Intravitreal bevacizumab in persistent retinopathy secondary to malignant hypertension

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Abstract

Purpose: To evaluate the efficacy and safety of intravitreal bevacizumab (IVB) injection in persistent retinopathy secondary to malignant hypertension (MHT).

Patients and methods: Single IVB injection of 1.25 mg/0.05 ml in 12 cases with persistent retinopathy secondary to MHT more than one month after control of MHT with pre and post injection evaluation of best corrected visual acuity (BCVA) and anatomical outcome up to sixth month and postinjection complications were evaluated.

Results: Progressive reductions in retinal hemorrhages, exudates, cotton-wool spots, and macular star were documented by photography, angiography, and central macular thickness (CMT) measured by optical coherence tomography (OCT) imaging. Decreased macular edema was the most common finding. Improvement or stabilization of visual acuity was noted in all cases.

Conclusions: In addition to proper medical management of MHT, IVB injection is an effective and safe approach to treat persistent retinopathy associated with MHT.

Abbreviations: MHT, malignant hypertension, IVB, intravitreal bevacizumab, BCVA, best corrected visual acuity, CMT, central macular thickness, OCT, optical coherence tomography

Keywords: Malignant hypertension, Malignant hypertensive retinopathy

Introduction

Hypertension is ranked as the fourth greatest mortality risk factor in the world. Acute hypertension of any cause can enter an accelerated or malignant stage. Three different levels of ocular fundus lesions are altered by arterial hypertension including hypertensive retinopathy, choroidopathy, and optic neuropathy.1

Keith et al. used the term malignant hypertension (MHT) for the first time in the English literature in 1928 when they reported on a series of patients with the presence of retinitis, marked hyper-tension, and fairly adequate renal function.2

By 1939, Keith et al. had classified patients with hypertensive retinopathy into 4 groups. They described the course and prognosis of these patients with hypertension according to the degree of retinopathy.

Group I was restricted to minimal constriction of the retinal arterioles with some tortuosity in mildly hypertensive patients. Group II included arteriovenous nipping, while group III included hemorrhaging and exudates. Group IV included papilledema.1,3

MHT is a clinical syndrome characterized by severe systolic and diastolic hypertension, usually appearing progressively over a period of several weeks to several months; it is often associated with significant and progressive deterioration in cardiac or renal function, and there is evidence of encephalopathy.4
World Health Organization (WHO) criteria are probably the most useful for MHT; it now differentiates hypertensive retinopathy on the basis of 2 grades of changes in the fundus, fundus hypertonicus and fundus hypertonicus malignus. Patients diagnosed as having malignant hypertension have severe hypertension with bilateral retinal hemorrhages and exudates. Papilledema, unless florid, is an unreliable physical sign and was of no additional prognostic importance in patients treated for hypertension who already had bilateral hemorrhaging and exudates. Diastolic blood pressure is usually greater than 130 mm Hg, but there is no absolute level above which MHT always develops and below which it never occurs. Bevacizumab is a humanized monoclonal antibody that competitively inhibits all isoforms of the VEGF-A family in the extracellular space. While bevacizumab is currently approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer, metastatic breast cancer, and non-small cell lung cancer, it is widely used as an off-label treatment for neovascular age-related macular degeneration and retinal vascular disorders including retinal vein occlusion and diabetic macular edema. Aim of our study was to evaluate efficacy and safety of intravitreal bevacizumab (IVB) injection in persistent retinopathy secondary to MHT.

### Patients and methods

A prospective non randomized case series study was done after acceptance of medical and ethical committees. All patients were informed that the therapy was off-label and the relevant consent form was signed by them. The study was carried out by single IVB injection 1.25 mg/0.05 ml in both eyes of 12 patients with persistent retinopathy secondary to MHT more than one month after control of malignant hypertension with pre and post injection evaluation of BCVA and anatomical outcome up to the sixth month and postinjection complications were evaluated.

All patients had visited an ophthalmologic clinic with the chief complaint of acute blurred vision and headache or referred from internal medicine. Data of patients were included when their color photographs of the fundus were judged to indicate hypertensive retinopathy grade III or grade IV according to Keith et al. classification of hypertensive retinopathy. There had to have been at least 2 successive high blood pressure readings recorded in the chart during the period when the symptoms occurred with diastolic blood pressure of 120 mm Hg or more and systolic blood pressure of 220 mm Hg or more according to WHO definition of MHT and we excluded patients with such diseases as diabetes mellitus, blood dyscrasia, and autoimmune and infectious diseases which can mimic the fundus findings of MHT.

