Suppression of Melanoma-Associated Neoangiogenesis by Bevacizumab

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Background: Bevacizumab, a potent antibody against the vascular endothelial growth factor (VEGF), has been shown to be effective for treatment of colorectal cancer. Recently, high effectiveness of bevacizumab in combination with paclitaxel has been reported in a single metastatic melanoma case. To our knowledge, we demonstrate for the first time the antiangiogenetic effect of bevacizumab in a patient with a vitreous melanoma metastasis.

Observations: A 68-year-old man with a vitreous melanoma metastasis of the left eye was treated with a vitrectomy combined with intravitreal bevacizumab application because of iris neovascularization and progressive epiretinal tumor plaques. Four days after the treatment, the melanoma-associated neovascularization completely disappeared, but it recurred after 6 weeks. Although repetitive administration of local bevacizumab produced the same antiangiogenetic effect, progression of the epiretinal tumor plaques could not be stopped with the local bevacizumab treatment.

Conclusions: Intraocular administration of the anti-VEGF drug bevacizumab causes immediate and complete regression of melanoma-associated angiogenesis. The rationale for the therapeutic strategy in our patient was an elevated level of VEGF in the vitreous cavity. Because we could not demonstrate a direct antiproliferative effect of bevacizumab on melanoma metastasis, bevacizumab seems most promising if evaluated in combination with antiproliferative agents.

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neovascular glaucoma led to the decision to perform a revitrectomy with silicone oil tamponade followed by an intravitreal injection of bevacizumab, 1.0 mg. Informed consent was obtained for the bevacizumab therapy. The patient was aware of the experimental nature of the treatment. The isolated compartment of the vitreous cavity allowed for a quantitative analysis of the VEGF concentration in the vitreous specimen of the revitrectomy (human VEGF enzyme-linked immunosorbent assay; DuoSet, R&D Systems, Minneapolis, Minnesota). The concentration was exceptionally high (VEGF, 0.226 ng/mL) in our patient compared with 3 control patients without neovascular disease in whom the VEGF levels were below the detection limit of the test (<0.031 ng/mL).

Four days after the injection of bevacizumab, the neovascularization of the iris had completely disappeared and the intraocular pressure could be controlled with topical antiglaucomatous therapy. After 6 weeks, recurrent iris neovascularization and progressive epiretinal tumor plaques were apparent, and therefore the bevacizumab injection in the anterior chamber was repeated 4 weeks later. Initially, the neovascularization regressed, but recurred again after 4 weeks accompanied by an increase of the intraocular pressure (Figure, C). Because of the initial effectiveness, the intravitreal bevacizumab injection was repeated. As before, iris neovascularization disappeared 4 days after the injection (Figure, D), and the intraocular pressure normalized. Visual acuity remained at a stable level, around 20/200. Despite the anti-VEGF treatment, however, the epiretinal tumor plaques had progressed (Figure, B). No further therapy was performed owing to a worsening of the patient’s general condition. He died 12 weeks later, 18 months after the onset of visual complaints.

Figure. Antiangiogenic but not antiproliferative effect of bevacizumab. A, Photograph of the retina (arrow) showing scattered pigmented epiretinal melanoma metastasis (arrowheads). B, Same retinal area as shown in panel A (arrow) 3 months later. Distinct progression of the epiretinal metastasis (arrowheads) exists despite repeated intraocular bevacizumab therapy. C, Pronounced melanoma-associated neovascularization of the iris (arrows). D, Complete regression of iris neovascularization 4 days after intravitreal application of bevacizumab.
The eye offers the unique opportunity to directly visualize neovascularization because of the transparency of the cornea. Owing to the uncommon manifestation of a melanoma metastasis within the vitreous cavity, we were thus able to closely follow the effect of intraocularly administered bevacizumab on melanoma-induced neovascularization of the iris. The rationale for the therapeutic strategy in our patient was an elevated level of VEGF in the vitreous cavity. Most interestingly, in the case presented herein, local administration of the anti-VEGF drug bevacizumab did not only stop neangiogenesis but even led to immediate and complete regression of melanoma-associated angiogenesis. The effect of bevacizumab was only temporary, and that most likely is explained by the production of new VEGF by the melanoma cells. But the antiangiogenic effect could be repeated by subsequent applications of the anti-VEGF drug. In our patient, bevacizumab could not prevent progression of the epiretinal tumor metastasis. Although an antiproliferative effect is controversially discussed, our findings are in accordance with in vitro experiments that did not find a major role for VEGF in melanoma cell proliferation.

Nevertheless, in vitro data suggest that VEGF overexpression is a common phenomenon in melanoma cells. Upregulation of VEGF—and hence increased angiogenesis—has been recently shown in melanoma cells undergoing malignant transformation induced by overexpression of the signaling protein Akt in vivo.

We therefore conclude that direct targeting of VEGF seems to be a promising therapeutic strategy in metastatic melanoma. Because we could not demonstrate a direct antiproliferative effect of bevacizumab on melanoma metastasis, bevacizumab seems most promising if evaluated in combination with antiproliferative agents. This hypothesis is supported by the effective combination therapy of paclitaxel and bevacizumab reported recently.

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**Study concept and design:** Jaissle. Acquisition of data: Jaissle, Henke-Fahle, and Szurman. Analysis and interpretation of data: Jaissle, Ulmer, Henke-Fahle, Fierlbeck, Bartz-Schmidt, and Szurman. Drafting of the manuscript: Jaissle and Szurman. Critical revision of the manuscript for important intellectual content: Jaissle, Ulmer, Henke-Fahle, Fierlbeck, Bartz-Schmidt, and Szurman. Administrative, technical, and material support: Jaissle, Henke-Fahle, and Szurman. Supervision: Ulmer, Fierlbeck, Bartz-Schmidt, and Szurman.

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**REFERENCES**