The treatment of malignant brain tumors in infants and very young children: An update of the Pediatric Oncology Group experience

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The survival of infants and very young children with brain tumors is significantly worse than that of older children, both overall and within specific tumor types. Not only are survivals poor, but infants tend to suffer the brunt of treatment-induced neurotoxicity. As such, since the mid-1980s the attention of the neuro-oncology community has been focused on this group of children. In 1986, POG[2] developed a novel approach for the treatment of infants and very young children with malignant brain tumors in which prolonged postoperative chemotherapy was given in an attempt to delay radiation (Duffner et al., 1993). In this report, the experience with "Baby POG" 10 years after the study opened will be reviewed and comparisons will be made with other treatment trials used in this age group.

Brain tumors, the most common solid malignancy in childhood, are fairly equally distributed among children 0–14 years of age with 12–16% occurring in children <2 years of age at diagnosis (Albright, 1985; Duffner et al., 1986; Tomita and McLone, 1985), and approximately 5% occurring in those <6 months of age (Cohen and Duffner, 1994). The location of brain tumors in very young children differs from the posterior fossa predominance of older children. This is especially true in the first 6–12 months of life, where supratentorial location is significantly more common. For example, in the Toronto Series, 71% of children <1 year of age with brain tumors were supratentorial, and in the French Series, 70% of brain tumors diagnosed at birth or in the first week were supratentorial (Asai, 1989; Jellinger, 1973). If analysis of location is restricted to malignant tumors, however, these proportions change, that is, the posterior fossa is the site of medulloblastoma (the most common malignant brain tumor in this age group) and the location of most ependymomas in the very young.

Tumor types vary according to age as well (Duffner et al., 1986). Although medulloblastomas are the most

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[2]Abbreviations used are as follows: ABMR, autologous bone marrow rescue; ABMT, autologous bone marrow transplantation; CCG, Children's Cancer Group; GTR, gross total resection; MOPP, mechlorethamine/vincristine/procarbazine/prednisone; PFS, progression-free survival; PNET, primitive neuroectodermal tumor; POG, Pediatric Oncology Group; SEER, Surveillance, Epidemiology, and End Results; UKCCSG, United Kingdom Children's Cancer Study Group.

[3]Kühl, J., Berthold, F., Bode, U., Deinlein, F., Graf, N., Henzo, G., Muller, A., Ottensmeier, H., Scheurlein, W., Wolff, J., and Riehm, H. (1998) Postoperative chemotherapy without radiation therapy in children less than three years of age with medulloblastaoma: German pilot trial HIT-SKK'92. Proceedings of the 8th Symposium of Pediatric Neuro-Oncology, May 6–9, Rome.

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common malignant tumor in children 0–14 years of age, ependymomas vary in frequency with age. They are the second most common malignant tumor in children <2 years of age, but are relatively unusual in children after the age of 5. The third most common malignant tumor identified by the SEER Registries in children <2 years of age is the high-grade astrocytoma, a grouping that includes glioblastoma multiforme, anaplastic astrocytoma, and malignant glioma (Duffner et al., 1986). Other than in the very young, this histology is rare until the 10-14-year interval.

Much of the epidemiologic data on childhood brain tumors is derived from the SEER Registries (Duffner et al., 1986). Since the 1980s, however, large numbers of children from the United States and Europe have been entered into treatment trials sponsored by the National Brain Tumor Consortiums. Although these data do not provide true epidemiologic information, they do identify which types of tumors are being referred for therapy. Thus, in the POG study of children <3 years of age with malignant brain tumors, the most common tumors were medulloblastomas followed by ependymomas, PNETs, and malignant gliomas (Duffner et al., 1993). The PNET category was not identified as a separate entity in the SEER Registry, and as such, incidence figures are not available. Moreover, PNETs are a particularly difficult group to analyze because of differences in histologic interpretation and classification. In the POG Study, for example, the term "primitive neuroectodermal tumor" excluded children with medulloblastomas and choroid plexus carcinomas, but included patients with pineoblastomas, cerebral neuroblastomas, and ependymoblastomas. In contrast, the CCG included medulloblastomas under the rubric of PNET (Geyer et al., 1994). Thus, interpretation of treatment results in this tumor histology is difficult. Malignant gliomas in the Baby POG I clustered in the very young, with 12 of 18 tumors occurring in children <6 months of age and only one child having a malignant glioma who was older than 24 months at diagnosis. Although low-grade astrocytomas, including pilocytic astrocytomas, are the most common tumor type in the first two years of life, they will not be specifically addressed in this report.

