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Chemotherapy For Retinoblastoma
A Current Topic

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Abstract

Retinoblastoma is the most common primary intraocular tumour in children, with an incidence of 1 in 15 000 live births. Treatment strategies for retinoblastoma have gradually evolved over the past few decades. There has been a trend away from enucleation (removal of the eye) and external beam radiation therapy toward focal 'conservative' treatments. Every effort has been made to save the child's life with preservation of eye and sight, if possible.

Primary enucleation continues to be the commonly used method of treatment for retinoblastoma. It is employed in situations where eyes contain large tumours, long standing retinal detachments, neovascular glaucoma and suspicion of optic nerve invasion or extrascleral extension. Most of these eyes either have or are expected to have no useful vision. Radiation therapy continues to be an effective treatment option for retinoblastoma. However, external beam radiotherapy has unfortunately been associated with secondary non-ocular cancers in the field of radiation (primarily in children carrying the RB-1 germline mutation). Ophthal-

mic plaque brachytherapy has a more focal and shielded radiation field, and may carry less risk. Unfortunately, its applicability is limited to small to medium-sized retinoblastomas in accessible locations. Cryotherapy and transpupillary thermotherapy (TTT) have been used to provide control of selected small tumours. TTT is an advanced laser system adapted to the indirect ophthalmoscope which provides flexible nonsurgical treatment for small retinoblastomas.

Recent research in the treatment of retinoblastoma has concentrated on methods of combining chemotherapy with other local treatment modalities (TTT, radiotherapy, cryotherapy). This approach combines the principle of chemotherapeutic debulking in paediatric oncology with conservative focal therapies in ophthalmology. Termed chemoreduction, intravenous or subconjunctival chemotherapy is used to debulk the initial tumour volume and allow for focal treatment with TTT, cryotherapy and plaque radiotherapy. Cyclosporin has been added to the chemotherapy regimen in several centres.

Other clinical settings where chemotherapy is considered are situations where the histopathology suggests a high risk for metastatic disease and where there is extraocular extension. There is no consensus that chemotherapy is needed when choroidal invasion is observed on histopathology. However, in patients where the retinoblastoma is noted beyond the cut end of the optic nerve or if there is disruption of the sclera with microscopic invasion of the orbital tissue, treatment has been helpful. Systemic and intrathecal chemotherapy with local and cranial radiotherapy has improved the survival of these patients. Most recently, the use of new chemotherapy modalities with haematopoietic stem cell rescue or local radiotherapy has increased the survival of patients with distant metastasis. Nevertheless, the prognosis of patients with central nervous system involvement is still poor.

1. Current Treatment Options for Retinoblastoma

Although retinoblastoma is the most common primary intraocular tumour in children, the treatment of this disease is a complex topic. Therapeutic plans usually require a multidisciplinary approach by a team consisting of ocular oncologists, paediatric oncologists and radiation oncologists. The most important goal is to save the child's life, followed by preservation of vision and the cosmetic use of the eye. Therapy is tailored to each patient, considering the size, location, number, laterality of tumour(s), the condition of the other eye, risk for metastasis and secondary cancers, and systemic status of the patient.[1-11] Treatment options include enucleation, external beam radiotherapy (EBRT), brachytherapy, laser photocoagulation, cryotherapy, thermotherapy, chemothermotherapy, intravenous chemoreduction, subconjunctival chemoreduction, and systemic chemotherapy for metastasis.[1-11]

Primary enucleation is the commonly used method of treatment for retinoblastoma. We recommend primary enucleation for patients with unilateral retinoblastoma in the following situations: eyes containing large tumours (20mm in base, 10mm in height), long standing retinal detachment, neovascular glaucoma, iris neovascularisation or seeding, suspicion of optic nerve or choroid invasion or extrascleral extension, and no expectation for useful vision.[12] Primary enucleation allows cure rates of 92% in most patients with unilateral retinoblastoma.[12,13] In bilateral retinoblastoma, standard therapy was enucleation in the advanced eye and EBRT in the less advanced eye.[14] However, in recent years this standard has changed with the advent of new investigational eye preserving treatment modalities.[1-3,14]

EBRT has been an effective treatment option for retinoblastoma.[15-18] In a recent series by Hungerford et al.[19] ocular salvage rate after EBRT was significantly improved compared with other series.[15-17] The rate of ocular salvage depended on the stage of the disease and the use of focal therapy for limited recurrence.[19-22] Recurrence after EBRT is a rare problem which usually develops within 4 years of treatment. It appears to be related to the stage of the disease and tumour size at the time of treatment.[19-22]

