

Treatment of Metastatic Retinoblastoma

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Purpose: The risk for death in patients with retinoblastoma is increased in those who present with metastatic disease, and the role of intensive chemotherapy and autologous hematopoietic stem cell rescue in these patients remains unclear.

Design: Nonrandomized interventional case series.

Participants: Four consecutive patients with metastatic retinoblastoma.

Methods: We treated four patients with retinoblastoma metastatic to the bone and bone marrow with intensive chemotherapy, consolidation with megatherapy, and autologous hematopoietic stem cell rescue. Chemotherapy included courses of carboplatin and etoposide alternating with cyclophosphamide, etoposide, and either carboplatin or cisplatin. Radiation therapy was delivered to areas of bone metastases.

Main Outcome Measures: Patient survival.

Results: All patients completed and responded to the scheduled therapy; complete response of the bone marrow disease was documented after two courses of chemotherapy in all cases. Two patients are long-term survivors.

Conclusions: The treatment described has been successful in obtaining disease-free survival in patients with metastatic retinoblastoma. *Ophthalmology* 2003;110:1237–1240 © 2003 by the American Academy of Ophthalmology.

In recent years, significant advances have been made in the treatment of retinoblastoma. However, rarely has retinoblastoma metastatic to the bones or to soft tissues other than the orbit been cured with chemotherapy and radiation therapy. For those patients with metastatic disease, a very intensive multimodality approach that incorporates intensive chemotherapy, radiation therapy, and transplantation of autologous

hematopoietic stem cells may be effective.^{1–12} Herein, we report our results with an intensive multimodality treatment of four patients with retinoblastoma metastatic to the bones and bone marrow.

Materials and Methods

Four patients with unilateral retinoblastoma developed metastatic disease to the bones and bone marrow 4 to 24 months after enucleation. Table 1 summarizes the demographics of the patients, as well as their treatments and outcomes. Systemic chemotherapy included courses of carboplatin and etoposide alternating with cyclophosphamide, doxorubicin, and either carboplatin or cisplatin. Autologous hematopoietic stem cells were harvested after two to four courses of chemotherapy, after complete response of the bone marrow disease had been documented. Radiation therapy to areas of bone metastases was administered after two courses of chemotherapy. Consolidation with megatherapy and autologous hematopoietic stem cell rescue were performed after 6 to 10 courses of chemotherapy. Informed consent was obtained from each patient's parents or legally authorized representative before treatment was started.

Results

All patients received the scheduled therapy. After two courses of chemotherapy, there was complete response of the bone marrow disease in all cases, and imaging demonstrated partial response of the bone metastases in all cases. Radiation therapy (1800–4600 cGy) was delivered after two courses of chemotherapy to all sites of bone and soft tissue metastases. Consolidation with megatherapy and autologous hematopoietic stem cell rescue was per-

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Table 1. Clinical Characteristics, Treatment, and Outcome of Patients with Metastatic Retinoblastoma

Age at Dx (mos), Race/Sex	Eye (R-E)	Primary Treatment	Histology	Age at Metastases (mos)	Sites of Disease	Treatment				
						Chemotherapy	EBRT	Response	HDCT	Outcome
17, W/M	R (Vb)	Enucleation	Choroid, optic nerve	24	Bone: orbit, skull; BM	(CYC/DOX/CDDP) × 1 (CBP/ETO) × 2 (CYC/DOX/CBP) × 2	46 Gy: orbit, skull base	CR	CBP+ ETO	Alive NED, 7+ yrs
27, W/M	R (IVb)	Enucleation	Choroid, ciliary body	31	Bone: orbit, skull; BM	(CYC/DOX/CDDP) × 5 (CBP/ETO) × 4 (CYC/DOX/CBP) × 1	41.4 Gy: orbit, skull	CR	BUS ₊ , CYC ₊ , MEL	Recurrence, CNS 38 mos, DOD 44 mos
34, H/M	L (NA)	Enucleation	NA	39	Bone: orbit, maxilla, mandible; BM; LN	(CBP/ETO) × 3 (CYC/DOX/CBP) × 3	36.5 Gy: orbit, maxilla, mandible	CR	CYC ₊ , ETO	Alive NED, 6+ yrs
36, W/F	R (Vb)	Enucleation	Choroid, sclera	60	Bone: orbit, skull; BM	(CBP/ETO) × 3 (CYC/DOX/CBP) × 3	18 Gy: neck 45 Gy: orbit, skull	CR	CYC ₊ , TOPO	Recurrence, BM/ovary 77 mos, CNS 87 mos, DOD 88 mos

Dx = diagnosis; R-E = Reese-Ellsworth group; EBRT = external beam radiation therapy; HDCT = high-dose chemotherapy; W = white; H = hispanic; M = male; F = female; R = right eye; L = left eye; NA = not available; BM = bone marrow; LN = lymph nodes; CYC/DOX/CDDP = cyclophosphamide 150 mg/m²/day × 7 days; doxorubicin 35 mg/m²/days × 1 day, cisplatin 100 mg/m²/day × 1 day; CBP/ETO = carboplatin 560 mg/m²/day × 1 day etoposide 150 mg/m²/day × 3 days; CYC/DOX/CBP = cyclophosphamide 150 mg/m²/day × 7 days, doxorubicin 35 mg/m²/day × 1 day, carboplatin 560 mg/m²/day; CR = complete response; CBP = carboplatin; ETO = etoposide; BUS = busulfan; CYC = cyclophosphamide; MEL = melphalan; TOPO = topotecan; NED = no evidence of disease; CNS = central nervous system; DOD = dead of disease.

formed after 6 courses of chemotherapy in 3 patients and after 10 courses in the fourth patient. Myeloablative regimens differed for each patient. Two of the four patients survived free of disease for >6 years after therapy. In the other two, disease recurred in the central nervous system and other sites. Toxicity of this treatment was as expected, with moderate myelosuppression and occasional episodes of neutropenic fever. One patient (patient 1) with *Candida albicans* sepsis received successful antifungal therapy. One long-term survivor (patient 3) developed deficiencies of growth and thyroid hormones secondary to radiation to the head and neck. Finally, toxicity from consolidation with high-dose chemotherapy and transplantation of autologous hematopoietic stem cells was tolerable, and engraftment of bone marrow was good.