Prior to the mid-1980s, the treatment for infants and very young children with brain tumors was surgery followed by radiation (with a 10–20% dose reduction according to age). The resulting poor survivals and significant neurotoxicity led some neuro-oncologists to consider withholding treatment entirely for these babies. This approach began to change in 1985 when van Eys et al. (1985) reported their experience in treating infants who had benign or malignant brain tumors with a regimen of postoperative MOPP therapy. Radiation was withheld in those children who did not develop progressive disease. Based on the promising early results of their work (van Eys et al.), the POG first piloted and then opened a group-wide study in 1986 in which prolonged postoperative chemotherapy and delayed irradiation was given to children with malignant brain tumors who were <3 years of age at diagnosis (Baby POG I). The chemotherapy included two cycles of cyclophosphamide and vincristine followed by a third cycle of cis-platinum and etoposide (VP-16). The POG did not believe there was sufficient evidence to withhold radiation entirely, but planned to defer radiation (if possible) to reduce neurotoxicity. As such, infants <2 years of age at diagnosis received chemotherapy for 2 years followed by radiation, and children between the ages of 2 and 3 years at the time of diagnosis received 1 year of chemotherapy followed by radiation. Dose reductions of radiation were given to those children in whom there was no evidence of residual disease following completion of chemotherapy. In the same year (1986), CCG began a randomized study for children with medulloblastoma, supratentorial PNETs, and malignant ependymomas using a regimen of eight drugs in 1 day. As part of that study, children <18 months of age were non-randomly assigned to receive eight drugs in 1 day. The investigators could choose either radiotherapy of the involved site after two cycles of chemotherapy or craniospinal radiotherapy 1 year after diagnosis and after the completion of maintenance chemotherapy (Geyer et al., 1994). This approach of delaying or eliminating radiation for infants with brain tumors was also being tried in Europe. In 1987, the German Pediatric Brain Tumor Study Group, in the HIT SKK87 study, piloted a postoperative chemotherapy regimen for children <3 years of age with malignant brain tumors with the goal of delaying radiation (Kühl et al., 1995). They used a very intensive chemotherapy regimen that included procarbazine, ifosfamide, intravenous/intrathecal methotrexate, cisplatin, cytarabine, and vincristine (Kühl et al., 1995). Finally, the UKCCSG piloted a regimen of postoperative chemotherapy and delayed or no radiotherapy for children <3 years of age with malignant brain tumors. Chemotherapy consisted of carboplatin, vincristine, cyclophosphamide, methotrexate, and cis-platinum (Lashford et al., 1996). Thus, in the 1980s there was a shift in the treatment of infants with brain tumors from the standard approach of surgery and radiation to that of prolonged postoperative chemotherapy and delayed, or in some cases the elimination of, radiation.

Overall Results

One hundred ninety-eight children <3 years of age with malignant brain tumors were treated in the Baby POG I Study. The 5-year PFS was 30 ± 4.9%, and the overall 5-year survival was 39.4 ± 3.9%. Most of the failures occurred during the first 6 months of chemotherapy with limited failures after 2 years. There was no difference in survival by age at diagnosis, that is, 0–23 months versus 24–36 months. Thus, in the overall population it did not appear that a delay in radiation of 2 years versus 1 year adversely affected survivals. It was of interest that in the final analysis there was no significant survival difference between those children with metastases at diagnosis compared with those without. The single most important predictor of survival was the degree of surgical resection. There were 57 children who had received a GTR (as determined by central review) and 113 in whom there had been less than a GTR. The 5-year survival for those who had had a GTR was 61.8 ± 7.0% versus those with a subtotal resection whose 5-year survival was 31 ±

4.8%. Forty-four children had had both a GTR and no metastases at diagnosis. Their 5-year survival was 65%.

The overall results of the Baby POG I cannot be compared with either the CCG or the German trials because neither has reported results of their study as a whole, but other studies are available for comparison. The UKCCSG studied the use of prolonged postoperative chemotherapy in an effort either to avoid or delay radiation (Lashford et al., 1996) in 28 young children with a variety of brain tumors. The treatment regimen included carboplatinum, vincristine, cyclophosphamide, methotrexate, and cis-platinum. Toxicities primarily resulted from administration of carboplatinum, and one child died a toxic death from infection. The overall survival at four years was 35%. The limited number of patients (28) versus 198 in the Baby POG I make comparisons unreliable. An important comparison is with the Royal Marsden experience with children <2 years old irradiated for brain tumors (Bloom et al., 1990). The 5-year survival for 35 irradiated children was 39%, and comparable to the Baby POG overall results despite the POG delay in radiation. As with the UKCCSG study, however, the number of patients in the Royal Marsden report was limited.

Other studies that do have large numbers of children tend to be registry reports and, as such, include benign and malignant tumors, with children treated on a variety of different regimens. The SEER Registries provided survival data on both benign and malignant brain tumors in children 0–14 years (1973–1980). The 5-year survival of children <2 years old with all brain tumors is 36% (Duffner et al., 1986). Farwell et al. (1978) also reviewed the SEER Registry data from Connecticut (1935–1974), and reported 5-year survivals of children <18 months of age at 23%. Stiller and Bunch (1992) reported a series of children <2 years old with brain and spinal tumors, both benign and malignant (1971–1985), from the population-based National Registry of Childhood Tumors (United Kingdom). Of 516 children, 13% died without treatment and 18% died within a month of surgery. Survivals ranged from 20 to approximately 36% (Stiller and Bunch, 1992). The results from the Baby POG I cannot be readily compared with the epidemiologic data derived from the SEER or the United Kingdom Registries, since treatments varied widely and benign tumors (as well as spinal tumors in the United Kingdom study) were included for analysis.