Abramson[23] suggested that children carrying the RB-1 germline mutation treated with EBRT had a 35% cumulative risk of a second non-ocular cancer in the radiation field by 30 years of age, whereas children who did not carry this germline mutation had a 6% risk. Cosmetic orbital deformities and cataracts occur in 90% of EBRT-treated retinoblastoma patients.[23] The cumulative probability of death from these second non-ocular neoplasms was reported to be 26% at 40 years.[24-26] This risk was also found to be dependent upon the age of the patient at the time of irradiation. Patients younger than 12 months had a much poorer prognosis than patients older than 12 months.[23] In contrast, Mohney et al.[27] found similar rates of secondary malignancies (30% at 40 years), but these malignancies were mostly outside the field of irradiation. They concluded that 'radiation technique and dosage' may have contributed to previous findings.[27]

Brachytherapy offers a more focal and shielded radiation field. The use of low energy ophthalmic plaques (e.g. ^{125}I, ^{103}Pd) should reduce the amount of irradiation to the orbital bones and soft tissues.[28-30] Solitary tumours up to 16mm in diameter were treated with plaques.[28] The location of the tumour is also an important factor. Plaque therapy of posterior pole tumours increased the risk of radiation retinopathy and optic neuropathy. Although plaque brachytherapy has been used as a primary treatment, it is more commonly a secondary therapy.[28] In certain cases, tumour control and ocular salvage can be achieved when the only other option is enucleation.

Argon, diode and xenon arch lasers are used for photocoagulation. Indications include tumours 4.5mm or less in base and 2.5mm or less in thickness (without vitreous seeds). It is directed to delimit the tumour and coagulate the tumour's vascular supply. The introduction of indirect ophthalmoscope laser photocoagulation systems and chemoreduction regimens have increased the utility of lasers for the treatment of retinoblastoma.[30]

Cryotherapy and heat-inducing thermotherapy modalities provide tumour destruction using infrared radiation, microwaves or ultrasound.[31] The goals are to deliver temperatures of 42 to 60°C for specific time durations. These temperatures can leave a gray-white scar at the site. Consequently, the settings of the laser (power and time) are modulated for each tumour. Secondary tractional or vaso-occlusive complications can occur within the choroid, retina, and optic nerve,

In selected patients, cryotherapy alone can be effective in the treatment of intraocular retinoblastoma.[31,32] Cryotherapy is usually employed to control local disease located at the equator or anterior to the equator, and when the tumour is mostly confined to the sensory retina. The best results with this therapy are seen in tumours measuring 3.5mm or less in base and 2mm or less in thickness without seeds. Clearly, cryotherapy is not recommended when there are extensive vitreous seeds over a localised retinal lesion.[31,32]

Recently, a number of researchers have become interested in the treatment of retinoblastomas by combining chemotherapy with other local treatment modalities; this has been termed 'chemoreduction'.[1-3,14] This approach combines the principle of chemotherapeutic debulking in paediatric oncology with the relatively noninvasive focal therapies used in ophthalmology. The driving force behind these new approaches is to avoid enucleation, and/or EBRT, to save vision, and to salvage more eyes. Chemoreduction also offers the potential to decrease the risk of secondary malignancies associated with EBRT in patients with RB-1 germline mutation. It also carries the risk of second-

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2. Chemotherapeutic Techniques

Chemotherapy [chlormethine (nitrogen mustard)] for retinoblastoma appeared in the literature in 1953.[33] Subsequent studies suggested that the alkylating agent triethylenmelanine, given by oral, intramuscular, intravenous or intra-arterial routes produced documented improvement in survival.[33-37] There was a decrease in usage of chemotherapy in patients with bilateral retinoblastoma between 1966 and 1980.[38] With advances in the treatment of other paediatric tumours, including neuroblastoma and rhabdomyosarcoma, in which chemotherapy has become standard for debulking solid tumours to allow localised radiotherapy or surgical excision, the interest for adjuvant chemotherapy for retinoblastoma was reborn.[4,34,39-47]

2.1 Chemoreduction

The term chemoreduction highlights the strategy of using systemic chemotherapy to shrink the tumour making it treatable with cryotherapy, laser photocoagulation or brachytherapy.[4,48] In 1976, Campinchi et al.[49] introduced the concept of 'chemoreduction,' by decreasing the size of retinoblastomas (with cyclophosphamide and vincristine) prior to either enucleation or radiotherapy. In subsequent years, other studies reported tumour regression following combinations of cyclophosphamide, vincristine, doxorubicin (adriamycin) and melphalan, and combinations of thiotepa, nimustine (ACNU) and cisplatin (heat therapy was added to this regimen).[39,49-50]

