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METHODS

Establishment of "retinoblastoma center" in a tertiary eye care center of Bangladesh - A new hope for retinoblastoma patients

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Retinoblastoma is the most common primary intraocular tumor in children with an incidence of 1:16,000 to 18,000 live birth. Worldwide newly detected cases per year are about 8000 and in India above 1400. It represents 11% of cancer that develops in the first year of life. The revolutionary management strategy has increased the survival rate of retinoblastoma above 95% in developed countries, and this rate is the highest among all pediatric cancers. But still, it is deadly cancer worldwide. Survival from retinoblastoma based on income >90% vs. 40% (in high to low-income countries). The incidence of metastasis is more in lower-income countries (32% vs. 12% in middle-income). Notably, Forty-three percent of the world's estimated cases reside in only 6 countries in Asia (China, Indonesia, Philippines, India, Pakistan, and Bangladesh). The mortality rate varies on different continents. Worldwide estimated death from retinoblastoma is more than 40%, and most of them are from Asia and Africa. Bangladesh is one of the developing countries in the South-East Asia region, and retinoblastoma constitutes 83% of all pediatric cancer under 4 years of age. For proper management of retinoblastoma with an international standard, the establishment of a retinoblastoma center consisting of ocular oncologist, clinical oncologist, radiation oncologist, pediatrician, oculoplastic surgeon, retina specialist, pediatric ophthalmologist, and ocularist is needed. Management includes proper diagnosis, treatment of the disease, genetic counseling, regular follow-up, rehabilitation of survivors, and screening of siblings. Chittagong Eye Infirmary & Training Complex is a tertiary eye care center and one of the referral centers of Bangladesh and is treating retinoblastoma since its inception. Due to the demand of time, the hospital has been reorganized with various facilities to serve retinoblastoma patients with a team approach in 2017. From January 2017 to March 2022, a total of 304 patients were diagnosed. Among them, 132 received vincristine, etoposide, and carboplatin (VEC) chemotherapy from this center, and 79 underwent enucleation with the long optic nerve. Besides treatment, the hospital is conducting sibling screening, visual and psycho-social rehabilitation for the RB survivors, and community awareness programs.

Keywords: retinoblastoma, retinoblastoma center, team approach

Introduction

Retinoblastoma the most common primary intraocular malignancy worldwide. It originates from primitive retinoblastoma, which arises from the inner neuroepithelial layer of the embryonic optic cup (1). About 200 years ago, in 1809, James Wardrop of Scotland described retinoblastoma as a distinct clinical entity (2). No age is immune to retinoblastoma but the most commonly affected age is below 2 years. It may be heritable or non-heritable. The tumor may present as bilateral or unilateral and may be multifocal or unifocal according to its heritance and penetration. Once, this tumor was uniformly fatal. Improvement of treatment facilities in the last two decades has changed the situation, and in the pediatric cancer group, the survival of retinoblastoma is the highest (3–5). It is a potentially

treatable disease with a survival rate better than 95% in developed countries (6). But still, retinoblastoma is deadly cancer worldwide, with an estimated death rate of more than 40% and most of them from Asia and Africa.

Current scenario

Among intraocular tumors of childhood, retinoblastoma is the commonest worldwide and in the first of life, it constitutes about 11% (3). The incidence rate is 1:16000 to 1:18000 live birth (7, 8). Every year in the world about 8,000 and in India above 1,400 new cases are detected (9). It has no racial or sex predilection and can affect various socio-economic groups equally. But lower socioeconomic groups present with more advanced stages.

Retinoblastoma may be unilateral (60%) or bilateral (40%). Some instances showed that children diagnosed with unilateral cases at a younger age have a higher probability of subsequent conversion to bilateral disease (10, 11). The mortality rates in different regions of the world are different. It is estimated that the highest mortality rate is in Africa (70%). The rates in other regions are Asia without Japan (39%), Japan (3%), North America (3%), Latin America (20%), and Oceania (10%) (6).

Approximately 43% of the global burden lives in 6 countries in Asia such as India, China, Indonesia, Pakistan, Bangladesh, and Philippines (12). Although the survival rate in developed countries is highly impressive, the survey shows that it depends on the income of the country as 90% vs. 40% (in high to low-income countries). Literature also shows that the occurrence of metastases is higher in low-income countries (32% vs. 12% in middle-income countries) (13).

