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Review: New horizons in retinoblastoma treatment: an updated review article

Fatemeh Azimi,[1] Reza Mirshahi,[2] Masood Naseripour[1,2]

[1]Eye Research Center, the Five Senses Institute, Iran University of Medical Sciences, Tehran, Iran; [2]Stem Cell and Regenerative Medicine Research Center, Iran University of Medical Sciences, Tehran, Iran

Retinoblastoma (Rb) is a rare childhood intraocular malignancy with an incidence rate of approximately 9000 children per year worldwide. The management of Rb is inherently complex and depends on several factors. The orders of priorities in the treatment of Rb are saving life, globe salvage and vision salvage. Rarity and the young age at diagnosis impede conducting randomized clinical trials (RCTs) for new therapeutic options, and therefore pre-RCTs studies are needed.

This review provides an overview of advances in Rb treatment options, focusing on the emergence of new small molecules to treat Rb. Articles related to the management and treatments of Rb were searched in different databases.

Several studies and animal models discussing recent advances in the treatment of Rb were included to have a better grasp of the biological mechanisms of Rb. Over the years, the principles of management and treatment of Rb have changed significantly. Innovations in targeted therapies and molecular biology have led to improved patient and ocular survival. However, there is still a need for further evaluation of the long-term effects of these new treatments.

Retinoblastoma (Rb) is a primary neuroectodermal tumor caused by immature retinoblasts, and accounts for 3% of all childhood cancers. It is the most common childhood intraocular malignancy [1]. The disease usually manifests as unifocal or multifocal tumors involving one or both eyes [2]. There are currently many effective modalities for Rb treatment, including focal treatments (laser therapy, cryotherapy, and radiotherapy), systemic chemotherapy, innovative new drug delivery methods (intravitreal and intra-ophthalmic chemotherapy), and enucleation to prevent extraocular extension and metastases and subsequent fatality [3]. The treatment of recurrent tumors depends on the extent of the disease, the laterality and number of tumor foci (unifocal, unilateral, multifocal), the size and location of the tumor, the presence of vitreous and subretinal seeding, the age and general health condition of the child, and the previous treatments. Both the International Intraocular Retinoblastoma Classification and Intraocular Classification of Retinoblastoma classification systems are used worldwide as the main intraocular Rb classification methods [4] (Table 1). Due to intra-tumoral heterogeneity, chemical-resistant phenotypes, and obstacles in drug delivery to the eye, Rb is still a major public health problem despite the continuous progress in its treatment, screening, and care [5].

In Rb, the tumor might initially be chemosensitive, but cross-resistance may ensue in the course of the treatment. The cross-resistance mechanisms are complex in nature and may differ from individual drug resistance. Drug resistance, especially in metastatic tumors, directly leads to treatment failure [6]. The main target of the traditional anti-tumor chemotherapeutic agents is cell division affecting the dynamics of the microtubules responsible for the mitotic spindle and DNA replication [7].

It is better to conduct clinical studies on the optimization of combination therapies (a treatment modality that combines two or more therapeutic agents) with a cytotoxic chemotherapeutic agent, another molecular targeting agent, or epigenetic-based or immune therapy [8]. The integration of anti-cancer drugs increases the effectiveness of the treatment compared to monotherapy due to critical pathways that basically decrease drug resistance. Moreover, tumor cells are often unable to adapt to the simultaneous toxic effects of two therapeutic agents combined [9].

However, combination therapies have limitations that should be considered in clinical trials. The design of combination trials may require pharmacodynamics studies and the collaboration of more than one pharmaceutical company to measure more than one biochemical or physiologic effect [10].

Correspondence to: Masood Naseripour, Department of Ophthalmology, Iran University of Medical Sciences (IUMS), Rassoul Akram Hospital, Niayesh Ave., 14455-364, Iran; Phone: 021 6655 8811; FAX: +98 21 66509162; email: masoodnp@yahoo.com

Table 1. Classification systems for intraocular retinoblastoma.

Eye Group	IIRC	ICRB	Therapy
A (very low risk)	All tumors are 3 mm or smaller, confined to the retina, and at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed	3 mm or smaller in greatest dimension Small tumors confined to the retina tumors are not near the foveola (the central "pit" of the retina) or the optic nerve No vitreous or subretinal seeding No retinal detachment	Laser photocoagulation Thermotherapy Cryotherapy Plaque radiotherapy
B (low risk)	Eyes with no vitreous or subretinal seeding Discrete retinal tumor of any size or location. Retinal tumors may be of any size or location not in group A Small cuff of subretinal fluid extending ≤5 mm from the base of the tumor	Larger tumor a. One or more tumors are >3 mm b. Macular location Tumor located ≤3 mm from fovea c. Juxtapapillary location Tumor located ≤1.5 mm from optic disc d. Additional subretinal fluid, Presence of subretinal fluid ≤3 mm from tumor margin Tumors are only in the retina No vitreous seeding No retinal detachment more than 5 mm from the tumor base	Laser photocoagulation Thermotherapy Cryotherapy Plaque radiotherapy Intravenous/intra-arterial chemotherapy
C (moderate risk)	Eyes with focal vitreous or subretinal seeding Discrete retinal tumors of any size and location. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque Up to one quadrant of subretinal fluid may be present	Focal subretinal fluid or seeding a. Localized subretinal fluid greater than 3 mm and less than 6 mm from the tumor b. Vitreous or subretinal seeding less than 3 mm from the tumor There is retinal detachment and it is more than 5 mm from the tumor base	Intra-arterial chemotherapy Intravitreal chemotherapy
D (high risk)	Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease Eyes with more extensive seeding than Group C Massive and/or diffuse intraocular disseminated disease including exophytic disease and >1 quadrant of retinal detachment. May consist of 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque-like	Diffuse subretinal fluid or seeding a. Subretinal fluid greater than 3 mm from the tumor b. Vitreous or subretinal seeding greater than 3 mm from the tumor	Intra-arterial chemotherapy Intravitreal chemotherapy Enucleation
E (very high risk)	Eyes that have been destroyed anatomically or functionally with one or more of the following: Irreversible neovascular glaucoma, massive intraocular hemorrhage, aseptic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis	Extensive tumor a. Tumor takes up more than 50% of the globe b. Neovascular glaucoma c. Opaque media from hemorrhage in anterior chamber, vitreous, d. or subretinal space e. Invasion of optic nerve, choroid (>2 mm), sclera, orbit or anterior chamber	Intra-arterial chemotherapy Enucleation Adjuvant intravenous chemotherapy if high-risk histopatho-logical features present

