https://doi.org/10.31925/farmacia.2022.6.5 **REVIEW**

INTRAVITREAL ANTI-VEGF THERAPY FOR OCULAR METASTASIS IN BREAST CANCER

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Manuscript received: June 2022

Abstract

Ocular metastases are the most common form of malignancy encountered in ophthalmology, in most cases associated with breast cancer as the primary tumour. Standard local therapy in case of ocular metastases that do not respond to systemic chemotherapy consists of external irradiation or brachytherapy, with multiple disadvantages related to the required logistics and multiple sessions as well as serious post-radiotherapy complications. The present systematic review discusses the efficiency and safety of intravitreal therapy with anti-vascular endothelial growth factor (anti-VEGF) agents used against choroidal metastases secondary to breast cancer. After an extensive search on PubMed, Google scholar and Web of science databases, 15 articles presenting data on 18 patients were included. The injected doses varied between 1.25 and 4 mg/session, with a monthly repetition of 3.9 ± 1.9 sessions. After treatment, it was reported that tumour size decreased in size in 94.5% of cases, the subretinal fluid decreased or resolved in 73.3% of cases, and vision improved in 61.1% of cases. The intravitreal injection of anti-VEGF agents as a simple and easy therapeutic approach that is free from the local ocular post-radiotherapy complications, can be considered a local adjuvant therapy to systemic chemotherapy.

Rezumat

Metastazele oculare sunt cea mai frecventă formă de malignitate întâlnită în oftalmologie, în cele mai multe cazuri asociate cu cancerul de sân ca tumoare primară. Terapia locală standard în cazul metastazelor oculare care nu răspund la chimioterapia sistemică constă în iradierea externă sau brahiterapia, cu multiple dezavantaje legate de logistica necesară și de multiplele ședințe și complicațiile grave ale radioterapiei. Prezentul review abordează eficiența și siguranța terapiei intravitreale cu agenți anti-VEGF (anti-factor de creștere endotelială) utilizați împotriva metastazelor coroidiene secundare cancerului de sân. În urma unei căutări extinse în bazele de date PubMed, Google Scholar și Web of Science, au fost identificate 15 articole care prezintă date despre 18 pacienți. Dozele injectate au variat între 1,25 și 4 mg/sesiune, cu o repetare lunară de 3,9 ± 1,9 ședințe. După tratament, s-a raportat că dimensiunea tumorii a scăzut în 94,5% din cazuri, lichidul subretinian a scăzut sau s-a remis în 73,3% dintre cazuri, iar vederea s-a îmbunătățit în 61,1% dintre cazuri. Injectarea intravitreană a agenților anti-VEGF poate fi considerată o terapie locală adjuvantă la chimioterapia sistemică.

Keywords: anti-VEGF, bevacizumab, ocular metastasis, breast cancer

Introduction

Breast cancer (BC) as a major global health burden is the most commonly diagnosed malignancy worldwide and the fifth cause of death [28]. Recent epidemiological studies found a prevalence of 24.5% for all cancers in women and 15.5% cancer deaths.

The incidence of BC is on the rise with 2.3 million new cases diagnosed in 2020 [46] being estimated to reach 4.4 million cases by 2070 [47]. However, recent developments in the therapy of BC and management of metastatic diseases, led to an increase in the 5-year breast-cancer-specific survival from 74.0% during 1975 to 1979 [19] to 90% in 2016, according to Surveillance, Epidemiology and End Results (SEER) data [9, 19, 20].

The estimated incidence of choroidal metastases in patients with disseminated BC varies from 2 to 13% in different studies [8, 52]. In a study by Wiegel *et al*. [52], asymptomatic BC choroidal metastasis (CM) was observed in 11% of patients with more than one affected organ and the risk factors associated with choroidal metastases were pulmonary and cerebral dissemination. Also, ocular metastasis was associated with advanced disease and adverse outcome [11, 25, 26, 52]. In a study on 46 cases, Kreusel *et al*. [26] found that CM occurrence in BC patients was associated with a mean survival of 13.1 months. Demirci *et al*. [11] studied 264 patients with CM and BC and found survival rates of 65% at 1-year and of 24% at 5-year follow-up.

