MEDULLOBLASTOMA is the most common malignant central nervous system tumor of childhood. Standard management has included surgical resection followed by craniospinal radiation therapy. Over the past decades, the survival rate of patients with medulloblastoma has progressively increased as diagnostic, surgical, anesthetic, and radiotherapy techniques have improved. These developments have been previously reviewed. Recent reports indicate 5-year survival rates of 50% to 70%, but the quality of life for survivors is impaired by neurointellectual and endocrinological sequelae, which are mainly due to whole-brain irradiation. The role of chemotherapy in the adjuvant setting was demonstrated by randomized studies. The potential benefits of protocols including chemotherapy prior to craniospinal radiation have been summarized by Packer. The rationale for this treatment schedule is that...
Chemotherapy may partially replace radiotherapy and permit a reduction in the cranial and spinal radiation dosage, resulting in fewer long-term sequelae.

Among chemotherapeutic regimens known to be effective in treating medulloblastoma, the “eight drugs in 1 day” (“8/1”) strategy of Bleyer, et al.,5 has been well documented.10,32 High-dose methotrexate has also been proposed.1,33 Both chemotherapeutic approaches are attractive for preirradiation treatment, as both cisplatin (part of the regimen of Bleyer, et al.) and methotrexate may enhance the effect of subsequent radiotherapy.4 In a previous pilot study our group replaced supratentorial prophylactic irradiation with this “sandwich” chemotherapy.6 This study was quickly stopped because of a very high rate of supratentorial recurrence. The aim of the present M7 study was to test both the feasibility and efficiency of a protocol including the same preirradiation chemotherapy with standard radiation doses to the posterior fossa and spinal axis but with reduced supratentorial doses.

Materials and Methods

Patient Population

Between March 1985 and September 1988, 70 successive patients under the age of 20 years with newly diagnosed medulloblastoma were treated at eight institutions in a multicenter French cooperative prospective nonrandomized study. There were 42 boys and 28 girls. The median age at diagnosis was 6 years (range 10 months to 19 years). Computerized tomography (CT) was obtained prior to surgery in all cases. A total surgical resection was attempted in all patients. The staging procedure was planned at Day 21 post-surgery and included clinical examination, review of the operative procedure, brain CT scan, cerebrospinal fluid (CSF) examination (after centrifuge preparation), and myelography. The classification system of Chang, et al.,9 was used for metastatic disease but not for preoperative local staging. Patients were assigned to two risk groups. Group A (standard risk) included patients with no local residue on CT, no brainstem involvement, no atypical cells in the CSF, and no metastasis, and who were more than 2 years of age. Group B (high risk) patients included those with incomplete removal of the primary tumor, brainstem involvement, and metastatic involvement. The seven children who were less than 2 years of age were in Group B. Two boys whose tumors were classified as ependymomas after central histological review were excluded from analysis.

Characteristics of the 68 children selected are summarized in Table 1. Among the 31 Group A patients, 21 underwent spinal radiological and/or cytological evaluation 2 to 30 days (median 14 days) after the beginning of chemotherapy.

Preirradiation chemotherapy was the same for the two groups. Chemotherapy was begun as soon as postoperative recovery was deemed good enough. Treatment consisted of two 8/1 regimens (Fig. 1) delivered as described by Pendergrass, et al.,32 on Days 7 and 21 and of two high-dose courses of methotrexate (12 g/m²) on Days 35 and 42. This was administered with prior intravenous hydration (1.4% sodium bicarbonate (100 ml/m² per hour until urine pH ≥ 7.5) in 500 ml of 5% dextrose over 4 hours) with prehydration (6 ml/kg sodium bicarbonate) and post-hydration (1.4% sodium bicarbonate and normal saline, 1:2) consisting of 3 L/m² for the first 24 hours after methotrexate and 2 L/m² per day for the next 48 hours. Oral leucovorin was begun 20 hours after the end of the methotrexate infusion at a dose of 15 mg every 6 hours for 12 doses. Methotrexate levels were monitored at the end of infusion and then after 24, 48, and 72 hours.

Routine neuroradiological evaluation was not required prior to the institution of radiotherapy, which began during the 5th week after surgery in Group B and after the last methotrexate infusion (7th week) in Group A (Fig. 2). The prescribed radiation doses were 50 to 55 Gy to the posterior fossa, 30 to 36 Gy to the spinal axis, and 27 Gy to the brain. Daily fractions were 1.6 to 1.8 Gy. Patients with focal metastatic disease received a 10-Gy boost to the lesion. Children under the age of 3 years received only 20 Gy to the hemispheres. Group B patients received postirradiation chemotherapy with four 8/1 treatments beginning 15 days after the end of radiation therapy and given every 4 weeks. Toxicities were recorded according to World Health Organization criteria.39 All diagnostic and therapeutic procedures were performed after informed consent of parents.

