Optic nerve relapse in a child with common Acute Lymphoblastic Leukemia treated with systemic anti CD-20 (Rituximab)

We describe a two- year old boy who was diagnosed with pre-B acute lymphoblastic leukemia (ALL). He developed a central nervous system (CNS) relapse with optic nerve involvement. Initially he was treated according to the ALL relapse protocol, including CNS radiotherapy. Despite an initial complete reponse, relapse occurred within six weeks of treatment. The leukemic blast cells were CD-20 positive and he was treated with systemic anti CD-20 therapy (Rituximab) with no CNS recurrence over a six-month period. He died due to a CD-20 negative bone marrow relapse. This case illustrates a potential role for Rituximab in pediatric CD-20 positive malignancies.

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Acute lymphoblastic leukemia is the most common form of childhood cancer with cure rates reaching 70-80%.[1] In children with common ALL up to 25% of cases have CD-20 positive leukemic blasts at presentation.[2]

Unlike CNS involvement, ocular complications in pediatric leukemia are rare. However, when they occur immediate diagnosis and treatment are necessary. Leukemic infiltration of the optic nerve may cause only minimal visual symptoms, despite massive involvement. The diagnosis can be made both clinically and with further opthalmological and radiological evaluation. Rituximab is a genetically engineered chimerical monoclonal antibody directed against the CD-20 antigen found on the surface of normal and malignant lymphocytes. Systemic anti CD-20 treatment has become increasingly important in the care of relapsed CD-20 positive non-Hodgkin lymphoma patients and has a potential role for those patients with CD-20 positive leukemias. Here we report a case of a *high risk* pre-B ALL, CD-20 positive patient, presenting with a second isolated CNS relapse with optic nerve involvement. Treatment was successful over a six-month period with Rituximab alone, without CNS or optic nerve recurrence. A CD-20 negative bone marrow relapse led to his death.

Report

A two year old boy was diagnosed with CD 20 positive pre-B ALL with a leukocyte count of 67×10^9/L, of which 98% were blasts. Cytogenetic studies and FISH analysis showed t(12; 17) without other chromosomal abnormalities. There was no central nervous system (CNS) involvement. He was treated according to the SNWLK (Dutch Pediatric Leukemia Society) ALL-high risk (HR)-9 protocol (Figure 1). Complete hematological remission was achieved following induction therapy. He developed an isolated CNS relapse two and a half years after the initial diagnosis, whilst off treatment. Cerebrospinal fluid (CSF) isolated cells were immuno-phenotypically identical to his initial marrow leukemic blasts. Morphological bone marrow analysis showed no evidence of relapse but due to a lack of molecular target, minimal residual disease could not be excluded. He received chemotherapy and CNS directed radiotherapy (total 24Gy), according to the POG-SIMAL-9 relapse protocol. As no HLA identical related donor was available he was not transplanted. Almost 3 years after the initial relapse, he developed

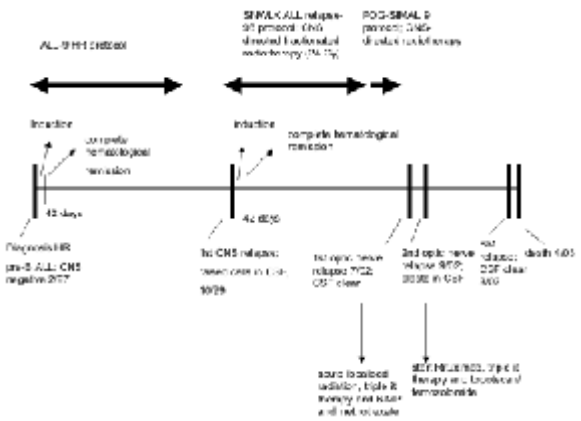

Figure 1. Case report: diagram illustrating the time sequence of the treatment in our patient.

