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Original Paper

High-dose Chemotherapy with Carboplatin, Etoposide and Cyclophosphamide Followed by a Haematopoietic Stem Cell Rescue in Patients with High-risk Retinoblastoma: a SFOP and SFGM Study

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This study investigates the role of high-dose chemotherapy with haematopoietic stem cell rescue as consolidation treatment in high-risk retinoblastoma (extraocular disease at diagnosis or relapse or invasion of cut end of optic nerve). 25 patients received high-dose chemotherapy including carboplatin (250 mg/m^2/day from day 1 to day 5 for the 6 first patients and 350 mg/m^2/day from day 1 to day 5 for the other patients), etoposide (350 mg/m^2/day from day 1 to day 5) and cyclophosphamide (1.6 g/m^2/day from day 2 to day 5) (CARBOPEC) followed by autologous haematopoietic stem cell rescue. 19 patients received this drug combination for chemosensitive extraocular relapse. The other 6 patients with histological high-risk factors were given this treatment as consolidation after enucleation and conventional chemotherapy. The three year disease-free survival was 67.1%. In 7 of the 9 relapsing patients, the first site of relapse was the central nervous system. All patients with central nervous system disease died except one. The main toxicity was haematological and digestive (mucositis and diarrhoea). 2 of the 13 evaluable patients had grade III and IV ototoxicity. One patient experienced an acute grade I reversible cardiotoxicity. The CARBOPEC regimen seems to be a promising therapeutic strategy in patients with high-risk retinoblastoma, especially those with bone and/or bone marrow involvement. This treatment did not improve the outcome of patients with central nervous system disease. © **1997 Elsevier Science Ltd.**

Key words: retinoblastoma, extraocular disease, high-hose chemotherapy
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INTRODUCTION

RETINOBLASTOMA USUALLY has a good prognosis in Western countries, but it is still a high-risk disease in some circumstances such as involvement of the cut end or subarachnoidal space of the optic nerve after enucleation [1, 2], orbital involvement [3] or distant metastatic disease [4, 5]. The prognosis is extremely poor in patients with central nervous system (CNS) disease. Therefore, new therapeutic strategies are needed in these high-risk patients.

Many studies have addressed the efficacy and tolerance of high-dose chemotherapy followed by autologous bone marrow transplantation in children with solid tumours especially in neuroblastoma [6, 7]. Cyclophosphamide has been shown to be very active as a single drug in extraocular retinoblastoma [8–10]. A more recent study of the activity of a combination of etoposide (VP16) and carboplatin in extraocular retinoblastoma showed a very high response rate [11]. The combination of high-dose VP16, carboplatin and cyclophosphamide has already been described as a high-dose

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chemotherapy regimen followed by autologous haematopoietic stem cell rescue in poor prognosis germ cell tumours in adults [12, 13]. Therefore, we used this chemotherapy combination as consolidation treatment in patients with high-risk retinoblastoma who had achieved complete or partial remission after initial conventional chemotherapy.

PATIENTS AND METHODS

Eligibility criteria

After parental informed consent, patients were eligible if they had metastatic disease (with or without CNS), isolated orbital disease initially or at relapse or histological high-risk factors after enucleation (involvement of cut end of optic nerve and/or its subarachnoidal space). In case of extraocular evaluable disease, at least a partial tumour response to conventional dose chemotherapy was required. Isolated positive CSF cytology, with normal central nervous system imaging, before CARBOPEC was not a criterion for exclusion.

According to these criteria, between October 1989 and September 1994, the intention to treat with this high-dose chemotherapy (HDCT) regimen was declared for 34 patients on a national level within the SFOP. 25 patients were included in this study. They were 19 males and 6 females. Their median age at the treatment by CARBOPEC was 34 months (range 9–125 months). Retinoblastoma was unilateral in 15 patients and bilateral in 10 patients. The time interval between initial diagnosis of retinoblastoma and treatment by CARBOPEC ranged from 4.5 to 120 months (median 16 months). Diagnosis of initial retinoblastoma and relapses has been asserted for all 34 patients by central histological review.

Included patients were divided into two groups:

Group 1. 6 patients received this high-dose chemotherapy as consolidation treatment after enucleation and adjuvant chemotherapy [2]. Their initial diagnosis and treatment are summarised in Table 1.

