Retinoblastoma: Intravenous Chemotherapy

11

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11.1 Introduction

The management of patients with intraocular retinoblastoma has changed dramatically in the past 20 years with the introduction of primary systemic chemotherapy. Before 1990, systemic chemotherapy had been used to treat patients with extraocular disease, with less than optimal results [1]. In the early 1990s, several investigators from North America and the United Kingdom began using chemotherapy agents that were effective against central nervous system tumors, to treat intraocular retinoblastoma [2–4]. The rationale was to achieve decrease in intraocular tumor volume with systemic chemotherapy (*chemoreduction*) so as to allow better tumor kill with local treatment using photocoagulation and cryotherapy (Fig. 11.1). Further, it was hoped that the use of chemotherapy would help to eliminate the need for external beam radiation therapy (EBRT) in this patient population susceptible to second malignancy [5, 6].

Systemic chemotherapy is indicated in unilateral intraocular retinoblastoma with high-risk features, bilateral intraocular retinoblastoma, extraocular retinoblastoma with local or regional spread, and metastatic retinoblastoma with or without central nervous system involvement (Box 11.1).

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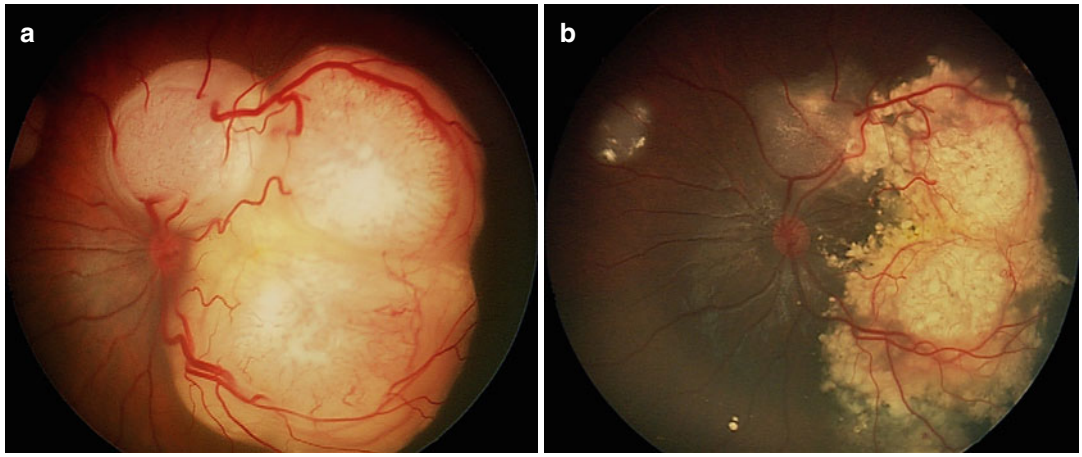

Fig. 11.1 Pretreatment group B retinoblastoma (**a**). Note reduction in tumor volume 3 weeks after the administration of the first cycle of carboplatin, etoposide, and vincristine (**b**). Focal consolidation may start at this time (concurrently with the second cycle of chemotherapy) or at the beginning of the third cycle. The goal of local consolidation is to treat the entire residual lesion with transpupillary thermotherapy (TTT) to assure that all tumor cells not killed by the chemotherapy will be eradicated. At least three sessions in which the residual lesion is completely covered by TTT is recommended (Chap. 10)

Box 11.1 Indications for Chemotherapy of Retinoblastoma

Intraocular retinoblastoma
Prophylaxis against metastasis following enucleation in the presence of histopathologic high-risk features
Extraocular retinoblastoma with local and/or regional spread
Metastatic retinoblastoma with or without CNS involvement
Trilateral retinoblastoma

11.2 Chemotherapy Regimens

Combination of carboplatin, etoposide, and vincristine (CEV) is the most common regimen used to treat retinoblastoma. A variety of other systemic chemotherapy combinations have been used [7–10]. They include carboplatin alone, carboplatin with vincristine, topotecan and vincristine, and carboplatin, teniposide, and vincristine. Doxorubicin, cyclophosphamide, and ifosfamide have also shown activity in retinoblastoma [11, 12]. Cyclosporine has been used in some studies in an effort to decrease chemotherapy resistance [8].

