Progression-Free Survival in Children With Optic Pathway Tumors: Dependence on Age and the Quality of the Response to Chemotherapy—Results of the First French Prospective Study for the French Society of Pediatric Oncology

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**Purpose:** To evaluate a strategy aimed at avoiding radiotherapy during first-line treatment of children with progressive optic pathway tumors (OPT), by exclusively administering multiagent chemotherapy during 16 months.

**Patients and Methods:** Between 1990 and 1998, 85 children with progressive OPT were enrolled onto this multicenter nationwide trial. Chemotherapy alternating procarbazine plus carboplatin, etoposide plus cisplatin, and vincristine plus cyclophosphamide was given every 3 weeks. At the time of relapse or progression, second-line chemotherapy was authorized before recourse to radiotherapy.

**Results:** Objective response rate (partial response [PR] + complete response [CR]) to chemotherapy was 42%. Five-year progression-free survival (PFS) and overall survival rates were 34% and 89%, respectively. The 5-year radiotherapy-free survival rate was 61%. In the multivariate analysis of the 85 patients that entered onto the study, factors associated with the risk of disease progression were age younger than 1 year at diagnosis (P = .047) and absence of neurofibromatosis type 1 (P = .035). In the multivariate analysis of the 74 patients that remained on study after the first cycle of chemotherapy, factors associated with the risk of disease progression were age younger than 1 year at diagnosis (P = .053) and no objective response to chemotherapy (P = .029). Three-year PFS was 44% in infants ≤1 year versus 66% in children older than 1 year. Three-year PFS was 53% in the absence of an objective response to chemotherapy versus 65% after a PR or CR.

**Conclusion:** A significant proportion of children with OPT can avoid radiotherapy after prolonged chemotherapy. Deferring irradiation with chemotherapy protocols did not compromise overall survival of the entire population or visual function.


OPTIC PATHWAY tumors (OPTs) account for 5% of childhood brain tumors. Approximately 65% of these tumors arise in children younger than 5 years of age.¹ Although OPTs are usually low-grade astrocytomas, their behavior is highly unpredictable, ranging from spontaneous regression to progressive visual and neurologic impairment culminating in death.²,³ The most appropriate therapeutic strategy has yet to be defined.⁴,⁵

Surgery is rarely indicated as first-line treatment for diffuse chiasmal and hypothalamic tumors. In these settings, radiotherapy is effective for tumor control, with overall survival (OS) at 5 years reaching 90%.⁶-⁸ Because of long-term radiation-induced side effects such as cerebral vasculopathy,⁹ cognitive impairment,⁸ or endocrine deficits,¹⁰ chemotherapy has been proposed to postpone or avoid radiotherapy, especially in young children.¹¹,¹²

In November 1990, the French Society of Pediatric Oncology (SFOP) initiated a prospective trial of chemotherapy in young children (ie, younger than 5 years of age) with progressive OPT. At progression, children received multiagent chemotherapy during 16 months but no irradiation, provided disease remained stable with chemotherapy treatment. If additional progression occurred, second-line chemotherapy or irradiation could be given depending on the patient’s age. In 1995, the age limit for eligibility for the trial was extended, especially for patients with neurofibromatosis type 1 (NF1). We report the long-term results of this approach in 85 children, with particular emphasis on prognostic factors and visual outcome.

**PATIENTS AND METHODS**

**Eligibility Criteria**

Only patients with progressive OPT were eligible for the study. Progression (ie, enlargement of the tumor volume exceeding 25%) could be defined...
radiologically and/or clinically (significant deterioration of vision or new neurologic signs). Patients with a newly diagnosed tumor and severe visual impairment or neurologic signs could also be included in the trial, as well as patients with metastases.

Surgery was permitted before study entry, either for relief of hydrocephalus with shunting, cyst drainage, or for debulking. In the latter case, progression of the residue was required before the initiation of chemotherapy.

The other inclusion criteria were age younger than 5 years (after 1995, older children until 15 years could be included in the trial, especially if they had NF1, which precludes the use of radiotherapy as first-line treatment); no prior exposure to chemotherapy or radiotherapy; normal auditory, hepatic, and renal functions; and informed consent obtained from parents or guardians of each child in accordance with institutional guidelines.

During this period, there was no other ongoing clinical trial for these patients. The trial was approved by the French Society of Pediatric Oncology and by the local review boards at the participating institutions.