Ocular metastases in BC are not life-threatening but they can have a major impact on vision by causing blindness and eye pain, thereby affecting the quality of life of the patients. The lifespan of patients with eye metastases is limited, so, complex invasive treatments are generally not indicated. The therapeutic decision is influenced by the level of activity and the location of the eye metastases. Local treatment is required when there is a risk of visual impairment despite systemic chemotherapy. The main objectives of the treatment of CM are prevention of eye pain and preservation of vision, thereby improving the quality of life of the patients [4, 32]. The optimal therapeutic approach is still a subject of debate as different therapeutic approaches have their specific advantages and limits.

External beam radiation therapy (EBRT) is the standard treatment for ocular metastasis and it is efficient in 85 - 93% of cases [13, 21, 50]. The usual dose considered in EBRT is 20 - 30 Gy fractionated in approximately 10 sessions. The major drawbacks include limited available resources, multiple visits required and time loss affecting the quality of life of the patients particularly in cases with multiple organ metastasis. Moreover, potential vision-threatening complications such as cataract, exposure keratopathy, iris neovascularization, radiation retinopathy and papillopathy have been reported in 12% of cases. Ruthenium-106 (^{106}Ru) plaque brachytherapy has an efficiency of 94%, but this method of targeted radiotherapy requires a surgical intervention to place the plaque and another intervention to remove it [13, 45]. As therapeutic alternatives, transpupillary thermotherapy with infrared diode laser and photodynamic therapy were used but indicated in small formations under 3.5 mm and minimal subretinal fluid [22].

Vascular endothelial growth factor (VEGF) exerts a proangiogenic role at the level of tumour cells, and affects vascular permeability. Metastatic BC has been associated with elevated serum VEGF levels [31]. Systemic intravenous bevacizumab (a VEGF monoclonal antibody) treatment was approved as an adjuvant to chemotherapy for metastatic BC [14]. Moreover, anti-VEGF agents are currently routinely used in a large array of chorioretinal diseases, such as diabetic retinopathy, age-related macular degeneration and retinal vein thrombosis. Recently, several authors have reported the efficiency of intravitreal anti-VEGF in treatment of ocular metastasis [6, 33, 53].

The present review discusses the safety and outcomes of intravitreal anti-VEGF therapy in ocular metastasis secondary to BC, in terms of the effect upon ocular pain, visual acuity and tumour size, based on the available literature.

Materials and Methods

Data extraction and analysis

A comprehensive search was carried out on PubMed, Web of Science and Google Scholar, by the search strategy: ("ocular" OR "choroid" OR "uveal metastasis") AND ("anti-VEGF" OR "Bevacizumab" OR "Ranibizumab" OR "Aflibercept") AND ("breast cancer"). All the original articles and case reports documenting patients with BC and ocular metastasis that underwent intravitreal anti-VEFG therapy, published in English language, were included in the present review. Meeting abstracts, commentaries, and book chapters were excluded. Also, a hand search was performed in the references of the relevant reviews on the topic.

Figure 1 displays the PRISMA flowchart of steps taken to prepare the present article. The articles were screened independently by two researchers. Any disagreement was solved by discussion. Papers which did not provide sufficient information regarding the intravitreal anti-VEGF therapy or its outcomes, were excluded.

All information regarding the age, tumoural status, other coexisting metastasis at the diagnosis of ocular dissemination, concurrent systemic chemotherapy, doses and timing of intravitreal anti-VEGF administered, ocular or general side-effects and other local therapies used were documented. The outcomes were evaluated in terms of changes in visual acuity (VA), size of intraocular tumour and subretinal fluid (SRF). For iris metastasis associated with neovascular glaucoma, regression of neovessels and ocular pain were also analysed. The data were analysed using Microsoft Excel (v. 2019) and SciStat® software (www.scistat.com).