Group 2. 19 patients received this high-dose chemotherapy for extraocular chemosensitive disease at diagnosis or relapse. Initial conservative therapy, enucleation, histological risk factors and site of relapse are detailed in Tables 2 and 3 [11, 14–16]: isolated orbital relapse in 7 patients, bone and/or bone marrow metastases [17] without central nervous system disease in 8 patients and metastases with central nervous system disease in 4 patients. External beam irradiation on the orbit was performed before high-dose chemotherapy in 4 patients and on vertebral metastases in 1 patient who presented paraplegia.

2 patients out of the 19 had already been previously treated for recurrent disease. One had been treated for ectopic pineal retinoblastoma [18] by surgery, 4 courses of VP16-carboplatin and 45 Gy irradiation on the pineal region (patient no. 11). The other had been treated for two subsequent orbital relapses by chemotherapy and radiotherapy [3] (patient no. 17).

The disease status before treatment by high-dose chemotherapy of patients from groups 1 and 2 was: complete remission (17 patients), partial remission (7 patients) and stable disease (1 patient) (Tables 1 and 2). CSF cytology was positive at the time of treatment with CARBOPEC in 2 patients (nos. 5 and 18). The tumour response rate to VP16-carboplatin of patients from group 2 has been previously evaluated in a phase II study [11].

9 patients out of 34 at high-risk disease were not included in the study. They were 6 males and 3 females. Their median age was 31 months (range 14–61 months). Retinoblastoma was unilateral in 6 patients and bilateral in 3 patients. The high-risk criteria of these non-included patients were: involvement of the cut end of optic nerve (2 patients), isolated orbital relapse (3 patients), bone and/or bone marrow metastases without central nervous system disease (3 patients) and metastases with central nervous system disease (1 patient) The reasons for their exclusion were: tumour progression after conventional chemotherapy (6 patients), cardiotoxicity of previous chemotherapy contra-indicating the use of high-dose cyclophosphamide [19, 20] (1 patient). All these patients received conventional chemotherapy. 5 patients out of 9 received previous radiotherapy on the orbit. Parental refusal prevented 2 other patients from inclusion. High-risk criteria, reason for exclusion, treatment and follow-up are summarised in Table 4.

Haematopoietic stem cell harvesting

After a median number of 3 courses of chemotherapy (range 2–7), bone marrow was harvested under general anaesthesia in 24 patients. Haematopoietic stem cells were harvested in peripheral blood in one patient. Haematopoietic stem cell specimens were evaluated for cellularity (mononucleated cells) and for the presence of colony-forming unit-granulocyte macrophage: CFU-GM/Kg ranged from 0.25×10^4 to 129×10^4 (median 14×10^4). For patients with bone marrow metastases, harvesting was achieved when bone marrow aspirations and biopsies showed complete remission. The specimens were cryopreserved in DMSO and were not purged [21].

The high-dose chemotherapy regimen

For the first 6 patients, the carboplatin dosage was 250 mg/m^2/day. Considering the good tolerance of the treatment, the

Table 1. *CARBOPEC after enucleation and adjuvant chemotherapy (group* 1*)*

Patient	Initial diagnosis	Previous chemotherapy	Previous orbit irradiation (Gy)	Status before HDCT	Post-HDCT irradiation (in Gy)	Follow-up (months)
1	cut end of optic nerve	2 VP-CARBO/2 CADO	50	C R		NED† (50)
2	cut end of optic nerve	2 VP-CARBO/2 CADO		C R	50 (Orbit)	NED (8)
3	cut end of optic nerve	2 VP-CARBO/2 CADO	45	C R		NED (55)
4	cut end of optic nerve	2 VP-CARBO/2 CADO		C R	45 (Orbit)	NED (33)
5	cut end of optic nerve	2 VP-CARBO/2 CADO		'C R'*	24 (Spinal axis)	DRD‡ (9)
6	disruption of ocular globe	2 VP-CARBO/2 CADO	36	C R		NED (26)

CADO: Cyclophosphamide 300 mg/m^2 day 1 to day 5. Vincristine 1.5 mg/m^2 at day 1 and day 5. Doxorubicin 60 mg/m^2 at day 5. VP CARBO: Etoposide (VP16) 100 mg/m^2 day 1 to day 5. Carboplatin 160 mg/m^2 day 1 to day 5. *This patient had a positive CSF cytology before CARBOPEC. †NED: no evidence of disease. ‡DRD: disease-related death (after progression within CNS in this patient). HDCT, high-dose chemotherapy.

