Retinoblastoma-Parents Role and Current Management Role in Increasing Survival

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Brief Introduction

Retinoblastoma is a cancer of the very young child; two-thirds of all cases of retinoblastoma are diagnosed before age 2 years, and 95% of cases are diagnosed before age of 5 yrs. Thus, a case may be classified as unilateral sporadic, bilateral sporadic, unilateral familial or bilateral familial. Bilateral and familial retinoblastoma are caused by a germline mutation and are thus a heritable tumor., Unilateral sporadic retinoblastoma is usually not heritable. Retinoblastoma arises from the retina, and its growth is usually under the retina and toward the vitreous. Involvement of the ocular coats and optic nerve occurs as a sequence of events as the tumor progresses. Invasion of the choroid is common, although occurrence of massive invasion is usually limited to advanced disease.

A "two-hit" model, as proposed by Knudson, was developed based on the finding that children with bilateral retinoblastoma developed multifocal, bilateral tumors at an earlier age than children with unilateral, unifocal tumors. According to the two-hit model, two events are necessary for the retinal cell or cells to develop into tumors. Overall, 85% of children with unilateral disease represent somatic events, but 15% represent the hereditary form with constitutional mutations in the RB1 gene. The RB1 gene was localized and then cloned based on rare children with retinoblastoma who carry a cytogenetically visible constitutional deletion at chromosome 13q14.

DIAGNOSIS

Accurate diagnosis in a child with suspected retinoblastoma is accomplished by taking a detailed history, physical evaluation, external ocular examination, slit lamp biomicroscopy and binocular indirect ophthalmoscopy with scleral indentation.

Parents role - Play a pivotal role in history part. The early they say about symptoms and signs the early we can diagnose and treat the child thereby increasing survival chances. Presentation correlates with laterality; patients with bilateral disease present at a younger age, usually in the first 12 months of life. Most cases present with leukocoria, which is occasionally first noticed after a flash photograph is taken by parent or relative. Strabismus is the second most common presenting sign and usually correlates with macular involvement. Very advanced intraocular tumors present with pain, glaucoma, or buphthalmos. As the tumor progresses, patients may present with orbital or metastatic disease. Metastases occur in the CNS or systemically (commonly in the bones, bone marrow, and liver).

EXAMINATION

Diagnosis of intraocular retinoblastoma is usually made without pathologic confirmation. An examination under anaesthesia with a maximally dilated pupil and scleral indentation is required to examine the entire retina. A very detailed documentation of the number, location, and size of tumors, the presence of retinal detachment and subretinal fluid, and the presence of subretinal and vitreous seeds must be performed. Additional imaging studies include bidimensional ocular ultrasound and magnetic resonance imaging (MRI) (preferred over computed tomography [CT] to avoid radiation exposure). Needle biopsy confirmation is rarely, if ever, necessary. Ancillary diagnostic studies can be helpful in confirming the diagnosis of retinoblastoma. Fluorescein angiography shows early vascularity and late hyperfluorescence of the tumour These imaging studies are important to evaluate extraocular extension and to differentiate

retinoblastoma from other causes of leukocoria.

Evaluation of the presence of metastatic disease also needs to be considered in the subgroup of patients with suspected extraocular extension by imaging or high-risk pathology in the enucleated eye (i.e., massive choroidal invasion or involvement of the sclera or the optic nerve beyond the lamina cribrosa). In these cases, bone scintigraphy, bone marrow aspirates and biopsies, and lumbar puncture are performed. Optic coherence tomography has been found useful in the detection of cystic retinoblastoma that might show less dramatic response to chemotherapy, and it is also helpful in the follow-up of patients to assess macular anatomy.

Genetic counselling is recommended for all patients with retinoblastoma.

GENETIC TESTING AND COUNSELLING

Blood and tumor samples can be tested to determine if a patient with retinoblastoma has a mutation in the RB1 gene. Once the patient's genetic mutation has been identified, other family members can be screened directly for the mutation. The RB1 gene is located within the q14 band of chromosome 13. Exon by exon sequencing of the RB1 gene demonstrates germline mutation in 90% of patients with heritable retinoblastoma.