While chemotherapeutic agents varied according to the preference of the paediatric oncologist, most of the current studies have relied on vincristine, etoposide and carboplatin (VEC).[1-3,51,52] In a recent study,[52] a mean decrease of 35% in tumour base and 49% in tumour thickness was found by using two cycles of a VEC regimen. The authors noted a complete tumour response in 25 patients (46%) and a partial response in 29 (54%). Subretinal fluid completely resolved in 50 patients. Systemic adverse effects were found to be both mild and short term.[52] In a second published study of 130 tumours in 52 eyes of 32 consecutive patients observed for at least 1 year after initiation of treatment, all patients had not received prior treatment for retinoblastoma, were not eligible for focal treatment modalities, and would have previously been treated by enucleation or EBRT.[12] Focal treatments were delivered after the second or third cycle of chemotherapy. 53 retinal tumours in 25 eyes of 18 patients received less than 6 months of the VEC regimen, and 77 retinal tumours in 27 eyes of 14 patients received 6 months of this regimen. Adjuvant treatments (laser, cryotherapy) were applied to 93% of the tumours, of which 2% recurred over the mean follow-up of 17 months. In those eyes with seeds before treatment, the addition of adjuvant treatment to VEC for 6 cycles was reported to decrease the vitreous seed recurrence from 75 to 0%, and the subretinal seed recurrence from 67 to 0%.

Although the indications for chemoreduction are not clearly established, these authors found that by using chemotherapy (VEC for 6 cycles) and carefully applied adjuvant treatment, the ocular salvage rate in Reese-Ellsworth group V patients was 78% and in 42% of cases, enucleation or EBRT were avoided.[52]

In another series,[53] 33 tumours of 11 eyes in 6 patients received 2-drug chemotherapy (carboplatin and etoposide) for 6 to 7 monthly cycles.[53] Eight larger tumours underwent dramatic regression, and 6 larger tumours were without growth or further treatment for 7 to 21 months after completion of therapy. No extraocular extension, local recurrence, or serious adverse effects were related to treatment (over a follow-up period ranging from 12 to 40 months).

The addition of cyclosporin to the chemotherapeutic regimen has been suggested to decrease the rate of recurrent retinoblastoma.[1] The logic behind using adjuvant cyclosporin in combination with chemotherapy for retinoblastoma arises from its role in countering multiantineoplastic drug resistance. *In vitro* studies have shown that 30% of previously untreated, enucleated retinoblastoma

cells demonstrate resistance to multiple antineoplastic drugs. This finding was correlated to the overexpression of the multidrug resistance gene P-glycoprotein (an ATP membrane transport protein).[54,55] P-glycoprotein enables cells to transport antineoplastic drugs from the intracellular space. Cyclosporin blocks the ability of P-glycoprotein to clear drugs from these cells *in vitro*.

In a clinical study of chemoreduction with adjuvant cyclosporin therapy, Gallie et al.[1] included 40 eyes of 31 bilateral retinoblastoma patients (the other eye was enucleated in 22 patients), who would have undergone EBRT or enucleation as standard treatment. A variable chemotherapeutic protocol was used for 3 to 12 months, according to the severity of disease. Whereas some patients received a regimen of vincristine and teniposide every 10 days, other patients received carboplatin, vincristine and teniposide every 3 weeks. Both groups of patients also received cyclosporin at a dose of 4 to 33 mg/kg increased to the maximal tolerated dose. Focal therapy was given after 2 cycles of chemotherapy and was repeated if necessary. At the end of a median follow-up of 2.75 years, 85% of eyes were relapse free and enucleation or EBRT was avoided in 35 of 40 eyes.[1] For the most severe tumours (Reese-Ellsworth group Vb), the local control rate was 88%. The authors proposed that the addition of cyclosporin enhanced the effectiveness of chemoreduction based on 2 findings. First, the local control rate of 85% was better than the 37% rate seen at the same centre using chemoreduction without cyclosporin.[51] Second, of the 9 patients who failed prior to chemotherapy, 7 had responses to the same regimen with adjuvant cyclosporin.

