Pharmacotherapy for Retinoblastoma

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Systemic chemotherapy has become the cornerstone of therapy for retinoblastoma. The advent of novel chemotherapeutic and antiangiogenesis agents together with new routes of drug administration including periocular, intravitreal and intra-ophthalmic artery injection will hopefully revolutionize the management of this sight-threatening and potentially fatal infantile ocular neoplasm.

Key words: Retinoblastoma; Pharmacotherapy; Chemotherapeutic Agents

INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy of infancy and childhood with an incidence of 1 in every 20,000 live births.1 During the 20th century, retinoblastoma was uniformly fatal. Early diagnosis and recent advances in the management of retinoblastoma particularly the use of chemotherapy have improved the prognosis of this fatal disease. Although this neoplasm has one of the highest cure rates among malignant tumors, it is almost invariably fatal if left untreated.1

Treatment modalities currently available for retinoblastoma can be classified as follows: (1) focal therapy including cryotherapy, conventional laser photocoagulation, transpupillary thermotherapy, photodynamic therapy (in vitro study), and plaque radiotherapy;2 (2) external beam radiotherapy;3 (3) systemic chemotherapy and (4) enucleation. With the advent of chemotherapy, radical methods of management such as enucleation and external beam radiation have been relegated to second and third lines of treatment. Chemotherapy is currently the most important treatment modality for globe salvage in retinoblastoma patients.

GENERAL CONSIDERATIONS

The goal of chemotherapy, in addition to globe salvage, is avoiding external beam radiation and its complications such as temporal bone atrophy, sicca syndrome, cataracts, radiation retinopathy, neovascular glaucoma and more importantly, the risk of secondary non-retinoblastoma tumors in the field of radiation.4 Systemic chemotherapy also improves survival in children with metastases. Treatment failure following chemotherapy generally occurs in eyes with advanced retinoblastoma with retinal or vitreous seeding and the appearance of subretinal fluid. The introduction of newer chemotherapy protocols has dramatically improved patient and eye survival as well as visual outcomes. Because of the limited number of retinoblastoma cases referred to ophthalmology centers and the need for combined treatment, it is difficult to assess the beneficial effects of any particular therapeutic modality.

Chemotherapy may be applied in a systemic or local manner. Systemic chemotherapy may be used for chemoreduction (CRD), as an adjuvant modality, or for treatment of metastases.5 Chemoreduction is defined as the pro-
cess of reducing tumor volume such that it becomes amenable to cure by local therapy; this concept has become an integral part in the current management of retinoblastoma.\textsuperscript{4,5} In patients with Reese-Ellsworth group 1-4 retinoblastoma, CRD coupled with sequential aggressive local therapy can minimize the need for enucleation and external beam radiation without significant systemic toxicity. Shields et al\textsuperscript{6} observed a globe salvage rate of 100\% using CRD plus adjuvant focal treatment in Reese-Ellsworth groups 1-4. According to the more recent International Classification of Retinoblastoma, globe salvage with CRD is achieved in 100\% of patients in group A, 93\% in group B, 90\% in group C, and 47\% in group D.\textsuperscript{6} Group E was not included in the analysis because most oncologists have avoided the use of CRD for this group because of the high risk of failure; most eyes with group E retinoblastoma have been enucleated.

**CHEMOTHERAPEUTIC AGENTS**

Chemotherapy alone is not curative and must be combined with intensive local therapy. Several chemotherapeutic agents including, methotrexate, cyclophosphamide, triethylene melamine (TEM), actinomycin, doxorubicin, cyclosporine, etoposide, vincristine, carboplatin and melphalan have been used for retinoblastoma chemotherapy.

Methotrexate has been used to treat retinoblastoma metastases to the central nervous system (CNS). Methotrexate is a folic acid analogue type antimitabolite which inhibits DNA, RNA and protein synthesis as a result of binding to dihydrofolate reductase. It is excreted in the urine. Adverse effects include hepatotoxicity and lung disease as well as renal failure and acute hematologic dysfunction in high doses. Intrathecal methotrexate 0.25 to 0.50 mg/kg is given every other day in CNS retinoblastoma until no tumor cells are present in the cerebrospinal fluid (CSF). While some prolongation of life may be seen in CNS retinoblastoma patients treated by methotrexate, such treatment has not been curative.\textsuperscript{7}

Cyclophosphamide is an alkylating agent of the nitrogen mustard type. It acts by cross linking DNA and RNA thereby inhibiting protein synthesis. It is eliminated by hepatic biotransformation and renal excretion. Oral and intravenous cyclophosphamide have been used for treatment of retinoblastoma but without any apparent value. The main side effect of cyclophosphamide is hemorrhagic cystitis.\textsuperscript{8,9}

