Consolidation Chemoradiotherapy and Autologous Bone Marrow Transplantation Versus Continued Chemotherapy for Metastatic Neuroblastoma: A Report of Two Concurrent Children's Cancer Group Studies

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Purpose: **To compare event-free survival (EFS) for patients with stage IV neuroblastoma who were treated with induction chemotherapy followed by additional courses of the same chemotherapy or by intensive chemoradiotherapy and autologous bone marrow transplantation (ABMT).**

Methods: **Two hundred seven children who were diagnosed with stage IV neuroblastoma after 1 year of age were given five to seven courses of induction chemotherapy consisting of cisplatin, etoposide, doxorubicin, and cyclophosphamide (CCC-321-P2). This chemotherapy was continued for 13 total courses for some patients, whereas intensive chemoradiotherapy with ABMT was given to others (CCG-321-P3). The decision to continue chemotherapy versus to consolidate with chemoradiotherapy was not randomized but was made by parents and physicians. Marrow used for ABMT was purged ex vivo and was free of immunocytologically detectable neuroblastoma cells.**

Results: **One hundred fifty-nine of 207 patients (77%) remained event-free during induction therapy. Of these, 67 received chemoradiotherapy/ABMT (CCG-321-P3) and 74 continued chemotherapy (CCG-321-P2). Using Cox regression analysis, the relative risk (RR) of an event after chemoradiotherapy/ABMT was estimated to be 58% of that for patients who continued chemotherapy (P = .01). Similarly, Kaplan-Meier analysis estimated EFS at four years for the chemoradiotherapy/ABMT and chemotherapy groups to be 40% and 19%, respectively (P = .019). Subgroups appearing to benefit from chemoradiotherapy/ABMT were those with only a partial tumor response to induction chemotherapy (RR = 0.43; P = .008; EFS, 29% *v* 6%) and those whose tumors had amplification of the N-*myc* gene (RR = 0.26; P = .112; EFS, 67% *v* 0%).**

Conclusion: **Consolidation with intensive, myeloablative chemoradiotherapy followed by purged ABMT may be more effective than continuing chemotherapy for patients with stage IV neuroblastoma.**

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METASTATIC neuroblastoma that is diagnosed after 1 year of age is almost always an aggressive malignancy.[1-11] Studies in recent years suggest that intensive, multimodal therapy provides some possibility of long-term survival.[12-20] Dose-intensive induction chemotherapy with surgery and local irradiation cytoreduces most tumors.[16,18,20] Consolidation with myeloablative chemotherapy or chemoradiotherapy followed by allogeneic bone marrow transplantation (BMT) or autologous BMT (ABMT) results in 15% to 40% of patients alive 4 years after transplantation.[13-19,21] Chemotherapy without myeloablative consolidation results in a 12% to 20% survival rate at 4 years.[7,10,22-29] The efficacy of myeloablative versus nonmyeloablative consolidation therapy has not been determined.

The Children's Cancer Group (CCG) recently completed pilot studies of chemotherapy (CCG-321-P2; 1986 to 1991) and myeloablative chemoradiotherapy (CCG-321-P3; 1985 to 1994) for children with high-risk neuroblastoma. In the latter study, hematopoiesis was restored using autologous marrow that had been purged ex vivo. The concurrent performance of these protocols resulted in children receiving uniform induction chemotherapy. Then, without randomization, they either continued this same chemotherapy or changed to chemoradiotherapy/ABMT. The large number of patients with stage IV disease enrolled onto these studies provides a relatively homogenous population to compare the efficacy of contin-

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ued chemotherapy versus consolidation with intensive chemoradiotherapy/ABMT.

Although this was not a randomized comparison of two regimens, each patient group was similar with respect to multiple characteristics. In addition, two analyses addressed a potential waiting-time bias,[30] whereby patients with less aggressive tumors would be more likely to receive chemoradiotherapy/ABMT, because this treatment was not an option if disease progression occurred during induction chemotherapy. Cox regression analysis treated time to ABMT as a time-varying covariate, and Kaplan-Meier analysis compared event-free survival (EFS) from the data of ABMT for chemoradiotherapy/ABMT patients to EFS from 8 months after diagnosis for chemotherapy patients still event-free at that time. Together, these analyses suggest that consolidation with myeloablative chemoradiotherapy/ABMT after induction chemotherapy provides more effective treatment for patients with stage IV neuroblastoma than does continuation of the same chemotherapy. Patients who particularly appear to benefit from chemoradiotherapy/ABMT are those with only a partial response after induction therapy and those with tumors that have amplification of the N-*myc* proto-oncogene.

