Malignant Lymphomas

The effects of rituximab treatment during pregnancy on a neonate

A 35-year old woman developed Burkitt´s lymphoma and was treated with rituximab and CHOP therapy early during pregnancy. Monitoring of rituximab concentrations and B-cell counts in the child revealed a transient complete B-cell depletion associated with high rituximab cord blood concentrations. B-cell recovery was fast, showing a regular immunophenotype without loss of CD20 antigen, no functional deficits and adequate vaccination IgG titers.

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Development of a malignant disease during pregnancy constitutes an exceptionally difficult situation for both the patient and the physician. Cytotoxic chemotherapy can result in multiple fetal abnormalities or spontaneous abortion especially if administered during the first trimester.[1-4] Administration of rituximab, a monoclonal anti-CD20 antibody, successfully used to treat B-cell lymphoma, may allow deferral of cytotoxic therapy but its safety profile in early pregnancy remains unknown.[5,6] We report the first data on rituximab concentrations and the subsequent impact of this drug on immune function in mother and child.

A 35-year old female was diagnosed with CD20$^+$ Burkitt´s lymphoma of the left breast in week 15 of pregnancy. The minimum stage was II$_E$A (hepatosplenomegaly suspicious but not proven by biopsy; no bone marrow involvement). In order to delay exposure of the fetus to antineoplastic drugs later into the second trimester of pregnancy, treatment was started in week 16 with four weekly infusions of rituximab (375 mg/m^2) and a minor response was documented by magnetic resonance imaging and ultrasound. Treatment was continued with four standard courses of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) at 3-week intervals followed by two courses of CHOP resulting in a complete remission in week 37. We did not use a methotrexate-containing regimen because of its known teratogenicity. No deviation from normal intrauterine development was registered in the child. In week 41 the patient delivered a healthy girl via cesarean section. By now, the 26-month old girl has been repeatedly seen by her pediatrician who reported completely normal growth and developmental status. The mother received high-dose therapy (BEAM) followed by autologous peripheral blood stem cell transplantation for consolidation 2 months after delivery and has remained in complete remission until now.

Serum levels of rituximab were measured by enzyme-linked immunosorbent assay (ELISA) as described earlier in two independent laboratories (Xendo Drug Development Services, Groningen, The Netherlands and Genentech, Basle, Switzerland).[7] Rituximab serum concentrations and lymphocyte counts of the mother and child were measured at birth, and at weeks +4 and +18 after delivery.

At the time of the birth, both the mother and child had very high serum levels of rituximab with a complete absence of B cells. The concentration of rituximab in the serum of the cord blood (32095 ng/mL) exceeded that in the mother's serum by three times (Table 1). There is so far little information about diaplancental transfer of monoclonal antibodies, but due to an active transport involving specific Fc-receptors at the placental barrier fetal concentrations of different physiological IgG types usually exceed maternal concentrations at full term.[8] As rituximab has a human IgG1/κ constant region, this mechanism might be involved in this case, too. Despite high rituximab concentrations in the neonate's blood, a fast B-cell recovery was seen during the weeks following birth. CD20 is expressed from pro-B-lymphocytes to adult B-cells, thus early B-cell precursors should not have been affected by rituximab treatment contributing to the fast B-cell recovery observed.[9,10] Up to the present age of 26 months, no overt infectious complications were reported for the child. IgG production in neonates begins subsequent to antigen contact after 4-6 months. Due to physiological hypogammaglobulinemia, the first 6 months after birth are the most vulnerable phase for bacterial infection. In our case, B-cell counts had been normalized by 4 months after birth and the period with low IgG might not have been longer than average.

Table 1. Lymphocyte counts and rituximab concentrations of the mother and child during pregnancy, at birth, and afterwards.

Time	*Mother*			*Child*		
week of pregnancy/ after delivery	*CD19$^+$ B-cells* (cells/μL)*	*CD3$^+$ T-cells† (cells/μL)*	*Rituximab serum level (ng/mL)*	*CD19$^+$ B-cells‡ (cells/μL)*	*CD3$^+$ T-cells§ (cells/μL)*	*Rituximab serum level (ng/mL)*
20	0	946	–	–	–	–
27	0	640	–	–	–	–
34	4	337	–	–	–	–
at birth	0	779	9750	0	93	32095
+4	0	759	–	70	6616	5399
+18	37	504	500	1460	5475	700

**normal range in adults: 120-400/μL; †normal range in adults: 1050- 1490/μL; ‡normal range in a child 3-6 months: 200-1100/μL; §normal range in a child 3-6 months: 1700-3600/μL.*

We conclude that a combination of immunotherapy and chemotherapy was safely administered during pregnancy without causing any malformation, developmental retardation or immune dysfunction in the child while producing a complete remission in the mother. These findings not only demonstrate an uneventful clinical

course after rituximab administration during pregnancy but also show that recovery from intrauterine B-cell depletion can be fast with no obvious long-term effects. Rituximab therapy is a viable option for deferring cytotoxic therapy early during pregnancy and might help to reduce the risk of fetal malformation or abortion.

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