Medulloblastomas

Sixty-two children with medulloblastomas in the Baby POG I were treated with postoperative chemotherapy and delayed radiation. A complete surgical resection was performed in 38%, whereas an incomplete resection was performed in 62%. Of those children in whom there was residual disease following surgery, 48% had either a complete or partial response to two cycles of cyclophosphamide and vincristine. The 5-year PFS was 31.8 ± 8.3%. Progressive disease tended to occur early, with most failures occurring in the first 6 months and no cases of progressive disease occurring after 2 years of therapy. The overall survival at 5 years was 39.7 ± 6.9%. Importantly, there was no difference in survival by age at diagnosis. Thus, the delay in radiation of 2 years versus 1 year did not have an impact on survival. The strongest prognostic indicator for survival was the ability to achieve a GTR. Of 20 children who had had a GTR, there was a 60% 5-year survival compared with 33 children who had had a subtotal resection in whom there was a 32% 5-year survival. There were 13 children who had had a GTR and no metastases at diagnosis. Their 5-year survival was 69%. This group is of particular interest because those children who had no evidence of disease following completion of chemotherapy received reduced neuraxis radiation of 2400 cGy, with 5000 cGy to the posterior fossa. Their survivals are comparable to older "good risk" children treated with full-dose radiation. Therefore, a reduction in neuraxis radiation from 36 to 24 Gy apparently did not adversely affect survivals (Duffner et al., 1993).

There were 46 children <18 months old with medulloblastomas in the CCG study of postoperative "eight-in-one" chemotherapy and delayed radiation (Geyer et al., 1994). The 3-year PFS was 22 ± 6%. Fifteen of the children had had a GTR and no evidence of metastases at the time of diagnosis. Thirty percent were alive and free of disease with a median follow-up of 72 months. Perhaps most interesting about the eight-in-one data is that approximately 20% of children with medulloblastomas had prolonged survivals, most of whom had received no radiation following completion of chemotherapy. The somewhat better results achieved in the Baby POG study, particularly among children with GTRs and no metastases, may reflect the fact that the eight-in-one regimen was less effective chemotherapy (probably because it was less intensive) than the agents and dosing chosen for the Baby POG.

Both the POG and the CCG studies planned to delay radiation. A somewhat different approach was taken in a pilot study from Philadelphia (1988–1990) in which 10 children 18–60 months of age with medulloblastoma and no disseminated disease were treated with 1800 cGy to the craniospinal axis, a posterior fossa boost of 5040–5580 cGy, and a chemotherapy regimen that consisted of weekly vincristine during radiation followed by vincristine, cis-platinum, and lomustine for eight cycles delivered every 6 weeks (Goldwein et al., 1993). This group of children was somewhat older than those in the Baby POG and the CCG studies, and excluded those <18 months old. Although only 10 patients were treated in this fashion, preliminary results were very encouraging with a 4-year survival of 69% (Goldwein et al., 1993).

Although the POG and the CCG delayed radiation, others have had the goal of eliminating radiation in young children. This concept was first promulgated by van Eys et al. (1985). Results of their study were recently updated by Ater et al. (1997). In this trial from 1976 to 1988, nitrogen mustard, vincristine, procarbazine, and prednisone were given to children <3 years of age with either medulloblastomas or ependymomas. Radiotherapy was not given unless there was evidence of progressive disease. Eight of the 12 children with medulloblastoma are still surviving without evidence of disease and of these 8, 6 never received radiation therapy. Three of 7

children who relapsed were salvaged. The resulting 5-year survival was 67%.

The Australian-New Zealand Childhood Cancer Study Group (1988–1989) also aimed to eliminate radiation, if possible. They treated children with medulloblastomas on a chemotherapy regimen that included carboplatinum and vincristine as well as the eight-in-one regimen. Radiation was only given in the face of tumor progression or recurrence. All 3 of the children with medulloblastomas had GTRs, and 1 of the 3 remained in complete response 51 months following diagnosis, in the absence of radiation. Two other children went on to develop progressive disease, and 1 died (White et al., 1993). In a more recent study from the same group, a different chemotherapy regimen was used. A combination of cyclophosphamide, vincristine, and etoposide produced very high response rates (82%) in medulloblastoma. Of the 16 patients with medulloblastoma, 7 remained alive (13–58 months) with a median of 25 months. None of these children were given radiation after completion of chemotherapy (White et al., 1998).

In the first HIT SKK87 study, postoperative chemotherapy and delayed radiation produced a 5-year survival rate of 50% in 30 children, but only 2 of 12 "cured" children had IQs over 85 (Kühl et al., 1995). Based on the results of this trial, the German Pediatric Tumor Study Group developed a treatment regimen (HIT SKK92) in which radiation was eliminated if possible in children without evidence of disease after chemotherapy. Chemotherapy consisted of cyclophosphamide, i.v. methotrexate, carboplatinum, vincristine, and intraventricular methotrexate. Thirty-five children <3 years of age were treated on this regimen. Nine of 15 children had a complete response of the primary tumor to chemotherapy, as well as 3 of 13 with solid CNS metastases, and 6 of 11 with cerebrospinal fluid dissemination. The 3-year event-free survival was 52%. Twelve children without evidence of disease were not irradiated.[3]

In all the reported studies—including those of van Eys et al. (1985), POG, and the CCG—progressive disease tended to occur very early, often within the first 3–6 months of treatment with chemotherapy, while late failures were uncommon.

