A patient with relapsed B cell non-Hodgkin lymphoma (NHL) infiltrating the Central nervous system (CNS) and resistant to chemotherapy was treated with intrathecal Rituximab (IT RTX), administered weekly for eight weeks at increasing doses, from 10 to 40 mg. After the second administration the patient showed significant clinical improvement and Cerebro spinal fluid (CSF) clearance of lymphomatous cells. A MRI scan performed after 30 days from the start of therapy showed full regression of lymphomatous infiltration. This report confirms the efficacy and safety of IT RTX in the treatment of CNS B-cell NHL.

**Keywords** Intrathecal Rituximab · Leptomeningeal lymphoma

**Introduction**

In patients with non-Hodgkin lymphoma (NHL), involvement of the central nervous system (CNS) is associated with adverse outcome [1]. The majority of NHLs, which involve the CNS, are B-cell lymphomas, which express the CD20-antigen [2]. Rituximab (RTX) is a chimeric monoclonal antibody against the B-cell specific CD20-antigen that has proven highly effective in the treatment of B-cell NHL [3]. When administered intravenously, RTX concentrations in the Cerebro spinal fluid (CSF) are very low and they are not increased significantly upon repeated intravenous (IV) administration [4]. Experimental preclinical models showed the safety of RTX administered into the CSF and have encouraged the intrathecal (IT) use of the drug in NHL with CNS infiltration [5]. However, the clinical experience reported so far is very limited [6–8].

**Clinical case**

A 30-year-old female with primary large B cell-NHL was diagnosed at our Institution in January 2005. The tumor involved the mediastinum with a bulky mass (>10 cm) infiltrating the pericardium, the right axillary nodes and the celiac tripod nodes (3 cm). Repeated bone-marrow biopsies and cytological examination of the CSF were negative. LDH level was over the upper limits. The ECOG performance status was 2 and the International Prognostic Index (IPI) score was 3. After a full course of chemotherapy according to the MACOP-B protocol (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), CT scan and PET-scan showed the complete regression of the tumor mass. The patient was then treated with intensification field radiotherapy consisting of fractionated 3600 cGy.
In August 2005 she was re-admitted with headache, facial paraesthesias, and leg weakness. Neurological examination showed bilateral trigeminal neuropathy, Lasegue sign, motor and sensory involvement of lumbo-sacral roots. MRI-Contrast-enhanced T1-weighted images showed bilateral thickening and enhancement of the trigeminal nerves, vestibule-cochlear nerves and lumbo-sacral roots. CSF examination showed the presence of 200 cell/μl represented by large lymphoid blasts CD20+/CD79a+ and small CD20 negative lymphocytes and monocytes. Total body CT-scan and bone marrow biopsy were normal.

The patient was treated according to the MAIT schedule with eight IT courses of Cytosine-Arabinoside (ARA-C) (40 mg) plus Methotrexate (MTX) (12 mg) and methylprednisolone (40 mg), (twice a week), and two courses of IV ARA-C (3 gr/sm) every 28 days. The neurological picture remained unchanged, and CSF, although showing significant cell reduction, disclosed persistence of lymphoma cells (>40 cells/μl). In October 2005 the patient presented a bilateral facial nerve paralysis and persisting signs of trigeminal and lumbo-sacral root involvement. MRI scan showed a contrast enhanced thickening of both trigeminal nerves and contrast-enhanced hyperintensity within the fundus of both internal auditory canals (Fig. 1). There was no evidence of complete or relative cranio-cervical junction blockade. CSF examination showed 80 cells/μl represented by lymphoid blasts.

By the end of October 2005, the patient gave her informed consent to start weekly IT RTX, administered through intralumbar route, according to the following schedule: starting dose 10 mg (2.5 mg/ml), 2nd dose 20 mg, 3rd dose 30 mg, 4th dose 40 mg. RTX was administered in 2 min infusions.

The patient showed no relevant side effect after RTX infusion up to the dosage of 30 mg. After the 40 mg infusion she experienced headache, cramps, severe back pain and leg weakness, which were successfully treated with anti-histaminic, dexamethasone and morphine. Because of this reaction, 30 mg was considered the maximum tolerated dose, and four more such doses were given. Neurological picture started to ameliorate after the second RTX infusion, while cytological examination of the CSF carried out 7 days after the second RTX showed a complete clearance of lymphoma cells (cells = 1/μl). The patient was also given a course of intravenous MTX 3 gr/m², administered on day 3 after the third infusion of IT RTX and repeated after 21 days. A MRI scan performed by the end of November 2005 showed full regression of lymphoma infiltration (Fig. 2).

The patient was subsequently treated with two cycles of chemotherapy according to the IEV schedule (ifosfamide, etoposide, epirubicin) followed by autologous peripheral stem cells transplantation in February 2006. At the last follow-up, in April 2006, she was in complete clinical remission, while brain and spinal MRI-scan, total-body CT-scan and CSF analysis were normal.

**Discussion**

We provide here further evidence that IT RTX is effective and safe in therapy of large B-cell NHL with CNS infiltration. The patient here described received such therapy for CNS relapse of large B-cell NHL with multiple cranial, lumbo-sacral and leptomeningeal involvement. While systemic and IT salvage chemotherapy with ARA-C and MTX were ineffective, treatment with IT RTX resulted in remarkable improvement of neurological symptoms and signs, changes of MRI picture and cellular clearance of CSF.