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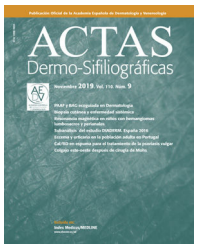

ORIGINAL ARTICLE

Experience With Bexarotene to Treat Cutaneous T-Cell Lymphomas: A Study of the Spanish Working Group of Cutaneous Lymphomas

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KEYWORDS
Bexarotene;
Retinoid;

Abstract
Background and objectives: Bexarotene has been approved to treat advanced stage cutaneous T-cell lymphomas (CTCL) since 1999. However, very few data have been published on its

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Cutaneous T-cell lymphoma;
Mycosis fungoides;
Sézary syndrome

long-term safety and efficacy profile. The aim of this study is to determine the tolerability to bexarotene and outcomes by collecting the 2nd largest case series to date on its long-term use vs CTCL.
Material and method: This was a multicenter retrospective review of 216 patients with mycosis fungoides (174), or Sézary syndrome (42) on a 10-year course of bexarotene alone or in combination with other therapies at 19 tertiary referral teaching hospitals.
Results: A total of 133 men (62%) and 83 women (38%) were included, with a mean age of 63.5 year (27–95). A total of 45% were on bexarotene monotherapy for the entire study period, 22% started on bexarotene but eventually received an additional therapy, 13% were on another treatment but eventually received bexarotene while the remaining 20% received a combination therapy since the beginning. The median course of treatment was 20.78 months (1–114); and the overall response rate, 70.3%. Complete and partial response rates were achieved in 26% and 45% of the patients, respectively. Treatment was well tolerated, being the most common toxicities hypertriglyceridemia (79%), hypercholesterolemia (71%), and hypothyroidism (52%). No treatment-related grade 5 adverse events were reported.
Conclusions: Our study confirms bexarotene is a safe and effective therapy for the long-term treatment of CTCL.

PALABRAS CLAVE
Bexaroteno;
Retinoide;
Linfoma cutáneo de células T;
Micosis fungoide;
Síndrome de Sézary

Experiencia con bexaroteno en linfoma cutáneo de células T: un estudio del Grupo Español de Linfomas Cutáneos (GELC)

Resumen
Antecedentes y objetivos: El bexaroteno está aprobado para el tratamiento de linfomas cutáneos de células T (LCCT) en estadio avanzado desde 1999. Sin embargo, se han publicado muy pocos datos sobre su seguridad y eficacia en el largo plazo. El objetivo del siguiente trabajo es determinar la eficacia y seguridad del bexaroteno en la serie de casos del Grupo Español de Linfomas Cutáneos (GELC) en su uso a largo plazo para el tratamiento de CTCL.
Material y método: Realizamos una revisión retrospectiva multicéntrica de 216 pacientes con micosis fungoide (174) o síndrome de Sézary (42) tratados con bexaroteno solo o en combinación con otras terapias en 19 hospitales universitarios de referencia en España durante 10 años.
Resultados: Se incluyeron 133 hombres (62%) y 83 mujeres (38%), con una edad media de 63,5 años (27-95). El 45% recibió monoterapia con bexaroteno durante todo el período de estudio, el 22% comenzó con bexaroteno pero posteriormente recibió una terapia adicional, el 13% estaba bajo otro tratamiento pero en algún momento se añadió bexaroteno y el 20% restante recibió una terapia combinada desde el principio. La mediana de duración del tratamiento fue de 20,78 meses (1-114). La tasa de respuesta global fue del 70,3%. Se lograron respuestas completas y parciales en el 26% y el 45% de los pacientes, respectivamente. El tratamiento fue bien tolerado; las toxicidades más frecuentes fueron la hipertrigliceridemia (79%), la hipercolesterolemia (71%) y el hipotiroidismo (52%). No se observaron efectos secundarios de grado 5 relacionados con el tratamiento.
Conclusiones: Nuestro estudio confirma que el bexaroteno es una terapia segura y eficaz para el tratamiento a largo plazo de CTCL.

Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin lymphomas originated from malignant T-lymphocytes initially located in the skin. Mycosis fungoides (MF) is its most common variant, and accounts for over half of all CTCLs reported, while Sézary syndrome (SS) is much rarer (5%). Current definition of these neoplasms is based on the 2018 update of the WHO-EORTC (World Health Organization – European Organization for Research and Treatment of Cancer) classification for primary CTCLs.[1] Although MF are SS are both considered incurable diseases, most of the patients will survive for many years. MF usually runs an indolent clinical course with a 5-year survival rate of 88%, whereas SS holds a poor prognosis, being the 5-year survival rate close to 36%. Furthermore, clinical stage at diagnosis predicts survival in MF: 65–85% of the patients have an IA or IB stage disease with a median survival of >12 years; stage IVB patients, however, have a median survival of <2.5 years.[2]

The treatment algorithm of CTCL is also based on the stage of the disease using the tumor-node-metastasis-blood (TNMB) staging system, which was

revised in 2007.[3] Early-stage disease (IA–IIA) is often managed with skin-directed therapies, such us topical corticosteroids, phototherapy (psolaren + ultraviolet A-PUVA, or narrow-band UV-B, (NBUVB), topical chemotherapy, total skin electron beam therapy, and localized radiation therapy. Advanced-stage disease (IIB–IVB) and refractory early-stage disease usually require systemic approaches including retinoids (mainly bexarotene), interferon α, histone deacetylase inhibitors (vorinostat, romidespin), targeted immunotherapy (denileukin diftitox, alemtuzumab, brentuximab vedotin, and recently mogamulizumab), chemotherapy, extracorporeal photopheresis, and haematopoietic stem cell transplantation.[2] Stagewise consensus recommendations have been made for the selection of the appropriate therapy.[4,5]

Bexarotene (Targretin®; Cephalon pharmaceuticals, Inc., Maisons-Alfort, France) is an X-receptor selective synthetic retinoid approved by the FDA in 1999 to treat CTCL in patients refractory to, at least, 1 prior systemic therapy. In Europe,[6] it was licensed in 2002. Bexarotene has a high affinity for retinoid X receptors (RXR, types α, β and γ) which, when activated, have antiproliferative and proapoptotic properties, inhibiting the growth of hematopoietic and epithelial tumor cell lines, and inducing a dose-dependent apoptosis of malignant lymphocytes.[7] Unlike other retinoids, bexarotene does not affect regulatory T-lymphocytes, Langerhans' cells of the skin, or keratinocytes, thus avoiding the well-known adverse events of immunosuppressive drugs.[8] Additionally, bexarotene can be administered orally, which is also a plus. It has proven to be effective for all stages of CTCL, with an overall response (OR) rate of 45% in clinical trials.[9,10] Hypertriglyceridemia and central hypothyroidism are the most common dose-related adverse events reported in 79% and 40% of the patients respectively, requiring individual drug dosing, and preventive usage of lipid-lowering agents and thyroid hormone replacement.[9,10] Adverse events require monitoring of laboratory parameters at the follow-up and are often well managed with concomitant drugs.[11] All retinoids are teratogenic.

The use of bexarotene for early- and advanced-stage disease is supported by 2 phase II/III clinical trials.[9] Nevertheless, data on its long-term tolerability and response in a real-life setting are scarce, with only a few cohort studies published in the literature.[12–17]

The aim of the present study is to retrospectively evaluate the outcomes of a 10-year course of bexarotene, its safety profile by collecting most patients treated with bexarotene by members of the Spanish Group of Cutaneous Lymphomas, and compare these results with data from the scientific medical literature currently available. As far as we know, this is the 2nd largest series ever reported after the one reported by Hamada et al. of patients with CTCL treated with bexarotene alone or in combination with other therapies.

Methods

This multicenter retrospective trial enrolled most adult patients with either MF or SS treated with oral bexarotene alone or in combination with other therapies at 19 tertiary referral Spanish teaching hospitals following the convenience sampling method (Fig. 1). A total of 216 patients were included in the study (174 of whom had MF and 42, SS). All patients fulfilled the diagnostic criteria of the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classifications for MF and SS. Proper diagnostic workup was performed in every patient who were staged according to the WHO/EORTC classification for primary cutaneous lymphomas, and the TNMB staging system was used for CTCL. The patients' treatment was left to the physician's criterion.

