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REVIEW

Rituximab in the Treatment of Primary Cutaneous B-Cell Lymphoma: A Review☆

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Abstract Rituximab is a chimeric mouse-human antibody that targets the CD20 antigen, which is found in both normal and neoplastic B cells. In recent years, it has been increasingly used to treat cutaneous B-cell lymphoma and is now considered an alternative to classic treatment (radiotherapy and surgery) of 2 types of indolent lymphoma, namely, primary cutaneous follicle center lymphoma and primary cutaneous marginal zone B-cell lymphoma. Rituximab is also administered as an alternative to polychemotherapy in the treatment of primary cutaneous large B-cell lymphoma, leg type. Its use as an alternative drug led to it being administered intralesionally, with beneficial effects. In the present article, we review the literature published on the use of rituximab to treat primary cutaneous B-cell lymphoma.
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PALABRAS CLAVE
Rituximab;
Linfoma primario cutáneo de células B;
Linfoma folicular;
Linfoma de la zona marginal;
Linfoma cutáneo primario difuso de células grandes tipo piernas;
Efectos secundarios

Rituximab en el tratamiento de los linfomas cutáneos B primarios: revisión

Resumen Rituximab es un anticuerpo quimérico murino-humano dirigido contra el antígeno CD20 presente en los linfocitos B normales y neoplásicos. Su uso en los linfomas cutáneos de células B ha ido en creciente desarrollo en los últimos años. Así se plantea como una alternativa a los tratamientos clásicos de radioterapia y cirugía en los linfomas de curso indolente, el linfoma folicular y el linfoma de la zona marginal. También se utiliza en el tratamiento del linfoma cutáneo primario de células grandes tipo piernas como alternativa a la poliquimioterapia. Su desarrollo como alternativa terapéutica ha llevado a su uso intralesional también con buenos resultados. En este artículo se revisa la literatura publicada del uso de rituximab en los linfomas cutáneos primarios de células B.
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Introduction

Primary cutaneous B-cell lymphomas (CBCLs) are a group of B-cell lymphomas localized in the skin at the time of diagnosis. According to the recent World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification, there are 3 main subgroups: follicular lymphoma (FL), marginal zone lymphoma (MZL), and cutaneous diffuse large B-cell lymphoma leg-type (CDLBCL-LT).[1] These account for approximately 20% to 25% of all primary cutaneous lymphomas. Most CBLCs (more than 80%) correspond to the 2 variants with an indolent course, FL and MZL.[2] The main characteristics of these 3 subgroups are summarized in Table 1.[3] Neither FL nor MZL follows a very aggressive course, and 5-year survival is greater than 95%.[1] Although prognosis is excellent, recurrence rates after treatment are high, ranging from 14% to 62%.[3] FL and MZL most frequently present as plaque or nodular lesions, occasionally with an anatomic distribution, with the trunk being the most frequent site (48.9%), followed by the face (26.4%).[4,5] Given the benign course of these cutaneous B-cell lymphomas and their frequent multifocal distribution, a conservative approach to treatment should be followed. The most widely used types of treatment are radiotherapy (RT) and surgery,[4,5] though these carry with them a risk of sequelae and are not ideal in the case of multifocal and/or recurrent lesions. Other therapeutic options therefore need to be explored. In absence of controlled clinical trials, there is no clear consensus on the best treatment for indolent CBCL.[3] CDLBCL-LT in contrast follows a rapidly progressing course with a high rate of recurrence and a tendency for extracutaneous dissemination; 5-year survival is 50%.[3] The lesions are located on the legs in more than 70% of patients, with presentation in the form of nodules or ulcerated tumors. Differential diagnosis should include systemic diffuse large cell non-Hodgkin lymphoma (NHL) with cutaneous involvement.[6] In recent years, systemic rituximab alone or in combination with chemotherapeutic agents has been introduced for the treatment of CDLBCL-LT.

Rituximab

Rituximab is a murine-human chimeric monoclonal immunoglobulin G antibody against the CD20 antigen present on almost all neoplastic and normal B-cells. It has been used successfully in the treatment of systemic B-cell NHL either as monotherapy or more commonly in combination with other chemotherapeutic agents.[7] In recent years, rituximab has been used by dermatologists with good outcomes in a range of skin diseases[8] and CBCLs.

In vitro studies of rituximab have shown this agent induces lysis of lymphoma B-cells by antibody-dependent

Table 1 Characteristics of the Most Common Primary Cutaneous B-Cell Lymphomas.

