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ORIGINAL REPORT

High-Risk Neuroblastoma Treated With Tandem Autologous Peripheral-Blood Stem Cell–Supported Transplantation: Long-Term Survival Update

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A B S T R A C T

Purpose
To provide an update on long-term survival of patients with high-risk neuroblastoma treated with tandem cycles of myeloablative therapy and peripheral-blood stem-cell rescue (PBSCR).

Patients and Methods
Ninety-seven patients with high-risk neuroblastoma were treated between 1994 and 2002. Patients underwent induction therapy with five cycles of standard agents, resection of the primary tumor and local radiation, and two consecutive courses of myeloablative therapy (including total-body irradiation) with PBSCR.

Results
Fifty-one patients have experienced relapse or died. Median follow-up time among the 46 patients who remain alive without progression is 5.6 years (range, 15.1 months to 9.9 years). Progression-free survival (PFS) rate at 5 years from diagnosis was 47% (95% CI, 36% to 56%), and PFS rate at 7 years was 45% (95% CI, 34% to 55%). Overall survival rate was 60% (95% CI, 48% to 69%) and 53% (95% CI, 40% to 64%) at 5 and 7 years, respectively. The 5- and 7- year PFS rates from time of first transplantation for 82 patients who completed both transplants were 54% (95% CI, 42% to 64%) and 52% (95% CI, 40% to 63%), respectively. Five patients died from treatment-related toxicity after tandem transplantation. Relapse occurred in 37 (42%) of 89 patients, mainly within 3 years of transplantation and primarily in diffuse osseous sites. No primary CNS relapse or secondary leukemia was seen. One patient developed synovial cell sarcoma 8 years after therapy.

Conclusion
High-dose therapy with tandem autologous stem-cell rescue is effective for treating high-risk neuroblastoma, with encouraging long-term survival. CNS relapse and secondary malignancies are rare after this therapy.

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INTRODUCTION

Over the last decade, intensification of consolidation therapy with autologous stem-cell rescue after myeloablative doses of chemotherapy with or without total-body irradiation (TBI) has contributed to the improved survival of children with high-risk neuroblastoma.[1-5] However, long-term cure rates remain low, presumably because of the emergence of resistant clones or persistence of minimal residual disease. Additionally, relapse in the CNS has emerged as a problem after some treatment regimens because more intensive treatment has resulted in better control of disease and longer progression-free intervals.[6,7] We report here the long-term results of a limited-institution, single-arm trial of induction chemotherapy and local control measures (surgery and local radiation), followed by rapid-sequence tandem high-dose (myeloablative) treatments (HDT) with peripheral-blood stem-cell rescue (PBSCR). The rationale and details of this study have been described elsewhere.[8,9] In designing this trial, we initially investigated the feasibility and toxicity of intensification of consolidation therapy using tandem transplantation. This protocol had the following three important characteristics: collection of peripheral-blood stem cells (PBSCs) early in therapy, presumably before significant genetic damage in hematopoietic stem and progenitor cells had occurred from the induction chemotherapy cycles; use of separate non–cross-reactive regimens for each myeloablative treatment; and rapid progression

from the first to the second HDT/PBSCR. In the pilot study, this regimen was found to be tolerable, with early results suggesting a low toxic death rate. In the initial 39 patients who were enrolled, 26 remained relapse free, with a 3-year PFS rate of 58% (90% CI, 40% to 72%).[8] We report here the long-term survival of an expanded group of patients treated with the same regimen.

PATIENTS AND METHODS

Patient Selection and Evaluation

Patients with high-risk neuroblastoma who had received no prior therapy or who had received only one course of chemotherapy (for intermediate-risk disease that was later reclassified) were offered this therapeutic protocol. These patients included those more than 1 year of age with International Neuroblastoma Staging System[10] stage 4 disease or stage 3 disease with *MYCN* amplification.[11] Beginning in 1999, the inclusion criteria were expanded to include infants less than 12 months of age with stage 3, 4, or 4s disease and *MYCN* amplification, and children more than 12 months of age with stage 3 disease and unfavorable Shimada histology[12] (1999 to 2002 only). Patients were consecutively enrolled onto this trial from 1994 to 1998; from 1999 to 2002, patients were treated "as per" the same regimen after the study had achieved its goal of determining feasibility. Children were treated at the following four centers: Dana-Farber Cancer Institute and Children's Hospital Boston, Children's Hospital of Philadelphia, Emory Children's Center, Atlanta, and Primary Children's Medical Center, Utah. Institutional review board approval for treatment on this study at each of the four centers was obtained. Parental informed consent was obtained both for treatment on and as per the trial.

