Intravenous cidofovir treatment for recalcitrant warts in the setting of a patient with myelodysplastic syndrome

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Abstract

Cidofovir is an acyclic nucleoside phosphonate with broad-spectrum activity against DNA viruses, including human papilloma virus (HPV). However, data on the efficacy of cidofovir in an immunosuppressive setting remain contradictory. We report for the first time on the promotion of the healing of recalcitrant warts in a patient with myelodysplastic syndrome with intravenous cidofovir treatment.

Introduction

Impaired immunity can interfere with the resolution of viral infections. Human papilloma virus (HPV) infection may occur in patients with active myelodysplastic syndrome (MDS), which is characterized by a monoclonal, dysplastic haematopoiesis, hyperactive bone marrow, blast access (pro-proliferative MDS) and an alteration of the immune system. In periods of neutropenia and low T-cell counts, HPV-induced lesions may be particularly resistant to antiviral therapies. MDS is a disease of the elderly and frequently pursues an indolent course. In children, MDS is often associated with cytogenetic abnormalities and a high incidence of progression into leukaemia. Benign courses of the disease are rare and therapeutic approaches essentially palliative. In addition, immunosuppression following allogeneic haematopoietic stem cell transplantation often facilitates the acquisition of infectious diseases and the extension of viral infections.

Case report

A 21-year-old Caucasian woman had been diagnosed with the indolent subtype of MDS in 1998 and had subsequently been treated with prednisolone, cyclosporin A, chemotherapy (5-azacytidine) and stem cell factor therapy (G-CSF). Parallel to therapy she noticed warts on her right hand. Lesions enlarged despite topical treatment with 5-fluoruracil (Verrumal®, Hermal, Hamburg, Germany) and Imiquimod (Aldara®, 3M, Neuss, Germany) over a 12-week period, respectively. Moreover, neither repetitive CO₂ laser sessions nor liquid nitrogen cryotherapy could prevent progression.

In March 2001, the patient presented to our dermatology department with extensive verrucous lesions on her upper trunk, shoulders and hands affecting the lateral nail folds. The tumour was large enough to encroach on the underlying nail matrix, causing nail dystrophy (fig. 1a). Biopsy showed papillomatosis, acanthosis, hyperkeratosis and cytopathological changes. HPV 27 was identified by
polymerase chain reaction. Platelet counts were decreased (thrombocytes 14/nL) and demonstrated morphological size abnormalities. Refractory anaemia and neutropenia varied in degree from mild to severe (e.g. leucocytes 2.5/nL, haemoglobin 8.5 g/dL on admission). Blasts were less than 5% in the bone marrow. T-helper cells were 423 cells/µL (546–1669) and total NK cells counted 40 cells/µL (190–808).

We started therapy with cidofovir (Vistide®, Pfizer, Karlsruhe, Germany) given intravenously once a week over a period of 2 weeks (375 mg, i.e. 3.5 mg/kg bodyweight) and then continued this low dosage regimen twice a month over a period of 18 weeks. To avoid nephrotoxicity, intravenous pre- and posthydration and 4 g probenecid were given at each infusion. No side-effects were observed, especially neither renal impairment nor apparent changes of haematologic parameters. Ophthalmological controls before and during treatment were normal.

Beginning on the sixth week, we registered a slow but gradual reduction of all lesions. Persistent lesions on her right hand were treated with CO₂ laser therapy; lesions on the left hand received no further treatment. The follow-up period of another 8 weeks showed a persisting effect with further reduction of verrucous lesions, leaving only minimal residual disease that later resolved completely (fig. 1b). During the 1-year follow-up time, the patient presented with new verrucous lesions in other locations easily approachable by CO₂ laser.

**Discussion**

To our knowledge, this is the first report of an effective systemic treatment of recalcitrant warts with cidofovir in MDS. Treatment of HPV-induced lesions is often difficult in cases with hidden localization, frequent reoccurrence or broad extension not being accessible to topical treatment.
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or surgical intervention. Systemic treatment would be helpful in these cases. In the presented case, extensive verrucous lesions were successfully treated with repeated cycles of intravenous cidofovir twice monthly.

Cidofovir is an acyclic nucleoside phosphonate with broad-spectrum activity against DNA viruses including cytomegaly, herpes, papova and pox viruses. To date, the systemic administration of cidofovir has only been approved for the treatment of cytomegalovirus (CMV) retinitis resistant to ganciclovir and foscamet in patients with AIDS, but several other clinical applications have been tried, i.e. in herpes and adenoviral infections, in mollusca contagiosa and in Kaposi sarcoma. However, major undesirable effects, such as nephrotoxicity, neutropenia, infections and ciliary body necrosis leading to ocular hypotonia and iritis/uveitis, as well as the actually high treatment costs, i.e. €1115.15 for 375 mg cidofovir in Germany, are significant limiting factors for the systemic cidofovir treatment.

Cidofovir was also proved to be effective against HPV. The mechanism of action in cells infected with HPV apparently differs from that of CMV. HPV utilizes host-cell DNA polymerase instead of a virally encoded polymerase. Although keratinocytes not infected with HPV show little or no decrease in growth when treated with cidofovir, infected cells show a marked decrease in cell growth. These infected cells have been shown to be trapped in the S phase, an indication of a halt of DNA synthesis. Cidofovir has further been demonstrated to induce DNA fragmentation and caspase-3 protease activity, a key early event in the induction of apoptosis, in HPV-positive cells. This pronounced growth inhibitory effect of cidofovir on HPV-infected cells includes malignant cell lines, as cidofovir has demonstrated activity against cervical carcinoma cells infected with HPV.

Until now, about 100 HPV genotypes have been identified in humans, and cidofovir has been used successfully in several HPV-induced conditions. Topical or intralesional application has been effective in HPV-related lesions of the gingiva, respiratory tract, anogenital infections, Bowenoid papulosis, and verrucae vulgares in HIV. In contrast, intravenous cidofovir therapy over 3 months was once reported to be inefficient in HPV 6- and HPV 11-positive respiratory papillomatosis, which only responded after combination therapy with interferon alpha-2b over 6 months. Moreover, intravenous application of cidofovir (four weekly doses) failed to reduce HPV 3- and HPV 10-positive lesions in epidermodysplasia verruciformis.

Comparing these cases with our observation, one may speculate that the partial nonresponsiveness of cidofovir documented in the past may either be the result of the shortness of treatment period or of a differential response of cidofovir on different HPV types. Lately, Hivnor et al. successfully treated recalcitrant warts in a patient with HIV with 10 cycles of cidofovir, which favours our theory of a long-term active regimen against HPV.

In conclusion, systemic cidofovir administered over 5 months may be effective in the treatment of HPV 27-positive recalcitrant warts in MDS. However, the severe potential side-effects and high costs limit its application. Therefore, the safer and less-expensive topical cidofovir 1% or 3% treatment of recalcitrant warts has rather to be considered in those selected patients in whom classical therapy regimens have failed.

References