	MFZ	FL	CDLBCL-LT
Clinical Characteristics	Young adults or adults Single or multiple plaques or tumors on the legs Frequent cutaneous recurrences Sometimes associated with *Borrelia burgdorferi* infection Extracutaneous involvement uncommon	Adults Solitary tumors or clusters of tumors on the head and trunk Cutaneous recurrence in 20% Extracutaneous spread in 5% to 10%	Single or multiple tumors on the legs; rarely present at other sites Frequent cutaneous recurrences Frequent extracutaneous spread
Histopathology	Diffuse or patchy infiltrate of small B cells Includes cells in marginal zone (centrocyte-like), lymphoplasmacytoid and plasma cells	Follicular or diffuse infiltrate or both Centrocytes and centroblasts	Infiltrated monomorphous with predominance of centroblasts and immunoblasts
IHC	CD79a+, Bcl-2+, Bcl-6-, CD10-, cyclin D1-, CD5-	CD20+, CD79a+, Bcl2-, Bcl-6+, MUM1-, CD10$^{\pm}$	CD20+, CD79a+, Bcl-6$^{\pm}$, CD10-, Bcl-2+, MUM-1+
Genetics	Clonal rearrangement of IgH 50% to 60% t(14-18) in a small percentage	IgH clonal rearrangement t(14;18) absent	Clonal rearrangement of IgH in most cases t(9:21)
Treatment	RT, surgery, IFN-α, rituximab Systemic CT reserved for generalized lesions or extracutaneous involvement (CHOP, R-CHOP)	RT, surgery, IFN-α, rituximab Systemic CT reserved for generalized lesions or extracutaneous involvement (CHOP, R-CHOP)	RT for solitary lesions Polychemotherapy: CHOP, R-CHOP Rituximab
5-year survival	> 95%	95%	50%

Source: Willemze et al.[1] and Cerroni et al.[4]
Abbreviations: CT, chemotherapy; FL, follicular lymphoma; IFN-α, interferon alfa; IgH, immunoglobulin H; IHC, immunohistochemistry; CDLBCL-LT, cutaneous diffuse large B-cell lymphoma leg-type; MZL, marginal zone lymphoma; RT, radiotherapy.

cell mediated cytotoxicity, complement activation, and direct induction of apoptosis. This mechanism does not depend on the immune system and occurs because the variable region of murine origin binds with high affinity to the CD20 antigen expressed on malignant B lymphocytes, halting their proliferation and inducing apoptosis probably through transmembrane calcium channels.[6] Rituximab has also been shown to induce an antigen-specific response in T cells by an immunization mechanism.[9] Additionally the drug is able to sensitize cells to the cytotoxic effects of other chemotherapeutic agents.[10]

Rituximab is also known to act via the bcl-2 protein. This marker is overexpressed in 85% of CDLBCL-LT and is considered one of the factors associated with worse prognosis.[11] In the case of systemic diffuse large cell lymphomas, the addition of rituximab to combinations based on anthracyclines is particularly beneficial for bcl-2 positive lymphomas, which had a worse prognosis before rituximab was available.[12]

Rituximab in Primary Cutaneous Lymphomas

Follicular Lymphoma and Marginal Zone Lymphoma

Primary cutaneous FL and MZL are cutaneous lymphomas with an indolent course despite the high rates of recurrence. It is therefore important to highlight that treatment should not be aggressive in most cases. The recommendations for management of LF and MZL include withholding treatment (*watchful waiting*), RT, surgery, or intralesional interferon alfa.[3] Sometimes, however, large, painful, disfiguring, or itchy multiple lesions may be present; watchful waiting is not an option and treatment should be administered. Moreover, in these situations, local skin interventions, such as surgery or RT, are not appropriate, particularly in the case of multiple lesions or lesions on sites such as the face or neck where the interventions might leave substantial esthetic sequelae. In these circumstances, other treatment alternatives, among them systemic or intralesional rituximab, have been used.

Tables 2 and 3 summarize the published cases of FL and MZL, respectively, treated with systemic rituximab. Table 4 summarizes the cases of FL and MZL treated with intralesional administration of rituximab.

In total, 44 cases have been published of cutaneous FL treated with intravenous rituximab (Table 2).[13–24] Regimens have ranged from the usual 4 infusions, once a week, with standard doses of 375 mg/m^2 to courses of up to 10 infusions. The complete response rate for all the published cases is approximately 77%, with a response duration ranging from 6 to 57 months. For MZL, 16 cases of systemic rituximab treatment have been published (Table 3),[14,18,21,25,26] with an overall complete response rate of 43% and a duration of response of between 6 and 75 months.

This apparently worse response to rituximab in patients with MZL is pending confirmation in the future in large prospective studies; if real, the difference could be due to several mechanisms that confer resistance to rituximab. A study has been published describing the lack of efficacy of rituximab in patients with noncutaneous MZL who also

Table 2 Published Cases of Follicular Lymphoma Treated with Intravenous Rituximab.

