrow with increased urinary catecholamine metabolites. Diagnosis, staging, and response assessments were performed according to International Neuroblastoma Staging System (INSS) criteria.³⁵ Centralized analysis of *MYCN* gene amplification (defined as more than 10 copies) by fluorescent in situ hybridization and Shimada histology classification was performed.^{36,37}

Patients ≤ 30 years of age at initial diagnosis and without prior systemic therapy were enrolled at one of five participating Children's Oncology Group (COG) institutions. High-risk neuroblastoma included patients with INSS stage 3, age ≥ 365 days with *MYCN* amplification and/or unfavorable histol-

ogy; INSS stage 3, 4, or 4S and age less than 365 days old with *MYCN* amplification; INSS stage 4 and age ≥ 547 days old; INSS stage 4, and age 365 to 547 days old with *MYCN* amplification, unfavorable histology, and/or diploidy; and age ≥ 365 days initially with INSS stage 1, 2, or 4S that progressed to stage 4 without interval chemotherapy.

The study protocol and consent forms were approved by each participating hospital's institutional review board, and signed informed consent was obtained from the patient or parents or guardian, as appropriate, after neuroblastoma diagnosis was confirmed. The protocol was activated on March 29, 2004, and was closed to accrual on November 30, 2005.

Treatment

Protocol therapy consisted of three phases: induction, consolidation, and maintenance (Fig 1). Induction included six cycles of chemotherapy administered every 21 days or thereafter when absolute neutrophil count (ANC) was ≥ 750/μL and platelet count was ≥ 75,000/μL. Granulocyte colony-stimulating factor 5 μg/kg/d was administered 24 hours after completion of chemotherapy until ANC was more than 1,500/μL. Doses were based on body-surface area for those who weighed more than 12 kg or on weight (kg) for those who weighed ≤ 12 kg. Topotecan dose was adjusted to achieve a topotecan lactone systemic exposure (ie, area under the curve [AUC]) of 50 to 70 ng/mL/hr. PBSC harvest occurred after cycle 2 or later, if clinically indicated. Surgical resection of residual primary tumor or sites of regional dissemination (nodal disease) occurred after cycle 5.

Patients with at least partial response (PR) at the end of induction, PBSC product of ≥ 1.5 × 10⁶ CD34+ cells/kg without evidence of tumor contamination as documented by immunocytochemical assay,³⁸ a cardiac shortening fraction of ≥ 28% or ejection fraction ≥ 55%, a creatinine clearance or glomerular filtration rate ≥ 60 mL/min/1.73 m², and serum creatinine less than 1.5 mg/dL proceeded to consolidation chemotherapy (carboplatin, etoposide, and melphalan).³⁹ On day 0, PBSCs were infused, and daily granulocyte colony-stimulating factor (5 μg/kg/d) was administered until engraftment (ANC > 2,000 × 3 days). External beam radiotherapy (21.6 Gy in 1.8 Gy fractions) beginning ≥ 28 days following PBSC infusion was administered to the presurgical gross tumor volume and sites of residual disease on the basis of computed tomography scan, magnetic resonance imaging, and/or metaiodobenzylguanidine (MIBG) scans performed at the end of induction. Maintenance isotretinoin began after day 66 after PBSC infusion and after radiation therapy for 6 months duration.⁴⁰

Adverse events were assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The treating institutions assessed tumor response by using the INSS response criteria³⁵ for chest, abdomen, or pelvic computed tomography scan, magnetic resonance imaging evaluation, iodine-123 [¹²³I]-MIBG scintigraphy, urinary catecholamine levels, and bone marrow aspirate and biopsy obtained from bilateral iliac crests. Response assessments occurred after induction cycle 2 and at end of induction, consolidation, and maintenance. Patients were followed until they met the criteria for being off study (death, loss to follow-up, entry into another COG therapeutic study, withdrawal of consent for further data submission, or secondary malignancy).