METHODS

Patients

Patients enrolled onto the CCG-321-P2 and CCG-321-P3 studies were 1 to 18 years old when diagnosed with neuroblastoma. Diagnosis and staging of neuroblastoma were performed at the patient's institution according to standard pathologic and clinical criteria used by the CCG.[31,32] Staging was as follows: stage III, tumor that extended in continuity beyond the midline, possibly with bilateral involvement of regional lymph nodes; and stage IV, remote disease that involved multiple sites, including bone, bone marrow, organs, soft tissues, or groups of distant lymph nodes. To provide a homogeneous patient population with respect to clinical stage, this report includes only the 207 patients with stage IV and not the 34 with high-risk stage III disease enrolled onto CCG-321-P2. All 67 stage IV patients who received CCG-321-P2 induction chemotherapy and then transferred to CCG-321-P3 chemoradiotherapy/ABMT are reported herein. A previous report,[13] which compared outcome for stage IV patients being consolidated with the cisplatin, etoposide, melphalan (PEM) plus total-body irradiation (TBI) chemoradiotherapy regimen (see below and Table 1) versus allogeneic BMT, reported earlier results for 33 of these stage IV ABMT patients. CCG-321-P3 also enrolled neuroblastoma patients treated by other induction chemotherapy protocols, but this report includes only those initially treated by CCG-321-P2. Informed consent for these studies was obtained according to the requirements of local institutional review boards.

Therapy

The composition of the CCG-321-P2 chemotherapy regimen is listed in Table 2, and that of the three myeloablative CCG-321-P3 chemoradiotherapy regimens are listed in Table 1. CCG-321-P2 was open for patient enrollment from September 1986 to January 1991 and CCG-321-P3 was open from October 1985 to February 1994. Patients could receive CCG-321-P2 chemotherapy for a total of 13 courses if disease progression or other events did not occur. Alternatively, at physician discretion, they could proceed to CCG-321-P3 chemoradiotherapy/ABMT (n = 67) or CCG-321-P1 chemoradiotherapy/allogeneic BMT (n = 18) after from three to nine courses of CCG-321-P2 (before 36 weeks after initiation of chemo-

Table 1. CCG-321-P3: Myeloablative Chemoradiotherapy Regimens

Day	Drug
VAMP-TBI regimen (1985-1988)	
−9	Cisplatin 90 mg/m^2/8 h
−8	No therapy
−7	Teniposide 150 mg/m^2/1 h; doxorubicin 45 mg/m^2/0.5 h
−6	Melphalan 140 mg/m^2/0.5 h
−5	Melphalan 70 mg/m^2/0.5 h
−4	Teniposide 150 mg/m^2/1 h
−3	TBI 3.33 Gy
−2	TBI 3.33 Gy
−1	TBI 3.33 Gy
0	ABMT
PEM-TBI regimen (1988-1990)	
−8	Cisplatin 30 mg/m^2/24 h, etoposide 100 mg/m^2/24 h
−7	Cisplatin 30 mg/m^2/24 h, etoposide 100 mg/m^2/24 h, melphalan 140 mg/m^2/0.5 h
−6	Cisplatin 30 mg/m^2/24 h, etoposide 100 mg/m^2/24 h, melphalan 70 mg/m^2/0.5 h
−5	Cisplatin 20 mg/m^2/24 h, etoposide 100 mg/m^2/24 h
−4	No therapy
−3	TBI 3.33 Gy
−2	TBI 3.33 Gy
−1	TBI 3.33 Gy
0	ABMT
CEM-TBI regimen (1990-1994)*	
−8	Carboplatin 160-300 mg/m^2/24 h, etoposide 125-200 mg/m^2/24 h
−7	Carboplatin 160-300 mg/m^2/24 h, etoposide 125-200 mg/m^2/24 h, melphalan 140/mg/m^2/0.5 h
−6	Carboplatin 160-300 mg/m^2/24 h, etoposide 125-200 mg/m^2/24 h, melphalan 70 mg/m^2/0.5 h
−5	Carboplatin 160-300 mg/m^2/24 h, etoposide 125-200 mg/m^2/24 h
−4	No therapy
−3	TBI 3.33 Gy
−2	TBI 3.33 Gy
−1	TBI 3.33 Gy
0	ABMT

*The doses of carboplatin and etoposide were escalated in the CEM-TBI regimen, and the lowest and highest levels are indicated.