The efficacy of the single-agent intravenous carboplatin for both intraretinal and intravitreous retinoblastoma chemoreduction therapy has been investigated.[57,58] Recently, Bechrakis et al.[59] showed the clinicopathological features of retinoblastoma after primary chemoreduction.[59] Five patients with sporadic bilateral retinoblastoma (Reese-Ellsworth group V disease) underwent planned enucleation of their functionally blind eye after 2, 3, 4 and 6 courses of primary chemotherapy with carboplatin, etoposide, cyclophosphamide and vincristine. All tumours were noted to exhibit a good response to the therapy and decreased in volume. One patient had a type 1 regression and 4 patients had either a type 2 or a type 3 regression pattern. Histopathological examination revealed complete tumour necrosis in 1 patient with type 1 regression after 3 courses of chemotherapy and in 1 patient with type 3 regression after 4 courses of chemotherapy. The remaining 3 patients with type 2 or 3 regression had histologically active proliferating tumour cells after 2, 3 and 6 courses of chemotherapy. They observed heterogeneity of retinoblastoma cells, presumably due to variable sensitivity to chemoreduction, and proposed that chemotherapy alone was not a reliable treatment for all retinoblastomas but offered the potential to become a first-line approach if combined with other focal treatments.

2.2 Chemothermotherapy

Heat has a potential synergistic effect with both chemotherapy and radiation for the treatment of systemic and ocular cancers.[60] Localised laser thermotherapy increased the binding of platinum to tumour DNA in a Greene melanoma model in rabbits treated with carboplatin.[60] The combination of heat and chemotherapy is called chemothermotherapy. In a retrospective, uncontrolled study by Murphree et al.,[2] 38 eyes were treated with primary chemotherapy (a single of dose of carboplatin every 28 days for an unspecified number of cycles). Heat was delivered via diode laser for 10 to 30 minutes at 300 to 700mW in a varying protocol from 4 sessions over 2 weeks postcarboplatin to a single session on day 0 of carboplatin. They found that chemothermotherapy was 100% effective for patients with Reese-Ellsworth group I and II cancer. Only 2 of 4 patients with group III responded and all group Vb patients failed to respond. Two hyperthermia sessions were determined to be the minimal effective therapy, and the second hyperthermia session given on day 3 of the cycle was thought to increase the effect of carbo-

platin by a local coagulative effect. The authors advised the use of chermothermotherapy only for group I tumours less than 6mm in base.

2.3 Chemoradiotherapy

Kingston et al.[14] evaluated the combined effect of chemotherapy and external beam radiotherapy in 14 patients with bilateral Reese-Ellsworth group V retinoblastoma. Before the initiation of radiotherapy, patients received 2 cycles of chemotherapy (vincristine, carboplatin, etoposide). Four eyes were primarily enucleated because of severe disease at presentation. It was noted that all patients demonstrated reduction in tumour size after 2 cycles of chemotherapy. At the median follow-up of 60 months, 2 children died from extraocular malignancies. Of the remaining 20 eyes, 6 required enucleation. The authors did not find an improved eye salvage rate (70%) compared with the 66% eye salvage rate with radiotherapy alone in their previous study, but the patients were noted to have more severe disease at baseline than the patients in the previous study.[14,19] Of the surviving patients, 6 of 9 group Vb eyes were preserved with chemoradiotherapy. Chemotherapy also has the potential to increase radiation adverse effects.

2.4 Subconjunctival and Intravitreal Chemotherapy

For the chemotherapy of intraocular retinoblastomas, an ideal dose distribution would involve the delivery of anticancer agents exclusively to the intraocular space of the affected eye. This would offer almost no systemic exposure to the drug and minimise the risks of short- and long-term systemic adverse effects. In a transgenic mouse model of hereditary retinoblastoma, intravitreal injections of carboplatin were found to inhibit intraocular tumour formation in a dose-dependent fashion.[61] Histopathological studies showed no evidence of tumour at the injection sites suggesting that intravitreal injections may be performed relatively safely. In a case report from Sweden,[62] 3 patients with only 1 remaining eye which contained recurrent retinoblastoma and extensive vitreous seeding, were treated with vitrectomy followed by intraocular chemotherapy. Two patients responded and the third had postoperative haemorrhage and required enucleation.

In light of the fact that intraocular procedures open the eye to orbital seeding, and a potential for subsequent extraocular extension, intravitreal chemotherapy and vitrectomy should be thought of as high risk procedures.

