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A Review of Outstanding Retinoblastoma Researches on RB1 Genes: Focus on Treatment by Non-ionizing and Ionizing Radiation

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ABSTRACT

Introduction Retinoblastoma (RB) is a malignant retinal tumor, which affects infants and children. This cancer happens through a mutation in the retinoblastoma tumor suppressor genes (RB1). Inactivation of RB1 has been observed in more than 97% of all retinoblastoma patients with mutations. In recent years, RB treatment has developed significantly. RB's treatment methods can be one or a combination of the following treatments, including chemotherapy, non-ionizing, or ionizing radiation. This article aimed to review each treatment method's role and its effectiveness in the treatment of RB. Several articles from 2004 to 2020 were reviewed in PubMed, Web of Science, Google Scholar, and Scopus, based on the RB treatments, of which 73 were selected for this study.

Conclusion It can be concluded that ionizing and non-ionizing radiation play an important role in treating retinoblastoma. It was also shown that a combination of radiation treatments is more effective than traditional therapeutic methods.

Ionized and non-Ionized radiations can be used as an effective treatment to cure retinoblastoma.

Keywords Retinoblastoma; Treatment; RB1 Gene; Ionizing Radiation; Non-Ionizing Radiation

CITATION LINKS

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Introduction

Retinoblastoma (RB) is a malignant retinal tumor that affects newborns and children [1-4]. The most common sign of this cancer is a white pupil reflex called leukocoria [3, 5, 6]. Most of the patients are at risk due to long-standing diagnosis [5]. Diagnosis of pediatric cancer is still dependent on clinical symptoms, which may be non-specific or sometimes appear in later stages. Therefore, there is a need to understand better molecules that provide less invasive, early, and effective detection of cancer [7]. Retinoblastoma happens by a mutation in the *RB1* gene. Mutations in both *RB1* alleles are essential in precursor retinal cells, with the first mutation may be germline or somatic, and the second, which is always somatic [1, 8, 9]. Early identification of *RB1* gene mutations in blood samples or somatic *RB1* mutations in tumors is important for the care and management of patients with retinoblastoma and their families [10]. Retinoblastoma accounts for approximately 11% of cancers occurring in the first year of life, with 95% diagnosed before 5 years of age [11]. Multiple studies indicated that age is an important risk factor of RB, while other investigations showed various factors could affect early detection of such disease, including racial, ethnic, and socioeconomic factors [11-16]. The low socioeconomic status will remarkably affect the degree of illness and outcomes of the eye due to the possibility of treatment limited by the access to primary and direct cancer care [17]. Some research showed that when the birth order increased, a decreasing risk was observed for other tumor types in the research except for retinoblastoma [18-21]. Some studies have been carried out to check clinical outcomes and treatment in children in southwestern China with retinoblastoma and distinguish the predictive factors for bad outcomes. The study showed that parents' and physicians' education for early retinoblastoma symptoms such as leukocoria, therapeutic strategy, and retinoblastoma treatment outcomes might improve early detection, improvement of compliance, and disease outcome [22, 23].

This study aims to investigate the effects of all types of radiation, both ionizing and non-ionizing, on RB treatment. In this research, the following question has been answered: How can ionizing and non-ionizing radiation be used as an effective method to cure RB cancer?

In this review, the original scientific articles published after 2000 on the effects of ionized and non-ionized radiation on retinoblastoma were reviewed through MEDLINE, PubMed, Web of Science, Google Scholar, and Scopus databases. Keywords "Radiation therapy" or Radiotherapy" or "Radiation" or "X-ray" or "Gamma-ray", AND "Retinoblastoma" AND, "Ionized" or "Non-ionized" or "Ionizing' or "Non-ionizing" were applied.

Original scientific articles published in English, as well as studies reporting the source of the radiation, dose, and sample size, were only selected (research criteria).

Eligible articles were comprehensively reviewed by one of the authors (Dr. M. Aljamal) based on the research criteria. The article's selection started with screening the title, abstract, and conclusion of the article; the next step, the articles that met the criteria were selected. Finally, 73 articles were selected for this study.

