ONKOLOGIE

Casuistic Contribution · Kasuistik

Onkologie 2001;24:491–494

Anti-CD20 Monoclonal Antibody (Rituximab) and Cidofovir as Successful Treatment of an EBV-Associated Lymphoma with CNS Involvement

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Key Words
Cidofovir · Rituximab · PTLD · Stem cell transplantation

Summary
Background: Epstein-Barr virus(EBV)-associated post-transplant lymphoproliferative disease (PTLD) is a serious complication after allogeneic hematopoietic stem cell transplantation (HSCT). Especially in cases with involvement of the central nervous system (CNS) treatment is difficult because the efficacy of most chemotherapeutic agents as well as EBV-specific cytotoxic donor T cells in liquor is uncertain. In the last years the anti-CD20 monoclonal antibody Rituximab was intensively investigated in the treatment of EBV-PTLD. However, only 8 patients with B-cell lymphoma and CNS involvement treated with Rituximab were reported. ***Case Report:*** A 24-year-old female patient with acute T-lymphoblastic leukemia in second complete remission had received allogeneic, unrelated, T-cell depleted HSCT. 10 months later an EBV-associated PTLD was diagnosed. Beside peripheral lymphomas and B symptoms the patient showed neurological symptoms. Examination of the cerebrospinal fluid (CSF) revealed a meningeosis lymphoblastica caused by the EBV lymphoma. Treatment with Rituximab and the antiviral drug Cidofovir led to complete remission with regression of the peripheral lymphomas and disappearance of the neurological symptoms. In addition, the PCR control on EBV DNA became negative in the plasma as well as in CSF. ***Conclusion:*** The combination of Rituximab and Cidofovir appears as an interesting alternative treatment in patients with EBV-associated PTLD and CNS involvement.

Schlüsselwörter
Cidofovir · Rituximab · PTLD · Stammzelltransplantation

Zusammenfassung
Hintergrund: Die Epstein-Barr-Virus(EBV)-assoziierte Posttransplantations-lymphoproliferative Disease (PTLD) ist eine gefürchtete Komplikation nach allogener hämatopoetischer Stammzelltransplantation (HSCT). Insbesondere bei Befall des zentralen Nervensystems (ZNS) ist die Behandlung auf Grund der unsicheren Liquorwirksamkeit der meisten Chemotherapeutika als auch von EBV-spezifischen zytotoxischen T-Spenderzellen schwierig. Der monoklonale Anti-CD20-Antikörper Rituximab wurde in den letzten Jahren bei Patienten mit EBV-PTLD intensiv untersucht. Allerdings wurde bislang lediglich von 8 Patienten mit ZNS-Befall eines B-Zell-Lymphoms berichtet, bei denen eine Therapie mit Rituximab erfolgte. ***Kasuistik:*** Eine 24-jährige Patientin hatte wegen einer akuten T-lymphoblastischen Leukämie in zweiter kompletter Remission eine allogen-unverwandte, T-Zell-depletierte HSCT erhalten. 10 Monate später wurde eine EBV-assoziierte PTLD diagnostiziert. Neben peripheren Lymphomen und B-Symptomen zeigte die Patientin neurologische Symptome. Die Liquoruntersuchung erbrachte den Befund einer Meningeosis lymphoblastica im Rahmen des EBV-Lymphoms. Die Behandlung mit Rituximab und dem Virustatikum Cidofovir führte zu einer kompletten Remission mit Rückbildung der peripheren Lymphome und Verschwinden der neurologischen Symptomatik. Außerdem wurde die PCR-Kontrolle auf EBV-DNA sowohl im Plasma als auch im Liquor negativ. ***Schlussfolgerung:*** Die Kombination von Rituximab und Cidofovir erscheint als eine interessante Therapiealternative für Patienten mit EBV-assoziierter PTLD und ZNS-Befall.

