

Antiangiogenesis in Ocular Oncology: More Than Meets The Eye

These agents have multiple applications in the management of chorioretinal vasculature conditions.

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It is well established that angiogenesis is essential for many physiologic and pathologic processes.^{1,2} Conversely, antiangiogenesis is a validated strategy to treat a number of disorders, including solid tumors and intraocular neovascular syndrome.³⁻⁵ Expression of the vascular endothelial growth factor-A (VEGF-A) gene and protein occurs in healthy ocular tissues, especially in the retina, and has been shown to be upregulated during neovascularization responses associated with proliferative retinopathies.⁶ VEGF-A concentration increases in the aqueous humor of eyes with intraocular neovascularization due to ischemic retinal diseases such as diabetic retinopathy, retinal vein occlu-

sion, radiation retinopathy, and in eyes with hemangioma or choroidal melanoma.⁷

SIDE EFFECTS OF RADIATION FOR TUMORS

Uveal melanoma is a rare tumor with a poor prognosis both in terms of local morbidity and high rates of mortality following systemic spread.⁸ Conservative treatment, using plaque brachytherapy or proton beam irradiation, is the standard choice for uveal melanoma with limited extension.⁸ Radiation retinopathy is a predictable complication after radiotherapy, most commonly in medium and large tumors.⁹

In 1,300 patients treated with plaque radiotherapy,

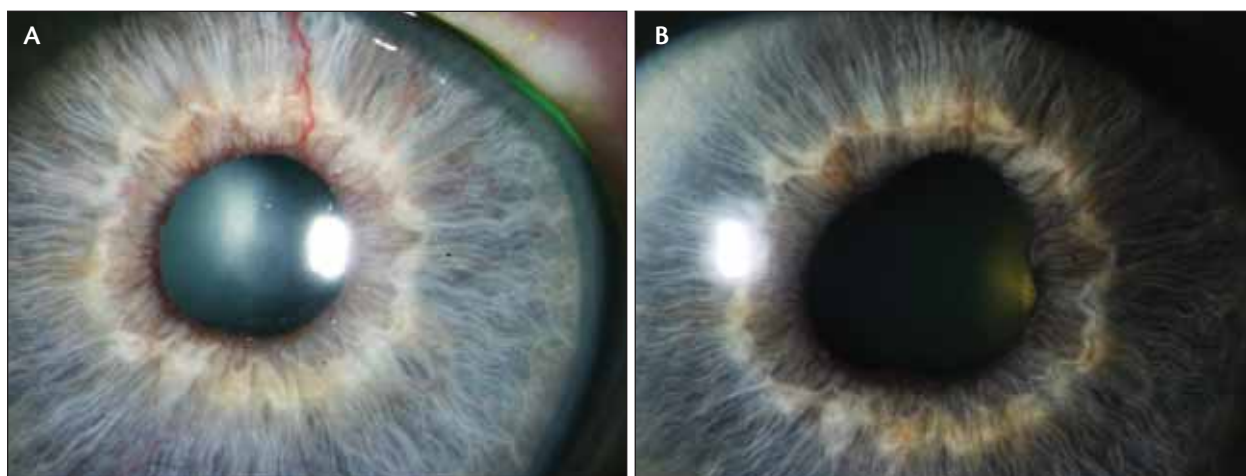


Figure 1. Anterior segment photography of a patient affected by neovascular glaucoma subsequent to I-125 brachytherapy for posterior uveal melanoma (A). The same patient 1 month after intravitreal injection of bevacizumab showed complete resolution of iris neovascularization (B).

radiation retinopathy was found in 46% at 5 years.¹⁰ The risk of radiation retinopathy is related to effective dose, the presence of systemic disease (eg, diabetes mellitus), and the use of radiation sensitizers (eg, chemotherapy).¹¹ The risk of radiation maculopathy, including macular ischemia and macular edema, is related to capillary abnormalities due to capillary endothelial cell loss.^{12,13}

The management of radiation macular edema continues to be challenging. Different authors have investigated treatment strategies for radiation macular edema including focal laser therapy, photodynamic therapy, and intravitreal triamcinolone.⁹ Recently bevacizumab (Avastin, Genentech, Inc.), a VEGF inhibitor, was found (in an off-label application) to decrease macular edema caused by central retinal vein occlusion and neovascular age-related macular degeneration.^{14,15}

MACULAR EDEMA

Finger et al¹⁶ evaluated intravitreal bevacizumab in the treatment of radiation retinopathy, particularly radiation maculopathy and macular edema. In this series, regression of radiation retinopathy (hemorrhage, exudates, intraretinal microangiopathy, and macular edema) was noted after treatment. The most consistent finding was decreased leakage from both preexisting and neovascular retinal vessels. These findings seem to be significantly different from the natural course of radiation maculopathy.

