Induction Chemotherapy and Conformal Radiation Therapy for Very Young Children With Nonmetastatic Medulloblastoma: Children's Oncology Group Study P9934

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ABSTRACT

Purpose

P9934 was a prospective trial of systemic chemotherapy, second surgery, and conformal radiation therapy (CRT) limited to the posterior fossa and primary site for children between 8 months and 3 years old with nonmetastatic medulloblastoma. The study was open from June 2000 until June 2006.

Patients and Methods

After initial surgery, children received four cycles of induction chemotherapy, followed by age- and response-adjusted CRT to the posterior fossa (18 or 23.4 Gy) and tumor bed (cumulative 50.4 or 54 Gy) and maintenance chemotherapy. Neurodevelopmental outcomes were evaluated and event-free survival (EFS) results were directly compared with a previous study of multiagent chemotherapy without irradiation (Pediatric Oncology Group [POG] trial 9233).

Results

Seventy-four patients met eligibility requirements. The 4-year EFS and overall survival probabilities were $50\% \pm 6\%$ and $69\% \pm 5.5\%$, respectively, which compared favorably to the results from POG 9233. Analysis showed that the desmoplastic/nodular subtype was a favorable factor in predicting survival. Our 4-year EFS rate was $58\% \pm 8\%$ for patients with desmoplasia. Whereas seven of 10 patients who had disease progression before CRT had primary-site failure, 15 of 19 patients who progressed after CRT had distant-site failure. Neurodevelopmental assessments did not show a decline in cognitive or motor function after protocol-directed chemotherapy and CRT.

Conclusion

The addition of CRT to postoperative chemotherapy in young children with nonmetastatic medulloblastoma increased event-free survival compared with the use of postoperative chemotherapy alone. Future studies will use histopathologic typing (desmoplastic/nodular versus nondesmoplastic/nodular) to stratify patients for therapy by risk of relapse.

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INTRODUCTION

One third of pediatric CNS tumors occur in patients younger than 5 years. Among the most common histologic diagnoses in this group are embryonal neoplasms such as medulloblastoma (MB).¹ Craniospinal irradiation (CSI) is a standard component of therapy in older children. Although CSI is effective, it is associated with an unacceptably high incidence of sequelae in very young children.²⁻⁴ Treatment protocols for infants and young children have relied on primary postoperative combination chemotherapy regimens with deferral or avoidance of irradiation. Despite this, survival for chil-

dren in this group has been suboptimal and neurocognitive sequelae remain high.^{2,5-9}

It has been reported that the use of methotrexate in the postoperative chemotherapy regimen favorably influences survival.¹⁰ However, the mean intelligence quotient of the surviving group in one series was significantly lower than that of healthy controls within the same age group, raising concerns about the neurotoxicity of methotrexate in the reported regimen.¹¹ Local failure as a component of failure was a substantial concern, and radiation therapy was used in at least 38% of patients who were successfully saved from treatment failure.¹¹

Considering reports demonstrating that conformal radiation therapy (CRT) could be safely administered in very young children with infratentorial ependymoma without the anticipated late effects,^{12,13} we hypothesized that the use of CRT would benefit very young children with nonmetastatic MB.

PATIENTS AND METHODS

Patients

Our Children's Oncology Group study P9934 enrolled children older than 8 months and younger than 3 years with institutionally diagnosed non-metastatic (M0) MB. The study was approved by the institutional review boards at each of the participating institutions. The patients' legal guardians consented to treatment and the patients themselves assented when age-appropriate. Protocol guidelines recommended maximal safe surgical removal of the primary tumor. The extent of resection was assessed using operative notes and by magnetic resonance imaging (MRI) obtained within 72 hours of surgery. The presence of any tumor on MRI or by surgical report was considered evidence of incomplete resection. Study inclusion criteria included age, central review of the histopathology of MB and posterior fossa primitive neuro-ectodermal tumor, absence of metastases, written informed consent obtained from legally authorized representative, no prior radiation or chemotherapy, and chemotherapy as per protocol administered within 6 weeks of definitive tumor surgery. MRI scans of the entire brain and spine were performed within 3 weeks before starting chemotherapy. Eligibility also required adequate hematologic and metabolic function.