Pharmacokinetically Guided Topotecan Dosing

Topotecan pharmacokinetics samples were obtained at all institutions, shipped overnight on dry ice, and analyzed at St. Jude Children's Research Hospital (SJCRH; North American patients) or on site at The Children's Hospital at Westmead (Australian patients) by using a method cross-validated with the SJCRH lab. Final dosage recommendations were calculated by the SJCRH laboratory and implemented on the next day after sample analysis.

Pharmacokinetic analysis was performed on day 1 of cycles 1 and 2. If pharmacokinetic analysis confirmed achievement of target (AUC 50 to 70 ng/mL/hr), no additional pharmacokinetic studies were performed. If the patient was outside the target range, topotecan dosage was adjusted for day 3, and the pharmacokinetic analysis was repeated. Dose adjustment was repeated on day 5 if the patient remained outside the target range, and pharmacokinetic studies were performed again on day 5. The initial dosage for cycle 2 was determined on the basis of the patient-specific pharmacokinetic data collected during cycle 1. Pharmacokinetic study times and results from the cycle 2 pharmacokinetic analyses were applied in the same manner as for cycle 1.

Sample Collection and Analysis

Samples (2.5 mL) were collected by using a limited sampling model: preinfusion, and 5 minutes, 2 hours, and 3 hours after the end of infusion. Whole blood was collected into a heparinized tube from a site contralateral to the site of topotecan infusion, plasma was processed, and topotecan lactone concentrations were measured. The lower limit of quantification for this high-performance liquid chromatography method was 0.25 ng/mL.³⁴

Pharmacokinetic Analysis

A two-compartment model was fit to the topotecan lactone plasma concentrations by using a maximum a posteriori Bayesian algorithm as implemented in ADAPT II.⁴¹ Estimated model parameters included the volume of the central compartment, elimination rate constant, and the intercompartment rate constants. Clearance and volume of distribution at steady state were calculated by using standard equations and the parameter estimates. A plasma concentration time profile was simulated from model parameters for each patient and the AUC_{0-∞} was calculated by using a log-linear trapezoidal method. Because of previously published data suggesting a linear disposition,^{42,43} topotecan dosage adjustments were made by using the following equation: adjusted dosage = (current dosage/current AUC) × target AUC.

Statistical Analysis

The pilot regimen was deemed feasible (primary end point) if induction rules were met: ≥ 25 patients received 75% or more of the intended cycles 3 to 6 chemotherapy doses, no more than one death related to toxicity during induction, eight or fewer patients experiencing dose-limiting toxicities (DLTs) during cycles 1 and 2, and no more than two patients with PBSC tumor contamination by immunocytochemical analysis or having less than 1.5 × 10⁶ CD34+ cells/kg collected. DLT was defined as inability to achieve ANC of more than 750/μL or platelet count of more than 75,000/μL by day 35 from the start of the cycle (unless there was documented tumor involvement of marrow); any grade 3 or higher nonhematopoietic, nonmucosal (mucositis/stomatitis) toxicity that did not resolve to grade ≤ 2 by day 35 of the cycle (excluding grade 3 anorexia or nausea); any grade 4 nonhematopoietic/nonmucosal toxicity (excluding grade 4 febrile neutropenia, anorexia, dehydration, vomiting) not attributable to infectious complication; or grade 4 mucositis requiring intubation.

Descriptive statistical analyses were performed to assess patient characteristics, toxicities, and secondary end points of topotecan pharmacokinetics, response, and survival. Event-free survival (EFS) and overall survival (OS) were calculated by using the Kaplan-Meier method⁴⁴ with SEs per Peto et al.⁴⁵ For EFS, time to event was calculated from the time of enrollment onto the study until the first occurrence of relapse, progressive disease, secondary malignancy, or death, or until the time of last contact if no event occurred. For OS, time to event was calculated from the time of enrollment onto the study until the time of death or until the time of last contact if the patient did not die. EFS and OS were compared with a log-rank test, and Kaplan-Meier curves were plotted. *P* values less than .05 were considered statistically significant.

