(18)

Effective treatment of cytomegalovirus retinitis and neuritis with retrobulbar ganciclovir after treosulfan-based autologous bone marrow transplant

Skuteczne leczenie zapalenia siatkówki i nerwu wzrokowego pozagałkowym podaniem gancyklowiru u dziecka po autologicznym przeszczepie szpiku z zastosowaniem treosulfanu

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Summary: We describe the case of a 16-month-old girl with neuroblastoma and chronic lymphocytopenia due to chemotherapy and treosulfan-containing megatherapy who developed cytomegalovirus retinitis and neuritis. Intravenous ganciclovir and anti-cytomegalovirus immunoglobulin were used with a transient benefit; however, retrobulbar gancyclovir resulted in a complete remission. This report emphasizes the need for close monitoring of viral infections in patients undergoing treosulfan-containing megatherapy, highlighting the immunosuppressive effects of this agent, and indicates the potential use of retrobulbar ganciclovir as the alternative method of drug delivery.

Key words: neuroblastoma, treosulfan, cytomegalovirus, retrobulbar therapy.

Streszczenie: W pracy przedstawiono przypadek 16-miesięcznego dziecka płci żeńskiej z neuroblastoma, z przewlekłym niedoborem krwinek białych, leczonego chemioterapią z następową megachemioterapią opartą na treosulfanie, u którego stwierdzono zakażenie cytomegalowirusem przebiegające pod postacią zapalenia siatkówki i zapalenia nerwu wzrokowego z utratą widzenia. Dożylna podaż gancyklowiru oraz immunoglobuliny przeciwko wirusowi cytomegalii przyniosła jedynie przejściową poprawę. Pozagałkowe podanie gancyklowiru spowodowało całkowitą remisję choroby. Raport ten podkreśla potrzebę ścisłego monitorowania zakażeń wirusowych u pacjentów poddawanych autotransplantacji oraz wskazuje na możliwość pozagałkowego zastosowania gancyklowiru jako alternatywnego sposobu podawania leku.

Słowa kluczowe: neuroblastoma, treosulfan, cytomegalowirus, terapia pozagałkowa.

Introduction

In immunocompromised patients cytomegalovirus (CMV) viremia and disease are major causes of morbidity and mortality. CMV infections usually manifest as enteritis, fever and bone marrow suppression, but can also affect lung, brain and eyes. CMV retinitis (CMVR) is a well-described event in immunosuppressed patients; it is particularly common in human immunodeficiency virus ((HIV) – acquired immune deficiency syndrome (AIDS) (1, 2). It can also occur in patients undergoing immunosuppressive therapies, either systemic, such as cancer therapy or transplant or local, such as intraocular steroids. Optic neuritis affects mainly young adults; the most common etiology is multiple sclerosis, followed by infection, autoimmune disorders, and drug-related vasculitis (3). Only a few reports have described CMV optic neuritis after hematopoietic stem cell transplantation (HSCT), and all cases have occurred after haplo- or allo-HSCT (4). CMVR rarely occurs after autologous hematopoietic stem cell transplant (aHSCT). CMVR usually manifests with hemorrhagic and necrotic changes without accompanying pain, and approximately 60% of patients have involvement of both eyes (5). CMV surveillance testing is not routinely recommended during and after aHSCT (5). Risk factors for CMV disease after aHSCT include CD34 selection, high-dose corticosteroids, the use total body irradiation or fludarabine as a part of the conditioning treatment (5).

Ganciclovir (GCV), known for over 20 years, inhibits CMV replication and is considered the standard therapy for CMV. Treatment usually requires long-term systemic administration; however, ganciclovir is commonly associated with significant side effects. Complications can be especially severe in patients undergoing transplant. Therefore, its use is very carefully considered and is reserved mostly for symptomatic CMV disease. Other currently available drugs, such as cidofovir and foscarnet, are also associated with significant toxicity (5). The major drawback of intravenous GCV administration is the poor blood-brain permeability due low lipophilicity, which can lead to subtherapeutical intravitreal concentrations (6). Intravitreal ganciclovir is recommended in adults with CMVR that is refractory to intravenous therapy; however, its use in children has not been adequately tested.

Here, we describe a case of successful treatment of CMVR and neuritis developing after treosulfan-based megatherapy in a child with neuroblastoma with retrobulbar injection of ganciclovir.