Table 2. CCG-321-P2: Chemotherapy Regimen

Day	Drug
1	Cisplatin, 60 mg/m^2/6 h
2	No therapy
3	Teniposide or etoposide, 100 mg/m^2/1 h; doxorubicin, 30 mg/m^2/.25 h
4	Cyclophosphamide, 900 mg/m^2/0.5 h
5	Cyclophosphamide 900 mg/m^2/0.5 h
6	Teniposide or etoposide 100 mg/m^2/1 h

therapy). The last patient to transfer from CCG-321-P2 induction therapy to CCG-321-P3 chemoradiotherapy did so in August 1991. Patients also could transfer from CCG-321-P2 to non-CCG protocols for myeloablative chemoradiotherapy and allogeneic BMT (n = 2) or ABMT (n = 11).

Patients who were to be transferred to CCG-321-P3 had their bone marrow harvested and purged ex vivo by sedimentation, filtration, and magnetic immunobeads.[33,34] All marrow samples used for ABMT were evaluated by immunocytology after purging and found to be free of detectable neuroblastoma cells (sensitivity = one tumor cell per 10^5 normal cells).[35] Surgery was performed at diagnosis and/or after four or five courses of chemotherapy to remove gross disease, if possible.[36,37] Local irradiation was given to the remaining gross abdominal or thoracic tumor (10 Gy) and to persistent bone lesions (20 Gy).

The response to CCG-321-P2 induction chemotherapy was determined according to international criteria after courses 3, 5, and 7 (or before chemoradiotherapy/ABMT) using bone scan, computed tomography, bone marrow aspirate and biopsy, and urine catecholamine metabolite determination.[32]

Statistical Analyses

Analyses of outcome used EFS as the end point, with an event being defined as death due to any cause or the occurrence of progressive disease or a second malignancy. Progressive disease was defined according to international criteria[32] as follows: (1) growth of an existing lesion by greater than 25%, (2) development of a new lesion or marrow metastases, or (3) increase in marrow metastases. Analyses took into account complexities caused by chemoradiotherapy/ABMT occurring at different times and by the requirement that patients be event-free to receive chemoradiotherapy/ABMT.

One analysis of the effect of chemoradiotherapy/ABMT on EFS was based on the Cox partial likelihood method.[38] With this approach, the time from diagnosis to ABMT was treated as a time-varying covariate to allow for the varying times at which chemoradiotherapy/ABMT took place.[39] Thus, at any time point (where time is defined as time since entry onto the CCG-321-P2 chemotherapy study), the event hazard rate experienced by patients who had not yet had an ABMT was compared with the event hazard rate of patients already transplanted at that time. In analyzing the effect of chemoradiotherapy/ABMT, the event hazard rates for these two groups of patients were assumed to differ by a constant factor, the relative risk (RR), the value of which is estimated in the analysis. All patients (n = 31) who received myeloablative therapy/BMT other than that of CCG-321-P3 were censored at the time this therapy was received, because removal from the comparative analysis would potentially bias results in favor of chemoradiotherapy/ABMT.

To determine if the RR of an event after chemoradiotherapy/ABMT versus chemotherapy differed between subgroups of patients (eg, those with N-*myc*–amplified or –nonamplified tumors), tests for differences in the RR by subgroup were performed. This was computed from the change in log likelihood when an interaction term between treatment and subgroup membership was added to the Cox regression model.

The log-rank statistic was used to compare Kaplan-Meier curves for the two treatment groups. A comparison of Kaplan-Meier curves starting from the date chemotherapy began and the date of ABMT would positively bias the analysis in favor of chemoradiotherapy/ABMT, since the chemotherapy group would include all patients with early events. Therefore, only chemotherapy patients who remained event-free for 8 months and then continued chemotherapy were compared with chemoradiotherapy/ABMT patients. Eight months was chosen since it was the median time from diagnosis to transplant for the chemoradiotherapy/ABMT patients. Of the patients who did not receive CCG-321-P3 chemoradiotherapy/ABMT, 48 progressed or died before 8 months, and 18 were transplanted before 8 months on other protocols, which left 74 in the chemotherapy group for Kaplan-Meier analysis (all patients are used in the Cox regression). Thirteen patients in the chemotherapy group received chemoradiotherapy/BMT after 8 months according to non–CCG-321-P3 protocols, and they were included but censored on the date of their BMT so that they contribute to the chemotherapy group outcome to that date. Patients in the chemotherapy group completed from three to eight courses of CCG-321-P2 chemotherapy (median, 6.5) before 8 months, whereas the ABMT group received from three to nine courses (median, five) of CCG-321-P2 chemotherapy before the time of ABMT.