Although a positive finding with current technology confirms susceptibility, a negative finding cannot absolutely rule it out. A multistep assay that includes the following may be performed for a complete genetic evaluation of the RB1 gene

- DNA sequencing to identify mutations within coding exons and immediate flanking intronic regions.
- Southern blot analysis to characterize genomic rearrangements.
- Transcript analysis to characterize potential splicing mutations buried within introns.

Genetic counseling is an integral part of the management of patients with retinoblastoma and their families, regardless of clinical presentation; counseling assists parents in understanding the genetic consequences of each form of retinoblastoma and in estimating the risk of disease in family members. The identification of genetically susceptible family members can lead to early diagnosis that cannot only be life saving but may avoid the need for enucleation of the affected eye. Genetic analysis also provides important information with regard to the risk for parents (and long-term survivors of retinoblastoma) to have additional children with retinoblastoma

MANAGEMENT

The most important objective in the management of a child with retinoblastoma is survival of the patient, and the second most important goal is preservation of the globe. The focus on visual acuity comes later, after safety of the patient and globe is established.

Standard Treatment Options for Unilateral Retinoblastoma and bilateral Retinoblastoma

1. Enucleation for large intraocular tumors, followed by risk-adapted chemotherapy when the eye cannot be saved.
2. Conservative ocular salvage approaches when the eye and vision can be saved.

- Chemoreduction with either of the following:
- Systemic chemotherapy with subtenon chemotherapy.
- Ophthalmic artery infusion chemotherapy.
- Local treatments including cryotherapy, thermotherapy,EBRT and plaque radiation therapy.

Enucleation :

Most children with unilateral retinoblastoma present with advanced disease, and most of them require enucleation. Other indications for enucleation are for children with bilateral disease where enucleation may be

indicated for the eye with the most advanced disease that does not respond to chemotherapy (rarely, enucleation is indicated for both eyes), for the eye that has failed all known effective therapies, when active tumor is present in an eye with no vision, when glaucoma is present as a result of neovascularization of the iris or tumor invasion into the anterior chamber, and when direct visualization of an active tumour is obstructed by conditions including haemorrhage, corneal opacity, or cataract . Enucleation is curative in 95% of patients with unilateral disease.

EBR therapy:

It is an effective means of curing retinoblastoma. The most common indication for EBR is for the eye in a young child with bilateral retinoblastoma who has active or recurrent disease after completion of chemotherapy and local therapies. Children with small tumors within the macula that do not respond to chemotherapy or have recurrent disease following chemotherapy can benefit from EBR. With EBR therapy, the entire tumor-bearing area of the globe is included along with at least 1 cm of the optic nerve. The prescribed dose to the tumor ranges from 42 Gy to 46 Gy, with the radiosensitive lens receiving significantly less

Chemoreduction:

It is a method of reducing tumour volume to allow for therapeutic measures that are more focused and less damaging. It has evolved to be an important measure in the initial management of retinoblastoma. The chemotherapeutic agents vary depending on the preference of the pediatric oncologist. We presently use carboplatin, etoposide, and vincristine. Other oncologists include only one agent (carboplatin) or two agents (vincristine, carboplatin) in their protocol. The chemotherapy regimen is generally given for 6 cycles to allow for adequate tumor reduction. Focal therapy to the individual tumors is delivered at cycle 2 after achieving adequate tumour reduction and subretinal fluid resolution. The objective of chemoreduction is to reduce tumour size so that focal treatments can be applied to a smaller tumour volume in order to preserve more vision and possibly avoid enucleation and external beam radiotherapy. It is reported that the retinoblastomas decreased a mean of 35% in tumor base and nearly 50% in tumor thickness after 2 cycles of chemoreduction. Subretinal fluid resolved in 76% of cases and both vitreous and subretinal seeds showed regression with the treatment.

Thermotherapy :

It involves the application of heat directly to the tumor, usually in the form of infrared radiation. A temperature between 45°C and 60°C is the goal of this therapeutic approach and is below the coagulative threshold and therefore spares the retinal vessels from coagulation . Thermotherapy alone can be used for small retinoblastomas that are 3 mm in diameter without vitreous or subretinal seeds.

Chemothermotherapy :

Larger tumours or tumours with subretinal seeds are usually treated with a combination of thermotherapy and chemotherapy. Tractional and vaso-occlusive complications that can be seen with thermotherapy alone appear to be less frequent when thermotherapy is used in combination with chemotherapy.

