J Neurol
DOI 10.1007/s00415-011-6190-y

LETTER TO THE EDITORS

Acute painful lumbosacral paresthesia after intrathecal rituximab

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Received: 18 May 2011 / Revised: 11 July 2011 / Accepted: 14 July 2011

Dear Sirs,

Central nervous system (CNS) recurrence of systemic aggressive B-cell lymphoma carries poor prognosis with median survival of 2–4 months and less than 10% 1-year survival after treatment with standard-dose chemotherapy and/or radiotherapy [1, 2]. Aiming to improve on these treatment results, we designed a phase II study to evaluate an intensive protocol including myeloablative treatment in CNS recurrence of systemic B-cell non-Hodgkin's lymphoma (NHL). This study (HOVON 80, Netherlands Trial Register, no. 1757) is an ongoing phase II study on the feasibility and efficacy of R-DHAP + HD-MTX (dexamethasone 40 mg days 1–4, cisplatin 100 mg/m^2 day 1, cytarabine 2 × 2 g/m^2 day 2, rituximab 375 mg/m^2 day 5, methotrexate 3 g/m^2 day 15), followed by autologous stem cell transplantation in patients with recurrent aggressive B-cell lymphoma with CNS localization. Rituximab is a chimeric anti-CD-20 antibody which has radically changed prospects for patients with systemic B-cell lymphoma [3, 4]. However, after intravenous administration it does not penetrate the blood–brain barrier well, and it has been postulated that intrathecal administration may improve results of treatment of leptomeningeal lymphoma [5, 6]. We therefore incorporated intrathecal rituximab into the protocol.

The patients we report herein were all treated according to protocol with systemic R-DHAP-MTX as described above, for three 28-day cycles. Additionally, intrathecal rituximab, containing no preservatives and without concurrent other agents, was administered via lumbar puncture after premedication with paracetamol 1,000 mg on days −1, 4, 8, 11, and 21 in the first cycle, four times in the second cycle, and three times in the third cycle. The first administration in each patient consisted of 10 mg rituximab; in subsequent administrations the dose was increased to 25 mg provided no toxicity had occurred. This dosing was based on prior publications [7, 8]. None of our patients experienced side-effects after the first intrathecal administration of rituximab, except for a minor sensation of pressure in the sacral area in one patient. However, after the first administration of 25 mg rituximab, 2 of the first 12 treated patients reported extremely painful paresthesia in the buttocks, legs, and feet immediately after administration, lasting 30–60 min. There were no neurologic deficits at the time, nor on follow-up, but blood pressure increased temporarily. After these adverse events the protocol was amended to dilution of rituximab in 0.9% saline to 5 mg/ml and additional premedication with antihistamines. The subsequently treated, 13th, patient suffered identical symptoms despite

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Published online: 10 August 2011

Table 1 Clinical characteristics of affected patients

Patient	1	2	3
Age (years)	49	48	58
CSF cellularity before i.t. rituximab	16×10^6/l	0.7×10^6/l	8.7×10^6/l
CSF lymphoma by cytology and/or flow cytometry	+	–	Not available/unevaluable
CSF cellularity after i.t. rituximab (4 days)	5×10^6/l	1.7×10^6/l	Not done
Best result of treatment	CRu	CR	CRu
Survival after AE (months)	8	>26	5.5

CRu Complete response unconfirmed, *CR* complete response, *CSF* cerebrospinal fluid, *AE* adverse event

the adapted protocol. Clinical characteristics of the patients are given in Table 1. The pain resolved completely in all patients within a few hours. However, they all refused further treatment with intrathecal rituximab, and further intrathecal therapy was changed to methotrexate, which was administered uneventfully. The rituximab dose in the protocol was subsequently reduced to 10 mg per administration, diluted as described above and combined with 4 mg intrathecal dexamethasone. Twelve additional patients were thus treated, and no further incidents of painful radiculopathy have occurred.

In a phase I study investigating intraventricular/intrathecal rituximab, the maximum tolerated dose was found to be 25 mg; at 50 mg, grade III hypertension was the dose-limiting toxicity and one of two patients thus treated additionally experienced transient diplopia, nausea, and vomiting [7]. A painful radiculopathy was described after intrathecal administration of 25 mg via lumbar puncture in one patient; the majority, however, had been treated intraventricularly. Antonini described one patient treated with 40 mg intrathecal rituximab in whom transient headache, cramps, back pain, and leg weakness occurred [9]. Schulz described six patients treated with 10–40 mg undiluted intra-CSF rituximab for CNS lymphoma, two of them via lumbar puncture; one of them suffered transient severe back pain and paraparesis during the first intrathecal administration of rituximab (25 mg) [8]. In this patient a high tumor load was present in the CSF and the authors assumed a tumor lysis syndrome. However, in none of our patients was high CSF cellularity present, making tumor lysis an unlikely explanation.

Both acute and subacute toxicities have been observed after intrathecal treatment with chemotherapeutic agents [10–13]. For methotrexate as well as (sustained-release) cytarabine an acute, reversible aseptic meningitis with fever, headache, backache, nausea, and vomiting has been described. Symptoms begin several hours after administration and can be prevented with oral or intrathecal dexamethasone in the majority of patients [10, 11]. An inflammatory reaction is a likely cause for the aseptic meningitis after methotrexate and cytarabine, but in rituximab the occurrence during or immediately after administration make an inflammatory reaction unlikely. We postulate a direct interaction with spinal nervous structures (radices?) as the most likely explanation for this adverse reaction to rituximab.

This very painful, though completely transient, adverse effect of intrathecal rituximab precludes intrathecal administration of higher doses via lumbar puncture. It has not been described after intraventricular administration, despite the fact that considerably more patients have been treated with rituximab via this route.

Acknowledgments The rituximab used in the study was provided free of charge by Roche. Financial support for the HOVON 80 study was obtained from the Dutch Cancer Society, project no. 2006-11. J.K.D. reports receiving travel grants from Roche.

Conflicts of interest Dr. Bromberg reports no conflicts of interest other than the above. Dr. Baars reports no conflicts of interest. Dr.van Imhoff reports no conflicts of interest. Dr.Enting reports no conflicts of interest. Dr. van den Bent has performed consultancy services for Roche.

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