11.3 Intraocular Retinoblastoma

The Reese-Ellsworth (R-E) classification system developed in the era of EBRT as the primary modality failed to reliably predict outcome with chemotherapy. To allow selection of a homogeneous population of patients to test current therapy approaches, which include chemotherapy, the International Classification System for Intraocular Retinoblastoma was developed (Chap. 3) [13]. This classification has been validated and is useful in predicting ocular outcome [14].

11.3.1 Group A and B Eyes

In general, eyes with group A tumors are treated with local therapy alone. Combination of systemic chemotherapy with CEV and local therapy has been successful in treating group B eyes (R-E stage I–III) [15]. Six courses of low-dose CEV or three courses of high-dose CEV have been used (Table 11.1). Ocular salvage rates of nearly 100 % can be achieved with CEV regimen and local therapy. With this success, attempts were made to minimize morbidity by eliminating etoposide. Investigators at St. Jude Children's

Table 11.1 Low-dose and high-dose treatment regimens

	Dose	
Drug	Low dose (mg/kg)	High dose (mg/kg)
Carboplatin	18.6	28
Etoposide	10	12
Vincristine	0.05	0.05
Course repeated every 21–28 days		

Research Hospital achieved an ocular salvage rate of 83 % in R-E group I–III eyes using eight cycles of vincristine and carboplatin [7]. Subsequently, the Children's Oncology Group conducted a study of two-drug regimen (vincristine and carboplatin) in group B tumors. This study was closed early due to more-than-expected number of failures.

11.3.2 Group C, D, and E Eyes

In spite of initial response with low-dose CEV regimen in eyes with subretinal or vitreous seeds, only 53 % of R-E group 4 and 5 eyes (group C, D, or E) were treated successfully without requiring EBRT and/or enucleation [15, 16]. Gallie et al. reported relapse-free rates of up to 89 % with the addition of cyclosporine to chemotherapy to reverse drug resistance [8]. Other groups were not able to reproduce the results of this pilot study. Subsequently, doses of the chemotherapy agents were increased in an attempt to achieve increased intraocular drug levels. This resulted in 66 % eye salvage at 5 years in one study, but nearly half the eyes required low-dose EBRT at recurrence [17]. In addition, subtenon or periocular carboplatin has been used to increase drug delivery to the vitreous where blood supply is poor. Preliminary studies using subtenon carboplatin and high-dose CEV showed improved ocular salvage rates [18]. Toxicities observed using this modality included periorbital fat atrophy resulting in mild to moderate cosmetic changes and restriction of extraocular movements [19]. Rare cases of optic atrophy have also been reported [18]. To further evaluate this strategy, the Children's Oncology Group opened a single-arm trial of systemic and subtenon chemotherapy for group C and D eyes. Unfortunately, this study was closed early due to poor accrual, and study results are awaited.

11.4 High-Risk Histopathology

The treatment of choice for unilateral group E eyes is enucleation. In 10–15 % of patients who undergo enucleation, tumor may involve one or more of the following and is considered to be high risk for metastatic disease: anterior chamber, massive choroidal involvement, and spread to ciliary body/iris, sclera, or optic nerve beyond lamina cribrosa (Chap. 16) [20–23]. If left untreated after enucleation, as much as 24 % of patients with high-risk features may develop metastatic disease, often leading to death [22].