Table 2. Therapy at initial diagnosis of patients included for relapse or advanced disease (group 2)

Patient	Laterality	Initial conservative treatment		Histological risk factors after enucleation	Treatment after enucleation
		Left eye	Right eye		
7	unilateral	—	radiotherapy	right: anterior chamber	no
8	bilateral	no	no	left: unknown histology right macroscopic extrascleral	radiotherapy (both eyes)
9	unilateral	no	—	left: choroid and anterior chamber*	no
10	unilateral	no	—	left: prelaminar involvement of optic nerve	no
11	bilateral	radiotherapy	no	right: intrascleral	no
12	bilateral	radiotherapy	no	right: intrascleral*	no
13	unilateral	no	—	left: retrolaminar involvement of optic nerve	no
14	bilateral	radiotherapy	no	left: prelaminar involvement of optic nerve	no
15	unilateral	no	—	left no histological risk factor	no
16	bilateral	no	radiotherapy	left: anterior chamber + choroid+intrascleral	radiotherapy
17	bilateral	radiotherapy + cryotherapy	radiotherapy + cryotherapy	no enucleation	no
18	unilateral	—	no	right: retrolaminar involvement of optic nerve	no
19	unilateral	—	no	right: retrolaminar involvement of optic nerve choroid + anterior chamber	no
20	unilateral	—	no	right: no histological risk factor	no
21	unilateral	—	no	right: choroid + intrascleral involvement of cut end of optic nerve	pre CARBOPEC chemotherapy (bone marrow involvement at diagnosis)
22	bilateral	radiotherapy	radiotherapy	left: prelaminar involvement of optic nerve	chemotherapy
23	bilateral	—	radiotherapy	left eye: no histological risk factor	no
24	bilateral	radiotherapy	radiotherapy	no enucleation	no
25	unilateral	no	—	left: involvement of cut end of optic nerve	radiotherapy+chemotherapy

*These patients were referred to SFOP centres at time of relapse.

other patients received 350 mg/m^2/day. It was administered in a 1 h infusion from day 1 to day 5. Etoposide was given at the dose of 350 mg/m^2/day in a 1 h infusion from day 1 to day 5. The cyclophosphamide dosage was 1.6 g/m^2/day in a 3 h infusion with hyperhydration and bladder protection by uromitexan from day 2 to day 5. Haematopoietic stem cells were reinfused on day 7. Seven days after the beginning of this high-dose chemotherapy, 14 patients received recombinant human granulocyte cell stimulating factor (G-CSF) and 1 received recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF).

Response and toxicity criteria

Toxicity and tumour response were graded according to the WHO classification. Tumour response to CARBOPEC was based on three-dimensional measurements for imaging accessible sites of the disease by CT scan or MRI. Histological biopsies were performed in all accessible residual masses. Complete remission of the bone marrow metastatic disease [17] was defined by the disappearance of tumour cells in cytological aspirations and/or in histological biopsies of the bone marrow. Cerebrospinal fluid cytology was also evaluated.

Haematologic toxicity was evaluated as the duration of grade IV neutropenia, grades III and IV thrombocytopenia, the number of platelets and red cell transfusions. In case of central nervous system disease or intra-ocular tumour, platelets transfusions were recommended to maintain platelet counts above 50×10^9/l. Nephrological and otological toxicities were assessed by the measurement of glomerular filtration rate and audiometric tests [22]. Cardiotoxicity was assessed by heart ultrasonography (left ventricular fractional shortening).

Further therapy

Radiotherapy was applied to the orbit in 6 patients, to the central nervous system and spinal axis in 6 patients and to the frontal brain and cervical region in 1 patient (Tables 1 and 3). The timing of this radiotherapy was within 4–9 weeks after CARBOPEC.

Statistics

Kaplan–Meier product limit estimates were used to assess the probability of overall survival and disease-free survival. Survival curves were estimated from the date of intention-to-treat. Patients were censored when last known to be alive; when patients had progressive disease and were lost to follow-up, they were considered as dead when tumour progression was recognised. For assessment of the disease-free interval, the endpoint was the outcome of a local or a metastatic event.