Pathology Review

Histologic confirmation of the diagnosis was not mandatory before study entry. All available slides (biopsy and partial resection specimens) were reviewed by a panel of four neuropathologists. Histologic subtypes and grading were according WHO criteria. Only low-grade (ie, grade 1 or 2) tumors were eligible for the trial.

Chemotherapy Regimen (Baby Brain SFOP [BBSFOP])

Chemotherapy consisted of three courses (A, B, and C) of two different drugs administered in seven three-course cycles. The planned duration of chemotherapy was 16 months. In course A, patients received carboplatin 15 mg/kg (450 mg/m²) in a 1-hour infusion on day 1 and procarbazine 4 mg/kg/d (120 mg/m²/d) orally on days 1 to 7. In course B, patients were administered etoposide 5 mg/kg/d (150 mg/m²/d) in a 1-hour infusion on days 22 and 23, and cisplatin 1 mg/kg/d (30 mg/m²/d) in a 3-hour infusion with mannitol plus saline on days 22 and 23. In course C, patients received vincristine 0.05 mg/kg (1.5 mg/m²) on day 43 and cyclophosphamide 50 mg/kg (1,500 mg/m²) in a 1-hour infusion on day 43. The next cycle was started on day 64. Doses were calculated in milligrams per square meter for children older than 3 years. The cumulated doses of each drug were 3,150 mg/m² for carboplatin, 5,880 mg/m² for procarbazine, 2,100 mg/m² for etoposide, 420 mg/m² for cisplatin, 10.5 mg/m² for vincristine, and 10.5 g/m² for cyclophosphamide.

All patients were fitted with a central line. Chemotherapy was administered in an outpatient clinic. More than 0.8 × 10⁹ granulocytes/L and more than 10⁵ platelets/L in hematologic reparation phase were mandatory for commencement of a new course. Patients did not receive granulocyte colony-stimulating factor. Doses were reduced by one third in the event of hematologic toxicity that postponed the start of the next course for more than 2 weeks. Platelet counts were maintained at more than 50 × 10⁹, with transfusion when necessary. This chemotherapy protocol was discontinued if disease progression occurred (ie, a more than 25% increase in the tumor volume and/or worsening of clinical signs) or unacceptable nonhematologic toxicity was present.

Other Treatments

Conservative surgery or shunting was possible before study entry and during chemotherapy. At the time of progression or relapse, second-line chemotherapy could be administered according to the patient’s age to postpone additional use of radiotherapy. Irradiation (50 to 55 Gy) was used only if progression occurred despite chemotherapy and was performed preferably in children older than 3 years without NF1.

At the end of the chemotherapy protocol, irradiation was not delivered to patients with a stable or shrinking residue.

Evaluation Procedures

Careful skin and ophthalmologic examinations verified the presence of NF1 at diagnosis and during treatment. The NF1 status was defined according to the consensus criteria published in 1988.

The ophthalmologic evaluation consisted of at least a fundus examination and, when feasible according to the patient’s age, measurement of visual acuity and visual field determination. Visual evoked potentials were also used to evaluate visual deficits when needed in the youngest patients.

Disease extent at diagnosis was assessed by a cranial magnetic resonance imaging (MRI). The locoregional extent of the tumor was defined according to the Dodge classification. Briefly, stage A corresponds to tumors limited to one optic nerve, stage B corresponds to tumors involving the chiasma with or without optic nerve involvement, and stage C corresponds to tumors with extension toward the hypothalamus or streaking along the visual pathways more posteriorly. The product of the three largest diameters of the solid part of the tumor was used to estimate the tumor volume. If intracranial metastases or suggestive clinical signs were present, the radiologic work-up was completed by a spinal MRI.

The neuroradiologic follow-up consisted of a cranial MRI study after each cycle (ie, every three courses) of chemotherapy until the second year after the start of treatment and every 6 months thereafter. Response was evaluated clinically and radiologically by the individual investigators during chemotherapy. All MRI files were centrally reviewed retrospectively using standard International Society of Pediatric Oncology criteria.

Because of visual deficits, neuropsychologic evaluation could not be performed routinely in all study patients nationwide. However, some of the patients were evaluated and the results have been presented elsewhere.