Mendelsohn et al.[63] studied intraocular carboplatin and etoposide concentrations after intravenous and local peribulbar placement in nonhuman primates. Primates were treated with (1) intravenous carboplatin, etoposide, vincristine, (2) peribulbar carboplatin, (3) episcleral balloon carboplatin. No measurable amount of etoposide was detected in the aqueous or vitreous humor after intravenous administration. The measured peak concentration of carboplatin after intravenous administration was 1% of the peak plasma value. Mean measured peak concentrations of carboplatin after epibulbar or episcleral balloon administration were 7.68- and 9.52-fold larger, respectively, than the concentration achieved after intravenous administration. The authors found that peribulbar and episcleral balloon administration of carboplatin was relatively safe and resulted in higher vitreous concentrations than intravenous administration. They emphasised however, that in a human eye with retinoblastoma, these results may be different.

Murray et al.[64] found a dose-dependent inhibition of intraocular tumours by subconjunctivally injected carboplatin in a transgenic retinoblastoma mouse model. No evidence of histopathological toxicity was noted.

3. Chemotherapy for Extraocular Retinoblastoma

Chemotherapy has an important role in the management of retinoblastomas with extraocular disease. Extraocular retinoblastoma may be localised to the soft tissues surrounding the eye or to the optic nerve beyond the margin of resection. However, further extension may occur into the brain and meninges with subsequent seeding of the spinal

fluid. Metastatic disease can involve the lungs, bones and bone marrow.

Several risk factors for micrometastatic disease, such as tumour size, length of the optic nerve stump, extent of choroidal invasion and degree of cell differentiation have been suggested.[65,66] Choroidal invasion has been considered as an important risk factor for metastatic disease, but the value of isolated choroidal invasion as a risk factor for metastatic disease was challenged.[67-69] It is unknown whether or not adjuvant chemotherapy decreases the risk of metastasis in patients with adverse histopathological risk factors. Moreover, histopathological risk factors such as the degree of differentiation or choroidal invasion cannot be determined in nonenucleated eyes. For this reason some investigators have treated all patients with nonenucleated eyes with chemotherapy.[70]

In a series by Schvartzman et al.,[71] a very low relapse rate was obtained in patients with only intraocular disease treated with enucleation or conservative treatment without adjuvant chemotherapy (51 out of 52 patients with tumours confined to the eye survived). They concluded that adjuvant chemotherapy is not needed for patients with only intraocular disease. In our review of the literature for this article, there were studies that suggested that the outcome of chemotherapy-treated patients was significantly worse than nonchemotherapy-treated bilateral retinoblastoma patients.[11,39] On the other hand, Kingston and others have proposed that the use of adjuvant therapy in children with adverse histological factors improved their survival and that is why metastatic diseases have been rarely seen over the past decade.[72-74]

A prospective multi-institutional study was designed to determine the benefits of adjuvant chemotherapy.[75,76] Starting in 1977, patients with group V retinoblastoma (Reese-Ellsworth classification) were randomised after enucleation, to receive either chemotherapy (cyclophosphamide and vincristine) or no chemotherapy (controls). 88 patients were enrolled, 41 on chemotherapy and 47 controls. At a median follow-up of 2 years, the overall survival rate was 91.3%; survival rates in the chemotherapy group and the control group were 87.6 and 95%, respectively. Overall, there were 7 relapses, 4 outside the CNS, the latter being equally distributed between chemotherapy recipients and controls. All relapses occurred within 1 year of diagnosis. All 7 had involvement of both the choroid and the optic nerve.

3.1 Chemotherapy in Patients with Optic Nerve Involvement

After enucleation, retinoblastoma can be found to invade beyond the edge of surgically transected optic nerve, or grow through the sclera. These cases are termed micrometastatic retinoblastoma. It is a major prognostic factor for recurrence.[77,78] The relapse rate has been reported to be as high as 80%.[78] While there is no consensus as to the best therapy for this group of patients, when micrometastatic extension is found (without overt evidence of metastatic disease), systemic chemotherapy with external beam irradiation is commonly employed.

Zelter et al.[70] used enucleation and systemic chemotherapy (cyclophosphamide, vincristine, doxorubicin) for tumours involving the optic nerve head, and additional brain radiotherapy and intrathecal chemotherapy (methotrexate, cytarabine and dexamethasone) for tumours extending beyond the cut optic nerve. At the end of a median 63 months follow-up (only unilateral disease), the overall survival rate was 100% (5 of 5 patients were alive) in patients with only optic nerve extension, and 75% (3 of 4 patients were alive) in patients with tumour involving the cut end of the optic nerve. In patients with bilateral disease, 1 patient with only optic nerve extension was free of disease, while of the other 2 patients (with tumour extending beyond the cut end of the optic nerve), 1 was alive at the end of a median 81 months follow-up.[70]

Chemotherapy was also used in a series of 51 patients with retinoblastoma.[79] Intravenous chemotherapy was given to all patients (including 32 unilateral, 19 bilateral tumours). Patients with retinoblastoma extending to the optic nerve head, choroid and emissaries received cyclophospha-

mide and vincristine in addition to local radiotherapy. Doxorubicin was added when there was extension beyond the cut optic nerve or through the sclera into the orbit. In patients with CNS involvement, intrathecal chemotherapy with methotrexate, cytarabine and hydrocortisone, and cranial radiotherapy was added. The overall survival rate was 90.6% for patients with unilateral and 84.2% patients with bilateral disease.