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Introduction

Dependent on additional risk factors the incidence of Epstein-Barr virus(EBV)-associated post-transplant lymphoproliferative disease (PTLD) varies from 1–25% [1–4]. A significantly increased incidence of PTLD after allogeneic HSCT was reported in patients with T cell depleted grafts, after intensive treatment of graft-versus-host-disease (GvHD), and in cases with advanced stages of acute GvHD (grades 3 or 4) [3, 5]. The pathogenetical model for the development of PTLD includes the increased proliferation of EBV-infected B lymphocytes and its insufficient immune control by T cells. In addition, genetic mutations in infected proliferating B lymphocytes lead to transformed malignant cells and the development of aggressive malignant lymphoma [6].

Both clinical course as well as morphology of these disorders are very heterogenous [3]. However, there is a high frequency of extranodal involvement [6]. Treatment strategies include withdrawal of immunosuppression [3], infusion of unselected donor leukocytes or EBV-specific cytotoxic donor T cells [1, 7–9], application of antiviral drugs and combination chemotherapy [10–13]. Moreover, the use of specific anti-B-cell monoclonal antibodies (anti-CD20, -CD21, -CD24) was intensively examined over the last years [4, 14–17]. We here report the successful treatment of an EBV-associated PTLD including CNS involvement with the combination of anti-CD20 monoclonal antibody Rituximab and antiherpesvirus agent Cidofovir.

Case Report

A 24-year-old female patient with acute T-lymphoblastic leukemia in second complete remission received T-cell depleted, HLA-DRQB1-micromismatched HSCT from an unrelated donor in February 1999. Conditioning regimen consisted of 1200 cGy fractionated total body irradiation, cyclophosphamide (60 mg/kg × 2), etoposide (30 mg/kg × 1) and antithymocyte globulin (ATG) Merieux (2.5 mg/kg × 4). The graft contained 8.8×10^6/kg CD34-positive cells. Following transplantation the patient received T-cell addback consisting of 1×10^5/kg and 1×10^6/kg CD3-positive cells, respectively, on days +14 and +21. GvHD prophylaxis was performed from day +15 to day +100 only with cyclosporine (CSA). Subsequently various complications as consequence of the immunodeficiency were diagnosed (esophagitis caused by reactivated CMV infection, ambilateral pneumonia with suspicion of aspergillosis, maxillary sinusitis). 9 months after transplantation the patient developed a histologically proven chronic GvHD of the skin and gastrointestinal tract (extensive disease) that was successfully treated with prednisolone. Because of unacceptable side effects (muscular atrophy, depression, insomnia) the application of prednisolone had to be stopped and from day +210 the immunosuppression was continued with CSA. 4 months later (day +312) the patient had to be admitted to hospital with peripheral lymphomas, B symptoms (fever up to 40 °C, weight loss of 6 kg in 3 months) and physical weakness. Neurological symptoms including tremor, hypersensitivity to light and touch, imbalances and insecurity in walking were observed. An ultrasound scan showed enlarged lymph nodes (cervical, axillary, inguinal) up to 2.4 cm in diameter. As signs of increased cell proliferation lactate dehydrogenase (LDH) as well as thymidine kinase (TK) levels in

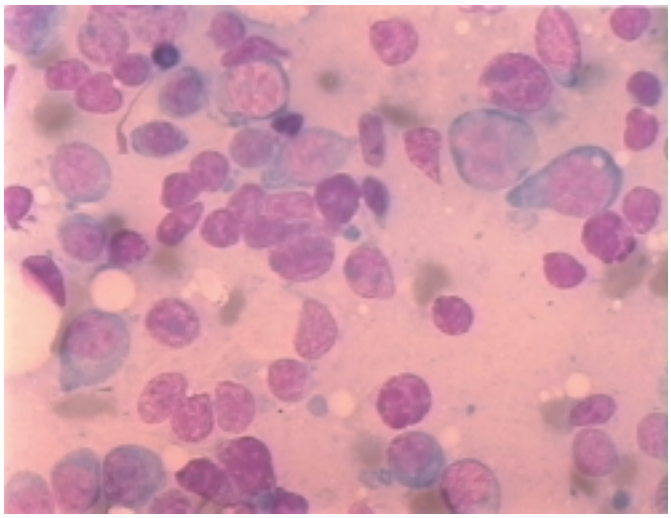
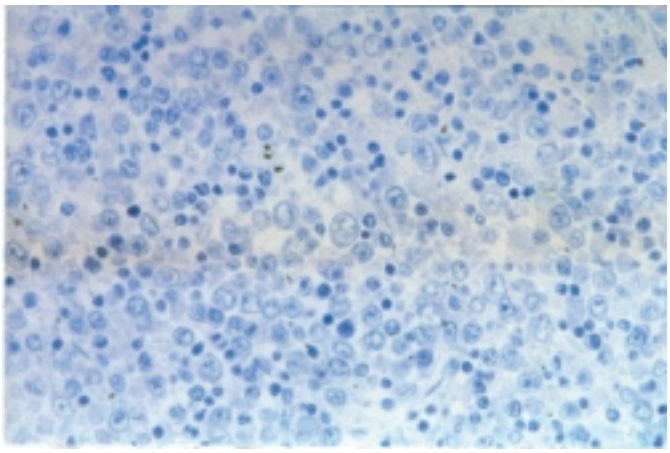


