Fatal course after administration of rituximab in a boy with relapsed all: a case report and review of literature

We are reporting on a 14-year-old boy with a very early relapse of pre-B acute lymphoblastic leukemia (ALL) and anaplastic astrocytoma WHO °III; the astrocytoma was subtotally resected and subsequently treated with irradiation and chemotherapy. The leukemic relapse was refractory to the administered salvage therapy. Therefore, treatment with the human anti-CD20 monoclonal antibody (MoAb) IDEC-C2B8 (*rituximab*) was initiated. After a small fraction of the standard dose (375 mg/m²) had been administered, the infusion had to be interrupted because of an acute attack of pain in the lumbar region. Two days later, after resumption of the therapy, he developed a fatal course of *systemic inflammatory response syndrome* (SIRS) and died, possibly due to uncontrollable cytokine release syndrome associated with sepsis. The fatal course will be discussed based on a review of the literature.

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The safety and efficacy of the chimeric monoclonal antibody *rituximab*, which specifically binds to the CD20 antigen on normal and malignant B lymphocytes, has been proven in many clinical trials. The mode of action of *rituximab* includes complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity.[1] The indication for *rituximab* includes mainly CD20+ Hodgkin- and Non-Hodgkin B-cell lymphoma with a lymphocytosis up to 5000/ μL. Only a few cases of treatment of acute lymphoblastic leukemia (ALL) with *rituximab* have been reported.[2,3] Between 84% and 95% of patients experienced treatment-related adverse events, approximately 90% of which were mild to moderate, most involving flu-like symptoms (fever, chills, nausea and asthenia).[4] Infusion-related cytokine release syndrome (CRS)[5,6] is the most frequent MoAb-specific adverse event of *rituximab*.4 The vast majority of infusion-related adverse reactions occurred with the first infusion and within the first 24 hrs; therefore close monitoring is imperative.4 The post-marketing surveillance database indicates 0.04–0.07% of patients with a fatal courses related to *rituximab* administration.[7]

Case report

We are reporting on a 14-year-old boy without tumor syndromes in the family history suffering from relapse of pre-B ALL and anaplastic astrocytoma WHO°III. Initially a pre-B ALL was diagnosed. A noticeable hyperdensity of the left gyrus cinguli in the cerebral MRI was considered as a leukemic infiltration. Combination chemotherapy was commenced according to the German CoALL-06-97 trial (high risk).[8] After induction chemotherapy, bone marrow (BM) puncture revealed complete remission but the cerebral lesion showed no change. A stereotactic biopsy confirmed an anaplastic astrocytoma WHO °III infiltrating the frontal brain. The tumor was resected incompletely and ALL chemotherapy was switched to mercaptopurine maintenance therapy. Treatment according to the national *HIT-GBM-D* trial was started.[9] Seven months after diagnosis of ALL he suffered a very early relapse. On day 15 of the ALL relapse protocol ALL-REZ BFM 2002,[10] BM-puncture revealed 80% lymphoblasts. He was referred to our department to receive *rituximab* and chemotherapy before BM transplantation.

Before the administration of *rituximab*, he had slightly elevated liver enzymes (ALT 117 U/l [normal <29 U/l]) and moderately elevated plasma LDH (790 U/l [normal < 377 U/l]). PBC showed a WBC of 1.5 /nl with 69% lymphoblasts. The CD-20 surface marker was expressed on 36% of lymphoblasts.

Rituximab (375 mg/m²) infusion was started at 13 mg/h (0.2 mg/kg/h), with the infusion rate progressively increased according to the patient's clinical condition. This therapy was accompanied by aggressive hydration, diuresis, prednisone, dimetinden maleate, allopurinol, and morphine.

Two hours later, after infusion of approximately 75 mg *rituximab*, the procedure was stopped because the patient complained of intolerable back pain in the lumbar region accompanied by tachycardia (180/min) and slight chills. The patient recovered quickly after the administration of morphine. The next day, after a second dose of morphine the clinical condition was inconspicuously. PBC showed an nearly unchanged WBC of 1.4 /nL, HGB 7,8 mg/dL, PLT 11 /nL and slightly elevated ALT 78 U/L, and elevated plasma LDH 1587 U/L. Two days later, *rituximab* infusion was resumed at a quarter of the previous infusion rate. After 9 hrs and infusion of approximately 230 mg *rituximab*, the patient developed an anaphylactoid reaction with arterial hypotension, tachycardia, and hypoxia. Adrenalin, dimetinden maleate, glucocorticoids, oxygen, and fluids were given and he was transferred to the ICU. Leukocytes were 0.3/nl with 7 % lymphoblasts, serum LDH rose to 2231 U/l, plasma ALT rose to 222 U/l [normal < 29 U/l], plasma AST rose to 309 U/l [normal < 23 U/l], plasma GGT rose to 80 U/l [normal < 48 U/l] and potassium was 2.7 mmol/l without other signs of tumor lysis syndrome (TLS).

Despite maximal intensive care support, hypotonia persisted and echocardiography revealed severely restricted left ventricular function (fractional shortening 21–23%). Vancomycin and cefotaxime were given because of suspected septicemia with leukocytopenia, fever and rising C-reactive protein (24 mg/dL). Even though the detected causative organisms (Streptococcus bovis and E. coli.) were sensitive towards the administered antibiotics, the patient's clinical condition deteriorated and he died of multiple organ failure 72 hrs after administration of the first dose of *rituximab*. The autopsy failed to provide any additional information beyond evidence of fat-embolism of the lungs and petechial bleedings in the skin, the mucous membranes, the peri- and epicard, the lungs, and the brain. Astrocytoma was infiltrating the corpus callosum and the fornix.

