

Treatment Results in Patients With Retinoblastoma and Invasion to the Cut End of the Optic Nerve

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Background. There is little information on the outcome of patients with retinoblastoma and tumor at the resection margin of the optic nerve. **Procedure.** Retrospective evaluation of three successive prospective protocols. Twenty-six consecutive patients were analyzed (International Staging System—IRSS—stage 2 = 21, stage 3 = 5) from three successive prospective protocols (1988–2006). Patients with stage 2 were enucleated upfront and those with stage 3 had neoadjuvant chemotherapy followed by enucleation and adjuvant therapy. Both groups received adjuvant chemotherapy and orbital radiotherapy after enucleation. Patients in protocol 1 received 1 year of the lower-dose chemotherapy regimen including cyclophosphamide, vincristine and doxorubicin along with intrathecal chemotherapy. Patients of protocols 2 and 3 received a more intense and shorter intravenous regimen including carboplatin and etoposide

alternating with cyclophosphamide, idarubicin and vincristine with no intrathecal treatment. The components of protocol 2 and 3 were similar except for the dose of carboplatin which was 10% lower in protocol 3. **Results.** Thirteen were treated in protocol 1 and 13 in protocols 2 and 3. The probability of event-free survival was 0.70 at 5 years. Events included: CNS relapse = 3, second malignancies = 3, death in complete remission = 2. There were no significant differences in outcome between protocols or stages. Endocrinological disturbances related to the hypothalamus–hypophysis axis were evident in 6/8 patients evaluated. Severe orbital sequelae occurred in 12 cases. **Conclusions.** A substantial number of patients with tumor at the resection margin of the optic nerve can be cured with current therapy; however, therapy related sequelae are frequent. *Pediatr Blood Cancer* © 2008 Wiley-Liss, Inc.

Key words: chemotherapy; optic nerve involvement; pathology; radiotherapy; retinoblastoma; surgery

INTRODUCTION

Optic nerve invasion beyond the lamina cribrosa is one of the most important risk factors for extraocular relapse in retinoblastoma [1–7]. In this situation, the risk for extraocular relapse increases significantly when the resection margin is invaded by tumor, since microscopic disease is left behind in the orbit [1]. In more advanced cases, the tumor invades massively the optic nerve making it evident on imaging studies, leading to overt macroscopic invasion at the time of diagnosis. However, detecting microscopical invasion of the optic nerve preoperatively with imaging studies is difficult [8]. Despite the fact that these are considered high risk patients, there is little published information on their outcome with modern treatment [2,4,9–11]. Survival rates as low as 20% have been reported for this group of patients in historical series, however they provide little information on treatment [1,2,4,10]. Modern studies are hampered by the rarity of this condition in developed countries, so few reports have information on more than 10 patients and significant conclusions are difficult to obtain, but current survival figures are probably higher [2,4,10,11]. Patients with this feature have been treated on prospective studies in our center since 1987 but each study included limited numbers of patients. We thus collected information in a larger cohort to conduct an investigation [12,13].

PATIENTS AND METHODS

The clinical records of all patients with retinoblastoma and tumor invasion to the resection margin of the optic nerve seen at our institution and included into three successive prospective protocols from January 1988 to December 2006 were analyzed. The first protocol was carried out from 1987 to 1993 [12], the second one from 1994 to 2001 [13] and the third one from 2002 to the present time. All studies were approved by the Institutional Review Board and parents or guardians signed informed consents. Patients with metastatic disease or preauricular adenopathy at diagnosis were excluded and only patients enucleated at our institution were included.

Patient Evaluation and Staging

After enucleation, all pathology specimens were processed under a previously reported procedure [14]. Massive choroidal invasion was considered when tumor cells invaded the choroid > 50% of its thickness or when >1 tumor cluster was noted [13]. Extent of disease evaluation included a contrast-enhanced head and orbit CT scan or MRI, lumbar puncture with examination of the cytopsin and bone marrow assessment, including a single bone marrow aspiration in the first study and bilateral bone marrow aspiration and biopsy from the second one onwards [15]. Immunocytology for GD2 expression on fresh tumor cells was used in all patients on the second and third protocols [15]. All cases were re-classified according to the International Retinoblastoma Staging System (IRSS) [16]. Patients were divided into two groups according stage that dictated the initial management. (1) Those with stage 2: this subgroup included those patients in whom invasion to the resection margin of the optic nerve was detected after pathological examination of an enucleated eye. (2) Those with stage 3 disease: including those patients in whom massive extraocular disease was evident on initial staging, including massive optic nerve enlargement (Fig. 1).

