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Retinoblastoma: Rare Plight in Pediatrics

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Abstract

Retinoblastoma is an eye cancer that typically develops in children before they touch 5 years. Incidence is low, with 1 in 20, 000 live births worldwide. The estimated incidence is variable ranging from 3.4 to 42.6 cases per million live births. Over 80% of cases are in low- and middle-income countries. Retinoblastoma is caused by changes in a gene called RB1. 40 percent of children with retinoblastoma have a hereditary form of the condition. 60 percent of children with retinoblastoma have a sporadic form of the condition, which cannot be passed to the next generation. Most retinoblastoma patients have a white pupil reflex, or leukocoria, instead of a normal black pupil or red reflex. Children with retinoblastoma have pain, red-eye, poor vision, inflammation of the tissue surrounding the eye, different coloured irises, and dilated pupil. Most cases (75%) involve only one eye (unilateral), and the rest (25%) affect both eyes (bilateral).

Management of retinoblastoma is individualized according to patient characteristics and preferences, with the main goals being to save the patient's life Treatment strategies for retinoblastoma involve intravenous chemo reduction, local administration routes of chemotherapy (eg, intra-arterial, intravitreal), focal therapy for tumor consolidation (eg, photocoagulation, thermotherapy, cryotherapy, plaque brachytherapy), external beam radiotherapy, and surgical enucleation.

Introduction

Retinoblastoma was initially described by Dr. James Wardrop in 1809. The tumor was first named RB by Verhoeff and has been referred to by that name since 1926. The incidence rate of retinoblastoma is low 1 in 18000 live births. It is a tumor of the developing retina that arises from primitive retinal stem cells or cone precursor cells [1]. The global retinoblastoma patient survival is calculated to be <30% [2]. RB is characterized by the abnormal phenotypic expression or loss of the tumor suppressor gene. The gene is located within the q14 band of chromosome 13. Leukocoria is the appearance of a white reflection through the pupil. Other common symptoms are strabismus and vision loss. Neovascularization, neovascular glaucoma, hyphema, pseudohypopyon, and vitreous haemorrhage may be observed in advanced cases [3]. Patients with evidence of invasive retinoblastoma should be treated with chemotherapy for 4 to 6 months to prevent metastases [4]. Orbital extension of retinoblastoma can lead to systemic dissemination via the blood vessels, lymphatic system or along the visual pathway to the brain. Overall incidence was 6.3% [5,6].

Table 1: *International Staging of Retinoblastoma*

Clinical Staging	Description
0	Patients treated conservatively
1	Enucleation based on histopathology
2	Enucleation, microscopic residual tumor
3	Regional extension Overt orbital disease Periauricular or cervical lymph node extension
4	Metastatic disease Haematological metastasis (single or multiple lesions) CNS extension (Prechiasmatic lesion, CNS mass, Leptomeningeal and CSF disease)

Table 2: *Signs and Symptoms of Retinoblastoma*

A pupil that looks white, instead of the normal black
A crossed eye, which is an eye looking either toward the ear or toward the nose
Poor vision
A red, painful-looking eye
An enlarged pupil
Different-colored irises

Differential Diagnosis

The most common pseudoretinoblastomas include persistent hyperplastic primary vitreous, Coats' disease and ocular toxocariasis. Fluorescein angiography is particularly useful in differentiating retinoblastoma from Coats' disease [7].

Diagnosis Imaging

B scan ultrasonography: confirms the presence of masses in the posterior segment of the eye. In retinoblastoma, the ultrasound should reveal an irregular mass, which is more echogenic than the vitreous, and commonly has fine calcifications.

Genetic Testing

Mutation testing is an essential investigation, and can be performed on peripheral blood and tumour tissue. Molecular genetic testing for RB1 mutations has 95% sensitivity [8].

Initiating Cure of Retinoblastoma

Enucleation: The technique of enucleation is to gently remove the eye intact without seeding the malignancy into the orbit.

Objectives: Current aim of treatment is to preserve life, vision preservation is secondary at this time. Retinoblastoma remains intraocular and curable for 3-6 months from the first sign of leukocoria.