RESULTS

Patients' Characteristics

Thirty-one patients were enrolled onto the study and all met eligibility requirements (Table 1). The majority of patients were male (81%) and age ≥ 18 months (84%), with median age at diagnosis of 30 months (range, 10 months to 9 years). One patient progressed to INSS stage 4 from stage 1 following only surgical resection, three patients had stage 3, and 27 patients had stage 4 neuroblastoma.

Table 1. Patient Characteristics With 3-Year EFS and OS

Characteristic	No.	%	3-Year EFS ± SE (%)	<i>P</i>	3-Year OS ± SE (%)	<i>P</i>
Stratum						
Newly diagnosed	30	97	39.1 ± 9.7	N/A	59.1 ± 9.5	N/A
Relapsed	1	3	1 event		1 death	
Age, months						
< 18	5	16	40.0 ± 31.0	.5608	40.0 ± 31.0	.2056
≥ 18	26	84	38.5 ± 10.1		61.5 ± 9.9	
Race/ethnicity						
White	23	88	39.1 ± 10.8		60.9 ± 10.6	
Black	2	8	1 event	N/A	1 death	N/A
Other	1	4	1 event		1 death	
Sex						
Male	25	81	32.0 ± 10.0	.2740	48.0 ± 10.4	.1873
Female	6	19	62.5 ± 22.1		100.0 ± 0	
INSS stage						
Not stage 4	4	13	25.0 ± 21.7	.4786	25.0 ± 21.7	.1522
Stage 4	27	87	39.7 ± 10.3		62.0 ± 9.9	
MYCN status						
Not amplified	15	60	26.7 ± 13.2	.2386	53.3 ± 13.8	.9987
Amplified	10	40	48.0 ± 17.3		46.7 ± 17.0	
Ploidy						
Hyperdiploid	9	50	33.3 ± 19.2	.6092	25.9 ± 15.8	.0652
Diploid	9	50	44.4 ± 16.6		77.8 ± 13.9	
Shimada histology						
Favorable	1	5	0 events	N/A	0 deaths	N/A
Unfavorable	21	95	47.1 ± 12.1		50.6 ± 11.9	
INPC MKI						
Low/intermediate	8	62	37.5 ± 21.0	.2795	37.5 ± 21.0	.3702
High	5	38	60.0 ± 21.9		60.0 ± 21.9	
INPC grade						
Undifferentiated/ poorly differentiated	11	85	54.5 ± 16.4	.1698	54.5 ± 16.4	.1698
Differentiating	2	15	2 events		2 deaths	

Abbreviations: EFS, event-free survival; INPC, International Neuroblastoma Pathology Classification; INSS, International Neuroblastoma Staging System; MKI, mitosis karyorrhexis index; N/A, not applicable; OS, overall survival.

Table 2. Topotecan Pharmacokinetic Analyses

Variable	No. of Patients			
	Cycle 1		Cycle 2	
	No.	%	No.	%
Pharmacokinetic studies	31		31	
Fixed-dose topotecan*	31		31†	
Dosing success	14		12	
Dosing failure	17		19	
Pharmacokinetic guided dosing‡	17		19	
Targeting success	12		14	
Targeting failure	5		5	
Total successes	26	84	26	84
Dosage to achieve target, mg/m ²				
Median	1.2		1.3	
Range	0.75-2.1		1.2-2.9	
Dosage to achieve target, mg/kg				
Median	0.06		0.11	
Range	0.04-0.1		0.04-0.13	

*Success if target area under the curve of 50 to 70 ng/mL/hr was achieved after protocol-defined dose (cycle 1 or cycle 2) or cycle 1–based pharmacokinetic analysis (cycle 2).

†Fixed dosage per protocol (n = 11) or dosage based on cycle 1 pharmacokinetic analyses.

‡Success if target area under the curve of 50 to 70 ng/mL/hr was achieved by pharmacokinetic-guided dosing.

