

## SHORT COMMUNICATION

## Intralesional Rituximab Treatment for Primary Cutaneous B-cell Lymphoma: Nine Finnish Cases

Liisa Väkevä, Annamari Ranki and Tarja Mälkönen

Department of Dermatology, Allergology and Venereal Diseases, University of Helsinki and Helsinki University Central Hospital, Center of Inflammation, Skin and Allergy Hospital, Meilahdentie 2, FIN-00250 Helsinki University Central Hospital, Helsinki, Finland. E-mail: liisa.vakeva@hus.fi

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Primary cutaneous B-cell lymphomas (PCBCL) are rare skin-defined non-Hodgkin lymphomas with no extracutaneous involvement at the time of diagnosis. They are classified into 3 major entities in the 2008 WHO-EORTC joint classification (1). These 3 most common types include primary cutaneous follicle centre lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT). PCBCL constitute approximately 25% of all skin lymphomas. It is important to distinguish between PCBCL and systemic B-cell lymphomas with skin involvement, since most PCBCL are low-grade malignancies with a 5-year survival of up to 95–99% (2).

The current treatment options for PCBCL (besides local treatments, e.g. topical corticosteroids, nitrogen mustard, bexarotene) include radiotherapy, surgical excision, chemotherapy, interferon- $\alpha$  and monoclonal antibodies (3–5). For aggressive forms, polychemotherapy is used.

Rituximab is a chimeric monoclonal immunoglobulin G antibody targeting CD20, which is expressed on normal and tumour B cells (6). Intravenous rituximab is commonly used in systemic low-grade B-cell non-Hodgkin lymphomas (7), whereas intralesional rituximab is being increasingly used as an alternative to conventional treatments (radiation or surgery) (5). No randomized studies are available on the efficacy of intralesional rituximab treatment, but there are some reports of the effect of intralesional rituximab in PCBL (8–15).

## PATIENTS AND METHODS

Of the 9 patients, 5 were male and 4 female. The mean age at diagnosis was 58 years. Three patients had PCMZL and 6 had PCFCL, confirmed by histology and immunohistology performed at the Dermatopathology Unit of Helsinki University Central Hospital

at the time of diagnosis. None of the patients had signs of lymph node or systemic involvement, based on computed tomography (CT). According to the ISCL/EORTC proposal on tumour-node-metastasis (TNM) classification of cutaneous lymphomas other than mycosis fungoides/Sézary syndrome, our cases varied in classes T1a–T2a, N0M0 (16). In all cases CD20 staining was positive and Bcl-2 was positive in marginal zone lymphoma-lesion patients. An immunoglobulin lambda gene clonal proliferation was confirmed in all of the patients with marginal zone lymphoma.

The basic treatment protocol was to inject 2 ml rituximab (Mabthera (10 mg/ml, Genetech Inc, Oseaside, USA)) intralesionally 3 times for a week for 4 weeks. This treatment schedule was modified in some cases, as described in the results section. With increased experience, we added pre-injectational paracetamol prophylaxis to the protocol. We followed each patient from the time of diagnosis until 28 Feb 2015.

## RESULTS

Nine patients with multiple cutaneous lesions or multiple cutaneous locations of PCBCL during 2008 to 2014 were treated with intralesional rituximab. Six patients had a solitary lesion. The most common therapy prior to intralesional rituximab was surgery, which 5 patients had undergone (Table I).

Six patients received only one rituximab treatment cycle, and 3 patient received multiple cycles. Primarily, all patients achieved complete response (CR) with intralesional rituximab. If re-treatment was needed, it was as successful as primary treatment. Follow-up time varied from 6 months to 8 years. The mean follow-up time was 4.1 years. Until the end of follow-up period 5 out of 9 patients had experienced relapse. In all patients relapses occurred in the same anatomical location as the primary lesion(s). The time to relapse after treatment is shown in Table I.

Table I. Main characteristics of patients with primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle centre lymphoma (PCFCL)

Sex/age, years	Type/stage	Previous treatment	Cycles	Cumulative dose, mg	Lesions	n	Localization	Response	Relapse/time after treatment, months	Total follow-up time, years
M/64	PCMZL/T1a	S+R	3	360	3		Thigh	CR	Yes/5–25	8.3
F/63	PCFCL/T2a	S	2	344	1		Neck/back	CR	Yes/34	8.0
M/19	PCFCL/T2a	S+R	4	155	4		Head	CR	Yes/6–18	1.7
M/66	PCMZL/T2a	None	1	600	3		Upper arm	CR <sup>a</sup>	Yes/11	6.3
F/52	PCFCL/T1a	None	1	147	1		Torso	CR	No	3.2
M/71	PCMZL/T1a	S	1	240	1		Shoulder/neck	CR	Yes/24	6.25
F/71	PCFCL/T1a	S	1	275	1		Back	CR	No	1.7
M/41	PCFCL/T1a	None	1	120	1		Head	CR	No	0.5
F/76	PCFCL/T1a	None	1	40	1		Head	CR	No	0.5

<sup>a</sup>Later developed papular eruption and mantle cell lymphoma. S: surgery; R: radiation.