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Fig. 1. Overt tumoral extension to the optic nerve (arrow) in a stage 3 patient.

Treatment

Stage 3 patients were given 2–3 cycles of preoperative chemotherapy in order to shrink the tumor to allow for a safer enucleation. Orbital extenteration was not done in any case. Adjuvant chemotherapy was prescribed for all patients. In the first protocol the chemotherapy regimen included standard doses of cyclophosphamide, doxorubicin, and vincristine along with intrathecal therapy (Table I, regimen 1) [12]. In the second and third studies, patients received regimen 2 including high dose carboplatin and etoposide alternating with cyclophosphamide, idarubicin and vincristine (Table I, regimen 2) [13]. Intrathecal therapy was omitted. Selected patients with overt extraocular disease were eligible for window therapy with investigational agents such as idarubicin ($n = 3$) [17]. Orbital radiotherapy was given within 2 weeks after enucleation. For radiation therapy, the children in

supine position were treated with photons from a linear accelerator by an isocentric technique at source-to-axis distance of 100 cm. The prescribed dose was 45 Gy in 25 fractions of 1.80 Gy/day. All patients were given sevoflurane for anesthesia and immobilized with head rest. The gross tumor volume and clinical target volume were covered by the 45 Gy isodose surfaces. The gross tumor volume was defined by orbital bones, optic nerve and included optic chiasma. Early in the study, eight patients were treated with lateral oblique field. The remaining 18 patients were treated with 3 anterior oblique fields by a wedge pair technique. Chemotherapy was not altered during radiotherapy.

Surviving patients of the second and third protocol were systematically evaluated for long-term sequelae in most cases including endocrinologic evaluation, cardiologic and audiologic tests annually beginning after 2 years of enucleation.

Statistical Analysis

Contingency tables were constructed and Chi-square or Fisher exact tests were used for categorical variables and Mann–Whitney test was used for continuous variables. Extraocular relapse (including orbital and metastatic relapse) and second malignancies, as well as toxic deaths were defined as event and event-free survival curves at 5 years were calculated according to Kaplan–Meier and survival status was updated to December 2007. Curve comparison was done with the log-rank test.

RESULTS

Patients Characteristics

Three hundred forty-five patients with retinoblastoma were admitted to our hospital in the period under study. Of these, 26 (7.5%) consecutive patients who fulfilled the inclusion criteria were analyzed. Median age at diagnosis was 31.7 months (range 4–61) and male/female ratio was 0.73. Median follow up was 83 months (range 12–186).

TABLE I. Description of Chemotherapy Regimens

Regimen 1 (12) (used for protocol 1)
Vincristine 0.05 mg/kg/day 1
Cyclophosphamide 40 mg/kg/day 1 (with hyperhydration and sodium 2-mercaptoethanesulfonate-MESNA)
Doxorubicin 0.67 mg/kg/days 1–3
Week 0
Vincristine 0.05 mg/kg/day 1
Cyclophosphamide 20 mg/kg/day 1 (with hyperhydration and MESNA)
Doxorubicin 0.67 mg/kg/days 1–3
Week 3, 6, 9, 12, 15, 18, 21
Vincristine 0.05 mg/kg/day 1
Cyclophosphamide 30 mg/kg/day 1 (with hyperhydration and MESNA)
Weeks 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, and 54
Intrathecal chemotherapy was given weeks 0, 1, 2, 3, 4, and 5 (methotrexate, cytarabine, and dexamethasone in an age-adjusted fashion [12])
Regimen 2 (13) (used for protocols 2 and 3)
Vincristine 1.5 mg/m ² /day 1 (0.05 mg/kg in children weighing <10 kg)
Cyclophosphamide 65 mg/kg/day 1 (with hyperhydration and MESNA)
Idarubicin 10 mg/m ² /day
Weeks 0, 6, 12, 18
Carboplatin 560 mg/m ² /days 1 and 2 (18.7 mg/kg for children weighing <10 kg) (in protocol 3, 500 mg/m ² /days 1 and 2 or 18 mg/kg in children weighing <10 kg)
Etoposide 100 mg/m ² /days 1, 2, and 3 (3.3 mg/kg for children weighing <10 kg)
Weeks 3, 9, 15, 21