reduced vision in the right eye, with infiltration of the right optic nerve extending to the optic chiasm. There were no blasts evident in the CSF. He received acute localized irradiation,[3] with initial complete regression of the tumor mass determined by follow-up MRI. Visual acuity did not improve. He subsequently received additional triple intra-thecal therapy, (methotrexate, cytosine arabinoside and prednisone) for local control. Systemic treatment consisted of oral 6-mercaptopurine and methotrexate only. Bone marrow transplantation (BMT) with an unrelated donor was planned. Two months later, at pre-transplant ophthalmologic examination there was only light perception in the right eye with marked papilla edema with hemorrhages and macular star formation. The visual acuity of the left eye was diminished with temporal pallor of the optic nerve head. An MRI showed thickening of the right optic nerve from its location in the orbital apex to just anterior of the optic chiasm, consistent with a relapse. CSF examination revealed scanty CD20 positive blasts but the marrow showed no evident infiltration. In consultation with the parents, as the prognosis after second central nervous system relapse is extremely poor,[4] a palliative regimen was advised and the BMT cancelled. The parents refused the option of an Omaya-reservoir.[5,6] In light of the CD 20 positivity of the blasts, Rituximab was given once a week for four weeks at a dose of 375 mg/m^2. It was decided to offer this modality of treatment in the hope of controlling the neurological sequelae in our patient with minimal treatment related toxicity. MRI evaluation at 1 week after completion of Rituximab showed a complete regression of the tumor, CSF analysis was clear of blasts. Further treatment consisted of monthly i.v. Rituximab together with triple intrathecal therapy, combined with alternating monthly oral Topotecan 2.4 mg/m2 and Temozolomide 180 mg/m2. Six months later he developed a CD-20 negative bone marrow relapse without evidence of optic nerve or CNS involvement and died peacefully at home.

Discussion

Rituximab is a genetically engineered chimerical monoclonal antibody directed against the CD-20 antigen found on the surface of normal and malignant lymphocytes. Given systemically in patients without CNS disturbances, approximately 1% of the administered dose can be detected in the CNS.[7,8] Recent literature supports the use of anti CD-20 monoclonal antibody therapy (Rituximab) in adult patients with CD-20 positive CNS lymphoma.[7,8] However, there is no literature available

about the pharmaco-dynamics and CNS distribution of Rituximab administered to patients following CNS directed radiotherapy or those with recurrent CNS relapses. We felt that our patient may have had a therapeutic response in light of a possible disruption in the blood brain barrier, which may have allowed for an increased penetration. This remains speculative as, unfortunately, we were not in a position to use labeled Rituximab and demonstrate this effect in vivo. Adverse effects have been reported with Rituximab but none occurred in our patient. The number of medical conditions where Rituximab can be used is developing rapidly.[9] Temozolamide and topotecan were given in addition to the Rituximab. Further studies with these drugs are needed in hematological malignancies.[10, 11] Ocular complications in pediatric leukemia are rare. However, when they occur immediate diagnosis and treatment are necessary. Ocular complaints including blurred vision or progressive visual loss may be caused by cataract, retinal complications (hemorrhages, infiltration, infarction or serous detachment), vitritis or optic nerve involvement and should be investigated without delay by an ophthalmologist.[3] Leukemic infiltration of the optic nerve may cause only minimal visual symptoms despite massive involvement. However, visual loss may be more severe when the infiltration is located more posteriorly. The diagnosis of optic nerve involvement in ALL can be made both clinically and with ophthalmologic and radiological evaluation. B-scan ultrasonography can be used for the early diagnosis of infiltration of the anterior part of the optic nerve.[12] The first CNS relapse in our patient was characterized by a high CNS blast count apparently without visual impairment. Interestingly, with the second CNS relapse the blast count was low but there was infiltration of the right optic nerve. This suggests a local lesion above the optic chiasma, which *seeded* blasts into the CSF, as seen in CNS lymphoma. Although this is a recognized complication of ALL it is relatively uncommon. As an ophthalmologist at the first CNS relapse did not see the patient, we cannot be sure about the duration of visual impairment. The left optic nerve was already pale at evaluation during the second relapse. As optic disc pallor is due to a very slow developmental process, the lesion may already have been present. Other causes for optic atrophy in this patient include Vincristine, intrathecal therapy and post irradiation. We feel that all children with relapsed ALL should always have a properly conducted fundoscopic examination in light of the potential treatment implications. If optic nerve leukemic infiltration is diagnosed and promptly treated with emergency radiation, vision in some, but not all, cases can be salvaged.[3] In conclusion, we consider Rituximab to be a new and useful drug for use in children with CD-20 positive malignant hematological disease such as non-Hodgkin lymphoma and some acute leukemias. Our patient initially had CD-20 positive leukemic blast, but the eventual marrow relapse was CD-20 negative. This might have been caused by evolution of the leukemia clone as often happens in targeted therapy in highly malignant cancers. We were not in a position to investigate the clonal evolution by molecular methodology, so this remains speculative, albeit clonal evolution has been proposed by other authors.[13]

Although an expensive modality of therapy, our patient illustrates that selective use of Rituximab improves the quality as well as the duration of life and is well tolerated in the palliative setting. Further studies are required to establish the optimal role of Rituximab in the treatment of pediatric CD-20 positive hematological malignancies

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