Triethylenemelamine was formerly used by direct injection into the carotid artery often in combination with radiotherapy but led to unfavorable responses and has been abandoned.\textsuperscript{7}

Dactinomycin (Actinomycin D) is an antineoplastic antibiotic which has been used in combination therapy for metastatic retinoblastoma. Although it does not lead to complete cure, prolongation of life has been achieved in some cases. Major adverse effects include bone marrow depression, nausea and mucositis. The dose is 10-15 mg/kg per day as 5 intravenous bolus doses.\textsuperscript{8,9}

Doxorubicin (Adriamycin) is also an antineoplastic antibiotic which binds to DNA and inhibits DNA and RNA synthesis. It has been used for treatment of systemic retinoblastoma. Major side effects are dose-related cardiotoxicity, extravasation, red urine, mucositis and alopecia.\textsuperscript{8,9}

**CURRENT STANDARD TREATMENT**

Systemic chemoreduction of intraocular tumors with carboplatin, usually in conjunction with etoposide and vincristine, followed by local therapy has become the standard conservative treatment for intraocular retinoblastoma worldwide.\textsuperscript{10}

Combination chemotherapy with vincristine sulfate, carboplatin and etoposide phosphate is usually administered in 6 cycles, but up to 13 cycles are sometimes required to control the disease.\textsuperscript{11} Cyclosporine has been added to these three agents in some institutions in order to overcome drug resistance.\textsuperscript{12} When combined with focal therapy such as laser or cryotherapy, this multimodality approach is generally quite successful for less advanced tumors.\textsuperscript{12}

Vincristine is a vinca alkaloid which specifically binds to $\beta$-tubulin and blocks its ability
to polymerize with α-tubulin and form microtubules. Cells blocked in mitosis undergo changes characteristic of apoptosis. Vincristine sulfate seems to be better tolerated by children than by adults who may experience neurological toxicity. The more severe neurological manifestations may be avoided or reversed either by suspending therapy or reducing the dose upon occurrence of motor dysfunction. Although neurotoxicity is the main side effect of vincristine sulfate, myelosuppression is less common than with vinblastine. Vincristine is given intravenously and precaution should be made to avoid extravasation. Treatment should be limited to cycles of combination therapy but maintenance therapy is not recommended in children.

Carboplatin (Paraplatin) is a platinum co-ordinator compound which crosslinks DNA similar to alkylating agents. It is eliminated by renal excretion. Major side effects include nephrotoxicity, ototoxicity, neuropathy, hypomagnesemia, hypersensitivity reactions and hepatotoxicity.

Etoposide inhibits DNA and is eliminated via hepatic biotransformation and excretion. Main adverse effects include allergic reactions, hepatotoxicity, CNS toxicity, hypotension, alopecia, acute myelogenous leukemia and mucositis in high doses.

For more advanced disease typically characterized by vitreous seeding, standard combination therapy is less successful with an ocular salvage rate of 25-60% beside the avoidance of both external beam radiation and enucleation for Reese Ellsworth group V-b disease.

In high dose chemoreduction, the dose of etoposide and carboplatin is increased. High dose chemotherapy has also been recently used for management of extraocular and orbital extension of retinoblastoma and in patients with optic nerve invasion.

Standard dose adjuvant chemotherapy can be administered after enucleation in patients with high-risk histopathologic characteristics predisposing the patient to metastatic disease. In a group of retinoblastoma patients who received post-enucleation adjuvant chemotherapy, the incidence of metastasis was 4% compared to 24% in the control group. Retinoblastoma patients with tumor cells in the CSF receive intrathecal methotrexate in addition to high dose adjuvant chemotherapy. Chemotherapy cycles are usually administered at 3-week intervals over a 6 month period but regimens vary in dosage and number of cycles at different oncology centers.

FOLLOW-UP SCHEDULE

The usual protocol is to visit the patients every 3-4 weeks until tumor control is achieved. Follow-up visits are scheduled every 2-3 months up to one year after tumor control, every 3-4 months during the second year, every 4-6 months until the age of 4-6 years, and annually thereafter.

NEW HORIZONS IN RETINOBLASTOMA PHARMACOTHERAPY

Novel Agents

Development of less toxic chemotherapeutic agents such as topotecan (Hycamtin) and novel agents like 2-deoxy D-Glucose (2-DG), a glycolytic inhibitor, as well as widespread adoption of intravitreal chemotherapy and intra-arterial chemotherapy may improve the cure rate of retinoblastoma in near future.