Present management protocol

The use of chemotherapy has changed the treatment protocol of retinoblastoma, which was mostly dependent on radiotherapy two decades back. The modern chemotherapy regimen has increased the survival rate up to 95 to 98% in developed countries (11). They are now more interested in sight preservation (14). But the situation is not so surprising in low and middle countries.

Management plan should consider the following:

- Presentation – either bilateral or unilateral;
- Grading of tumor and staging of the patent; and
- Extent of metastasis – local or distant.

The treatment options are presented below in tabulated form in **Table 1**. After all these efforts, enucleation remains the gold standard for some cases of unilateral retinoblastoma.

TABLE 1 | Treatment options for retinoblastoma.

Treatment options	
Local therapy	Laser photocoagulation (Green laser) Transpupillary thermal therapy(Diod laser) Cryo therapy
Chemotherapy	Local chemotherapy • Intravitreal • Intracameral • Periocular Intravenous chemotherapy Intra- arterial chemotherapy Intrathecal chemotherapy
Radiation therapy	Plaque radiation therapy(Brachytherapy) External beam radiation therapy Proton beam therapy
Surgery	Enucleation (Intraocular) Exenteration (Extraocular)

FIGURE 1 | Before and after treatment with I/V chemotherapy, Lt enucleation followed by the prosthesis.

FIGURE 2 | Preparing chemotherapy in the ward.

Chemotherapy for retinoblastoma

Nowadays, chemotherapy became the mainstay of treatment for retinoblastoma. There are various types of chemotherapy.

The different indications of chemotherapy are shown in Table 2.

Role of systemic chemotherapy

Currently one of the main management protocols for retinoblastoma is intravenous chemotherapy in conjunction with local therapy. There are different chemotherapeutic agents and different combinations. From 1996, 6 to 12 cycles of vincristine sulfate, etoposide phosphate, and carboplatin are used in most RB centers as prime chemotherapeutic agents at an interval of 3 to 4 week. (15–18).

The advantages of intravenous chemotherapy are as follows:

- Intraocular tumor control
- Retinal detachment (RD) subsidies
- Save both the globe and sight
- Prevents –Pinealoblastoma and metastasis in case RB of the high-risk group

Non-ocular second cancer risks are also reduced.

Chemotherapy schedule for intraocular retinoblastoma

Day 1: Vincristine + Etoposide + Carboplatin

Day 2: Etoposide

Standard dose chemotherapy (3-4 weekly intervals, 6 cycles):

Vincristine 1.5 mg/m22 (0.05 mg/kg for children <36 months of age and maximum dose <2 mg), etoposide 150 mg/m (5 mg/kg for children <36 months of age), and carboplatin 560 mg/m2 (18.6 mg/kg for children <36 months of age).

TABLE 2 | Indications of chemotherapy.

Intravenous	Intraocular retinoblastoma • Bilateral • Some unilateral Orbital retinoblastoma High risk retinoblastoma Metastatic retinoblastoma
Intra-arterial	Intraocular retinoblastoma as primary treatment(Group B and C) Refractory intraocular retinoblastoma as secondary treatment.
Periocular	Recurrent or residual vitreous seeds Bilateral retinoblastoma with poor prognosis at diagnosis. In cases with contraindication of systemic chemotherapy
Intravitreous	Recurrent vitreous seeds Residual vitreous seeds
Intracameral	Seeds in the anterior segment not responding to systemic chemotherapy.
Intrathecal	CNS metastasis - if CSF is positive

FIGURE 3 | Group counseling.

High-dose chemotherapy (3-4 weekly intervals, 6–12 cycles):

Vincristine 0.025 mg/kg,

Etoposide 10-12 mg/kg,

Carboplatin 28 mg/kg

Management of retinoblastoma also includes proper follow-up, genetic counseling, rehabilitation of survivals, and screening of siblings.

Situation in Bangladesh

Sarwar et al. mentioned retinoblastoma, leukemia, and bone tumors (malignant) as the most common malignancies in the 0 to 14 years age group among Bangladeshi children in his "Epidemiology of childhood and adolescent cancer in Bangladesh, 2001–2014." Retinoblastoma constitutes 83% of cancer in 0-4 years age group (19).