Statistical Analysis

OS rates were estimated using the Kaplan-Meier method, from the first day of chemotherapy to death or the date of the last follow-up visit for patients who were still alive. Progression-free survival (PFS) rates were estimated using the above-mentioned method from the first day of chemotherapy to the time of documented failure (date of progression for patients whose disease progressed before achieving a complete response [CR], or time of relapse or death for the others) or to the last follow-up visit for patients in whom disease remained stable or who did not experience relapse. The radiotherapy-free survival rates were estimated using the Kaplan-Meier method from the first day of chemotherapy to the start of irradiation or to the date of death, both of which were considered as treatment failures, or to the date of the last follow-up visit for patients who were still alive without having received radiotherapy. The 95% CIs for survival rates were estimated using the Rothman method.

Follow-up data were updated in October 2002. Median follow-up was estimated with the Schemper method. Statistical differences in PFS rates were tested by the two-sided log-rank test. Relative risks were estimated with their 95% CIs using a Cox model both in the univariate and in the multivariate analysis. Adjusted relative risks were estimated in the final model including the variables that attained significance in the multivariate analysis. The first prognostic factor analysis was performed on the whole population. The second analysis was restricted to patients without disease progression after one cycle to test the impact of the best response to chemotherapy on the risk of failure. For this second analysis, responses were pooled as either good (CR or partial response [PR]) or poor (all the other cases: stable disease or a minor response). To compare the proportions of patients with different outcomes relative to a given risk factor, we used the Mantel-Haenszel χ² test, which is preferred when testing the significance of a linear relationship between two ordinal variables. If significant results are observed, the interpretation is that increases in one variable are associated with increases (or decreases for negative relationships) in the other that are greater than would be expected by chance of random sampling.
RESULTS

Description of the Population

Between November 1990 and December 1998, 85 children with progressive OPT entered onto the study. There were 38 boys and 47 girls. Twenty-three children (27%) met the National Institutes of Health diagnostic criteria for NF1. The median age at diagnosis was 17 months (range, 1 day to 123 months), whereas children with NF1 were significantly older (34 v 13 months; \( P = .01 \)).

Chemotherapy was initiated at diagnosis in 52 patients (61%) because vision was threatened (in 32 of 52 patients) or neurologic symptoms were severe (in 20 of 52 patients). Chemotherapy was initiated after a period of surveillance in the other 33 children (39%), either after radiologically evaluated progression in 21 children or after clinical deterioration in 12 children (threatened vision in eight children and severe neurologic signs in four children). At the start of treatment, neurologic signs were increased intracranial pressure in 23 children, motor deficit or pyramidal signs in 13 children, and seizures in three children. Thirteen children had a diencephalic syndrome and three showed precocious puberty. Five children had proptosis. The median age at the start of chemotherapy was 33 months (range, 4 to 164 months); children with NF1 were significantly older (36 v 14 months; \( P = .01 \)). Fourteen (16%) children were older than 5 years when they started receiving chemotherapy.

At the start of treatment, nine patients had metastases or multicentric disease. Fifty-eight patients (68%) had large tumors extending beyond the chiasm; that is, class C in Dodge’s classification. Only two patients had a Dodge A tumor.

Tumor specimens were obtained in 50 patients by biopsy (\( n = 31 \)) or a partial resection (\( n = 19 \)). The central review of more than 80% of the samples always confirmed the diagnosis made by the local pathologist. The histologic type was juvenile pilocytic astrocytoma in 38 patients (76%). The remaining patients were equally distributed between fibrillar astrocytoma and low-grade astrocytoma not otherwise specified.

Response to Chemotherapy

After a central review of all radiologic follow-up MRI studies, 36 patients (42%) had at least 50% tumor shrinkage as the best response to chemotherapy. Fifteen children had a minor response, and 23 children had stable disease as the best response. Only 11 patients never responded to chemotherapy.

In the 51 children who had significant tumor shrinkage (i.e., at least 25%), this response was evidenced during the first two cycles in 50% of the patients and during the first four cycles in 75% of the patients.

The response rate was correlated with the tumor extent, as described in the Dodge classification (\( P = .0467 \), Mantel-Haenszel \( \chi^2 \) test). Disease progression occurred in 17% of patients with Dodge C tumors after one cycle, compared with 4% of patients with Dodge A and B tumors. A good response (i.e., more than 50% of tumor shrinkage) was observed in 56% of Dodge A and B tumors and in only 36% of Dodge C tumors.

The response rate was not correlated with age or with the presence of metastases. However, 23% of children younger than 1 year experienced disease progression after one cycle of chemotherapy compared with only 8% of those age 1 year and older (\( P = .0864 \), Mantel-Haenszel \( \chi^2 \) test).