Topotecan Pharmacokinetic Analyses and Dose Adjustments in Cycles 1 and 2

The population's average topotecan lactone clearance was 26.4 L/h/m² (range, 10.2 to 60.9 L/h/m²). The inter- and inpatient variabilities in topotecan systemic clearance assessed by using a mixed effects model were 23% and 30%, respectively.

A total of 56 pharmacokinetic studies were performed in 31 patients during cycle 1, and 54 studies were performed in 31 patients during cycle 2 (Table 2). After cycle 1 fixed topotecan dose, 16 (52%) of 31 analyses were within the target range (dose success). Cycle 2 topotecan dose was based on the cycle 1 dose that successfully achieved the target AUC or was calculated on the basis of the final pharmacokinetic study; 12 (39%) of 31 analyses were dose successes. Fourteen patients required a dose adjustment during cycles 1 and 2. Pharmacokinetically guided topotecan dosing achieved the target AUC in 84% of patients in either cycle 1 or cycle 2. Only one patient did not achieve the target AUC during either cycle 1 or cycle 2. Twelve patients (39%) and 18 patients (58%) required an increase in topotecan dose during cycle 1 and cycle 2, respectively. The median topotecan dosages required to achieve the target AUC in cycles 1 and 2 were 1.2 mg/m²/d (range, 0.75 to 2.1 mg/m²/d) and 1.3 mg/m²/d (range, 1.2 to 2.9 mg/m²/d), respectively.

Stem-Cell Harvest

PBSCs were successfully collected in 30 patients ($> 1.5 \times 10^6$ CD34+ cells/kg). One patient had disease progression before PBSC collection and went off therapy. Median PBSC collection was 31.1×10^6 CD34+ cells/kg (range, 1.8 to 541.8×10^6 CD34+ cells/kg) collected over a median of 1 day (range, 1 to 3 days), with 27 collections occurring before cycle 3. Three patients had less than 4×10^6 CD34+ cells/kg collected; one patient had CD34+ cells/kg collected following cycle 5 of induction at the physician's discretion. No tumor

contamination was detected in the PBSC products by immunocytochemical analysis performed centrally (n = 29) or at a local institution (n = 1).

Toxicities

No DLTs or deaths related to toxicity occurred during induction. Only one patient required a dose reduction of more than 25% of the intended chemotherapy doses (in cycle 6) because of prolonged myelosuppression. Table 3 lists reported grade 3 or higher key toxicities during induction cycles 1 to 2 and 3 to 6. The majority of patients experienced grade 3 or 4 hematopoietic toxicity and febrile neutropenia throughout induction. Mucositis involving the oropharynx or lower intestinal tract and documented infections were more common during cycles 3 to 6 (30% and 46.7%, respectively) compared with cycles 1 and 2 (9.7% and 9.7%, respectively).

Table 3 also summarizes reported grade 3 or higher nonhematopoietic toxicities experienced during consolidation. Thirteen patients (54%) developed increases in liver transaminase levels, three in the setting of systemic infection. One patient died after consolidation with

Table 3. Observed Induction and Consolidation Toxicity

Toxicity	Cycle			
	1 and 2 (n = 31)		3 Through 6 (n = 30)	
	Count	Incidence (%)	Count	Incidence (%)
Induction grade 3 or 4 toxicity*				
Hemoglobin	23	74.2	22	73.3
Neutrophils/granulocytes (ANC/AGC)	25	80.6	25	83.3
Platelets	24	77.4	25	83.3
Mucositis/stomatitis/colitis/enteritis/diarrhea	3	9.7	9	30.0
Febrile neutropenia (fever of unknown origin without infection, ANC $< 1 \times 10^9$; fever $\geq 38.5^\circ\text{C}$)	22	71.0	20	66.7
Infection (clinical or microbiologic diagnosis) with grades 3 to 4 neutrophils, ANC $< 1.0 \times 10^9$	3	9.7	9	30.0
Other infection	0	0.0	5	16.7
Consolidation grade 3, 4, or 5 toxicity (n = 24) *				
Mucositis/stomatitis/colitis/enteritis/diarrhea			7	29.2
Febrile neutropenia (fever of unknown origin without infection, ANC $< 1 \times 10^9$; fever $\geq 38.5^\circ\text{C}$)			8	33.3
Infection (clinical or microbiologic diagnosis) with grade 3 to 4 neutrophils, ANC $< 1.0 \times 10^9$			11	45.8
ALT			13	54.2
AST			13	54.2
Bilirubin (hyperbilirubinemia)			1	4.2
Hypoxia			3	12.5
Pleural effusion (nonmalignant)			1	4.2
Renal failure			1	4.2

Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count.