Treatments

After confirmation of the diagnosis, patients underwent induction therapy consisting of five cycles of standard chemotherapeutic agents. The treatment plan has been reported in detail previously,[8] and the overall schema is summarized in Figure 1. Patients received a total of 4 g/m² of cyclophosphamide, 200 mg/m² of cisplatin, 1 g/m² of carboplatin, 10 g/m² of ifosfamide, 1,650 mg/m² of etoposide, 3 mg/m² of vincristine, and 150 mg/m² of doxorubicin during induction. PBSC collection was performed after recovery from the second or third cycle of chemotherapy; most patients had PBSC collected after the third cycle. The median number of collections was two (range, one to four collections). For patients treated at the Dana-Farber Cancer Institute and Children's Hospital Boston during 1994 to 1998 and for all patients treated at Children's Hospital of Philadelphia, CD34⁺ selection was performed on the PBSC (n = 42). Resection of the primary tumor was undertaken after the fourth or fifth cycle of induction therapy. Local irradiation was administered in

patients with gross or microscopic residual disease after surgery. Full restaging was not performed after induction. Criteria for proceeding to transplantation were absence of progressive disease and acceptable organ function. Each of the HDTs was fully myeloablative, and the regimens included etoposide 2.4 g/m², cyclophosphamide 3.6 g/m², and carboplatin 2 g/m² (HDT1), and melphalan 180 mg/m² with 12 Gy of TBI in fractions of 1.5 Gy each (HDT2; Fig 1). The median infused dose per stem-cell transplantation was approximately 7 × 10⁶ CD34⁺ cells/kg. After the report of Matthay et al[4] in 1999 demonstrating the superior outcome of patients treated with 13-*cis*-retinoic acid, this drug was added to the regimen as standard of care. Charts were reviewed to determine last date known alive, date and sites of relapse, and occurrence of secondary malignancies. Institutional review board approval was obtained for chart review.

Statistical Analysis

Descriptive statistical analysis was performed to assess patient characteristics. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and CIs were calculated using Greenwood's formula.[13] PFS was defined as the time from diagnosis and from date of first transplantation to progression or relapse of primary tumor or death, whichever occurred first. Patients who were alive without relapse were censored at the time last known alive and relapse free (April 2005). OS was defined as the time from diagnosis or first transplantation to death. Secondary malignancies were not counted as events.

RESULTS

Patient Characteristics

Ninety-seven patients with high-risk neuroblastoma were treated according to this protocol. Patient characteristics are listed in Table 1. The median age at diagnosis was 35 months (range, 6 months to 18 years). There was one patient who was less than 12 months of age at diagnosis, and 14 patients were between 12 and 18 months of age. Eighty-seven patients (90%) had stage 4 disease. *MYCN* amplification was observed in 53% of the tumors analyzed. Of the 10 patients with stage 3 disease, six had tumor *MYCN* amplification.

Six of the 97 patients developed progressive disease during induction and did not receive myeloablative therapy. Additionally, two patients did not receive high-dose therapy because of parental wishes. Eighty-two (93%) of the remaining 89 patients underwent two courses of myeloablative therapy. Seven patients received only one course either because of toxicity (three patients) or parental choice
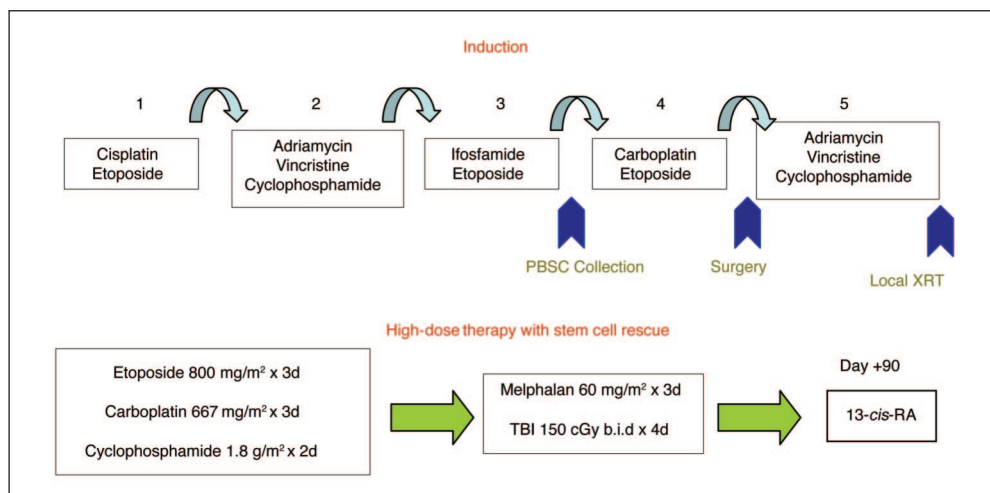