Risk of bias

The papers analysed in the present review were case reports comparable in terms of diagnosis, therapeutic approach and follow-up. However, there were differences in the biological types of BC of the patients, concurrent chemotherapy, absence/presence of systemic bevacizumab, and the dose and timing of intravitreal injections, which may be a significant source of bias. Moreover, in some cases, authors reported another local therapy, such as EBRT, transpupillary thermotherapy (TTT), or indocyanine green mediated photothrombosis (IMT).

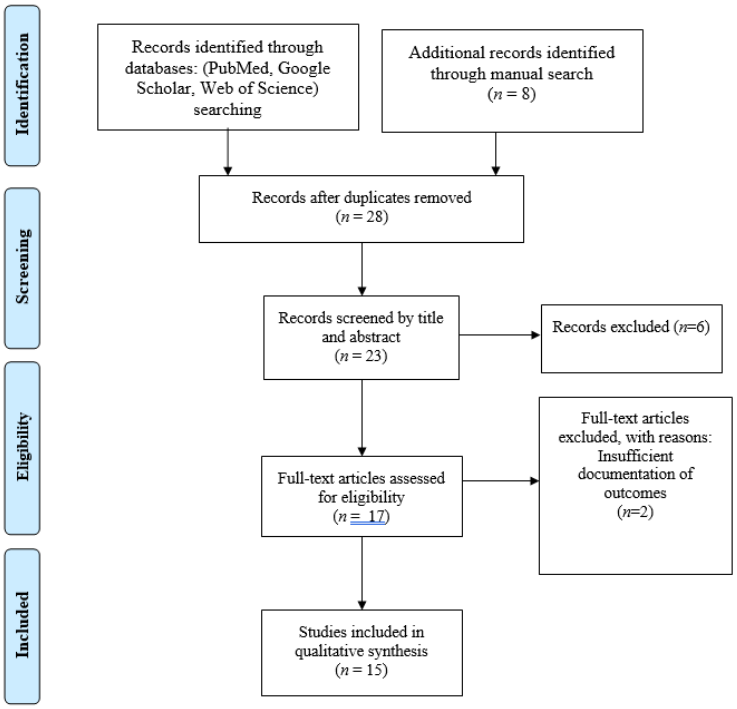

Figure 1.
PRISMA flowchart of the present study

Results and Discussion

After duplication removal, and application of inclusion and exclusion criteria, 15 articles presenting data from 18 patients (22 eyes) were included and analysed. The relevant information abstracted from the reviewed articles are presented in Tables I and II.

Table I

General description of the articles included in the present review

First author, year	Affected eye	Age (years)	Systemic metastases	Ocular mts.	Systemic chemotherapy	Ocular treatment	Initial visual acuity	Final VA	Tumour size	SRF	Follow-up (months)
Augustine H, 2014 [6]	RE	75	liver, bone, brain	choroid, single	concurrent (capecitabine, transtuzumab, denosumab)	IVB 1.25mg, monthly, 4 doses	20/125	20/25	decreased	resolved	8
Mansour AM, 2012 [33]	LE	49	NA	Choroid + optic disc	previous	IVB 2.5mg monthly, 3 doses	20/20	20/40	decreased	persisted (probably damaged RPE)	22
Yao HY, 2010 [50]	LE	50	lung, lymph nodes	Choroid, single	concurrent (paclitaxel, gemcitabine)	IVB 2.5mg, 1 dose	CF	20/30	decreased	resolved	24