Schvartzman et al.[71] reported that 10 out of 11 patients with invasion of the optic nerve up to the cut end, and 11 of 14 patients with invasion of the optic nerve beyond the cut end, survived at the end of the median follow-up time of 39 months. They used systemic chemotherapy (cyclophosphamide, doxorubicin, vincristine) in patients with invasion of the optic nerve up to the cut end, and systemic and intrathecal chemotherapy (methotrexate, cytarabine and dexamethasone) and orbital radiotherapy in patients with tumours involving the optic nerve beyond the point of transection. Their results suggested that cranial radiation could be avoided in patients with tumours involving the optic nerve beyond transection. The combination of tumour beyond the cut end of the optic nerve plus full choroidal invasion was associated with a higher risk of relapse.[77] Invasion of the optic nerve beyond the lamina cribrosa but not extending beyond the cut end was a less significant risk factor.

Few reports effectively deal with the question of whether these patients need adjuvant chemotherapy or radiation. However, in a retrospective study, the mortality rate in patients treated with enucleation alone was reported to be as high as 42%.[67] Zelter, Schvartzman, and others suggested that systemic chemotherapy alone may be used for tumours invading up to the cut end of the optic nerve or choroidal invasion.[4,19,71,80-82]

3.2. Chemotherapy in Patients with Orbital Extension

In reports from large centers, orbital extension of intraocular retinoblastoma or orbital recurrence after enucleation occurred in up to 12% of all retinoblastomas.[83,84] Orbital extension of retinoblastoma had been associated with higher mortality rates ranging from 94 to 100%, with a mean survival of 14 months.[37,74,85] MacKay et al.[86] reported that regardless of whether therapy was given, affected patients died within 5.8 months on average, and in an earlier study,[87] Merriam found an average survival of 3.5 months. Reese reported that none of his 25 patients survived when treated with exenteration and EBRT.[88] However, this dismal prognosis was challenged by several studies and observations. Grabowski[84] reported a disease-free state in 10 of 12 patients after a mean follow-up of 44 months by using chemotherapy, whole brain irradiation, and intrathecal chemotherapy (when CNS metastases were present). Although there is no standard treatment for extraocular retinoblastoma, therapy usually involves enucleation of the globe, orbital radiotherapy, and intensive systemic chemotherapy.[89] Most investigators have suggested that survival is improved when chemotherapy is used in combination with radiation therapy.[34,89] A variety of agents have been investigated, including chlormethine, triethylenemelamine, cyclophosphamide, cisplatin, etoposide, vincristine, dactinomycin, doxorubicin, nitrosoureas (lomustine and nimustine), methotrexate, and fluorouracil.[89,91-93]

Doz et al.[83] reported their results in 33 patients who received combinations of systemic and intrathecal chemotherapy, and orbital and cranial irradiation. They noted that increasing the intensity of chemotherapy dose resulted in a shorter duration of treatment and an avoidance or reduction in orbital radiation. In a more recent report,[90] they concluded that intensive chemotherapy using platinum compounds, epipodophyllotoxins, cyclophosphamide, doxorubicin, and vincristine could be used to treat patients with orbital retinoblastoma even when associated with CNS metastases. They preferred carboplatin in chemotherapy protocols for its ability to penetrate better into bone marrow and CNS. They found that the plateau phase of the survival curve was reached at 15 months, with a survival rate of 34 ± 8%. They also showed that the disease-free interval was longer when patients had

no CNS disease. A total of 20 of the 21 recurrences occurred within 1 year after diagnosis of orbital involvement.

In a phase II study,[91] 2 courses of etoposide and carboplatin were used for relapses in extraocular retinoblastoma. Four partial responses were obtained, 1 patient stabilised, and 1 progressed after 2 courses of this regimen. These investigators also added systemic chemotherapy regimens [cyclophosphamide, vincristine and doxorubicin (CADO), carboplatin, etoposide and cyclophosphamide (CARBOPEC)], radiotherapy and brain irradiation for patients with progressive disease. They observed nonevolutive disease in 4 patients, disease-related death in 1, and progressive disease in another patient. The follow-up of patients ranged from 3 to 50 months.