Although three chemoradiotherapy regimens were tested in the CCG-321-P3 study (Table 1), EFS after 36 months was not significantly different for the three regimens (teniposide, doxorubicin, melphalan, and cisplatin (VAMP)-TBI, 38%; PEM-TBI, 52%; carboplatin, etoposide, and melphalan (CEM)-TBI, 50%; P = .59). Therefore, data for patients treated according to these three regimens (VAMP-TBI, n = 8; PEM-TBI, n = 33; CEM-TBI, n = 26) were pooled for analysis of EFS.

Interim Analyses of Data

Studies CCG-321-P2 and CCG-321-P3 did not involve randomizations, and they were not originally designed to yield a direct comparison between chemotherapy and ABMT. No formal mechanism for the timing of analysis of the chemotherapy versus chemoradiotherapy/ABMT question was instituted, and the present analysis must be regarded as a retrospective review. Early results from this same retrospective comparison were presented in May 1993, and a brief report published in the meeting proceedings.[40] The preliminary analysis in 1993 was based on follow-up evaluation of these patients to June 1992, approximately 10 months after the last patient was transferred for transplantation on CCG-321-P3. At the time of the early analysis, there was a suggestion of a benefit to patients in the chemoradiotherapy/ABMT group; however, this was not significant (P = .27) based on the follow-up data available at that time. Some other information regarding this comparison was also described in a more recent survey of the CCG experience with myeloablative therapy in neuroblastoma.[41] This survey indicated that the previously reported analysis now yielded (with further follow-up evaluation) a statistically significant benefit for ABMT, but did not give any data to support this statement. The current analysis is based on follow-

up data to January 17, 1994, 29 months after the last patient was transferred from CCG-321-P2 to CCG-321-P3 for transplantation, and represents a final report on this comparison.

In interpreting a retrospective analysis, the primary difficulty is in evaluating two issues: (1) whether selection biases may have been present in the way that patients were chosen for treatment, and (2) once the analysis has been performed, whether statistically significant results are more likely to be published than are insignificant findings. The fact that these data have been analyzed more than once has an impact on the interpretability of the results only if the decision to publish these data at this time (as opposed to some other time, or never) is a function of the size of the differences recorded. The analysis described here deals with one specific selection bias issue (the selection of patients who are alive and in remission), but no retrospective analysis can fully address either question 1 or 2.

The median follow-up durations for the chemoradiotherapy/ABMT and chemotherapy groups are 40 and 35 months, respectively. Tests of tabular data used the Pearson χ^2 statistic. All P values reported are for two-tailed alternatives. The Epilog statistics package (Epicenter Software, Pasadena, CA) was used for all calculations. Data files for the current analysis were closed on July 17, 1994, and a cutoff date for analysis of January 17, 1994 was used to insure that event and survival data were reported completely.

RESULTS

Patients and Response to Induction Chemotherapy

Two hundred seven children who were diagnosed with stage IV neuroblastoma after 1 year of age were enrolled onto CCG-321-P2. Clinical and laboratory characteristics for all patients (n = 207), for those who remained event-free 8 months after diagnosis and then continued with CCG-321-P2 chemotherapy (n = 74), and for those who remained event-free 5 to 11 months after diagnosis and then received CCG-321-P3 myeloablative chemoradiotherapy/ABMT (n = 67) are listed in Table 3. There were no significant differences between the chemotherapy and chemoradiotherapy/ABMT groups for any of the characteristics.

For the 207 children, the Kaplan-Meier estimate of EFS at 8 months after diagnosis was 77%. While CCG-321-P2 induction chemotherapy was effective against 44% of stage IV tumors (complete or very good partial response), it was only moderately effective (partial response) or ineffective (no response, progressive disease or death) against 56%. Thus, metastatic neuroblastomas diagnosed after 1 year of age were heterogeneous in responding to this induction chemotherapy.

Continued Chemotherapy Versus Consolidation With Chemoradiotherapy/ABMT

The EFS of patients who continued to receive chemotherapy was compared with that of patients who received chemoradiotherapy/ABMT. Cox regression analysis estimated the RR of an event after ABMT as 58% of that observed for patients who continued with chemotherapy (P = 0.013; Table 4). Kaplan-Meier analysis estimated the EFS rates for patients treated with chemoradiotherapy/ABMT versus continued chemotherapy to be 40% and 19%, respectively, at 4 years (P = 0.020; Fig 1A).