Brachytherapy :

Brachytherapy involves the placement of a radioactive implant (plaque), usually on the sclera adjacent to the base of a tumor. Iodine-125 (125I), gold, and more recently ruthenium have been used . The intention is to deliver a dose of 4,000 - 4,500 cGy transclerally to the apex of the tumor over a period of 2-4 days. This treatment is limited to tumours that are 16 mm in base and 8 mm in thickness, and can be used as the primary treatment or, more frequently, in patients who had failed initial therapy including previous EBR therapy. This modality can also be used when there is a peripheral tumour with focal vitreous seeding around it. Relative

contraindications include larger tumours and those that involve the macula. . Side effects are less common than with EBR and include optic neuropathy, radiation retinopathy, and cataract formation.

Laser Photocoagulation:

Laser photocoagulation is recommended only for small posterior tumors . The treatment is delivered with an argon or diode laser or a xenon arc. The purpose of this treatment is to coagulate all the blood supply to the tumour . Effective therapy usually requires 2-3 sessions at monthly intervals. Complications of this treatment include retinal detachment, retinal vascular occlusion, retinal traction, and preretinal fibrosis

Cryotherapy :

Induces tumour tissue to freeze rapidly, resulting in damage to the vascular endothelium with secondary thrombosis and infarction of the tumour tissue. Cryotherapy may be used as primary therapy for small peripheral tumours or for small recurrent tumours previously treated with other modalities. Tumours are typically treated three times per session, with one or two sessions at monthly intervals. Ninety percent of tumours 3 mm in diameter are cured permanently, and complications are few and rarely serious . Transient conjunctival edema and transient localized serous retinal detachments can occur. Vitreous hemorrhage can be observed in large or previously irradiated tumors.

Subconjunctival Chemoreduction for Retinoblastoma :

Children with advanced retinoblastoma in both eyes or in their only remaining eye are generally treated with systemic chemoreduction and a local periocular boost of subconjunctival carboplatin

ARET12P1 (NCT02097134) (Intra-arterial Melphalan in Treating Younger Patients With Unilateral Retinoblastoma): This pilot clinical trial is studying whether unilateral Group D retinoblastoma, or retinoblastoma affecting one eye that has spread to the vitreous fluid, can be treated with intra-arterial injection. This may provide children with unilateral retinoblastoma a lower chance of needing surgery to remove the eye and reduce the severity of treatment side effects.

Treatment Options for Extraocular Retinoblastoma

Orbital and locoregional retinoblastoma: Treatment includes systemic chemotherapy and radiation therapy; with this approach, 60% to 85% of patients can be cured. Because most recurrences occur in the central nervous system (CNS), regimens using drugs with well-documented CNS penetration are used. Different chemotherapy regimens have proven to be effective, including vincristine, cyclophosphamide, and doxorubicin and platinum- and epipodophyllotoxin-based regimens, or a combination of both.

CNS disease: -Systemic chemotherapy and CNS-directed therapy.

-Systemic chemotherapy followed by myeloablative chemotherapy and stem cell rescue

Trilateral retinoblastoma-Systemic chemotherapy followed by surgery and myeloablative chemotherapy with stem cell rescue.

-Systemic chemotherapy followed by surgery and radiation therapy

Extracranial metastatic retinoblastoma: Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy

Treatment options for progressive or recurrent intraocular retinoblastoma include the following:

1. Enucleation.
2. Radiation therapy (external-beam or plaque radiation therapy).
3. Local treatments (cryotherapy or thermotherapy).
4. Salvage chemotherapy (systemic or intra-arterial).

Treatment options for progressive or recurrent extraocular retinoblastoma include the following:

1. Systemic chemotherapy and radiation therapy for orbital disease.
2. Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy for extraorbital disease

SUMMARY

Imaging techniques and a variety of treatment modalities have resulted in vast improvements in the management of children with retinoblastoma. There is widespread acknowledgment that awareness of the symptoms of the disease by parents and early detection accompanied by early intervention will significantly reduce visual and systemic morbidity and mortality. Molecular genetic studies with identification of germline mutations have made a tremendous impact on the management of the disease.

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