RESULTS

Overall and disease-free survival (Figure 1)

Eight out of 25 patients relapsed within a median of 10 months after the high-dose chemotherapy (range 5–26 months) (Tables 1 and 3). 17 patients are alive without evidence of disease. The plateau phase of the disease-free survival curve was reached at 26 months with a disease-free survival of 67.1% (standard error 0.09). Median follow-up of disease-free survivors is 46 months (range 8–74 months). The distribution of these 17 patients according to the reason of their inclusion is: 5 patients alive with NED out of 6 treated

Table 3. CARBOPEC after conventional chemotherapy for chemosensitive relapses and advanced disease (group 2)

Patient	First site of relapse	Time of relapse† (months)	Previous chemotherapy	Previous irradiation	Status before HDCT	Post-HDCT irradiation	Follow-up (months)	Relapse post-ABMT
7	isolated orbital relapse	83	VP-CARBO CADO	orbit 45 Gy	PR		NED (74)	
8	isolated orbital relapse	20	VP-CARBO CADO	orbit 45 Gy	CR		NED (27)	
9	isolated orbital relapse	3	PE-CADO 5-FU-Cisplatin	orbit 43 Gy	SD		PD‡ (5)	Orbit
10	isolated orbital relapse	11	VP-CARBO CADO		PR	orbit (50 Gy)	NED (46)	
11	isolated orbital relapse	5	VP-CARBO CADO		PR	orbit (50 Gy)	NED (25)	
12	isolated orbital relapse	1	PE CADO	left orbit 45 Gy	PR	right orbit (50 Gy)	NED (69)	
13	isolated orbital relapse	3	VP-CARBO CADO		PR	orbit (50 Gy)	NED (57)	
14	bone metastasis chest wall	119	VP-CARBO CADO		CR		NED (50)	
15	bone metastases (humerus-tibia-femur)	13	VP-CARBO CADO		CR		NED (11)	
16	bone metastases (mandible)	27	VP-CARBO CADO		CR		NED (37)	
17	bone metastases (temple)	42	VP-CARBO CADO		CR		NED (36)	
18	bone metastases (radius + sphenoid)	15	VP-CARBO CADO	vertebral 15 Gy metastases	'PR'*	Spinal axis and CNS (36 Gy)	DRD (10)	CNS§
19	orbital relapse bone metastases (forehead)	6	PE CADO		CR	orbit (50 Gy)	NED (70)	
20	bone metastases (occiput)	8	VP-CARBO CADO		CR	Spinal axis and CNS (36 Gy)	DRD (13)	CNS
21	bone marrow metastases	advanced disease at diagnosis	VP-CARBO CADO		CR	Spinal axis and CNS (35 Gy)	DRD (20)	CNS
22	CNS disease	79	VP-CARBO CADO		CR	Spinal axis and CNS (35 Gy)	DRD (10)	CNS
23	CNS disease cervical nodes	89	VP-CARBO		CR	Frontal brain/cervical region	NED (63)	
24	spinal axis metastases	72	VP-CARBO VP-ENDOXAN		PR	Spinal axis and CNS (38 Gy)	DRD (26)	CNS
25	CNS disease	14	VP-CARBO CADO		CR	Spinal axis and CNS (36 Gy)	DRD (7)	CNS

*This patient had a positive CSF cytology before HDCT. †Time interval between diagnostic and relapse. ‡PD, progressive disease. §CNS, central nervous system. PE: Cisplatin 100 mg/m^2 at day 1; Teniposide (VM26) 160 mg/m^2 at day 3. CADO, cyclophosphamide 300 mg/m^2 day 1 to day 5; vincristine 1.5 mg/m^2 at day 1 and day 5; doxorubicin 60 mg/m^2 at day 5. VP endoxan: etoposide 50 mg/m^2 day 1 to day 5; cyclophosphamide 2 g/m^2 day 2 to day 4; VP CARBO, etoposide (VP16) 100 mg/m^2 day 1 to day 5; carboplatin 160 mg/m^2 day 1 to day 5; SD, stable disease; PR, partial recovery; CR, complete recovery.

Table 4. *Non-eligible high-risk patients*

Patient	Initial diagnosis	Chemotherapy	Irradiation	Reason for non-inclusion	Follow up (months)
26	Cut end of optic nerve	2 VP-CARBO/2 CADO	Orbit (26 Gy)	Progression (CNS)	DRD (12)
27	Orbital and bone relapse	2 VP-CARBO/2 CADO	No	Progression (CNS)	DRD (15)
28	Orbital relapse	6 courses of 8 drugs in 1	Orbit (50 Gy)	Parental refusal	DRD (38)
29	Metastases with CNS disease	2 VP-CARBO/2 CADO	No	Progression (CNS)	DRD (11)
30	Bone marrow metastases	2 VP-CARBO/2 VP-ENDOXAN	No	Cardiotoxicity	DRD (25)
31	Orbital relapse	2 VP-CARBO/2 CADO	No	Progression	DRD (4)
32	Orbital relapse	2 HD MTX-2HD Ara-C*+IT† 2 PE/2 CADO+IT	Orbit (50 Gy)	Parental refusal	Lost to follow up/ NED (51)
33	Cut end of optic nerve	2 VP-CARBO/2 CADO	Orbit (40 Gy)	Progression (CNS)	DRD (4)
34	Orbital and bone relapse	2 VP-CARBO/1 CADO	Orbit (50 Gy)	Progression (CNS)	DRD (4)

PE: cisplatin 100 mg/m^2 at day 1; teniposide (VM26). CADO: cyclophosphamide; vincristine 1.5 mg/m^2 at day 1 and day 5; doxorubicin 60 mg/m^2 at day 5. 8 DRUGS IN 1: vincristine 1.5 mg/m^2 at day 1; methylprednisone 300 mg/m^2 at day 1; lomustine 75 mg/m^2 at day 1; procarbazine 75 mg/m^2 at day 1; hydroxyurea 1500 mg/m^2 at day 1; cisplatin 100 mg/m^2 at day 1; aracytine-C 300 mg/m^2 at day 1; cyclophosphamide 300 mg/m^2 at day 1. VP endoxan: etoposide 50 mg/m^2 day 1 to day 5; cyclophosphamide 2 g/m^2 day 2 to day 4. VP CARBO: etoposide (VP16) 100 mg/m^2 day 1 to day 5; carboplatin 160 mg/m^2 day 1 to day 5. *2 HD MTX: two courses of high-dose methotrexate (8 g/m^2); 2 HD Ara-C: two courses of high-dose aracytine C. †IT intrathecal chemotherapy using methotrexate and aracytine C.

for histological high-risk factors after enucleation, 6 patients alive with NED out of 7 treated for isolated orbital relapse, 5 patients alive with NED out of 8 treated for metastases without central nervous system disease and 1 patient alive with NED out of 4 treated for metastases with central nervous system disease.

8 patients presented an extraocular relapse after CARBOPEC: one patient from group 1 (histological high risk factors) and 7 patients from group 2 (orbital and/or metastatic disease). The reason for their eligibility was: involvement of cut end of optic nerve in one patient (no. 5), isolated orbital relapse in one patient (no. 9), metastases without central nervous system disease in 3 patients (nos. 18, 20 and 21) and metastases with central nervous system disease in 3 patients (nos. 22, 24 and 25). 2 of these relapsing patients had positive CSF cytology at the time of treatment with CARBOPEC (nos. 5 and 18). The site of first relapse was the central nervous system in 7 patients and orbit in 1 patient (no. 9). One patient (no. 17) presented an intraocular relapse: he had been treated for bone metastases without central nervous system

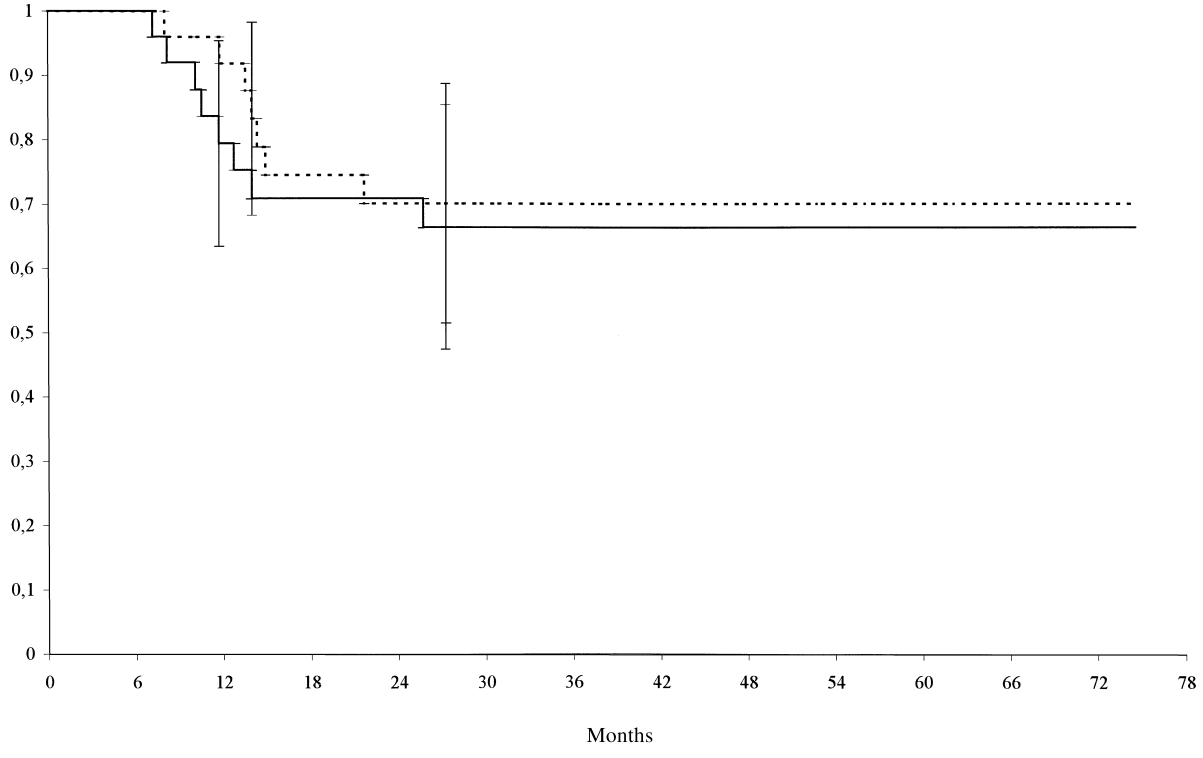

Figure 1. Overall survival (broken line) and disease-free survival (solid line) of the 25 patients treated by CARBOPEC regimen. The plateau phase of the disease-free survival (DFS) curve was reached at 26 months with a DFS of 67.1% (standard error 0.09).

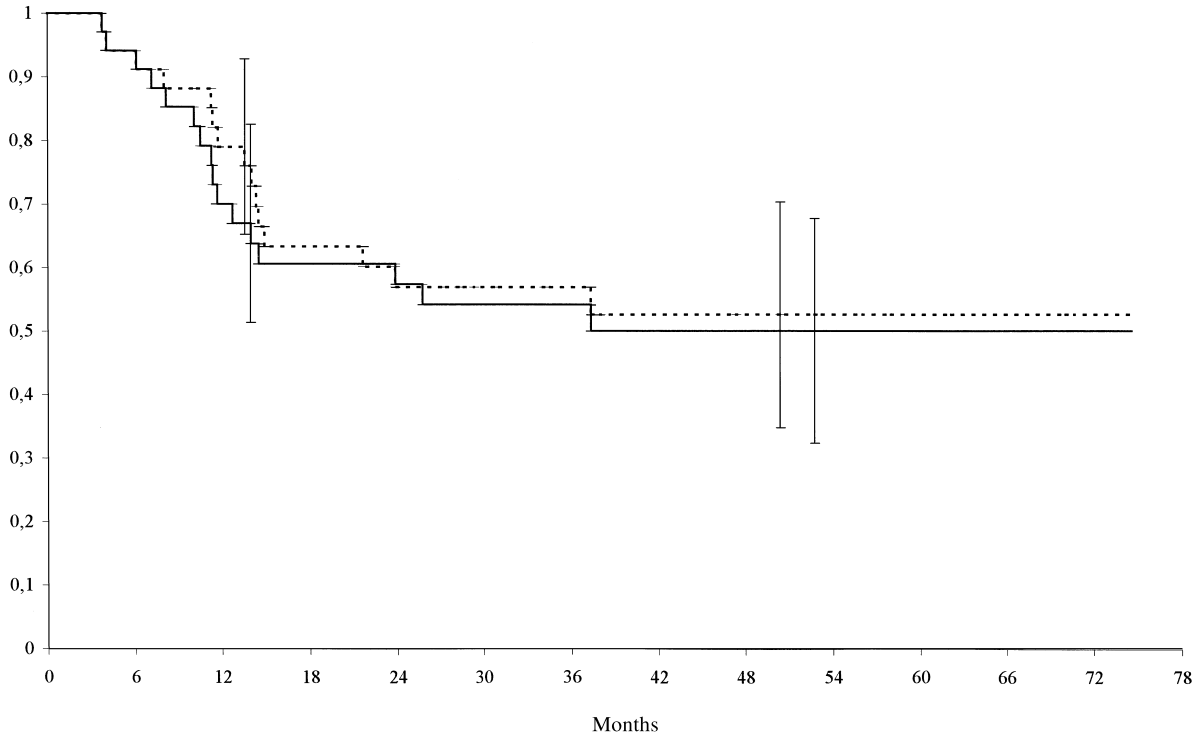

Figure 2. Overall survival (broken line) and disease-free survival (solid line) of the 34 high-risk patients. 9 patients among 34 did not receive this treatment. The reasons for their exclusion were: tumour progression after conventional chemotherapy (6 patients), cardiotoxicity of previous chemotherapy contraindicating the use of high-dose cyclophosphamide (1 patient) and parental refusal (2 patients). The plateau phase of the disease-free survival (DFS) curve is reached at 37 months with a DFS of 50% (standard error 0.09).

disease. The eye relapse occurred 24 months after HDCT. Local therapy using a radioactive disc was performed. This patient is alive without evidence of disease and a follow-up of 34 months after HDCT.

8 patients among the 9 excluded died of retinoblastoma progression in the central nervous system with a median of 12 months from the date of the intention to treat (range 4–51 months). One patient (no. 32) was lost to follow-up, without progressive disease, at 51 months from the date of the intention to treat (Table 4). The plateau phase of the disease-free survival curve, of all 34 high-risk patients, was reached at 37 months with a disease-free survival of 50% (standard error 0.09) (Figure 2).

Tumour response

Tumour response was evaluable in 8 sites in 8 patients. 6 of them had isolated orbital residual image, the significance of which is difficult to interpret. The 17 other patients were in complete remission before treatment by CARBOPEC. Median time for evaluation after CARBOPEC was 5 weeks (interval 4–9 weeks). 2 patients showed complete remission (nos. 7 and 18) and 6 patients a stable disease (nos. 9, 24, 10, 11, 12 and 13). CSF cytology remained positive after treatment with CARBOPEC in 2 patients (nos. 5 and 18).

Toxicity

The median duration of grade IV neutropenia was 14 days (range 10–47). All patients had fever: the duration of a temperature above 38°C ranged from 2 to 19 days (median 8 days). There were 4 positive blood cultures. One patient (no. 9) had a grade IV systemic infection due to *Candida albicans* and needed to be transferred to an intensive care unit. All patients received parenteral antibiotic and antifungal therapy: the duration of parenteral antibiotic therapy ranged from 5 to 45 days (median 18 days). Intravenous antifungal drugs were administered over a median duration of 11 days. Median duration of grade IV thrombocytopenia was 19 days (range 11–39 days). There was no grade IV haemorrhage. The number of platelet transfusions ranged from 2 to 19 (median 4) and the number of erythrocyte transfusions ranged from 2 to 9 (median 4). All patients except one had mucositis and needed a morphine-based therapy. 14 patients had a grade III diarrhoea; 1 patient had severe diarrhoea due to cryptosporidia infection.

12 patients were evaluable for long-term nephrotoxicity: there was no decreased glomerular filtration rate. 13 patients were evaluable for ototoxicity: two (nos. 24 and 13) developed, respectively, grade III and grade IV ototoxicity. Both had previously received cisplatin. Only 1 patient out of the 25 evaluable developed acute grade I reversible cardiac toxicity (patient 7) and received a digitalic-based therapy for eight weeks. No haemorragic cystitis, veno-occlusive disease or interstitial pneumonia occurred in these patients.

DISCUSSION

Extra-ocular disease and involvement of the cut end of optic nerve in retinoblastoma are still high-risk situations. Retinoblastoma is a highly chemosensitive disease. The use of high-dose chemotherapy including various combinations of cyclophosphamide, etoposide, cisplatinum, vincristine, doxorubicin and/or melphalan, sometimes associated with total body irradiation, has already been reported in individual

cases in retinoblastoma [23–25]. However, the long-term outcome of a series of patients treated by a single protocol of high-dose chemotherapy has never been assessed.