Treatment

Children received four 4-week courses of induction chemotherapy, each consisting of cyclophosphamide, vincristine, cisplatin, and etoposide. This was followed by consideration for second surgical resection if residual disease was present. Patients without evidence of progression during induction chemotherapy received age- and response-adjusted CRT. Finally, a maintenance course of chemotherapy was administered, consisting of four alternating cycles of cyclophosphamide and vincristine followed by oral etoposide. More information about the histopathology central review, radiation planning and treatment, and the chemotherapy schema delivered is available in the Appendix (online-only).

Evaluations

During treatment, toxic effects were monitored with appropriate laboratory assessments and imaging studies and were graded according to the US National Cancer Institute's common toxicity criteria version 2. Disease status was assessed by centrally reviewed MRI of the head and spine using standard methods. Patients were monitored by routine cytologic examination of the lumbar CSF; the presence of any tumor cells in the CSF was considered positive. After completion of treatment, follow-up examinations were done every 3 months for the first 12 months, every 4 months for the next 12 months, every 6 months for the next 12 months, and then once every year.

Neurodevelopmental Assessments

Patients' families were contacted and asked to complete a battery of telephone-based interviews and questionnaires.¹⁴⁻¹⁹ A designated primary caregiver was asked to complete interviews at registration and at specified periods before induction chemotherapy; before CRT; and at 12, 24, 36, and 48 months postdiagnosis. At registration, the primary caregiver was asked to recall their child's best ever obtained development before onset of symptoms from the brain tumor. The median time for recall of baseline best function was 25 days (range, 7 to 90 days). The phone interview employed the WeeFIM (Uniform Data System for Medical Rehabilitation, Amherst, NY) system.¹⁹ Functional quotients and age-adjusted norms were generated for the domains of self-care, mobility, and cognition.

Formal neuropsychological testing was performed at three time points to coincide with the phone-based interviews: immediately before radiation therapy (within 1 month of beginning radiation therapy), at 24 ± 1 month after diagnosis, and 48 ± 1 month after diagnosis. Intellectual functioning was

assessed using an age-appropriate instrument (Bayley Scales-II or Wechsler Preschool and Primary Scale-Revised).^{14,17,18}

The results of the WeeFIM analysis will be detailed in this article. More detailed results of neurodevelopmental assessments will be the subject of a separate article.

Statistical Analysis

The primary objective of this phase III historical control study was to determine whether the proposed therapy was more effective than the combined treatments given to children of the same age and with the same extent of disease. The primary end point for the evaluation of treatment efficacy was event-free survival (EFS), and it was defined as the time to disease progression, disease relapse, occurrence of a second neoplasm, or death from any cause measured from the time of study enrollment. The secondary end point was time to death from any cause, from which actuarial overall survival (OS) probability was calculated. The design called for 65 eligible patients enrolled onto the study in 5 years. Based on a one-sided log-rank test with 5% type I error, accounting for minimal failure rate after 2 years, and with a follow-up period of 2 years on the last patient, this study has at least 80% power to detect a 1.8-fold reduction in the failure rate under a proportional hazard assumption or an improvement in 2-year EFS from 25% in study 9233% to 46% in P9934.²⁴ Nonparametric EFS and OS curves were calculated using the product-limit (Kaplan-Meier) estimates, with SEs via the Greenwood formula. Multivariate Cox regression analysis was used to analyze possible prognostic factors for the risk of recurrence. The factors included in the analysis are age, gender, extent of resection, residual tumor, tumor site, and histopathologic subtype. A significance level of .05 was used.

A mixed-effects growth curve model using all available data was chosen for the longitudinal analyses of neurodevelopmental assessments, with an unstructured covariance pattern to account for the correlation within patients. The resultant model described the rate of change in neurodevelopmental function, allowing for the possibility that change may not be constant over time. It also accounted for between-patient variability by incorporating the rate of change for each patient into the model. The particular method we used for fitting growth curves was a piecewise linear regression model. The change in functional quotient was modeled as a linear function over short intervals of time. For the model fitting, we allowed the slope to change at pre-CRT, 12, 24, 36, and 48 months after enrollment.

RESULTS

Patient Characteristics

Between October 2000 and June 2006, 82 patients were enrolled onto this study from 64 separate institutions. Eight children were considered ineligible on central review: five had discordant diagnoses on histopathology review, two had evidence of metastases on radiology review, and one had inadequate imaging. The characteristics of the eligible patients enrolled onto this study are listed in Table 1. The median follow-up for patients alive at last contact was 4.8 years.