Fig 1. Schema of induction and high-dose therapy before autologous stem-cell rescue. PBSC, peripheral-blood stem-cell collection; XRT, radiation; d, days; TBI, total-body radiation 13-*cis*-RA, 13-*cis*-retinoic acid.

Table 1. Clinical and Biologic Characteristics of the Patient Cohort		
Characteristic	No. of Patients	%
Age		
< 12 months, *MYCN* amplified	1	1
12-18 months	14	14
MYCN amplified	12	
> 18 months	82	85
Stage		
3	10	10
MYCN amplification	6	
Unfavorable histology	4	
4	87	90
MYCN gene copy number		
Nonamplified	43	47
Amplified	48	53
Unknown	6	
Primary site		
Abdominal, nonadrenal	36	38
Adrenal	52	55
Cervical/paraspinal	7	7
Unknown	2	
No. of transplantations		
0	8	8
1	7	7
2	82	85

(four patients). Five children died of toxicity during tandem transplantation, and one child died 3 months after HDT/PBSCR from unknown causes but had no evidence of disease near the time of death. Causes of toxicity-related deaths included veno-occlusive disease (n = 1), sepsis (n = 1), and viral infections with Epstein-Barr virus and cytomegalovirus (n = 3).

Risk of Relapse and Survival Analysis

A total of 51 patients have experienced relapse or died at the time of this report. This includes 45 patients who had relapsed or progressive disease plus six patients who died of toxicity or other causes. The median follow-up time for patients without event (ie, relapse or death) was 5.6 years (range, 15.1 months to 9.9 years). The 3-year PFS rate of the 97 patients treated on this protocol was 55% (95% CI, 44% to

64%), with the PFS remaining relatively stable at 5 and 7 years (Table 2; Fig 2). Among the 89 patients who received at least one course of HDT/PBSCR, 46 (51%) are currently alive and relapse free. PFS rates at 3, 5, and 7 years from time of first transplantation were 59% (95% CI, 47% to 68%), 51% (95% CI, 40% to 61%), and 49% (95% CI, 37% to 59%), respectively. The PFS at 7 years was not substantially different from the PFS at 5 years. However, the OS rate was noted to decrease between 5 and 7 years, with a rate of 62% (95% CI, 51% to 72%) at 5 years and 52% (95% CI, 37% to 65%) at 7 years. When the subset of 82 patients who underwent two courses of HDT/PBSCR was analyzed, the 3-, 5-, and 7-year PFS rates from time of first transplantation was 61% (95% CI, 50% to 71%), 54% (95% CI, 42% to 64%), and 52% (95% CI, 40% to 63%), respectively. OS rates are listed in Table 2.

Thirty-seven (42%) of 89 patients who underwent one or two transplantations had relapse of disease after consolidation. Twenty-eight (75%) of the 37 patients who experienced relapse have died of disease. There were no late toxic deaths; all deaths after 3 months from transplantation were from progressive disease. There was no difference in survival (OS and PFS) between patients whose stem cells were selected for CD34 positivity and patients whose cells were not (P = .33 and P = .58, respectively). Neither *MYCN* amplification nor stage influenced PFS (P = .3 and P = .72, respectively) or OS (P = .81 and P = .44, respectively). Among patients with stage 4 disease, there was a marginally significant difference in PFS between children ≤ 18 months of age and children more than 18 months of age (P = .08). Survival comparisons between patients in the two age groups with *MYCN*-nonamplified tumors were unfeasible because almost all of the patients (13 of 14 patients) ≤ 18 months of age with stage 4 disease had *MYCN*-amplified tumors.