Discussion

We have shown that patients with metastatic retinoblastoma benefit from a multimodal approach that incorporates intensive multiagent chemotherapy and radiation therapy with consolidation with high-dose chemotherapy and transplantation of autologous hematopoietic stem cells. Despite the rarity of metastatic retinoblastoma, strong evidence supports the use of this multimodal approach, and two series have shown that metastatic retinoblastoma can be cured with intensive chemotherapy.^{4,11} Dunkel et al¹¹ recently reported long-term survival in four patients with retinoblastoma metastatic to the bones and bone marrow after use of the N-6 regimen, an intensive regimen similar to the one we report. Like their patients, all four patients in our series achieved complete remission of the bone marrow disease after only two courses of chemotherapy; this result confirms the exquisite chemosensitivity of extraocular retinoblastoma^{4,6,8,11,12} and the importance of intensive chemotherapy

to achieve an early major cytoreduction of the tumor burden. However, despite the early good responses, disease recurred in two of our patients, and they died of disease of the central nervous system, a complication that continues to represent the major obstacle to improved outcome of patients with metastatic retinoblastoma.⁶ There are no effective treatments for patients with central nervous system disease from the spread of retinoblastoma, and chemotherapy delivered intrathecally has not provided any advantage.⁷

In addition to the administration of repeat cycles of intensive chemotherapy, the consolidation of the response with high-dose chemotherapy and rescue with autologous hematopoietic stem cells seems to be beneficial.^{4,11,12} However, the exact role of consolidation with megatherapy is difficult to assess because of the low number of patients and the absence of randomized studies. Nevertheless, some evidence suggests that consolidation is effective in treating other metastatic pediatric neuroectodermal tumors, such as neuroblastoma¹³ and, less clearly, Ewing's sarcoma,¹⁴ thus supporting the role of consolidation in retinoblastoma. In this regard, the selection of drugs to be used in the megatherapy regimen is important. The most successful regimens have included carboplatin, with or without etoposide, and incorporation of alkylating agents seems to have a major effect.^{4,11} Alkylating agents, such as melphalan, busulfan, and thiopeta, seem to have an increasing role in the consolidation regimens for metastatic neuroblastoma and Ewing's sarcoma,^{14,15} and there is evidence that their incorporation in the regimen favorably affects outcome.¹⁶

Finally, in addition to the intensive systemic therapy, radiation therapy may be used after chemotherapy to consolidate areas of known (or suspected) involvement of bone

or soft tissue. However, the exact role of radiation therapy in the treatment of distant metastases is unclear.

Metastatic disease represented a recurrence after primary enucleation in all four of our cases. In the three evaluable cases, the enucleated eye showed histologic features suggestive of a high risk for metastatic disease, such as massive choroidal involvement or infiltration of the optic nerve, ciliary body, or sclera. It is possible, therefore, that adjuvant chemotherapy could have prevented the development of metastatic disease. However, the exact frequency of metastatic disease after enucleation for retinoblastoma is not known in relation to the extent of invasion by the tumor of the optic nerve,^{17–19} choroid,^{20–23} ciliary body–iris,^{24,25} or sclera.²⁶ Multiple references to risk factors for prognosis have evolved over the past 15 years.^{27–33} Various publications have indicated that disease of the optic nerve head and of the choroid may be interdependently related to the development of metastatic disease.^{19,22} Involvement of the ciliary body–iris by tumor suggests additional risk for metastatic disease via vascular and lymphatic routes; these metastases can involve lymph nodes, bones, and bone marrow.^{22,23} Involvement of tumor beyond the lamina cribrosa has been associated with an increased incidence of metastases, yet these patients have most likely also had other intermediate- or high-risk pathologic features.¹⁹ Orbital extension of retinoblastoma may have a better prognosis than previously reported.^{6,24} Chemotherapy with carboplatin/etoposide, cyclophosphamide/doxorubicin, or both has been successful in concert with radiation for treating retinoblastoma in patients with high-risk pathologic features.^{4,34,35} Therefore, postenucleation adjuvant chemotherapy should certainly be considered for patients with high-risk features, as noted previously.^{26,27} However, prospective, preferably randomized, cooperative studies should be performed to better define the histologic risk factors and the role of adjuvant chemotherapy. This is the approach currently being considered by the Children's Oncology Group. Finally, metastatic retinoblastoma is very rare in the United States, and lessons regarding the most appropriate treatment are available only through cooperative, multi-institutional studies, such as the current Children's Oncology Group initiative. In developing nations, where the incidence of retinoblastoma is higher than in the United States, more patients present with high-risk or metastatic disease because of delay in diagnosis. It is in these countries that greater efforts must be made for earlier diagnosis.

In summary, long-term survival can be achieved with the use of an intensive multimodal approach in patients with high-risk and metastatic retinoblastoma that does not involve the central nervous system. However, new approaches are needed for the treatment of patients with trilateral retinoblastoma and with disease of the central nervous system.

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