The management of patients with high-risk features has varied from close observation to, more commonly, treatment with six courses of the low-dose CEV regimen. Recent chemoprophylaxis studies have shown encouraging results [24]. Honavar et al. reported on 80 patients with unilateral sporadic retinoblastoma who had high-risk pathologic features postenucleation [22]. Two of 46 patients who received adjuvant chemotherapy developed metastatic disease when compared with 8 out of 34 patients who did not receive chemotherapy. Uusitalo et al. reported on 129 patients with unilateral disease treated at the University of California, San Francisco, and the University of Miami [20]. Eleven patients with postlaminar involvement or tumor at the cut end of the optic nerve were treated with chemotherapy. None of those patients developed metastatic disease. This spurred the Children's Oncology Group to propose a uniform treatment protocol for patients with high-risk pathology to better understand the role of each of these features and the outcome of patients. Of the 312 patients enrolled, 93 had high-risk features confirmed by central histopathological review. These patients received six cycles of low-dose CEV. After a median follow-up of 1.9 years, only one patient with high-risk feature developed extraocular relapse [25].

11.5 Therapeutic Approaches to Extraocular Retinoblastoma

The treatment of extraocular retinoblastoma is discussed in more detail in another chapter (Chap. 17). Survival of patients with retinoblastoma depends on extent of disease. In the United States, where the majority of patients have intraocular disease, overall survival is reported at 90 %. In contrast, extraocular retinoblastoma is associated with a very poor outcome [26]. Extraocular retinoblastoma can be divided into three categories: regional extraocular disease (optic nerve involvement at the cut end of the enucleated eye, orbital or periauricular involvement), distant metastatic disease without CNS involvement, and CNS disease. In order to compare outcomes of extraocular retinoblastoma, Chantada and colleagues have developed an international staging system for retinoblastoma (Chap. 5) [27]. The historical event-free survival rates at 1 year are 40 % for patients with orbital disease, 20 % for patients with metastatic disease, and 0–5 % for CNS-positive patients [28].

11.5.1 Regional Extraocular Disease (Stages 2 and 3)

Traditionally, patients with orbital disease have been treated with surgery with or without irradiation and have fared poorly. The addition of conventional-dose chemotherapy to the treatment regimen has improved survival considerably. Recent reports confirm that conventional chemotherapy and external beam irradiation can cure patients with regional extraocular disease (orbital and/or preauricular disease or optic nerve margin positivity). Investigators in Argentina treated 15 patients with orbital or periauricular nodal disease with chemotherapy (cyclophosphamide, doxorubicin and vincristine or vincristine, idarubicin, cyclophosphamide, carboplatin, and etoposide) [11]. This was followed by external beam irradiation (45 Gy) up to the chiasm in patients with orbital disease and to the involved nodes in patients with preauricular lymphadenopathy. They reported a 5-year event-free survival of 84 %. Chantada et al. reported event-free survival of 70 % at 5 years in 26 patients with optic nerve involvement treated with the above chemotherapy regimens and orbital irradiation. Events included CNS relapse in 3, second malignancy in 3, and death in remission in 2 patients [28]. Investigators in Brazil treated 61 patients with regional extraocular disease using chemotherapy and an external beam radiation therapy dose of 40–50 Gy to the orbit. Triple intrathecal chemotherapy was also administered. Therapy was successful in 20/32 patients with orbital disease and 22/29 with optic nerve margin positivity [12].

