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Recent Management of Retinoblastoma- A Review Article

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Review Article

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Abstract: Retinoblastoma is the commonest primary intraocular malignancy of childhood. Reported incidence varies from 1 in 15,000 to 1 in 18,000 live births. Early detection and treatment of retinoblastoma can not only salvage the eye and vision but also the life of the patients. The management of retinoblastoma needs a multidisciplinary panel approach. Various treatment options include enucleation, radiotherapy like external beam radiation (EBRT), focal therapy like cryotherapy, laser photocoagulation, transpupillary thermotherapy (TTT), systemic chemotherapy, chemoreduction etc. Over the past two decades there has been tremendous advancement in the treatment of retinoblastoma like intra-arterial chemotherapy, intra-vitreal chemotherapy periocular chemotherapy etc. The purpose of this article is to highlight the recent updates in the treatment of retinoblastoma.
Keywords: retinoblastoma, intra-arterial chemotherapy, intra-vitreal chemotherapy.

INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy in children affecting 1 in 15000 live births. The estimated incidence varies from 3.4 to 42.6 cases per million live births [1]. Reported incidence ranging from 1 in 15000 to 1 in 18000 live births [2]. There is no racial or gender predisposition in the incidence of retinoblastoma. Retinoblastoma is bilateral in about 25 to 35% of cases [3]. The average age at diagnosis is 18 months, unilateral case being diagnosed at around 24 months, and bilateral cases before 12 months [3]. Early detection and treatment of retinoblastoma can not only salvage the eye and its sight, but also live of the patient. Retinoblastoma must always be considered in the differential diagnosis for any child presenting with leucocoria, strabismus, red eye or a cellulitis like symptoms.

The main objective of management of retinoblastoma can be divided into three catagories. The primary objective is the survival of the patient, secondary objective is preservation of the globe and the tertiary objective is preservation of function (vision).The management of retinoblastoma needs a multidisciplinary team approach including an ocular oncologist, paediatric oncologist, radiation oncologist, radiation physicist, genetist and an ophthalmic oncopathologist [4].

MANAGEMENT PROTOCOL

Current management protocols include management of intraocular retinoblastoma, orbital retinoblastoma and metastatic retinoblastoma. The management strategy depends on the stage of the disease. Management of retinoblastoma is highly individualized and is based on several considerations- ages at presentation, laterality, tumour location, tumour staging, visual prognosis, systemic condition, family and societal perception, prognosis and cost effectiveness of treatment in a given economic situation [4].

Management of intraocular retinoblastoma

- Focal therapy(cryotherapy, laser photocoagulation, transpupillary thermo therapy)
- Trans sclera thermotherapy6, plaque radiotherapy
- Local therapy (EBRT, enucleation)
- Systemic therapy (chemotherapy)
- Adjuvant therapy

Management of orbital retinoblastoma:

- EBRT
- High dose chemotherapy
- Enucleation
- Exenteration

Management of Metastatic retinoblastoma

- High dose chemotherapy

- High dose chemotherapy with autologous stem cell rescue.

EVOLUTION IN THE TREATMENT OF RETINOBLASTOMA

Once retinoblastoma was considered almost to be fatal. But there were reports of survival following enucleation in late 1800s and early 1900s. Following enucleation Radiation as a treatment modality was reported in 1903, which became the preferred treatment modality(from external beam to proton beam and brachytherapy etc) till 1990s. Later the concept of photocoagulation was developed to treat small tumour in 1950s by Meyer and Schwickerath in Germany. To treat small peripherial tumours cryotherapy was introduced as a treatment option by Linkoff in 1960s.

Systemic chemotherapy has become popular as a treatment of choice for intraocular retinoblastoma since mid 1990s as because it causes dramatic reduction in tumour size with a high survival rate. But in many cases it fails to cure the disease alone where it has to be combined with radiation, laser, cryo even enucleation. Combined therapy has been shown to have better globe salvage rates than chemotherapy alone in both early as well as advanced retinoblastoma [5, 6]. Another treatment option which includes chemoreduction with transpupillary thermotherapy achieved tumour control in 83% of REgroup 5 tumours. Retinoblastoma less than REgroup 5 showed 100% control [7].

Despite so much advancement in the treatment of retinoblastoma, enucleation is still the treatment of choice in many cases of retinoblastoma. Primary enucleation is still the treatment of choice for advanced intraocular retinoblastoma with neo-vascularization of iris, secondary glaucoma, anterior chamber invasion, tumour occupying >75% of the vitreous volume, orbital inflammation, hyphaema or vitreous haemorrhage [8]. It is the standard treatment for retinoblastoma of ICRB group E. Adjuvant therapy following enucleation has been shown to decrease metastasis even in advanced retinoblastoma [9].