Author/Year	Number of Patients	Number of Infusions	Response	Duration of Response, mo	Remarks
Heinzerling 2000[13]	3	1, 2, 4	2 PR/1 CR	5, 12, 10	Urticarial reaction in the tumors Disappearance of B cells from peripheral blood
Gellrich 2001[14]	2	4-8	PR	9	
Kennedy 2004[15]	2	4	PR, CR	6, 7	
Lacouture 2005[16]	1	4	CR	24	Treatment of recurrence after RT
Fink-Puches 2005[17]	2	3, 4	CR, CR	24, 14	One patient had cutaneous recurrence at a different site
Gellrich 2005[18]	8	8-10	6 CR, 2 PR	7-30	Shows histological cure
Errante 2006[19]	1	8	CR	NS	Urticarial reaction
Gitelson 2006[20]	2	4	CR	17-39	One of these, maintenance therapy every 2 months for 8 months
Kerl 2006[21]	1	4	CR	18	No recurrence
Morales 2008[22]	10	4	8 CR, 2 PR	6-31	Maintenance, variable for each patient
Valencak 2009[23]	11	6	CR	6-57	Treatment of multifocal lesions, not candidates for RT or surgery
Brunet-Posenti 2011[24]	1	4	CR	NS	Edematous infusion reaction
Total	44	1-10	34 CR/10 PR 77% CR	6-57	

Source: Heinzerling et al.[13] and Brunet-Posenti et al.[24]
Abbreviations: CR, complete response; NS, not specified; PR, partial response; RT, radiotherapy.

Table 3 Published Cases of Marginal Zone Lymphoma Treated with Intravenous Rituximab.

Author/Year	Number of Patients	Number of Infusions	Response	Duration of Response, mo	Remarks
Soda 2001[25]	1	4	PR	6	Multiple lesions, rituximab used first-line
Gellrich 2001[14]	2	4-8	PR	9	Maintenance treatment
Gellrich 2005[18]	1	8	PR	23	Recurrence after 23 months
Kerl 2006[21]	1	4	CR	24	No recurrence, no maintenance therapy
Morales 2008[22]	5	4-6	1 CR, 2 PR, 1 SD, 1 IR	6-23	Maintenance treatment in 3 of the patients
Valencak 2009[23]	5	4-6	4 CR, 1 PR	17-75	Additional treatment in 2 of the patients
Seker 2010[26]	1	8	CR	13	All multinodular

Source: Gellrich et al.[14]; Gellrich et al.[18]; Kerl et al.[21]; Morales et al.[22]; Valencak et al.[23]; Soda et al.[25]; and Seker et al.[26]
Abbreviations: CR, complete response; IR, incomplete response; PR, partial response; SD, stable disease.

received chemoimmunotherapy.[27] One of the hypotheses is that malignant B cells acquire new mutations that confer resistance to rituximab-induced apoptosis. Thus, in a study of 4 patients with recurrent disease, an increase in bcl-2 activity was observed after rituximab treatment.[28] Variations in the site of B-cell binding to rituximab have also been seen. Patients with certain genotypes at the antibody binding site appear to respond better to treatment with rituximab and disease-free periods are longer. This polymorphism in the expression of the CD20 antigen in malignant B cells may define a subgroup of patients with innate resistance to rituximab.[29]

Recurrences after treatment with intravenous rituximab, in both patients with FL and with MZL, are frequent (20% and 50%, respectively). However, recurrences of CBCL are frequent with all treatment types except surgery and RT.[3] Thus, authors such as Gellrich et al.[18] propose more prolonged treatments of 8 cycles instead of 4, as better response rates (90%) and remission rates are obtained; however, the benefits of prolonging treatment are not clearly demonstrated due to the small number of patients studied. In a subsequent study of 16 patients, Valencak et al.[23] reported complete response in 62% of indolent CBCL treated with intravenous rituximab and proposed that 4 cycles would be sufficient. The authors highlighted the lack of studies that support the need to extend treatment. Likewise, the published studies do not provide clear indications as to whether re-treatment with rituximab after recurrence might be beneficial, as has been demonstrated in systemic FL.[30,31]

Most studies define complete response as disappearance of all cutaneous lesions, which are assessed clinically with regular follow-up of the patients. Some studies have, however, also evaluated histologic response of the lesions[14,18,25] by means of a skin biopsy after treatment. These studies report the presence of an infiltrate of CD8-positive T cells,[14] with decreased CD20 expression.[25] Gellrich et al.[18] took biopsies from 8 of the treated patients with complete response and found that despite a complete clinical response, only 6 had complete histologic response.

