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A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement

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Summary:

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation. Since retinoblastoma is highly chemosensitive, dose-escalation of chemotherapeutic agents with stem cell support should be promising. We report our experience with high-dose chemotherapy (HDC) and autologous stem cell transplantation (SCT) in patients with metastatic retinoblastoma. Five patients with metastatic retinoblastoma underwent HDC with autologous SCT following conventional chemotherapy and local radiation therapy. Stem cells (bone marrow in four and peripheral blood stem cells in one) were collected after marrow involvement was cleared. Melphalan was a key drug in all patients, and was administered in combination with other agents such as cisplatin, cyclophosphamide, carboplatin or thiotepa. Three patients are currently alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT. They had no central nervous system (CNS) involvement. The two patients who died of disease had CNS involvement. No long-term sequelae of HDC have been noted. Our treatment strategy using HDC appears to be effective for treating metastatic retinoblastoma without CNS involvement.

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Retinoblastoma, the most common ocular malignancy in childhood, develops in infants, and the incidence is one in 160 000–20 000 births in Japan.[1] Many therapeutic modalities have been employed, and retinoblastoma has become one of the curable pediatric solid tumors. Nevertheless, the prognosis of extraocular retinoblastoma with metastasis to bone/bone marrow (BM) or the central nervous system (CNS) remains very poor.[2] Such high-risk populations include involvement of the cut end of the optic nerve, extrascleral spread into the orbit, lymphatic or hematogenous dissemination, CNS involvement and trilateral retinoblastoma. The overall occurrence of extraocular retinoblastoma was 4.8% of all patients at an institution.[3] Since retinoblastoma is highly chemosensitive, a treatment strategy that includes the dose-escalation of chemotherapeutic agents and stem cell support should be promising. We treated five patients with metastatic retinoblastoma using high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (SCT), and three patients are currently alive and disease-free. Although our experience is very limited, our experience suggests the feasibility of a prospective study.

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Patients and methods

Five patients received HDC for extraocular retinoblastoma between March 1986 and November 2000 at the National Cancer Center Hospital of Japan (NCCH), and the data reported reflect the last patient contact as of January 2004. All patients originally were treated with radiation therapy and/or enucleation for intraocular disease at NCCH. The clinical characteristics of the patients are described in Table 1. After completion of the initial series of local ophthalmic therapies in NCCH, four of the five patients developed metastatic recurrence, as reported elsewhere.[4–6] Only one patient had BM metastasis at the initial diagnosis. Staging studies included computed tomography and magnetic resonance imaging of orbits and brain, histopathologic evaluation of BM aspiration and cytologic examination of cerebrospinal fluid (CSF). All patients were classified as having stage III/IV disease by the grading system of Grabowski and Abramson.[7] After the diagnosis of metastatic diseases was established, all patients were treated with conventional chemotherapy with or without radiotherapy and surgical enucleation (Table 2). Systemic chemotherapy included courses of vincristine, cyclophosphamide and doxorubicin with or without cisplatin alternating with cisplatin and cyclophosphamide, or

Table 1 Patients characteristics

UPN	*Sex*	*Age at diagnosis*	*Involvement*	*Metastases at diagnosis*	*Treatment*	*Metastases after therapy*
1	F	3 months	Bilateral	None	Right: 50.7 Gy radiation Left: enucleation	Brain (optic chiasm), spinal cord (L1)
2	M	10 months	Bilateral	None	Right: 49.4 Gy radiation Left: enucleation	Brain (ethmoid and sphenoid sinus), bilateral cervical LNs
3	F	41 months	Left	None	Left: 46 Gy radiation + HIT	Right temporal bone, marrow (70%)
4	F	16 months	Right	Marrow	Right: enucleation + 6 Gy radiation + chemotherapy	
5	F	18 months	Right	None	Right: 46 Gy radiation + enucleation + HIT + PC + CTT + IVI	Right orbit, marrow (50%)

UPN = unique patient number; HIT = heat-inducing thermotherapy; PC = photocoagulation; CTT = chemothermotherapy; IVI = intravitreal injection.

Table 2 Therapy and outcome

UPN	*Cx. after Mets*	*Rx. after Mets*	*SCT from relapse (mos)*	*Conditioning (mg/m^2)*	*Stem cell source*	*Result*	*Meta. after SCT (mos)*	*Sequelae*
1	VCR/CY/ADR $\times 2$ CY/CDDP $\times 1$	Spine 40 Gy, cranium 25 Gy + boost 15 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Spinal cord at Th12-L1 level (24 mos)	NE
2	VCR/CY/ADR $\times 3$ CDDP/ETO $\times 2$	Cranium 40 Gy + boost 20 Gy, spine 21 Gy, cervical LNs 40 Gy	5	CDDP 90, CY 120 mg/kg, L-PAM180	BM	DOD	Rt. cervical LN (4 mos)	NE
3	VCR/CY/ADR $\times 4$ CDDP/ETO $\times 2$	Focal site 40 Gy	7	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (113 +)	None	None
4	VCR/CY/ADR $\times 3$ CDDP/ETO $\times 3$	—	6	L-PAM 180, VP-16 800, CBDCA 1600	BM	NED (107 +)	None	None
5	VCR/CY/ADR/ CDDP $\times 3$ CBP/ ETO $\times 4$	—	7	L-PAM 160, CY 120 mg/kg, TEPA 500	PBSC	NED (38 +)	None	None