Topotecan is a topoisomerase inhibitor which binds to topoisomerase 1-DNA and prevents relegation of its single-strand breaks. The pharmacologic effects of topotecan have been confirmed in the LHBeta Tag murine model of retinoblastoma in a recent study by Tsui et al. The authors demonstrated that subconjunctival administration of topotecan enabled the formation of a depot sufficient to provide clinical effects for 3 weeks after treatment. Topotecan is excreted in urine and has no liver toxicity. Major side effects include bone marrow depression, mucositis, nausea and alopecia. Although periocular topotecan has been used up to a maximum dose of 2 mg using a #25 gauge needle, dose limiting toxicity has not been reached so far and further studies are necessary to determine its effects on retinoblastoma. Other novel nonchemotherapeutic agents have been investigated in murine models.
use of vascular targeting therapy, popularized for age-related macular degeneration, has been explored in the LHBeta tag murine model of retinoblastoma. Jockovich et al. recently reported that mice treated with subconjunctival carboplatin injections, external beam radiation and the vascular targeting agents combretastatin A4 and anecortave acetate had high levels of apoptotic cell death with minimal necrosis. These effects were seen on histopathologic analysis 1 week after treatment with carboplatin and external beam radiation but as early as 1 day in the vascular targeting group, indicating that combined therapy may maximize synergistic therapeutic effects. Authors from the same laboratory have also recently reported the use of 2-DG as an adjuvant to chemotherapy in the treatment of murine retinoblastoma. The rationale behind this approach was that solid tumors containing hypoxic regions associated with slowly proliferating cells do not respond to standard chemotherapy. When 2-DG was combined with carboplatin, a marked decrease in tumor burden was observed that was significantly more profound than when either agent was used alone. Immunohistochemical studies indicated that hypoxic tumor cell populations were markedly reduced by carboplatin and 2-DG and by 2-DG alone indicating that 2-DG effectively killed hypoxic tumor cells in vivo. The authors suggested that this drug may hold promise for adjuvant therapy in human patients. Clinical trials using 2-DG in combination with chemotherapy are already in process in lung, breast and bone cancers.

Anti-VEGF agents such as bevacizumab are likely to be of benefit in the treatment of retinoblastoma. Bevacizumab has been demonstrated to suppress angiogenesis and growth of retinoblastoma both in vitro and in vivo.

New Routes of Drug Administration

One of the main problems surrounding chemotherapy is that chemotherapeutic agents may not be able to penetrate the blood-retinal barrier when administered systemically. Moreover, because of side effects, high dose systemic chemotherapy is potentially dangerous. One method to circumvent this problem is to deliver chemotherapy locally providing trans-scleral drug penetration and high intraocular concentrations. Periocular chemotherapy (subconjunctival, subtenon, retrobulbar) and intravitreal injection are being explored as means of minimizing systemic exposure to chemotherapeutic agents for treatment of intraocular retinoblastoma. However, only carboplatin has been widely used in children with retinoblastoma by this route. Although virtually devoid of systemic toxicity, it may induce severe local adverse effects including orbital fibrosis and optic nerve atrophy. Therefore, the introduction of safer drugs or delivery systems for periocular use is necessary.

Carboplatin delivered subconjunctivally has been demonstrated to be efficacious for management of retinoblastoma especially in the presence of vitreous seeds because it can penetrate the sclera and achieve effective concentrations in the vitreous cavity, however the response may be short-standing. This modality is currently under trial. Kaneko and Suzuki have shown that intravitreal injection of melphalan can cure about 50% of eyes with vitreous seeding that have failed to respond to other methods including external beam radiotherapy.

In addition to above-mentioned routes, another significant progress in the treatment of intraocular retinoblastoma is the development of a technique for direct intra-arterial infusion of chemotherapeutic agents including melphalan in which successful cannulation of the ophthalmic artery was performed. There were minimal local complications such as lid edema and conjunctival injection in patients who did not subsequently undergo radiation therapy. The promising results of this study suggest that many globes which are currently enucleated may be salvageable with minimal local and systemic toxicity. This will be particularly useful for situations in which bilateral enucleation seems necessary or in cases in which reluctance to enucleation may predispose to metastatic disease in children whose lives could otherwise be saved.
CONCLUSION

Although enucleation is still commonly employed for treatment of intraocular retinoblastoma, recent advances in the field of ophthalmic oncology such as introduction of novel agents and new routes of drug administration will revolutionize the management of this fatal and sight-threatening disease in future. In the clinical realm it is expected that the advent of less toxic chemotherapeutic agents such as topotecan, 2-DG and antiangiogenesis agents as well as periocular, intravitreal and intra-arterial routes of administration of chemotherapeutic agents will improve cure rates. This will hopefully decrease or eliminate the need for enucleation and external beam radiation with its associated complications. Possible side effects of these new modalities such as an increased incidence of non-ocular cancers, require further studies.

REFERENCES