Advances in the development of targeted therapy and biomolecular tumor pathways have improved the survival rates in developed countries [11]. Despite the fact that developing countries have lower Rb survival rates, the horizon in such countries is promising, and the results are encouraging [12].

Advances in biomedical research have led to a better understanding of the biology of tumors through the study of genomics, proteomics, epigenetics, and the microenvironment. New research is thus constantly being sought to obtain newer targeted treatment options with minimal complications and maximum effectiveness against Rb. The US Food and Drug Administration (FDA) has recently approved the clinical use of targeted therapeutic agents for various types of cancer [13].

Targeted therapeutic agents exert their anti-cancer effects through a variety of mechanisms, including inhibition of proliferation, induction of apoptosis, suppression of metastasis, regulation of immune function, and reversal of multi-drug resistance [14]. Considering the young ages of Rb patients and the rarity of the disease, the behaviors of isolated cell cultures need to be studied to understand the biology of tumor cells in the body. Cell cultures are used to create new diagnostic tests and new treatments for Rb. The most important Rb cell lines primarily used in Rb research include Y79 (the first Rb cell line), Weri, Rb355, Rb116, SNUOT-Rb1, and HXO-Rb44 [15–20]. In this article, the successes and challenges of incorporating molecularly targeted therapies, tubulin-modifying molecules, immunotherapy, high-mobility group A (HMGA) protein, vitamin D analogs, angiogenesis inhabitation, neurotransmitter pathway disruption, arsenic trioxide, EDL-155, gene therapy, local drug delivery systems, new hydrogel implant, ncRNAs, aqueous humor markers, exosomes, and MLN4924 (pevonedistat) in the management of Rb are highlighted (Table 2).

Searches for relevant articles were conducted at the PubMed, Scopus, Embase, and Google Scholar electronic databases. The searches were limited to English articles. The mesh term keywords that were used for the electronic-database searches were “advances OR treatment OR targeted therapies” AND “Retinoblastoma.” The included articles reported original studies and new Rb treatments.

DISCUSSION

Molecularly targeted therapy: Molecularly targeted therapies are relatively new, and many questions about how and when to combine them in the first-line Rb treatment remain unanswered [21]. The first tumor suppressor gene to be identified and cloned was *RB1*, but there is currently no effective molecularly targeted treatment for Rb [22]. However, there has been significant progress in the understanding of tumor biology, leading to the discovery and development of small molecules for the treatment of Rb, including new targeted therapies such as MDMX-p53 response inhibitors (nutlin-3a), spleen tyrosine kinase (SYK) inhibitors, histone deacetylase (HDAC) inhibitors [3], and CEP1347 (small-molecule kinase inhibitor) [23].

MDMX-P53 response inhibitors—Nutlin-3A was discovered by Vassilev et al. [24] in 2003 to inhibit p53-murine double minute (MDM2/MDM4) interaction when they screened a chemical library. It is a cis-imidazole analog involved in the activation of p53, a tumor-inhibiting protein, and attenuates tumor cell viability both in vivo and in vitro [25]. Nutlin-3A is currently being studied in a phase 1 clinical trial for Rb treatment [25,26]. Subconjunctival nutlin-3A in a mouse model of Rb has a reduced tumor burden especially in combination with topotecan (TPT) [25]. However, it should be noted that due to the blood-retinal barrier in Rb, the effective entry of many drugs, such as nutlin-3A, is hindered [25,27].

Epigenetic mechanisms: SYK and HDAC inhibition—The proto-oncogene tyrosine-protein kinase (also known as spleen tyrosine kinase [SYK]), although not normally expressed in the human retina, is upregulated in 100% of Rb tumor specimens and leads to tumor cell survival [28]. Inhibition of SYK by BAY-61–3606 and R406 could result in tumor cell death in Rb, and an in vivo study of subconjunctival BAY-61–3606 injection with systemic TPT in orthotopic xenograft mice has shown its effectiveness in inhibiting Rb cell proliferation [28]. In addition, recent studies have demonstrated that the mediators of SYK are the B-cell chronic lymphocytic leukemia/lymphoma 2 (Bcl-2) protein families [29].