Fig. 1. Cytological examination of cervical lymph node showed immunoblasts with partial differentiation to plasma cells (100:1; Pappenheim's stain).



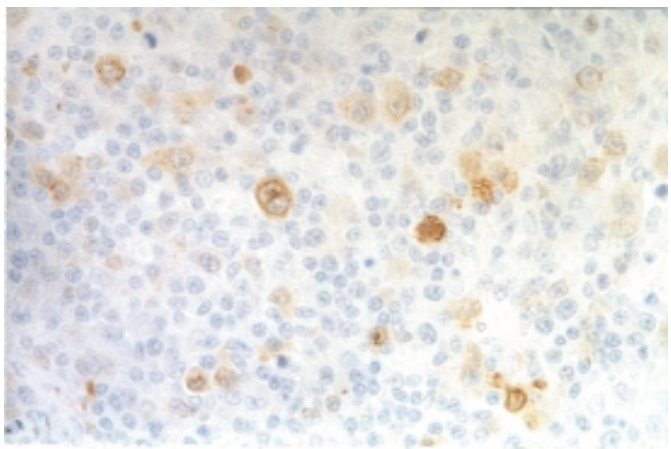


Fig. 2. A. Histological examination revealed polymorphous B-cell proliferation type of EBV-associated PTLD. The majority of tumor cells are large blasts with prominent nucleoli and pale basophilic cytoplasm (200:1, Giemsa). **B.** The tumor cells were positive for EBV-latent membrane protein-1 (200:1; ABC method).

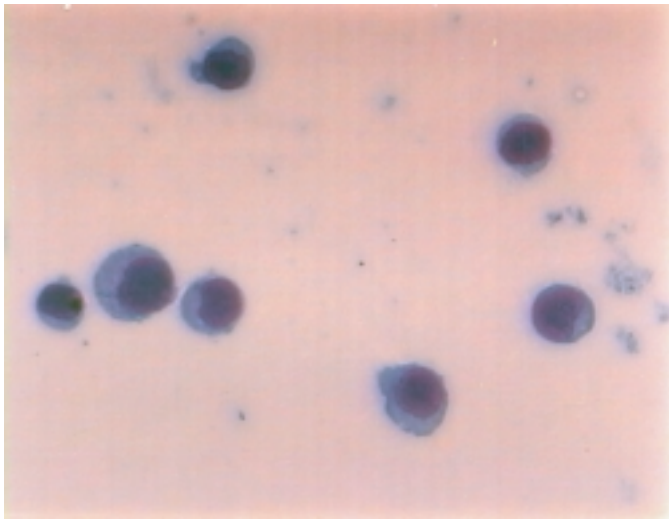


Fig. 3. Cytological detection of polymorphic immunoblasts and plasmoblastic cells in the cerebrospinal fluid (meningeosis lymphoblastica caused by EBV-PTLD) (100:1; Pappenheim's stain).

the serum were significantly increased. In contrast, the CD4 count in the peripheral blood (43 cells/mm^3) and the CD4/CD8 ratio (0.17), respectively, were considerably reduced.