In a study by Goble et al.,[92] orbital recurrence of retinoblastoma was treated with an excisional biopsy of the tumour mass, followed by orbital radiotherapy and systemic (cyclophosphamide, cisplatin, vincristine, methotrexate, and etoposide) and intrathecal (methotrexate) chemotherapy in 5 patients. They followed these patients for between 8 and 84 months and all remained alive, although their previous study reported that 9 of 10 patients died because of the disseminated disease.[93] All these deaths occurred within 2 years. Three of 4 exenterations performed for orbital recurrence were found to be histopathologically incomplete. These authors suggested that orbital exenteration was unlikely to achieve complete surgical removal of all recurrent tumour. They concluded that differences in survival between their studies were due to more aggressive treatment in the latter study.[92,93]

3.3 Chemotherapy for Patients with Distant Retinoblastoma Metastasis

Direct tumour-extension into the CNS and metastatic disease are the most common causes of death in patients with retinoblastoma.[82,94] Early diagnosis and treatment has decreased the incidence of metastatic retinoblastoma in developed countries. In the USA, haematogenous or lymphatic dissemination of retinoblastoma is found in less than 10% of cases.[67] Metastases are most frequently found in the bone and bone marrow. Additional sites include the paranasal sinuses, salivary glands, lymph nodes, subcutaneous tissue, liver, spleen, pleura, and testes.[77,95,96]

Multi-agent chemotherapy for metastatic retinoblastoma was first published by Wolff et al.[75] Subsequent series concentrated on the use of cyclophosphamide. Other agents have been incorporated in combination including: triethylenemelamine, doxorubicin, vincristine, cytarabine, dacarbazine, lomustine, hydroxycarbamide, fluorouracil, methotrexate, uramustine, chlorambucil, prednisolone, dactinomycin, and melphalan.[97-4] In the few studies which evaluated the use of single agents in the treatment of metastatic retinoblastoma, cyclophosphamide was one of the only drugs proven to be active in phase II studies in extraocular retinoblastoma, along with ifosfamide, doxorubicin and platinum compounds.[75,76,100-83] Thus, the combination of high dose cyclophosphamide, vincristine and carboplatin offers the possibility of additive activity for these drugs. In some centres, this drug combination has been used in high-risk retinoblastoma patients (orbital relapse or metastases) as consolidation treatment after complete or partial remission induced by initial conventional chemotherapy.[105] Melphalan, amsacrine (m-AMSA), mitoxantrone, cis-diamminediacquaplatinum (DDP), fluorouracil, teniposide, peptichemio, chlorambucil, uracil, chlormethine, and hydroxycarbamide failed to produce an improvement in survival.[102,103]

Doz et al.[91] reported that among 10 patients with assessable soft tissue mass surrounding bone metastases, tumour response was complete in 8 patients and partial in 2 patients after 2 courses of vincristine and carboplatin therapies in a phase II study. Later, these patients received systemic chemotherapy (CADO or CARBOPEC regimens) and brain irradiation as further treatment. However, 4 patients developed CNS involvement and died between 4 and 19 months later.

Zelter et al.[70] used enucleation, local radiotherapy and systemic chemotherapy (cyclophospha-

mide, doxorubicin, cisplatin and epipodophyllotoxin for 3 courses) in patients with distant metastasis. Their survival rate at the metastatic disease was 25% in unilateral patients and 0% in patients with bilateral retinoblastoma.

Schvartzman et al.[71] reported that only when malignant invasion of preauricular lymph nodes was the only manifestation of metastatic disease did their patients have good survival after treatment. Their patients were treated with systemic chemotherapy (cyclophosphamide, doxorubicin, vincristine, cisplatin, etoposide) and local radiotherapy. All of these patients had long term survival and gave a good response to less intensive therapy. However, most patients with distant metastasis demonstrated a transient complete response rate, but then relapsed in 13 months and died.

In a patient with of disseminated metastatic retinoblastoma, a preoperative regimen consisting of etoposide, cisplatin, high dose melphalan and total body irradiation followed by autologous bone marrow transplantation was suggested as a potentially curative approach.[104] The patient was disease-free for 17 months after this regimen.[105] Namouni et al.[106] studied high dose chemotherapy with haematopoietic stem cell rescue as a consolidation treatment in high risk retinoblastoma patients. They used CARBOPEC followed by autologous haematopoietic stem cell rescue in 25 patients. The 3-year disease-free survival was 67.1% but all patients with CNS disease died. They concluded that the CARBOPEC regimen appeared to be a promising therapeutic strategy for patients with high risk retinoblastoma (especially those with bone and/or bone marrow involvement). This therapy did not work in patients with CNS involvement.

