Rapid complete response using intrathecal rituximab in a patient with leptomeningeal lymphomatosis due to mantle cell lymphoma

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Mantle cell lymphoma (MCL) is a B-cell lymphoid tumor that expresses CD20 and is associated with a poor prognosis. Central nervous system involvement has been associated with particularly dismal outcome. We report a 62-year-old male with MCL and meningeal lymphomatosis. The patient was treated with intrathecal rituximab (IT-R) 25 mg every third day for five doses with clearance of tumor after the third dose. Systemic therapy consisted of R-HyperCVAD alternating with rituximab, high-dose methotrexate, and cytarabine every 21 days, with IT-R on day 1 of each chemotherapy cycle. The patient was consolidated with an autologous stem cell transplant and remains in remission 23 months later. The use of IT-R and conventional intrathecal chemotherapy in MCLs is discussed here. *Anti-Cancer Drugs* 19:917–920 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Mantle cell lymphoma (MCL) is a lymphoid tumor that arises in the follicular mantle zone with characteristic features of expression of pan B-cell markers (CD19, CD20, and CD22), T-cell marker CD5, overexpression of bcl-1, and a *t*(11;14).There are two histologic presentations according to WHO classification: classic variant, which is composed of a homogeneous population of small-to-medium cells with scanty cytoplasm, variable irregular nuclei, and low proliferation index, and the blastoid or blastic variant [1]. The overall survival is poor in classic MCL [2–7] and even worse in the blastic variant [3,8].

The incidence of central nervous system (CNS) or leptomeningeal (LM) involvement is highly dependent on the histology. Bollen *et al.* analyzed the risk of CNS involvement and observed that it was higher in high-grade and intermediate non-Hodgkin lymphoma (NHL) than low-grade NHL [9]. The incidence of CNS involvement at presentation of MCL ranges from 1.6 to 11% [2,8,10,11]. CNS involvement at diagnosis in the blastic variant has been reported in 6% of cases [8]. Most series report that the incidence of CNS involvement increases over time [10–14]. The survival in patients affected by CNS/LM involvement is dismal despite intensive treatment with local and/or systemic therapy [10–13].

We present a male patient with blastic variant MCL and LM lymphomatosis. He was treated using intrathecal rituximab (IT-R) and systemic chemotherapy plus rituximab.

Case report

On June 2005, a 62-year-old male presented with generalized adenopathy, hepatomegaly, splenomegaly and drenching night sweats, and weight lost (6 kg in 2 months). Biopsy of an inguinal node showed blastic variant MCL, confirmed by immunohistochemistry (CD5+, CD20+, CD19+, Cyclin D1+, bcl-2+, bcl-6–, and CD10–). He was in stage IV with hepatic and bone marrow involvement, and also had leukemic cells detected in peripheral blood by flow cytometry. Upper and lower endoscopy were negative. Lactate dehydrogenase was elevated (560 IU/l, upper limit of normal: 190 IU/l) and β-2-microglobulin was 5 ng/dl (upper limit of normal: 1.9 ng/dl). Because of persistent headaches, he underwent a head computed tomography scan and a lumbar puncture. The scan was normal. The cerebrospinal fluid (CSF) protein level was elevated and atypical mononuclear cells were reported (200 cell/μl); those cells were confirmed as lymphoid and positive for CD5, CD20, CD19, lambda light chain restricted, and negative for CD23, CD10, and CD3 (Fig. 1a). The patient was treated on a protocol using IT-R in aggressive

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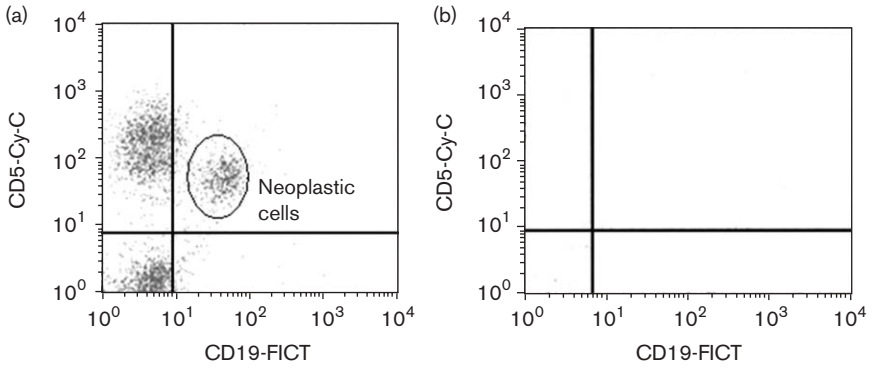
Fig. 1



Flow cytometry before and after treatment with intrathecal rituximab (IT-R) in a patient with leptomeningeal involvement in mantle cell lymphoma (MCL). (a) Before treatment. Detection in cerebrospinal fluid of neoplastic cells positive for CD19 and CD5, by flow cytometry. They were CD20 positive and light chain restricted and negative to CD10 and CD23 compatible with MCL (not shown). (b) After treatment. The liquor was analyzed using the same antibodies panel at diagnoses (CD19/CD5, CD23, CD10, CD20) after three doses of IT-R. The flow cytometry analysis was done before the third dose of IT-R (25 mg).