Intravitreal injection of 1.25 mg/0.05 ml bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) was given after full asepsis in the operation room. Injection was done in both eyes in 2 successive days. It was injected into the vitreous cavity through the superotemporal quadrant, 4 mm from the limbus using 30-gauge needles with post injection check of intraocular pressure. The patient was reviewed from internal medicine. Data of patients were included when their color photographs of the fundus were judged to indicate hypertensive retinopathy grade III or grade IV according to Keith et al. classification of hypertensive retinopathy.

| Table 1. Clinical finding of patients with malignant hypertension retinopathy. |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Patient (n)**             | **Gender**      | **Age in years**| **Symptoms**    | **Past history**| **BP in mm Hg** | **Etiology**     | **Initial BCVA Log MAR OD/OS** | **Final BCVA Log MAR OD/OS** |
| 1                           | Female          | 63              | Blurred vision     | +ve             | 225/160          | Essential hypertension | 0.3/0.2/0.3               | 0.8/0.8/0.8               |
| 2                           | Male            | 45              | Headache         | +ve             | 220/125          | Renal hypertension | 0.3/0.4/0.4               | 0.8/0.8/0.8               |
| 3                           | Male            | 54              | Blurred vision     | +ve             | 230/140          | Renal hypertension | 0.4/0.4/0.4               | 0.8/1.0/0.8               |
| 4                           | Female          | 28              | Headache         | –ve             | 220/130          | Pheochromocytoma | 0.3/0.3/0.3               | 0.8/0.8/0.8               |
| 5                           | Female          | 27              | Headache         | –ve             | 240/160          | Preeclampsia      | 0.5/0.5/0.5               | 0.8/0.8/0.8               |
| 6                           | Female          | 64              | Blurred vision     | +ve             | 225/140          | Renal hypertension | 0.2/0.3/0.3               | 0.6/0.6/0.6               |
| 7                           | Male            | 49              | Blurred vision     | +ve             | 220/130          | Essential hypertension | 0.5/0.5/0.5               | 0.8/0.8/0.8               |
| 8                           | Male            | 39              | Blurred vision     | –ve             | 235/145          | Renal hypertension | 0.2/0.2/0.2               | 0.5/0.6/0.6               |
| 9                           | Male            | 58              | Headache         | –ve             | 230/135          | Essential hypertension | 0.4/0.4/0.4               | 0.8/0.8/0.8               |
| 10                          | Female          | 27              | Blurred vision     | –ve             | 220/130          | Preeclampsia      | 0.3/0.3/0.3               | 0.8/1.0/0.8               |
| 11                          | Female          | 52              | Headache         | +ve             | 225/130          | Renal hypertension | 0.2/0.2/0.2               | 0.8/0.6/0.6               |
| 12                          | Male            | 54              | Blurred vision     | +ve             | 220/125          | Essential hypertension | 0.3/0.4/0.4               | 0.8/1.0/0.8               |
| Mean                        |                 | 42.9            |                  |                 | 226/137          |                  | 0.3/0.3/0.3               | 0.8/0.8/0.8               |

Statistics: SPSS 17 was used for statistical analysis and (P < 0.05) was considered as statistically significant and (P > 0.05) was considered as statistically insignificant.
Results

Twelve patients were included in our study (Table 1). There were 5 males and 7 females. The study included 5 patients with no history of hypertension (group 1), while 7 patients had a known history of hypertension (group 2). The ages ranged from 27 to 58 years in group 1 and 45 to 64 years in group 2. Systolic blood pressures ranged from 220 to 240 mm Hg in group 1 and 220 to 235 mm Hg in group 2. Diastolic blood pressure ranged from 130 to 160 mm Hg in group 1 and 125 to 160 mm Hg in group 2. Patients in group 2 had a hypertension history with or without receiving medication for it. They had been warned that they had poorly controlled blood pressure, and it had been suggested that they visit their internists for further treatment.

There were no significant differences in ages, or systolic and diastolic blood pressures between the 2 groups. (p > 0.05). Case 6 (group 2) developed renal failure 3 months after MHT was diagnosed, although she was admitted for intensive medical blood pressure control. Two patients in group 2 experienced cerebral vascular accidents during the period when MHT was diagnosed. No ocular or systemic complications related to bevacizumab were noted during the entire course of follow-up except subconjunctival hemorrhage in six eyes.

The initial BCVA is that at the time of presentation of the patients to an ophthalmology clinic and the final BCVA is that after one injection of IVB by the sixth month.

Clinically there were variations in fundus pictures between retinal hemorrhages, exudate, cotton wool spots. All patients have macular edema, macular star was present in 4 patients and disc edema was present in 5 patients (Fig. 1up). In the final visit sixth month post injection there was disappearance of macular and disc edema, macular star, exudates, cotton wool spots and hemorrhages except some hard exudates or cholesterol deposits remained in 4 patients and some retinal pigmentary changes in 3 patients (Fig. 2 up right and left).

One month after the control of malignant hypertension ten patients had persistent macular star in both eyes and four patients showed persistent papilledema in both eyes. Six weeks after IVB injection all macular star disappeared (statistically highly significant p < 0.001) and two patients only showed persistent disc swelling after 6 weeks of IVB injection (statistically significant P < 0.05) (Fig. 2).

