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Recent advances in management of retinoblastoma: A review

Bhavna Chawla, Gautam Lokdarshi, Sushmita Pathy

Bhavna Chawla, Gautam Lokdarshi, Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi 110029, India
Sushmita Pathy, Department of Radiotherapy, IRCH, All India Institute of Medical Sciences, New Delhi 110029, India
Author contributions: Chawla B contributed to the conception and design, literature search, writing the article, critical revision of the article; Lokdarshi G and Pathy S contributed to writing the article, literature search; all authors final approval of the article.

Correspondence to: Bhavna Chawla, MS, Additional Professor, Ocular Oncology and Pediatric Ophthalmology Service, Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. bhavna2424@hotmail.com
Telephone: +91-11-26593088
Fax: +91-11-26588919
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Abstract

The management of retinoblastoma has evolved significantly over recent years. Current treatment options aim to preserve the globe as well as vision with minimum morbidity. High resolution imaging has improved tumor detection and is useful for prognosticating cases and monitoring response to treatment. Targeted chemotherapy such as intra-arterial and intra-vitreal chemotherapy has shown promising results and these routes are being increasingly employed world-wide for globe preservation. The advent of new radiotherapy techniques has led to improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. This review aims to highlight newer advancements in the field of diagnosis and management of retinoblastoma that have been introduced in recent times, with a special emphasis on globe-preserving therapy.

Key words: Retinoblastoma; Recent advances; Chemotherapy; Radiotherapy

Core tip: The management of retinoblastoma has improved significantly over the past few decades. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The purpose of this article is to review the literature on various key developments in the field of retinoblastoma, with particular emphasis on globe-conserving treatment.

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INTRODUCTION

The diagnosis and management of retinoblastoma (RB) often presents as a challenge to the ophthalmologist. Recent advances have contributed towards improving the clinical outcome of the most common intraocular malignancy seen in children. Evolution in imaging techniques has facilitated accurate diagnosis and staging

of RB. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The introduction of intra-arterial and intra-vitreal chemotherapy in recent times has shown encouraging results. The advent of newer radiotherapy techniques have led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. The purpose of this article is to review the literature on various key developments in the field of RB, with particular emphasis on globe-conserving therapies. A brief overview of these recent advances is highlighted below.

IMAGING

Imaging plays a key role in the diagnosis of RB. With the introduction of high-resolution three-dimensional (3D) Fast Spin Echo (FSE) magnetic resonance imaging (MRI) and high resolution ultrasound, the diagnosis of RB is no longer a dilemma. Although computed tomograph scan is very useful in detecting calcification which can sometimes be missed on ultrasonography, it has been reported that high-resolution three-dimensional (3D) FSE T2 weighted imaging with thin sections (0.4 mm) and high Signal to Noise Ratio (SNR) can also detect calcification[1]. Gradient-echo T2 weighted MRI is also effective in detecting calcified structures[1]. Recently, it has been observed that the difference in Apparent Diffusion Co-efficient values on diffusion-weighted MRI can be helpful in differentiating between viable and necrotic tumor[2]. In addition, this modality can also be used to monitor the response of tumor to chemotherapy in cases of trilateral RB as well as in those eyes that are treated with globe salvaging therapies[2,3]. The presence of vitreous haemorrhage can pose difficulty in delineating the tumor, which can be overcome by T1-weighted MR images without the use of gadolinium-based contrast material[4]. Apart from its diagnostic value, MRI is also an established imaging modality for staging of RB[5]. Contrast-enhanced T1-weighted MR imaging with fat saturation is recommended to rule out optic nerve involvement as well as extra scleral involvement[6]. The sensitivity and specificity of MR imaging for depicting post-laminar optic nerve invasion has been reported to range from 50%-90%[4,5]. A retrospective study by Song *et al*[7] in cases of unilateral RB concluded that focal strong enhancement and enlarged optic nerve on MR films had better correlation with optic nerve invasion than optic nerve enhancement, tumor size and tumor location[7]. It is noteworthy that in some children, this enhancement can be due to aseptic cellutis or inflammation of soft tissues rather than true invasion[8]. A short course of systemic steroids and repeat MR imaging facilitates accurate staging in such cases and has been found to be useful in guiding further management[8].

Another application of imaging in RB is the use of high resolution ultrasound to detect the tumor in the fetus at its earliest stage[9]. Investigators have used high resolution ultrasound at 37 wk of gestation to detect a 2-3 mm elevated lesion in a fetus at risk of heritable RB[9]. Being a rapidly growing tumor, doubling time for RB is considered approximately 15 d[10]. Therefore, it has been suggested that infants proven to carry the family's *RB1* mutant allele can be delivered a few weeks early, to optimize the chances of retaining good vision with minimally invasive therapy[11].