A second analysis restricted events to progressive disease by censoring five therapy-related deaths among the chemoradiotherapy/ABMT group and one among the chemotherapy group at the time they occurred. This analysis was performed to compare the antitumor activity of each therapy. The RR of progressive disease with chemoradiotherapy/ABMT was 50% of that with continued chemotherapy (P = .002; Table 4). Kaplan-Meier analysis, after censoring therapy-related deaths, gave similar results, with 43% and 19% estimated EFS rates for the chemora-

Table 3. Patient Characteristics and Response to Induction Chemotherapy

Characteristic	All Patients		Chemotherapy Group		Chemoradiotherapy/ABMT Group	
	No.	%	No.	%	No.	%
All patients	207	100	74	100	67	100
Age at diagnosis, years						
1-2	46	22	21	28	11	16
> 2	161	78	53	72	56	84
Bone metastases at diagnosis						
Absent	74	36	31	42	20	30
Present	133	64	43	58	47	70
Bone marrow metastases at diagnosis						
Absent	50	24	23	31	13	19
Present	157	76	51	69	54	81
Tumor N-*myc*						
Not amplified	72	76	25	78	29	83
Amplified	23	24	7	22	6	17
Resection of primary tumor (at diagnosis or end of induction chemotherapy)						
Gross complete resection	112	54	41	55	48	72
Partial resection	31	15	12	16	10	15
Biopsy only	27	13	11	15	4	6
None	37	18	10	14	5	8
Response to induction therapy (8 months after diagnosis)*						
CR	84	41	45	61	32	48
VGPR	6	3	3	4	3	4
PR	66	32	23	31	32	48
NR	3	1	3	4	0	0
PD	48	23	0	0	0	0

NOTE. Variables were compared for chemotherapy v chemoradiotherapy/ABMT groups using the Pearson χ^2 test, and no significant differences were found.

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

*Responses were assessed after courses 3, 5, and 7 of CCG-321-P2 induction chemotherapy as described in the Methods.[32]

Table 4. Comparison of EFS for Children With Stage IV Neuroblastoma Who Received Consolidation Chemoradiotherapy/ABMT Versus Continued Chemotherapy

	Cox Regression			Kaplan-Meier§		
	RR			% EFS at 48 Months		
	RR*	95% CI	P†	ABMT	Chemotherapy	P
All patients	0.58	0.39-0.88	.013	40	19	.020
Therapy-related deaths censored	0.50	0.32-0.77	.002	43	19	.004
Response to induction therapy‡						
CR or VGPR	0.61	0.34-1.10	.103	50	27	.114
PR	0.43	0.23-0.80	.008	29	6	.011
Tumor N-*myc*‡						
Not amplified	0.98	0.52-1.85	.960	28	26	.893
Amplified	0.26	0.05-1.36	.112	67	0	.066
Age at diagnosis, years						
1-2	0.70	0.22-2.22	.540	62	60	.720
> 2	0.48	0.31-0.77	.002	35	5	.003
Bone metastases at diagnosis						
Absent	0.59	0.29-1.22	.154	45	35	.557
Present	0.58	0.35-0.96	.034	37	18	.063
Bone marrow metastases at diagnosis						
Absent	0.76	0.32-1.77	.522	42	41	.776
Present	0.54	0.33-0.87	.011	39	17	.019

Abbreviation: CI, confidence interval.

*RR of an event among patients who received chemoradiotherapy/ABMT v those who continued chemotherapy.

†Significance of RR estimate for chemoradiotherapy/ABMT v chemotherapy groups.

‡RR estimate is significantly different ($P < .10$) for these subsets, but not others. Likelihood ratio χ^2 test results were as follows: CR or VGPR (RR = 0.61) v PR (RR = 0.43), $P = .074$; N-*myc* not amplified (RR = 0.98) v amplified (RR = 0.26), $P = .010$.

§Kaplan-Meier analysis determined the probabilities of EFS from the date of ABMT for the chemoradiotherapy/ABMT group and from 8 months after diagnosis for the chemotherapy group, and groups were compared using the log-rank statistic. Both groups included only patients who were event-free survivors at the time analysis began. The median follow-up time from the beginning of the analysis for event-free survivors is 40 months (range, 28 to 66) for the chemoradiotherapy/ABMT group and 35 months (range, 3 to 80) for the chemotherapy group.

diotherapy/ABMT and chemotherapy groups ($P = .004$; Table 4 and Fig 1B). These results suggest that, as a group, patients with stage IV disease had a better outcome if intensive chemoradiotherapy/ABMT consolidation was provided after induction chemotherapy than if the same chemotherapy was continued.

Response of Patient Subgroups to Continued Chemotherapy Versus Consolidation With Chemoradiotherapy/ABMT

All patients with stage IV neuroblastoma who are diagnosed after 1 year of age have high-risk disease, but these tumors respond differently to induction therapy, as demonstrated in this study. Although subgroups cannot yet be precisely defined by laboratory or clinical tests, some were chosen to test the possibility that one or the other of the postinduction strategies may be most effective against certain subgroups of tumors. Variables used to define subgroups included N-*myc* gene amplification, age, bone and bone marrow metastases at diagnosis, and tumor response to induction therapy (Table 4).