A larger series of 21 patients with radiation retinopathy (edema, hemorrhages, capillary dropout, and neovascularization) and a subjective or objective loss of vision was recently reported by the same author.¹¹

Angiographic findings revealed closure of intraretinal microangiopathy; decreased vascular transudation, edema, and exudates; and resolution of retinal hemorrhages after treatment. The reduction of macular edema related to bevacizumab treatment was the most consistent finding associated with improvement in vision. At the last examination, visual acuity was stable or improved in 86% of patients, findings that were attributed to retrieval of the functional anatomy of the macular nerve fibers.¹¹ Conversely, there was no apparent effect on capillary nonperfusion.

Mason et al⁹ reported 10 consecutive patients with macular edema due to radiation retinopathy after plaque radiotherapy for choroidal melanoma. After a single intravitreal bevacizumab injection, mean foveal thickness decreased with only modestly improved best-corrected visual acuity (BCVA).

In our experience, intravitreal bevacizumab treatment provided excellent short-term resolution of radiation-induced macular edema but only a modest short-term BCVA gain (unpublished data). Restoration of normal macular anatomy appears to be insufficient, in the majority of cases, to obtain normal visual function, despite normal macular appearance. Data from Mason et al⁹ suggest that radiation-induced capillary nonperfusion may be responsible for the minimal improvement in BCVA.

RON

Radiation-induced optic neuropathy (RON) is an uncommon, albeit devastating, complication of radiation exposure to the visual pathways.¹⁷ Early RON can

occur within several weeks of irradiation and is characterized by acute inflammation leading to optic nerve pallor.¹⁷ In contrast, late RON occurs years after treatment and has been characterized by irreversible vasculitis, necrosis, and optic disk pallor.¹⁷

Histopathologic analysis of RON reveals necrosis, exudates, and obliterative endoarteritis (loss of endothelial cells and thickened vessel walls).^{18,19} On the optic disk, radiation can result in ischemia, neovascularization, and leakage.²⁰ Intravitreal bevacizumab was reported to be effective in short-term RON resolution accompanied by improvement in visual acuity in a short-term follow-up.²⁰

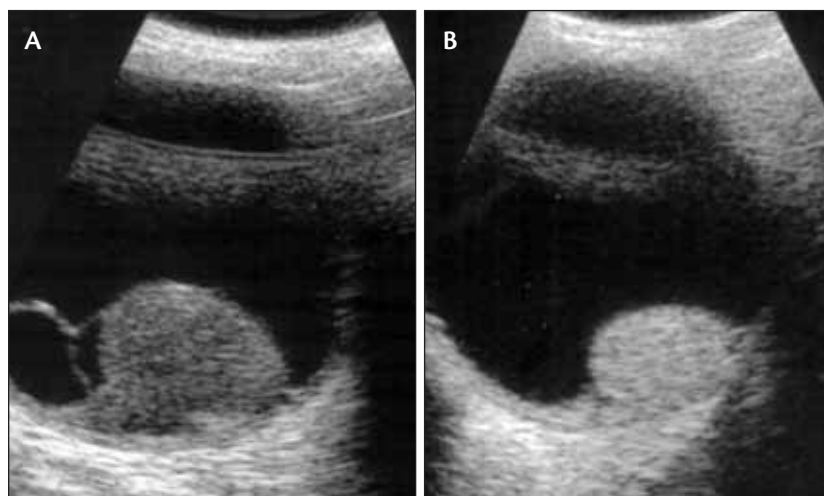


Figure 2. B-Scan ultrasonography of a patient affected by choroidal melanoma with persistent serous retinal detachment after I-125 brachytherapy (A). The same patient 4 months after intravitreal injection of bevacizumab showed complete resolution of subretinal fluid, decreased tumor thickness, and increased tumor reflectivity (B).

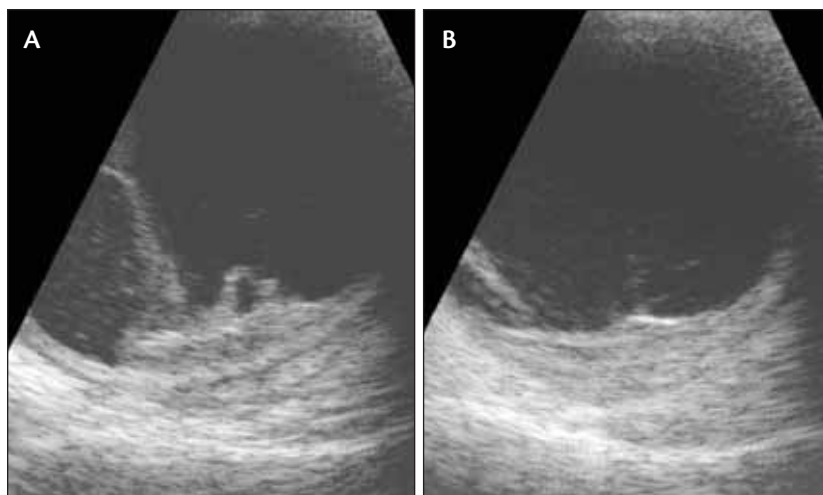


Figure 3. B-Scan ultrasonography of a patient affected by familial exudative vitreo-retinopathy with large, perilesional SRD (A). The same patient 2 months after intravitreal injection of bevacizumab showed marked resolution of subretinal fluid, decreased tumor thickness, and increased tumor reflectivity (B).