First author, year	Affected eye	Age (years)	Systemic metastases	Ocular mts.	Systemic chemotherapy	Ocular treatment	Initial visual acuity	Final VA	Tumour size	SRF	Follow-up (months)
Zako M, 2012 [53]	RE	51	bones, lymph nodes, mediastinal, ovary	Choroid + optic disc + RD	concurrent (paclitaxel, gemcitabine, letrozole, tamoxifen, cyclophosphamide) + Bevacizumab	IVB 2.5mg, 1 dose	0.5	0.05	decreased	resolved	13
Amselem L, 2007 [3]	RE	57	lung, bone	choroidal, single	previous	IVB, 4 mg, 1 dose	10/200	20/60	decreased	persisted	1
Maudgil A, 2015 [34]	RE LE	43 62	bone, lung, lymph nodes NA	choroid, multiple choroid+ iris	concurrent (Both cases)	Case1: PDT, IVB 1.25 mg monthly, 3 doses, EBRT Case 2: EBRT, IVB 1.25 mg monthly, 3 doses	6/18 6/18	6/60 6/60	Increased decreased	NA persisted	6 1
Fenicia V, 2014 [13]	LE LE	39 54	NA lung, bone	choroid, singles (both cases)	concurrent (tamoxifen) concurrent (docetaxel)	IVB 1.25 mg monthly, 2 doses IVB 1.25 mg monthly, 4 doses	20/50 20/25	20/20 20/20	decreased (both cases)	resolved (both cases)	6 (death) 12 (death)
Lin CJ, 2015 [29]	BE	34	liver	Choroid, multiple	Concurrent (cetuximab)	TTT + IVB 4mg, weekly, 3 doses	RE:20/40 LE:20/20	BE:20/20	Decreased BE	Decreased BE	6
Jun JW, 2022 [20]	LE	60	lymph nodes, liver, bone, brain	Optic disc	concurrent	IVB 1.25 mg, monthly 3 doses + 2.5 mg monthly, 2 doses	20/50	NA	decreased	decreased	< 1
Arevalo JF, 2012 [5]	RE BE	47 70	NA NA	Choroid, single Choroid, multiple	concurrent	IMP + IVB 4 mg single dose (both cases)	RE: CF RE:20/25 LE:HM	RE:20/100 RE:20/40 LE:CF	Decreased decreased	Resolution resolution	4 7
Seidman CJ, 2017 [42]	LE	47	liver, lung, brain	Iris, multiple + NV glaucoma	concurrent	IVB 1.25 mg monthly, 3 doses	20/32	20/50	Decreased, NV remitter, IOP normalized	Not applicable	3
Lin IH, 2021 [30]	BE	48	bone, liver, lung	choroid + orbit + optic nerve (RE)	concurrent + bevacizumab	LE: IVB 2.5 mg + EBRT for orbital mts (3 Gy/fraction, 10 fractions, 10 days)	RE: no LP LE: 20/120	RE: LP LE:20/20	LE: decreased, almost disappeared	LE: resolved	6
Bernaducci I, 2015 [7]	BE	52	bone, liver, lung	choroid, single	NA	EBRT maximal dose (1 year before) + IVB 1.25 mg 1 dose in RE	RE: LP LE: 6/12	RE: CF	decreased	resolved	1 (death)

First author, year	Affected eye	Age (years)	Systemic metastases	Ocular mts.	Systemic chemotherapy	Ocular treatment	Initial visual acuity	Final VA	Tumour size	SRF	Follow-up (months)
Akinci GE, 2019 [1]	LE	65	bone marrow, lungs, brain	iris, single	concurrent	IVB 1.25 mg, 5 dose in 8 months (monthly 3 times, bimonthly afterwards)	20/20	20/20	decreased, NV remitter, IOP normalized	Not applicable	12
Vale S, 2018 [51]	LE	72	bone, liver, lung, lymph node, adrenal gland	iris, single, NV glaucoma	initiated at iris mts diagnosis	IVB 1.25 mg single dose	CF	20/80	decreased, NV remitter, IOP normalized	Not applicable	10 (death)