Chemoradiotherapy/ABMT appeared more effective for children who had only a partial response after induction chemotherapy, as the RR of an event after chemoradiotherapy/ABMT was estimated to be just 43% of that for patients who continued chemotherapy ($P = .008$; Table 4 and Fig 1C). Comparison of the RR estimates using the likelihood ratio χ^2 method for patients with a partial response (RR = 0.43) versus a complete or very good partial response (RR = 0.61) also gave evidence that the patients with partially responsive tumors benefited more from chemoradiotherapy/ABMT than did those with more responsive tumors ($P = .074$).

N-*myc* gene analysis was performed on neuroblastomas from 95 of 207 patients, and 23 tumors had genomic amplification. Among 23 patients with N-*myc*–amplified tumors, 10 developed progressive disease during the first 8 months after diagnosis, and the estimated EFS rates 8 months after diagnosis for patients whose tumors had versus did not have amplification of N-*myc* was 65% versus 83% ($P = .048$). Data from the 13 patients who remained event-free were used for comparison of postinduction therapies. The RR of an event after chemoradiotherapy/ABMT was estimated to be 26% of that for pa-

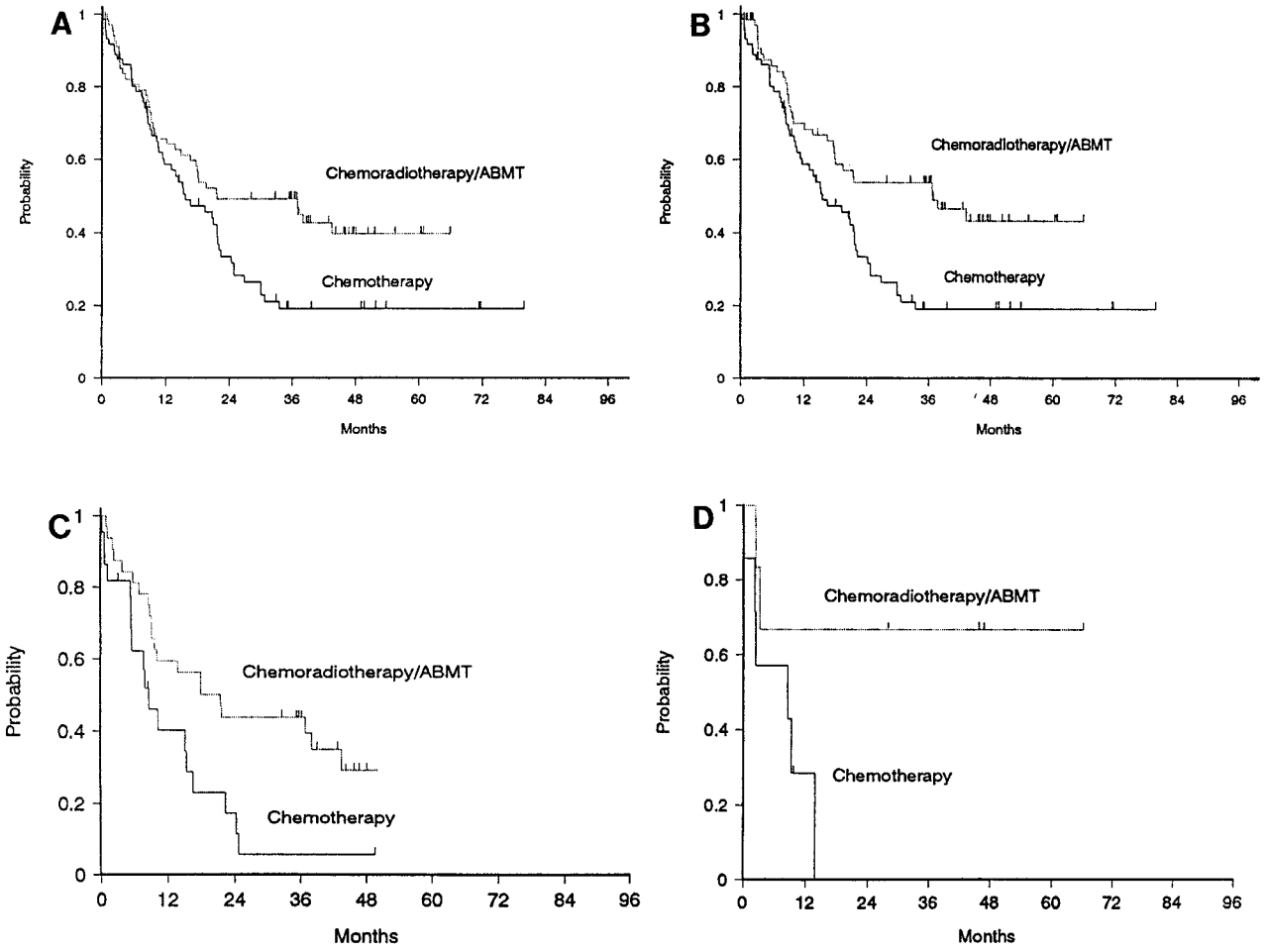

Fig 1. EFS for stage IV neuroblastoma, chemoradiotherapy/ABMT *v* continued chemotherapy. (A) All patients (P = .020); (B) all patients, censoring therapy-related deaths (P = .004); (C) patients with partial response to induction chemotherapy (P = .011); (D) patients with amplified N-*myc* (P = .066). Patient numbers are provided in Table 3.

tients who continued with chemotherapy (Table 4). This large difference was not significant (P = .112), probably due to the relatively small number of patients in this subset. However, comparison of the RR estimates for patients with nonamplified (RR = 0.98) versus amplified tumors (RR = 0.26) using the likelihood ratio method indicated that patients with N-*myc*–amplified tumors benefited more from chemoradiotherapy/ABMT than did those with nonamplified tumors (likelihood ratio χ^2, P = .010). Kaplan-Meier analysis also suggested an advantage for those patients treated with chemoradiotherapy/ABMT (EFS, 67% *v* 0%; P = .066; Table 4 and Fig 1D).

Other subgroups that had a significantly lower risk of an event with chemoradiotherapy/ABMT included those diagnosed after 2 years of age and those with bone and/or bone marrow metastases at diagnosis (Table 4). However, likelihood ratio χ^2 tests showed that the benefits of chemoradiotherapy/ABMT for the compared subgroups (eg, 1 to 2 years *v* > 2 years; bone metastases absent *v* present; bone marrow metastases absent *v* present) were not significantly different.

DISCUSSION