Bcl-2 is a protein known to prevent apoptosis and to help in cell viability. Bcl-2 inhibitors (especially MCL-1 inhibitors) can be a novel therapeutic candidate due to their upregulation in Rb, and are also being developed as a treatment for other cancers [30]. HDAC inhibitors are another class of targeted anti-cancer therapies currently being investigated in phase 1 clinical trials that may be effective as a targeted treatment for Rb [31]. Several properties of HDAC inhibitors make them potential candidates for the treatment of Rb. First, the epigenetic profile of Rb exhibits dysregulation compared to normal retinoblasts [28]. Second, HDAC inhibitors have selective cytotoxic effects on tumor cells, and tumor cells with dysregulated E2F1 activity are sensitive to HDAC inhibition [32]. Finally, numerous studies have shown that HDAC inhibitors have synergistic effects with other agents in the treatment of Rb [28]. Cells with higher E2F1

activity and with overexpression of pro-apoptotic agents are highly sensitive to HDAC inhibitors. Rb cells have high E2F1 activity, and Rb-derived cell lines are particularly sensitive to HDAC-induced apoptosis. Recent studies have suggested that HDAC inhibitors may specifically inhibit Rb tumor cell proliferation and therefore have less systemic toxicity than other chemotherapeutic agents [33].

Small-molecule kinase inhibitor: CEP1347 is a promising candidate for cancer stem cell-targeted therapy [34]. It is a semi-synthetic compound that protects various nerve cells against various insults leading to apoptosis, and subsequently improves the survival of dopamine neurons [35].

CEP1347 is a safe drug that inhibits mixed-lineage kinases and activates apoptotic pathways in the pathogenesis of Parkinson's disease [34]. It selectively inhibits MDM4 expression and activates the p53 pathway, leading to anti-proliferative effects on the Rb cells [23]. Currently, none of the drugs acting on Rb by activating p53, including nutlin-3A, have a strong clinical potential. However, as CEP1347 may be able to pass through the blood-retinal barrier, it is a potential candidate for the treatment of Rb and other cancers in which the *P53* gene is intact [23].

Tubulin-modifying molecules: Vincristine (VCR), also known as leurocristine and Oncovin [36], is a first-line chemoreduction agent for Rb that was first isolated in 1961 [37]. Its mechanism of action is inhibition of microtubule assembly [38]. Therefore, Rb tumor cells may show similar sensitivity to other tubulin-modifying compounds. Some studies have revealed that VCR in combination with TPT [39] and carboplatin (CBP) [40] is effective for the treatment of advanced intraocular Rb. Chemotherapy is the standard treatment for Rb, but chemotherapy agents such as VCR, etoposide (ETP), and CBP may lead to drug resistance and treatment failure [41].

Table 2. New advances in management of retinoblastoma.

New therapies	Examples of applications
Molecularly targeted therapies	MDMX-p53 response [3,25,26], spleen tyrosine kinase (SYK) inhibitors [3,28,29], histone deacetylase (HDAC) inhibitors [3,28,33], CEP1347 (small-molecule kinase inhibitor) [23]
Tubulin Modifying molecules	Paclitaxel (PTX) [44]
Immunotherapy	CAR-T cell therapy [53] Signal transducer CD24 [59] Nucleolin (NCL) protein [61,62]
High mobility group A (HMGA) protein	HMGA aptamer (NCLAb–HMGAap) [68,69]
Vitamin D analogs	Calcitriol [71,79,80]
Angiogenesis inhabitation	Celastrol nanomicelles (CNMs) [87] Ribavirin [20]
Neurotransmitter pathway disrupting	Transfection of AP-2α and AP-2β expression into Rb cells to induces apoptosis [98]
Arsenic Trioxide	Arsenic trioxide (white arsenic or As2O3; ATO) [18]
EDL-155	an isoquinoline derivative [102]
Gene therapy	HSV- TK / GCV(Herpes Simplex Virus-Tyrosine Kinase / Ganciclovir) [19,104] Oncolytic adenovirusVCN-01 [106]
Local drug-delivery systems	Poly lactic-co-glycolic acid (PLGA) [117,118] Gold-based nanoparticles [126,127] Dendrimer [133]
New hydrogel implant	Local drug delivery [134]
Non- coding RNAs (ncRNAs)	lncRNAs [139-151] miRNAs [158-161]
Aqueous humor markers	circulating tumor cell (CTC) and cfDNA-based fluid biopsies [171,172]
Exosomes	nanoparticles derived from cell membranes containing RNA, microRNA, lipids and proteins [175]
MLN4924 (Pevonedistat)	Pevonedistat, a neddylation inhibitor [180]

Paclitaxel (PTX) was first obtained from the *Taxus brevifolia* (Pacific yew) in 1971 and was approved for medical use in 1993 [42]. It is a taxane that causes marked apoptosis in tumor cells by affecting the tubulin dynamics [43].

Paclitaxel is used to treat breast cancer, ovarian cancer, and small cell lung cancer. Recent studies have demonstrated its potential therapeutic effects in Rb [44]. Its mechanism of action is inactivation of the intracellular proteins necessary for cell survival and function, which results in cell death [45]. Subconjunctival injection of paclitaxel effectively inhibits intraocular tumor burden in the human luteinizing hormone (β subunit; LH beta) Tag Rb model. The main barriers to the use of paclitaxel as an Rb chemotherapy regime are its toxicity [46] and its formulation [47].