RE: right eye; LE: left eye; IVB: intravitreal bevacizumab;; SRF: subretinal fluid; PDT: photodynamic therapy; TTT: transpupillary thermal therapy; IMP: Indocyanine green mediated photocoagulation; NV: neovascularization; EBRT: external beam radiotherapy; CF: counting fingers; LP: light perception

All patients were females, mean ± SD age 54.1 ± 11 years, with a previous history of metastatic BC. At the moment of ocular dissemination diagnosis, all patients presented multiple organ metastasis, most commonly localized in bone (55.5%), the lungs (50%) and the liver (44.4%). The reason for presentation in all cases mild [13, 32, 49] severe [3, 5, 46, 47] and 16.6% of cases had ocular pain. The choroid was the most frequent site of metastatic dissemination (14 cases, 77.7%), followed by iris and optic disc. In 10 cases (55.5%) the lesions were solitary, with a slight predominance of the left eye involvement (Table II).

Table II

Pooled characteristics of the patients reported by the reviewed articles

No of cases	18 cases (22 eyes)
Age	54.1 ± 11 (34 - 75 years)
Systemic metastases at presentation	Lung: 9 (50%) Bone: 10 (55.5%) Liver: 8 (44.4%) Brain: 4 (22.2%) Lymph nodes: 5 (27.7%) Other: 2(11.1%) Not acknowledged: 5 (27.7%)
Laterality:	LE: 9 (50%) RE: 5 (27.7%) BE: 4 (22.3%)
Location of ocular metastasis	Choroid: 14 (77.7%) Iris: 4 (22.2%) Optic nerve: 4 (22.2%) Orbit: 1 (5.5%)
Number	Single: 10 (55.5%) Multiple: 8 (44.4%)
Chemotherapy	Concurrent: 15 (83.3%) Previous: 2 (11.1%) Not acknowledged: 1 (5.5%)
Systemic Bevacizumab	2 (11.1%)
IVB dose ± number of doses	1.25 mg/0.05 mL: 10 cases (55.5%); 3.9 ± 1.9 doses repeated monthly (1 - 8 doses) 2.5 mg/0.1 mL: 4 cases (22.2%); 1.5 ± 1 doses (1 - 3 doses) repeated monthly 4 mg/1.6 mL: 4 cases (22.2%); 1.5 ± 1 doses (1 - 3 doses) repeated monthly
Associated therapies	TTT: 1 case (5.5%) EBRT: 3 cases (16.6%) IMP: 1 case (5.5%)

Effect on visual acuity	Increased: 11 out of 18 cases (61.1%) Decreased: 6 out of 18 cases (33.3%) Not acknowledged: 1 out of 18 cases (5.5%)
Effect on tumour size	Decreased: 17 out of 18 cases (94.5%) Increased/no change: 1 out of 18 cases (5.5%)
Effect on SRF in choroidal +optic nerve metastases	Decreased/ remitted: 11 out of 15 cases (73.3%) Persistent: 3 out of 15 cases (2%) Not acknowledged: 1 out of 15 cases (6.6%)
Effect on NV in iris metastases	Regression: 3 out of 3 cases (100%)
Mean follow-up (months)	8.2 ± 6.6 (1 - 24 months)

TTT: thermal transpupillary thermotherapy; IMP: Indocyanine green mediated photothrombosis; IVB: intravitreal bevacizumab; EBRT: external beam radiotherapy; SRF: subretinal fluid; NV: neovessels

The diagnosis was based on clinical ophthalmoscopic exam, the CM displaying an irregularly shaped creamy yellowish appearance with mottling of the pigment epithelium and visible prominence. Imagistic investigation, such as fluorescein angiography, ocular B-scan and optical coherence tomography confirm the elevation of the choroidal mass, and the presence of the sub-retinal fluid (SRF), intraretinal fluid or exudative retinal detachment.

