Review Article

Local Chemotherapy for Retinoblastoma

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The new treatment modalities of retinoblastoma have been very effective in saving the vision, salvaging the globe and improving the life expectancy of patients. The treatment options include chemotherapy, that can be intravenous chemotherapy, periocular chemotherapy, intravitreal chemotherapy and intra-arterial chemotherapy, and local modalities i.e. transpupillary thermotherapy, cryotherapy, laser photocoagulation, radiation treatment using plaque brachytherapy or external beam radiation therapy (EBRT). The most common intravenous chemotherapy drugs are carboplatin, vincristine, and etoposide. The drugs for periocular chemotherapy are Topotecan and carboplatin. For intravitreal chemotherapy the most commonly used drugs are methotrexate, topotecan and melphalan. For intra-arterial chemotherapy drugs used are melphalan, topotecan and rarely carboplatin. The treatment options can be used as single treatment or as adjuvant to consolidate treatment, depending upon the stage of disease. Advanced stages of disease and orbital involvement have poor prognosis.

Key words: Retinoblastoma, Chemotherapy, Treatment.

In childhood malignancies Retinoblastoma (Rb) is the most common intraocular malignancy. It is more common in children before three years of age. Retinoblastoma may be unilateral or bilateral, unilateral retinoblastoma is more common. It may be heritable or non-heritable. Retinoblastoma may present as endophytic or exophytic tumor. Diagnostic methods include examination under anesthesia, indirect ophthalmoscopy, B scan, CT scan, MRI scan and retcam imaging. Treatment of retinoblastoma is improving its outcomes and there is lot of progress. The new treatment modalities of treating retinoblastoma have been very effective in saving the vision, salvaging the globe and improving the life expectancy of patients[1]. The treatment options include chemotherapy, that can be intravenous chemotherapy, periocular chemotherapy, intravitreal chemotherapy and intra-arterial chemotherapy, and local modalities i.e. transpupillary thermotherapy, cryotherapy, laser photocoagulation, radiation treatment using plaque brachytherapy or external beam radiation therapy (EBRT). The most common intravenous chemotherapy drugs are carboplatin, vincristine, and etoposide. The drugs for periocular chemotherapy are Topotecan and carboplatin. For intravitreal chemotherapy the most commonly used drugs are methotrexate, topotecan and melphalan. For intra-arterial chemotherapy drugs used are melphalan, topotecan and rarely carboplatin. The treatment options can be used as single treatment or as adjuvant to consolidate treatment, depending upon the stage of disease. Advanced stages of disease and orbital involvement have poor prognosis.

CLINICAL FEATURES

Patients with Retinoblastoma (RB) may have different clinical presentations including strabismus and leukocoria. In initial evaluation, it is important to differentiate RB from other similar diseases by using ultrasonography. Coats disease, toxocariasis and persistent fetal vasculature (PFV) are common differential diagnosis of RB. Recently 111 cases were analyzed for suspected RB, in which 68% patients were found to have RB, while rest of the 32% patients had other diseases with an alternate diagnosis of (PFV) 31% and Coat's disease (29%)[2].

Classification of retinoblastoma has changed with advancement in treatment strategies. In the past Reese-Ellsworth (RE) classification of retinoblastoma has been used to predict globe salvage and external beam radiation was the primary treatment modality at that time[3]. However, the R-E classification didn't address sub-retinal and vitreous seeding. In order to predict better treatment outcomes, a modified classification was developed by adopting local consolidation treatment and chemo reduction. Thus, the International Classification of Retinoblastoma was developed, with primary focus on focal and diffuse vitreous and sub-retinal seeds[4,5].

EPIDEMIOLOGY

In pediatric ocular malignancies, RB is highly curable tumor[6]. Many epidemiological studies on RB showed that tumor affects 1 in 16000-18000 births approximately while 7000-8000 new RB cases are being reported annually worldwide[7,8].

Retinoblastoma is an important primary intraocular tumor. The annual incidence rate of retinoblastoma is approximately 3.5 per million for children younger than 15 years of age[9] and 11.8 per million for children younger than 4 years[5,7]. The combined incidence rate for children younger than 14 is estimated to be 53 – 60 per million[6,9]. In United States the survival rate approaches 100% while in other developing countries it is much lower. Survival rate is 80 – 89%[10-20], 83%[17], 81%[18,19] and 48% in Latin America, Iraq, China and India respectively[20]. It is much lower 20 – 46% in Africa[21,22]. Additionally, with the increasing population, especially in Africa and Asia, retinoblastoma is "getting more importance[6].

