Review Article

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Retinoblastoma: A Glance

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Abstract

Retinoblastoma (Rb) is a widely spreading malignant condition during childhood across the globe. It is an intraocular tumor developing from immature cells of retina. Since retina is an outgrowth of neural tissue, advancing tumor poses threat of spread of malignant cells to orbit and neural tissue of brain. Tumor arises as a result of mutation in Rb1 gene located on chromosome 13 or due to amplification of somatic MYCN. Clinical presentation of tumor is characterized by 'leukocoria'. Accurate diagnosis and wisely opting the therapeutic approach with minimum side effects and good prognosis is indeed the best way to deal with this malignancy.

Keywords: Retinoblastoma, Leukocoria; Chromosome 13; RB1 Gene; 13q14 Deletion.

Introduction

One of the commonest intraocular malignancy among children is retinoblastoma (Rb). It is a primary malignant disease which solely occurs in childhood. [1]. Tumor is usually diagnosed by the age of 2-5 years [2,3]. By so far, mainly two varieties of retinoblastoma are common, heritable and non-heritable [4].

Hereditary type of Rb results from mutation in Rb1 gene. Non-hereditary type occurs when autonomous somatic mutations or epigenetic silencing via methylation takes place. Apart from these, retinoblastoma can result from amplification of somatic MYCN [4]. Heritable form accounts for 40% whereas those arising from de novo germline mutations account 80% of retinoblastoma [5]. Hereditable form usually presents as bilateral or multifocal ocular involvement but it may also manifest as unilateral or unifocal [6]. Earlier sign and symptoms are observed in bilateral compared to that of unilateral retinoblastoma [7, 8]. Heritable cases are more likely to emerge with primitive neuroectodermal tumor [9,10]. Malignancies of eye, orbit, nasal cavities, soft tissue sarcomas and osteosarcomas are often found positive in retinoblastoma patients. These patients are also at greater risk for developing carcinomas of skin and brain [11-13].

Individuals suffering from hereditary type are at higher risk of developing second primary tumor [14]. A study on patients under follow-up treatment of retinoblastoma reveals that 38% developed second primary tumor, amongst those who were treated by radiation.

Whereas among those who did not underwent any kind of radiotherapy, only 21% developed a second tumor [11]. Another study shows second tumors are more likely to emerge in those who received external beam radiation therapy and chemotherapy [15]. It has been shown that proton radiotherapy offers lower risk for second tumor when compared with conventional photon radiotherapy. The only disadvantage associated with proton radiotherapy is that long term follow-up is required [16].

The above data is clearly suggests that retinoblastoma is linked with various types of cancers and also that certain treatment modalities lead to risk

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for developing a second primary tumor.

Genetics

Retinoblastoma is tumor of genetic origin. Tumor arises from immature cells of retina. Mutation of Rb1 gene on chromosome 13 results in hereditary form of retinoblastoma. Pattern of growth and development of a cell is controlled by chromosomal genetic code. Mutation in this genetic code can result in development of malignancy. Heritable type of Rb tumor is more often bilateral [17]. Minor fraction of patients suffering from retinoblastoma show deletion of band 13q14. Nearly 20% of Rb patients reveal either monosomy 13 or band 13q14 deletion. Significant amount of patients exhibit trisomy 1q and i(6p) [18]. Some studies reveal that those who survived inherited form of tumor have high risk for developing non-ocular tumors. High percentage of Rb patients who had undergone enucleation exhibit histopathological risk factors and clinical predictors [19,20].

Rb1 gene is cloned tumor suppressor gene. This gene encodes for a protein which regulates cell cycle in negative manner. Heterochromatin is stabilized by this protein for maintenance of chromatin structure as a whole. The gene is active in hypo phosphorylated form and binds transcription factor E2F1 [21,22]. Required condition for development of malignancy is alterations in both the alleles of Rb1 gene. In non heritable variety of tumor both of the mutations take place in somatic cells, hence is not inherited to the child [23-25]. All individuals suffering from hereditary form of this tumor are heterozygous for alterations in Rb1 gene. Heritable form of retinoblastoma is passed as autosomal dominant trait. These patients are at great risk for developing a second primary tumor especially those who have undergone external beam radiation therapies. Numerical figures of mean of Rb tumor foci is inconsistent in carriers of mutant Rb1 alleles and depends upon extent of functions of normal allele. Genetic modification alters the phenotypic expression of heritable form of the disease [26-29].

