

Intraventricular treatment of relapsed central nervous system lymphoma with the anti-CD20 antibody rituximab

Most patients with primary central nervous system (CNS) lymphoma or systemic non-Hodgkin's lymphoma (NHL) involving the CNS relapse after an initial response to treatment, often presenting with leptomeningeal disease.¹ Since the majority of these lymphomas are B-cell neoplasms expressing the CD20 surface antigen treatment with the chimeric monoclonal antibody (Mab) rituximab might be a new therapeutic option.²⁻⁴ Here, we report on 6 patients with relapsed CNS B-cell lymphoma who were treated with intraventricular or intrathecal applications of rituximab. One of these cases has already been reported.⁵

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The primary objective of these individual case studies was to evaluate the feasibility and safety of intraventricular administration of rituximab. Treatment was not uniform since the dose of rituximab was intensified during the course of treatment (Table 1). From a pharmacological point of view the intraventricular route of administering rituximab might be superior to the intrathecal route. However, ethically the implantation of an Ommaya reservoir for an experimental individual therapy would have been unjustifiable. Therefore we gave intraventricular treatment to those patients who had an Ommaya reservoir implantation in accordance with a recently reported new treatment protocol for primary CNS lymphoma.⁶ In order to define the most effective but tolerable single dose, intraventricular injections of 10-40 mg rituximab in a volume of 1-4 mL were administered over two minutes via

an Ommaya reservoir or intrathecally. Before administration of intraventricular rituximab an equivalent volume of cerebrospinal fluid (CSF) was removed. Drug clearance from the CSF was determined in 4 patients by measuring rituximab levels in the CSF and blood by ELISA after intraventricular administration. Patients were closely monitored immediately following drug administration and daily until the end of therapy. Neurotoxicity was evaluated using the National Cancer Institute common toxicity criteria and Minimal-Mental Status examination. Informed consent was provided according to the Declaration of Helsinki.

Four patients with primary CNS lymphoma and two with systemic NHL and cerebral involvement were treated. Two patients received both intravenous and intraventricular rituximab, the other four patients received intraventricular (n=2) or intrathecal (n=2) treatment only (Table 1). Four patients suffered from leptomeningeal lymphoma involvement established by leptomeningeal gadolinium enhancement in MRI (n=1) or malignant cells in the CSF (n=3). Intraventricular rituximab was efficient in patients with leptomeningeal lymphoma. Total clearance of malignant cells in the CSF was proven histologically in patients with previously detectable malignant cells in this site (patients # 1, 2 and 6). Leptomeningeal lymphoma nodules disappeared following intraventricular rituximab treatment in patient # 5 (Figure 1). However, solid parenchymal lymphomas progressed (patients #1 and 4) or showed were only a minor response (patient #3).

As reported for cynomolgus monkeys and patients with CNS lymphoma who were treated with intravenous rituximab,^{4,7,8} monoclonal antibody levels in the CSF of patients #1 and 3 in our study reached 1% or less of the corresponding rituximab serum concentrations (Table 1). The potential efficacy of intravenous rituximab in CNS tumors seems to be limited. Maximal CSF concentrations of up 460 to 1550 µg/mL observed within two hours of intrathecal administration in

Table 1. Patients' characteristics, treatment and response to intraventricular rituximab.

| Age | Disease | Treatment | Max. CSF concentrations Post i.v. Ritux. | Max. CSF concentrations post i.vent Rituximab | Side effects | Response | |
|-----|---------|--|--|--|------------------------|---|--|
| 1 | 66 | PCNSL + meningeal involvement | 1×375mg/m ² weekly×2w rituximab i.v. 2×10-40 mg weekly×2w rituximab i.vent. | 0.38µg/ | 10 µg/mL (after 24h) | nausea chills, hypotension NCI Grade I | Total clearing of meningeal tumor cells; parenchymal progress |
| 2 | 62 | PCNSL + meningeal involvement | 1×10mg weekly ×4w rituximab i.th | n.d. | n.d. | – | Total clearing of meningeal tumor cells |
| 3 | 33 | DLBCL with cerebral metastasis | 1×375mg/ m ² weekly×2w rituximab i.v. 2×25-30 mg weekly×5w rituximab i.vent. | not detectable | 2.9µg/mL (after 48h) | – | Minor parenchymal response |
| 4 | 66 | PCNSL | 3×25-30mg weekly ×2w rituximab i.vent. | n.d. | 35.4 µg/mL (after 24h) | – | Parenchymal progress |
| 5 | 70 | PCNSL + meningeal involvement | 3×25-35mg weekly×3w rituximab i.vent. | n.d. | 1.9 µg/mL (after 48h) | – | Complete remission of leptomeningeal involvement |
| 6 | 30 | Burkitt's lymphoma + meningeal involvement | 2×25mg weekly×1w; 3×25 mg weekly×2w rituximab i.th. | n.d. | n.d. | Severe pain attack, paraparesis NCI Grade III | Total clearing of meningeal tumor cells for 4 weeks |

CSF measurements were done 24h and 48 h after administration of rituximab. n.d. not done; PCNSL: primary central nervous system lymphoma; DLBCL: diffuse large B-cell lymphoma w week; i.v.: intravenous; i.vent.: intraventricular via an Ommaya reservoir; i.th.: intrathecal.