Intravenous treatment with rituximab is safe and generally well tolerated, particularly in comparison with other traditional chemotherapeutic agents. The adverse effects

Table 4 Published Cases of Follicular Lymphoma Treated with Intralesional Rituximab.

Author	Number of Lesions/Type	Prior Treatment	Response	Duration of Response, mo	Recurrence
Heinzerling 2000[13]	2 FL	2/2	2 PR	0-12	2/2
Paul 2001[36]	2 FL	1/2	2 CR	12	0/2
Fink-Puches 2005[17]	3 FL/4 MZL	1/7	6 CR/1 PR (MZL)	12-27	4 (3 MZL, 1 FL)/7
Roguedas 2005[37]	1 FL	1/1	CR	12	1/1
Kerl 2005	3 FL/3 MZL	4/6	6 CR	3-14	2 (1 FL, 1 MZL)/6
Kyrtsonis 2006[38]	2 MZL	0/2	2 CR	36-44	2/2
Park 2010[39,a]	1 MZL	0/1	CR	26	0/1
Peñate 2012[40]	18 FL/17 MZL	25/35	14/18 CR in FL 11/17 CR in MZL	3-48	6/14 CR in FL 4/11 CR in MZL

Source: Fink-Puches et al.[17]; Kerl et al.[21]; Heinzerling et al.[35]; Paul et al.[36]; Roguedas et al.[37]; Kyrtsonis et al.[38]; Park et al.[39]; and Peñate et al.[40]
Abbreviations: CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; PR, partial response.
[a] Pediatric case.

Table 5 Adverse Effects of Systemic Rituximab.

Cutaneous Effects	Rash
	Pruritus
	Urticaria
	Bacterial infections
	Lichenoid reactions
	Paraneoplastic pemphigus
	Steven-Johnson syndrome/toxic epidermal necrosis
	Vesicular/blistering dermatitis
Systemic Effects	Fatal infusion reaction (first 24 h)
	Tumor lysis syndrome
	Hepatitis B reactivation (can be fulminant)
	Severe cardiac arrhythmias
	Renal failure (can be fatal)
	Hypersensitivity reactions
	Others: sick serum disease, rheumatoid-like inflammatory arthritis syndrome, vasculitis, mucositis

Source: Scheinfield[32]

are summarized in Table 5.[32] The most frequently reported cutaneous effects are mild, usually in the form of rash or urticaria, which occur in approximately 15% of patients. Serious side effects such as paraneoplastic pemphigus or Steven-Johnson syndrome appear in fewer than 2%. Of interest is the occurrence of wheals around the skin lesions in FL treated with systemic rituximab; this is thought to be due to the release of inflammatory cytokines.[13,19] The risk of reactivation of hepatitis B virus is also of particular interest in patients with chronic infection as the event can potentially be fatal.[26,33] The American Hepatology

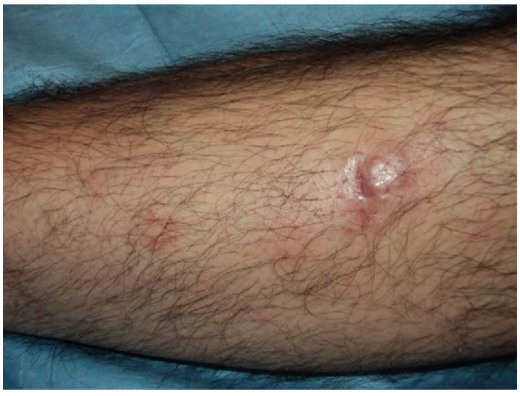

Figure 1 Image of a patient with marginal zone lymphoma in the leg.

Guidelines recommend the use of lamivudine as prophylaxis for up to 6 months after finishing treatment with intravenous rituximab in carriers of HbsAg.[34] Some authors suggest this prophylactic period should be extended to up to 2 years after finishing treatment, given that late reactivation of hepatitis B has been reported.[26]

In most studies, intravenous rituximab is considered the treatment of choice for multifocal lesions and also for lesions on the face and scalp, as RT may cause alopecia and irreversible cutaneous effects, such as poichyloderma or atrophy.[19,26]

In recent years, the use of intralesional rituximab has become widespread for FL and MZL. The aim is to make treatment more comfortable and accessible while minimizing side effects (Figs. 1 and 2). The published cases of treatment of FL and MZL with intralesional rituximab

Table 6 Cutaneous Diffuse Large B-Cell Lymphoma Leg-Type, Treated With Rituximab Monotherapy.

