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ORIGINAL REPORT

Long-Term Results for Children With High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-*cis*-Retinoic Acid: A Children's Oncology Group Study

Katherine K. Matthay, C. Patrick Reynolds, Robert C. Seeger, Hiroyuki Shimada, E. Stanton Adkins, Daphne Haas-Kogan, Robert B. Gerbing, Wendy B. London, and Judith G. Villablanca

From the University of California at San Francisco School of Medicine, San Francisco, CA; the Childrens Hospital Los Angeles and the University of Southern California Keck School of Medicine; and the Children's Oncology Group Statistics and Data Center, Los Angeles, CA; the South Carolina Cancer Center, Columbia, SC; and the University of Florida and Children's Oncology Group Statistics and Data Center, Gainesville, FL.

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Corresponding author: Katherine K. Matthay, MD, University of California School of Medicine, 505 Parnassus Ave, Room M647, San Francisco, CA, 94143-0106; e-mail: matthayk@peds.ucsf.edu.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
We assessed the long-term outcome of patients enrolled on CCG-3891, a high-risk neuroblastoma study in which patients were randomly assigned to undergo autologous purged bone marrow transplantation (ABMT) or to receive chemotherapy, and subsequent treatment with 13-*cis*-retinoic acid (*cis*-RA).

Patients and Methods
Patients received the same induction chemotherapy, with random assignment (N = 379) to consolidation with myeloablative chemotherapy, total-body irradiation, and ABMT versus three cycles of intensive chemotherapy. Patients who completed consolidation without disease progression were randomly assigned to receive no further therapy or *cis*-RA for 6 months.

Results
The event-free survival (EFS) for patients randomly assigned to ABMT was significantly higher than those randomly assigned to chemotherapy; the 5-year EFS (mean ± SE) was 30% ± 4% versus 19% ± 3%, respectively ($P = .04$). The 5-year EFS (42% ± 5% *v* 31% ± 5%) from the time of second random assignment was higher for *cis*-RA than for no further therapy, though it was not significant. Overall survival (OS) was significantly higher for each random assignment by a test of the log(−log(.)) transformation of the survival estimates at 5 years ($P < .01$). The 5-year OS from the second random assignment of patients who underwent both random assignments and who were assigned to ABMT/*cis*-RA was 59% ± 8%; for ABMT/no *cis*-RA, it was 41% ± 7%; for continuing chemotherapy/*cis*-RA, it was 38% ± 7%; and for chemotherapy/no *cis*-RA, it was 36% ± 7%.

Conclusion
Myeloablative therapy and autologous hematopoietic cell rescue result in significantly better 5-year EFS and OS than nonmyeloablative chemotherapy; *cis*-RA given after consolidation independently results in significantly improved OS.

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INTRODUCTION

Children with high-risk neuroblastoma have poor long-term survival despite intensive multimodal treatment.[1] Previous studies attributed improvement in outcome to the use of myeloablative cytotoxic therapy with autologous bone marrow transplantation (ABMT). However, because these studies were not prospectively randomized, selection bias may have influenced the results.[2-4]

From 1991 to 1996, the Children's Cancer Group compared myeloablative chemotherapy and radiotherapy plus purged ABMT with continuing intensive chemotherapy without ABMT in a randomized study. Because of the high risk of relapse from minimal residual disease, each cohort underwent a second random assignment to test the efficacy of 13-*cis*-retinoic acid (*cis*-RA), a known differentiating agent for neuroblastoma, to prevent relapse.[5-7] The initial outcome, which was reported in 1999, showed a significant difference in 3-year event-free survival (EFS) for the group randomly assigned to myeloablative therapy and ABMT compared with the group randomly assigned to continuing chemotherapy (CC), although overall survival (OS) was not significantly different.[8] There was also a statistically significant advantage in EFS for patients randomly assigned to *cis*-RA, regardless of whether they had undergone ABMT or received CC. This report describes long-term outcome, more

than 8 years after completion of accrual, with analysis of prognostic factors.

PATIENTS AND METHODS

Of 539 eligible patients who had newly diagnosed high-risk neuroblastoma and who were aged 1 to 18 years, 434 patients had stage 4 neuroblastoma; 72 had stage 3 neuroblastoma with one or more of the following: *MYCN* oncogene amplification, serum ferritin ≥143 ng/mL, and unfavorable histopathology; one patient (aged older than 1 year) had stage 2 neuroblastoma with *MYCN* amplification; 13 patients had stage 1 or 2 disease but developed bone metastases after resection only; and 19 patients younger than 1 year had stage 4 disease and *MYCN* amplification. Parents or guardians provided written informed consent, and the study was approved by local institutional review boards. Enrollment occurred between January 1991 and April 1996.