Intravitreal anti-VEGF protocol

The protocol used for intravitreal anti-VEGF therapy was similar in all cases. After singing an informed consent to the off-label use of the drug, the patients underwent topical anesthesia. The injection of bevacizumab 25 mg/mL (Avastin; Genentech, San Francisco, California, USA or Avastin®, Roche, Inc., Basel, Switzerland) was done through the pars plana, 3.5 - 4 mm from the limbus, using a 28 - 30 gauge needle. Most authors used a common dose of 1.25 mg/0.05 mL bevacizumab, monthly, which is also currently administered with minimal side-effects for other chorioretinal pathologies, such as age-related macular degeneration, diabetic retinopathy or retinal vein thrombosis. The mean (± SD) numbers of injections were 3.9 ± 1.1 for each case. However, significant improvement in VA and tumour reduction could be observed in most cases at the 1-month follow-up.

Other authors considered a higher dose (of 2.5 mg or 4 mg of bevacizumab) more appropriate as justified by diffuse or multiple metastatic spread, involvement of the optic disc, or poor vision due to increased SRF accumulation with retinal detachment (Table I).

Intravitreal route for anti-VEGF delivery was preferred to anterior chamber injections in cases of iris metastasis. Intravitreal delivery ensures longer persistence of the drug at the ocular level and on the other hand, spread of the metastatic cells along the needle trajectory is prevented [1].

Outcomes of intravitreal anti-VEGF breast cancer-related choroidal metastasis

No general or ocular side-effects were reported. The efficiency of the intravitreal bevacizumab therapy was analysed in terms of functional and anatomical outcomes.

The tumour size decreased after IVB (intravitreal bevacizumab) therapy in 94.5% of cases. Only one study [34] reported failure of IVB therapy in a case of CM; the patient was on general hormonal replacement therapy and was previously treated with photodynamic therapy (PDT), with further reactivation of the ocular tumour. As tumour size continued to increase despite 3-month IVB (1.25 mg/0.05 mL), she was later successfully treated with EBRT. However, the authors reported in the same case-series, a patient who was apparently not responsive to EBRT, but reached tumour regression after 3-month IVB with no improvement in VA.

The IVB therapy was associated with decreased SRF in 73.3% (11 out of 15 cases). The persistence of SRF despite tumour regression was explained by Mansour *et al*. [33] by a possible previous severe damage to the retinal pigmentary epithelium due to CM [33]. In iris metastasis, tumour size decreased and neo-vascularization of the iris regressed in all 3 cases. The quality of life of the patients improved after IVB treatment, with ocular pain relief and normalization of the intraocular pressure.

IVB therapy led to an increase in VA at the end of the follow-up period in 61.1% (11 out of 18 cases). Adverse visual outcome after IVB was statistically significantly associated with multiple CM (5 cases, 83.3%; $p = 0.018$, chi^2 test). Cases that presented choroid with optic disc metastasis, or iris metastasis were more likely associated with decreased vision at the end of the follow-up period than cases with CM only; however, the correlation was not statistically significant ($p = 0.088$).

Ocular metastasis is the most frequent ocular malignancy, the primary tumour is BC (40 - 47%) followed by lung cancer (21 - 29%) [4, 32]. In female patients, for 77% of the cases, BC is the primary source for ocular metastasis [20]. Choroid is a structure that is richly vascularized, irrigated by 80 - 85% of the ocular flow, lacks lymphatic drainage, and escapes the strict control of blood-retinal barrier. These anatomical peculiarities make it the most frequent site of hematogenous metastatic dissemination at the eye

level. The short posterior ciliary arteries are the preferential route for embolic cells due to their rich supply. Less frequent locations are iris (in 9% of cases) and ciliary body (in up to 2% of cases) [4, 32, 44]. The involvement of the optic nerve, retina or vitreous body is extremely rare. Optic disc infiltration is known to occur either due to direct extension of a choroidal tumour which is located close to the optic disc, or less frequently, due to a spread of neoplastic cells to the circulation of the optic nerve head by blood route [27, 33, 44, 45]. Retinal metastases are extremely rare, due to the existence of retinal-blood barrier, and vitreous body may be affected either by the inflammation of the internal limiting membrane or seeding from the retina [4].