Author/Year	Number of Patients	Number of Infusions	Response	Duration of Response, mo	Remarks
Heinzerling 2000[13]	5	4	1 CR/2 PR/2 PD	6-13	No side effects of note
Sabroe 2000[42]	1	4	PR	3 months	Cycle repeated, but recurrence after 3 weeks
Aboulafia 2001[43]	1	4	CR	NS	No side effects of note (RT and polyCT avoided)
Garbea 2002[44]	1	7	PD	0 months	Adverse effects: fever, herpes zoster
Bonnekoh 2002[45]	1	8	CR	8 months	No side effects of note (RT and polyCT avoided)
Viguier 2002[46]	1	4	CR	15 months	Recurrence, treated with R-CHOP
Zinzani 2003[47]	1	4	CR	8 months	No side effects
Brogan 2003[48]	3	4	1 CR/2 PD	6 months	Combined with RT
Gellrich 2005[18]	1	8	PD	0 months	
Lacouture 2005[16]	1	4	CR	17 months	Recurrence after RT
Pedraz 2005[49]	1	4	CR	Not specified	
Fenot 2010[50]	8	4	3 CR/3 PR/3 PD	26-28 months	5 patients retreated with R-CHOP

Source: Lacouture et al.[16]; Gellrich et al.[18]; Heinzerling et al.[35]; Sabroe et al.[42]; Aboulafia[43]; Garbea et al.[44]; Bonnekoh et al.[45]; Viguier et al.[46]; Zinzani et al.[47]; Brogan et al.[48]; Pedraz et al.[49]; and Fenot et al.[50]

Abbreviations: CR, complete response; CT, chemotherapy; NS, not specified; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease

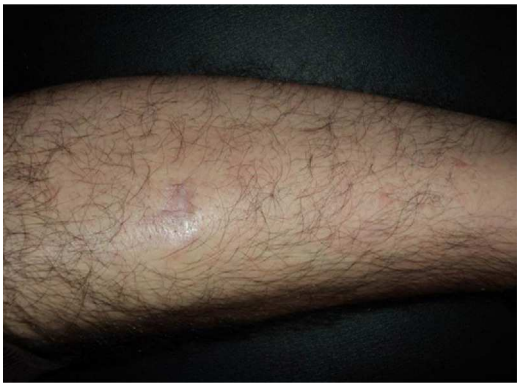

Figure 2 Resolution after 3 injections, each a week apart, of intralesional rituximab (10 mg/mL).

are summarized in Table 6.[17,21,35–40] The complete response rates with this treatment in indolent B-cell lymphomas are somewhat greater than those achieved with intravenous administration. Response rates range from 83% to 89%, but the recurrence rate after treatment remains high (40% to 62%).[3] In most studies, regimens of between 10 and 30 mg per lesion (diluted to 10 mg/mL) are used, up to 3 times a week and in cycles of up to 12 weeks, according to response. The most frequently reported side effect is injection-site pain.[17,21,35–39] Of particular note given the large number of patients included is a recent study published by the Spanish Cutaneous Lymphoma Group, who retrospectively analyzed the outcomes of intralesional rituximab treatment of indolent cutaneous B-cell lymphoma in several hospitals.[40] A total of 35 patients were included, 17 with MZL and 18 with FL. A mean of 2 lesions were treated per patient. Most patients were treated with 3 injections per week for 1 week in every month. A complete response rate of 74% was found—slightly below that reported in previous studies.[3] Mean disease-free survival was 114 weeks. Side effects were detected in 54% of the patients, with the most common being injection-site pain. A small number of patients had fever presenting between 6 and 12 hours after the injection, although the effect was transient and observed most often in the first injections. Some of the most important findings in this study are that there were no apparent factors predictive of response or differences in responses according to underlying disease (MZL or FL), in contrast to the case when the drug is administered systemically.

The conclusion from these studies is that intralesional use of rituximab is becoming more widespread in selected patients with low-grade CBCL in view of the convenience, lower dose, and fewer side effects.

Cutaneous Diffuse Large B-cell Lymphoma, Leg-Type

CDLBCL-LT occurs less frequently than the other 2 types of CBCL discussed above. This type accounts for approximately 1% to 3% of all primary cutaneous lymphomas and, unlike FL and MZL, follows a more aggressive course with frequent extracutaneous spread and recurrence after treatment. Prognosis is intermediate with a 5-year survival rate of approximately 50%.[3] Factors indicative of poor prognosis in cutaneous large B-cell lymphomas include onset at an early age, ulceration, and positive staining for multiple myeloma oncogene (MUM) 1 and bcl-2, while expression of bcl-6 is associated with good prognosis.[41] However, these findings are open to debate because the series of cutaneous large B-cell lymphomas include some forms of FL, which is typically bcl-6 positive and has a better prognosis. In contrast, CDLBCL-LT is typically MUM-1 positive and has a worse prognosis. The expression of one of these proteins may not therefore be a prognostic factor in itself, but rather related to diagnosis of 2 different lymphomas with different prognoses.