Treatments for retinoblastoma

Due to a mutation of 1 of 2 RB1 genes in all somatic cells, the patients with hereditary retinoblastoma are in danger of inducing secondary cancer [24]. The various aspects must be considered in choosing the suitable treatment options for retinoblastoma, which can be included: unilateral/bilateral case, size and location of the lesion, the possibility of losing the vision, and hereditary nature of this disease [4]. The most common treatment methods for retinoblastoma are chemotherapy, ionizing radiation (external radiation therapy and brachytherapy), and non-ionizing radiation (laser photocoagulation). Some treatment methods of most unilateral cases and some bilateral cases have reduced the use of external beam radiotherapy and systemic chemotherapy such as ophthalmic artery chemosurgery and intravitreous chemotherapy; therefore, the most metastatic disease can be curable now [25]. In this paper, the treatment option for retinoblastoma is reviewed to study each treatment method's efficiency on RB treatment.

Chemotherapy treatment

Chemo-reduction treatment played an important role as a conservative option in children with intraocular retinoblastoma and even in children with advanced cases of this disease [26]. The charts of 58 consecutive patients with hereditary retinoblastoma treated between January 1996 and August 2005 were reviewed. Wilson *et al.* found that young patients treated using systemic chemotherapy for RB may effectuate small previously undetected lesions by slowing their growth [27]. Zhao *et al.* divided children with retinoblastoma into groups D and E in 29 treatment centers and found that using chemotherapy before enucleation may not has the impact or the benefit for the patient. On the contrary, the enucleation could minimize the risk of the spread of cancer to other organs. While Post-enucleation chemotherapy showed an effective method to improve children's survival rate with high-risk histopathology [28]. Systemic chemotherapy may increase morbidity and the risk of inducing a secondary malignancy [29]. Besides, it is the strongest risk factor for second malignancies outside the periorbital region. Therefore, instead of systemic chemotherapy, another treatment option was

recommended to reduce the risk effect after this treatment method [30]. Intravenous chemotherapy (IVC) is an effective way to treat early-stage retinoblastoma, especially classified under groups A, B, and C, where the studies showed that the survival rate could reach 100% but still for RB groups D and E requires enucleation with IVC. In this study, 249 cases were examined [31, 32]. IVC is related to some systemic side effects that cannot be avoided, such as hearing loss, which might induce myelogenous leukemia [33, 34]. Another method was Intra-arterial chemotherapy (IAC), where this method was introduced basically for advanced cases of retinoblastoma after the intravenous chemotherapy has failed in the treatment process. Therefore, some centers tried to use the IAC method as a primary treatment for advanced cases of RB and showed significant improvement to prevent the enucleation option [35-40]. Recently, intravitreal chemotherapy has shown an effective way to control vitreous seeds. Several studies have been conducted to check the effectiveness of this treatment, and they found that intravitreal chemotherapy is a reliable and efficient method for the treatment of vitreous cases [41-46].

Non-ionizing radiation treatment

The treatment of cancer and cure options are limited in some cases. For example, when the tumor is inoperable [47]. New Findings show that targeting and treating cancer by non-ionizing radiation is a new important goal in cancer treatment. Although electromagnetic fields (EMFs) have been used in medical applications for diagnostic or therapeutic purposes, non-ionizing EMF's can be considered as a novel method in treating cancer cells [47]. There are varieties of new treatment strategies, which use electroporation for the treatment of cancer. The electro-gene transfer method was used to benefit from delivering genes, guiding the immune system against the tumors [47]. Electrochemotherapy is another strategy that uses electroporation to deliver a chemotherapeutic agent, and irreversible electroporation uses the electroporation to induce necrosis [27, 28]. Other methods were suggested using temperature to treat cancer, such as cryotherapy, which induces thermal necrosis by freezing and radiofrequency ablation [48].