Treatment

All patients received five cycles of induction with cisplatin, doxorubicin, etoposide, and cyclophosphamide plus surgery and received radiotherapy for residual local and metastatic disease, as previously described.[8] Patients in the ABMT group received carboplatin (1,000 mg/m^2) and etoposide (640 mg/m^2) as continuous infusions over 96 hours; melphalan (140 mg/m^2 on day −7 and 70 mg/m^2 on day −6); and total-body irradiation (3.33 Gy daily on days −3, −2, and −1) followed by infusion of immunomagnetically purged bone marrow and granulocyte-macrophage colony-stimulating factor. Patients in the CC group received three cycles of cisplatin (160 mg/m^2), etoposide (500 mg/m^2), and doxorubicin (40 mg/m^2), as continuous infusions over 96 hours with bolus ifosfamide (2,500 mg/m^2 on days 0 to 3) and granulocyte colony-stimulating factor. The first random assignment was performed just before the third cycle of induction therapy (median, 60 days after diagnosis) for patients without progressive disease (PD). After ABMT or CC (median, 288 days after diagnosis), patients without PD or histologically confirmed disease were randomly assigned to receive six cycles of *cis*-RA (160 mg/m^2/d in two divided doses for 14 days every 28 days) or no further therapy. Disease extent was assessed by international neuroblastoma response criteria at diagnosis, end of induction, after CC or ABMT, and after *cis*-RA.[9]

Statistical Considerations

The study design included two separate sequential random assignments in a quasi-factorial design. Patients with PD before week 8 were ineligible for the first random assignment. Patients with PD or histologically confirmed disease at the completion of ABMT or CC were ineligible for the second random assignment. Patients ineligible for the first random assignment were non–randomly assigned to CC (NRCC). If these patients remained progression free without documented tumor after CC, they were eligible for the second random assignment but were not included in the intention-to-treat analysis of the first random assignment.

A permuted-block design was used for random assignment of approximately equal numbers of patients from each of two strata (stage 3 or 4) to ABMT or CC. The second random assignment was balanced with respect to patients from each group of the first random assignment and non–randomly assigned patients who were ineligible for transplantation.

Similarities between groups were assessed with Fisher's exact test. Outcome analyses used life-table methods according to the Kaplan-Meier method and associated statistics.[10] SEs of the life-table estimates of EFS and OS were calculated according to Peto et al.[11] The primary end point was EFS calculated from time of random assignment. An event was defined as relapse, disease progression, death, or second neoplasm. A two-sided log-rank test, robust to deviations from proportional hazards, was used to compare survival curves. For situations in which the assumption of proportional hazards was obviously violated, survival curves were compared at a fixed point in time by using a two-sided test of a log(−log(.)) transformation of the survival estimates at the 5-year time point.[12] Treatment regimens were compared by intention-to-treat analyses. A Cox proportional hazards model was used to identify prognostic factors. P less than .05 was considered statistically significant except for the two-sided test of the log(−log(.)) transformation of the survival estimates, in which $P < .025$ was considered statistically significant.

RESULTS

Patient Characteristics

Of 539 eligible patients, 379 participated in the first random assignment, and 258 participated in the second. Patient characteristics of the randomly assigned groups were comparable at baseline ($P > .05$; Appendix Table A1, online only). Patients in the group that was non–randomly assigned to chemotherapy differed from randomly assigned patients in the higher percentage of stage 3 (21% *v* 12%; $P = .02$) and lower median age (2.6 *v* 3.1 years; $P = .01$; Appendix Table A1). Detailed characteristics and outcomes for patients with stage 3 disease are reported in a separate manuscript. Outcomes for all randomly assigned high-risk patients are reported below.

Random Assignment and Actual Treatment Received

Of the 539 eligible patients, 190 were randomly assigned to CC, and 189 were assigned to ABMT. Of those assigned to ABMT, 129 actually received ABMT according to protocol; of those assigned to CC, 150 received chemotherapy according to protocol. The assigned treatment was not received in 100 patients. Fifty-two patients had PD before they could receive assigned therapy (28 in CC group; 24 in ABMT). Two patients died after random assignment but before they could receive the assigned treatment. The remaining 46 patients did not receive assigned therapy because of physician or parent decision. Among patients without PD, compliance with the first random assignment was 86%. All analyses were performed on the basis of the assigned treatment.