None of the 13 children with diencephalic syndrome remained progression free during follow-up; time to progression was between 2 and 86 months. Five of them have a preserved vision; that is, visual acuity of the best eye is \( \geq 3 \).

PFS and OS (Table 1)

Survival curves are depicted in Fig 1. The median follow-up of the population was 6.5 years (range, 1.8 to 11.5 years) after the start of chemotherapy. PFS rates for the whole population were 79% (69% to 86%) at 1 year, 52% (42% to 63%) at 3 years, and 34% (24% to 45%) at 5 years.

Eleven patients died, all after disease progression. In 10 patients, tumor progression was the cause of death; in one patient, bacterial ventriculitis was the cause of death after shunting performed for disease progression. OS rates for the whole population were 96% (90% to 99%) at 1 year, 91% (82% to 95%) at 3 years, and 89% (81% to 94%) at 5 years.

BBSFOP Chemotherapy Failures and Salvage Treatment

During follow-up, 54 patients (67%) experienced tumor progression or relapse. Eighteen of these treatment failures (including the 11 in whom disease progression was evidenced after one cycle of chemotherapy) occurred during chemotherapy after a median interval of 3 months (range, 1 to 14 months). Among the 11 patients with early progression during the first cycle (i.e., the first 3 months), the disease could be transiently controlled with second-line chemotherapy in only one patient. Eight patients were irradiated, usually after failure of second-line chemotherapy. Four of the 11 patients died and five others are blind at last follow-up visit.

At last evaluation, 28 patients had received radiotherapy either after tumor progression (\( n = 25 \)) or after the physician’s decision (\( n = 3 \)). Irradiation was given as second-line treatment in 12
patients or after failure of the other salvage treatment consisting of chemotherapy and/or surgery in 13 patients. The second-line chemotherapy commonly used was the vincristine-carboplatin regimen described by Packer et al. Twenty-nine of the 54 children who experienced a relapse (54%), achieved at least disease stabilization with this second-line regimen, as shown in Figure 1, in which PFS and radiotherapy-free survival curves are compared. For the 25 patients treated with irradiation for a median interval of 35 months (range, 4 to 70 months) from the start of chemotherapy, it was possible to postpone radiotherapy for a period of two cycles of BBSFOP chemotherapy instead of seven, necessitating withdrawal of the drug. No allergy to carboplatin or to cisplatin was observed. No acute ototoxicity was encountered and all patients (95% CI, 65% to 83%) were alive and radiotherapy free 3 years from the start of treatment, and 61% (95% CI, 50% to 72%) were still alive and radiotherapy free at 5 years (Fig 1).

Prognostic Factor Analysis

The results of the univariate and multivariate analyses of PFS for the 85 patients enrolled onto the study (Table 2) showed that age younger than 1 year and the absence of NF1 were the only independent adverse prognostic factors. Tumor extent, as defined by the Dodge classification, was only of marginal prognostic significance. Initial progression was rarely seen in small tumors and occurred in only one of 27 Dodge A and B tumors compared with 10 of 58 Dodge C tumors ($P = .0467$, Mantel-Haenszel $\chi^2$ test).

The results of the univariate and multivariate analyses of PFS for the 74 patients without progressive disease after one cycle of chemotherapy (Table 3) showed that age younger than 1 year and a poor response to chemotherapy (ie, stable disease or a minor response) were the only independent adverse prognostic factors. NF1 was only significantly associated with the prognosis in the univariate analysis.

It was thus possible to identify a subgroup with a particularly poor prognosis, namely the 11 patients younger than 1 year with less than a PR to chemotherapy observed any time after start of the treatment (ie, before the fourth cycle in 75% of the patients). All of these 11 patients experienced disease progression during the first 42 months after the start of chemotherapy, whereas 62% (range, 48% to 75%) of the patients 1 year and older with a good response to chemotherapy were still alive and progression free 3 years after the start of chemotherapy (Fig 2).

Toxicity

Chemotherapy had to be stopped because of toxicity in three patients (severe hyponatremia in two patients and renal failure in one patient). One toxic death related to shunt infection occurred in a patient with tumor progression during the first cycle of chemotherapy. Among the 1,265 courses administered, 241 (19%) were complicated by febrile neutropenia lasting less than 1 week (7%); documented infections (7%), two-thirds of which occurred in the absence of neutropenia; thrombocytopenia and anemia requiring transfusions were experienced by 2% in each case, respectively; and a procarbazine-related skin rash (1%), necessitating withdrawal of the drug. No allergy to carboplatin was observed. No acute otoxicity was encountered and all planned courses including cisplatin were administered.