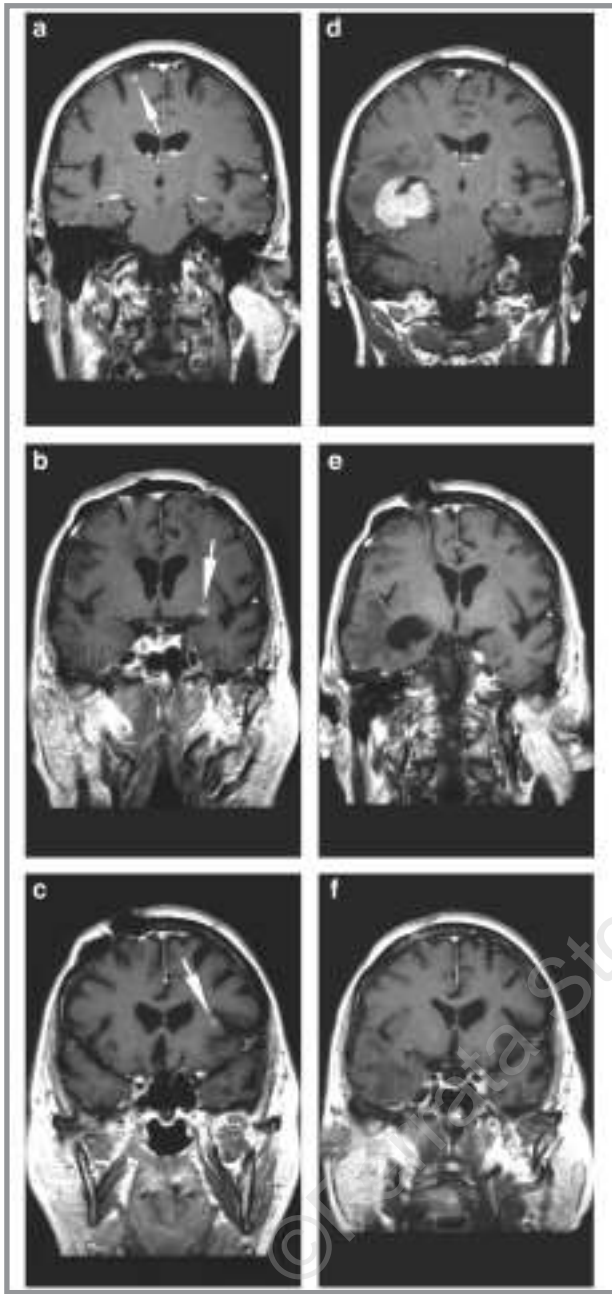


Figure 1. T1-weighted MRI with gadolinium before (a-c) and after (d-f) intraventricular rituximab treatment. Arrows point to leptomeningeal lymphoma nodules. An extensive parenchymal lymphoma relapse occurred after treatment (d-f).

cynomolgus monkeys⁸ suggest rapid drug clearance of rituximab from the CSF (Table 1). To improve and sustain the therapeutic efficacy of rituximab in CNS lymphomas, higher continuous concentrations in the CSF might be necessary. The maximal CSF concentrations observed in our patients are given in Table 1. Systemic use of rituximab was omitted due to the low rituximab levels reached in the CSF (in patients #1 and 3). Reversible side effects such as nausea and chills were observed immediately after intraventricular administration of 40 mg rituximab in patient #1. In patient #6 the levels of

malignant lymphoma cells increased from 210 to 920 cells/ μ L under intrathecal treatment with 50mg Ara-C thrice weekly. Following two intrathecal applications of rituximab of 25 mg in one week, there was a sustained clearance of lymphoma cells in the CSF. This patient suffered severe back pain and paraparesis during the first intrathecal application of rituximab, but these symptoms resolved fully within four hours. Acute neurotoxicity was probably related to a high tumor cell burden in the CSF and rapid tumor cell lysis after administration of rituximab.⁹ No further neurotoxicity was recorded in the remaining five patients. Mini-Mental Status examination remained stable in all patients. Overall survival ranged from two to 14 months (4,10,12,18,14, and 2 months). Time to progression was between two and 16 weeks (8, 16, 12, 2, 6, and 6 weeks).

These data suggest that intraventricular application of rituximab may have a role in the treatment of leptomeningeal disease in patients with CNS lymphoma. Future studies should investigate dose intensification of intraventricular rituximab treatment, the pharmacokinetics of this monoclonal antibody as well as combination with other chemotherapeutic drugs or radiotherapy.

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References

- McAllister LD. Primary central nervous system lymphoma: a review. *Curr Neurol Neurosci Rep* 2002; 2:210-5.
- Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma: clinical presentation, pathological classification, molecular pathogenesis and treatment. *J Neurol Sci* 2000;181:1-12.5.
- Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. *Ann Oncol* 2003; 14:520-35.
- Ruhstaller TW, Amsler U, Cerny T. Rituximab: active treatment of central nervous system involvement by non-Hodgkin's lymphoma? *Ann Oncol* 2000;11:374-5.
- Pels H, Schulz H, Mancke O, Hom E, Thall A, Engert A. Intraventricular and intravenous treatment of a patient with refractory primary CNS lymphoma using rituximab. *J Neurooncol* 2002;59:213-6.
- Pels H, Schmidt-Wolf IG, Glasmacher A, Schulz H, Engert A, Diehl V, et al. Primary CNS lymphoma: results of a pilot/phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol* 2003;21:4489-95.
- Harjunpaa A, Wiklund T, Collan J, Janes R, Rosenberg J, Lee D, et al. Complement activation in circulation and central nervous system after rituximab (anti-CD20) treatment of B-cell lymphoma. *Leuk Lymphoma* 2001;42:731-8.
- Rubenstein JL, Combs D, Rosenberg J, Levy A, McDermott M, Damon L, et al. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. *Blood* 2003; 101:466-8.
- Winkler U, Jensen M, Mancke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217-24.