*Only the maximum grade of toxicity per patient per type of toxicity is counted within the given time period.

Table 4. Response Assessment

Reporting Period	CR	VGPR	PR	MR	NR	PD	Not Evaluable*	Not Evaluated
Cycles 1 and 2 (n = 31)	2	1	9	9	8	1	0	1
End induction (n = 31)	7	8	11	2	1	1	1	0
End consolidation (n = 24)*	8	8	5	0	0	1	2	0

Abbreviations: CR, complete response; MR, mixed response; NR, no response; PD, progressive disease; PR, partial response; VGPR, very good partial response.

*One patient removed from protocol therapy prior to end of induction per physician discretion; two patients with death related to toxicity during consolidation.

myeloablative chemotherapy because of sinusoidal obstructive syndrome and another died from complications of renal failure.

Feasibility

In summary of the primary end point, all of the induction feasibility rules were met: delivery of intended cycles, no deaths related to toxicity or DLTs, and sufficient PBSC collection with no detectable tumor contamination.

Responses

Table 4 lists the number of overall responses for induction and consolidation therapy. A best overall response of complete response (CR), very good partial response (VGPR), or partial response (PR) was achieved in 12 (40%) of 30 evaluated patients following two cycles of induction, 26 (83.8%) of 31 at end of induction, and 21 (87.5%) of 24 at completion of consolidation. Twenty-four patients proceeded to consolidation. The reasons for removing patients from protocol therapy before consolidation were progression (n = 1), physician discretion (n = 2), less than PR to induction (n = 2), prolonged delay in beginning consolidation due to viral infection (n = 1), and parental refusal (n = 1).

Survival Analysis

Fourteen of the 31 patients were alive at last follow-up. Sixteen patients relapsed or progressed, and thirteen of those subsequently died. Four of the 17 deaths on this study were first events. Causes of death included disease (n = 15) and stem-cell transplantation–related complications (n = 2).

The median follow-up time for the 11 patients who did not experience an event was 4.5 years (range, 2.0 to 5.4 years). The overall 3-year EFS and OS rates were $37.8\% \pm 9.4\%$ and $57.1\% \pm 9.4\%$, respectively (Fig 2). No statistically significant difference in outcome was found by patient characteristics (Table 1).

DISCUSSION

The induction regimen from the COG ANBL02P1 study demonstrates tolerability and feasibility of delivering a dose-intensive TopoCy regimen to newly diagnosed patients with high-risk neuroblastoma. The regimen uses a dose-intensive chemotherapy backbone previously described by Kushner et al¹⁰ (Memorial Sloan-Kettering

Fig 2. Event-free survival (EFS) and overall survival (OS) for all patients (N = 31). The numbers at risk at the start of years 1 to 5 are given along the curves.

Cancer Center [MSKCC] regimen) and used in the completed COG A3973 study.¹³ The MSKCC regimen's initial induction cycles—high-dose cyclophosphamide plus doxorubicin and vincristine—cause significant mucosal and infectious toxicities¹⁰ similar to those observed during ANBL02P1 cycles 3 to 6. In comparison, dose-intensive TopoCy rarely caused severe mucositis and documented infection and did not limit the ability to deliver the subsequent intended dose-intensive chemotherapy.