Only 12% to 20% of children diagnosed with metastatic neuroblastoma after 1 year of age achieve long-term survival with conventional chemotherapy.[2-10,42] Dose-intensive chemotherapy appears to be important for tumor response,[16] and one study of 24 patients achieved an 87.5% complete or very good partial response rate.[20] Intensive consolidation therapy also is likely to have an

important role. Indeed, some patients become long-term survivors following consolidation with myeloablative chemotherapy or chemoradiotherapy, but at least 60% develop recurrent tumor.[14,15,17,43,44] Although numerous investigations of consolidation with myeloablative therapy have been performed, there is little information to compare this strategy to consolidation with nonmyeloablative therapy.[45-47] The primary analysis in this report evaluates the efficacy of these two postinduction therapies for patients with stage IV neuroblastoma.

Our data, which are derived from two concurrent studies of the CCG, suggest that consolidation with myeloablative chemoradiotherapy/ABMT is more effective than continued multiple courses of chemotherapy. Although this was not a randomized comparison of the two therapies, the large number of stage IV patients over 1 year of age at diagnosis entered onto the study (n = 207), the relatively large number who either continued chemotherapy (n = 74) or switched to chemoradiotherapy/ABMT (n = 67), the similarity of the two groups, and statistical analyses that minimized effects of nonrandom selection support the validity of this conclusion. This is the largest group of patients with stage IV disease for which comparison of two postinduction therapies has been possible.

These data provide the first comparison of two postinduction treatment strategies for subgroups of patients with stage IV disease. The strongest benefit from chemoradiotherapy/ABMT appeared to be for those who were in partial response after induction treatment (RR = 43%; P = .008). Chemoradiotherapy/ABMT also may be more beneficial than chemotherapy for patients with N-*myc*–amplified tumors (RR = 0.26; P = .112). Although this large apparent difference in risk was confirmed by Kaplan-Meier analysis (EFS, 67% *v* 0%), neither was statistically significant, probably due to the small number of patients with amplified tumors. However, comparison of the RR estimates for patients with amplified versus nonamplified tumors using the likelihood ratio χ^2 test indicated that those with amplified tumors benefited more from chemoradiotherapy/ABMT than did those with nonamplified tumors. Other subgroups that appeared to have a higher EFS from chemoradiotherapy/ABMT included patients who were older than 2 years and those who had bone and bone marrow metastases. No significant improvement in EFS with chemoradiotherapy/ABMT was demonstrated for patients diagnosed between 1 and 2 years of age and for those in complete or very good partial response at the time of chemoradiotherapy/ABMT.