One patient developed secondary acute lymphoblastic leukemia 50 months after the start of chemotherapy, which consisted of two cycles of BBSFOP chemotherapy instead of seven, followed by two second-line courses of chemotherapy including.

### Table 1. Summary of Outcome With a Median Follow-Up of 6.5 Years (range, 1.8 to 11.5 years)

<table>
<thead>
<tr>
<th>Survival</th>
<th>Overall Survival (%)</th>
<th>95% CI</th>
<th>Radiotherapy-Free Survival (%)</th>
<th>95% CI</th>
<th>Progression-Free Survival (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>96</td>
<td>90% to 99%</td>
<td>92</td>
<td>84% to 96%</td>
<td>79</td>
<td>69% to 86%</td>
</tr>
<tr>
<td>3 year</td>
<td>91</td>
<td>82% to 95%</td>
<td>75</td>
<td>65% to 83%</td>
<td>52</td>
<td>42% to 63%</td>
</tr>
<tr>
<td>5 year</td>
<td>89</td>
<td>81% to 94%</td>
<td>61</td>
<td>50% to 72%</td>
<td>34</td>
<td>24% to 45%</td>
</tr>
</tbody>
</table>

*11 deaths.
†34 patients were treated with radiotherapy or died.
‡In 54 patients, progression, relapse, or death occurred.

### Table 2. Relative Risks of Failure According to Initial Characteristics (n = 85, in 54 patients, progression, relapse, or death occurred)

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients %</td>
<td>3-Year PFS (%) 95% CI</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>59 69</td>
<td>61 48% to 72%</td>
</tr>
<tr>
<td>≤1</td>
<td>26 31</td>
<td>34 19% to 53%</td>
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<tr>
<td>Neurofibromatosis type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62 73</td>
<td>42 31% to 54%</td>
</tr>
<tr>
<td>Yes</td>
<td>23 27</td>
<td>82 62% to 93%</td>
</tr>
<tr>
<td>Dodge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A and B</td>
<td>27 32</td>
<td>66 47% to 81%</td>
</tr>
<tr>
<td>C</td>
<td>58 68</td>
<td>46 34% to 59%</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; PFS, progression-free survival.
*Reference category.
†Relative risks and $P$ values are estimated in multivariate analysis adjusted on age and neurofibromatosis type I.
continuous oral etoposide 3 weeks per month for a total of 8 months. This patient is alive and in remission of the leukemia.

Visual and Neuropsychologic Outcome

At the last follow-up visit, 11 children were blind. Visual acuity could be measured accurately in 46 of the 63 survivors who were not blind (73%). Failure to assess visual acuity was mainly because the patient was younger than 5 years of age at the time of evaluation. Twenty-eight children (60%) had poor vision (ie, visual acuity of the better eye below 3/10), and 18 (40%) had relatively preserved vision (ie, visual acuity of the better eye equal or above 3/10). The two patients with Dodge A tumors (ie, isolated optic nerve involvement) both showed PRs to chemotherapy with correction of the proptosis, and at last follow-up their visual acuity is 10/10 for both eyes.

Visual outcome was correlated with the response to chemotherapy (P = .0034, χ² test). Among the 36 children with a good response to chemotherapy, 18 (50%) had a visual acuity 3/10 in the best eye (ie, preserved vision) at the last follow-up visit. Among the 49 children with a poor response or progression of the tumor during chemotherapy, only 14 (28%) had a visual acuity 3/10 in the best eye.

Complete neuropsychologic evaluation is ongoing in the different participating centers and preliminary results in a subset of treated patients were presented recently.17 In this report, full-scale intelligence quotient scores of children treated with chemotherapy alone for an OPT were shown to be in the normal range.

DISCUSSION

Conservative management of OPT in children often includes the use of adjuvant therapy with irradiation or chemotherapy.5 These tumors are usually curable with irradiation.7,8 However, late effects are of particular concern in young children, who account for the majority of the patients affected by this disease.8 Low-grade gliomas are also sensitive to various chemotherapy drugs or combinations.23-29 Several groups have thus developed novel therapeutic approaches using chemotherapy to delay or avoid irradiation in young children with OPT. This study reports the largest series of homogeneously treated OPT with an extended follow-up of more than 6 years after the start of chemotherapy.