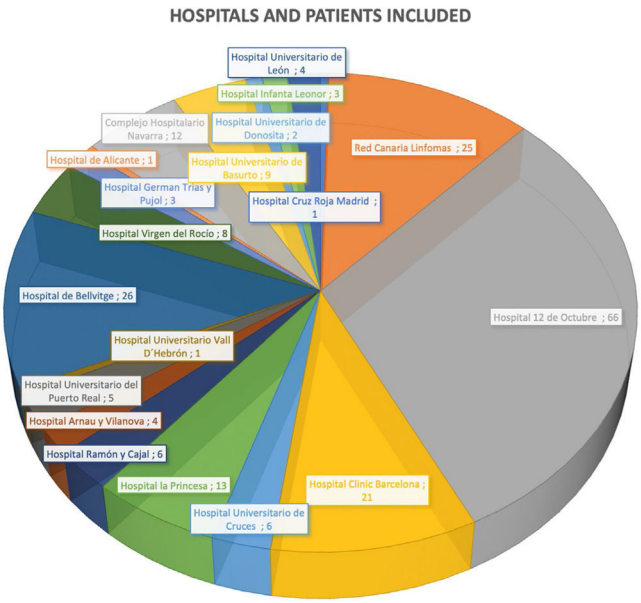

Figure 1 Spanish hospitals participating in the study and no. of patients on bexarotene in each center.

Patients received 75-mg bexarotene capsules with a varying dose of 150 mg/m^2 up to 300 mg/m^2 once a day. Dosage was individualized based on the clinical response and manageable adverse events. Both the lipid profile and the thyroid hormone levels were also measured periodically, and most patients received lipid-lowering agents and thyroid hormone replacement concomitantly to prevent or treat the aforementioned laboratory adverse events.

Bexarotene-related adverse events were then recorded and graded based on the National Cancer Institute common terminology criteria for adverse events (CTCAE v.4.0). As for the clinical outcomes, a complete response (CR) was considered in the absence of evidence of disease in the skin or extracutaneous organs for, at least, 1 month. Partial responses (PR) were $\geq$50% reductions in the area of skin lesions for, at least, 1 month, whereas progressive disease (PD) meant $\geq$ 50 increases in skin lesions, or blood, lymph node or visceral involvement. Overall response (OR) included both CR and PR. Stable disease (SD) was defined as no significant changes in either the skin, or extracutaneous clinical signs. This study is in full compliance with the criteria established by the Research Ethics Committee (Reg – 20070601).

Table 1 Patient characteristics and previous therapies.

Sex, N (%)	
Man	133 (61.6)
Woman	83 (38.4)
Age, years (min–max)	
At bexarotene initiation	63.5 (27–95)
At CTCL diagnosis	55.22 (13–94)
Stage, N (%)	
IA	41 (19.2)
IB	78 (36.4)
IIA	5 (2.3)
IIB	40 (18.7)
IIIA	16 (7.5)
IIIB	6 (2.8)
IVA	25 (11.7)
IVB	3 (1.4)
Previous therapies, N (%)	
None	21 (9.7)
Topical corticosteroids	177 (81.9)
PUVA	113 (52.3)
NBUVB	29 (13.4)
IFN-α	53 (24.5)
Radiation therapy	36 (16.7)
Methotrexate	22 (10.2)
Topical chemotherapy	21(9.7%)
Retinoids	20 (9.3)

Results

Patient and disease characteristics. Prior treatment history

The patients' characteristics and previous therapies are shown in Table 1.

Treatment modalities and dosage

The patients' body surface area (BSF) was used to determine optimal bexarotene dose at the beginning to later individualize and adjust such dosages. Data are shown in Table 2, and concomitant therapies in Table 3.

Table 3 Combination therapies used concomitantly with bexarotene.