A total of 319 patients completed consolidation therapy without PD. Of these, 130 were randomly assigned to *cis*-RA, and 128 were assigned to no further therapy. Of the remaining 61 patients, 37 had histologically documented residual disease and were nonrandomly assigned to *cis*-RA. The parents of 24 patients declined the second random assignment, so those patients are not analyzed here. Fifty-two percent of the patients who were randomly assigned to ABMT and 55% of those who were randomly assigned to CC underwent the second random assignment (98% compliance).

The overall 5-year EFS and OS rates ± SE from the time of enrollment for all 539 patients were 26% ± 2% and 36% ± 2%, respectively (Fig 1A). Survival rates for patients with stage 4 disease were slightly lower than the overall cohort (Fig 1B). The median follow-up time of patients alive without an event was 7.7 years (range, 130 days to 12.8 years). The data on which these analyses are based include 91.3% of the expected information (ie, the number of events expected).

Outcomes of ABMT Versus CC

The EFS for patients randomly assigned to ABMT was significantly higher than those randomly assigned to CC, as 5-year EFS rates were 30% ± 4% and 19% ± 3%, respectively ($P = .0434$; Fig 2A). By using the log-rank test to measure the overall difference between the curves, the OS for patients in the ABMT group was not statistically significantly higher than for the patients in the CC group; the 5-year OS rates from the time of random assignment were 39% ± 4% and

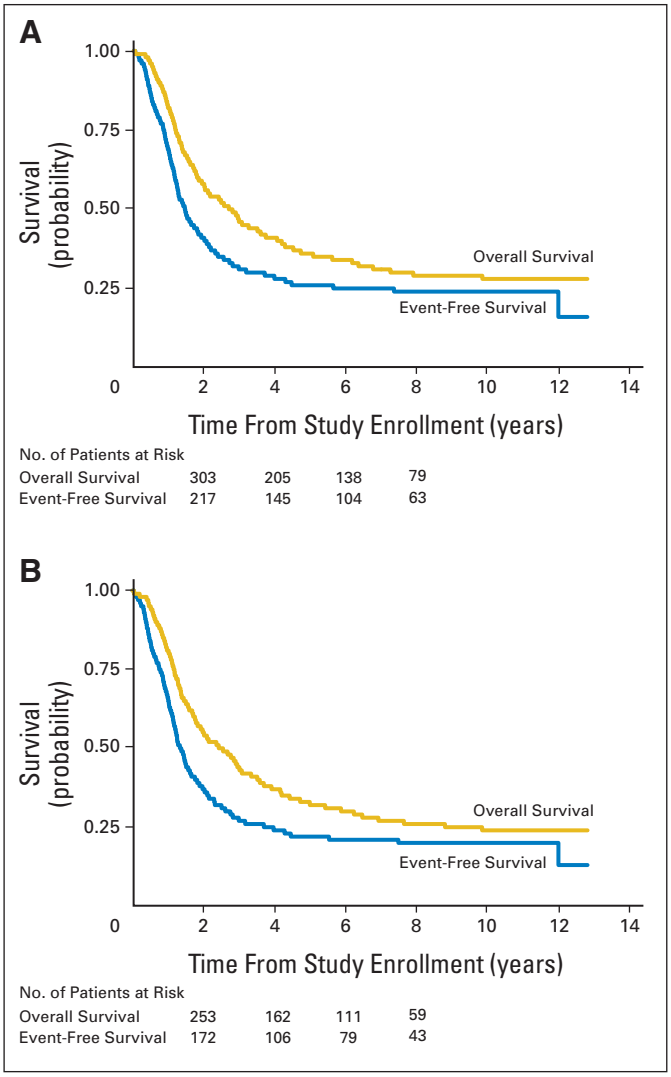

Fig 1. (A) Event-free survival (EFS) and overall survival (OS) for all patients (N = 539). (B) EFS and OS for patients with stage 4 disease (n = 466).

