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Intravitreal sustained-release ganciclovir implants for severe bilateral cytomegalovirus retinitis after stem cell transplantation

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ABSTRACT

Purpose: To describe the treatment of cytomegalovirus (CMV) retinitis with intravitreal sustain-release ganciclovir devices in a 16-year-old patient in third remission of acute lymphoblastic leukemia after stem cell transplantation.

Methods: The patient received a stem cell transplant from an unrelated bone marrow donor after which he contracted a serious CMV infection manifested in the lungs and retinae. His immune system at this time was almost completely depleted. Implantation of a sustained-release ganciclovir device was performed in both eyes when retinitis progressed in spite of aggressive antiviral intravenous treatment.

Results: No per- or postoperative complications were noted. Infiltrates, hemorrhages and macular edema present preoperatively dissolved over a period of six months. The final visual acuity was 1.0 in both eyes. The patients immune system and lung function slowly recovered during the same time period.

Conclusions: The intravitreal ganciclovir implant provides safe and effective therapy against CMV retinitis, and should be considered in patients acquiring the infection after stem cell transplantation.

Key words: acute lymphoblastic leukemia (ALL) – bone marrow transplant (BMT) – immune reconstitution – immunosuppression – stem cell transplantation (SCT) – vitreoretinal surgery.
Fig. 1. Fundus appearance after implantation of intravitreal sustained-release ganciclovir implants. (A and B) Five days after implantation. In the right (A) and left (B) fundi, multiple hemorrhages and whitish infiltrates can be seen in all quadrants. Macular edema is present in both eyes. The visual acuity (VA) is 0.04 in the right and 0.3 in the left eye. (C and D) Two months after implantation. One hemorrhage is still present in the right eye (→), but none can be found in the left eye. No infiltrates are present, but a macular edema is evident in both eyes. The VA is 0.6 in the right and 0.9 in the left eye. (E and F) Six months after implantation. No hemorrhages, infiltrates or macular edema can be seen. Minimal retinal atrophies in the right eye (→) is the only remaining sign of the CMV retinitis. The VA is 1.0 in both eyes.
The implantation procedure was, with a few exceptions, identical to the one described by Sanborn et al. (1992). The patient was put under general anesthesia. The ganciclovir containing device (Vitratome of Bausch & Lomb Surgical Inc., Clar- emont, California, USA) was prepared by trimming the anchoring strut and passing a double armed 9-0 nylon suture through the base. A conjunctival peritomy was performed in the lower temporal quadrant and a 5-mm limbus parallel sclerotomy was made 4 mm from the limbus with a microvitreoretinal blade. The device was now grasped with smooth forceps and introduced into the vitreous cavity. The anchoring suture was passed through either side of the scleral incision and tied. Ad- ditional 9-0 nylon sutures were placed to close the wound and the conjunctiva was closed with 8-0 vicryl sutures. Bethameta- sone and gentamicin were injected subcon- junctivally. An indirect fundus examina- tion was performed confirming the proper position of the implants. No peroperative complications were noted.

Five days after implantation the fun- dus appeared unchanged from preoperative examination and the patient had a VA of 0.04 RE and 0.3 LE (Figs 1A and B). The pathological findings in the fundus subsequently diminished, and the visual acuity 19 days postoperatively was 0.7 in both eyes. Two months after surgery, the VA was 0.6 RE, and 0.9 LE (Figs 1C and D). Most hemorrhages and all infiltrates had disappeared at this time, but exudative lesions were still present in both maculae (Figs 1C and D). Six months after implantation (11 months after the SCT), the VA was 1.0 in both eyes, and no macular edema, infiltrates or hemorrhages could be seen (Figs 1E and F). Minimal retinal atrophies could be detected in the right eye as the only remaining sign of the CMV retinitis. At no time did the patient report any dis- comfort locally or visual field disturb- ances from the implants.