Immunotherapy:

CAR T-cell therapy—Chimeric antigen receptor T cells (CAR T cells) are T cells that have been genetically engineered to produce chimeric or fusion proteins through recombinant DNA technology on the T cells for use in immunotherapy. In CAR T immunotherapy, the T cells are modified to identify and more effectively target and destroy tumor cells. CD171 (neural cell adhesion molecule L1), also known as L1CAM, was first identified in 1984 by Rathjen and Schenker in post-mitotic mice neurons cells [48]. L1CAM is expressed in Rb cells and plays an important role in the adhesion-mediated proliferation and chemoresistance of tumor cells [49]. GD2 (a b-series ganglioside disialoganglioside) is expressed in tumors of neuroectodermal origin, including human melanoma, neuroblastoma, and Rb [50,51], with a limited expression in natural tissues [52]. CD171- and GD2-specific CAR T cells are highly activated by Rb cell collision and are highly efficient against Rb cells in vitro depending on the expression of the target antigen. CAR T-cell therapy can improve the treatment strategies for metastatic Rb.

The antigens on the targeted tumor cells are destroyed upon treatment with CAR T cells, but sequential antigen modification in CAR T-cell therapy increases its ability to kill Rb cells. This approach provides the basis for in vivo studies to select the most useful regimens and target compounds for the development of CAR T-cell therapy for Rb [53].

Signal transducer CD24—Cluster of differentiation 24 (CD24) or heat-stable antigen CD24 (HSA) is a highly glycosylated protein that binds to membrane lipid raft microdomains through a glycosylphosphatidylinositol anchor [54]. Recent studies have shown that CD24 positivity is associated with poor prognosis in many types of tumors, including glioma [55], hepatocellular carcinoma [56], and breast cancer [57]. CD24 is highly expressed in Rb and is thus a potential indicator or predictor of the severity and prognosis of the disease. A positive association between CD24 and the chemotherapeutic response of Rb cells to VCR-based chemotherapy has recently been found [58]. However, the cellular mechanisms involved in CD24 activity in Rb are still unclear. CD24 inhibition can reduce autophagy activation via the PTEN/Akt/mTORC1 pathway, thus increasing VCR sensitivity. It facilitates a new therapeutic target for Rb chemotherapy [59].

Nucleolin protein: The nucleolin (NCL) protein is a small nucleolar RNA termed U20 that is expressed differently on the surfaces of tumor cells, connects ligands, and regulates carcinogenesis and angiogenesis [60]. NCL is expressed in Rb tumor tissues and cell lines more than in the normal retina. Cell proliferation using aptamers (oligonucleotide or peptide molecules) is significantly inhibited in Rb cell lines (Y79 and WERI-Rb1) [61]. Nucleolin aptamer (NCL-APT) treatment downregulates the apoptosis protein inhibitors and alters the serum cytokine, tumor miRNA-18a, and serum miRNA-18a levels. The effect of NCL-APT and locked nucleic acid-modified NCL-APT on the Rb tumor was successfully tested using Y79 xenografts of nude mice [61,62].

A powerful method of accurately measuring the metabolites in tissues and examining the lipid changes between normal and cancerous tissues is lipid imaging using desorption electrospray ionization mass spectrometry (DESI-MS) [63]. It is potentially helpful for studying the biology of retinal diseases. DESI-MS can also potently grade cancer stages, identify the margin of the surgical tumor, and examine tumor lipogenesis [63,64]. DESI-MS is used in NCL-APT therapy to observe the changes in the phosphatidylcholine levels in Rb cell lines and tumor tissues. Therefore, NCL-APT-based targeting is a useful treatment strategy in Rb especially in conjunction with DESI-MS for monitoring the therapeutic responses [61].

HMGA protein: The HMGA protein is overexpressed in Rb and is associated with the invasion and metastasis of the disease [65]. Aptamers, siRNAs, or DNA minor groove binders such as natropsin can optionally target HMGA proteins and mRNA transcripts [66]. siRNA causes apoptosis in cancer cells by targeting HMGA2 [67]. Another approach is HMGA aptamer therapy in Rb, which reduces cell proliferation by activating the TGFb-SMAD4-mediated apoptotic pathway. In addition, combining the HGMA2 aptamer with ETP has a synergistic effect [68]. The third option for targeting HMGA in Rb cells is NCL antibody-mediated delivery of HMGA aptamer (NCLAb–HMGAap) [69].

Recent studies have demonstrated that conjugate NCLAb–HMGAap has unbeatable features, such as easier synthesis, superior conjugation, higher rate of cellular internalization in WERI-Rb1 cells through receptor-mediated internalization, and increased cytotoxicity (more than 50-fold) in WERI-Rb1 compared to free HMGA aptamer and NCLAp–HMGA2si conjugate [69].

Vitamin D analogs: There is ample evidence of the role of vitamin D in cancer growth and development. The mechanism of the anti-cancer activity of vitamin D is regulation of apoptosis, angiogenesis, cell differentiation, proliferation, and migration [70]. However, the applicability of vitamin D therapy to Rb has not been established due to the lack of preclinical models and the possibility of vitamin D toxicity [71]. In 1966, due to the observation of calcification in regressed tumors, Verhoeff proposed the use of vitamin D for the treatment of Rb [72]. Since then, several studies have assessed the effects of vitamin D analogs on Rb [73–75].

Vitamin D appears to act as a protective agent in the eye through ubiquitously expressed receptors, where its local production and activation is possible due to the presence of the required enzymes [76]. Vitamin D analogs may produce anti-tumor effects on Rb by targeting the hedgehog signaling pathway [77].