A major concern about delaying or eliminating radiation in children with medulloblastoma has been the question of whether radiation will be effective as salvage therapy if the tumor recurs. Investigators from St. Jude's attempted to address this concern in a report published in 1994 by Gajjar et al. Thirteen children <3 years of age with medulloblastoma had been treated with maximal surgical resection followed by preradiation chemotherapy. Eleven children developed progressive disease during chemotherapy. Six had a complete response to "salvage" radiation therapy, and of these, 3 were alive 48–104 months post-diagnosis. Another 2 had repeat surgery at the time of recurrence and were then given radiation therapy. They remained alive and free of disease 91 and 107 months after diagnosis. Thus, salvage with radiation appears to be possible (Gajjar et al., 1994). Similarly, Ater et al. (1997) reported 3 of 7 children with recurrent medulloblastoma, initially treated with MOPP therapy, who were salvaged with either radiotherapy (2) or cis-platinum (1). In contrast, Fisher et al. (1998) reported less encouraging results in a mixed group of children, less than 3 years of age, who had failed chemotherapy. Thirty-five children received salvage therapy with radiation plus or minus chemotherapy. The overall 2-year survival following relapse was 29% and, for those who received radiation therapy alone at relapse, was 21% (Fisher et al., 1998). Thus, in these studies, salvage with radiation was possible in 20–40% of patients. Another approach to improve salvage has been the use ABMR (discussed in more detail later in this article). The French Society of Pediatric Oncology reported a 50% 2-year event-free survival in 20 young children with medulloblastoma who developed progressive disease during chemotherapy. Salvage was accomplished by ABMR with busulfan and thiotepa, followed by radiation (Dupuis-Girod et al., 1996).

The results of prolonged postoperative chemotherapy and delayed or no radiation in young children with medulloblastomas have offered mixed results. These studies suggest that medulloblastomas in infants are chemosensitive and, as with older children, most have suggested that a GTR measurably improves survival. There also appears to be a subcategory of good risk children with medulloblastoma who may be effectively treated with prolonged postoperative chemotherapy and who can have radiation withheld. For those children who fail during chemotherapy, 20–40% may be salvaged with radiation, chemotherapy, or ABMT.

Ependymomas

The Baby POG I study treated 48 children <3 years of age with intracranial ependymomas. Thirty-one were <2 years of age at diagnosis and received 2 years of chemotherapy followed by radiation, whereas 17 were 24–36 months of age at diagnosis and received chemotherapy for 1 year followed by radiation. Of 25 children who had residual disease after surgery, there was a 48% complete or partial response to two cycles of cyclophosphamide and vincristine. The first published account of the Baby POG reported overall survivals at 3 years of 61.8% (Duffner et al., 1993). These optimistic results did not persist, however, since unlike children with medulloblastomas in whom failures tended to occur early, children with ependymomas developed progressive disease over several years. When these data were recently updated, prognostic factors became apparent. As with medulloblastomas, the degree of surgical resection was important. Five-year survivals for children who had a GTR were 66% compared with only 25% in those children who had a subtotal resection (Duffner et al., 1998a). Another important prognostic factor was age at diagnosis. Unlike children with medulloblastomas in whom there was no difference in PFS or overall survival according to age at diagnosis, there was a significant difference between the two age groups in children with ependymomas. The 1-year survival rates of 87 and 94% in Groups A (0–24 months) and B (24–36 months), respectively, began to change at 2 years, when survivals were 67 and 82%, respectively. A significant divergence in survivals

according to age was noted, so that by 5 years, Group A (children who had received chemotherapy for 2 years) had only a 25.7% survival compared with 63.3% in Group B (children who had received 1 year of chemotherapy). These differences in survival, according to delay in radiation, persisted even in children considered to have the best prognosis, that is, those who had a GTR and no metastases at diagnosis. Although the 5-year survival rate for the 16 children in this grouping was 62.5%, the 8 children who were 24–36 months of age at diagnosis had 5-year survival rates of 87.5%, whereas the 8 children <24 months of age had a 5-year survival rate of only 37.5%. We concluded that the delay of radiation of more than 1 year adversely affected survival, since other potential factors differentiating the younger versus the older children—such as degree of surgical resection, pathology, and metastases—were not significantly different. These data also suggested that while ependymomas may be chemotherapy-sensitive tumors, they are not chemocurative. Radiation may be able to be deferred, but usually cannot be eliminated (Duffner et al., 1998a).

The CCG eight-in-one regimen was given to 15 infants with malignant ependymomas (Geyer et al., 1994). Although the POG Study did not identify a difference in prognosis based on pathology, that is, malignant or not, the CCG treated only children with malignant ependymomas. Thus, whether these groups are truly comparable is unclear. The 3-year PFS was 22%. As in the POG study, children with ependymomas continued to develop progressive disease over several years (Geyer et al., 1994).