3.4. Chemotherapy for Patients with CNS Involvement

CNS involvement usually occurs by direct extension through the optic nerve, via access to the cerebrospinal fluid (CSF), or by vascular invasion with haematogenous spread.[95] If CNS involvement is suspected at the time of presentation, it can be detected through lumbar puncture with cytospin analysis of the CSF.[94,95] To date, the prognosis for children with CNS retinoblastoma has been poor. Remissions have been obtained with combinations of oral lomustine and intrathecal methotrexate.[75,76,85]

Doz et al.[91] reported that among 4 patients with CNS disease, 3 had partial remission and 1 had a complete remission after 2 courses of vincristine and etoposide in a phase II study. They needed CARBOPEC and cranial irradiation therapy as further therapy. Although 2 patients died, 2 were being followed up between 19 and 51 months. Although Zelter et al.[70] used systemic and intrathecal chemotherapy and cranial radiation for CNS involvement, the survival rate in their study was 0%. Schvartzman et al.[71] also found his overall survival rate to be 0% for patients with CNS involvement. Although they exhibited an initial response to treatment, patients usually relapsed within 13 months of diagnosis. The authors used systemic and intrathecal chemotherapy and cranial irradiation. They suggested that their dose of radiation therapy might have been too low to control the CNS disease effectively, and that this population might benefit from a more intense radiation therapy.

3.5. Chemotherapy for Patients with Trilateral Retinoblastoma (Pinealoblastoma)

Trilateral retinoblastoma describes the association of bilateral retinoblastoma and neuroblastic tumour in the pineal gland or other midline structures. It is a major cause of mortality in children within the first 5 years after diagnosis of bilateral retinoblastoma.[107] Magnetic resonance imaging and computed tomography are essential to this diagnosis. The successes seen with intensive chemotherapy for the treatment of neuroblastoma and medulloblastoma with vincristine, cyclophosphamide and etoposide combined with intrathecal methotrexate led to their adoptation in the treatment of trilateral retinoblastoma.[107]

The treatment of 57 patients has been described in the literature.[108-111] Seven of these were treated with chemotherapy alone, with an average survival time of 24.6 months, and 3 of them were still alive.

When intrathecal therapy was incorporated into the regimen, 14 died with an average survival time of 19.8 months and 4 were still alive. The combination of chemotherapy and radiation was used for 23 of these patients resulting in an average survival time of 11.7 months. One patient was still alive.

The recent success with cisplatin and carboplatin-based chemoreduction of intraocular retinoblastoma also suggests that platinum-based chemotherapy for trilateral retinoblastoma may improve survival.[109] Radiation therapy alone was used in 10 patients with an average survival time of 6.5 months. Experience with trilateral retinoblastoma shows that radiation in doses greater than 50Gy may result in lengthened survival time.[109] Surgical resection in combination with radiotherapy and chemotheray was performed in 14 patents with an average survival time of 11.1 months and 2 were still alive. Platinum-based chemotherapy with intrathecal therapy and neural axis radiation therapy is most commonly used for the treatment of trilateral retinoblastoma.[109]

4. Conclusion

In developed countries, early diagnosis and treatment (enucleation and/or radiation therapy) has provided greater than 92% cure rates for patients with retinoblastoma. With the primary goal of saving life vastly improved, the secondary goals of preservation of vision and the cosmetic use of the eye have achieved greater importance.

Following the example of paediatric oncologists, new chemotherapy techniques are being investigated to save vision and spare children from enucleation. Chemoreduction has been used to shrink intraocular retinoblastomas, followed by secondary alternative therapies (radiation, laser therapy, cryotherapy) used to destroy residual tumours. Choices of chemotherapeutic agents and routes of administration continue to evolve; while scattered reports of secondary haematological malignancies have been attributed to chemotherapy. The long term efficacy, risks and adverse effects attributed to chemoreduction are currently being investigated within the framework of a multicentre, prospective, randomised clinical trial.

Chemotherapy (often combined with external beam radiation therapy) continues to be a mainstay in the treatment of patients with metastatic retinoblastoma. Clearly, systemic chemotherapy offers these patients their best chance for life.

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