Table 3: *Indications for enucleation*

Unilateral retinoblastoma or bilateral RB with Reese-Ellsworth stage V disease (damage to the entire retina.)
Tumour invasion in optic nerve, choroid, AC, pars plana, or orbit.
Painful glaucoma with loss of vision.
Tumour was unresponsive to other forms of conservative treatment.
Inability to examine retina secondary to vitreous huge or cataract following conservative therapy.

PMMA, hydroxyapatite, and polyethylene implants are commonly used 4 to 6 weeks after enucleation [9].

Current Approaches in Chemotherapy

Chemotherapy is used in the treatment of both intraocular and extraocular RB, and its administration may be systemic, subconjunctival, intra-arterial or intravitreal. The main objectives of RB treatment are firstly patient survival, the protection of the eye, and finally visual function. All tumors situated at the posterior pole or in the mid-peripheral retina, with a diameter of 15mm or more without vitreous seeding are managed by chemotherapy.

Table 4: *Goals of Chemotherapy*

Reduction of tumor size → RD dealt with focal therapy is the standard of care in early-stage disease. Reduce the use of EBRT (external beam radiation therapy) which reduces second malignancies and orbitofacial growth anomalies in early stage.
Reduce the need of enucleation in early stage.
Reduce the risk of local and systemic relapse in advanced stage.
Improve survival in metastatic disease.

The most common chemotherapy protocol used currently consists of vincristine, etoposide, and carboplatin. Autologous stem cell transplant with high-dose chemotherapy remains the only curative option for metastatic disease. HDAC inhibitors (Belinostat , Droxinostat , Givinostat , Panobinostat , Mocetinostat Abexinostat) etc reduce cell survival in human retinoblastoma cell lines and significantly reduced tumor burden. N-myc is amplified in 10% of human retinoblastoma cases and, therefore, such inhibitors may prove useful in the treatment of a subset of retinoblastoma patients.

Nutlin 3A is a small molecule inhibitor of the MDM2/ MDMX and p53 interaction, which was found to be able to induce cell death in human retinoblastoma cell lines [10].

Chemotherapy Regimens

Table 5: *Drug regimens*

Cisplatin; Cyclophosphamide
Carboplatin and Vincristine
Intra-arterial Melphalan
Periocular Topotecan
Carboplatin, Etoposide, and Vincristine for High-risk disease
Thiotepa, Cisplatin, Cyclophosphamide, Radiotherapy, ASCT

VCE (Vincristine, Carboplatin, Etoposide): 6 cycles Vincristine* Intravenous infusion (push) Day 1 < 36 months 0.05 mg/kg > 36 months 1.5 mg/m2 Carboplatin Intravenous infusion (1 hour) Day 1 < 36 months 18.6 mg/kg > 36 months 560 mg/m2 Etoposide Intravenous infusion (1 hour) Days 1, 2 < 36 months 5 mg/kg > 36 months 150 mg/m2. (Long term treatment is essentially required).

Side effects related to systemic chemotherapy include bone marrow suppression, alopecia, autotoxicity and nephrotoxicity.

[11] Lobaplatin is the third-generation platinum compound with DNA alkylating activity, producing interstrand DNA crosslinks, which result in apoptosis. Lobaplatin overcomes some forms of cisplatin resistance in preclinical tumour models. Lobaplatin significantly inhibited the growth of RB by suppressing tumor cell proliferation by inhibiting the E2F1/Cdc25a/Cdk2 signalling pathway [12].

Vitamin D and its analogues 1,25(OH)2D3, exhibit strong antiproliferative effects on different malignant cell types

Bevacizumab demonstrated a significant suppression of angiogenesis and growth of retinoblastoma in both *in vitro* and *in vivo* models, the compound is likely to be beneficial in the treatment of retinoblastoma.

Tigecycline significantly inhibits proliferation and induces caspase-dependent apoptosis in retinoblastoma cells.