Ater et al. (1997) recently updated the M.D. Anderson Cancer Center regimen in which MOPP chemotherapy without radiation was used as the primary postoperative approach treatment for infants with brain tumors. In that study, there were 5 children who had ependymomas. Two of the 5 were long-term survivors (at 13 and 16 years).

The Australia-New Zealand study of vincristine, etoposide, and intensive cyclophosphamide was used in 14 children with ependymomas. Seven of the children were evaluated for response, and 6 achieved either a complete responseor partial response (86%). Five of the children survived a median of 35 months (24–42 months). Interpretation of these results is hampered because of the limited duration of follow-up. Nonetheless, their response rates are better than any previously reported for this tumor type (White et al., 1998).

Clearly, the most important indicator of survival in ependymomas is the degree of resection. Thus, future trials must focus on methods of increasing the number of children who have received GTRs.

Malignant Gliomas

The Baby POG I study treated 18 children <3 years of age with either glioblastoma multiforme, anaplastic astrocytoma, or malignant glioma (Duffner et al., 1996). Of the 10 children who had residual tumor following surgery, 6 had partial responses to two cycles of cyclophosphamide and vincristine. The PFS rates at 1, 3, and 5 years were 54.25, 43, and 43%, respectively, with overall survivals at 5 years of 50%. What is perhaps most interesting in this group is that 4 children were not irradiated after the 24 months of chemotherapy (due to parental refusal) and, to date, none have developed recurrent disease. Also interesting was that the degree of surgical resection, the presence or absence of metastases, or pathology had no influence on survival. Because the sample size was small, however, the significance of these findings may be questioned.

In contrast to the promising results of the Baby POG Study, the CCG found less encouraging responses to eight-in-one treatment in their 39 children <2 years of age with malignant gliomas (Geyer et al., 1995). The objective response to two cycles of chemotherapy was 24%. Despite this, overall survivals of 51% were reported. Unlike the POG Study in which there did not appear to be a difference in survival based on pathology, the CCG reported that children who had anaplastic astrocytomas had a 44% PFS compared with children with glioblastomas in whom there was a 0% PFS. This study included children with spinal tumors as well as 3 children who had posterior fossa malignant gliomas, whereas the Baby POG only entered intracranial tumors. Moreover, in the POG Study if malignant gliomas were located in the brainstem, they were analyzed as part of the grouping of "brainstem gliomas." These differences may have undue influence when the total number of patients is so limited.

PNETs and Pineoblastomas

The category of PNETs is a conundrum. Pathologists and neuro-oncologists at times consider this entity to include medulloblastoma and at other times view them separately (Duffner and Cohen, 1997). The POG has viewed PNETs and medulloblastomas as distinct entities and hence reported results separately. In contrast, the CCG views medulloblastomas as PNETs. The situation is further confounded by the fact that, even among supratentorial PNETs, some groups include pineoblastomas, while others exclude them. Indeed, in the initial Baby POG report, pineoblastomas were part of the analysis of the results of the PNETs. We later separated the pineoblastomas for analysis because their behavior appeared to be different.

Eleven infants with pineoblastomas were treated on the Baby POG I (Duffner et al., 1995). They ranged in age from 1–35 months, and 8 of 11 were <12 months old at diagnosis. This group fared the worst of all children on the POG Study. All failed chemotherapy. Nine failed in the primary site, and of those 8 children in whom a metastatic work-up was performed at the time of progression, virtually all had evidence of leptomeningeal disease. Six children received radiation following failure on chemotherapy, and all failed either in the primary site, the leptomeninges, or extraneurally. All of the children died, with survivals following diagnosis ranging from 4–13 months. These dismal results were echoed in a report from the CCG in which 8 young children with pineoblastomas were treated with the eight-in-one chemotherapy regimen. All devel-

oped progressive disease a median of 4 months from the start of treatment (Jakacki et al., 1995). Thus, in the two relatively large studies of infants with pineoblastomas, results are extremely discouraging. At this point chemotherapy does not appear to be an effective option. Unfortunately, radiation was not effective as salvage.

PNETs

Seventeen children with non-medulloblastoma nonpineoblastoma PNETs were treated in the Baby POG I. The overall survival rate at 5 years was 27%. As with the other tumor groups (with the exception of the ependymoma group), failures tended to occur early in the course of treatment. Degree of surgical resection significantly influenced survival in these patients as well. There were 4 children who had had a GTR and 9 children who had a subtotal resection. The differences in 3-year survival rates were 100 versus 11%. Thus, in this group, as in the others, the influence of surgery on survival appears to be substantial (although the small sample size makes interpretation difficult).

The CCG also performed a randomized trial for children 1.5–19.3 years of age with supratentorial PNETs in which craniospinal radiation was followed by either eight cycles of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, vincristine, and prednisone versus up-front eight-in-one chemotherapy followed by radiation and then eight additional cycles of eight-in-one (Cohen et al., 1995). Twelve children were between the ages of 1–3 years of age. Three-year PFS was 25 ± 13% compared with 53 ± 9% for children >3 years old. These results included children with pineoblastomas. In the study as a whole, neither chemotherapy offered a survival advantage (Cohen et al., 1995).