With the chemotherapy-first approach used in our study, 75% of the patients were alive without irradiation at 3 years and 61% were alive without irradiation at 5 years. The median interval between the start of therapy and irradiation for the 25 patients in whom it was finally delivered was 35 months. Only one study in the literature evaluated the same parameter and found a similar delay in the delivery of irradiation with vincristine and etoposide chemotherapy.30

In addition, deferring irradiation did not jeopardize OS of these children with documented progressive OPT. The 89% OS rate at 5 years observed in our study is in the range of OS rates of previous studies in which irradiation was used before adequate chemotherapy became available for these tumors.6,8 Moreover, visual outcome after treatment is comparable to previous reports of patients treated with radiotherapy.6,8

Objective response to chemotherapy attained 42% in this trial, which is in the range of the rates obtained in most of the other
studies published to date.12,27,30 Only one recent study reported a higher response rate in a small cohort of patients with a vigorous regimen consisting of 10 monthly cycles of cisplatin and etoposide.28 However, this study also included low-grade glioma of various locations outside the optic pathway and response to chemotherapy may depend on tumor site.

The interval between the start of treatment and the first measurable response was delayed because 50% of these responses occurred after the second cycle of chemotherapy. This slow response is consistent with previous reports on the use of chemotherapy in this disease.12,28,30

In our study, the tumor extent at diagnosis correlated with the response rate. Most of the children who did not continue the BBSFOP regimen after one cycle because of tumor progression had a Dodge C tumor. A classic log-rank test found no correlation, however, between 3-year PFS and the Dodge stage. Indeed, the risk of treatment failure was not proportional during follow-up: children with large tumors tended to experience treatment failure earlier but not more often as a whole. This may explain why the log-rank test appears limited in its capacity to analyze this variable.31

The two main risk factors for an adverse outcome with the BBSFOP regimen, when considered before treatment, were age younger than 1 year and the absence of NF1. For the 74 children who continued to receive chemotherapy after one cycle, because they had at least stable disease at the first evaluation, the multivariate analysis revealed two main risk factors of paramount importance for a poor outcome: age younger than 1 year and the absence of a good response to chemotherapy. NF1 has been widely shown to influence the natural history of OPT. Once OPT is diagnosed in NF1 children, tumor progression may not always occur, even without treatment.32-34 Moreover, with therapy, children with NF1 fare better than children who are not affected by this type of phakomatosis.8,30

Only one multi-institutional study also explored the correlation between response to therapy and outcome in 78 children with low-grade gliomas of various locations, but no correlation was found.15 Age younger than 1 year was also found to be an important prognostic factor in the recent report by Massimino et al28 using a cisplatin-etoposide regimen.

Toxicity induced by the BBSFOP regimen was mild and rarely required discontinuation of therapy. Of note, allergy to carboplatin was not observed, in contrast to other carboplatin-based regimens for which allergy was the main reason for discontinuation of therapy.12,35 This could be explained either by the lower cumulated dose of carboplatin or by the insertion of other courses without carboplatin in our regimen. Despite relatively high cumulated doses of alkylating agents, to date, only a few therapy-related second cancers have emerged with the BBSFOP regimen, even after an extended follow-up.36 Nevertheless, future trials may need to address whether the intensity of chemotherapy can be decreased, especially in children with good prognostic features. Indeed, patients with NF1 have a good PFS with chemotherapy but probably have a higher risk of therapy-related leukemia.37,38

In conclusion, the multidrug regimen described in this trial is an effective treatment for children with OPT that allowed us to avoid or defer irradiation in a significant proportion of patients. In this study, it was possible to identify a subgroup of patients with a particularly poor prognosis, namely infants younger than 1 year who did not achieve a good response (ie, CR or PR) to chemotherapy. All of these patients experienced relapse, usually during the first 3 years after the start of treatment. More intense chemotherapy regimens may be beneficial to this subgroup. Because children with good responses to chemotherapy had a better PFS, stable disease with chemotherapy may no longer be considered as sufficient in these patients. Given that many children experienced a relapse after first-line chemotherapy, we were able to demonstrate that it was possible to further delay irradiation by administering second-line chemotherapy when necessary. Alternatives to carboplatin-based regimens warrant additional investigation. The identification of strong risk factors for failure of a chemotherapy-first approach, as evidenced in this study, raises the question of a risk-adapted treatment.

ACKNOWLEDGMENT

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APPENDIX

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

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES