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METASTATIC RETINOBLASTOMA: SINGLE INSTITUTION EXPERIENCE OVER TWO DECADES

CORRESPONDENCE:

Maria Antonietta De Ioris MD

Ospedale Pediatrico Bambino Gesù IRCCS

Piazza S.Onofrio 4 , 00165 Roma, Italy

Tel: +39 06 6859; Fax+39 06 6859

deioris@opbg.net

Raffaele Cozza MD ¹, Maria Antonietta De Ioris MD ¹, Ilaria Ilari MD PhD ¹, Rita Devito MD ², Paola Fidani MD ¹, Luigi De Sio ¹, Francesca Demelas MD ¹, Antonino Romanzo MD ³, and Alberto Donfrancesco ¹

¹Division of Pediatric Oncology Unit, Ospedale Pediatrico Bambino Gesù, Rome, Italy

²Department of Pathology, Ospedale Pediatrico Bambino Gesù, Rome, Italy

³Division of Ophthalmology, Ospedale Pediatrico Bambino Gesù, Rome, Italy

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ABSTRACT

Background: Metastatic spread in retinoblastoma is a rare occurrence in developed countries but still associated with a poor prognosis.

Patients and Methods: Medical records of all metastatic retinoblastoma diagnosed during a 20-year period were retrospectively reviewed.

Results: 6 patients out of 104 presented a metastatic disease with an incidence at diagnosis of 2%. Three had a metastatic disease at diagnosis, one patient a trilateral retinoblastoma and 2 a metastatic spread after enucleation. All but one were sporadic retinoblastoma. Central Nervous System (CNS) involvement was reported in 5 patients while one patient had an intra-orbital lesion and bone and bone marrow spread. Different treatment strategies were administered based on local treatment plus chemotherapy and radiotherapy with or without high dose chemotherapy. Ifosfamide/carboplatin/etoposide (ICE) regimen was administered in 3 patients resulting in a partial response. Out of 6 patients, 4 died and 2 patients are alive at 60 and 63 months from diagnosis. Both children with a long follow-up were treated with high dose chemotherapy. All but one patients with CNS involvement died; the survivor was a patient with pineal involvement..

Conclusion: This retrospective review confirms a curable strategy based on local treatment and conventional plus high dose chemotherapy. Patients with CNS involvement remain incurable.

INTRODUCTION

Retinoblastoma is the most common childhood intra-ocular cancer accounting for approximately 4% of all paediatric malignancies. The survival is over 95% in developed countries whereas it is estimated that only 50% of children with retinoblastoma survive worldwide. This discrepancy is due to earlier detection in developed countries whereas retinoblastoma is often detected when extra-ocular or metastatic spread was occurred in developing countries. [1]

Overt extra-ocular extension without metastasis presents a 5-year overall survival of 55-80 % while the metastatic disease had a poor prognosis with conventional strategies. [2-3] Recently, in developed countries, an intensive treatment based on conventional and high dose chemotherapy is proposed to metastatic patients. [4-6] However metastatic retinoblastoma still remain a clinical challenge in paediatric oncology.

The aim of this report is to describe the clinical-pathological characteristics, treatment and the outcome of patients with metastatic retinoblastoma diagnosed during a 20-year period at Ospedale Pediatrico Bambino Gesù (OPBG).

PATIENTS AND METHODS

Between January 1988 and December 2007, 104 retinoblastoma patients were diagnosed or referred to OPBG; out of them six patients presented a metastatic disease.

The clinical records of metastatic patients were reviewed to identify the clinical characteristics and a complete clinical history. The retrospective review included data concerning clinical presentation, age, sex, family history of retinoblastoma and/or other malignancies, ocular stage according to Reese Ellsworth system, anatomic sites of metastases and treatment at diagnosis and at relapse including ophthalmic therapy, chemotherapy and radiotherapy. All patients were restaged according to current International Retinoblastoma Staging System (IRSS) proposed by Chantada et al. in 2006. [7]

The slides of enucleated eyes were reviewed retrospectively by the same pathologist (RD). Tumour extension within the choroids, sclera and optic nerve was reported.

RESULTS

During a 20-year period 104 retinoblastoma patients were treated at OPBG from those, 6 cases presented a metastatic disease. Out of 6, 2 had a metastatic disease at diagnosis, one patient had a trilateral retinoblastoma, 2 children with unilateral retinoblastoma presented a metastatic spread after enucleating and the later patient with bilateral retinoblastoma presented a metastatic progression during conservative treatment. All but one was sporadic retinoblastoma; the hereditary retinoblastoma was a trilateral retinoblastoma.

The incidence of metastatic disease in this series is 6/104 (5.8%); during the study period 101 new diagnoses were performed at OPBG and of them only 2/101 (2%) presented a metastatic spread.

Out of 6 children, 3 showed a bilateral and 3 a unilateral disease.

The characteristics of patients including stage according to the Reese-Ellsworth group, stage, local therapy and treatment for metastatic disease were resumed in table 1.

Tab 1: Patients characteristics and treatment at metastatic spread

Pt	Sex	Age	IE	RE Stage	Pathological Risk Factors	Stage	TID	Metastatic Disease	Metastatic Site	Therapy (for Metastatic Disease)	Outcome
1	F	24	R	Vb	Scleral, extrascleral and nerve involvement	NE	E	6 m from dx	Orbit, CSF, meningeal	Chemo/XRT	Dead (28)
2	M	46	B	NK	NK	NE	E, Chemo	12 m from dx	CSF, meningeal	Chemo	Dead (5)
3	M	110	R	Vb	Massive choroid, scleral, extra scleral and nerve involvement	IV b3	E	at dx	CSF	Chemo/XRT	Dead (8)
4	F	59	B	Vb and III	Scleral, extrascleral and nerve involvement	IV b3	E, OT	at dx	CSF, meningeal	Chemo/XRT/HDC	Dead (16)
5	M	3	B	L IIIb, R Vb	NK	NE	E, OT	15 m from dx	Pineal	Chemo/HDC/XRT	Alive (63+)
6	F	18	L	Vb	Choroid infiltration	NE	E	6 m from dx	Orbit, bone, bone marrow	Chemo/HDC/XRT	Alive (60+)

Legend: Pt, patient; Age at dx in months; IE, involved eye; dx, diagnosis; m, month; R, right; L, left; B, bilateral; RE, Reese-Ellsworth; NK, not known; Stage according to International Retinoblastoma Staging System only for metastatic patients at diagnosis, NE not evaluable; TID, treatment of intra-ocular disease; E, enucleation; OT, ophthalmic treatment; Chemo, chemotherapy; CSF, cerebrospinal fluid; XRT, radiotherapy; HDC, high dose chemotherapy; Outcome months from metastasis diagnosis

Two patients (patient 3 and 4) presented a metastatic spread to CNS at diagnosis; the age was 110 and 59 months respectively. Enucleation was performed in patient 3 with unilateral disease while the bilateral patient (patient 4) underwent enucleation after 4 courses of chemotherapy. In both patients two courses of ifosfamide, carboplatin and etoposide (ICE, ifosfamide $1800 \text{ mg/m}^2/\text{day}$ for 5 days with a total dose 9000 mg/m^2 , carboplatin at $400 \text{ mg/m}^2/\text{day}$ for 2 days with a total dose 800 mg/m^2 and etoposide at $100 \text{ mg/m}^2/\text{day}$ for 5 days with a total dose 500 mg/m^2) were administered resulting in partial response. In patient 3, the ICE courses were followed by two course of cyclophosphamide, etoposide, carboplatin and thiotepa (CECAT) with a concomitant intrathecal chemotherapy based on metotrexate (MTX), cytarabine (Ara-C) and prednisone (PDN) during ICE and CECAT courses but he presented a progressive disease after the second CECAT course with a retro bulbar lesion. Although radiotherapy was administered on bulky disease up to $39,6 \text{ Gy}$ with cranial-spinal prophylaxis, this patient had a rapid meningeal spread and died 8 months from diagnosis. The patient 4 received two courses based on vincristine, doxorubicin and cyclophosphamide after the first 2 ICE courses. After enucleation of most affected eye, 2 courses based on cyclophosphamide and etoposide and radiotherapy on orbit up to 45 Gy were administered. He finally underwent a consolidation regimen based on etoposide 600 mg/m^2 , thiotepa 750 mg/m^2 and cyclophosphamide 120 mg/kg (ETC) followed by autologous bone marrow transplantation (ABMT) and Peripheral Blood Stem Cell (PBSC) rescue. The patient relapsed 5 months from the end of treatment on SNC and bone marrow and died 16 months after diagnosis.

An 18-month child (patient 5) had a hereditary trilateral retinoblastoma. He was treated for a bilateral retinoblastoma diagnosed at 3 month of age, with left eye enucleation and ophthalmic therapy. This asymptomatic patient presented a pineal mass on a routine magnetic resonance imaging (MRI) performed 15 month from initial diagnosis. Conventional chemotherapy (etoposide, MTX, vincristine and cyclophosphamide) and tandem courses of high dose chemotherapy (carboplatin/etoposide and thiotepa/L-PAM) followed by PBSC rescue according to AIEOP SNC 9501 protocol were administered followed by cranial radiotherapy (34 Gy with a boost up to 42Gy on pineal region) resulting in a complete remission without surgery. The child is alive at 63 months from metastatic spread diagnosis.

Three patients were treated after a metastatic spread. Two patients (patient 1 and 6) with unilateral retinoblastoma presented a metastatic relapse 6 months from diagnosis and the last patient with bilateral retinoblastoma had a metastatic spread after 12 months from diagnosis. The first patient (patient 1), prior treated only with enucleating at OPBG, presented an intra-orbital relapse. After a complete removal of orbital lesion, the parents refused further chemotherapy and radiotherapy treatment. She presented a second relapse 16 months from diagnosis and was treated with two carboplatin/etoposide courses and a cyclophosphamide, vincristine and doxorubicin course with a partial response. After partial removal of intra-orbital lesion and 3 etoposide, vincristine and cyclophosphamide courses, a local progression and bone metastasis were observed. She died 28 months from onset. The patient 6 presented an intra-orbital relapse with metastatic spread to bone and bone marrow after enucleating. After surgical removal of intra-orbital lesion and one carboplatin/doxorubicin/cyclophosphamide course, she was referred to OPBG. She received 4 ICE courses achieving a complete remission and then high dose chemotherapy based on ETC with PBSC rescue and radiotherapy up to 45 Gy on orbital region were administered. She is alive at 60 month from diagnosis.

The latter patient (patient 2), treated in another hospital for bilateral retinoblastoma, was admitted in OPBG Emergency Room for seizure due to a menigeal spread. He received a chemotherapy

regimen based on cyclophosphamide plus doxorubicin courses and cisplatin plus teniposide courses with intrathecal chemotherapy (MTX/Ara-C/PDN); this patient presented a resistant disease with a rapidly progression at CNS and died 5 months since diagnosis.

Out of 6 patients, 4 died of progressive disease within 2 years from diagnosis and 2 patients are alive at 60 and 63 months since diagnosis. Both children with a long follow-up were treated with enucleation and/or focal ophthalmic therapy; conventional chemotherapy and high dose chemotherapy followed by PBSC rescue; radiotherapy was administered on bulky disease. All patients with CNS spread –except of the trilateral retinoblastoma- died.

ICE regimen, at least 2 courses, were administered in 3 patients resulting in a partial response in all; two patients with CSF disease presented a negative CSF after 2 ICE courses while the patient with hematogenous metastasis presented a complete response in all metastatic sites after 4 ICE courses. ICE regimen was well tolerated with a manageable toxicity and good dose intensity. A total of 8 ICE course were administered with a median time from courses of 28.5 days (range 21-37).

Ocular stage according to Reese Ellsworth system and pathological risk factors were reported for 5 out of 6 patients; all patients presented an advanced Reese Ellsworth stage and at least one pathological risk factor (Table 1). All patients presented a stage IV according to the recent staging system proposed for retinoblastoma by Chantada et [7] (Table 1); patients with regional extension according to recent staging system were excluded.

DISCUSSION

Metastatic spread in retinoblastoma is a rare occurrence in developed countries. Jubran et al [8] reported an overall occurrence of 4.8% in a series of patients treated at the Children's Hospital Los Angeles while extra ocular retinoblastoma accounted of 20% of all retinoblastoma in a Brazilian series [2] and extra-orbital metastatic spread was observed in 11% in a Mexican series [3]. In developing countries, the higher incidence of metastatic spread is due to a late referral and consequently a delayed diagnosis as suggested by some authors. [2,3,9] In our series we reported an

overall occurrence of 5.8% while 2% (3/101) of new diagnosed retinoblastoma presented a metastatic spread at onset. The two patients with metastatic spread at diagnosis were older than whole retinoblastoma population, median age 13 month, confirming the pivotal role of early diagnosis to prevent metastatic spread. A prompt diagnosis with an accurate detection of pathological risk factors followed by adapted chemotherapy prevents metastatic spread as suggested by some authors in the last decades. [3,10-12].

As suggested by Jubran et al [8] the patterns of metastatic disease are four including trilateral retinoblastoma, regional metastasis, extension into the CNS, and distant metastasis with different outcome.

Orbital and loco regional metastasis are curable with intensive chemotherapy, surgery and local radiotherapy. [13-16] Moreover, in the recent IRSS [7], regional extension is not considered as metastatic disease.

Trilateral retinoblastoma is diagnosed in 3-4% of patients occurring more frequently in patients with bilateral disease and/or family history of retinoblastoma who are less than 1 year of age; in these patients a screening for a pineal tumour is suggested. [1, 17] The trilateral retinoblastoma was successfully treated and the long follow-up confirms the chance to cure trilateral retinoblastoma with an aggressive treatment as reported by Jubran et al [10] although large series (more than 5 patients) reported a discouraging outcome. [17-20]

All patients with CNS metastasis died, except of the trilateral retinoblastoma. As reported in recent published series, CNS patients succumb for progressive disease while survivors are anecdotal [2, 3, 8-9] despite intensive treatment including high dose chemotherapy [6,8]. The CNS involvement remains major prognostic factor and actually an effective strategy to cure have not been yet identified.

Extra CNS metastatic disease presents a poor prognosis with conventional chemotherapy [2, 14] while a multidisciplinary treatment that includes a consolidation with high dose chemotherapy seems a promising strategy [4-6, 20-21] as observed in one relapsed disseminated retinoblastomas.

The current guidelines propose for metastatic retinoblastoma an intensive chemotherapy treatment plus high dose chemotherapy followed by PBSC rescue or ABMT and radiotherapy on bulky disease.[13] Recently, a COG protocol has started accrual in COG centres and some international institution; this protocol according to Memorial Sloan Kattering experience [5] is based on induction phase with vincristine, cisplatin, etoposide and cyclophosphamide followed by high dose chemotherapy based on carboplatin, etoposide and thiotepa plus radiotherapy.

Considering our experience with ICE regimen and literature data, we proposed four ICE courses in extraocular retinoblastoma; this intensive chemotherapy was followed by radiotherapy on bulky disease plus high dose chemotherapy followed by PBSC rescue or ABMT in metastatic patients. From 1998 ICE regimen was proposed to metastatic retinoblastoma as adopted for different neuroectodermal tumours [22-23] at OPBG with a clinical response in all cases. In our experience the addition of ifosfamide seems improve the well-known effectiveness of carboplatin/vepeside [25]; recently Antoneli et al [15] improved the survival of retinoblastoma with orbital involvement with the addition of ifosfamide/etoposide to chemotherapy with etoposide/cisplatin.

We have choosen as conditioning regimen thiotepa in association with etoposide and cyclophosphamide. Different conditioning regimens were used for metastatic retinoblastoma. [4-6, 20-21]. Thiotepa seems an interesting option considering its good penetration of cerebrospinal fluid [29] and it was integrated in conditioning regimen with carboplatin alone or with etoposide [5, 21] or cyclophosphamide/mephalan [20] or cyclophosphamide and vepeside. [8]

As Los Angeles group [8] we did not include platinum compound in conditioning chemotherapy in order to minimize potential hearing problems in patients with an existing visual impairment and yet treated with carboplatin in induction phase. In the induction phase we have preferred carboplatin than cispatin for the less important ototoxicity.

This retrospective review of metastatic spread in retinoblastoma patients is carried out on a population diagnosed during a long time span and consequently different treatments were proposed;

moreover the criteria for staging are diverse during this long period. Nevertheless only patients stage IV according to recent IRSS were considered for this report.

In conclusion the occurrence of metastatic spread in retinoblastoma is rare and associates with a delayed diagnosis even in developed countries. A multidisciplinary treatment strategy that includes an intensive induction phase and high dose chemotherapy in patients with disseminated retinoblastoma (bone, bone marrow, CNS) may improve the outcome. However the prognosis of patients with CNS involvement remains dismal and need new therapeutic option.

Further cooperative studied would clarify the best therapeutic strategy in different metastatic patterns.

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