However, the mechanism of vitamin D analogs in the treatment of Rb is still unknown and needs further investigation. The upregulation of p53 and p21, though, was observed in the Y79 cell line following vitamin D analog therapy [71], which is related to an increased Bax protein concentration and a decreased Bcl-2 content [78]. Both in vitro and in vivo models have been used to investigate the anti-tumor effect of vitamin D analogs, including calcitriol.

Calcitriol (1, 25-dihydroxyvitamin D3), which is normally produced in the kidney, is the active form of vitamin D. It inhibits the growth of Y79 cells in vitro [79] and minimized the tumor burden in both xenograft and transgenic mouse Rb models [71,79,80]. Despite the efficacy of calcitriol in both these models of Rb, its use as a treatment for Rb is limited due to its systemic toxicity (hypercalcemia and renal toxicity) [71,81].

Angiogenesis inhibition: Angiogenesis is known to be a major driving force in various tumors [82]. As Rb is an angiogenesis-dependent tumor, anti-angiogenic therapy is expected to have a positive effect on it [83]. Tigecycline, niclosamide, and quercetin have recently been investigated and have been determined to be potential candidates for the treatment of Rb by suppressing Rb cell proliferation through the modulation of angiogenesis pathways [84]. Anti-angiogenic compounds play an important role in Rb treatment. First, Rb is a completely vascularized tumor that depends on its vascular supply, and second, vascular endothelial growth factor (VEGF) is over-expressed in Rb cells and Rb patients [83].

Bevacizumab (Avastin) obtained FDA approval for use in certain types of cancer [85]. Bevacizumab reduces the tumor microvascular density twofold, which reduces Rb growth by 75% without significant systemic toxicity [83]. Angiogenesis inhibitors are safe for the adult retina, but there are concerns regarding their use in children with Rb due to their potential impact on the ocular development [86].

Celastrol nanomicelles: Celastrol nanomicelles (CNMs, 27.2 mg/kg/2 days) [87] are traditional Chinese medicine components with strong anti-tumor [88], anti-inflammatory, and anti-angiogenic activities [89]. Celastrol nanoparticles (NPs) inhibit the growth of retinoblastoma SO-Rb50 cells in humans by inducing apoptosis. In recent studies, CNMs were able to inhibit the growth of Rb in a mouse model by preventing neovascularization, which may be relevant to the inhibition of the VEGF pathway and of hypoxia-induced HIF-1α. CNMs may be a potent alternative for Rb treatment [87].

Ribavirin: One of the potentially eukaryotic translation initiation factors (eIF) that plays a key role in the development and transformation of various cancers is eIF4E [90]. However, few studies have investigated its potential role in Rb treatment [20]. Angiogenesis is one of the key pathways in Rb tumor survival and metastasis. Bevacizumab and pigment epithelium-derived factor result in angiogenesis inhibition in Rb, with negligible systemic toxicity [83,91]. Ribavirin is a pharmacologic eIF4E function inhibitor [92] that targets angiogenesis and potentially suppresses VEGF-induced migration by disrupting capillary network formation. Mechanistically, ribavirin decreases the protein but not the mRNA levels of c-Myc, cyclin D1, and VEGF and inhibits the eIF4E function in Rb cells. The combined use of ribavirin and CBP leads to an efficacious treatment with a greater potential for inhibiting Rb than the use of single drugs separately [20].

Neurotransmitter pathway disruption: The growth of Rb by disrupting the pathways of neurotransmitter receptors, transporters, and biosynthetic enzymes, which are expressed in human Rb, can be reduced both in vivo and in vitro [93]. Mixtures of genes commonly found in the cells of retinal progenitors and differentiated retinal neurons (photoreceptors and amacrine cells) are also expressed in human Rb. Amacrine cells are interneurons that form synapses with ganglion or bipolar cells, which are distributed in the innermost part of the inner nuclear layer of the retina and play a critical role in processing visual signals [84]. Thirteen

well-defined drug agents targeting major neurotransmitter pathways were tested in vitro, and it was found that monoaminergic amacrine cell transporter inhibitors, along with fluphenazine and chlorpromazine injections for 3 consecutive weeks, prevent the proliferation of Rb cell lines (Weri, Y79, and Rb355) [93].

Activator protein-2 (AP-2, a family of transcription factors, with AP-2α, AP-2β, AP-2δ, AP-2ε, and AP-2γ) has a regulatory role in biologic functions, including differentiation, cell proliferation, apoptosis, and carcinogenesis [94,95]. In the amacrine cells in fetal chickens, mice, and humans, the AP-2 family is expressed in the early stages of the development of the retina [95,96]. Co-expression of AP-2α/AP-2β is observed in a high percentage of amacrine cells [95]. The AP-2 expression scheme in the Rb cell lines mimics the amacrine cell differentiation patterns [97]. Transfection of AP-2α and AP-2β expression into Rb cells induces apoptosis and inhibits proliferation [98].

Arsenic trioxide: Arsenic trioxide (white arsenic or As_2O_3; ATO) was approved for medical use by FDA in 2000 for relapsed/refractory acute promyelocytic leukemia [99,100]. ATO is thought to function through mechanisms distinct from those of traditional chemotherapeutic agents (e.g., the reactive oxygen species due to oxidative damage leading to apoptosis) and is not prone to drug resistance [101].