Patterns of Relapse and Development of Secondary Malignancies

Of the 97 patients who started on therapy with this regimen, six experienced progression in metastatic sites during induction. Thirty-seven patients who completed at least one transplantation experienced progression or relapse after transplantation. Twenty-five (68%) of 37 relapses occurred within the first 2 years after transplantation, and 11 of 12 remaining relapses occurred in years 3 and 4. One relapse occurred at 6 years from first transplantation. Of 48 patients who

Table 2. OS and PFS of Patients Treated With HDT/PBSCR								
Survival	Median Survival Time (years)	3-Year Rate		5-Year Rate		7-Year Rate		
		%	95% CI	%	95% CI	%	95% CI	
Survival from time of diagnosis for all patients, N = 97								
PFS	3.9	55	44 to 64	47	36 to 56	45	34 to 55	
OS	7.4	72	62 to 80	60	48 to 69	53	40 to 64	
Survival from time of first transplantation for patients who received at least one transplantation, n = 89								
PFS	5.2	59	47 to 68	51	40 to 61	49	37 to 59	
OS	Not reached	72	61 to 80	62	51 to 72	52	37 to 65	
Survival from time of first transplantation for patients who received tandem transplantation, n = 82								
PFS	Not reached	61	50 to 71	54	42 to 64	52	40 to 63	
OS	Not reached	74	62 to 82	64	52 to 74	54	38 to 67	

Abbreviations: OS, overall survival; PFS, progression-free survival; HDT/PBSCR, high-dose treatment with peripheral-blood stem-cell rescue.
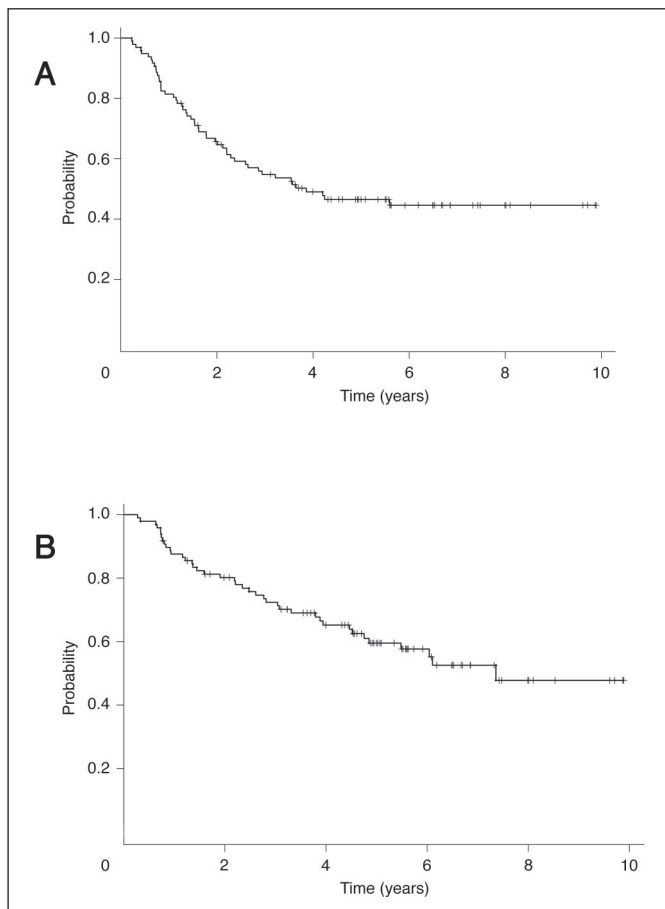
Fig 2. (A) Progression-free survival and (B) overall survival from diagnosis of 97 patients with high-risk neuroblastoma.

survived in complete remission at least 3 years from first transplantation, seven have experienced relapse.

The majority of relapses occurred at metastatic sites and included bone (n = 27), bone marrow (n = 13), liver (n = 2), and lung (n = 1; patients had multiple sites of relapse). Isolated local relapse was rare and occurred in only three patients. One patient had an isolated lymph node relapse out of the radiation field. Of the 31 patients who experienced metastatic relapse, nine experienced relapse in the primary site as well. No relapses primary to the CNS were seen.