Disease Progression and Other Events

Thirty-seven patients experienced events as recorded by their treating institutions. Tumor progression was reported in 32 patients and was confirmed by central review in 29. Tumor progression could not be documented in three patients; all were alive at the time of analysis. Two patient deaths were reported by the treating institution without imaging documentation of disease progression. One patient died as a result of infection 2 weeks after the start of chemotherapy; two patients developed secondary malignancies (T-cell acute lymphoblastic leukemia and acute myelodysplastic syndrome), which were possibly treatment related though neither malignancy carried the characteristic molecular genetic markers.

Table 1. EFS and OS by Patient and Tumor Characteristics

Characteristic	No. of Patients	%	4-Year EFS		4-Year OS	
			Rate	P	Rate	P
Age, months						
< 12	12	16	83 ± 11	.03	92 ± 8	.08
≥ 12	62	84	43 ± 7		65 ± 6	
Sex						
Male	40	54	54 ± 8	.54	63 ± 8	.43
Female	34	46	46 ± 9		76 ± 7	
Race/ethnicity						
White	60	81	43 ± 7	.07	68 ± 6	.28
Black	6	8	100 ± 0		100 ± 0	
Other/unknown	8	11	62 ± 17		60 ± 18	
Extent of resection						
Gross total	55	74	53 ± 7	.30	75 ± 6	.13
Subtotal	15	20	40 ± 13		53 ± 13	
Unknown*	4	5				
Residual tumor						
No residual	48	65	57 ± 7	.09	78 ± 6	.06
Residual	23	31	39 ± 10		57 ± 10	
Unknown*	3	4				
Primary tumor site						
Cerebellar hemisphere	19	26	79 ± 10	.03	84 ± 9	.10
Vermis/intraventricular	45	61	41 ± 8		63 ± 7	
Other/mixed/unknown*	10	13				
Histologic pattern						
Desmoplastic/nodular	39	53	58 ± 8	.008	79 ± 7	.003
Nondesmoplastic/nodular	13	17	23 ± 12		31 ± 16	
Unknown*	22	30				

Abbreviations: EFS, event-free survival; OS, overall survival.

*Not included in survival analysis.

Patterns of Failure

Among the 29 patients with documented disease progression, there was a striking difference in the pattern of failure related to the timing of CRT (Table 2). Primary site failure was a component of failure in seven of 10 patients who progressed before CRT. In four patients, progression was exclusively confined to the posterior fossa. In contrast, failure outside of the posterior fossa occurred in 15 of 19

patients who progressed after CRT. The most common sites of involvement were the frontal lobes and spinal theca caudal to C2. There were no treatment failures in the irradiated occipital or temporal lobes. One patient experienced recurrence in the posterior fossa at 4.8 years and one developed primary site failure at 5.3 years. Three patients in our series, one before and two after CRT, experienced neuraxis dissemination of disease in which primary site failure was not identifiable. Central review of individual radiation dosimetry was used to determine the dose at the site of initial failure (Fig A1, online only).

Table 2. Sites and Timing of Recurrence by Central Review

Site of First Recurrence	Failures Before CRT	Failures After CRT
Primary site only	4	1
Primary site and metastatic to posterior fossa	1	0
Primary site and metastatic to spine	1	0
Primary site and CSF involvement	1	0
Sites of metastatic disease	0	0
Posterior fossa	0	1
Frontal region only	0	3
Spine only	1	3
Frontal region and metastatic to spine	0	7
Spinal and CSF involvement	1	1
CSF involvement	0	1
Widespread metastatic disease	1	2
Total	10	19

Abbreviations: CRT, conformal radiation therapy.

Outcome

Figure 1 illustrates the EFS and OS rates for the 74 eligible children treated in this study and for the subset of M0 MB patients ages 8 to 36 months who were treated on POG 9233. Four-year EFS and OS probabilities on our trial P9934 were 50% ± 6% and 69% ± 5.5%, respectively. This compared favorably to the EFS of 25% ± 5.5% and OS of 46% ± 6% on POG 9233, based on children of the same age ($P = .0085$ and $P = .0075$, respectively). However, further comparison of these two studies shows that the distribution of baseline variables was significantly different for extent of resection and the histologic diagnosis of desmoplastic and nodular tumor MB. The proportion of patients who had gross total resection and desmoplastic/nodular tumor MB on our trial was significantly higher than on POG 9233. Fifty-five (79%) of 70 patients had gross total resection on our trial compared with 32 (51%) of 63 patients on POG 9233 (χ^2 P value =

Fig 1. (A) Comparison of overall survival (OS) and event-free survival (EFS) and (B) analysis by desmoplasia in trials P9934 and Pediatric Oncology Group 9233.