SCT = stem cell transplantation; BM = bone marrow; CNS = central nervous system; LN = lymph node; NED = no evidence of disease; DOD = dead of disease; NE = not evaluable; VCR/CY/ADR = vincristine 1.5 mg/m^2/day $\times$ 1, cyclophosphamide 600 or 800 mg/m^2/day $\times$ 2, doxorubicin 40 mg/m^2/day $\times$ 1; CDDP/CY = cisplatin 90 mg/m^2/day $\times$ 1, cyclophosphamide 1200 mg/m^2/day $\times$ 1; CDDP/ETO = cisplatin 20 mg/m^2/day $\times$ 5, etoposide 100 mg/m^2/day $\times$ 5; VCR/CY/ADR/CDDP = vincristine 1.5 mg/m^2/day $\times$ 1, cyclophosphamide 1200 mg/m^2/day $\times$ 1, doxorubicin 40 mg/m^2/day $\times$ 1, cisplatin 18 mg/m^2/day $\times$ 5; CBP/ETO = carboplatin 120 mg/m^2/day $\times$ 5, etoposide 100 mg/m^2/day $\times$ 5; L-PAM = melphalan; VP-16 = etoposide; CBDCA = carboplatin; TEPA = thiotepa.

cisplatin and etoposide, or carboplatin and etoposide. After complete response of tumor involvement in the BM, autologous BM cells were collected from four patients, autologous blood stem cells from one patient, respectively. The nonpurged stem cells were cryopreserved. All patients also received one to five intrathecal injections of methotrexate at a variable dose of 5–12.5 mg/dose, concomitant with systemic chemotherapy. Radiation therapy was given in four patients to sites that had harbored bulky disease at early stage after the diagnosis of metastasis. All patients were prepared for HDC with SCT after achieving complete remission, which was evaluated by imaging studies, BM aspiration and/or CSF examination. We harvested BM cells or peripheral blood stem cells, if a BM aspirate had no tumor cells on morphologic analysis before harvesting. We did not apply minimum residual disease (MRD) studies on BM cells or peripheral blood stem cells. Conditioning regimens for all patients contained melphalan 180 mg/m^2 as a key drug. Concomitant agents were cisplatin 90 mg/m^2 and cyclophosphamide 120 mg/kg (case 1, 2), etoposide 800 mg/m^2 and carboplatin 1600 mg/m^2 (case 3, 4), or thiotepa 500 mg/m^2 and cyclophosphamide 120 mg/kg (case 5). The collected BM cells ($1.0–1.7 \times 10^8$ total nucleated cells/kg) or peripheral blood stem cells (4.7×10^6 CD34 + cells/kg), which were unmanipulated, were infused approximately 24 h after completion of the conditioning chemotherapy. Granulocyte-colony stimulating factor was administrated intravenously once daily from day +5 or +7, and was continued until engraftment of neutrophils was established (case 3–5).

Results

Engraftment

Engraftment of neutrophils, defined as the first of two consecutive days of an absolute neutrophil count of at least 0.5×10^9/l, occurred 18, 26, 10, 14 and 11 days, respectively, after stem cell rescue. Platelet engraftment, defined as the first of 2 consecutive days of an absolute platelet count of at least 50×10^9/l sustained without transfusion, occurred 67, 32, 11, 51 and 16 days, respectively, after stem cell rescue.

Toxicities

All patients developed severe mucositis with oropharyngeal pain (WHO grade 3) after SCT. Only one patient had elevated transaminase levels greater than five times normal (case 5). All patients developed febrile neutropenia without a detectable pathogen, which subsided within 7 days by antibiotic treatment. No other acute toxicities associated with SCT were observed.

Patient survival

All three patients without CNS metastasis are alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT (case 3–5). They are alive without complications, except for orbital growth retardation because of local irradiation and surgical enucleation. Two patients died of recurrent diseases 4 and 48 months, respectively, after SCT (case 1, 2). There was no second malignancy in this series.