The CCG also treated 11 children <18 months of age with supratentorial nonpineoblastoma PNETs with eight-in-one and delayed or reduced volume radiation (Geyer et al., 1994). The PFS was 55%. Thus, the POG and CCG studies both demonstrated that while pineoblastomas in very young children have a poor prognosis, some children with nonpineoblastoma supratentorial PNETs may have prolonged survivals.

New Approaches

One of the clear outcomes of the early baby studies has been the ability to identify prognostic factors. Although there are some disagreements, particularly as to the influence of leptomeningeal disease, the ability to achieve a GTR has uniformly been identified as a strong indicator of survival. Advances in imaging and surgical techniques have increased the number of children who are surgically made disease-free, but there are children in whom residual disease still remains despite attempts at maximum surgical resection. There is now convincing evidence that postoperative chemotherapy may reduce the vascularity of some tumors such as choroid plexus carcinomas, making complete surgical resection possible at the time of "second-look" surgery (Razzaq and Cohen, 1997).

The "Baby" studies in the 1980s were developed in response to very real concerns over radiation-induced neurotoxicity, especially in the face of volumes which included the craniospinal axis. As noted, this led to trials either to delay or eliminate radiation. Over the past decade, advances in radiation techniques have offered a third possibility, that of focused or 3-dimensional conformal radiation. This technique offers the possibility of reducing the radiation dose to the auditory apparatus and the temporal lobes, thereby potentially limiting the damage to both hearing and cognition (Kun, 1997).

Bone Marrow Transplantation

In recent years there has been increasing interest in the use of high-dose chemotherapy with ABMT or stem cell rescue for children with recurrent brain tumors. Guruangan et al. (1998) reported the use of myeloablative chemotherapy with ABMR in children <6 years of age with recurrent brain tumors. To be eligible for the study, the children had to have a recurrent malignant brain tumor with minimal residual disease of <2 cm of tumor diameter. The myeloablative therapy in this trial was carboplatinum, thiotepa, and etoposide in 16 patients; thiotepa and etoposide in 3; and thiotepa, etoposide, and 1,3-bis(2-chloroethyl)-1-nitrosourea in 1. Ten of 20 patients had a 3-year event-free survival of 47 ± 14% and an overall survival of 43 ± 13%. Seven of the 10 patients also received radiation (Guruangan et al., 1998).

High-dose chemotherapy with ABMR has been used by the French Society of Pediatric Oncology since 1987 for children with recurrent disease. Twenty young children with medulloblastomas who had developed progressive disease on conventional chemotherapy received high-dose chemotherapy followed by ABMT with busulfan and thiotepa. There was a reported 75% radiologic response rate to the chemotherapy. Those children who had a primary relapse received local radiation therapy after transplantation. For the 20 patients so described, the event-free survival was 50%. In this study, the goal was to prevent the need for craniospinal radiation in a young population of patients. The approach was particularly effective in children who had localized recurrence, but was not as effective for those children who had evidence of disseminated disease (Dupuis-Girod et al., 1996).

In addition to trials of ABMR in recurrent disease, ABMR is also being studied in newly diagnosed young children. Mason et al. (1998a) reported the results of 62 children <6 years of age enrolled in a trial for newly diagnosed malignant brain tumors. After surgery, the children received induction with cis-platinum, vincristine, etoposide, and cyclophosphamide. The children only went on to ABMT if they were either free of disease following completion of chemotherapy; if after chemotherapy, second-look surgery allowed them to be made free of disease; or if they had stable tumor, but were to receive radiation after consolidation. Thirty-seven children received consolidation chemotherapy ABMT, and 15 overall remained free of disease progression. An additional 3 died of treatment-related complications. The 3-year overall and event-free survivals were 40 and 28%,

respectively. Nineteen children of the original 62 received radiation: 17 for progressive disease and 2 for residual disease at the time ABMT. Among children with medulloblastomas, which included 12 children <3 years of age, there was a 38% 2-year event-free survival (95% CI, 11–65%). In this study, radiotherapy was not administered to 18 children who completed consolidation, and of these, 17 remained alive without evidence of progressive disease. Thus, this study suggests ABMT may allow the reduction or elimination of radiation in some children and, as such, deserves further evaluation.

Less encouraging was the report from Mason et al. (1998b) on ABMT in children with recurrent ependymomas. Fifteen children (5 months to 12 years of age) were treated with thiotepa, etoposide, carboplatinum, and ABMR. Five died of treatment-related toxicity, and 8 died of progressive disease. Only 1 child remained alive 25 months following ABMR, and that child has had subsequent progressive disease (Mason et al., 1998b). Similarly poor results were reported by the French Society of Pediatric Oncology (Grill et al., 1996) in a group of 16 children with refractory or recurrent ependymomas. Busulfan and thiotepa was followed by ABMR. There were no radiologic responses and toxicity was severe, including one death.