The ion-ionizing radiation with nanosecond pulsed electric fields (nsPEFs) has shown a brilliant treatment method at local sites [41]. In this study, results were obtained among 12 treated cases, in which 10 out of 12 cases were performed at immediate follow-up, 8 out of 10 cases at short-term follow-up, and 6 out of 10 cases at long-term follow-up, the presence of the active caspase (one of the apoptosis hallmarks), Yo-PRO-1 uptake (which probably identifies apoptotic cells), and propidium iodide (PI) uptake (which act as the measure of membrane integrity) were investigated in B16f10 cells. Their findings showed that nsPEFs induced cell death in 90-95% of cells in murine B16f10 melanoma, murine E4 squamous carcinoma, murine Hep16, and human HepG2 hepatocellular carcinoma [41]. In other researches, it has been shown that photodynamic therapy (PDT) could also act as a suitable clinical method for cancer treatment. It contains a local or systemic administration of a photosensitizer, followed by irradiating a target lesion with a certain wavelength of non-ionizing light, which results in oxidative photo-damage and finally the targeted death cells [49, 50]. The importance of infrared (IR) therapy has also grown rapidly in recent years [51-54]. Two kinds of therapies are usually employing the lights at red and near-infrared wavelengths (600–100 nm) to modulate biological activity, which can be classified as Low-level light therapy and Photobiomodulation (PBM) therapy. The Low-level light therapy (LLLT) acts as a treatment method using a low intensity of light, so the effect is based on response to the light and not due to heat or thermal effect, and it uses a variety of light sources, especially low-power lasers to kill cancer cells [55, 56]. While Photobiomodulation (PBM) therapy technique uses a form of light therapy that utilizes non-ionizing forms of light sources, like light-emitting diodes (LEDs) and lasers in the visible and infrared spectrum. This non-thermal process has suitable therapeutic outcomes, including alleviating pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration [55, 56]. IR-induced physiological effects are claimed to be due to two basic kinds of photo acceptor: cytochrome c oxidase (CCOX) and intracellular water [55, 56]. The water dynamics in membranes, mitochondria, and/or cells absorb the IR photons, which converts light into signals that can stimulate biological processes [57]. During cancer, patients can be exposed to a variety of radiation types. Low doses of ionizing radiation are used for medical imaging applications (1–10 mGy).

On the other hand, high doses of radiation play an important role in cancer radiotherapy to destroy malignant tissue (fractionated up to a local dose of 80 Gy) [55, 58-60]. In new research in 2018, it is pointed that ionizing and near-infrared radiation can both play a well therapeutic role in cancer treatment [61, 62]. Ionizing radiation is typically used for non-invasive malignant tissue reduction, but near-infrared photobiomodulation is applied for narcotic approaches, such as pain reduction or impairment of wound healing [61, 62]. Combined exposure of these two irradiation types is finally suitable for cancer patients. The research suggested that the cancer patients treated with X-rays should be prevented from uncontrolled near-infrared (NIR) irradiation, while controlled double-treatment could provide an alternative therapy approach, exposing the patient to less radiation [61, 62]. A brief table summarizes some previous studies on the response of retinoblastoma

disease to non-ionizing radiation (Table 1).

Ionizing radiation treatment

Telomeres are nucleoprotein sets that protect the linear chromosomes from fusion and decomposition and play an important role in maintaining DNA integrity [61, 62]. The shortening of telomeres due to DNA replication leads to aging of the cell in most somatic cells [63, 64]. Telomerase is a unique ribonucleoprotein reverse transcriptase that synthesizes telomeric repeats [63, 64]. Normal somatic cells contain low telomerase activity (TA). On the other hand, 90% of all malignant cells express TA; thus, telomerase is one of the malignancy hallmarks [63, 64]. Activation of telomerase is considered important for malignant transformation and is essential for protecting the malignant clone [63, 64]. Obtaining a better understanding of the molecular mechanism of telomerase activation by ionizing radiation in retinoblastoma cells is important because patients suffered from retinoblastoma and treated with ionizing radiation are at risk for secondary cancers [63, 64]. DNA damage induced by ionizing radiation at doses of 2-5 Gy could increase telomerase activity while using doses greater than 10 Gy might decrease telomerase activity in Y79 cell lines [65].