Other pathology risk factors present in enucleated eyes of the study group included: choroidal invasion in 19 (massive in 11), scleral invasion in 11 (trans-scleral 7) and anterior segment invasion in 7. Nine patients had bilateral retinoblastoma. Of them, seven had one eye enucleated at diagnosis and the remaining eye treated conservatively with external beam radiotherapy (EBRT) ($n = 6$) or chemoreduction and followed by EBRT and ophthalmological therapy ($n = 1$). The two remaining patients underwent simultaneous bilateral enucleation. One patient with bilateral retinoblastoma had stage 3 disease in one eye and a Reese-Ellsworth Group V in the contralateral eye. Conservative treatment was attempted but the eye had to be ultimately enucleated. Overall four patients ultimately had bilateral enucleation. The pathology examination of the second enucleated eye had: tumor in the resection margin of the optic nerve in one case who received simultaneous bilateral enucleation and had subsequently a CNS relapse, the remaining ones had intraocular disease (one of them with choroidal invasion).

Outcome According to Stage

Twenty-one patients had presumed intraocular disease by CT scan and tumor at the resection margin of the optic nerve was found after pathological examination of an initially enucleated eye (stage 2). In four of them (three early in protocol 1 and one in protocol 2), the optic nerve stump was shorter than 2 mm at pathological examination. In two of them, the child presented with severe buphthalmia and enucleation proved to be difficult. Two cases were enucleated at our center by another ophthalmologist without the preoperative diagnosis of retinoblastoma and a short optic nerve stump was obtained. All four survive disease-free, but one of them had a low grade glioma at the radiation field (described below). The median optic nerve length, measured by the pathologist after fixation of the eyeball was 4.1 mm (range 0–14). Measurements of the optic nerve stump taken by the ophthalmologist in the operating room are not available. The remaining five patients had overt invasion to the optic nerve detected at diagnosis (stage 3), so they received preoperative chemotherapy. Overall, 13 patients were treated on protocol 1 (events $n = 3$) and 13 in protocols 2 and 3 (events $n = 5$).

Events Description

The most common adverse events were disease relapse and second malignancies. In all three cases with CNS relapse, patients presented with leptomeningeal dissemination at a median time of 10 (range 9–11) months from diagnosis and all died with progressive disease despite a second line treatment was attempted. Three patients had a second malignancy: two of them developed a secondary acute myeloid leukemia and were reported elsewhere [18]. Both cases died of leukemia. One case had a low grade glioma developing at the ipsilateral side from the irradiated eye at 15 years after diagnosis. The tumor could be completely resected and the patient survives with a follow up of 38 months. Two patients died while in complete remission. One of them because of parental abuse and no tumor could be found at autopsy. The remaining patient with the chromosome 13q14 syndrome at the time of diagnosis died during adjuvant therapy for sepsis during a chemotherapy-induced neutropenic episode.

Survival Estimates

The 5-year probability (P) event-free survival (EFS) and P overall survival (OS) were 0.7 (95% confidence interval—CI 0.53–0.87) for the whole population. When only disease recurrence was considered, there was no significant difference ($P = 0.87$; 95% CI 0.75–0.99). Since protocols 2 and 3 were very similar and the number of patients included in each was small, they were compared together to protocol 1. However, there were no significant differences ($P_{EFS} = 0.71$; 95% CI 0.47–0.95) versus 0.67 (95% CI 0.42–0.92).

Treatment Related Sequelae

Eight surviving patients had a complete sequelae evaluation. No significant audiological toxicity occurred. One patient had a mild decrease of the shortening fraction at the echocardiogram (included in the first protocol). Six out of eight patients had endocrinological sequelae. Central hypothyroidism was present in four patients: isolated central hypothyroidism was present only in one case, while in the others was associated with ACTH deficiency ($n = 1$), early puberty ($n = 1$), and in one patient hypogonadism and growth hormone deficiency. Isolated GH and ACTH deficiency were present in one patient each. All patients had severe cosmetic sequelae because of the combined effect of irradiation and enucleation. Twelve had at least one plastic surgery procedure to alleviate the cosmetic appearance.

DISCUSSION

Our results showed in a relatively large cohort that a significant number of patients with retinoblastoma and tumor at the resection margin of the optic nerve can become long-term survivors with the use of an intensive intravenous chemotherapy regimen that was helpful for replacing intrathecal drugs. In our series, despite having a higher tumor burden, patients with stage 3 achieved a comparable disease-free survival to those with stage 2. Since chemotherapy regimens were similar, we may assume that the prescription of preoperative chemotherapy immediately after diagnosis avoiding the delay that a surgical procedure might have caused, could be an explanation for these results. This approach was previously published by the Institut Curie group but in their institution, preoperative chemotherapy was followed by a combined ophthalmological–neurosurgical approach to achieve a complete resection of a longer stump of the optic nerve. The results were encouraging in a limited patient series with massive involvement of the optic nerve [19].