11.5.2 Metastatic Retinoblastoma Without CNS Involvement (Stage 4a)

Historically, patients with metastatic retinoblastoma were treated with conventional doses of chemotherapy and radiation therapy, and despite some reports of long-term survival, the majority of the evidence pointed to a grim prognosis. This was confirmed by the Argentine and Brazilian investigators referenced above with reports of 0/26 and 1/14 survivors with distant metastatic disease, respectively [11, 12]. Namouni et al. reported the results of 25 patients with metastatic retinoblastoma treated with high-dose carboplatin, etoposide, and cyclophosphamide followed by autologous stem cell rescue (ASCR) [29]. Five of 11 patients (45 %) without CNS metastasis at diagnosis were event-free survivors at 11–70 months after high-dose chemotherapy. Dunkel et al. reported on four patients with metastatic retinoblastoma without CNS involvement treated with high-dose carboplatin, thiotepa, and etoposide with ASCR after complete response to conventional doses of chemotherapy. All four were event-free survivors from 46 to 80 months following diagnosis [30]. Matsubara et al. from Japan reported on five patients with metastatic retinoblastoma treated with conventional-dose chemotherapy and irradiation to bulky sites followed by high-dose chemotherapy with a variety of chemotherapy combinations and ASCR [31].

The three patients without CNS involvement are long-term survivors with no evidence of disease at 113, 107, and 38 months from the time of transplant.

Evidence suggests that high-dose chemotherapy with ASCR is associated with improved survival for patients with metastatic retinoblastoma not involving the CNS. The optimal high-dose chemotherapy combination remains to be determined; however, the inclusion of thiotepa may decrease the risk of CNS recurrence due to the excellent penetration of this agent into the CNS.

11.5.3 Metastatic Retinoblastoma with CNS Involvement (Stage 4b)

There are fewer data on survivors of retinoblastoma with CNS metastatic disease or patients with pineal involvement (trilateral retinoblastoma). Antoneli et al. described seven patients with CNS disease at the time of diagnosis, none of whom survived despite treatment with chemotherapy and irradiation of the whole brain and spine to 36 Gy [12]. Chantada et al. reported on 21 patients with CNS metastatic disease who were treated with conventional-dose chemotherapy and irradiation: 24 Gy to the brain and 18 Gy to the spine [11]. None of those patients survived. Recently, two survivors were reported in a multi-institutional retrospective series of eight patients, following high-dose chemotherapy with ASCR [32].

11.5.4 Trilateral Retinoblastoma

Trilateral retinoblastoma occurs in 3 % of patients and is diagnosed more commonly in patients with bilateral disease who are less than 1 year of age (Chap. 20) [33]. Amoaku et al. reported no cure in five patients with trilateral retinoblastoma, including three patients treated with chemotherapy ± radiation therapy [34]. Jubran et al. described three patients with trilateral disease. One patient survived following a complete resection of the pineal tumor followed by induction chemotherapy, high-dose chemotherapy, and ASCR [26]. Dunkel et al. reported 13 patients with trilateral retinoblastoma treated with two cycles of induction chemotherapy consisting of vincristine, cisplatin or carboplatin, cyclophosphamide, and etoposide, followed by high-dose chemotherapy and ASCR [35]. Five patients survived event free at a median of 77 months of follow-up.

Although the evidence to support high-dose chemotherapy and ASCR for patients with CNS involvement is not strong, the poor prognosis and the young age at diagnosis justify intensive chemotherapy. While the optimal regimens are not known, international collaborative studies are needed to improve the outcomes of patients with metastatic retinoblastoma. The ongoing Children's Oncology Group ARET0321 prospective multinational study in patients with extraocular retinoblastoma aims to answer this question.

11.6 Chemotherapy Agents

Carboplatin is a member of a family of cytotoxic compounds based on elemental platinum (Fig. 11.2). It acts by interrupting DNA replication and disrupting cell division by forming cross links with DNA [36]. Its serum decay pattern is triphasic, with initial, middle and terminal half-lives of 12–24 min, 1.3–1.7 h and 22–40 h. Approximately 90 % is excreted in the urine in 24 h. Common toxicities associated with carboplatin are myelosuppression (most notably thrombocytopenia), nausea and vomiting, renal and ototoxicity. Renal and ototoxicity are dose related, and have not been seen to date with doses utilized for intraocular retinoblastoma [37, 38]. Some patients have reported a metallic taste in the mouth and rarely patients develop electrolyte disturbances or a peripheral neuropathy.