The use of myeloablative consolidation chemotherapy and autologous bone marrow infusion improves EFS of high-risk neuroblastoma.^{2,46,47} PBSCs carry less burden of collection⁴⁸ and are less likely to contain tumor cells⁴⁹ than bone marrow although the optimal timing of PBSC collection remains controversial. Our study confirmed prior results from Bensihom et al⁵⁰ that sufficient PBSC cells without tumor contamination can be harvested after two cycles of chemotherapy. Sufficient numbers of stem cells were harvested for a minimum of two PBSC infusions in all but one patient, which was essential when planning the current COG tandem transplantation study. The occurrence of secondary malignancy following intensive neuroblastoma therapy⁵¹ may be related to the mutagenic potential of induction alkylator or topoisomerase 1 inhibitor chemotherapy, further providing a rationale for earlier PBSC harvest.

Kretschmar et al¹⁸ reported no improvement in outcome when adding cyclophosphamide and topotecan to neuroblastoma induction therapy. However, topotecan doses were significantly lower than those used in ANBL02P1 (0.75 mg/m²/d) and may not provide maximal antitumor activity.^{31,32} Indeed, the response rate observed following two cycles of ANBL02P1 TopoCy are similar to the response rate in recurrent disease following lower-dose topotecan.³⁰ Within the context of the entire ANBL02P1 induction regimen, patients achieved an overall response rate of 84% and 15 (48%) of 31 patients achieved CR or VGPR. These induction response rates are similar to metastatic response of CR in 17 of 44 patients observed in a multicenter trial⁵² and the 47% CR or VGPR response rate observed with the European Neuroblastoma Study Group 5 (ENSG5) cooperative trial.¹² These similarities highlight the need for a larger phase III clinical trial to more accurately assess the efficacy of the ANBL02P1 induction regimen.

ANBL02P1 and previous pediatric topotecan trials demonstrate marked interpatient variability in clearance suggesting that pharmacokinetically guided dosing may be of clinical benefit.^{33,53} We were able to achieve the target exposure in 84% of patients. The median topotecan dose required to achieve the target AUC (cycle 1, 1.2 mg/m²/d; cycle 2, 1.3 mg/m²/d), achieved by either a dose increase or decrease, supports the use of 1.2 mg/m²/d dosing administered daily for 5 days in future trials. The ANBL02P1 trial was not intended to assess the maximum tolerated topotecan dose that could be combined into induction therapy. Higher topotecan (6 to 8 mg/m² per cycle) and cyclophosphamide dosages (approximately 4,200 mg/m² per cycle) have been successfully administered to patients with recurrent neuroblastoma.^{28,29} Future trials incorporating a higher topotecan dosage into induction therapy may be warranted given ANBL02P1 results, although feasibility studies may be needed given the risk for increased mucositis²⁴ and infection associated with higher topotecan dosages.³⁰

ANBL02P1 confirmed the feasibility of incorporating pharmacokinetically guided dosing in an international multi-institutional clinical trial among institutions equipped with personnel and resources to perform real-time sampling and processing. However, in this patient population, more inpatient variability in topotecan clearance was observed than in previous studies. Changing clinical factors (eg, renal function, extent of disease, concomitant medications) may account for some of this variability,⁵⁴ but since this was, to the best of our knowledge, the first COG study of its kind, unfamiliarity with logistic aspects of the study also may have contributed to the greater inpatient variability observed. Regardless, our study shows that although feasible, current real-time sampling techniques are time and labor intensive and are not likely to be feasible in a COG group-wide study because most sites do not have the appropriate infrastructure. Ultimately, methods must be developed to individualize therapy without burdening the health care system, either by minimization of the number of topotecan samples required or determination of a population model to predict topotecan exposure.

The feasibility of PBSC harvest and tolerability of the ANBL02P1 induction regimen support further investigation of its efficacy in a

phase III clinical trial. However, suboptimal response still occurs in a subset of patients with neuroblastoma. Future trials need to translate our improved understanding of the neuroblastoma genetic signature by introducing novel molecularly targeted therapy. The tolerability of the topotecan-containing induction regimen provides a backbone regimen on which to add such agents.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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