In order to avoid leaving a tumor remnant at the distal end of the optic nerve, enucleation should be performed by an experienced ophthalmologist capable of obtaining at least 10 mm of optic nerve stump [20]. However, this could be a challenge in buphthalmic eyes, as happened in two of our cases. When only a minimal portion of the optic nerve is resected, the distal extension through the remaining optic nerve is not known and it could be probably less than in cases when tumor is seen after obtaining an appropriate stump. This feature may occur because of lack of awareness of the ophthalmologist that the enucleated eye had retinoblastoma (one case in our series) or technical difficulties making impossible to obtain a longer stump. It may be argued that our patient population had a short optic nerve length. It is usually recommended to obtain at least 10 mm of optic nerve on enucleation of eyes with retinoblastoma and the mean

TABLE II. Treatment Outcome in Series With More Than 10 Patients With Tumor at the Resection Margin of the Optic Nerve

First author (reference)	Period	Patient number	Treatment	Survival
Zelter (9)	1981–1986	13	Adjuvant chemotherapy with vincristine, doxorubicin and cyclophosphamide, orbital and CNS radiation	6/13
Kopelman (6)	1922–1959	137	Unknown	19.7%
Messmer (5)	1956–1986	19	Unknown	8/19
Magrann (1)	1922–1986	51	Radiation ± chemotherapy	22%
Antoneli (4)	1987–2000	29	Adjuvant systemic and intrathecal chemotherapy, orbital radiotherapy	22/29
Khelifaoui (11)	1977–1990	17	Various regimens, orbital radiotherapy	10/16 (1 lost to follow up)
Stannard (25)	1983–2000	13	Chemotherapy (various regimens) brachytherapy	5/13

value for our population is somewhat shorter. However, the length of the optic nerve stump is critically influenced by the time when it is measured [21]. When measurements of the optic nerve stump taken by the ophthalmologist at the operating room are compared to those obtained by the pathologist, there is 30% difference in length due to fixation [21]. In our study, we measured the optic nerve length even later; it was done by the pathologist at the microscope after fixation and staining, so the actual length is not comparable to other series. However, in our series, four patients had less than 2 mm of optic nerve stump and we decided to give the same treatment than in those with tumor at the resection margin with an adequate optic nerve stump. The limited patient number included in our study invalidates any definitive conclusion but none of the patients with short optic nerve stump had a relapse and one had a treatment-related secondary malignancy, emphasizing the need to develop strategies to minimize this phenomenon since these patients might have been over-treated.

There is no agreement on what the best treatment for these patients is, but most centers use adjuvant treatment with chemotherapy and orbital radiotherapy [2,4,7,22]. Given that CNS relapse is the most common event, an ideally effective regimen should target the CNS with drugs with good penetration to it. Some groups advocated the use of intrathecal chemotherapy which are not the most active agents for retinoblastoma and are potentially neurotoxic [2,13,22]. Our treatment regimens resulted in a low relapse rate with or without intrathecal chemotherapy. The traditional approach for the post-enucleation treatment of these patients included adjuvant systemic and intrathecal chemotherapy along with radiotherapy [7,23]. However, many groups recently avoided intrathecal chemotherapy [13,19]. The survival rate for these patients ranged from 40% to 70% (Table II). The addition of an alkylating agent to the combination of carboplatin and etoposide is also controversial. Antoneli et al. [24] reported that the addition of ifosfamide and etoposide to a platinum containing regimen may improve results in patients with orbital invasion. Other reports also supported the use of prophylactic cranial radiotherapy [9,25]. However more recent series withdrawn prophylactic cranial radiation and kept orbital radiotherapy (including the chiasm in the radiation field) at a dose of 40–45 Gy [13,19]. However, despite using limited radiation, severe orbital hypoplasia and endocrinological dysfunction leading to hypopituitarism was seen in most our patients. Neuroendocrine abnormalities secondary to CNS radiotherapy have been reported and the growth hormone and the FSH/LH axes have been described as the most vulnerable to radiation damage [26]. However, in our series, the TRH–TSH axis appeared to be the most frequently affected one. A larger group of retinoblastoma patients after orbital

radiotherapy treatment should be studied to fully characterize this complication. Our patient population suffered from other significant long-term sequelae including three cases of secondary malignancies. Therefore, despite our results being satisfactory in terms of survival, more effective and less toxic treatments should be developed for this high risk population.

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