Plasmaaustausch-Therapie in der Behandlung einer Rituximab induzierten progressiven multifokalen Leukencephalopathie (PML) - ein potentieller Ansatz in der Behandlung einer lebensbedrohlichen Nebenwirkung

C. A. Burchardt[1], S. Wienzek-Lischka[2], H. Hackstein[2], G. Bein[2] und M. J. Rummel[1]

[1] Abteilung Hämatologie, Med klinik 4/5, Universitätsklinikum Giessen, [2]Institut für Transfusionsmedizin, Universitätsklinikum Giessen

Background

PML is a rare opportunistic disease that is most commonly associated with acquired immunodeficiency syndrome and results from reactivation of latent JC polyoma virus (JCV). In 2009 Carson et al.[1] reported 57 cases after Rituximab (R) therapy in HIV negative patients. Meanwhile there exists a black box warning for PML and the use of R. No curative therapy for PML exists, treatment is mostly supportive. In Natalizumab induced PML removal of the drug via plasma exchange is an important part of the therapy. Here we report the first successful case of R removal with a plasma exchange therapy accompanied by our CDC - based assay (B cell cross match assay, Wienzek – Lischka et al[2]) for monitoring efficient R removal from patients plasma.

Methods

For monitoring anti-CD20 antibody concentration during plasmapheresis we established a method based on CDC-technique. Isolated B-cells and dilution series of patients (pts) serum (from undiluted up to 1:100000) were incubated on tersaki plates described in the following CDC-protocol. The same assay was carried out with a dilution series of rituximab solution in known concentration.

Complement dependent cytotoxicity test (CDC):

Lymphocytes from healthy volunteer blood donors were purified of whole blood samples using Ficoll-PaqueTM method. For separation of B cells we use a B cell purification kit (Rosette Sep, Stemcell Technologies, Grenoble, France). After isolation lymphocytes were incubated with at 56°C inactivated patient`s serum for 30 minutes. Complement was added for 60 min. After staining and fixation with Fluoroquench, positive or negative reactions can be distinguished.

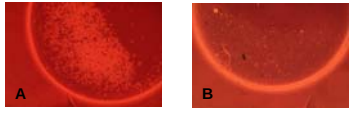

Fig.1A and B:
Complement dependent cytotoxicity test
viable B cells (*neg. reaction A)* and lysed B cells (*pos. reaction ,B)*

Case

A 70 year old white man with severe comorbid conditions (IDDM, small cell lung cancer in 2007, meningioma) and a history of marginal zone lymphoma (first diagnosed in 08/2003 and diagnosis of relapse in 04/2009) was admitted with diagnosis of a R induced PML to our department.

Case (continued)

From April 2009 to Sept 2010 he received 6 cycles of R-Bendamustine therapy (R 375 mg/m2 on day 1, Bendamustine 90 mg/m2 on day 1+2) and 4 cycles of R-maintenance therapy (375 mg/m2 each cycle, last administration Sept 2010). Patient achieved a good partial remission as demonstrated in a CT scan. Neurological symptoms first ocurred in November 2010. At this time, 6 weeks after the last R administration, he presented with paraparesis of the legs and paresis of the left arm. Corresponding demyelinaton signs were observed in MRI of the brain and backbone.

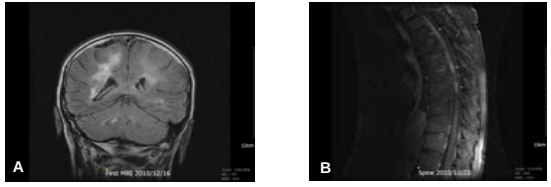

Fig. 2 A and B:
MRI before PE therapy (T2 Flair, A) and Spine (B)