The central nervous system is the main site of failures: 7 of our patients relapsed in the central nervous system. 3 received this high-dose chemotherapy for metastases involving the central nervous system. 3 other patients were treated for metastases without central nervous system disease: 2 (nos. 18 and 20) had a parameningeal intracranial bone extension (patient no. 18 who also presented a positive CSF cytology before CARBOPEC) and one (no. 21) had involvement of the cut end of the optic nerve at diagnosis of retinoblastoma, for which he did not receive radiotherapy on the orbit before CARBOPEC. The seventh patient (no. 5) who relapsed in the central nervous system was treated for histological high-risk factors and also showed positive CSF cytology before CARBOPEC. This high-dose chemotherapy regimen was used in 2 patients with positive CSF cytology since isolated positive CSF cytology, without progressive disease on central nervous system imaging, was not considered as failure to respond. Currently and in the light of these first results, the occurrence or persistence of positive CSF cytology is considered as failure to respond and these patients are not treated by this high-dose chemotherapy regimen.

Despite initial tumour response to conventional chemotherapy, the consolidation by active drugs with central nervous system radiotherapy did not prevent relapses within the central nervous system in our patients. Initial treatment of patients with central nervous system disease often included doxorubicin which does not cross the blood–brain barrier and therefore is not effective in central nervous system sites of retinoblastoma. This might partially explain the failure of the treatment in these patients.

The effectiveness of high-dose chemotherapy as consolidation after enucleation, adjuvant chemotherapy and local radiotherapy on the orbit region in case of involvement of cut end of optic nerve is not easy to assess. We used CARBOPEC in these patients because of the high risk of central nervous system relapse [3]. In case of isolated orbital relapse, consolidation with CARBOPEC and external beam irradiation of the orbit seems to be effective with an encouraging rate of long-term disease-free survivors (7 patients are alive with NED out of 8).

However, comparable results have been reported with a combination of conventional chemotherapy and radiotherapy in patients with involvement of the cut end of the optic nerve or with isolated orbital disease [5, 26]. High-dose chemotherapy in these two particular indications seems to be a therapeutic alternative for extra-ocular disease in retinoblastoma. The good tolerance of this high-dose chemotherapy combination resulted in a relative short duration of treatment by conventional dose chemotherapy: median duration 4 months (range 3.6–5 months) in our patients.

Patients with distant metastatic disease, especially in the bone and bone marrow without central nervous system involvement, are seldom cured with conventional chemotherapy [5]. In 4 of our 8 patients, distant metastatic disease did not involve skull bones. 3 of these 4 patients are alive with NED (the fourth [no. 21] relapsed in the central nervous system). The 4 other patients had metastatic disease within the skull: one of them (no. 17) had a temple extracranial tumour and the three others had intracranial bone metastases with negative CSF cytology and no central nervous system disease. 2 of these 3 patients with intracranial bone metastases (nos. 18 and 20) died after relapse in the central nervous system; the third one (no. 19: frontal bone metastases and orbital disease) had his forehead intracranial tumour included in the orbit irradiation volume. This patient is alive with NED. The central nervous system relapses of 2 patients with intracranial bone metastases might lead to the hypothesis of parameningeal extension in extraocular retinoblastoma and thus the relevance of local radiotherapy.

The role of external beam irradiation in high-risk retinoblastoma depends on the location of the disease. External beam irradiation of the orbit region still has an important role in the treatment of the involvement of the cut end of optic nerve after enucleation and orbital relapse. Central nervous system irradiation, as is currently performed, does not cure central nervous system disease. Despite the high risk of central nervous system involvement in retinoblastoma, the relevance of radiotherapy to the central nervous system [27] must be debated in very young children because of the high risk of central nervous system irradiation related neurotoxicity [28]. We think that local radiotherapy may be combined with the treatment of patients with intracranial bone metastatic extension.

The main acute toxicities of this high-dose chemotherapy regimen were haematological and digestive. Myelosupression due to this high-dose chemotherapy regimen might be shortened by the use of peripheral blood haematopoietic stem cells and haematopoietic growth factors.

The long-term toxicity related to carboplatin was only otological in our evaluable patients. Both patients with grade III or IV ototoxicity had received cisplatin-based chemotherapy before treatment with CARBOPEC. Finally, cyclophosphamide, carboplatin and VP16 are known to be mutagenic and may be responsible for second tumours [29, 30] especially in patients with a constitutional abnormality of the retinoblastoma gene. The patients treated by this drug combination should be carefully followed up.

We conclude that the combination of high-dose carboplatin, etoposide and cyclophosphamide is effective in patients with high-risk retinoblastoma, especially those with chemosensitive distant metastatic disease, but without involvement of the central nervous system. CNS disease cannot be cured with this high-dose chemotherapy combination. Acute toxicity is manageable. Long-term toxicity and especially the occurrence of a second tumour must be carefully investigated in these patients.

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