.001). Thirty-nine (75%) of 52 patients had desmoplastic/nodular tumor MB on P9934 compared with 20 (49%) of 41 patients on POG 9233 ($\chi^2 P = .01$). Comparing the EFS between P9934 and POG 9233 after the stratification of extent of resection still showed the P9934 regimen had a greater benefit than the POG 9233 regimen (stratified log-rank $P = .02$). However, this was not the case for the comparison stratified by desmoplastic/nodular tumor MB versus other subtypes of MB (stratified log-rank test $P = .812$). Comparing each stratum reveals some evidence of a difference in the desmoplastic/nodular tumor MB group but not in the nondesmoplastic/nodular tumor MB group (Fig 1). It is important to note that our study was not designed to prospectively detect differences in each stratum, and the power to detect a difference in each stratum was low owing to the small sample size. The 4-year EFS for patients with desmoplastic/nodular tumor MB was $34\% \pm 11\%$ and $58\% \pm 8\%$ on POG 9233 and P9934, respectively (log-rank P value = .24). The 4-year EFS in nondesmoplastic/nodular tumor patients was $14\% \pm 7\%$ and $23\% \pm 12\%$ on POG 9233 and P9934, respectively (log-rank $P = .92$). There were 22 patients from each study who did not have specimens that were adequate for the evaluation of desmoplasia. There was no significant difference in outcome between patients who were evaluated versus those who were not. In the cohort of patients who did not have evaluation, patients enrolled onto P9934 had a more favorable outcome than the cohort enrolled onto POG 9233 (log-rank $P = .04$).

Prognostic Factors

Table A1 (Appendix) summarizes 4-year EFS and OS rates based on age, gender, extent of resection, residual tumor, tumor site, and histopathologic subtype. Univariate analyses showed that the following individual factors were significantly associated with better EFS: younger age, cerebellar hemisphere lesions, and desmoplastic/nodular pattern. Age and desmoplastic/nodular pattern were significantly correlated with OS. To determine the independent value and the relative risk (RR) of the significantly correlated prognostic factors, a multivariate Cox regression analysis was performed. The presence of a desmoplastic/nodular pattern was the only factor independently associated with outcome (Fig 2). It was significantly more common in tumors occurring in children younger than 1 year old than in older children. Ten (91%) of 11 patients younger than 1 year had desmoplastic/

Fig 2. Estimated mean functional quotient for cognition, mobility, and self care versus time from enrollment (weeks). (A) Mean cognitive functional quotient; (B) mean mobility functional quotient; and (C) mean self-care functional quotient.

nodular patterns compared with 29 (71%) of 41 patients who were older than 1 year old. The RR for progression and relapse was 2.8 times higher (95% CI, 1.3 to 6.3) for the patients with nondesmoplastic/nodular tumors than for those with desmoplastic/nodular tumors. The multivariate analysis of OS also showed that presence of a desmoplastic/nodular pattern was the only factor independently associated with OS. The RR for death was 3.62 times higher (95% CI, 1.3 to 10.0) for the nondesmoplastic/nodular patients than for the desmoplastic/nodular patients.

Toxicity

Myelotoxicity was the most frequently reported adverse effect. One treatment-related death occurred secondary to a fungal infection during the first course of induction. Grade 4 toxicities were confined mainly to the expected myelotoxicity of the induction regimen. No child had symptoms of irradiation-induced acute neurotoxicity.

Neurodevelopmental Follow-Up

Obtaining adequate direct neuropsychological data on cooperative group studies for infant brain tumor patients has proved to be difficult. In an attempt to overcome these barriers, this study used a telephone-based assessment approach in conjunction with validated parental reports and an abbreviated direct formal neuropsychological battery.