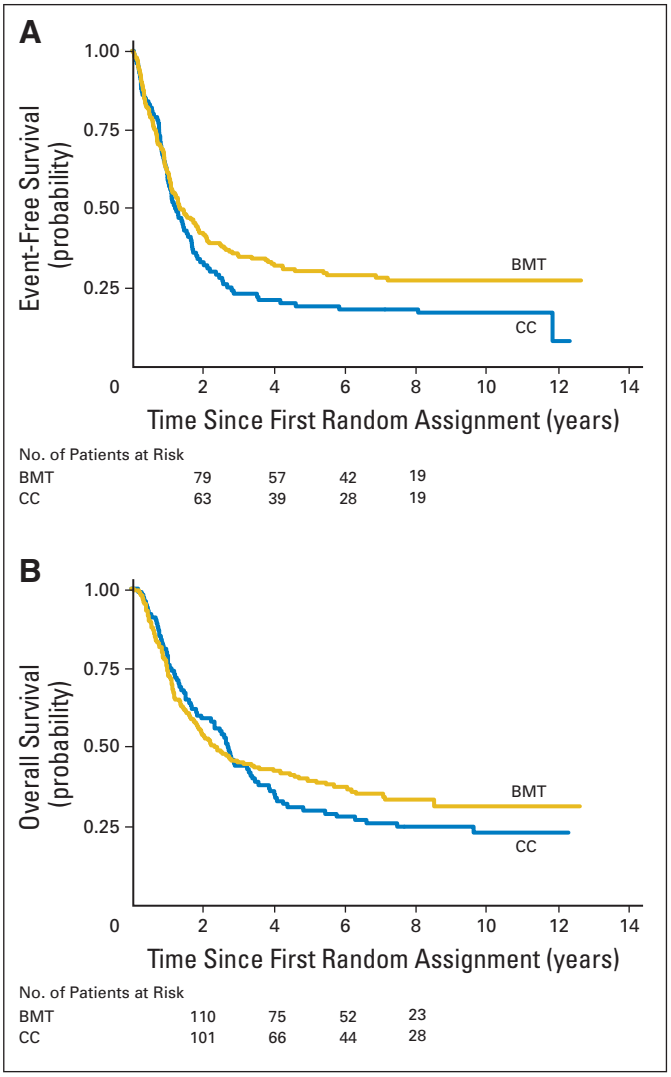

Fig 2. (A) Event-free survival for patients randomly assigned to continuing chemotherapy (CC; n = 190) versus autologous bone marrow transplantation (BMT; n = 189). $P = .0434$. (B) Overall survival for patients randomly assigned to CC (n = 190) versus BMT (n = 189). $P = .3917$ by log-rank test; $P < .0001$ by test of the log(−log(.)) transformation of the survival estimates at 5 years.

30% ± 4%, respectively ($P = .3917$; Fig 2B). However, in patients who survived more than 3 years, there appears to be a benefit of ABMT. At 5 years, the curves are significantly different ($P < .0001$) in a test of the log(−log(.)) transformation of the survival estimates. The results were similar within stage 4 patients; EFS and OS rates for ABMT were 26% ± 4% and 37% ± 4%, respectively, versus 16% ± 3% and 28% ± 4%, respectively, for CC, though there were no statistically significant differences when using a log-rank test between any treatment groups.

Effect of Subsequent Therapy With cis*-RA*

There was a trend that associated improved EFS for patients who were randomly assigned to *cis*-RA versus no *cis*-RA, though it was not statistically significant; 5-year EFS rates from time of random assignment were 42% ± 5% versus 31% ± 5%, respectively ($P = .1219$; Fig 3A). Both the *cis*-RA and no *cis*-RA groups had EFS rates that were significantly higher than patients with documented residual disease who were non–randomly assigned to *cis*-RA, who had a 5-year EFS rate of 6% ± 4% ($P = .0025$ and $P < .0001$, respectively). The trend for a better outcome with *cis*-RA continued for OS. Although the OS curve for patients who received *cis*-RA was not statistically significantly higher than that of the patients who received no *cis*-RA, (5-year OS from the time of random assignment, 50% ± 5% *v* 39% ± 5%, respectively; $P = .1946$; Fig 3B), the OS for *cis*-RA was significantly higher in a test of the log(−log(.)) transformation of the survival estimates at 5 years ($P = .0006$). Both the *cis*-RA and no *cis*-RA group had OS rates that were significantly higher than the patients who were nonrandomly assigned to *cis*-RA (n = 37) and who had a 5-year OS rate of 21% ± 8% ($P = .0052$ and $P = .0003$, respectively). Within stage 4, the 5-year EFS rates for *cis*-RA versus no *cis*-RA were 36% ± 5% and 26% ± 4%, respectively ($P = .2577$), and the 5-year OS rates for *cis*-RA versus no *cis*-RA were 44% ± 5% and 36% ± 5%, respectively ($P = .4538$).