In the present review article, metastatic tumours affected the left eye more, but the difference was not statistically significant ($p = 0.081$, chi^2 test). Laterality of ocular metastasis has been studied by several authors, but with conflicting results. While some researchers found a higher prevalence for the left eye [43], suggesting a more direct pass for the tumoural cells from aorta *via* left carotid artery, others found lesions in the right eye more frequently [2, 25], or observed no significant difference in distribution [44, 24].

Many studies have reported that systemic bevacizumab is an effective treatment for systemic BC metastases. Neovascularization and angiogenesis are important processes for tumour growth and secondary disseminations. Vascular endothelial growth factor (VEGF) is the ligand for the VEGF receptor 2, and has emerged as a key potential target for the pharmacological inhibition of tumour angiogenesis. In addition, VEGF can regulate important signal pathways related to tumourigenesis, including the function of tumour stem cells and the origin of tumour cells [18]. The discovery of anti-VEGF agents has been a milestone in combating many oncological diseases, such as digestive, breast or non-small cells lung cancer. Bevacizumab as a recombinant humanized anti-VEGF monoclonal antibody, can effectively bind VEGF molecules family and inhibit binding of the VEGF to its receptors Flt -1 (R-VEGF1) and KDR (R-VEGF2), at the surface of endothelial cells. It has an important anti-tumoural role by inhibiting angiogenesis, tumour cell migration and metastasis [23, 49].

The first anti-VEGF agent developed was bevacizumab and it was successfully implemented, with moderate systemic toxicity, in the therapy of colorectal cancer [16, 37, 35]. However, the present indications for systemic bevacizumab in metastatic BC are a subject of controversy due to severe systemic effects and limited evidence regarding the increase in the survival of these patients [15, 38, 41]. The potential systemic effects of anti-VEGF treatment include the development of thromboembolic events, rise in systemic arterial blood pressure, ventricular dilatation, and contractile dysfunction. However, multiple studies reported a very low incidence in intravitreal use, ranging between 1.3 and 5% for different anti-VEGF agents. None of the patients included in the present review experienced any ocular of general side-effects after IVB therapy. Moreover, IVB therapy proved to be efficient in reducing tumour size in 94.5% of cases and improving vision in 61.1%.

In the present days, healthcare systems are more and more preoccupied by the economic burden, in terms of costs vs efficacy of the treatment [39, 40]. Thus, IVB might be a valuable alternative to radio-therapy for ocular metastases secondary to BC.

This review has some limitations. The reported cases received different doses of IVB varying between 1.25 and 4 mg/session, along with different systemic treatments. BC is a highly heterogeneous disease caused by genetic and epigenetic mutations [17], with different responses to chemotherapic agents [12] that make the results of a certain therapy difficult to generalize. Favourable effects, in terms of tumour regression were observed even at small doses of 1.25 mg (0.05 mL), proving its anti-angiogenic and anti-permeability effects on angiogenesis in CM. Synergistic effects of IVB with concurrent chemotherapy, such as paclitaxel, may also play an important role in achieving tumour regression [53]. Moreover, some of the patients included in the review article received also systemic bevacizumab, which might augment the effects of the IVB alone [29, 53].

Conclusions

Intravitreal anti-VEGF therapy could be a safe and efficient alternative to radiotherapy in CM secondary to BC, which cannot be managed by systemic chemo-therapy. The method is simple, takes only some minutes, could be performed easily on ambulatory basis and repeated monthly if necessary. The advantage of this treatment is the avoidance of long-duration radiotherapy, hospitalization, or surgery. Longer studies on larger numbers of patients are necessary to establish appropriate doses and timing.

Conflict of interest

The authors declare no conflict of interest.

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