Case report

An 8-month-old infant was diagnosed at the Department of Surgical Oncology for Children and Youthery, Institute of Mother and Child, Warsaw, with *N-MYC* amplified neuroblastoma after she presented with a large abdominal mass. She had metastatic disease in the liver, bones and bone marrow. She received treatment using a high-risk regimen including cisplatin, doxorubicin, cyclophosphamide, vincristine, carboplatin and etoposide. Because of the rapid progression of the liver metastases, the patient received 600 cGy to the liver. Local treatment was completed with surgery of the primary tumor. The patient was transferred to the Department of Pediatric Oncology, Hematology and Bone Marrow Transplantation, Wroclaw Medical University where due to prior liver irradiation and persistent hepatomegaly and elevated liver aminotransferase activity it was decided that busulfan administration should be avoided in the megatherapy regimen prior to aHSCT. An alternate conditioning regimen was proposed, including treosulfan (days -5 to -3, daily dose 12 g/m^2) and melphalan (day -2, dose 140 mg/m^2). The graft contained 2.7 million CD34 cells/kg and was infused on day 0. Neutrophil recovery >500/uL was achieved on day +12, and the patient was discharged in good overall condition on day +16. Two weeks after discharge, during a routine ophthalmic examination changes in both eyes were noticed (retinitis, floaters, and blurred vision). CMV PCR assay was positive in blood and urine. Intravenous ganciclovir was started, given daily at therapeutic levels for 42 days, and was later decreased to maintenance levels for 5 weeks. Clearance of the virus in blood and urine was achieved. During maintenance therapy, new inflammatory changes in the retina and neuritis were detected. Intravenous ganciclovir was again increased to therapeutic dose (7.5 mg/kg/day for 34 days), and anti-CMV immunoglobulin (400 mg/kg on days 1, 2 and 7; 200 mg/kg on day 14, and 500 mg/kg every 2 days for 10 doses) was also administered. This resulted in clearance of the virus from blood and urine, and regression of the inflammatory changes in both retinas. The patient then continued her oncological care with radiation therapy to the tumor bed and cis-retinoic acid. After the second cycle of retinoid acid, an increased CMV load in the blood was noted. Ophthalmic examination revealed acute viral conjunctivitis in both eyes. Otherwise the anterior segment was normal. A diffuse inflammatory infiltration in the vitreous was seen behind the crystalline lens (progressed significantly during two days) (Fig. 1). The details eye fundus not visible but noticeable yellow-white areas of retinal necrosis surrounded by haemorrhages (pizza pie symptom) typical of CMV retinitis. Ocular therapy considered due to rapid advance of the intraocular inflammation. The patient received retrobulbar injections of ganciclovir (50 mg) at the Department of Ophthalmology, Military Institute of Aviation Medicine in Warsaw. Outstanding response noted after 3 days, with the majority of vitreous infiltrations resolvation and CMV retinitis improvement. Palpebral edema was observed two days after the injection resolved almost completely on the third day. Due to numerous foci of active retinitis retrobulbar ganciclovir injection was repeated after 10 days. The sings of retinitis resolved after next 10 days. However, the diffused and dispersed pigmentary mottling areas were still present (Fig. 2). The blood remained positive for CMV for additional 10 weeks. The patient developed a cataract in the right eye 7 months after treatment, and underwent cataract surgery with vitrectomy. The patient is now 3 years after receiving retrobulbar injection of ganciclovir. She does not reveal any signs of active CMV infection and remains in remission of her neuroblastoma.

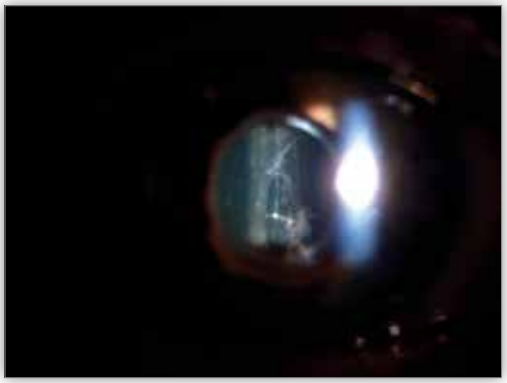

Fig. 1. Diffuse inflammatory infiltration seen in the vitreous behind the crystalline lens of the right eye in the active stage of inflammation.

Ryc. 1. Rozsiane nacieki zapalne w ciele szklistym za soczewką oka prawego widoczne w aktywnej fazie zapalenia.