Figure 4 displays the EFS for the patient subset that participated in both random assignments and identifies the time to an event from

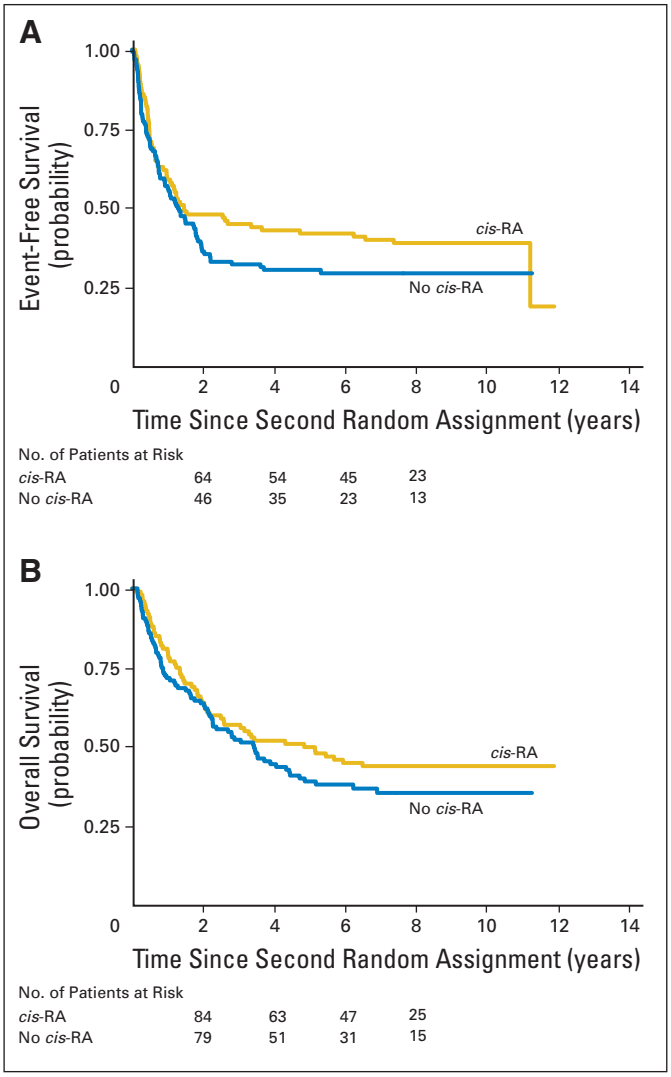

Fig 3. (A) Event-free survival for patients randomly assigned to 13-*cis*-retinoic acid (*cis*-RA) (n = 130) versus no *cis*-RA (n = 128). $P = .1219$. (B) Overall survival for patients randomly asigned to *cis*-RA (n = 130) versus no *cis*-RA (n = 128). $P = .1946$ by log-rank test; $P = .0006$ by test of the log(−log(.)) transformation of the survival estimates at 5 years.