The biopsy and subsequent cytological examination of a cervical lymph node first confirmed the suspicion of an aggressive non-Hodgkin's lymphoma with detection of immunoblasts (fig. 1). Histologically a polymorphe EBV-PTLD was diagnosed (fig. 2A) with detection of CD20-, partially also CD30-positive blasts, expression of immunoglobulin kappa- and lambda light chains as well as the EBV-antigen LMP-1 (latent membrane protein) (fig. 2B). The clonality could be proven by detection of the rearrangement of the immunoglobulin heavy chain gene. In addition, the examination of the cerebrospinal fluid (CSF) revealed a polymorphic meningeosis lymphoblastica as cause of the neurological symptoms (fig. 3). A magnetic resonance tomography (MRT) scan of the skull showed meningeal irritations in the area of the frontal brain. The polymerase chain reaction (PCR) was positive for EBV-DNA in the peripheral blood and in CSF.

First, immunosupression with CSA was stopped on day +312. Because of the preexisting chronic GvHD as well as the unsatisfactory results with cytotoxic agents, we started a treatment with Rituximab (375 mg/m^2 i.v. on days +316, +323, +330, +337) [Europe: Mabthera®, Hoffmann-La Roche, Grenzach-Wyhlen, Germany; USA: Rituxan®, IDEC Pharmaceuticals, San Diego, CA; Genentech, San Francisco, CA] and Cidofovir (5 mg/kg i.v. on days +317, +324, +331) [Vistide®, Pharmacia & Upjohn, Erlangen, Germany]. Subsequently we observed a rapid improvement of the general condition of the patient with complete regression of the peripheral lymphomas and disappearance of the neurological symptoms. The patient was discharged from hospital on day +338. The PCR control on EBV-DNA first became negative only in the plasma while it still remained positive in CSF (day +337). Therefore, we continued outpatient the application of Cidofovir on days +348 and +362. Subsequently, also in CSF the PCR on EBV-DNA became negative (day +378).

Until day +440 the patient remained well without any signs of a nodular or CNS relapse of the EBV-lymphoma. However, an ambilateral pneumonia caused by Aspergillus fumigatus was diagnosed. After development of an ARDS the patient died on day +458 as a consequence of a multiorgan failure.

Discussion

EBV-associated PTLD is a serious complication in patients with allogeneic HSCT after myeloablative as well as after dose-modified conditioning. Treatment of choice is immunotherapy with immediate withdrawal of immunosuppression on the one hand and infusion of unselected donor leukocytes or EBV specific cytotoxic donor T cells on the other hand [1, 3, 8]. However, the potential alloreactivity of unmanipulated donor cells as well as the problems of a immediate availability of unrelated donors can limit this therapeutic option [1, 7]. Beside cytotoxic agents and various antiviral drugs [10–13], positive results of the use of the monoclonal anti-CD20 antibody rituximab were repeatedly reported [4, 16, 17].

The situation of our patient with CNS involvement appeared difficult for different reasons. First, beside the discontinuation of the immunosuppression an intensive immunotherapy (including DLI) was impossible (preexisting GvHD, unrelated donor). Treatment with chemotherapeutic agents was not likely to be successful, since the results in patients with PTLD are frequently unsatisfactory [6, 18]. On the other hand a very limited number of cytotoxic drugs are able to cross the blood-brain barrier [19]. Although the ability to penetrate into the CNS is unknown with Rituximab [19, 20], we decided to use this antibody because of its repeatedly reported effectiveness in EBV-associated PTLD [4, 16, 17]. In addition, in patients with CNS involvement by B-cell lymphoma the systemic and/or intraventricular application of Rituximab were described occasionally [20–24]. We combined Rituximab with Cidofovir, its antiviral efficiency against EBV having been already examined [25, 26]. The clinical course of our patient could indicate that Rituximab is effective not only in cases with nodular manifestation of EBV-LPD. We have seen that this antibody is active also in CNS despite low concentrations in the CSF in comparison to serum levels described by several authors [20, 22, 24].

Conclusion

As seen in our patient with meningeosis lymphoblastica caused by a malignant EBV-associated lymphoma, it is possible to achieve complete remission without any systemic or intrathecal cytotoxic chemotherapy. This shows that the disturbance of the blood-brain-barrier, frequently observed in patients with CNS involvement, seems to play an important role. Therefore, the systemic use of Rituximab in conventional doses appears to be an interesting alternative treatment in patients with EBV-associated PTLD and CNS involvement.

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