Secondary cancers were rare in this group of patients. One patient developed a synovial cell sarcoma 8 years after initial diagnosis of neuroblastoma. Another patient developed myelodysplasia with clonal trisomy 8 and with normal peripheral-blood counts 5.6 years after diagnosis. Overt secondary leukemia was not seen in these patients.

DISCUSSION

We reviewed the treatment outcomes for a large cohort of patients with high-risk neuroblastoma who were uniformly treated with a single induction regimen followed by consolidation with either one (n = 7) or two (n = 82) courses of myeloablative therapy. With a median follow-up of 5.3 years, the PFS rate from diagnosis of patients

treated with this regimen was 47% (95% CI, 36% to 56%) at 5 years. Patterns of relapse included diffuse disease, primarily bony; diffuse and local disease; and rarely, local disease only. We have seen no primary CNS relapses. Secondary malignancies included a synovial cell sarcoma and myelodysplasia with trisomy 8. There were no cases of overt secondary leukemia.

Myeloablative therapy became the standard of care in the United States after the Children's Cancer Group compared the outcome of 189 patients randomly assigned to receive myeloablative chemotherapy with autologous bone marrow transplantation with the outcome of 190 patients who were randomly assigned to receive chemotherapy alone (3-year PFS rate ± SE: 34% ± 4% v 22% ± 4%, respectively; $P = .034$).[4] If one myeloablative course increases survival rates, could tandem transplantation improve on the outcome? The earliest work attempting to answer this question used a double harvest/double graft approach with purged bone marrow support, with an OS rate of 32% at 5 years in a high-risk group of patients.[14] In an analysis of 546 patients with advanced neuroblastoma from the European Bone Marrow Transplantation Solid Tumor Registry, a 5-year PFS rate of 24% was reported for 436 patients who underwent a single procedure compared with 33% for 110 patients who underwent double megatherapy ($P = .05$).[3] In another study in which 17 high-risk neuroblastoma patients were treated with triple-tandem cycles of high-dose therapy with PBSCR and local irradiation, the 3-year PFS rate was 57%.[15] In the present report, patients who underwent double high-dose therapy had a 3-year PFS rate from time of first transplantation of 61%, and 5- and 7-year PFS rates of 54% and 52%, respectively. Whether or not this is significantly better than single myeloablative therapy regimens will require a larger, phase III randomized study. The Children's Oncology Group has designed a phase III study, which is currently under development, to test the effect of tandem HDT/PBSCR on PFS in patients with high-risk neuroblastoma.

Our treatment regimen contains many features that might have influenced outcome. For example, induction therapy was novel in that it incorporated newer agents (carboplatin and ifosfamide) into a standard backbone of anthracycline, cisplatin, and cyclophosphamide, building on the experience of the Pediatric Oncology Group.[16,17] Isolated local relapse was rare in our cohort, perhaps because of aggressive surgical debulking as well as the use of local irradiation in addition to TBI.[18-20] The use of PBSC as opposed to the use of bone marrow as a source of support after myeloablative therapy may have contributed to improved survival. Similar to other reports,[21] we have reported significantly faster hematopoietic recovery associated with higher number of hematopoietic cells infused with PBSCT, which is an effect that was seen in both HDT/PBSCR.[8] PBSC may also be cleaner, with less chance of reinfusing tumor cells.[9] Other potential explanations for our observed outcomes include bias as a result of patient selection (all patients were cared for at major urban tertiary care centers) and limited sample size.

The absence of CNS relapse in itself could also have contributed to the improved survival rate in our cohort. With improved survival in metastatic neuroblastoma, the incidence of CNS relapse has increased.[6,22] In a retrospective analysis of 251 patients with neuroblastoma, none of whom had CNS disease at diagnosis, 4.3% were found to develop CNS relapse.[6] Development of CNS disease was associated with lumbar puncture in the presence of known bone marrow involvement, suggesting that circulating or epidural microscopic tumor cells may have seeded the craniospinal axis.[6] Lumbar puncture at

diagnosis was not performed as a part of our study, which may, in part, explain the absence of CNS relapse in this group. In addition, the CNS relapses mentioned in the earlier referenced study[6] could have been a result of the non-TBI regimens that were used in these patients. In another retrospective analysis of 434 children with stage 4 disease, 5.3% had the CNS as the site of first recurrence, which occurred in the first 18 months after diagnosis.[22] Some of these patients were treated with regimens that included TBI. The estimated risk of CNS recurrence was 8% at 3 years, with no significant change in risk over a 15-year period of follow-up. In this study too, a significant risk factor for CNS recurrence was lumbar puncture at diagnosis, in addition to ages 2 to 3 years and MYCN gene amplification. Our follow-up has been over 5 years, allowing sufficient time for CNS recurrence to occur. Thus far, no evidence of CNS relapse has been documented.