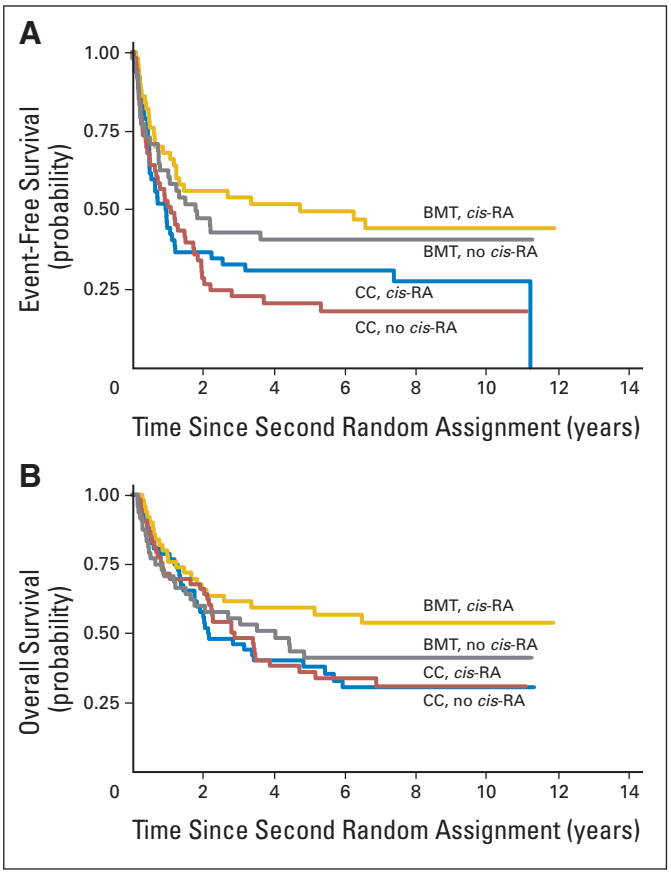

Fig 4. (A) Event-free survival for patients who participated in both the first and second random assignments (autologous bone marrow transplantation + 13-*cis*-retinoic acid [*cis*-RA] [n = 50] versus continuing chemotherapy (CC) + no *cis*-RA [n = 53]). $P = .0038$. (B) Overall survival for patients who participated in both the first and second random assignments (autologous bone marrow transportation + *cis*-RA versus CC + no *cis*-RA) $P = .0540$.

the time of second random assignment. The 5-year EFS rate for patients who were randomly assigned to ABMT and *cis*-RA (n = 50) was 50% ± 8% and was 20% ± 6% for patients assigned to CC and no *cis*-RA (n = 53; $P = .0038$). The 5-year OS rate for patients who were randomly assigned to ABMT and *cis*-RA (n = 50) was 59% ± 8% and was 41% ± 7% for patients assigned to ABMT without *cis*-RA (n = 48); the rate was 38% ± 7% for patients assigned to CC and *cis*-RA (n = 52) and was 36% ± 7% for patients assigned to CC and no *cis*-RA (n = 53; $P = .054$ for the OS of ABMT/*cis*-RA *v* CC/no *cis*-RA). There was no evidence of statistical interaction between treatments of the second random assignment and the first random assignment ($P = .8239$), and the order of the treatment group outcomes makes clinical sense. Treatment with the combination of ABMT and *cis*-RA appears superior to the other combinations. This should be interpreted with caution, because the study was not designed to identify a superior treatment combination in this fashion.

Association of Induction Response and Long-Term Outcome

Of 462 patients who were assessable for induction response, 265 (57%) were complete response (CR)/very good partial response (VGPR), and 197 (43%) were at least partial response (PR). The EFS for the CR/VGPR patients was significantly greater than that of the patients who were at least PR ($P < .0001$; Table 1). Within each treatment group in the first phase of the study, CR/VGPR patients had statistically significantly higher EFS at $P < .0001$. However, the CR/VGPR patients did not have statistically significantly better EFS rates than the patients who were at least PR within the treatment groups of the second phase of the study that tested *cis*-RA (Table 1).

Of the 405 first events, 378 were relapse or PD. Of these 378 patients, 67 patients underwent ABMT after going off protocol therapy and had a 5-year OS of 17% ± 5%.

Prognostic Variables

The potential prognostic factors analyzed included International Neuroblastoma Staging System stage, age, *MYCN* status, pathology, ferritin, and response to induction chemotherapy (Appendix Table A2, online only). In both the overall patient cohort

Table 1. Comparison of EFS and OS Rates by Level of Response Overall and Within Treatment Groups

Response	No. of Patients	5-Year EFS Rate (%)	5-Year EFS SE	*P*
Overall				
CR/VGPR	265	35	± 3	< .0001
≥ PR	197	15	± 3	
CC				
CR/VGPR	92	27	± 5	< .0001
≥ PR	80	10	± 3	
ABMT				
CR/VGPR	99	40	± 5	< .0001
≥ PR	74	19	± 5	
cis-RA				
CR/VGPR	86	46	± 6	.2800
≥ PR	34	32	± 8	
No *cis*-RA				
CR/VGPR	87	29	± 6	.9807
≥ PR	28	32	± 9	

Abbreviations: EFS, event-free survival; OS, overall survival; CR, complete response; VGPR, very good partial response; CC, continuing chemotherapy; PR, partial response; ABMT, autologous bone marrow transplantation; *cis*-RA, 13-*cis*-retinoic acid.