Table 1 Outcomes after treatment with IT-R in primary/secondary aggressive lymphoma

Author	Number of cases	Histological diagnostic	Site of disease/number of cases	Site of best response: (% CR)	Type of therapy	Survival median (ranges) in months
Rubenstein *et al.* [18]	10	Primary/secondary DLBCL	Parenchyma + LC/5	LC: 6/9 (66.7)	Rituximab	CR: 14.25 (9–33.5)
		Relapsed/refractory	Parenchyma alone/1 LC alone/4	Parenchyma: 1/6 (16.7)	Phase I 10–50 mg	PR: 2 (0.27–5.25) Failure: 0.71 (0.32–1.1)
Antonini *et al.* [16]	1	Secondary	Cranial/peripheral nerves + LC	LC: 1/1 (100)	Rituximab	
		DLBCL		Peripheral nerve: 1/1 (100)	10–40 mg	6 (alive)
		Relapsed				
Schulz *et al.* [17]	6	Primary/Secondary DLBCL	Parenchyma + LC/3	LC: 4/4 (100)	Rituximab	11 (2–18)
		Relapsed/refractory	Parenchyma alone/2 LC alone/1	Parenchyma: 0/5 (0)	10–40 mg	
Present case	1	Secondary MCL At initial diagnosis	LC/1	LC: 1/1 (100)	Rituximab 25 mg	23 (alive)

Twelve (75%) of 16 patients affected in leptomeningeal compartment achieved a complete response after treatment with rituximab (doses commonly used range from 25 to 30 mg).
CR, complete response; DLBCL, diffuse large B-cell lymphoma; IT-R, intrathecal rituximab; LC, leptomeningeal compartment; MCL, mantle cell lymphoma; PR, partial response.

lymphoma. He went on to receive two more doses as treatment (25 mg) with IT-R (three doses in total). Follow-up flow cytometry of the CSF was negative for malignant cells with only a few T-cells (29% CD4 + and 71% CD8 +) detected (Fig. 1b). Two additional doses were delivered after tumor clearance. The IT-R treatment was complicated by severe neuropathic pain, which decreased over the course of treatment.

The patient received systemic chemotherapy with R-HyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating each 21 days with high-dose methotrexate, cytarabine and systemic rituximab, and IT-R consolidation on day 1 of each cycle. The patient achieved a systemic complete systemic response confirmed by computed tomography scan, positron emission tomography scan, bone marrow biopsy, and normal laboratory values. He was consolidated with an autologous peripheral blood stem cell transplant. He remains in complete remission 25 months after completion of therapy.

Discussion

We present a patient with MCL who had LM involvement at diagnosis. Conventional chemotherapy with methotrexate, cytarabine, and/or steroids has been associated with poor outcome with a median survival of less than 5 months in some series [2,10–12]. Therefore, the use of IT-R has been explored as an alternative therapy.

CNS and/or leptomeningeal compartment (LC) involvement in MCL is uncommon. Ferrer *et al.* [10] observed it in only 1.6% cases at diagnosis and Segal *et al.* [2] observed it in 7%. Valdez *et al.* [11] reported a much higher incidence (10 of 25 patients, i.e., 40%) of CNS involvement, but this may reflect selection bias as only the 25 patients (of 108) with CSF samples were included. Interpretation of incidence figures is further complicated by the lack of immunohistochemical confirmation of CNS involvement [2,10,12]. Hedge *et al.* [14] reported that among 51 patients newly diagnosed with aggressive lymphoma, 22% had occult CSF involvement (11 detected by flow cytometry and only one by morphology) . The actuarial risk of CNS/LC involvement has been estimated at 5 years in 26% (CI 95%: 10–42%) [10]. CNS involvement was more frequent in relapsed/refractory disease, blastic histology, Ki-67 expression over 50%, high lactate dehydrogenase, intermediate and high-risk international prognostic index, leukemic phase, and two or more extranodal sites [2,10–13].

The outcome of treatment in different series using conventional IT-chemotherapy (methotrexate and/or cytarabine and/or steroids) is dismal [2,10–13]. Of thirteen patients only two achieved a complete remission (survival: 19 and 24 months), with one of them later dying of relapse after autologous transplant [2,11]. The remaining patients had a median survival of less than 5 months [10–13].

The patient presented here had almost all high-risk features of CNS involvement including blastic histology, high lactate dehydrogenase, high-risk international prognostic index, leukemic phase, and more than two extranodal sites. Because of the poor results with conventional chemotherapy, the patient was treated with IT-R. Rituximab is a chimeric monoclonal antibody directed against CD20. It is used as part of the systemic therapy of patients with NHL. The initial studies using IT-R in animal models showed it was feasible and safe [15]. IT-R use has been reported in humans with primary or secondary CNS involvement by diffuse large B-cell lymphoma [16,17]. Rubenstein conducted a phase I study using IT-R for primary/secondary CNS/LC involvement in diffuse large B-cell lymphoma and/or intraocular lymphoma [18]. One of its mechanisms of action is by complement-dependent cytotoxity [19]. There are some reports in the literature supporting that rituximab cannot effectively cross the blood–brain barrier [20,21]. However, the CNS has cells capable of synthesizing complement proteins, allowing the drug to exert its therapeutic effect [22]. In fact, after the administration of systemic rituximab, complement activation can be detected in the CSF (more dramatically, if there is damage to the blood–brain barrier and in older individuals) [20,23,24].

The optimal dose of IT-R has been studied by Rubenstein *et al.* [18]. Unfortunately, this patient was treated before this data was available. We selected 25 mg based on data published by the German group [16]. Schulz *et al.* observed more side effects when using doses over 30 mg, including the occurrence of neuropathic pain. This may be related to complement activation in the LM compartment.

This patient received his CNS therapy before systemic therapy. IT-R produced a rapid response before systemic treatment, but it is likely that the systemic therapy, including his autologous transplant, was important in consolidation of the response.

This is the first report describing the use of IT-R for the treatment of LM lymphomatosis in MCL. The experience with using IT-R in lymphoma is presented in the Table 1. Seventy-five percent of this group achieved a complete response.

We conclude that IT-R was safe and effective in treating LM lymphomatosis due to MCL in this patient. This approach may warrant further evaluation in a prospective clinical trial.

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