Acute Lymphoblastic Leukemia

Rituximab plus chemotherapy in children with relapsed or refractory CD20-positive B-cell precursor acute lymphoblastic leukemia

We treated three children with relapsed or refractory CD20 positive B-cell precursor acute lymphoblastic leukemia with rituximab in combination with chemotherapy, which produced a decreasing or persistent low positive minimal residual disease load. Two children subsequently underwent allogeneic stem cell transplantation and remain in complete remission at days +399 and +332.

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Rituximab is an approved, widely and successfully used genetically engineered chimeric antibody for the treatment of CD20 positive B-cell non-Hodgkin's lymphomas (NHL), mainly in adult patients.[1,2] Its efficacy has recently been demonstrated in single pediatric patients with mature B-NHL[3] and B-cell acute lymphoblastic leukemia (ALL).[4] We report on three children with relapsed or refractory CD20 positive B-cell precursor ALL (BCP-ALL) according to EGIL criteria[5] with a cytologic and molecular response to rituximab (375 mg/m^2 per application) given in combination with salvage therapy according to ALL-REZ-BFM treatment protocols. Remission was assessed by conventional cytological methods and by quantification of minimal residual disease (MRD) at a submicroscopic level using clonal markers detecting T-cell receptor or immunoglobulin gene rearrangements at a sensitivity level of at least 10^{-3}.

Patient #1, a 7-year-old boy was referred from another country because of a primary common-ALL with bilateral testicular involvement resistant to protocols CCG-1961 and CCG-1941. Treatment was switched to ALL-REZ-BFM therapy[6] without any significant cytological response to this therapy. Rituximab was added before the third intensive polychemotherapy course (R2) and before a subsequent course deriving from the ALL-BFM 2000 protocol for high-risk patients (HR-1') (Schrauder *et al.*, *submitted*). Cytologically, the boy achieved a complete remission during which residual disease monitored by two clonal markers (Vδ2Ja29; (VH3)D2JH6) decreased to a level of 10^{-3}-10^{-4}. The boy was allografted from an HLA-matched sibling following myeloablative conditioning with total body irradiation (TBI). After an uneventful course, he remains in complete remission at day +399 post transplant.

Patient #2, a 7-year old girl with pre-B-ALL and amplification of the *AML1* gene achieved a complete remission after treatment according to the medium risk branch of the ALL-BFM-2000 protocol but experienced a late isolated bone marrow relapse two years after completion of first-line therapy. She was then treated according to the S2 branch of the ALL-REZ-BFM 2002 protocol, and achieved a cytological complete remission after the fourth block of salvage therapy but had persistently high levels (>10^{-3}) of MRD. By the addition of rituximab prior to two subsequent multidrug chemotherapy courses, R1 and R2, MRD decreased below the sensitivity level of 10^{-4} (markers VκII-kde, VH1D3(JH6), Vδ2δd3). She was allografted in second complete remission and remains in continuous remission at day +332 post-transplant with limited chronic graft-versus-host disease and bronchiolitis obliterans.

Patient #3, a 5-year old girl with *TEL-AML1* positive common-ALL was treated according to the ALL-BFM-95 protocol. Forty-four months after diagnosis, a combined *TEL-AML1* positive bone marrow and central nervous system relapse occurred. During the course of intensive salvage therapy she experienced a severe infection while pancytopenic, suffered from pulmonary and cerebral hemorrhage necessitating cardiopulmonary resuscitation, and developed a persisting hemiparesis. Having achieved a second complete remission, she relapsed again 6 months after completion of salvage therapy. Treatment according to ALL-REZ-BFM 2002 resulted in a third cytological complete remission and allogeneic hematopoietic stem cell transplantation from an unrelated donor was performed following myeloablative conditioning with TBI, VP-16 and anti-lymphocyte globulin. She remained in complete remission until day +458 when another com-

Table 1. Response to salvage chemotherapy combined with rituximab in three children with relapsed or refractory ALL.

*CD20$^+$ leukemic blasts in BM**		*Patient #1 80%*			*Patient #2 34%*			*Patient #3 64%*	
Blasts (%) in BM/MRD	Block	BM	MRD	Block	BM	MRD	Block	BM	MRD
before salvage therapy		66%	n.d.		95%			38%	
after cytoreductive prephase	n.d.			V	98%	n.d.	V	CR	n.d.
after 1. cycle	1. F1	60%	n.d.	1. F1	55%	n.d.	Rituximab	CR	$<10^{-4}$
after 2. cycle	2. F2	60%	10^{0}	1. F2	19%	10^{-1}	**1.** F1	CR	$<10^{-4}$
after 3. cycle	**1.** Rituximab	40%	10^{0}–10^{-1}	II-IDA	27%	10^{-2}–10^{-3}	**1.** F2	CR	$<10^{-4}$
after 4. cycle	1. R2	26%	10^{0}–10^{-1}	1. R1	CR	10^{-1}–10^{-2}	**2.** F1	CR	$<10^{-4}$
after 5. cycle	**2.** Rituximab	CR	10^{0}–10^{-1}	1. R2	CR	10^{-2}–10^{-3}	**2.** F2	CR	$<10^{-4}$
after 6. cycle	1. HR1'	CR	10^{-3}–10^{-4}	**1.** Rituximab	CR	10^{-3}			
after 7. cycle	1. HR2'	CR	10^{-3}–10^{-4}	2. R1	CR	$<10^{-4}$			
after 8. cycle	prior to HSCT	CR	10^{-4}	**2.** Rituximab	CR	$<10^{-4}$			
after 9. cycle				2. R2	CR	$<10^{-4}$			

*BM: bone marrow; HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; n.d.: not done; *no serial immunophenotyping was performed.*

bined relapse (*TEL-AML1* positive with additional secondary cytogenetic aberrations) was diagnosed. She received cytoreductive chemotherapy and repeated intrathecal cytostatic injections. During the subsequently administered infusion of rituximab, a generalized seizure occurred. By magnetic resonance imaging and lumbar puncture cerebral hemorrhage, thrombosis and encephalitis were excluded. Within the next days she fully recovered and therapy was continued with conventional chemotherapy according to the ALL-REZ-BFM 2002 protocol. The molecular response to treatment was confirmed using three markers (Vκ I-Kde, κintron-kde, Vγ9-Jγ12). She remains in cytological remission with stable low MRD positivity ($<10^{-4}$) now for ten months.

All the patients described here presented with relapsed or resistant ALL and received heterogeneous pre-treatment, including allogeneic hematopoietic stem cell transplantation in one patient. In these patients, an intensification of conventional chemotherapy was limited by the occurrence of severe myelosuppression. Therefore, an antileukemic agent with a different mechanism of action and without myelosuppressive effect was needed. Here, we show that the addition of rituximab to conventional salvage therapy was feasible and could lead to a cytological remission and reduction of MRD in patients with CD20 positive BCP-ALL (Table 1). Persistence of MRD in children with relapsed ALL has been shown to be of major prognostic impact for an unfavorable outcome.[7] Furthermore, the MRD status prior to allogeneic hematopoietic stem cell transplantation is known to be a strong predictor for subsequent relapse in these patients.[8] Therefore, MRD reduction is important for a more successful course after such transplants.[9] Thus, the determination of MRD kinetics in children with recurrent ALL may be used to initiate experimental approaches with monoclonal antibodies, such as rituximab for CD20 positive leukemia, early during the course of treatment in selected pediatric patients. Systematic prospective trials with larger series of patients will be required to confirm these preliminary results.

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