Growth failure, hypothyroidism, and lack of pubertal progress have been observed among the survivors of this protocol. A subset of these patients who have undergone neuropsychological testing showed a lack of morbidity, with excellent neurocognitive functioning.[23] A comprehensive analysis is underway to report on the late effects of this treatment regimen.

Treatment-related myelodysplasia and leukemia have been reported to occur between 7 months and more than 16 years (median, 2 years) after neuroblastoma diagnosis in patients treated with dose-intensive therapy.[24] In our series of patients, only one patient developed myelodysplasia (almost 6 years after diagnosis). This patient had a clonal trisomy 8, which is a genetic abnormality that is not uncommon in post-therapy–related myelodysplasia.[25] With the alkylator dose-intensity contained in this regimen, more incidents of treatment-related myelodysplasia/leukemia would have been expected. Explanations for the lack of secondary leukemia in our patients may include the collection of PBSC early in induction therapy and the use of TBI as part of HDT2, thus ablating leukemogenic hematopoietic precursors.

Secondary malignancies are not uncommon in long-term survivors of neuroblastoma. In a study of 544 neuroblastoma patients with an average follow-up time of 15 years, 12 (2.2%) developed secondary malignancies compared with the 1.19% expected from general population rates.[26] The most frequent secondary solid tumors were thyroid and breast cancers[27,28] attributed to external radiotherapy and occurring between 2 and 21 years after neuroblastoma diagnosis. One patient in our series developed a synovial cell sarcoma 8 years after treatment for neuroblastoma. Because all of the patients described in our study received diagnostic metaiodobenzylguanidine (MIBG), local radiation to the primary tumor, or TBI as part of high-dose therapy, the future occurrence of secondary malignancies is expected.

Induction response, in particular MIBG response, has been correlated in other studies with improved outcome.[29] Unfortunately, we had little data on induction response rates in this cohort, with only limited information on MIBG response at end of induction. During the long time period during which patients were cared for with this regimen, the standards of scanning changed; early patients had no MIBG scans, some later patients had ^{131}I-MIBG scans, and more recent patients underwent modern ^{123}I-MIBG scanning. Longer follow-up on this small number of more recent patients may be informative. Other risk factors such as MYCN gene status and stage did not predict outcome, but the sample size is limited.

Deaths from neuroblastoma have usually been early events; less than 5% occurred more than 3 years from diagnosis, and less than 1% occurred after 5 years.[30,31] Late recurrences have also been rare, with most of the relapses of neuroblastoma typically occurring within 2 years after therapy.[32] With advances in treatment, an increase in the incidence of late recurrences may be seen.[32,33] In our study, late relapses continue to be rare; the largest proportion of patients (68%; 25 of 37 patients) who experienced relapse did so less than 2 years from first transplantation. Only one patient has experienced relapse 5 years or later after diagnosis, with 29 patients at risk. It is still possible that patients may experienced relapse because it has been reported that relapses have been observed as late as 7 years after megatherapy.[33] Therefore, longer follow-up of patients in this series will determine whether this regimen merely arrests the disease until recurrence at some later point or holds the promise of long-term cure. The results of a prospective randomized trial now in development by the Children's Oncology Group comparing single with tandem consolidations may clarify the role that intensification of consolidation has in contributing to long-term outcomes.

In conclusion, despite the improved long-term survival rates seen in patients treated with tandem myeloablative therapy, more than 50% of children with high-risk disease still are not cured. One of the methods for further improvement in survival may be the tailoring of treatment according to response after induction.[5,30] In fact, to more effectively improve induction, up-front topotecan and cyclophosphamide are being incorporated in a future Children's Oncology Group study for newly diagnosed high-risk neuroblastoma patients. Eradication of minimal residual disease may also contribute to better long-term survival through the use of postconsolidation therapy with differentiating agents, targeted antibody therapies, and biologic response modifiers. Finally, detection of molecular aberrations by high-throughput approaches needs to be prioritized in an effort to identify new therapeutic targets.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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