Toxic Effect of Intravitreal Carboplatin Detected by Flattened Electoretinogram in A Patient with Retinoblastoma Treated by Chemoreduction and Local Treatments

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Abstract

Purpose: The first report of electroretinographic changes following the intravitreal injection of carboplatin in a patient with retinoblastoma

Case report: Recurrent tumors after chemoreduction and adjunctive local treatment in an infant with familial unilateral retinoblastoma, group C, was treated with intravitreal carboplatin (10 µg) injections.

Results: The tumor was regressed after 3 injections. Flat electoretinogram (ERG) amplitude was noted following the intravitreal injection of carboplatin. After one year tumor-free period in this case, visual acuity (VA) in the affected eye was 20/800 despite a flat ERG.

Conclusion: Intravitreal carboplatin can effectively treat intraretinal tumor recurrences but de-novo recurrent tumors could not be prevented. Intravitreal injections of carboplatin can cause retinal toxicity and flat ERG.

Keywords: Retinoblastoma, Chemoreduction, Intravitreal Carboplatin, Flattened Electoretinogram

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Introduction
Retinoblastoma is the most common intraocular malignancy in children. Treatment approaches for retinoblastoma have changed dramatically in the past years. There has been an effort to increase the use of chemotherapy and focal treatments to avoid the use of external beam radio-therapy, mainly because of the growing awareness of other malignancies in retinoblastoma patients with germinal disease. Common systemic chemotherapy (Vincristine, Etoposide, and Carboplatin (VEC)) like radiation is associated with some serious adverse effects. Some trends to local chemotherapy (Subconjunctival carboplatin or intraocular chemotherapy) with some considerable results, are documented in the treatment of retinoblastoma.

Intravitreal carboplatin was proposed as an efficient treatment of retinoblastoma on laboratory animal eyes. To the best of our knowledge, this report is the first report of electroretinographic changes after intravitreal injection of carboplatin in human eye.

Case report
A 24-month-old Iraqi girl presented with leukocoria in the right eye (OD) for the last 3 months (Figure 1A). He had the family history of retinoblastoma in her father and a cousin who were treated by enucleation. The left eye (OS) was normal. The right eye (OD) had no fixation. There was a large macular retinoblastoma measuring 12×12×2.5 mm with some subretinal seedings [Group C in international classification of retinoblastoma (ICRB)]. The intraocular pressure (IOP) was normal in both eyes. Six cycles of VEC chemoreduction with adjuvant consolidation - thermal laser therapy - were administered (Figure 1B).

Two months after complete chemotherapy (Six cycles), 15 new foci of intraretinal tumors (0.5 to 3 mm in dimensions) appeared around the main regressed tumor (Figure 1C). IOP was 25 mmHg in OD with C/D ratio of 0.5 and 12 mmHg in OS. She was treated by Timolol. The baseline electroretinogram (ERG) (Metrovision MonElec 1-France) was normal for both eyes (Figure 2A). Her parents were informed about the new situation and different treatment options. They refused enucleation. Three more cycles of VEC chemotherapy were administered. One month later (May 2006) after getting the informed consent 20 mg, subtenon carboplatin plus 10 µg/0.1 ml intravitreal carboplatin through pars plicata with 30 gauge needle after AC tap (Carboplatin vial - Ebewe Austria) were injected. Twenty days later (June 2006), 0.7 C/D ratio with no significant changes in the lesions were observed. Latanoprost (Xalatan) was added. The second intravitreal carboplatin (10 µg/0.1 ml) was injected. The main tumor was regressed (Type III regression) and all but two intraretinal lesions were regressed (Type IV regression) (Figure 1D). ERG (September 2006) showed marked decrease of b and a-wave amplitudes (Figure 2B) and IOP was 17 mmHg at this time. The third intravitreal carboplatin (10 µg/0.1 ml) was injected. Examination in October 2006 showed inactivity of the main tumor and all recurrent foci were regressed. IOP was normal (Figure 1E). Latanoprost (Xalatan) was discontinued and the third ERG in December 2006 showed the same changes with more decrease in the b-wave (Figure 2C).

Two months later, fundus examination of OD showed 4 foci of de-novo recurrences inferiorly and nasally about 0.7 mm in diameter and thickness which were ablated by cryotherapy and diode indirect photocoagulation. Three additional cycles of VEC therapy were administered. The fourth ERG (January 2007) was nearly flat with extinguished a and b-waves (Figure 2D). After 12 months of follow-up, the eye remained stable with no further recurrences occurred. The best corrected vision was 20/800, despite the flat ERG.
Figure 1. The fundoscopic appearance of the retinoblastoma tumor treated with chemoreduction and multiple adjunctive treatments

(A) Fundus photograph of the right eye before intravitreal injection of carboplatin and after six cycles of chemoreduction (Vincristine, Etoposide, and Carboplatin). The main tumor was regressed (Type III regression). (B) Fundus photograph of the right eye after second intravitreal injection of carboplatin. The main tumor was regressed (Type III regression). (C) Foci of de novo intraretinal tumors in the mid-periphery of retina (D) The resulted scars of the tumors after injection of intravitreal carboplatin (E) Flat scar of the peripheral lesions after the third intravitreal carboplatin

Figure 2. The electroretinogram of the retinoblastoma tumor treated with chemoreduction and multiple adjunctive treatments including intravitreal carboplatin

(A) Nearly normal baseline electroretinogram of the right and left eyes after six chemotherapy cycles (B) The electroretinogram of the right eye after second injection of intravitreal carboplatin shows marked decrease of both b and a-wave amplitudes. Note that the decrease in the b-wave is more prominent. (C) The electroretinogram after third intravitreal injection of carboplatin shows more decrease in a and b-wave amplitudes in the right eye. (D) The fourth electroretinogram, two months after the third intravitreal carboplatin showed a flat electroretinogram.
Discussion

Despite the improved therapeutic indices achieved with systemic chemotherapy, complete tumor control is difficult in most patients with advanced stages of retinoblastoma. Local treatment of retinoblastoma is a new era in the treatment of this malignant tumor. Ericson and Rosengren pioneered using intravitreal injections of chemotherapeutic agents for treatment of retinoblastoma in 1960. They concluded that irreversible ERG changes were not seen in the injected eyes.\(^4\) Ueda showed that an intravitreal Melphalan (10 µg) had no adverse effect on ERG and the retinal structure.\(^5\) Harbour reported the effectiveness of intravitreal carboplatin on retinoblastoma tumors and the maximum safe dose of intravitreal carboplatin in rabbits was reported to be 10 µg and in murines 4 µg.\(^5\)

To our knowledge, this report is the first reported case of intravitreal injections of carboplatin in human. In our case, the recurrent lesions were treated with some successes by intravitreal carboplatin, but significant changes were seen on ERG. Although the multiple intravitreal lesions may cause some changes in the viability of the retina, the high intravitreal titer of carboplatin (Subtenon and intravitreal injection of carboplatin at the same time) was also considered as the main cause of the toxic retinal reaction manifested by a flat ERG. The globe was preserved with some vision in one year follow-up period.

In this limited and short term experience, the intraocular injection of carboplatin did not prevent the occurrence of the new lesions. Although intravitreal carboplatin could cure small new lesions in this patient, flattening of ERG was a significant disadvantage. More laboratory and clinical studies for finding the effective intravitreal safe doses of carboplatin or other chemotherapeutic agents are needed.

Conclusion

Although, the intravitreal carboplatin can be an efficient way for eradicating the recurrent retinoblastoma tumors but it may cause retinal toxicity.

References