CHEMOTHERAPY

Although enucleation is accepted as the standard treatment for advanced tumors, local and site selective delivery of chemotherapeutic drugs has shown encouraging results in salvaging the globe as well as vision in many eyes otherwise destined for enucleation. These newer therapeutic approaches are discussed briefly.

Super-selective intra-arterial chemotherapy

This novel approach has evolved rapidly over the last few years and has shown encouraging results in both early and advanced tumors[12,13]. Being a site directed therapy, it has considerably fewer systemic side-effects in comparison to conventional intra-venous chemotherapy. Over the last few decades, the selectivity of the technique has improved from using sites such as the internal carotid artery, supra-orbital artery and superficial temporal artery, to the currently used ophthalmic artery[14-18]. Melphalan is the drug of choice for intra-arterial chemotherapy and heparin (70 U/kg) is the anticoagulant used. There is no standardised dosing schedule, however, the conventional dose ranges from 3-5 mg per sitting[13,16,17]. Recently, Abramson *et al*[16] and Gobin *et al*[17] have recommended intra-arterial chemotherapy as a safe and effective treatment for advanced intra-ocular RB. Although intra-arterial chemotherapy has the advantage of fewer systemic side effects as compared to intravenous chemotherapy, some investigators consider melphalan as a more toxic agent than those drugs which are used for intravenous chemotherapy[19]. Exposure to fluoroscopy related radiation and ophthalmic artery occlusion are other concerns[19]. It has been suggested that a selective ophthalmic artery angiogram instead of carotid angiogram can be used to minimise radiation exposure[13]. Though not yet established as a primary treatment, intra-arterial chemotherapy has also been used as a first line treatment in less advanced cases of intraocular RB[12]. There are other investigators who consider it as a part of a multi-modal therapeutic approach[13,18]. Intra-arterial chemotherapy has been reported to be associated with an overall success rate of 55%-100% in salvaging the globe, in addition to the advantage of very low systemic toxicity[12,13]. Recently, Francis *et al*[20] have demonstrated that Carboplatin ± topotecan ophthalmic artery chemosurgery (OAC) can allow for prompt regression of tumors and can be curative as a single agent in combination with focal techniques, with ocular survival of 89.9% at two years. Furthermore, Carboplatin ± topotecan infusions have low hematologic and ocular toxicity and no statistically significant influence on electroretinogram responses, and can be used in conjunction with melphalan-containing OAC[20]. It has been recommended that children, especially

less than 6 mo of age at the start of treatment with carboplatin, should routinely undergo thorough long-term audiologic monitoring[21]. Recently, a single-centre retrospective study has compared the relative incidence of new intraocular lesions after treatment with carboplatin through intravenous (systemic) and OAC in naïve eyes, or those with prior treatment (systemic chemotherapy/external beam radiotherapy)[22]. The incidence reported were 56%, 2.4% and 8% respectively[22]. The systemic chemotherapy treated patients had multiple new lesions within months of treatment, as compared to fewer new lesions in the OAC group[22]. It was noted that previously irradiated eyes showed delayed appearance of new lesions. The new lesions were more common at a younger age and were usually located in the peripheral retina, which can be explained by the centrifugal development of retina[22].

Intravitreal chemotherapy

Another local route for drug delivery that has shown promising results in RB is intra-vitreal chemotherapy (IViC)[23,24]. However, this route is recommended only as salvage therapy for recurrent or recalcitrant vitreous seeds and should not be considered as a primary treatment[19]. In a study by Munier *et al*[23] in RB cases with recalcitrant vitreous seeds, melphalan was injected intravitreally in a dose of 20-30 μg (0.1 mL of 0.2 mg/mL) using anti-reflux procedure, followed by triple freeze-thaw cryoapplication to sterilize the needle track[23]. The procedure was carried out every 7-10 d and was repeated upto eight injections if a response could be documented, until complete seed fragmentation was observed or complete response was achieved[23]. Complete response was established if the seeds (1) completely disappeared (vitreous seeding regression type 0); or were converted into (2) refringent and/or calcified residues (vitreous seeding regression type Ⅰ); (3) amorphous, often non-spherical, inactive residues (vitreous seeding regression type Ⅱ); or (4) a combination of the last two (vitreous seeding regression type Ⅲ)[23]. The authors recommended that IViC could be repeated if vitreous recurrence occurred[23]. In their study, a success rate of 84.14% at 2 years was achieved[23]. A localised peripheral salt-and-pepper retinopathy at the injection site was the only complication noted in 10 eyes (43%)[23]. Another retrospective study on intra-vitreal chemotherapy by Shields *et al*[24] showed 100% (11/11) success rate with 1 to 4 cycles of monthly IViC (melphalan 20-30 μg) at 2 year follow-up[24].