INTRA-ARTERIAL CHEMOTHERAPY

Over the past two decades there is tremendous advancement in the treatment of retinoblastoma with the trend away from systemic chemotherapy towards more selective chemotherapy is underway.

Japanese physicians in 2004 introduced the treatment of retinoblastoma called intra-arterial chemotherapy by injecting melphalan into the ophthalmic artery. During the temporary occlusion of the Internal carotid artery, a small catheter is passed into the ophthalmic artery and then inject the chemotherapeutic agrents directly in to the ophthalmic artery. This procedure is more effective, faster, better and safer then systemic chemotherapy. This procedure is performed in 187 patients (563 intra-arterial chemotherapy) with no reported serious complications. The common complications reported were mild transient bradycardia, periorbital erythema and swelling [10].

Later another technique was introduced by Abramson *et al*. [11, 12] which allowed repeated cannulation of the ophthalmic artery with advanced retinoblastoma without occluding the distal cerebral blood flow at the time of infusion. The studies using this technique reported significant tumour control and restoration of vision in children with RE group 5. No severe side effects were reported. In this study only one patient required enucleation.

A more recent study done by Marr *et al*. in 2012 [13] reported the use of three drugs in this intra-arterial treatment with carboplatin, melphalan, and topotecan. Survival at 24 months was 75%. Shields et al in their large study reported successful treatment using this regimen. These studies report showed that selective intra-arterial chemotherapy with carboplatin, melphalan and topotecan is effective in the treatment of retinoblastoma and decreases the toxic effect during treatment. No deaths or strokes have been reported but in some cases vision-threatening vascular complications have been repoted.

BRIDGE CHEMOTHERAPY

In 2012 Gobin YP *et al*. [14] in their study reported that sequential intravenous chemotherapy followed by intra-arterial chemotherapy called bridge chemotherapy for young infants with retinoblastoma may be considered in eyes in which cannulation of ophthalmic artery is not possible.

INTR-VITREAL CHEMOTHERAPY

This treatment is found to be effective at a low cost but the potential for tumour dissemination through the needle tract following intra-vitreal penetration has limited its use. 90.4% and 100% patient survival rate respectively was repoted by a recent study of intravitreal melphalan [15]. T Ghassemi F *et al.* [16] in their study reported effective treatment with intravitreal combination melphalan (40microgram in 0.04 ml of diluent) and topotecan (8-20microgram in 0.04 ml of BSS). No cases of episcleral or orbital extension were reported in this study.

PERIOCULAR CHEMOTHERAPY

Posterior subtenon delivary of carboplatin has been demonstrated to be efficacious in the management of RE Group VB retinoblastoma with vitreous seeds because it can penetrate the sclera and achieve effective concentrations in the vitreous cavity [17].

Abramson *et al.* demonstrated subconjunctival carboplatin in ICRB group c and d eyes [18]. Periocular Topotecan has also been tried as adjuvant therapy in patients with retinoblastoma [19].

TREATMENT OF EXTRAOCULAR EXTENSION

Extraocular retinoblastoma is considered almost always fatal. But there are reports of success with neoadjuvant chemotherapy followed by surgical debulking and chemotherapy or radiation where indicated.

For systemic metastasis management include high dose of chemotherapy with radiation therapy and high dose of chemotherapy with autologous stem cell rescue. High dose of chemotherapy involves high dose of vincristin, cisplatin, cyclophasphamide and etoposide for four cycle followed by one cycle of high dose of carboplatin, thiotepa and etoposide [20].

NEWER TREATMENT OPTIONS

The newer treatment includes genetic therapy and viral vectors. A recent study demonstrated the use of viral vector to infect the retinoblastoma cells from enucleated eye [21]. This procedure has been under research to find out as possible mechanism to target retinoblastoma cells directly. Another recent study evaluated the efficacy of subconjunctival nanoparticle carboplatin in transgenic mice [22].

Inhibition of glycolysis with with 2-deoxy-d-glucose targets the cellular mechanism that hypoxic tumour cells used for survival. Hence the inhibition of glucose metabolism in hypoxic environment is being studied as a possible treatment for cancer treatment [23].

A recent study has evaluated the potential effect of VEGF inhibitor bevacizumab (Avastin, Genentech) on angiogenesis and tumour growth factor of retinoblastoma in vitro and in vivo showed 75% reduction in tumour growth without significant systemic toxicity [24].

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