Furthermore, it has been shown that telomerase activity is increased 12-24 hours after the radiation dose of less than 10 Gy [65]. Although the extent of activation or inhibition of telomerase with ionizing radiation depends on the cell type and the experimental setting, the mechanism of regulating telomerase in a radiation-dose dependent manner is still poorly understood [65]. The latest researches on *RB1* have shown that the mutation on chromosome 13q is often present in retinoblastoma tumors [65]. The *RB1* gene has an important role in regulating the cell cycle, cell differentiation, cell aging, apoptosis, and growth suppression [66-68]. Yang *et al.* reported that *RB1* could be functionally inactivated through many kinds of mechanisms, such as deregulated phosphorylation and direct sequestration by oncoproteins and the loss of *RB1* function leads to a breakdown in genome integrity [66-68]. The E2F group of transcription factors also has an important role in DNA repair. E2F1, known as the most important founding member of the E2F transcription factor family, promotes the recruitment and/or retention of repair factors, such as XPA and XPC, at the sites of DNA breaks and can repair DNA double-strand breaks (DSBs) [69-73]. The RB1-E2F1 complex is formed as a response to DNA damage and is recruited to the sites of DNA DSBs [69-73]. To analyze the DNA repair efficiency of exogenous RB1, SO-Rb50 cells transfected with the pcDNA3.1-Rb1 or pcDNA3.1-vector were exposed to ionizing radiation [137Cs (dose rate, 0.67 Gy/min)] [69-73]. The viability of RB1 of 50 cells was measured. It has been found that DNA repair efficiency was significantly increased following radiation-induced damage [69-73]. External beam radiotherapy has been a standard treatment option for large-sized lesions and intraocular retinoblastoma, but it markedly increases secondary cancer risk. A summary of some studies that have been conducted to study the efficiency of ionizing radiation on Retinoblastoma treatment (Table 2).

Table 1) Researches conducted to study the efficiency of non-ionizing radiation in the treatment of retinoblastoma disease

Research	Specifications
Beebe *et al.* 2009 [49]	
Irradiated samples:	Tumor cells
Radiation source:	nsPEFs
Dose:	one or ten 60ns or 300ns pulses at various electric fields
Analysis time after radiation:	Decreased
Sample count:	Decreased
Results:	Results show four coincident apoptosis markers in the major population (85-95%) of cells
Conclusion:	nsPEFs can induce cell responses that indicate apoptosis induction
Wei *et al.* 2016 [52]	
Irradiated samples:	Y79 and WERI-Rb1
Radiation source:	Laser
Dose:	10, 30, and 50 J/cm2
Analysis time after radiation:	48 hrs
Sample count:	Decreased
Results:	The viability of Y79 cells decreased
Conclusion:	The beacon showed an efficient imaging capability on retinoblastoma cells and increased cell apoptosis after PDT in vitro.
Wei *et al.* 2016 [52]	
Irradiated samples:	Tumor cells
Radiation source:	Laser
Dose:	633-nm (30 J/cm2) over 5 min
Analysis time after radiation:	72 hrs
Sample count:	Decreased
Results:	The apoptosis of tumor cells increased
Conclusion:	The beacon showed an efficient imaging capability on retinoblastoma cells and increased cell apoptosis after PDT in vitro.
Aerts *et al.* 2010 [53]	
Irradiated samples:	3 RB1 models
Radiation source:	Laser
Dose:	100 and 600 mW (75 and 50 J/cm2)
Analysis time after radiation:	<70 days
Sample count:	No effect
Results:	Successful treatment of RB with PDT is likely to depend on the tumor's parameters like location and size.
Conclusion:	They still do not have a full understanding of the mechanisms of action of PDT in RB.

Continue of Table 1) Researches conducted to study the efficiency of non-ionizing radiation in the treatment of retinoblastoma disease

Research	Specifications
Walther *et al.* 2014 [54]	
Irradiated samples:	Y79; WERI Rb1 cell lines and PRE cells
Radiation source:	Laser
Dose:	60 J/cm2 and 100 mW/cm2
Analysis time after radiation:	0 and 30 and 60 hrs
Sample count:	No effect
Results:	The immune system's activation, combined with the low resistance mechanism, makes PDT an ideal cancer curative treatment. However, many technical limitations are linked to the dozen clinically approved photosensitizers and limit their use too few applications.
Conclusion:	PDT can be a therapeutic option for the treatment of retinoblastoma and also a promising therapeutic alternative.
Konig *et al.* 2018 [61]	
Irradiated samples:	Human fibroblasts
Radiation source:	Near Infrared(NIR) & X-Ray
Dose:	600–1400 nm for 30 min & 90 kV, 33.7 mA, 5.23 Gy/min
Analysis time after radiation:	During 24 hrs
Sample count:	Decreased
Results:	NIR Pretreatment Delays Repair of X-ray-induced DSBs
Conclusion:	Cancer patients treated with X-rays should be prevented from uncontrolled NIR irradiation. Nevertheless, controlled double-treatment could be an alternative therapeutic way.