Statistical Analysis

Disease-free survival was considered to be the time elapsed from the date of surgery to the first documented evidence of treatment.
failure. All causes of death were included in the analysis of disease-free survival. The probabilities of survival were computed by the Kaplan–Meier product-limit method and the log-rank test was used to compare differences in survival rates among subgroups of patients.

**Follow-Up Examination**

After completion of treatment, follow-up examination was standardized and included clinical examination, brain CT or magnetic resonance (MR) imaging, and CSF sampling on a 4-month basis for the first 2 years, on a 6-month basis during the 3rd year, and then yearly. At the time a recurrence was detected, complete neuroimaging of the neuraxis and CSF sampling were performed. Psychocognitive testing was not strictly standardized by the protocol and was determined at the discretion of the managing physician. However, academic achievements and social activity were carefully recorded.

**Results**

**Surgical Outcome**

A ventriculoperitoneal shunt was placed in 38 children with hydrocephalus 1 to 16 days (median 5 days) before surgery. In three children, it was placed 4, 7, and 19 days postoperatively. Table 2 summarizes the extent of resection as judged by the surgeon and by postoperative CT. Computed tomography was performed within 10 days after surgery in all but nine patients who had radiological evaluation of the posterior fossa 11 to 22 days postsurgery. According to the classification of Laurent, et al., 50 patients (74%) were graded S0, 11 (16%) were S ≥ 1, and seven (10%) were graded Sx. One child who had a partial resection with gross residue (S3) had a neurological impairment without radiological evidence of disease progression after two courses of 8/1 treatment and underwent reoperation; his clinical recovery was very slow. He did not receive methotrexate infusion and started radiation therapy at Day 141.

**Chemotherapeutic Regimen**

The times from surgery to successive courses of the initial chemotherapy are summarized in Fig. 3. Hematological toxicity was considered acceptable. The percentage of patients who developed Grade 4 neutropenia after the first, second, third, and fourth courses of chemotherap-
Nine recurrences (36%) were in the posterior fossa (total resection in four patients, subtotal resection in three, partial resection in one, and biopsy only in one). Five recurrences (20%) were supratentorial and occurred in patients who had received 30.6 Gy (one M0 and one M1 metastasis classifications) and 27 Gy (one M0 and two M3) to the brain. Nevertheless, two of the latter (one M0 and one M3) can be correlated with an eye shield set too high. Thus, in only one supratentorial recurrence could a reduction in radiation dose be implicated. Five recurrences (20%) were in the spine (two with supratentorial involvement as well). However, one of these patients (M3) was 17 months old and received only 16.1 Gy to the neuraxis. The remaining four children (one M0, one M1, one M3, and one with doubtful myelography at diagnosis) were to receive the correct dose to the spinal cord (34 to 36 Gy), but one patient had tumor recurrence in the mobile gap between medullary fields. Among four patients who showed recurrence on CSF testing but who had no detectable spinal disease, three had been irradiated with electron beam energy of less than 17 MeV. Of eight children under 3 years old (range 14 to 27 months), disease progression was observed in three; in one case in the supratentorial region and in the spine, and in two cases in the posterior fossa.

Survival Data

The probabilities of 3-, 5-, and 7-year disease-free survival were 67%, 62%, and 59% (± 13%), respectively, for the selected population (68 patients); 74%, 74%, and 62% (± 21%) for Group A (31 patients); and 60%, 57%, and 57% (± 16%) for Group B (37 patients). No significant difference in survival rate was observed between Group A and Group B (Fig. 5). Univariate analysis showed that a very young age, quality of resection, and radiation dose to the brain had no prognostic value in this series. The 7-year disease-free survival rates in children more or less than 2 years of age were 58% ± 14% and 55% ± 32%, respect-
Feasibility of the Treatment Regimen

Follow-Up Data

Three patients were lost to follow up at 59, 62, and 83 months, respectively, following diagnosis. One patient from Group A developed a supratentorial meningioma 88 months after diagnosis. No leukemia or myelodysplasia was recorded. Long-term sequelae and quality of life with a longer follow-up period will be reported separately. At this time, among 38 patients evaluated who are in complete remission, 18 are considered to have normal or subnormal (reasonable achievement delays) academic performance (median age at diagnosis 12 years), 15 have learning disabilities and are enrolled in special education classes (median age at diagnosis 5.5 years), and five have important neurocognitive handicaps and need institutional care (median age at diagnosis 4.5 years). Twenty-two patients received or are receiving growth hormone therapy.