TREATMENT

The treatment options having less systemic side effects, better outcomes in term of saving vision, salvaging the eye and improving the life expectancy of the patient are getting more popularity and are used more frequently mostly in first world countries. Local chemotherapy is more targeted and is discussed further:

Selective Intra-Arterial Chemotherapy: (SIAC)

The need of selective intra-arterial chemotherapy is very high because of less systemic side effects although systemic chemo therapy and consolidation with focal treatments may have good treatment outcomes but on the other hand systemic chemotherapy may have very fatal side effects, so selective intra-arterial chemotherapy (SIAC) is one of the best options in which chemotherapy drug is delivered to the eye through ophthalmic artery and it is most targeted[19]. SIAC has minimal side effects as compared to systemic chemotherapy. In Japan in 2004, scientists used a novel technique named as Selective Ophthalmic Artery Infusion (SOAI), in which drug was delivered at distal part of ophthalmic artery through trans femoral approach[20,21]. SOAI was later modified by Abramson and Gobin in which chemo drug was delivered in ophthalmic artery that was more precise and he named it super selective intra-arterial chemotherapy (SIAC)[22]. The drug used by them was Melphalan for SIAC and no serious side effects were observed. Gobin et al used SIAAC in bilateral and unilateral advanced stage[23]. SIAC has high safety in terms of systemic and local side effects[24]. Role of IAC in recurrent disease was studied and it was observed that SIAC with melphalan alone or combined with Topotecan has very encouraging outcomes and tumor control was achieved in 75% of cases and in 67% cases the globe was successfully salvaged[25].

Chen M et al. presented the IAC outcomes in infants less than three months of age. Tumor regressed in 12 eyes out of 13 after 28 months. They reported this treatment as very promising for infants less than three months having retinoblastoma[26]. Shields et al studied the outcomes of IAC with melphalan in cases where intra-vitreal melphalan was given before or after IAC. They observed high success in globe salvage when IAC is consolidated with intra vitreal chemotherapy[27]. Leal-Leal et al. gave topotecan and melphalan combine SIAC in advanced stages of tumor and they reported 55% prevention of enucleation in their patients[28].

A short study conducted in India showed complications and outcomes of SIAC in local patients. They used melphalan (3 mg/5 mg/7.5 mg) and topotecan (1 mg) (n = 4) or melphalan (3 mg/5 mg/ 7.5 mg) alone (n = 2). A mean of three IAC sessions were given in each eye. They observed vitreous hemorrhage and diffuse choroidal atrophy in one case and they had good treatment response[29].

Periocular Chemotherapy

Carboplatin injection has been used for control of RB as periocular therapy along with systemic chemotherapy. Periocular injection of Topotecan

0.18 mg/kg has been advocated in recent years in adjuvant with systemic chemotherapy. In comparison with intravenous route, same level of periocular chemotherapy can be achieved in 30 min within vitreous and doses that are 6 – 10 times that of intravitreous route with effect lasting for hours. To deliver the chemotherapy common route being used are subconjunctival or subtenon's space location. Because of recurrences of disease, periocular therapy is usually combined with systemic therapy in order to enhance the local dose in vitreous. Complications of this local therapy include ecchymosis, periocular edema, ocular muscle fibrosis causing squint, atrophy of orbital fat and optic disc atrophy. Long-term complications have not observed and yet to be published[30].

Intravitreal Chemotherapy

Vitreous seeds usually respond poorly to systemic chemotherapy, because of low drug concentration in vitreous due to being an avascular structure. Intra-vitreal chemotherapy is basically used as salvage therapy in cases of persistent vitreous seeds[31]. The recommendations by Inomata and Kaneko were that melphalan is the most effective drug for seeds in retinoblastoma[33].

Munier et al[33] also used melphalan for vitreous seedlings in retinoblastoma in a dose of 20 – 30 µg/ 0.1 ml. The technique of intravitreal injection of melphalan was given 3-3.5 mm from limbus and triple thaw cryotherapy was done at injection site soon after taking out the needles to prevent needle tack seeding. The globe is rotated so that drug may be distributed in the vitreous equally. Shield et al described high success rate of intravitreal chemotherapy and showed 100 percent results in 24 months follow up.[34] Topotecan can also be used for intra-vitreal chemotherapy in vitreous seedlings in concentration of 8 – 20 µg/0.04 ml and it has longer half-life than melphalan. Combination of intra-vitreal chemotherapy is also practiced. The effect of intravitreal topotecan (8 – 20 µg of topotecan dissolved in 0.04 mL of balanced salt solution) combined with melphalan (40 µg of melphalan in 0.04 mL of diluent) was found to be safe in 9 eyes by Ghassemi et al[35]. There are side effects of intra-vitreal chemotherapy that have been studied by different authors and found that safe dose 20 – 30 µg has preservation of normal retinal functions as studied on electroretinogram (ERG), while others reported decreased ERG amplitudes indicating permanent retinal toxicity[36].

CONCLUSION

Local chemotherapy for retinoblastoma is safe and effective.

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