The guidelines for management of CBCL, issued by the EORTC, recommend treatment of CDLBCL-LT with polychemotherapy with or without rituximab (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone [CHOP]-like or R-CHOP regimens). In localized disease, the recommended treatment is RT, which shows good response rates.[3] There are 25 cases in the literature of CDLBCL-LT treated with rituximab in monotherapy (summarized in Table 6).[13,16,42–50] Regimens of 4 to 8 infusions were used with or without local RT in the tumors. The complete response rate of the published cases is 48%, but this response is only maintained for more than 6 months in 4 of the patients, that is, 18%, and so recurrences after treatment are frequent (82%). In all cases, treatment was well tolerated, without significant side effects.

The role of rituximab as monotherapy in CDLBCL-LT is not well defined; the results reported in the literature suggest that there is a marked initial response but recurrences and disease progression are frequent.

The recommended treatment with CHOP or CHOP-like polychemotherapy in CDLBCL-LT obtains complete response rates of 81%, but once again recurrence rates are high at 54%.[3] Some authors therefore recommend the use of intravenous rituximab as a less aggressive option that is better adapted to older patients.[16,43,45,49] Despite the recommendations of the WHO-EORTC, some authors have wondered whether intensified treatments with greater toxicity really improve prognosis in these patients. Most suggest that the treatment of choice should be tailored and adapted to the age of the patient, with rituximab considered as a palliative measure.

Other B-Cell Lymphoproliferative Processes

There has been a report of a case of cutaneous intravascular large B-cell lymphoma treated with R-CHOP with complete clinical and histologic response maintained for 6 months. These results appear promising, as this is a very aggressive lymphoma. However, given the rarity of the condition, it is difficult to establish treatment protocols.[51]

There is also a published case of pseudo-B-cell lymphoma refractory to conventional therapies that responded well to intralesional rituximab.[52]

Conclusions

Rituximab is an anti-CD20 antibody that is increasingly used in the treatment of CBCL. Good response rates are obtained in indolent B-cell lymphomas, FL, and MZL, for

both the intravenous and intralesional route of administration, although recurrence is frequent. Rituximab is not the preferred treatment, but it should be considered in patients with multiple and/or recurrent lesions at visible sites where radiotherapy or surgery may leave sequelae or scars. Intralesional use has become widespread in recent years with similar outcomes to intravenous use, but with fewer side effects and a lower cost. More studies are needed to establish the usefulness and the optimal protocol in other B-cell cutaneous lymphomas. In the future, molecular predictors of response, new clinical trials, and new combinations with existing treatments or other monoclonal antibodies may help define the role of rituximab in the treatment of CBCL.

Ethical Responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed their hospital's protocol on the publication of data concerning patients and that all patients included in the study have received sufficient information and have given their written informed consent to participate in the study.