Etoposide is an epipodophyllotoxin and acts as a topoisomerase II inhibitor (Fig. 11.3). It blocks the enzyme by stabilizing DNA cleavage complexes and preventing its catalytic activity. After an intravenous dose, the terminal half-life of etoposide, in patients with normal

renal function, is 6–8 h. Approximately 40 % of administered etoposide is excreted unchanged in the urine. The remainder is metabolized in the liver. Ninety-six percent of etoposide is bound to albumin in plasma. Common toxicities include nausea and vomiting, alopecia, stomatitis, bone marrow suppression, and fatigue. Hypotension (related to rate of infusion) and hypersensitivity rarely occur with this agent. Etoposide-induced secondary malignancy occurs in approximately 2–4 % of patients exposed. There are no statistical differences in the pharmacokinetics between patients who develop secondary acute myelocytic leukemia (AML) versus those who do not. It has been shown that cumulative dose and schedule of etoposide administration may be factors in the development of AML [39].

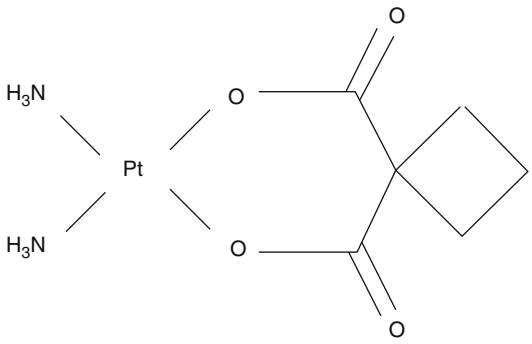

Fig. 11.2 The chemical structure of carboplatin. A DNA alkylating agent, carboplatin stops tumor growth by cross-linking guanine nucleobases in DNA double helix strands, rendering them unable to uncoil and separate for replication

Vincristine is an alkaloid isolated from *Vinca rosea* (periwinkle) (Fig. 11.4). It binds to tubulin, disrupting microtubules and inducing metaphase arrest [40]. Its serum decay pattern is triphasic, with initial, middle, and terminal half-lives of 5 min, 1.3 h, and greater than 24 h, respectively. It is excreted in the bile and feces. It is a potent vesicant. Common toxicities include alopecia, constipation, jaw and abdominal pain, blurred vision, ptosis, diplopia, clumsiness, and peripheral neuropathy.

11.7 CEV Regimen Toxicity

The regimens containing these three drugs have been largely well tolerated. The long-term toxicity of chemotherapy particularly in the setting of