Another study "Predicted Trends in the Incidence of Retinoblastoma in the Asia-Pacific Region" by Usmanov RH, Kivelä T stated that in the Asia-Pacific region, about 90% of patients with retinoblastomas reside in China, Indonesia, India, Pakistan, Bangladesh, Philippines, Iran, Vietnam, Japan, and Afghanistan that is only in ten countries. They stated that in 2012, the detected case of retinoblastoma in Bangladesh was 184.

In Bangladesh, there are few tertiary centers where treatment of retinoblastoma is available but not total care. For this reason, patients have to move to different centers for further treatment. Most of the patients are lost in this way and ultimately endangers the life of children. Also, parents are not aware of the white pupil, so most patients are late presenters, and this sometimes creates difficult situations for health facilitators. These problems are almost the same in other Asian countries. Important problems are as follows (12) general people are less aware of RB, which causes delayed presentation.

- National Screening Program on RB has not started even in a developed country.
- Lack of specialization in the field of RB with a very few organized centers.
- Lack of accessibility and lack of information.
- Social facts, economical issues, religious beliefs, and gender biasness.
- Poor compliance to treatment.
- Non-availability of single-center multi-disciplinary team approach.
- Counseling and support group deficiency.
- Prosthetic shell fitting clinics lacking in most hospitals.

What we are doing at Chittagong Eye Infirmary?

Chittagong Eye Infirmary and Training Complex is a tertiary eye care center and a referral center in Bangladesh. From the very beginning, we are treating retinoblastoma. This institute started a multidisciplinary team approach to management in 2017. The management team consists of an ocular oncologist (Retinoblastoma specialist), oculoplastic surgeon, retina specialist, pediatric ophthalmologist, pediatrician, oncologist, anesthesiologist, and ocularist. Along with medical and surgical treatment, we are doing genetic and general counseling, screening of siblings, and rehabilitation. We are serving RB patients following international standards but at a free of cost or at a minimal cost. Services available at Chittagong Eye Infirmary are shown in **Table 3**.

TABLE 3 | Services available at Chittagong Eye Infirmary for RB patients.

Name of Services	
1. Proper diagnosis	
2. Treatment	Chemotherapy • Intravenous • Periocular • Intravitreal Surgeries • Enucleation • Exenteration Local therapy • Cryo therapy • Green Laser • TTT
3. International standard follow-up schedule	
4. Genetic and general counseling	
5. Screening of sibling	
6. Visual and psycho-social rehabilitation	
7. Awareness program	
8. Reliable histopathology and proper data preservation service	

In the last 5 years (2017-2022). we have diagnosed 304 cases of retinoblastoma, and among them, 132 children received vincristine, etoposide, and carboplatin chemotherapy. Notably, 79 children underwent enucleation with the long optic nerve. In the meantime, we trained our junior doctors and midlevel personnel for taking care of these patients. In the COVID situation, we continued the treatment facilities with extra care for parents and accompanying persons on the hospital campus, 40 children received chemotherapy and local therapy, and 17 surgeries were performed under an emergency protocol between February 2020 and April 2021.

As treatment cost is always a burden for a family, we, therefore, provided the services at free of cost or at a minimal cost from the beginning of the center. Both Children Eye Cancer Foundation of Germany (KAKS) and Chittagong Eye Infirmary is supporting the treatment, food, and accommodation cost under a project named "CEITC-KAKS chemotherapy project".

The schedule of chemotherapy, physical condition of patients, and their reports are monitored regularly by telephone and using different apps such as WhatsApp, IMO, messenger, etc. Many children need a blood transfusion as an adverse effect of chemotherapy. For managing these situations, we have a blood donor team also.

In 2019, this institution started transpupillary thermotherapy (TTT) treatment, and 94 children received TTT up to March 2022.

Conclusion

Treatment of retinoblastoma is a long-running process, and a team approach is needed for proper management. The cumulative treatment cost of this disease is high. So treatment cost is a burden for families as most families belong to low and middle income. Our hospital is bearing most of the costs of these families and providing services at international standard. We are taking further measures for our improvement. To make this effort successful, donations and support from individuals, institutions, governments, and different NGOs are needed. One-stop services for retinoblastoma will increase treatment compliance, and more lives can be saved.

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