Seven scheduled follow-up phone assessments were performed unless the patient experienced an event leading to withdrawal from study. Thirteen patients were lost to developmental follow-up owing to failure of registration at the beginning of treatment. The number of patients tested with telephone assessments and questionnaires at each time point is listed here: baseline, 61 patients; before chemotherapy, 61 patients; pre-CRT, 54 patients; at 12 months, 40 patients; at 24 months, 34 patients; at 36 months, 30 patients; at 48 months, 30 patients. In contrast, 60% patients (37 of 61 potentially eligible) were registered for direct formal neuropsychological battery before CRT (baseline), then only 35% patients (12 of 34 of those potentially eligible) were tested at 24 months after registration, and only 16% (five of 30 of the potentially eligible) were tested at 48 months.

The results of WeeFIM assessments are expressed as means and standard deviations of functional quotients. A globally normal WeeFIM quotient is considered more than 79, mild delays 70 to 79, moderate delays 55 to 69, and severe delays less than 55.

Appendix Table A1 shows the categorization of cognitive, mobility, and self care functional quotient over time. The majority of infants fell within the normal-to-mild delay range in WeeFIM functional quotients at baseline, suggesting a significant delay in development before the diagnosis of a tumor. Figure 2 shows the estimated mean functional quotient for each domain over time. There was a decline in functional quotient from baseline to preirradiation in all three domains. The decline was more profound in mobility and self care. The estimated rates of decline for mobility, self care, and cognition during the first 16 weeks were -2.43 , -2.18 , and -1.39 points per month, respectively. After 16 weeks, the mean self care functional quotient increased but never returned to baseline levels. The mean at 36 months was 72.4 (95% CI, 64.6 to 80.2). In contrast, the mean mobility functional quotient increased dramatically to baseline levels at 36 months (86.2; 95% CI, 77.7 to 94.8). There was a smaller early decline in the cognitive functional quotient compared with mobility and self care,

and the quotient remained stable after 16 weeks. The mean cognitive functional quotient at 36 months was 73.1 (95% CI, 66.9 to 79.3).

In summary, although developmental progress continued in these infants over time, the population remained impaired relative to normal children. Importantly, no significant or consistent decline in either cognitive or motor functioning as measured by phone-based methods including the WeeFIM could be directly attributed to the delivery of chemotherapy or CRT.

DISCUSSION

The estimated survival rates among the 74 patients treated in our study compare favorably with the results of the historical study POG 9233, in which chemotherapy alone was the primary treatment. Although the introduction of conformal radiotherapy has most likely contributed to the improved survival rates obtained in this study, other improvements over time (technical improvement, staging, risk definitions, residual tumors, and histology) could also have contributed to improved survival rates.

Like other contemporary studies, our study has confirmed that very young children with desmoplastic/nodular MB have superior survival rates compared with those with classical MB. Histologic subtype was the only independent prognostic factor by multivariate analysis.²⁰

It has been reported that postoperative chemotherapy including high-dose intravenous and intrathecal methotrexate is a promising treatment for MB in young children without metastases.¹¹ However, moderate-to-severe leukoencephalopathy was found in the majority of patients in the reported cohort and the results of intelligence quotient tests on survivors were significantly lower than the results observed in healthy control subjects of the same age group. The same study was not able to identify the independent contributions of the disease, surgery, or chemotherapy to the adverse effects on neurocognitive function.

Over a 4-year post-treatment time frame, we did not observe a clinically significant decline in either cognitive or motor function after the delivery of chemotherapy and CRT. It is possible that decreasing quotients might be detected after a longer follow-up period. The significant declines in developmental and functional skills, compared with the premorbid baseline, suggests that surgery and/or the effects of the tumor have a more profound impact than we have previously recognized.

Taking into consideration recent promising results with chemotherapy alone since this study completed accrual, it has become unclear whether the application of CRT is required for children with localized desmoplastic MBs. Certainly, a potential drawback to this approach is the subsequent difficulty in using radiation for relapse strategies. However, it should be noted that with the exception of two patients, no initial recurrence was observed at sites that received a minimum of 12 Gy during the 6-week course of CRT. The pattern of relapse involving predominantly frontal regions is also of interest given that all patients were in a prone position during operation. Taken together with the lack of evidence of declines in either cognitive or motor function, these data are provocative and may prompt a reassessment of the role of irradiation in high-risk infants with these tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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