Table 2. Multivariable Analyses of Prognostic Factors Within Treatment Groups

Treatment Group	No. of Patients†	Prognostic Factors by Outcome* EFS	OS
CC	137	*MYCN* amplification Response < VGPR Stage 4	*MYCN* amplification Response < VGPR Stage 4
ABMT	155	Response < VGPR Ferritin > 143 ng/mL	*MYCN* amplification Response < VGPR
cis-RA	92	*MYCN* amplification Stage 4	*MYCN* amplification Stage 4
No *cis*-RA	88	*MYCN* amplification Stage 4	*MYCN* amplification

Abbreviations: EFS, event-free survival; OS, overall survival; CC, continuing chemotherapy; VGPR, very good partial response; ABMT, autologous bone marrow transplantation; *cis*-RA, 13-*cis*-retinoic acid.
*Listed prognostic factors were significantly prognostic of worse outcome ($P < .05$).
†Number of patients with complete data for the given significant prognostic factor.

and the subset of patients with stage 4 disease, factors prognostic of lower EFS and OS rates in univariate analyses included stage 4 disease, *MYCN* gene amplification, unfavorable tumor histopathology, elevated serum ferritin (> 143 ng/mL), and less than a very good partial response (< VGPR) to induction chemotherapy. Older age (< 547 days [n = 92] *v* ≥ 547 days [n = 447])[13] was prognostic of lower EFS in the overall cohort and in the patients with stage 4 disease, but it was not prognostic of lower OS in either cohort (Appendix Table A2).

Multivariable analyses revealed that response ($P < .0001$), *MYCN* status ($P < .0001$), histology ($P = .0064$), stage ($P = .0016$), and ferritin level ($P = .0392$) were prognostic of EFS in the 247 patients with complete data for all factors, whereas only response ($P < .0001$), *MYCN* status ($P < .0001$), histology ($P = .0131$), and stage ($P = .0232$) were prognostic of OS in 269 patients with complete data. For International Neuroblastoma Staging System stage 4, response, *MYCN* status, and histology were prognostic of both EFS and OS in the 222 patients with complete data. Multivariable analyses of prognostic variables within each treatment arm showed that *MYCN* amplification was the factor most often prognostic of worse outcome (Table 2). Neither age ≥ 547 days nor unfavorable histology were prognostic in any of the arms.

Toxicity, Second Malignant Neoplasms, and Deaths

Treatment-related toxicity data were unchanged from the prior report.[8] Second malignant neoplasms occurred in four patients, which included one patient with each of the following: T-cell acute lymphoblastic leukemia 5.0 years after study enrollment (not a first event) in a patient randomly assigned to CC; acute myeloblastic leukemia as a first event 2.7 years after enrollment in a patient randomly assigned to ABMT; clear-cell carcinoma as a first event at 2.5 years in a patient non–randomly assigned to CC; and follicular carcinoma of the thyroid as a first event at 7.3 years in a patient randomly assigned to ABMT. Only the last of these patients received *cis*-RA.

Of 365 deaths, causes were progressive disease (n = 297), treatment (n = 57), and unknown (n = 11). Fifteen of the treatment-related deaths occurred on protocol therapy (during induction, five; during BMT, 8; during CC, 1; during *cis*-RA, 1), 8 occurred during early follow-up, and the remainder occurred in patients who had relapsed and who had received nonprotocol therapy. Treatment-related deaths occurred in similar proportions in patients who were actually treated with ABMT (22 of 122) versus with CC (22 of 138; $P = .7408$), and the proportion of treatment-related deaths also was similar in patients with *cis*-RA (9 of 70) and without *cis*-RA (7 of 78; $P = .5973$).

DISCUSSION

This long-term analysis with an 8-year median follow-up validates our previously reported results that showed the unequivocal benefit of myeloablative therapy in high-risk neuroblastoma. There is a trend for consistently better outcome for each randomly assigned therapy separately, for all patients and for those with stage 4 disease, and for both EFS and OS, although this is statistically significant by log-rank comparison only for the ABMT versus CC random assignment for EFS. By using a comparison of the log(−log(.)) transformation of the survival estimates at 5 years, OS was significantly higher for each random assignment separately, and OS was higher for the ABMT and the *cis*-RA groups. Because more than 91% of the expected events are already observed, the results of this analysis are stable. For patients who underwent both random assignments, the EFS and OS were significantly higher for patients assigned to ABMT and *cis*-RA compared with those assigned to CC and no *cis*-RA.