In our experience, bevacizumab appears to be effective in reducing optic nerve edema, with modest and transient improvement in visual acuity (as in macular edema), but remains useless in the treatment of the ischemic component of this disease. Moreover, VEGF protects retinal ganglion cells against oxidative-stress-induced cytotoxicity.²¹ This neuroprotection may rely on the glutathione reductase pathway and it is blocked by anti-VEGF agents.²¹

Triamcinolone acetonide may theoretically obtain similar results to VEGF inhibition, without the risk of blocking neuroprotection in ischemic retinal and optic nerve tissue, if the aim of the treatment of RON (and maculopathy) is only to reduce tissue edema and intraretinal leakage. A multicenter study on the influence of ranibizumab (Lucentis, Genentech, Inc.) and intravitreal triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) is under way, but it is limited to the treatment of radiation-induced maculopathy.

SRD, IRIS NEOVASCULARIZATION, AND NEOVASCULAR GLAUCOMA

Serous retinal detachment (SRD) in posterior uveal melanoma may be present at the time of diagnosis and increases after radiotherapy.⁷ It is strictly related to retinal and tumor ischemia.⁷ SRD in posterior uveal melanoma may depend on the intraocular VEGF level.⁷ Sheidow et al demonstrated expression of VEGF-A in 94% of uveal melanomas; the levels, however, were low (staining was weak in 62% of tumors).²²

Stitt et al²³ revealed that the tumor was not the sole

source of VEGF-A production and that the retina may be a source of VEGF-A, as they found increased production of VEGF-A mRNA in ganglion cells and inner nuclear layers of the retina. Missotten et al⁷ also suggested that both tumor tissue and retina are sources of aqueous VEGF-A, and they observed increased VEGF-A expression in detached retinal tissue. Intraocular VEGF levels also seem to be related to the persistence of peritumoral serous retinal detachment after radiotherapy due to the subretinal leakage from abnormal tumor vessels stimulated by tissue ischemia.³ These data underline that a close pathophysiologic relation exists between tumor dimension, post-treatment ischemia, SRD, and neo-

vascular glaucoma in eyes with posterior uveal melanoma treated with radiation therapy.

Vasquez et al²⁴ reported the effect of intracameral bevacizumab in the treatment of neovascular glaucoma and exudative retinal detachment after brachytherapy in a patient affected by choroidal melanoma. One week after injection, there was regression of the iris and angle neovascularization. Intracameral bevacizumab injection was repeated monthly for an additional 3 months. One month after the last injection, the retinal detachment resolved, but the visual acuity remains no light perception.

In our case series, intracameral and intravitreal injection of bevacizumab appeared to be effective in the treatment of iris neovascularization and neovascular glaucoma, causing a rapid response of pathological vessels in all treated patients (Figure 1).²⁵ Retreatment, however, remains necessary every few months. Long-term follow-up is needed to obtain more information about the appropriate retreatment timing and long-term side effects of this approach. SRD appears less sensitive to anti-VEGF agents compared with neovascular glaucoma (Figure 2).²⁵ Moreover, the role of radiotherapy alone in the resolution of SRD must be considered in patients treated with both intravitreal anti-VEGF injection and radiotherapy. Indeed, radiation therapy alone may either resolve or increase SRD in conservatively treated posterior uveal melanoma.²⁶

ADDITIONAL USES

Anti-VEGF agents have also been used in selected cases as intravitreal local chemotherapy for metastatic

tumors to chorioretinal tissues. Kuo et al²⁷ reported a case of a 65-year-old woman with posterior pole metastases arising from colorectal adenocarcinoma successfully treated with intravitreal bevacizumab. The presumed mechanisms for the response are the antiangiogenic and antipermeability effects of bevacizumab on the new tumor vessels, and this was supported by fluorescein angiography changes.

While angiogenesis inhibitors are already widely used to treat retinal disease in adults, only limited reports are currently available for the use of anti-VEGF agents in pediatric vitreoretinal diseases such as retinopathy of prematurity, Coats disease, familial exudative vitreoretinopathy, and retinopathy of incontinentia pigmenti (Figure 3). Sun et al²⁸ reported a case of stage 4 Coats disease in a pediatric patient who was unresponsive to scleral buckling and subretinal fluid drainage. The patient was treated with intravitreal injection of an anti-VEGF agent. After injecting the anti-VEGF agent (pegaptanib sodium; Macugen, OSI/Eyetech) the elevated VEGF levels markedly decreased and exudative retinal detachment improved. More recently, Jun et al²⁹ reported the resolution of severe macular edema in adult Coats disease using intravitreal triamcinolone and bevacizumab injections.

SUMMARY

The use of anti-VEGF agents has opened a panoply of new options for patients with diseases involving chorioretinal vasculature, and further investigation is required to elucidate their optimal application.²⁷ Identification of proangiogenic growth factors in the presence of uveal or retinal tumors may provide an opportunity for therapeutic intervention, particularly in the period immediately following radiation therapy, which may reduce the incidence of secondary enucleation. ■

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