Topoisomerase inhibition (Idarubicin, Epirubicin) is highly effective in retinoblastoma chemo reduction. Intravenous doxorubicin showed both partial and complete responses. A larger study demonstrated an overall response rate of 60% fostamatinib a TKI has been evaluated for RB. Arsenic trioxide (As2O3; has been proved effective in early RB

Methotrexate has been used to treat retinoblastoma metastases to the central nervous system [13].

Highly oriented mesoporous silica nanoparticles (MSN) have also been evaluated for RB treatment. Camptothecin-loaded mesoporous nanoparticles functionalized with the monosaccharide galactose or mannose in combination with one photon or two photon excitation photosensitizers for photodynamic therapy.

Gene therapy: In a phase 1 study, intravitreal injections of an adenovirus vector containing HSVtk followed by treatment with ganciclovir were shown to be safe and effective against vitreous seeds [14].

Table 6: *Types of chemotherapies*

Intra-arterial chemotherapy	Intravitreal chemotherapy
The various agents used for IAC in RB include melphalan, carboplatin, topotecan, and methotrexate. Transient neutropenia develops in 11% patients	Intravitreal chemotherapy with Thiotepa is another well-established targeted therapy accounting for one of the important current treatment modalities for retinoblastoma manifesting vitreous seeds but did not gain popularity due to the risk of tumor metastasis.
Transient neutropenia develops in 11% patients and severe complications include vitreous haemorrhage in 13-27%. Local side effects at the injection site and carotid spasm can also occur.	Satisfactory results have also been reported with an intravitreal methotrexate, carboplatin and topotecan. Extraocular tumor dissemination through the needle track with subsequent metastasis was perhaps the most feared serious event

Periocular means chemotherapy “beside the eye”. This injection may be sub tenon space or subconjunctival. The drugs used are usually carboplatin or topotecan [15].

Table 7: *Indications of External Beam Radiotherapy*

Lesions close to macula or optic nerve.
Larger tumors with vitreous seeding.
Recurrent disease.
Adjuvant postoperative radiotherapy after enucleation in high risk pathologic features.
Palliative radiotherapy - Progression after chemo reduction.

Conventional EBRT in the showed local control rates of 41-56%, with eye survival rates of 60-100% [16].

Thermotherapy

Indicated for small tumors outside retinal arcade < 3mm diameter and 2 to 3mm thick without vitreous or sub-retinal seeds produces control rates of 86%. Complications include focal iris atrophy, peripheral focal lens opacity and retinal vascular obstruction. Transpupillary thermotherapy with diode laser has largely supplanted laser photocoagulation in the modern armamentarium of retinoblastoma treatment [17].

Photocoagulation

Light is focused through dilated pupils under GA and the feeding vessels are coagulated which results in the involution of the tumor. Used for small primary or recurrent tumor in the posterior part of retina < 2.5 mm thick and < 4.5 mm diameter [18].

Exenteration

It is an extremely disfiguring surgery. Upfront exenteration is now obsolete. It is currently performed only in those cases of primary/recurrent orbital disease that fail to respond to neoadjuvant chemotherap [19].

Cryotherapy

A trans-scleral cryoprobe cooled by nitrous oxide is used to double or triple freeze-thaw and destroy the tumour and underlying choroid. Ice crystals lyse the tumour cell membranes. Indications include treatment of small tumors and foci of subretinal or preretinal seeds. Focal therapies have the inherent advantage of eradicating focal areas of tumor formation in the retina without any risk of regional or systemic side effects [20].

Conclusion

A worldwide network dedicated to children and families affected by retinoblastoma is emerging. Mortality from retinoblastoma in the United States is approximately 3%, however, in developing countries is close to 60%.

Management of retinoblastoma is individualized according to patient characteristics and preferences, with the main goals being to save the patient's life and to preserve useful vision. In developing countries, retinoblastoma is accompanied by a high mortality rate due to delayed diagnosis. The best treatment is, and will always be, early treatment. Despite the significant cure rate associated with multimodal therapies for retinoblastoma, there is still a pressing need to develop new therapies that preserve vision and avoid the late effects of currently available interventions. The survival rate of Retinoblastoma in advanced countries is significantly better than in less developed countries.

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