The mean pre injection Log MAR was +0.5 and mean post injection after the 6 month was +0.1 which was statistically significant (p < 0.5) (Fig. 3).

As regards the mean preinjection CMT in OCT the mean was 350 μm in group 1 and 390 μm in group 2 and mean post injection at the final visit after 6 months was 180 μm in group 1 and 210 μm in group 2.

For all patients the mean preinjection CMT was 375 μm and the mean post injection after 6 months was 195 μm which is statistically significant (P < 0.05) (Fig. 4).

As regards fluorescein leakage both groups 1 and 2 had diffuse macular edema, alternate hyper and hypofluorescence in the posterior pole with disc leakage in 5 patients. All patients showed absence of flourescine leakage at the sixth month post injection.

Discussion

Our study included persistent hypertensive retinopathy secondary to malignant hypertension with systolic blood pressure more than 220 mm Hg and diastolic blood pressure more than 220 mm Hg in which hypertension then became controlled but with persistence of the retinopathy.

Fundus findings in systemic diseases such as systemic lupus erythematosus, diabetes mellitus, and other collagen
vasculopathies may be similar to those in hypertensive retinopathy. The overlapping findings in malignant hypertensive retinopathy and in diabetic retinopathy can be confusing. MHR can cause optic nerve head swelling; and the optic nerve head will appear hyperfluorescent with fluorescein angiography. The typical microaneurysms with FFA strongly suggest diabetic retinopathy. The exudative retinopathy manifested in diabetes tends to affect the deep capillaries, while hemorrhaging accumulates in the outer plexiform and inner nuclear layer. However, the hemorrhaging due to hypertension frequently arises from the superficial capillaries in the nerve fiber layer. All of these changes distinguish hypertensive retinopathy from that which is primarily diabetic. A systemic survey, including blood pressure and glycosylated hemoglobin (HbA1c), can provide an important clinical differential diagnosis. That was why we excluded patients with systemic diseases whose fundus manifestations might have caused confusion.

We did not find significant relation between severity of hypertension and degree of drop in initial visual acuity or extent of retinopathy and this may be due to our inclusion criteria that all patients have blood pressure more than 220/120 although proper medical control of MHT was essential for both systemic and ocular improvement. This differs from the study done by Browning et al. who found that the worst visual prognosis was associated with the highest presented blood pressure, the worst visual acuity at presentation, and the longest duration of symptoms. It is likely that the visual prognosis is affected by factors present at the time of presentation, this may be due to lower categories of blood pressure, So, early recognition is essential. In our group 1 patients, the visual prognosis was satisfactory when the blood pressure and underlying disease were controlled.

Case 6 (group 2) developed renal failure 3 months after MHT was diagnosed, although she was admitted for intensive medical blood pressure control. Two patients in group 2 experienced cerebral vascular accidents during the period when MHT was diagnosed.

Figure 2. Six months later after IVB injection and blood pressure was under control. The retinopathies showed nearly complete regression except for mild disc swelling and lower pictures showing the corresponding OCT in the macula.

Figure 3. Comparison of Log MAR pre and 6 month post injection.

Figure 4. Comparison of CMT pre and 6 month post injection.
Clinically we found in our study one month after the control of malignant hypertension that ten patients had persistent macular star in both eyes and four patients showed persistent papilledema in both eyes. Six weeks after IVB injection all macular star disappeared (statistically highly significant $p < 0.001$) and two patients only showed persistent disc swelling after 6 weeks of IVB injection (statistically significant $P < 0.05$).

It seems that there were more complications in group 2 patients. Maybe those patients had had a relatively longer duration of high blood pressure, and that resulted in more complications and related poorer prognoses.

In our study the mean pre injection Log MAR was $+0.5$ and mean post injection after 6 month was $+0.1$ which was statistically significant ($p < 0.5$)

As regards the mean preinjection CMT in OCT the mean was 350 $\mu$m in group 1 and 390 $\mu$m in group 2 and mean post injection at final visit after 6 months was 180 $\mu$m in group 1 and 210 $\mu$m in group 2.

For all the patients the mean preinjection CMT was 375 $\mu$m and the mean post injection after 6 months was 195 $\mu$m which is statistically significant ($P < 0.05$).

This improvement is in agreement with many studies about improvement of retinopathy, vision, and CMT with injection of intravitreal bevacizumab 1.25 mg/0.05 ml.$^{12,13}$

Once hypertensive retinopathy is suspected in a patient with acute vision decrease in both eyes, blood pressure should be checked immediately. A detailed fundus examination and frequent blood pressure monitoring are mandatory.

Conclusions

In addition to proper medical management of MHT, IVB injection is an effective and safe approach to treat persistent retinopathy associated with MHT.

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References