Right to privacy and informed consent. The authors declare that patient data do not appear in this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swendlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
2. Willemze R. Primary cutaneous B-cell lymphoma: classification and treatment. Curr Opin Oncol. 2006;16:425–31.
3. Senff N, Noordijk E, Kim Y, Bagot M, Berti E, Cerroni L, et al. European Organization for Research and Treatment of Cancer and International Society of Cutaneous Lymphoma consensus recommendations for the manegement of cutaneous B-cell lymphomas. Blood. 2008;112:1600–9.
4. Cerroni L, Gatter K, Kerl H. The illustrated guide of skin lymphoma. 3rd ed. Willey-Blackwell; 2011.
5. Bogle MA, Riddle CC, Triana EM, Jones D, Duvic M. Primary cutaneous B-cell lymphoma. J Am Acad Dermatol. 2005;53:479–84.
6. Shan D, Ledbetter JA, Press OW. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. Blood. 1998;91:1644–52.
7. Molina A. A decade of rituximab. Improving survivial outcome in non-Hodgkin's lymphoma. Annu Rev Med. 2008;59:237–50.
8. España A, Ornilla C, Panizo C. Rituximab en dermatología. Actas Dermosifiliogr. 2012, in press.
9. Selenko N, Maiddic O, Draixier S, Berer A, Jager U, Knapp W, et al. CD20 antibody (C2B8)-induced apoptosis of lymphoma cells promoted phagocytosis by dendritic cells and cross-priming of CD8+ cytotoxic T cells. Leukemia. 2001;15:1619–26.
10. Bello C, Sotomayor EM. Monoclonal antibodies for B-cell lymphomas: rituximab and beyond (ASCO meeting). Hematology. 2007:233–42.
11. Grange F, Petrella T, Beylot-Barry M, Joly P, D'Incan M, Delaunay N, et al. Bcl-2 protein expression is the strongest independent prognostic factor of survival in primary cutaneous large B cell lymphomas. Blood. 2004;103:3662–8.
12. Grange F, Beylot-Barry M, Courville P, Maubec E, Bagot M, Vergier B, et al. Primary cutaneous diffuse large-B-cell lymphoma leg-type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol. 2007;143:1144–50.
13. Heinzerling LM, Urbanek M, Funk JO, Peker S, Bleck O, Neuber K, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer. 2000;89:1835–44.
14. Gellrich S, Muche JM, Pelzer K, Audring H, Sterry W. Anti-CD20 antibodies in primary cutaneous B-cell lymphoma. Initial results in dermatologic patients. Hautarzt. 2001;52:205–10.
15. Kennedy GA, Blum R, Mc Cormack C, Prince HM. Treatment of primary cutaneous follicular center lymphoma with rituximab: a report of two cases. Australas J Dermatol. 2004;45:34–7.
16. Lacouture ME, Baron JM, Jani AB, Laumann AE, Soltani K. Treatment of radiation-relapsing primary cutaneous B-cell lymphoma with an anti-CD20 monoclonal antibody. Clin Exp Dermatol. 2005;30:46–8.
17. Fink-Puches R, Wolf IG, Zalaudek I, Kerl H, Cerroni L. Treatment of primary cutaneous B-cell lymphoma with rituximab. J Am Acad Dermatol. 2005;52:847–53.
18. Gellrich S, Muche JM, Wilks A, Jash KC, Voit C, Fisher T, et al. Systemic eight-cycle anti-CD20 monoclonal antibody (rituximab) therapy in primary cutaneous B-cell lymphomas-an applicational observation. Br J Dermatol. 2005;153:167–73.
19. Errante D, Bernadi D, Bianco A, de Nardi S, Salvagno L. Rituximab-related urticarial reaction in a patient treated for primary cutaneous B-cell lymphoma. Ann Oncol. 2006;17:1720–1.
20. Gitelson E, Al-Saleem T, Millenson M, Lessin S, Smith MR. Cutaneous B-cell lymphoma responds to rituximab: a report of five cases and review of the literature. Leuk Lymphoma. 2006;47:1902–7.
21. Kerl K, Prins C, Saurat JH, French LE. Intralesional and intravenous treatment of cutaneous B-cell lymphoma with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. Br J Dermatol. 2006;155:1197–200.
22. Morales AV, Advani R, Horwitz SM, Riaz N, Reddy S, Hoppe RT, et al. Indolent cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol. 2008;59:953–7.
23. Valencak J, Weihsengruber F, Rappersberger K, Trautinger F, Chott A, Streubel B, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: response and follow-up in 16 patients. Ann Oncol. 2009;20:326–30.
24. Brunet-Posenti F, Franck N, Tamburini J, Jacobelli S, Avril MF, Dupin N. Focal rituximab induced edematous reaction at primary cutaneous follicle lymphoma lesions: case report and literature review. Dermatology. 2011;223:200–2.
25. Soda R, Costanzo A, Cantonetti M, Orlandi A, Bianchi L, Chimenti S. Systemic therapy of primary cutaneous B-cell lymphoma, marginal zone type, with rituximab, a chimeric anti-CD20 monoclonal antibody. Acta Derm Venereol. 2001;81:207–8.
26. Seker M, Ustaalioglu BB, Bilici A, Yildirim ME, Kefeli U, Barisik NO, et al. Eight-cycle rituximab therapy resulted in complete remission in primary cutaneous marginal zone lymphoma. Leuk Res. 2010;34:160–3.
27. Lossos IS, Morgensztern D, Blaya M, Alencar A, Pereira D, Rosenblatt J. Rituximab for treatment of chemoinmmunotherapy naïve marginal zone lymphoma. Leuk Lymphoma. 2007;48:1630–2.