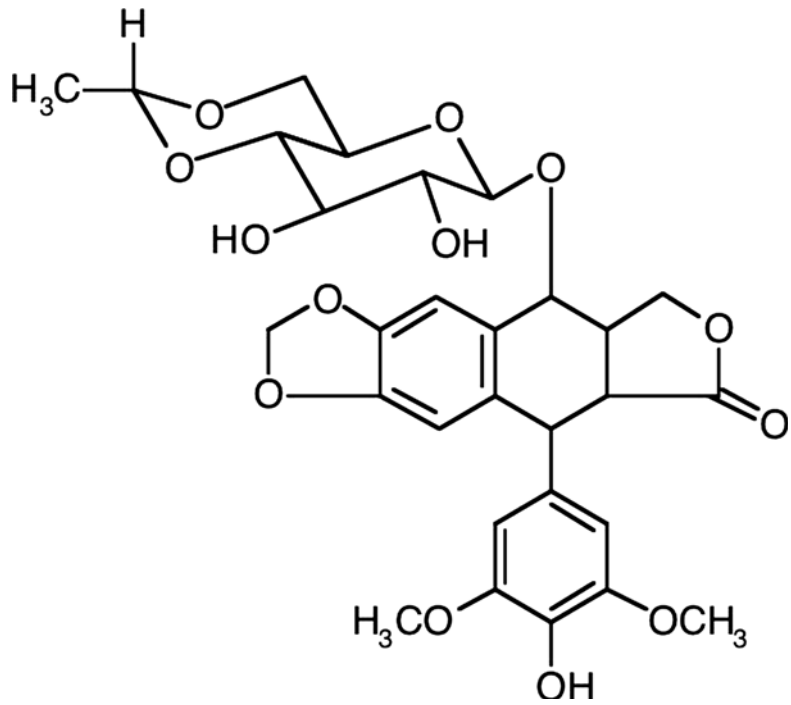

Fig. 11.3 The chemical structure of etoposide. An inhibitor of the nuclear enzyme topoisomerase II, etoposide is essential for DNA replication. Topoisomerase II is required to remove normally occurring knots and tangles in the genetic material

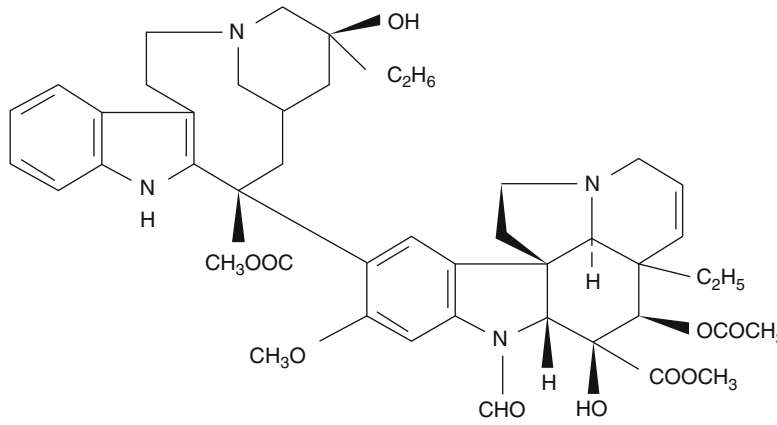

Fig. 11.4 The chemical structure of vincristine. Vincristine is an inhibitor of microtubule formation and disruptor of mitotic spindle formation

patients with a cancer predisposing condition is still not fully known.

Common expected toxicity. Myelosuppression is the most common toxicity occurring in almost 100 % of the patients, with nearly half of the patients requiring blood product transfusion and uncomplicated febrile neutropenic hospital admissions [41]. The addition of granulocyte-stimulating factor has shortened the period of neutropenia and consequently improved the toxicity profile of chemotherapy regimens. Some investigators have reported feeding problems and gastrointestinal disturbance during therapy but that is largely transient and resolves with the cessation of chemotherapy [15].

Uncommon serious toxicity. Ototoxicity is uncommon in children treated with CEV regimen [37, 38]. In an analysis of 164 patients who received carboplatin-based regimen for retinoblastoma, Lambert et al. did not find hearing loss attributable to treatment [37]. In a report from Italy, only 2 of 175 children treated with carboplatin required hearing aids [38]. Caution should be exercised when dosing children less than 10 kg. They should receive chemotherapy dose based on body weight rather than body surface area, as using body surface area has shown to increase the incidence of hearing loss [42].

Though the cumulative doses of carboplatin and etoposide are low in retinoblastoma therapy, development of secondary AML or MDS is a concern. There have been a few reports of myelodysplastic syndrome or secondary acute myeloid leukemia in patients treated with systemic chemotherapy for intraocular retinoblastoma [43, 44]. Gambos et al. surveyed major retinoblastoma centers in Americas and Europe [43]. Thirteen patients with secondary AML were identified. Twelve patients had previous chemotherapy, and eight of them had an epipodophyllotoxin (etoposide or teniposide). Many of these patients were from Latin America and received much higher doses than are used in the standard CEV regimen. In a retrospective review of 245 patients treated with CEV, Turaka et al. found one patient with AML who was treated with EBRT and chemotherapy [45]. None of the patients who received chemotherapy alone developed AML.

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