ATO inhibits the growth of Rb cell lines (both Y79 and SNUOT-Rb1) at high and low levels of concentration through apoptosis and differentiation, respectively. Weekly intravitreal injection of 0.1 μM or 5 μM ATO minimized the tumorigenesis in the SNUOT-Rb1 cells in orthotopic xenograft mice and showed no change in retinal thickness despite a more pronounced decrease at higher doses. Moreover, inflammatory cells were not observed in ATO treatment in the choroid, retina, or vitreous [18].

EDL-155: EDL-155, an isoquinoline derivative, was found to have high concentrations and to be effective in vivo, but it was found to have relatively weak potency in cultured Y79 cells [102]. In a Y79-Luc Rb xenograft mouse model, the tumor burden was significantly reduced with the periocular administration of EDL-155 (20 mg/kg/day in 0.1% dimethyl sulfoxide in saline) within 4 consecutive days, without any toxic side effect. EDL-155 disrupts the mitochondrial function and causes autophagy, thereby killing Rb cells [102].

Gene therapy: Gene therapy is the therapeutic transfer of nucleic acid polymers into diseased cells for the treatment of an underlying disease [103]. Suicide gene therapy includes the process of transferring the gene materials of a virus or of bacteria into tumor cells to convert a non-toxic compound to a lethal drug. A phase 1 study showed that intravitreal injections of adenovirus vectors including herpes simplex virus-tyrosine kinase (HSV-TK), along with ganciclovir (GCV), is safe and effective in vitreous seeding [104]. Also, HSV-TK/GCV can lead to the significant destruction of retinal tumor cell lines [19]. Despite these promising results, the use of this approach in gene therapy as a first-line treatment for Rb is unlikely, and it may be useful as a complement to the standard therapy for refractory vitreous seeding [104].

VCN-01 is a clinically oncolytic adenovirus that is genetically engineered from type 5 (Ad5) modified adenovirus and is used to inhibit the proliferation of cancer cells with a high content of free E2F1, following the dysfunctional Rb1 pathway [105]. It successfully annihilated chemoresistant specimens in vitro and effectively killed cancer cells derived from mouse Rb xenograft models. A recent study has shown that VCN-01 is safe in mice and juvenile rabbits [106]. According to the preliminary phase 1 results from Rb patients treated with intravitreal VCN-01, there was evidence of viral replication in the tumor cells, which led to anti-tumor activity in vitreous seeds of Rb. This treatment causes localized vitreous inflammation without any systemic inflammation.

The intravitreal injection of VCN-01 in xenograft models of Rb improved the ocular survival rate compared to the conventional chemotherapy, and inhibited micrometastatic spread to the brain. These promising results suggest that the development of oncolytic adenoviruses targeting Rb1 may provide selective and independent treatment options for Rb [106].

Local drug delivery systems: Over the past decade, nanotechnology-based drug delivery systems for cancer therapy have made significant progress by providing site-specific delivery options and increasing bioavailability [107]. Various materials have been widely used as intraocular drug carriers, such as dendrimers, liposomes, biodegradable polyesters, mesoporous silica, and gold NPs [107]. These modified particles can target specific cells. In addition, they can be designed to increase the therapeutic efficacy of the drug molecules and ensure the continuous release of the drug contained in them [108].

The use of NP-based systems enhances drug delivery to the posterior part of the eye. It also expands the intravitreal half-life of chemotherapeutic agents [109]. The rapid development of nanotechnology has allowed the use of intelligent nanosystems for cancer imaging, targeted drug delivery, and cancer regression monitoring in post-treatment oncology. In personalized nanomedicine (at least pre-clinically), drug delivery systems including NPs are used [110].

NPs as alternative drug delivery systems for systemic administration provide an essential substrate for improving the ocular transmission of therapeutic agents such as melphalan (MEL) by maintaining the stability of the drug, decreasing the need for frequent prescribing, targeting only cancerous tissues, having a long-term curative effect, minimizing complications, and reducing the number of invasive procedures and the need for the systemic administration of MEL [111]. Surface-modified NP formulations, when used in vivo, may improve Rb treatment. Surface-modified NPs with ligands such as MPG or TET1 pave the way for overcoming in vivo delivery challenges and increase the effectiveness of MEL [111].

Polylactic-co-glycolic acid: Polylactic-co-glycolic acid (PLGA) is especially used in ocular therapy due to its biocompatibility, favorable degradation, and approved clinical applications [112]. Previously, PLGA NPs were used as vectors for the intraocular delivery of active agents such as flurbiprofen [113].

Flurbiprofen-rich NPs showed a greater anti-inflammatory effect than the available eye drops in animal models of ocular inflammation, indicating that NPs increase the bioavailability of flurbiprofen. Surface-modified NPs and MPGs have a greater effect on Rb cells than unmodified NPs [111].

Other available drugs are anthracyclines (doxorubicin, idarubicin), which destroy cancer cells through DNA intercalation and inhibition of topoisomerase, and also have the ability to inhibit metastatic Rb [114]. The intravitreal injection of doxorubicin encapsulated in poly-β-hydroxybutyrate-based microspheres in rabbit ocular tissue showed reduced toxicity to the surrounding natural structures [115]. In addition, encapsulation reduces the peak doxorubicin level compared to free doxorubicin in ocular tissues. The ex vivo transscleral release of doxorubicin encapsulated in PLGA polymer NPs or liposomes (Doxil®, Tibotec Therapy) demonstrated that doxorubicin is easily released in the sclera isolated from humans, but its encapsulation (both in PLGA and liposomes) reduces the rate of transmission [116]. PLGA NPs were studied on Y79 Rb cell lines for the delivery of doxorubicin [117] and ETP [118] and may be prominent candidates for continuous drug delivery models.