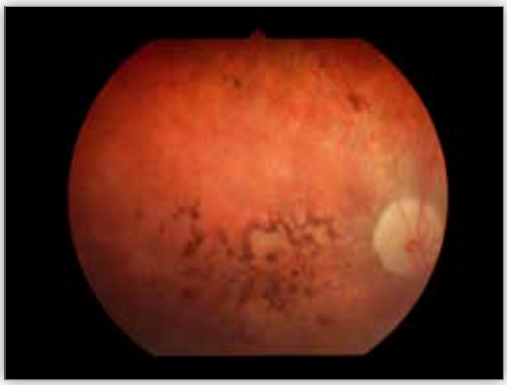

Fig. 2. Right eye fundus at 3 weeks after the first retrobulbar injection of ganciclovir. Complete resolution of intravitreal infiltration. Diffuse and dispersed chorioretinal cicatricial foci with pigmentary mottling are seen on the eye fundus.

Ryc. 2. Dno oka prawego po 3 tygodniach od pierwszego podania pozagałkowego gancyklowiru. Całkowite ustąpienie nacieków zapalnych. W siatkówce i naczyniówce widoczne rozproszone bliznowate ogniska z przebarwieniami.

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Discussion

We report the case of CMV retinitis and neuritis in a child with neuroblastoma and treatment-related chronic lymphocytopenia, who was successfully treated with retrobulbar administration of ganciclovir after previous failure of the systemic antiviral therapy.

Intravenous ganciclovir is a standard of therapy for CMV; however, viral resistance develops in 2.2% to 15.3% in patients, and is associated with larger areas of retinitis and increased loss of vision (1). Forcarnet and cidofovir are commonly used after ganciclovir treatment failure; however, both are associated with severe renal toxicity (renal tubular necrosis), which limits their use in patients after BMT (5). The optimal therapy for children with CMV retinitis and neuritis has not been defined. In young immunocompromised patients with CMV retinitis the recommended treatment includes ganciclovir and CMV IVIG. In cases of poor response, foscarnet is usually added. Treatment is continued until recovery positive cells to $>500/mm^3$ and $>15\%$. Some authors have shown successful treatment of adult AIDS patients with CMV retinitis with intravitreal ganciclovir, foscarnet or cidofovir (1). However, data on the use of intravitreal ganciclovir in children is very limited, with only seven cases reported in two infants, four children with acute lymphoblastic leukemia, and one patient with immunodeficiency syndrome (7, 8).

In our patient, because of rapid disease progression after intravenous therapy local administration was considered. Two forms of intraocular delivery are available: intravitreal injection of ganciclovir 0.4–2.0 mg/0.1 ml 1–2 times weekly, or implantation of sustained-release intraocular device (Vitrasert). Vitrasert is the new intraocular implant containing a minimum of 4.5 mg of ganciclovir, which is designed to release the drug into the vitreous over a 5 to 8 month period of time. However, both forms of intraocular therapy have had serious contraindications. Both Vitrasert and intraocular injections are contraindicated in cases of external infection or severe thrombocytopenia because of increased risk of bacterial endophthalmitis, macular edema or intraocular hemorrhages and less frequently retinal detachment and cataract. Given the circumstances, we elected to proceed with retrobulbar injections of ganciclovir. This route of administration prevents the complications of intraocular therapy and it is known to deliver high levels of the injected drug into the vitreous because the intraocular penetration is not inhibited by blood retinal barrier. The dose of 50 mg of ganciclovir was empirically chosen because it was 25 times higher than the recommended dose for intraocular injection and was similar to recommended systemic therapy. While this is a very valid option for children, retrobulbar injections should be performed very carefully because of diminished orbit volume in small children and the possibility of complications such as retrobulbar hemorrhage, accidental perforation of the globe or optic nerves injury, bradycardia or extraocular nerve palsies.

The role of CMV infection after aHSCT is underrated, as shown in the presented case. New alkylating drugs with immunosuppressive activity against T lymphocytes and antigen-presenting cells (9, 10), like treosulfan, might have be contributed to the development of CMV retinitis in our patient. While this case might be seen as anecdotal, the risk of opportunistic infections may be increased in patients receiving treosulfan, a drug that is preferred in second transplantations to reduce of intensity conditioning protocols, and in patients after abdominal radiotherapy to avoid hepatic venooclusive disease.

In summary, retrobulbar administration of ganciclovir is a good alternative in children with CMV retinitis not responding to standard treatment or in children in whom the systemic use of ganciclovir is limited by its toxicity.

Acknowledgements

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