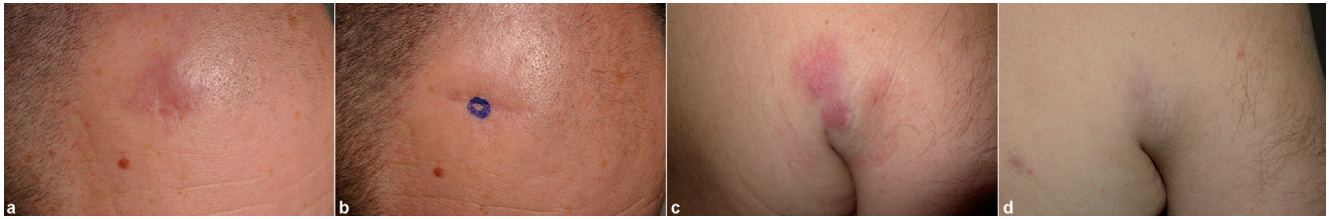


Fig. 1. Primary cutaneous follicle centre lymphoma (PCFCL) on the forehead. Lesion (a) before and (b) after 12 intralesional injections of rituximab. Response was confirmed by punch biopsy. Primary marginal zone lymphoma (c) before and (d) after 12 intralesional rituximab injections on the shoulder.

Our primary protocol was to administer rituximab, in a dose of approximately 2 ml (10 mg/ml) per lesion 3 times a week for 4 weeks, depending on the size of the lesions (Fig. 1). In some patients it was not possible or necessary to follow this protocol: if the lesions were on the forehead or the skull, it was technically difficult to inject a large volume of rituximab. Also, in 4 patients the lesions responded early in the cycle and not all injections were needed. The cumulative dose of injected rituximab ranged from 60 to 600 mg depending on the patient. Two patients also underwent radiation therapy after relapse with rituximab. The side-effects were minor irritation on the injection side and fever (4/9) up to 38°C on the day of treatment. Due to this, we added paracetamol prophylaxis to the treatment protocol. One patient developed urticarial-like lesions on and around the injection site at the beginning of his 4<sup>th</sup> cycle.

Two patients (one with PCFCL and one with PCMZL) had a previous history of *Borrelia burgdorferi* infection and one patient had had 3 lymphocytomas before the PCFCL diagnosis. One lesion (PCMZL) tested positive with borrelia-polymerase chain reaction (PCR) and rituximab treatment was effective only after administration of amoxicillin, 2 g/day for 21 days. One patient with PCMZL later developed systemic mantle cell lymphoma.

## DISCUSSION

PCBCLs are indolent lymphomas, which have a good prognosis and a tendency to relapse. The existing guidelines are based on retrospective studies and small case report series (5). Currently, local radiotherapy and surgery are recommended as first-line therapy in both PCFCL and PCMZL, whereas intralesional rituximab is considered as a second-line, alternative therapy. Considering the indolent nature of the disease, the treatments should not be devastating and even a “treat as needed” concept is acceptable. The good cosmetic results of intralesional rituximab injections favour this treatment mode over surgery and radiation therapy.

Intralesional rituximab is also well tolerated with minor side-effects. One of the most common side-effects of intravenous rituximab is short-term fever, occurring in 4 of our patients regardless of paracetamol prophylaxis. One of our patients developed an urticarial-type reaction and one a hydroa-vaccini-forme-like eruption.

The number of patients reported here (i.e. 9) is small, but as far as we know it includes all patients treated with intralesional rituximab in Finland. The largest previous study reported is by Penate et al. (9) with 35 patients. In this study, most of the patients had previous treatments and the most common sites of the lesions were head, neck and trunk. The CR rate varied between 65% and 78% and median follow-up time was 84 weeks. Our results reflect the same tendency, but in total, we followed up patients for 8 years.

Previous reports of PCBCL treated with intralesional rituximab have shown a relatively high incidence of recurrences. This is related to the tendency of PCBCL to relapse. We have also treated one large facial lymphocytoma with intralesional rituximab with good results (data not shown). Our results show that intralesional rituximab injections are a reasonable option for radiation therapy in selected cases. The treatment can be repeated several times and it is more cost-effective than intravenous rituximab treatment. Relapses are common and different treatment modalities and maintenance therapies may be considered in the future.

*The authors declare no conflicts of interest.*

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