Gold NPs: Gold NPs are highly absorptive of near-infrared light and can kill cancer cells due to their unique physical properties [118]. Moreover, light-activated drug secretion can be achieved by using gold NPs that bind to chemotherapeutic agents [119]. Gold nanocages are surrounded by a smart polymer; the nanocages absorb light and change in response to heat, causing the polymer to break down and release doxorubicin [120]. Gold NPs can also easily cross the blood-retinal barrier and do not cause significant cytotoxicity [121]. Gold liposomes and virus-like NPs containing TPT have been administered intravitreally in rabbit models of vitreous seeds [122].

Fibrin glue: Fibrin glue, a biodegradable carrier, is another injectable that is currently being tested as a delivery system for chemotherapy agents [123]. CBP [124] and TPT [125] secreted from fibrin stocks have both been shown to maintain their biologic activity against cultured Rb cells and to reduce the tumor volume in a transgenic mouse model of Rb [126]. In another study, fibrin sealants allowed the continuous transfer of CBP to the ocular tissues and were rapidly cleared in vivo [127]. Clinical studies have also shown promising results for TPT conjugated with fibrin [128].

Dendrimers: Dendrimer macromolecules (synthetic polymers) are spherical macromolecules 1–100 nm in size, with three different domains [129]. They have controllable shapes, sizes, surface properties, and voids and can be considered suitable candidates for drug delivery systems because they control the physical and chemical environment during their synthesis [130] and because of their appropriate design parameters, reproducibility and optimization, and ability to overcome drugs' physicochemical limitations (e.g., solubility, specificity, stability, biologic distribution, and therapeutic efficacy). Dendrimers are also capable of eliminating biologic barriers such as the first pass effect, immune cleaning, cell infiltration, and off-target interactions [131].

The effect of dendrimers as drug delivery systems in ophthalmology has also been studied. They play an effective role in the transmission of drugs to the intraocular tissues [132]. A recent study reported the successful injection of the subconjunctival polyamidoamine dendrimer G3.5 into transgenic Rb mice without toxicity. Also, higher doses of NPs can even lead to reduced tumor burden in the untreated contralateral eye. Another study showed that dendrimer NP-based CBP significantly minimized the tumor load compared to free CBP in a mouse model of Rb [133].

New hydrogel implant: The new hydrogel implant can deliver low-molecular-weight hydrophilic anti-tumor drugs such as TPT and VCR in therapeutic doses. It can prevent the strong complications of systemic or intravitreal/intra-arterial chemotherapy by facilitating lower exposition, long-term medicinal action, and transscleral drug delivery (bypassing the bloodstream) and by reducing the cytotoxicity/necrosis risks (with controlled drug release at the site of drug use) [134]. The purpose of the new hydrogel implant is the direct delivery of anti-tumor drugs to the globe. This implant has two components: an inner hydrophilic layer of 2-hydroxyethyl

methacrylate (HEMA) filled with the drug and an outer hydrophobic layer of 2-ethoxyethyl methacrylate to protect the healthy tissue from in vivo exposure to the chemotherapy agent [134].

A recent study assessed the stability of VCR and TPT, their transmitting properties, and the properties of HEMA-based hydrogels. The study showed that VCR is generally more stable while the drug concentration, medium type, and temperature affected the stability of TPT. The best results were obtained in water with a higher concentration at 4 °C and in the RPMI 1640 culture medium [134]. On the basis of the obtained results, it was recommended that the new hydrogel implant be used as a potent therapeutic tool for the delivery of topical medications in the treatment of Rb and other ocular disorders.

ncRNAs: ncRNAs are transcripts that are not converted to proteins. They are scattered throughout the human genome and are also abnormally regulated in tumor cells. They are commonly located in fragile regions, in heterozygosity loss sites, and in breakpoint regions. They indicate a new series of genes involved in tumorigenesis [135,136]. ncRNAs are divided into two categories according to function: those with an oncogenic function and those acting as tumor suppressors [137]. They are also classified into two groups on the basis of the length of their sequence: short ncRNAs, with a maximum length of 200 nucleotides, and long ncRNAs (lncRNAs), which are transcripts with more than 200 nucleotides [138]. Recently obtained evidence has shown that lncRNAs are involved in many cellular processes, such as cell proliferation, differentiation, migration, and invasion. Multiple lncRNAs, including BANCR [139], AFAP1-AS1 [140], NEAT1 [141], XIST [142], PlncRNA-1 [143], HOTAIR [144], PANDAR [145], DANCR [146], and THOR [147], cause the progression and metastasis of Rb, but some lncRNAs, such as MEG3 [148], MT1JP [149], and H19 [150], play a tumor-suppressive role.

New evidence also suggests that some lncRNAs, such as MALAT1, H19, and BANCR [149,151,152], are beneficial in the diagnosis and prognosis of Rb. lncRNA has differential expression in Rb and normal tissues, making it a potential biomarker for the diagnosis of Rb. It may also be a potential target for Rb therapy. The most studied class of ncRNAs is the microRNAs (miRNAs), which are about 22 nucleotides long and involved in regulating the expression of more than 60% of all genes [153]. They are also a group of small ncRNAs with independent promoters posited in intergenic sites [154], but they can also be transcribed in introns with the same host gene promoter [155]. They play an important role in cellular physiology and functions and are also involved in the development of various cancers by regulating the expression of the target genes; thus, they have been suggested as attractive biomarkers of tumors for the detection of Rb [153,155]. There are several evidences that the deregulation of different miRNAs is involved in different stages of Rb [156]. Recent studies have reported that miRNAs such as miR-30, miR-let-7e, miR-21, miR-204, and miR-320 are dysregulated in Rb patients and have been recommended as diagnostic biomarkers for Rb detection [157–159].