The general condition of the patient, i.e. his lung capacity, gradually improved seven months after the stem cell trans- plantation (SCT) and oxygen require- ment was discontinued. He was, however, kept on systemic intense combined anti- viral therapy. By this time, CMV quanti- tative PCR analysis of the body excretes showed weak positive reaction, but gene sequencing of the CMV isolate verified ganciclovir-resistant C607Y genotypic mutation. As clinical improvement and immune recovery was already evident (by reoccurrence of PHA tested T-cell reac- tivity and CD4 count reaching the so called ‘magical’ 0.2 × 109/L limit), all sys- temic antiviral treatment was stopped. At follow up, 11 months after the SCT, the general condition of the patient was com- pletely restored. Immunological screening showed CD4 count at the lower limit of the normal range and PHA-induced T- cell stimulatory response was normal.

Discussion

The introduction of ganciclovir and fos- carnct has radically changed the poor prognosis of CMV retinitis. One of the more recent additions to the armamen- tarium of treatments is the sustained-re- lease intravitreal ganciclovir implant which has been successfully used in AIDS patients (Sanborn et al. 1992; Martin et al. 1994). Reported complications of the operation include endophthalmitis, extrusion of the implant, retinal detach- ment, vitreous hemorrhage and place- ment of the implant in the suprachoroid- al space (Sanborn et al. 1992; Anand et al. 1993). We found the implant pro- cedure fairly simple to perform, and did not experience any per- or postoperative complications during the six-month fol- low-up in the patient reported here.

Intravitreal administration of ganciclo- vir is a treatment for CMV retinitis only, and cannot be given as single therapy when systemic infection is present. On the other hand intravitreal ganciclovir is more efficient in treating CMV retinitis than intravenous (i.v.) administration of the drug (Young et al. 1998), which is well illustr- ated in our patient who received both foscarnet and ganciclovir i.v., but still pro- gressed in his retinitis. Additionally, local ganciclovir therapy minimizes the hazard- ous side-effects of i.v. ganciclovir (bone marrow suppression) and foscarnet (nephrotoxicity), and has shown very little, if any, adverse effects on the ocular tissues (Charles & Steiner 1996; Young et al. 1998). The sustained-release device re- mains active for six to seven months, after which time it can be replaced or supple- mented by a second device at a different operation site if sustained therapy is re- quired (Morley et al. 1995).

Reports on the implant being used in patients suffering from CMV retinitis after bone marrow transplant are few and include only the adult population (McAuliffe et al. 1997). To our knowl- edge the present case represents the first pediatric patient treated with the gan- ciclovir implant after stem cell transplan- tation.

Cytomegalovirus infection in the im- munosuppressed patient represents a re- activation of a latent primary infection. When and if immune competence is re- gained, the virus is controlled and the CMV virus returns to its previously lat- ent stage. A reconstitution of the immune system is thus of utmost importance in any immunosuppressed patient displaying signs of active CMV infection.

Our patient was CMV positive at the time of his stem cell transplant but the donor was not. As a consequence, no im- munologic memory was established in the donor immune system and the CMV in- fection was reactivated since the patients own immune cells were obliterated by the conditioning and postgrafting immuno- suppressive treatment. The very slow re- constitution of the immune system in spite of the early discontinuation of im-
munosuppressive therapy allowed the CMV to ravage systemically, in the lungs and retinas. Antiviral therapy under such conditions is directed at stopping the progress of the disease until immunological reconstitution is achieved. The rapid improvement of the CMV retinitis of our patient suggests that the intravitreal ganciclovir implant controlled the CMV retinitis directly, but the long duration of the sustained-release preparation also gave the patient enough time to reconstitute his new immune system, without irreversible damage to the retina.

To summarize, we have illustrated that the intravitreal sustained-release ganciclovir device can be effective in treating CMV retinitis in a severely immunosuppressed patient. We suggest that the device should be considered not only in adult patients suffering from AIDS but also in young patients with CMV retinitis after stem cell transplantation.

References


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