Cytomegalovirus encephalitis/retinitis in allogeneic haematopoietic stem cell transplant recipient treated successfully with combination of cidofovir and foscarnet


Abstract: We report an 18-yr-old female patient with repeated CMV reactivations after HSCT treated by several pre-emptive courses of virostatic therapy. Seven months after HSCT, she developed CMV encephalitis/retinitis. Initial therapy with GCV and hyperimmune globulin failed, and later on GCV-resistant strain was detected. Continual increase of CMV DNA in peripheral blood led us to combined therapy with CDV and FCV, which was successful and free of severe renal toxicity. To our best knowledge, this is the first reported case of successful CMV treatment with a combination of CDV and FCV.

Key words: cytomegalovirus - transplantation - ganciclovir resistance - cidofovir - foscarnet

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CMV disease remains serious complication following allogeneic HSCT. Recent approach to prevent CMV disease is based on regular PCR monitoring and initiation of pre-emptive therapy with virostatics in positive but still asymptomatic patients. Unfortunately, treatment possibilities in HSCT recipients are seriously limited by bone
marrow suppression during GCV treatment (1, 2) and nephrotoxicity in FCV (3, 4) and CDV (5). Especially, combination of FCV and CDV together is considered highly toxic.

Case report

We report a girl diagnosed with AML in February 2003 at the age of 16 yr. Following therapy according to protocol BFM AML 98, she achieved complete remission. However, in January 2005, relapse of leukaemia was diagnosed. She was then successfully treated according to protocol AML REZ 2004 and was indicated to allogeneic HSCT from an unrelated donor in a second haematological remission of AML.

In June 2005, she underwent peripheral blood SCT using human leukocyte antigen allele mismatched 7/10 (B, Cw, Cw), CMV seronegative unmanipulated graft from a male donor. Cellularity of the graft was as follows: $12.9 \times 10^9$ nucleated cells/kg body wt, $11.12 \times 10^6$ CD34+ cells/kg body wt and $302.1 \times 10^6$ CD3+ cells/kg body wt. The conditioning regimen consisted of oral busulphan 16 mg/kg bw, cyclophosphamide 120 mg/kg body wt and melphalan 140 mg per square metre. GvHD prophylaxis consisted of ATG (rabbit ATG, Fresenius), standard short term methotrexate and cyclosporine A. She engrafted with granulocytes $>500 \times 10^9$/L on day (D) +16 and platelets $>20 \times 10^9$/L on D +26 with last transfusion of platelets being performed on D +19. Acute GvHD grade II was presented on D +61 (skin and gut involvement) and was successfully treated with methylprednisolone 1 mg/kg/day. As a good response was observed, the steroids were gradually tapered off and finally discontinued on D + 105 with no signs of GvHD reactivation. On D + 150, she developed skin rash and because of suspected skin GvHD, we initiated therapy with methylprednisolone in the dose of 1 mg/kg/day. Skin biopsy was performed but was inconsistent with GvHD, therefore steroids were discontinued three wk later. Until D + 210 cyclosporine was gradually tapered and discontinued with no signs of GvHD reactivation since.

We considered this patient to be at a high risk of CMV reactivation as the donor was CMV seronegative and patient was seropositive mononucleated 7/10 (B, Cw, Cw), CMV seronegative unmanipulated graft from a male donor. Cellularity of the graft was as follows: $12.9 \times 10^9$ nucleated cells/kg body wt, $11.12 \times 10^6$ CD34+ cells/kg body wt and $302.1 \times 10^6$ CD3+ cells/kg body wt. The conditioning regimen consisted of oral busulphan 16 mg/kg bw, cyclophosphamide 120 mg/kg body wt and melphalan 140 mg per square metre. GvHD prophylaxis consisted of ATG (rabbit ATG, Fresenius), standard short term methotrexate and cyclosporine A. She engrafted with granulocytes $>500 \times 10^9$/L on day (D) +16 and platelets $>20 \times 10^9$/L on D +26 with last transfusion of platelets being performed on D +19. Acute GvHD grade II was presented on D +61 (skin and gut involvement) and was successfully treated with methylprednisolone 1 mg/kg/day. As a good response was observed, the steroids were gradually tapered off and finally discontinued on D + 105 with no signs of GvHD reactivation. On D + 150, she developed skin rash and because of suspected skin GvHD, we initiated therapy with methylprednisolone in the dose of 1 mg/kg/day. Skin biopsy was performed but was inconsistent with GvHD, therefore steroids were discontinued three wk later. Until D + 210 cyclosporine was gradually tapered and discontinued with no signs of GvHD reactivation since.