Late Effects of Therapy

The adverse effects of radiation therapy are most severe in the very young (Duffner and Cohen, 1991). Of all the serious consequences of radiotherapy, the greatest concerns have focused on the long-term effects of radiation on cognition. In one study for example, Suc et al. (1990) retrospectively evaluated 20 long-term survivors diagnosed and irradiated for brain tumors before 3 years of age. The children were followed for more than 5 years. Eighty-five percent had impaired cognition and 55% required special education. Suc et al. (1990) attributed the significant neurocognitive deficits in 7 children to cranial irradiation (doses ranging from 30–35 Gy). The need for prospective assessments of neurocognitive function became apparent when the baseline developmental testing of children in the Baby POG I revealed that, prior to treatment, the distribution of scores of global cognitive development was abnormal, with 45% scoring 15 or more points below the norm and 29% scoring 30 points or more below the norm. After 1 year of therapy, there was no significant change in the distribution of scores. Had there been no baseline data, the 1-year results would have been misinterpreted. Unfortunately, the analysis of the intellectual data obtained in the Baby POG has not yet been finalized. That information ultimately will be extremely helpful in trying to determine whether a delay in radiation of 1 or 2 years has a positive impact on cognitive abilities. Although neither POG nor CCG have published long-term effects data from their baby studies, several pilot studies have reported interesting results. Ater et al. (1997) followed the infants treated on van Eys's regimen of postoperative MOPP chemotherapy. They found that those 6 children who had not received radiation had IQs within the normal range, with a mean IQ of 101, whereas those 5 children who had required radiation not only had lower IQs, but their IQs continued to decline over time. Their mean IQ at 5.8 years was 85, but it declined to 63 by 10 years.

Another study supported Ater's results. Nine children <2 years of age with brain tumors were treated with postoperative chemotherapy, but no radiation. Developmental testing revealed that their IQs ranged from 72 to 130, with the majority in the normal range. In contrast, of those children who had received radiation (11 children), profound delay was identified in 3, 4 had IQs above 80, and only 1 was considered to have "normal" function (Cohen et al., 1993). Thus, although the data are limited, it appears that chemotherapy is far less neurotoxic than cranial irradiation in the young child. Another interesting question for future studies is whether a reduction in the dose of neuraxis radiation would be associated with fewer long-term adverse effects. Goldwein et al., (1993) evaluated children <5 years of age who had medulloblastomas and treated them with 1800 cGy neuraxis radiation with a posterior fossa boost of 5040–5580, as well as a chemotherapy regimen that included vincristine, cisplatinum, and lomustine. Six children survived at least 1 year, and their mean IQ of 103 was essentially unchanged from baseline. In addition, 5 children were tested at baseline 2 years after radiation, and their IQs did not decline despite the longer follow-up. Thus, a reduction in the dose of neuraxis radiation may limit neurologic sequelae, at least in the short term. These data must be viewed circumspectly, however, since it is well-known that the changes associated with cranial irradiation are progressive over many years (Hoppe-Hirsh et al., 1995). One of the most interesting studies awaiting analysis in terms of long-term effects is that of the German Pediatric Brain Tumor Study Group. Their results with medulloblastoma, as noted earlier in this article, are among the best reported in the literature. The investigators, however, have used very intensive chemotherapy that has included both intraventricular and i.v. high-dose methotrexate. The investigators believed that methotrexate would be far less likely to produce leukoencephalopathy if given in the absence of radiation. This concept may need to be revisited, however, since we recently discovered that some children with acute lymphoblastic leukemia who had not been irradiated and who never had evidence of CNS disease developed leukoencephalopathy when treated on a POG protocol that used i.v. high-dose methotrexate given every 2 weeks. These results raise the question of whether the infants on the German HIT Program will be at risk for leukoencephalopathy.

The data that will be forthcoming from the POG in the next several months regarding the long-term effects of therapy on growth and thyroid function from the Baby POG I will be extremely important. Although hypothyroidism, if recognized, can be treated effectively with replacement therapy, the adverse effects of spinal radiation on the growth of young children are not reversible with growth hormone therapy. These are important quality-of-life issues, but not of the same magnitude as the issue of intellectual devastation. It will be crucial for the next cycle of national studies to determine ways in which

the long-term effects of therapy can be assessed frequently and accurately. Since these studies were virtually all developed as a response to concerns over neurotoxicity, it must be determined whether changes in treatment have actually improved quality of life.

Conclusions: What Has a Decade of Baby Studies Taught Us?

The research on infants with brain tumors over the past 15 years has led to a greater understanding of tumor biology and the varying responses to therapy of different tumor types. Perhaps most importantly, the studies have identified both poor and good risk patients, allowing stratification,as has been done with older children. Because babies tended to have a worse prognosis, they were previously automatically considered a poor prognosis group. Although this is generally true, even within this high-risk group, we now are able to identify those with good prognostic factors, such as those who have received a GTR and those who have had no evidence of metastases.

The information we have learned about babies with malignant gliomas is intriguing. There is clearly something unique about infants with high-grade gliomas, particularly those with glioblastomas, since some have extremely chemotherapy-sensitive tumors. Why this same remarkable chemosensitivity does not occur in older children or adults with glioblastomas remains a conundrum. If we could understand why this occurs, we might have a clue as to how to treat older children and adults more effectively.