Sub-conjunctival /sub-tenon chemotherapy

It has been observed that systemic chemotherapy alone may not be sufficient to treat Group C (eyes with focal vitreous or subretinal seeding and discrete retinal tumors of any size and location) and Group D (eyes with diffuse vitreous or subretinal seeding and/or massive, nondiscrete endophytic or exophytic disease) cases[25,26]. Local injections of chemo-therapeutic agents like sub-tenon or sub-conjunctival carboplatin have been used with varying degrees of success, usually as an adjuvant to systemic chemotherapy to avoid enucleation and external beam radiotherapy in cases of group C and group D retinoblastoma with vitreous/subretinal seeds. The Children's Oncology Group recommends use of 20 mg sub-tenon carboplatin along with chemoreduction and focal consolidation for Group C and D tumors[27]. Leng *et al*[28] have reported a favourable outcome with the use of sub-conjunctival carboplatin in RB tumors that progressed despite ablative therapy[28].

RADIATION THERAPY

Despite the established role of radiotherapy (RT) in RB, treatment modalities were shifted to primary chemotherapy combined with local treatment options such photocoagulation, cryotherapy and thermotherapy[29,30]. The high incidence of radiation induced growth deformities and second malignancies was attributed to external beam radiotherapy and RT was therefore reserved for tumours refractory to chemotherapy and local therapies. However, the assessments of risk by RT were based on outcomes of radiation delivery in the old era[31,32]. In recent times, there has been substantial advancement in radiation therapy and the advent of newer radiotherapy techniques has led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. These newer radiotherapy techniques which include intensity modulated radiotherapy, stereotactic radiotherapy volumetric modulated arc therapy (VMAT), proton therapy, and helical tomotherapy (HT) provide highly accurate radiation delivery[33].

Proton beam therapy provides uniform dose coverage of the target and unlike photon beams, has no exit dose and distributes no energy beyond the target. These unique properties reduce the incidence of late effects of radiation. A study by Sethi *et al*[34] compared the risk of second malignancies in survivors of RB treated with photon and proton radiation therapy[34]. The observed 10 year cumulative incidence of RT induced second malignancies were significantly different in proton and photon modalities ($P = 0.015$)[34]. However, proton therapy is expensive and is currently not widely available. In another study on the dosimetric comparison of various RT techniques by Eldebawy *et al*[33], it was concluded that inverse image guided radiotherapy using VMAT or HT provides superior conformity index and improved orbital bone and brain sparing[33].

Plaque Brachytherapy is commonly used for recurrent and residual disease after failure with chemotherapy and local therapy. The American Brachytherapy Society Ophthalmic Oncology Task Force (ABS-OOTF) recommends primary brachytherapy for unilateral anterior lesions[35]. Small tumours less than 15 mm in base and up to 10 mm in thickness in the absence of vitreous seeding are eligible[35]. The choice of radionuclide is decided according to local availability and intraocular dose distribution. I^{125} and Pd^{103} are used in North America, whereas I^{125} and Ru^{106} are used in Europe. Dosimetry of plaques presents a unique challenge which is due to the steep dose gradient within the tumour and presence of criti-

cal structures within few millimetres of the radioactive source. However, the TG-129 reports that adoption of heterogeneous dose calculation methods in clinical practice would result in dose variation of > 10% and requires careful assessment[36].

GUIDELINES FOR PATIENT FOLLOW-UP

After completion of therapy, regular follow-up is extremely important in these children in order to detect any recurrence of tumor, new lesion, or metastatic disease. It is recommended to follow-up all affected cases till the age of 16 years and to conduct screening of unaffected relatives or mutation carriers till the age of five (reference: 2013 Copyright American Cancer Society) or seven years (reference: NHS England/E04/S(HSS)/a, Copyright NHS Commissioning Board, 2013).

To summarize, the management of RB has evolved significantly over the last few years. Worldwide, there is an increasing trend towards preservation of the globe and vision in RB affected children. Newer advancements in diagnostic and therapeutic modalities have resulted in improved treatment outcomes in these children. Familiarity with these diagnostic and treatment modalities is essential for optimum management.

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