PML diagnosis was supported by detection of JCV with polymerase chain reaction (PCR) in cerebrospinal fluid. Total WBC was normal (6.4 g/l), but severe lymphopenia (0.7 g/l) was observed. IgG, IgM and IgA levels were not measurable, B cells were not detectable, CD4-pos. lymphocyte count was low (99 /µl). We initiated therapy with Mefloquine because of its anti JCV activity (Brickelmaier et al.[3]) and with Mirtazapine as a hypothesized gate for JCV in glial cells (O´Hara et al.[4]). 100g of Intravenous Immunoglobulins were substituted. Because the R concentration was very high, we started PE therapy to remove R. Measurement of R level is routinely not available and no commercial kit for monitoring of a PE therapy exists. Therefore we used our CDC based assay to monitor R concentration in pts. serum. Pretreatment R level was 30.8 µg/ml, after 7th aphaeresis 6.15 µg/ml and at the end of PE therapy (14th aphaeresis) 1.83 µg/ml. Our findings obtained with CDC-based assay were in a good match with the test results from Roche International.

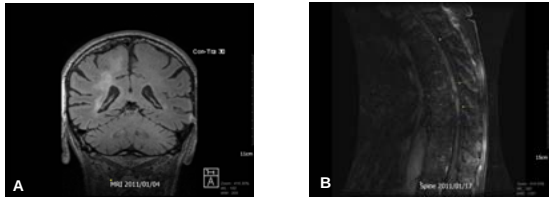

Fig. 3 A and B:
MRI after 7th Apheresis (A) and at the end (14th Apheresis) of PE therapy (B)

Case (continued)

Neurologic symptoms of the patient improved within first 2 weeks. MRI scans showed improvement of the lesions as well and JCV PCR in cerebrospinal fluid became negative. Lymphopenia disappeared and CD4 count increased up to 183 /µl. Patient was transferred into a rehabilitation program to improve his mobility and 4 weeks later he was discharged to home. Unfortunately, he died 2 weeks later due to pneumonia.

PE Therapy	Dilution of pts serum showing a positive reaction in B cell CDC	R serum concentration [µg/ml]	JC Virus PCR from cerebrospinal fluid	Lymphocytes [µl]	CD 4 + cells [µl]	IgG [g/l]
before PET	1 : 50	30,8	pos	960	99	< 1,6
7th PET	1 : 10	6,15	n. d.	1620	n. d.	2,2
14th PET	1 : 2	1,83	neg	1560	183	6,4

Tab. 1: Ritiximab serum concentrations, Dilution of pts. Serum and immunologic parameters during PE therapy

Conclusions

Rising use of R in hematologic malignancies (maintenance therapy in NHL e. g.) and chemotherapy induced immunosuppression is an increasing risk for development of PML. Bloomgren et al.[5] estimated an incidence of < 1/1000 up to 11/1000 for natalizumab treated pts depending on 3 risk factors:

- negative or positive anti JC virus antibodies before treatment
- use of immunosuppressants
- duration of treatment

For PML in pts with hematologic disorders and R treatment these data do not exist. In our ongoing Stil (Study group indolent lymphomas) NHL 07 2008 (MAINTAIN) trial we found an PML incidence of 2,44/1000 during induction treatment with 6 cycles of R-Bendamustine (unpublished data). Until today the only effective therapy for PML is immune reconstitution.

- To accelerate immunoresponse, rapid elimination of R with PE therapy appears as a new additional and useful tool and warrants further investigation.
- Therefore StiL is going to initiate a PML Registry for pts with hematologic disorders.
- Our CDC dependent assay is a rapid and immediate available method for monitoring PE therapy of pts with serious adverse events of R treatment.

References

[1]Carson et al., Blood, 14 May 2009, Vol. 113, Nr. 20
[2]Wienzek-Lischka et al., Abstract 41, DGI 2011
[3]Brickelmaier et al., Mult Sclerosis 2008; 14: Suppl 1: S44, abstr.
[4]O´Hara et al., Virus Res 2008; 132: 97-103
[5]Bloomgren et al., NEJM 2012, 366: 870-80

Contact information: alexander.burchardt@innere.med.uni-giessen.de or + 49 641 985 42651

Disclosure Information: C. A. B.: Honoraria from Roche and Mundipharma
M. J. R.: Honoraria, Advisory Role and Financing of Scientific Research from Roche and Mundipharma