Our findings emphasize the need to identify subgroups, since the relative efficacy of myeloablative and nonmyeloablative therapy may vary depending on the tumor subgroup. Clinical and tumor biologic parameters that can be defined at diagnosis, such as metastatic sites, histopathology,[1] N-*myc* gene status,[9] nerve growth factor receptor (*trk*A) expression,[48-50] P-glycoprotein expression,[51,52] nm23/nucleoside diphosphate kinase expression,[53,54] and tumor-cell quantity in marrow,[35] could define subgroups. Tumor response assessments that include sensitive evaluation of the response of marrow metastases with immunocytology[35] and polymerase chain reaction[55] techniques also may define subgroups whose tumor cells vary in their sensitivity to chemotherapy.

While our analysis indicates that chemoradiotherapy/ABMT may be better than continued chemotherapy for some patients, caution is warranted, and our results must be regarded as suggestive, rather than definitive. First, without randomization, unknown selection factors may bias the comparisons. For example, patients were not transferred to the chemoradiotherapy/ABMT study until after a purged autologous bone marrow sample had been obtained. However, there were no statistically significant differences between the two groups with respect to several factors that were analyzed, and there even were higher percentages of patients who were older than 2 years, who had bone and bone marrow metastases, and who had only a partial response at the conclusion of induction therapy in the chemoradiotherapy/ABMT group (Table 3). Second, late relapses may occur in either group, which could alter conclusions. However, to date, the latest relapse in a stage IV patient has been 43 months after ABMT, and the median follow-up durations for the chemoradiotherapy/ABMT and chemotherapy groups are 40 and 35 months, respectively. Last, chemoradiotherapy/ABMT could appear better than continued chemotherapy if the chemotherapy was quite ineffective. However, EFS for our chemotherapy group was similar to that reported for other contemporary chemotherapy studies.[22,25,28]

Three other reports have compared myeloablative and nonmyeloablative consolidation therapy for children with stage IV neuroblastoma. One randomized trial with a total of only 65 patients suggested that myeloablative chemotherapy/ABMT was most effective.[45] Two concurrent, nonrandomized studies performed by the Pediatric Oncology Group showed no difference in survival for 49 patients who received chemoradiotherapy/BMT compared with 67 patients who received chemotherapy.[46] However, the BMT group was heterogenous, with 32 being transplanted in first remission according to protocol and 17 being transplanted according to local protocols or after first remission. The latter could have had a significant nega-

tive impact on outcome after chemoradiotherapy/BMT, since patients who are treated with chemoradiotherapy/BMT after disease progression generally are less likely to survive than those who are treated before disease progression.[17,21,56] In a nonrandomized study of 110 patients by the Study Group of Japan, the EFS rates were 50% and 38.8% after 5 years for those who received myeloablative therapy/BMT and chemotherapy, respectively.[47]

A definitive comparison of consolidation with myeloablative versus nonmyeloablative therapy will come from the current randomized testing of these approaches by the CCG (CCG-3891). In this study, which will randomize 180 patients over 5 years to each of two treatment arms, the primary analysis will be based on an intent-to-treat comparison. All patients, who are randomized at 8 weeks after diagnosis to one of the two treatments, will be used in the outcome analysis for that treatment, even if progressive disease or death occurs before treatment or if therapy is changed. This will allow the use of standard statistical techniques such as the log-rank test or test of proportions, rather than the more complicated time-varying covariate analysis used for the present study.

While outcome for some patients with metastatic neuroblastoma appears to have been improved by consolidation with intensive, myeloablative therapy, it is clear that still more effective induction and consolidation therapies are required. Only 44% of our patients were in complete or very good partial response at 8 months, and 23% had already developed progressive disease. By 4 years after chemoradiotherapy/ABMT, 58% of transplanted patients had relapsed. Induction therapy should achieve a greater than 80% complete response rate, and this is likely to require intensive chemotherapy with hematopoietic growth factor and possibly stem-cell support. The best strategy for consolidation has not yet been defined; however, our data suggest that intensive, myeloablative therapy warrants further development and clinical testing. Nonmyeloablative postinduction chemotherapy, if used, should be more intensive than that used in this study. Even with maximally intensive induction and consolidation therapies, small numbers of tumor cells will probably survive in some patients. Thus, development of postconsolidation therapy that is effective against neuroblastoma cells that survive maximal chemotherapy and irradiation will have an important role in improving survival for patients with stage IV neuroblastoma.

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APPENDIX

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