Discussion

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation therapy.[2,8] Honavar *et al*[9] have shown that postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting high-risk histopathologic characteristics.[9] Several centers have used conventional-dose chemotherapy and radiation therapy for hematogenously spread extraocular disease. Despite some reports of long-term event-free survival,[7,10] the bulk of the evidence suggests that the prognosis remains poor with such an approach.[11]

A limited number of studies and case reports have suggested that HDC with autologous stem cell rescue might be beneficial for patients with metastatic retinoblastoma (Table 3).[12–20] Namouni *et al*[14] conducted a study of HDC consisting of carboplatin, etoposide and cyclophosphamide (CARBOPEC) followed by autologous SCT in 25 patients, including 12 patients with distant metastases. Among eight children with bone and BM metastases, five survived between 11 and 70 months disease free, while three patients with CNS metastases relapsed in the CNS after HDC and died. Thus, the CARBOPEC regimen appeared to be effective only for patients with bone and/or BM involvement of retinoblastoma. Dunkel *et al*[16] reported four retinoblastoma patients with orbit and BM metastases who underwent HDC consisting of carboplatin and thiotepa with or without etoposide. All patients survived event-free for 46–80 months after the diagnosis of metastatic disease. They concluded that this treatment strategy is effective for metastatic retinoblastoma without CNS involvement. Rodriguez-Galindo *et al*[19] reported four retinoblastoma patients with bone and BM metastases, treated by intensive systemic therapy. Although they did not mention an effectiveness of HDC, they concluded that the use of intensive multimodal approach in patients with metastatic retinoblastoma without CNS involvement could achieve long-term survival.

The important component in HDC is the alkylating agents, which have favorable toxicity profile. There are some reports that thiotepa is effective for high-risk retinoblastoma and other malignancies.[16,19,21,22] As it penetrates well into the brain, as demonstrated by similar drug levels in CSF and in serum after intravenous injection bolus use, we should consider the high-dose thiotepa in the attempts of HDC in disseminated retinoblastoma, particularly with CNS involvement. However, we used not thiotepa but melphalan for HDC. High-dose melphalan and SCT have been used to treat neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma in children.[23–26] In addition, Inomata and Kaneko[27] suggested that retinoblastoma was most sensitive to melphalan based on a colony assay on double agar layers. Kaneko treated six patients with intraocular retinoblastoma that recurred after irradiation therapy by injecting 40 mg/m^2 of melphalan into the ipsilateral intracarotid artery, and by applying ocular hyperthermia (45°C, 1 h).[5] Two patients were cured (no recurrence for more than 10 years) with a single treatment procedure while preserving adequate visual function. Based on their observation, we selected melphalan as a key drug for HDC. We should consider that not only thiotepa but also melphalan is an effective agent of HDC for retinoblastoma. As other agents, busulfan and nitrosurea drugs

Table 3 High-dose chemotherapy for retinoblastoma

Author (year)	*n*	*Marrow involvement (+/−)*	*Bone Metastasis (+/−)*	*CNS Metastatsis (+/−)*	*High-dose chemotherapy*	*Result*
Namouni *et al* (1997)[14]	12	1/11	7/5	4/8	CARBOPEC	6 alive
Dunkel *et al* (2000)[16]	4	3/1	4/0	0/4	CTE 3, TC 1	4 alive
Kremens *et al* (2003)[19]	5	4/1	2/3	0/5	CTE 4, BCyE 1	5 alive[a]
Rodriguez-Galindo *et al* (2003)[20]	4	4/0	4/0	0/4	CE 1, BuCyM 1, CyE 1, CyTopo 1	2 alive
Jubran *et al* (2004)[3]	4	1/3	2/0	1[b]/3	CTE	2 alive
Our cases	5	2/3	2/3	2/3	CDDP-CyM 2, MEC 2, TCyM 1	3 alive

[a]One alive after relapse.
[b]Pineal.
CARBOPEC = carboplatin + etoposide + cyclophosphamide; CTE = carboplatine + thiotepa + etoposide; TC = thiotepa + carboplatin; BcyE = busulfan + cyclophosphamide + etoposide; CE = carboplatin + etoposide; BuCyM = busulfan + cyclophosphamide + melphalan; CyE = cyclophosphamide + etoposide; CyTopo = cyclophosphamide + topotecan; CDDP-CyM = cisplatin + cyclophosphamide + melphalan; MEC = melphalan + etoposide + carboplatin; TCyM = thiotepa + cyclophosphamide + melphalan; DOD = dead of disease.

(nimustine, ranimustine), which are effective because of their capacity to cross the blood–brain barrier, have been used for retinoblastoma.[28,29]

We conclude that our treatment strategy that includes high-dose melphalan with autologous SCT and local irradiation is effective in patients with metastatic retinoblastoma without involvement of the CNS, although a wide variation in the HDC regimen made it difficult to judge the objective safety and efficacy of autologous SCT. A safer and more effective modality is required to better control CNS involvement. The possible risk of late sequelae secondary to additive toxicity by HDC and cranial radiation should be critically evaluated. Since metastatic retinoblastoma is a rare disease, a larger cooperative study is needed to clarify the safety and efficacy of this HDC strategy.

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