Table 2) Researches conducted to study the efficiency of ionizing radiation in the treatment of retinoblastoma disease

Research	Specifications
Ram *et al.* 2009 [63]	
Irradiated samples:	Tumor cells
Radiation source:	X-Ray
Dose:	2 to 8 Gy
Analysis time after radiation:	Up to 48 hrs
Sample count:	Not mentioned
Results:	Telomerase was activated
Conclusion:	Radiation up-regulates telomerase activity in cancer cells, and the Telomerase activation due to radiation may be a way of treating cancer
Akiyama *et al.* 2013 [65]	
Irradiated samples:	Y79 cells
Radiation source:	X-Ray
Dose:	2 and 5 and 10 Gy
Analysis time after radiation:	Up to 8 hrs
Sample count:	G2/M checkpoint increased
Results:	DNA damage induced by IR at doses of 2–5 Gy increased telomerase activity in Y79 cells, but DNA damage induced by IR at doses greater than 10 Gy might decrease telomerase activity.
Conclusion:	Different activation ways may be responsible for telomerase regulation.

Continue of Table 2) Researches conducted to study the efficiency of ionizing radiation in the treatment of retinoblastoma disease

Research	Specifications
Wilson *et al.* 2011 [68]	
Irradiated samples:	RB fibroblast strains
Radiation source:	ɣ Ray (662 KeV)
Dose:	0 (sham) or 50 cGy or 1 Gy
Analysis time after radiation:	<26 hrs
Sample count:	Decreased
Results:	The cells' inability to proliferate during continuous low-dose-rate irradiation at higher dose rates correlated with cell cycle redistribution and checkpoint-induced arrest in the radiosensitive G2 phase of the cell cycle.
Conclusion:	The RB1 Radio-sensitivity increased
Yang *et al.* 2013 [69]	
Irradiated samples:	SO-Rb50+pcDNA3.1-RB1
Radiation source:	X-Ray
Dose:	0 and 2.5 and 5 Gy
Analysis time after radiation:	0, 2.5, 8, 24 hrs
Sample count:	Decreased
Results:	Rb1 did not affect non-homologous end joining (NHEJ) activity, although it significantly promoted the homologous recombination (HR) pathway
Conclusion:	The RB1 radiosensitivity and instability increased
Guo *et al.* 2010 [73]	
Irradiated samples:	Human fibroblasts and E2Fs
Radiation source:	UVA, UVB, UVC
Dose:	290 nm
Analysis time after radiation:	Up to 8 hrs
Sample count:	Depending
Results:	E2F1 stabilization in response to DNA damage contributes to the induction of apoptosis
Conclusion:	E2F1 results in the inefficient repair of UV-induced DNA damage. It can inhibit apoptosis and increase survival in response to UV radiation

Conclusion

Many evidence suggests that ionizing and non-ionizing radiations have different mechanisms to destroy cancer cells and play an important role in treating RB. This paper gives a brief overview of some important mechanisms of radiation for cancer therapy. Early theoretical work suggested that radiation therapy included X-ray, Gamma-ray, and other ionizing radiation, leading to cancer cells' destruction. More recent work suggests that applying Infrared, Laser, electromagnetic radiation, and other non-ionized radiation would induce the overall damages and increase radiation efficiency. The results confirm that the combination of the treatments is more effective than traditional therapeutic methods.

The mutations of *RB1* genes are the cause of retinoblastoma. Thus, if these genes could regenerate

themselves by being activated again, this cancer can be cured. The future idea is to use electromagnetic radiation (ionizing or non-ionizing) to reactive the *RB1* genes.

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