Several critical miRNAs, such as hsa-miR-373, hsa-miR-181a, hsa-miR-125b, and hsa-let-7b, cause Rb progression and metastasis. They might act as tumor suppressors by co-regulating CDK6, CDC25A, and LIN28A. Some miRNAs, such as hsa-miR-25, hsa-miR-18a, and hsa-miR-20a, might exert their function by co-regulating BCL2L1 [160]. Few studies, however, have evaluated the circulation of miRNAs as diagnostic and prognostic biomarkers in Rb [161]. Thus, further research is needed to identify miRNAs and circulating miRNAs that are suitable candidates for the treatment and diagnosis of Rb [162].

Aqueous humor markers: Unlike other cancers, Rb cannot be classified through biopsy. Thus, it does not have any genetic tumor marker [163]. Tissue biopsy is contraindicated in Rb largely because it is invasive and poses a risk of extraocular tumor spread [164]. Nonetheless, studies of tumors in enucleated eyes have provided abundant information regarding the genetics of Rb [165].

Aqueous humor (AH) as an “alternative tumor biopsy” [167] addresses the problems associated with tissue biopsy. The recently shown cell-free tumor DNA (cfDNA) in AH has a potential biomarker role [168]. AH paracentesis is now a standard protocol during administrations of intravitreal chemotherapy for Rb patients. Anterior chamber paracentesis is conducted before the intravitreal injection of the chemotherapy agent to induce transient hypotony and therefore prevent the reflux of tumor cells during injection [169]. It has been found in recent studies that the reproducible AH samples reflect the genomic status of the tumor and Rb somatic chromosomal copy number alterations (SCNAs), which are involved in Rb tumorigenesis. The recurrent SCNAs of Rb in the AH predict the tumor’s response to globe salvage therapy [170], Hence, these results show that a 6p gain in the AH is a strong prognostic biomarker for poor clinical response to treatment [170]. Thus, circulating tumor cell- and cfDNA-based fluid biopsies in the blood or other fluids can now be used clinically for the management of Rb without the need for enucleation [171,172].

Exosomes: A new biomarker called exosome has been introduced in fluid sampling to monitor tumor progression

and drug resistance. Exosomes are NPs derived from cell membranes (30–100 nanometers in diameter) and contain RNA, miRNA, lipids, and proteins. Their microvesicles secreted by invasive tumor cells can be found in a variety of body fluids [173]. In recent years, numerous investigations have been made to show that there is a relationship between proteins' and peptides' levels of expression and different pathological diseases [174]. In a recent study, exosomes from Rb tumors and tumor seeding in the vitreous humor from Rb cell lines were isolated using high-resolution mass spectrometry [175]. This paves the way for the definition of exosomal markers as potential diagnostic and potential markers of prognostic and therapeutic targets in Rb.

MLN4924: Neddylation or adding Nedd8 modifies post-translational protein and has been linked to cancer development in 1997 [176]. MLN4924, also known as pevonedistat, is a neddylation inhibitor currently being studied on solid tumors [177] and blood malignancies [178] in phase I clinical trials.

The members of the choline family are the physiologic substrates of neddylation. The neddylation of all cullins is effectively blocked by MLN4924 and leads to the accumulation of their substrates, thus causing multiple cellular reactions, including cell cycle arrest, apoptosis, aging, and cell-type dependent-manner autophagy [179].

A recent study showed that in Rb, MLN4924 potently prevents Rb1 loss (Rb1null) and MYCN amplification. The maximum tolerable dose for intravitreal MLN4924 is 10–30 µg [180].

In addition, S-phase kinase-associated protein 2 (SKP2) has been identified as a potential therapeutic target [181]. A recent study demonstrated that the loss of SKP2 destroys Rb1null cells. Thus, intravitreal MLN4924 is an excellent new therapy for Rb, killing cancer cells by removing SKP2 complexes [180].

Conclusion: Despite the availability of various treatments for Rb, there is still an urgent need for new therapeutic options to prevent the delayed side effects of the current interventions and to maintain the patient's vision to the extent possible. Rb treatment options have evolved rapidly in recent years by changing the paradigm from the standard treatment protocols to targeted chemotherapy agents.

Targeted therapy is a promising treatment for various kinds of cancer. New Rb treatments and modalities have been explored, such as the use of new transporters and pathways for the local delivery of therapeutic agents and targeted molecular therapies. According to the available literature, anti-tumor drugs with molecular targeting are effective in treating Rb. Recent studies have predicted that future combinations of new targeted chemotherapeutic agents with local delivery, including CBP, TPT, and MEL, will increasingly play an important role in the management of Rb by creating safe and effective treatments that can help better control tumors while maintaining the patients' vision.

Despite the advances in the management of Rb in recent years, there are still some fundamental limitations in the clinical use of the new targeted therapies and delivery pathways. The long-term effects of these new treatment options also need to be further evaluated. It is hoped that with the benefit of better insight into the relationship between Rb cell biology and the future development of targeted and less toxic therapies, non-responder Rb cases will be a thing of the past.

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