Search strategy and selection criteria

Published data for this review were identified by searches of NCBI PubMed over the past 15 years using *CD20 monoclonal antibody*, *rituximab*, *cytokine release syndrome* as keywords without any restrictions on language of publication. Also, references to relevant articles in the authors' own and the manufacturer's databases were used.

Review of literature

Rituximab therapy is associated with possible adverse events like tumor lysis syndrome (TLS) or cytokine-release syndrome (CRS) (see Table 1). Patients with high cell counts and a high mitotic index are at high risk for TLS after any kind of cytoreductive therapy in cases of

Table 1. Case reports on fatal courses after rituximab.

B-Cell NHL	TLS	Abou Mourad Y *et al.*[12]
B-cell CLL	CRS	Lim LC *et al.*[18]
B-Cell NHL	CRS ??	Nikolaidis[25]
B-Cell NHL	Tumor cell agglutination	KunzmannV *et al.*[27]

leukemia or lymphoma.[11] In the literature, *rituximab* has been held responsible for both severe and moderate courses of TLS.[12-14]

Besides TLS, the most predictable MoAb-specific side effects are systemic flu-like symptoms, headache, fever, sweat, skin rash, shortness of breath, hypotension, nausea, and asthenia. In general, CRS known from therapy with MoAbs15 occur mostly during the first infusion of MoAbs.11 Severe hypotension, bronchospasm and hypoxia leading to death have been reported. [4,11,16-18] The pathophysiology of these reactions appear to be related to CRS, potentially leading to cytokine-associated systemic inflammatory response syndrome (SIRS).[19,20] Clinically severe courses of CRS21 after MoAbs therapy are known from similar agents like Muronomab,[5,22] Basiliximab,23 CAMPATH-1H or *rituximab*.[18] However, reports of cases of fatal CRS after *rituximab* therapy are uncommon.[4,18,20,24,25] The underlying mechanism of CRS is related to changes of serum cytokine levels due to rapid injection of the antibody. CRS is characterized by an increase of inflammatory cytokines such as IFN-γ, IL-8 and TNF-α occurring about 90 min after the first infusion.[19,17,26] In severe cases of CRS after *rituximab*, a 5 to 10-fold increase in liver enzymes, elevation of d-dimers, lactate dehydrogenase and prolongation of protrombine time are also commonly observed.20 Patients with peripherally higher number of tumor cells (>50×10^9/l) are more likely to develop severe infusion-related reactions including fever, chills, nausea, dyspnea and hypotension.[19, 24] Data on treatment with *rituximab* in children suffering from ALL are scant.[2,3]

Lim et al. report on a fatal CRS in a 71-year-old woman with Rai stage I B-cell chronic lymphocytic leukemia (B-CLL) and high leukemic cell burden.[18] She was started on *rituximab* at a very low initial dose. After a gradual increase during the second hour, she experienced rigors. Despite discontinuation of *rituximab* infusion, she became hypotensive with mild breathlessness and basal pulmonary crepitations. The patient suffered from progressive cardiopulmonary deterioration and died of cardiopulmonary collapse without signs of a TLS 9 hrs after administration of *rituximab*.

Kunzman *et al.* report on a 65-year-old man with pretreated B-CLL and high circulating lymphocyte counts.[27] Refractory to standard chemotherapy, he was admitted for *rituximab* therapy. Pretreatment WBC was 271.0 nl. Because of the high leukemic cell burden, the antibody was started at a reduced infusion rate of 2.5 mg/h for the first 2 hrs and gradually increased. After 6.5 hrs, the patient developed tachycardia, acetaminophen-resistant fever, and chills with decline of WBC. *Rituximab* therapy was discontinued. Unfortunately, three hours after cessation, the clinical condition deteriorated with progressive hypotension, dyspnea, tachypnea, and hypoxemia with basal crepitations in his lungs, progressive confusion and enuresis. In spite of intensive care support, the patient died of cardiopulmonary failure 13 hrs after initiation of *rituximab* infusion. Based on histopathologic findings, the authors provide evidence that tumor cell agglutination could have been responsible for severe infusion-related adverse events during *rituximab* treatment.

Discussion

Although the efficiency of *rituximab* is not clearly proven in ALL we decided to make a therapeutic attempt in face of the desperate condition of our patient. The exact mechanism and cause of the fatal progressive course after *rituximab* cannot clearly be explained. The reason for the massive back pain attack after the first infusion of *rituximab* remains unclear. After the second infusion, there was no evidence of TLS or massive leukemic cell agglutination. Therefore, it seems plausible that our patient sustained progressive CRS leading to a fatal SIRS. In severe cases of CRS after *rituximab* a 5 to 10-fold increase of liver enzymes, lactate dehydrogenase and a often a prolonged prothrombine time have been described.[20] In our patient, we observed a 10-fold increase of liver enzymes and lactate dehydrogenase. The prothrombine time was normal possibly due to the administration of fresh frozen plasma. However, the circumstantial course remains vague. In addition, *rituximab*-induced leukocytopenia could have promoted a systemic infection as indicated by increasing CRP and the detection of Streptococcus bovis and E. coli. A contradiction to this assumption would be the fact that *in vitro* tested antibiotics were not effective.

In our opinion, the most likely explanation for the unexpected fatal course is a SIRS on the basis of a massive CRS, potentially in combination with septicemia. Unfortunately, no serum-cytokine levels were measured in order to support the evidence of a CRS. In contrast to our patient, it is reported that *rituximab*-related CRS occurs mainly with the first infusion and within the first 24 hrs.4 Hence, it is essential that the infusion-related reaction be monitored continuously even though the manufacturer's post-marketing surveillance database indicates that just 0.04–0.07% of patients will experience a fatal course related to *rituximab* administration.7

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