28. Jaziheri AR, Vega MI, Bonabid B. Development of rituximab resistant lymphoma clones with altered cell signalling and cross-resistance to chemotherapy. Cancer Res. 2007;67:1270–81.
29. Weng WK, Lewy R. Two immunoglobulin G fragment C receptor polymorphims independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol. 2003;21:3940–7.
30. Hainsworth JD. Prolonging remission with rituximab maintenance therapy. Semin Oncol. 2004;31:17–21.
31. Fierro MT, Savoia P, Quaglino P, Novelli M, Barberis M, Bernengo MG. Systemic therapy with cyclophosphamide and anti-CD20 antibody (rituximab) in relapsed primary cutaneous B-cell lymphoma. J Am Acad Dermatol. 2003;49:231–87.
32. Scheinfield N. A review of rituximab in cutaneous medicine. Dermatol Online J. 2006;12:3.
33. Ozguroglu M, Bilici A, Turna H, Sendengecti S. Reactivation of hepatitis B virus infection with cytotoxic therapy in non-Hodgkin lymphoma. Med Oncol. 2004;21:67–72.
34. Idilman R. Lamivudine prophylaxis in HBV carriers with haematological malignancies who receive chemotherapy. Antimicrob Chemother. 2005;55:828–31.
35. Heinzerling LM, Dummer R, Kempf W, Schimd MH, Burg G. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol. 2000;136:374–8.
36. Paul T, Radny P, Koder SM, Paul A, Blaheta HJ, Garbe C. Intralesional rituximab for cutaneous B-cell lymphoma. Br J Dermatol. 2001;144:1239–40.
37. Roguedas AM, Watier H, Paintaud A, de Muret A, Vaillant L, Machet L. Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. Br J Dermatol. 2005;152:541–4.
38. Kyrtsonis MC, Siakantaris MP, Kalpadakis C, Dimopoulou MN, Vassilakopoulos TP, Kontopidou FN. Favorable outcome of primary cutaneous marginal zone lymphoma treated with intralesional rituximab. Eur J Haematol. 2006;77:300–3.
39. Park MY, Jung HJ, Park JE, Kim YG. Pediatric primary cutaneous marginal B-cell lymphoma treated with intralesional rituximab. Eur J Dermatol. 2010;20:533–4.
40. Peñate Y, Hernández-Machín B, Pérez-Méndez LL, Santiago F, Rosales B, Servitje O, et al. Intralesional rituximab in the treatment of indolent primary cutaneous B-cell lymphomas. An epidemiologic observational multicenter study: the Spanish Working Group on Cutaneous Lymphoma. Br J Dermatol. 2012;167:174–9, in press.
41. Hallerman C, Niermann C, Fisher RJ, Schulze HJ. New prognostic relevant factors in primary cutaneous diffuse large-B-cell lymphomas. J Am Acad Dermatol. 2007;56:588–9.
42. Sabroe RA, Child FJ, Woolford AJ, Spittle MF, Russel-Jones R. Rituximab in cutaneous B-cell lymphoma: a report of two cases. Br J Dermatol. 2000;143:157–61.
43. Aboulafia DM. Primary cutaneous large B-cell lymphoma of the legs: a distinct clinical pathologic entity treated with CD20 monoclonal antibody (rituximab). Am J Clin Oncol. 2001;24:237–40.
44. Garbea A, Dippel E, Hildenbrand R, Bleyl U, Schadendorf D, Goerdt S. Cutaneous large B-cell lymphoma of the leg masquerading as a chronic venous ulcer. Br J Dermatol. 2002;146:144–7.
45. Bonnekoh B, Schulz M, Franke I, Gollnick H. Complete remission of a primary cutaneous B-cell lymphoma of the lower leg by first line monotherapy with de CD20 antibody rituximab. J Cancer Res Clin Oncol. 2002;128:161–6.
46. Viguier M, Bachelez H, Brice P, Rivet J, Dubertret L. Cutaneous B-cell lymphoma treatment with rituximab: two cases. Ann Dermatol Venereol. 2002;129:1152–5.
47. Zinzani PL, Stefoni V, Alinari L, Vianelli N, Baccarani M. Rituximab in heavily pretreated cutaneous B-cell lymphoma. Leuk Lymphoma. 2003;44:1637–8.
48. Brogan BL, Zic JA, Kinney MC, Hu JY, Hamilton KS, Greer JP. Large B-cell lymphoma of the leg: clinical and pathological characteristics in a North American series. J Am Acad Dermatol. 2003;49:223–8.
49. Pedraz J, Delgado Y, Ballestero M, Fraga J, Carcía-Díez A, Fernández-Herrera J. Cutaneous large B-cell lymphoma of the leg. Actas Dermosifiliogr. 2005;96:237–40.
50. Fenot M, Quereux G, Brocard A, Renaut J, Dreno B. Rituximab for cutaneous diffuse large B-cell lymphoma leg-type. Eur J Dermatol. 2010;20:753–7.
51. Park GH, Kim CH, Chung WK, Won CH, Chang SE, Lee MW, et al. Primary cutaneous intravascular large B-cell lymphoma treated with combination chemotherapy and complicated by rituximab-induced interstitial lung disease. Acta Derm Venereol. 2010;90:296–8.
52. Martin SJ, Duvic M. Treatment of cutaneous lymphoid hyperplasia with the monoclonal anti-CD20 antibody rituximab. Dermatology. 2011;223:200–2.