Two other randomized trials showed a significant improvement in EFS for patients who received myeloablative therapy compared with chemotherapy or with no further treatment. Neither of these randomized trials showed a significant advantage for OS, despite the comparison to no further therapy in one study and to low-dose oral

maintenance therapy in the other study.[14,15] The 5-year EFS rate for all patients on CCG-3891 was 30% compared with 38% for the European Neuroblastoma Study Group 1 study, in which the random assignment occurred later and was limited to patients who achieved good response. The improvement in OS was significant in the European Neuroblastoma Study Group 1 study when analysis was restricted to patients with stage 4 disease who were older than 1 year of age.[15] The more recent German study that used peripheral blood stem cells and incorporated immunotherapy resulted in a 5-year EFS rate of approximately 38%.[14] Although CCG-3891 incorporated total-body irradiation in the conditioning regimen, neither European study used this modality, and there was no apparent detriment to EFS. Because of increased late effects with total-body irradiation,[16] it has been deleted in the majority of current high-risk neuroblastoma trials.

Outcome was improved additionally with *cis*-RA compared with no further therapy, and there was a significant increase in the 5-year OS by the log(−log(.)) transformation. This study likely showed more benefit than the study reported by Kohler et al,[17] because the latter used a much lower dose of *cis*-RA than was shown effective in preclinical studies.[18] Although the rate of occurrence of events and deaths appeared similar between the two therapies within the first 2 years after transplantation, *cis*-RA appeared beneficial in patients who survived, event free, beyond 2 years from transplantation. One possible explanation is that *cis*-RA is effective only against minimal residual disease and does not prevent recurrence from larger amounts of tumor. Therefore, a test at a fixed point in time is appropriate for the measurement of the late benefit of *cis*-RA instead of the log-rank test, which equally weights all parts of the survival curves. By using the test of the log(−log(.)) transformation of the survival estimates at 5 years, OS was significantly improved for patients who were randomly assigned to receive 13-*cis*-RA ($P = .0006$).

Characteristics that were significant for all patients in univariate analyses of EFS and OS included stage, serum ferritin, *MYCN* gene copy number, histopathology, and response to induction therapy.[8] Prognostic variables for EFS in multivariable analyses for all randomly assigned patients for the first random assignment of ABMT versus CC were response to induction, whereas *MCYN* amplification and response were significant for OS. The importance of disease response has been reported in other analyses of myeloablative therapy,[19] though some suggest intensive consolidation can overcome this difference.[20] Retrospective multivariable analyses of 529 patients who were on an European Bone Marrow Transplant registry found that the only significant factors for EFS were presence of disease by MIBG scan or persistent bone marrow disease at the end of induction.[21] *MYCN* status and stage disappear as prognostic variables for EFS in the patients who underwent ABMT in our study, similar to other reports. For the second random assignment that tested *cis*-RA, the most constant significant variables for both EFS and OS in both arms were *MYCN* amplification and disease stage 4. Response to induction lost significance, perhaps because eligibility for the *cis*-RA random assignment excluded documented persistent disease.

In conclusion, long-term follow-up of this randomized trial showed significantly better 5-year EFS and OS rates for myeloablative therapy with purged ABMT than for non–myeloablative chemotherapy, and *cis*-RA given after intensive therapy resulted in significant improvement in 5-year OS rates, regardless of the type of consolidation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Katherine K. Matthay, C. Patrick Reynolds, Robert C. Seeger, E. Stanton Adkins, Daphne Haas-Kogan
Provision of study materials or patients: Katherine K. Matthay, Hiroyuki Shimada, Daphne Haas-Kogan, Wendy B. London
Collection and assembly of data: C. Patrick Reynolds, Hiroyuki Shimada, Robert B. Gerbing
Data analysis and interpretation: Katherine K. Matthay, C. Patrick Reynolds, Robert C. Seeger, E. Stanton Adkins, Robert B. Gerbing, Wendy B. London, Judith G. Villablanca
Manuscript writing: Katherine K. Matthay, C. Patrick Reynolds, Judith G. Villablanca
Final approval of manuscript: Katherine K. Matthay, C. Patrick Reynolds, Robert C. Seeger, Hiroyuki Shimada, E. Stanton Adkins, Daphne Haas-Kogan, Robert B. Gerbing, Wendy B. London, Judith G. Villablanca

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