Diagnosis

Precise diagnosis is an important tool in management of the disease. Thorough history and external examination of eye of suspected patient reveals a lot about the disease. Diagnosis is made by recognizing the classic appearance of retinoblastoma (leukocoria), which varies with different stages of tumor. Earliest clinical stage of Rb presents as faint, slightly translucent lesion with basal dimensions less than 2 mm. As tumor grows, retinal blood vessels are dilated and a stage ahead of it exhibits foci of calcification. Large tumors exhibit the characteristic appearance of leukocoria which is produced due to reflection of light from white tumor mass. Retinoblastoma may be endophytic or exophytic on the basis of growth pattern. Endophytic cases present white, hazy mass which obscures blood vessels of retina, as tumor grows from retina to vitreous humor. While as in case of exophytic type, growth is from retina to sub retinal space. Endophytic type of growth pattern often stimulates endophthalmitis, andexophytic type usually leads to retinal detachment. Less frequently Rb may be characterized by flat retinal infiltration by malignant cells, without any visible tumor mass [30].

Although, a confirmation is achieved by binocular indirect ophthalmoscopy with scleral indentation and slit lamp bio microscopy. In order to accurately locate all the tumor, procedures are performed under anesthesia. Needle biopsy may be done in necessary cases. Vascularity of retinal blood vessels can be seen through fluorescin angiography. Tumor and calcification can be diagnosed via ultrasonography and computed tomography. Optic coherence tomography may be valuable in cystic cases of Rb. Optic nerve and brain tissue may be evaluated through magnetic resonance imaging to assess extent of lesion [30,31].

Management

A treatment therapy of retinoblastoma aims primarily at saving the life of patient. Other goals are preserving the eyeball and then securing the vision as far as possible. Management type alters according to stage of tumor, its location, risk of subject for second primary tumor and laterality. Chemo reduction has emerged out as one of the important treatment modality for reducing the tumor volume. Various chemotherapeutic agents such as etoposide, carboplatin, vincristine are commonly used. Basic concept of using chemo reduction is to diminish the tumor mass so that focal therapy can be applied over a small area in order to secure maximum vision and to avoid radiation therapy and enucleation [32]. One major issue associated with chemo reduction is recurrence of sub retinal and vitreous seeds [33]. A study reveals that during 7 years of follow-up treatment, recurrence percentage of tumor was 45%, in those treated with chemo reduction alone. Whereas, it was 22%, those were provided chemo reductionalong with thermotherapy or cryotherapy [34]. Systemic route is preferred in advanced cases of the disease. Patients are given subconjuctival carboplatin [35].

Another mode of treatment is focal therapy. These are mainly applied when tumor mass has been reduced through chemo reduction. These include laser photocoagulation, thermotherapy, cryotherapy and plaque radiotherapy. Laser photocoagulation is used to treat small tumors located posterior to the equator.

It is not very commonly used as its outcome depends on vascular coagulation. And for the same reason it is not used when patient is receiving chemoreduction. Here, indirect ophthalmoscopic argon or green diode laser is employed to treat the tumor mass [36]. Whereas, in thermotherapy diode infrared laser beam, conveying temperature range between 42°C to 60°C, is used to treat the tumor. It produces synergistic effect when used in conjunction with chemoreduction as well as with radiation therapy [37].

Cryotherapy utilizes triple freeze-thaw at interval of one month. Disadvantage with this treatment modality is that it fails in presence of vitreous seeds [38]. In case of failure of cryotherapy, plaque radiotherapy is employed. It is used in case of large tumor mass. In this mass is irradiated trans-sclerally, where a radioactive implant is placed over sclera, on the base of tumor [39].

External beam radiation therapy is one of the effective modes of treatment for retinoblastoma since Rb is radiosensitive. It is often employed in advanced stages of the disease. But main drawbacks of therapy are recurrence of tumor and stimulation of second tumor in irradiated field [40, 41].

Enucleation is the option preferred when tumor has advanced to greater extent and there is chance of involvement of other important structures such as optic nerve, orbital cavity. In this therapy, eyeball is carefully removed out of the orbital cavity, being precautious of not seeding any malignancy in orbit and replaced with an implant [42].

Conclusion and Future Prospectus

Now a day's retinoblastoma has emerged as a challenge to diagnose and treat. Prime task is to reach on precise diagnosis via careful examination. Next essential is to fix up a therapeutic approach with good prognosis. Patient age, size, location, extent, laterality of tumor mass are some of the factors to be considered while choosing treatment modality. Chemoreduction along with different forms of focal therapies has definitely improved the prognosis of retinoblastoma in past few years.

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