In contrast to the better prognosis of infants with glioblastomas, young children with pineoblastomas do far worse than their older counterparts. At the present time, there does not appear to be an effective way to treat these infants. Why the older children fare so much better is unclear.

The large grouping of supratentorial PNETs remains difficult to analyze, because as mentioned previously in this article, there are differences from study to study as to which patients are included or excluded under this rubric. Some children, however, are long-term survivors of supratentorial PNETs and even in this group, there is an advantage to GTR. At this time, patient numbers are too limited to allow firm recommendations as to the efficacy of any particular treatment approach.

Ependymomas are the second most common malignant brain tumor in children <3 years referred to the cooperative cancer groups. The experience with these children over the past decade has taught us important lessons about ependymomas in the very young. Ependymomas are a primary surgical problem. The differences in survival between those children who have had a GTR and those with less than a GTR are significant in virtually all the studies reported to date. We have also learned that ependymomas are sensitive to certain forms of chemotherapy, most dramatically demonstrated in the Australian-New Zealand vincristine/etoposide/cyclophosphamide study where a response rate of 86% was reported. We have learned from these studies, however, that although ependymomas may be chemotherapy-sensitive, they are not chemocurative, and radiation cannot be safely eliminated in most cases. Finally, we have relearned that children with ependymomas tend to develop progressive disease after several years, in striking contrast to other infant tumors in which failures tend to occur early. Therefore, promising reports of PFSs and overall survivals at 2 and 3 years are apt to be illusory at best. As a result of these lessons, a reasonable approach might be maximal surgery followed by chemotherapy; second-look surgery to achieve a GTR; focused radiation to the tumor bed; and finally, a regimen of chemotherapy for perhaps 8–12 months.

Certainly, the group of tumors with which we have had the greatest experience over the past decade has been infant medulloblastomas. In this group of children as well, important lessons have been learned. As with older children, a GTR has the strongest influence on survival. The studies over the past decade have clearly confirmed that medulloblastomas are chemosensitive tumors and that even leptomeningeal disease can be effectively treated at times with parenteral chemotherapy. Unfortunately, the studies have also demonstrated that despite chemosensitivity, failures tend to occur early, typically during the first 3–6 months of chemotherapy. If we analyze those children now considered to be good risk, that is, those who have had a GTR and no metastases, survival rates are extremely encouraging. In the Baby POG I, the population of children has a 69 ± 14.5% 5-year survival, which has been unchanged since the 30-month interval. In the German HIT study in which children were not irradiated after chemotherapy, the event-free survival of 15 patients without residual tumor and no metastases after neurosurgery was 79%.[3] Similarly, excellent results were reported by Kalifa et al. (1995) in good-risk young children with medulloblastomas who received chemotherapy and no radiation and who had a 3-year overall survival of 92%. These very encouraging results for infants with good-risk medulloblastomas treated with postoperative chemotherapy (often in the absence of radiation) contrast with the relatively poor results found by the CCG eight-in-one trial. In that study, there was only a 30% event-free survival with a median follow-up duration of 72 months for equivalent good-risk infants (Geyer et al., 1994). With this sole exception, those children considered to be good risk, even in infancy, may have extremely good survivals. It is possible that this group of children may not require radiation orthat radiation should be restricted only to the tumor bed. Alternatively, infants with medulloblastoma who have not had a GTR and/or have metastases at diagnosis have a far worse prognosis. It is in this population that high-dose chemotherapy with either ABMT or stem cell rescue is being considered by some groups, whereas earlier focused radiation is being considered by others.

During the past decade, there has been a concentrated effort to develop effective, less toxic approaches for infants with brain tumors. The large studies from the 1980s and early 1990s laid the ground work, demonstrating for the first time that chemotherapy could be used as the primary postoperative treatment in malignant brain tumors. The second group of studies from the CCG

and the POG (1992–1996), although closed, are not yet mature enough for analysis, but they both built on the original studies of the 1980s by intensifying drug dosages and eliminating radiation in patients with no residual disease. The studies being developed for the late 1990s and 2000 will, for the first time, have divergent approaches with an emphasis on ABMTin one group as opposed to a regimen of chemotherapy, second-look surgery, and conformal radiation in the other. The questions that will need to be answered by the next group of infant studies will be, among others: Which children may safely have radiation either withheld or limited in volume? Will high-risk children be more effectively treated with high-dose chemotherapy and ABMR, or will it be more advantageous to bring radiation back into the schema at an earlier time along with adjuvant chemotherapy? And, how do we better assess the acute and long-term effects of these regimens? In the Baby POG I, a study primarily developed to reduce the late effects of therapy, five children developed second malignancies, including three cases of lymphoproliferative disease (likely secondary to the prolonged use of etoposide and cis-platinum) (Duffner et al., 1998b). Will second malignancies also be reported with increasing frequency with other chemotherapy regimens? What will be the long-term outcome of young infants subjected to ABMR compared with those receiving conformal radiation? Will either approach improve survival, and which approach will be more effective in limiting neurotoxicity?

The studies of the past decade have been important in helping us better understand this difficult group of tumors. Achieving a balance between quality of life and improving survivals should remain the paramount goal of the next decade of baby studies.

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