We considered this patient to be at a high risk of CMV reactivation as the donor was CMV seronegative and patient was seropositive pre-SCT. Monitoring of viral loads from the whole blood was performed using the quantitative real-time PCR technique on weekly basis starting at D +7 following HSCT. The obtained viral loads were normalized to 100 000 human genomic equivalents obtained by quantification of albumin gene. During the clinically apparent CMV disease, we started to monitor the viral load two or three times a week and we tested both blood and plasma. CMV DNA was detected for the first time on D +20, and on D +27, the viral load crossed our threshold for treatment (1000 normalized viral copies). We started the pre-emptive therapy with GCV (5 mg/kg twice daily) and since that time she was treated with different virostatics almost continuously until D +311 (see Fig. 1a). Six months later during the ongoing treatment with FCV (maintenance dose of 90 mg/kg/day), we detected further increase of CMV DNA load in peripheral blood. At that time, she suffered from a headache and visual acuity decreased bilateral to 0.6. Therefore, we performed the lumbar puncture with positive detection of CMV in CSF about 2 600 000 viral copies/mL. Clinical suspicion of FCV-resistant viral strain and presence of symptomatic CMV disease led us to change the therapy to combination of GCV, CDV (5 mg/kg/wk) and hyperimmune globulin instead of combination of GCV, FCV and hyperimmune globulin. Ophthalmological examination confirmed retinitis of both eyes related most probably to CMV (Fig. 2). Thirteen days later, the viral load increased despite this therapy (see Fig. 1a). We suspected the presence of GCV-resistant CMV strain because of which we changed the therapy to combination of FCV (120 mg/kg/day) with CDV (5 mg/kg/wk with probenecid) and closely monitored renal function parameters as both drugs are known to be nephrotoxic (3, 4). Besides virostatics, we continued with administration of CMV hyperimmune globulin (Cytotect, Biotest, Germany). Clinical status slightly improved. Being aware of potential kidney toxicity, two wk later, we switched the therapy back to GCV, CDV and hyperimmune globulin. Shortly afterwards, we observed another peak in the CMV load, which decreased below our threshold one wk later and stayed there since that time (see Fig. 1a). In total, we administered four doses of CDV. The concomitant treatment of FCV and CDV lasted nine days.

The patient currently has no signs of CMV infection. Her blood counts are completely normal and she started to produce CMV-specific antibodies. Repeated ophthalmological examination revealed irreversible changes in retina because of CMV infection. Final visual acuity dropped to 0.1 in the right eye and to 0.5 in the left eye.

We retrospectively documented the presence of GCV-resistant CMV strain in the stored DNA samples with the method described by Chou.
et al. (6), which is based on the analysis of gene for viral phosphotransferase (UL97). We proved the presence of GCV-resistant strain in the samples obtained from peripheral blood and CSF during the episode of encephalitis/retinitis (Fig. 1a). It explains the insufficiency of therapy with GCV at that time.

We also analyzed the renal parameters before, during and after the treatment with CDV. We did not observe any proteinuria but only mild increase of serum creatinine above our reference range during the treatment with FCV and CDV (Fig. 1b). Later on, creatinine levels returned to virtually normal values.

Reconstitution of cellular immunity and of specific T lymphocytes in particular plays a key role in the resolution of CMV reactivation. Therefore, we analyzed the kinetics of lymphocytes detected in peripheral blood in connection to immunosuppressive treatment and CMV reactivation. During the therapy with steroids, the lymphocyte count decreased to almost undetectable counts. After short lasting steroid therapy was discontinued, lymphocyte counts again started to increase (see Fig. 1c). Retrospectively, we consider the skin rash to be potentially related to the administration of FCV as was already published elsewhere (7). The final resolution of clinical problems was observed only after recovery of lymphocyte counts (see Fig. 1c).

Concomitant administration of CDV and FCV proved to be safe and successful in the management of life-threatening CMV disease in our patient. Since the resolution of clinical problems in the immunocompromised patients is related to reconstitution of cellular immunity, a significant contribution of cellular immunity acting synergically with the virostatic therapy on the improvement of encephalitis in our patient cannot be ruled out. Nevertheless, the reconstitution of
Fig. 2. The figure documents retinal necrosis, retinal haemorrhages, perivascular infiltration and focal vascular irregularity caused by CMV retinitis in the posterior pole of the right eye.

lymphocyte count was truly apparent only after the decrease of CMV load during the virostatic treatment followed by final resolution of the infection (see Fig. 1c). Therefore, not only ongoing reconstitution of lymphocyte count, but also combined virostatic therapy was probably involved in controlling of the infection and favourable outcome.

This case made us introduce the detection of GCV-resistant strains in similar cases, which we are now able to prospectively modify the virostatic therapy. Moreover, recently we have also started to monitor reconstitution of CMV-specific lymphocytes.

To our knowledge, this is the first published successful use of combined therapy with CDV and FCV. We did not observe signs of severe nephrotoxicity either during or after the therapy. We are aware that most patients with CMV disease following HSCT are – unlike our patient – on immunosuppressive therapy that includes nephrotoxic drugs such as cyclosporine A or tacrolimus but our experience may vindicate concomitant use of CDV and FCV in particular patients.

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References