Discussion

Feasibility of the Treatment Regimen

The toxicity of the treatment given before irradiation was generally mild and led to acceptable delays between surgery and radiotherapy. However, the occurrence of one fatal and one life-threatening infection emphasizes the potential difficulty of managing chemotherapeutic treatment during the postoperative period in some patients. In 25% of patients, the toxicity of postirradiation chemotherapy resulted in long intervals between different courses of treatment. This points up the problem of hematological recovery after irradiation of the spinal axis at standard doses.

Prognostic Factors and Staging Problems

Patient age at diagnosis of less than 2 years was not an adverse prognostic factor in our series. This finding, which is in contrast to many reports,14 might reflect the equal distribution of standard-risk and high-risk patients between patients under and above 2 years of age. Total versus subtotal resection has been reported to have a documented significance15,19,38 that we did not observe. In many reports the incidence of local recurrence ranges from 29% to 70%.16,19,25 The low incidence of recurrence (3% ) observed in our series is probably related to the high rate of total tumor removal.

The proportion of high-risk patients varies widely (range 21% to 75%) in recent series.16,19,25,29 Selection criteria are often different between series and in large multicenter studies full initial staging is not available for all patients, making it difficult to know exactly how many patients fit current poor-risk criteria. In our series, the number of patients misstaged (two) or possibly misstaged for subjective reasons or insufficient investigations (11) represented almost 20% of the whole population, but they were equally divided between the two groups. The outcomes of Groups A and B were the same, but this result must be interpreted cautiously because 16 of 37 high-risk patients received more than 30 Gy to the supratentorial region. Our proportion of high-risk patients (Group B) and of patients with metastasis were 54% and 31%, respectively. In some reports, the better results for high-risk groups correlate with a lower proportion (20%) of patients with metastasis classifications of M1 to M3.19,30

Tumor dissemination at diagnosis is known to be an adverse prognostic factor.2,14,21,30 The 45% 7-year disease-free survival rate of our patients classified as M1 to M3 compares favorably with other series in which data on survival of patients with metastasis is available.16,19 A nonsignificant difference was found between M0 and M1 to M3 patients. However, this comparison has limited value because the M0 group is heterogeneous with regard to treatment (31 patients from Group A and 15 from Group B).

An additional problem in postoperative chemotherapy regimens in the treatment of medulloblastoma is the optimum timing of staging procedures. In this study early delivery of chemotherapy might have reduced tumor dissemination in some patients in Group A who were investigated late (for example, by clearing chemosensitive tumor cells from the CSF), leading to understaging and consequently undertreatment of a proportion of high-risk patients. This may have contributed to the lack of observed difference between Groups A and B in terms of survival. The early start of chemotherapy is logical in this treatment strategy, in order to limit the delay between surgery and radiotherapy. Furthermore, experimental data have suggested that the effectiveness of nitrosourea administration varies in inverse ratio to the time elapsed after surgery.37 This problem of staging accuracy can be avoided if the whole neuraxis is evaluated, which should, whenever possible, be at the time of preoperative MR.
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imaging. In our opinion, when this is not possible for medical or technical reasons, spinal evaluation and CSF sampling should be performed no later than 15 days after surgery.

Rationale for Chemotherapy and Reduced-Dose Radiation Therapy

Whether chemotherapy benefited these children and improved the potentially poor prognosis of patients in Group B cannot be evaluated in this study. Our results are comparable to the better results recently reported in terms of disease-free survival, both for the whole population and the two subgroups. Late recurrences occurred in the study arm without continuing chemotherapy, a fact observed in other reports. A number of studies have demonstrated the usefulness of chemotherapy in high-risk groups. In standard-risk groups, although data are less convincing, chemotherapy is recommended by many authors. The improved but still imperfect results obtained in “good-risk” patients are not a definitive argument for depriving these patients of the potential benefit of chemotherapy.

The question of whether radiotherapy can be at least partially replaced by adequate chemotherapy remains open.

Data with regard to reducing radiation dosage are controversial. On one hand, good results have been reported to date in most series using 25 Gy to the neuraxis, either alone or in combination with chemotherapy for brain tumors: a new approach and rationale for preradiation chemotherapy. Med Pediat Oncol 11:213, 1983 (Abstract)


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