Concomitant therapies	*N*
None	101
Topical steroids	3
Phototherapy	41
IFN-α	15
Methotrexate	5
Radiation therapy	8
Topical chemotherapy	7
Extracorporeal photopheresis	5
Phototherapy + IFN-α	8
Methotrexate + IFN-α	1
Phototherapy + radiation therapy + topical chemotherapy	1
Topical steroids + topical chemotherapy	3
Phototherapy + topical chemotherapy	2
IFN-α + radiation therapy	3
Topical steroids + radiation therapy	1
Topical steroids + radiation therapy + phototherapy + IFN-α	1
Topical steroids + radiation therapy + phototherapy + methotrexate	1
Topical steroids + radiation therapy + phototherapy	1
Topical steroids + radiation therapy + methotrexate + IFN-α + topical chemotherapy	1
Topical steroids + phototherapy + IFN-α + topical chemotherapy	1
Phototherapy + IFN-α + radiation therapy	3
Radiotherapy + topical chemotherapy	1
Phototherapy + methotrexate + radiation therapy	1
Phototherapy + radiation therapy	1
Topical steroids + methotrexate + topical chemotherapy	1

Clinical response

CRs, and PRs were achieved in 26% and 45% of the patients, respectively. Therefore, the OR rate was 70% (CR + PR = OR). A total of 13% of the patients showed SD while 17% showed progression despite bexarotene therapy. The median initial response time was 8 months. Time to partial and com-

Table 2 Bexarotene dosage and duration of therapy and treatment schedule (note that data of 12 patients are missing).

	Median	Min	Max
Body surface (m^2)	1.81	1.38	2.36
Initial bexarotene dose (mg/day)	246.56	75	675
Maximal bexarotene dose (mg/day)	363.62	75	750
Period on bexarotene therapy (months)	20.78	1	114
			N (%)
Bexarotene monotherapy			92 (45.1)
Ongoing bexarotene therapy			44 (21.6)
Other therapies plus bexarotene added later			27 (13.2)
Combined therapy			41 (20.1)

Table 4 Time to achieve clinical response.

	Median (months)
Time to initial response	7.57
Time to partial response	21.10
Time to complete response	27.11

plete responses was 21 months and 27 months, respectively (Table 4).

Response rates and time to achieve them varied depending on the clinical stage (Table 5). It took longer to achieve both partial (23 months) and complete responses (30 months) in the early vs the late-stage group (14 and 19 months, respectively). Overall, early-stage patients were on bexarotene for longer periods of time (24 months) vs late-stage patients (10 months).

In relation to combined treatments, we only found that PUVA treatment prior to bexarotene increased the rate of patients with PRs (from 43% up to 47.3%) while the rate of patients with DP dropped (from 20.6% down to 13.4%). Stable patients also went up 4%, but they are not very significant data on this regard.

A total of 44% of our patients remained on bexarotene maintenance therapy (doses were very variable based on response, adverse events, and patient comorbidities, often ranging from 150 mg/m^2 up to 300 mg/m^2) when study data were collected.

Adverse events (Table 6)

The most common adverse events reported were hypertriglyceridemia (79%), followed by hypercholesterolaemia (71%). A total of 197 patients required lipid-lowering drugs (146 and 51 patients received these drugs before and after starting bexarotene, respectively). Fibrates, statins, and omega-3 fatty acids were administered to 160, 145, and 50 patients, respectively.

Hypothyroidism was diagnosed in 52% of the patients. Overall, 205 patients received thyroid supplementation, which was added preventively in 121 patients prior to bexarotene therapy. In the remaining 84 patients, it was added after starting bexarotene.

No grade 5 adverse events were reported.

Discussion

The use of bexarotene was approved based on 2 phase II/III clinical trials[9,10] conducted among 58 patients with early stage-disease (stages I–IIA) and 94 patients with advanced-stage disease (stages IIB–IVB). However, studies showing the safety and efficacy profile in a real-life setting are scarce. As far as we know this is the 7th cohort of patients with CTCL on bexarotene reported in the medical literature currently available. First, Abbott et al. published their 5-year experience with bexarotene in 66 English patients in 2009. Shortly after that, Väkevä et al. published their 10-year experience with bexarotene in 37 Finnish patients in 2012, while Quéreux et al. reported their 10-year experience in 32 French patients in 2013. Finally, Sokolowska-Wojdylo et al. conducted a similar study on their 5-year results in 21 Polish patients in 2016. There are 2 more Japanese series available: Fujimura et al. (29 patients), and Hamada et al. (267 patients), including many types of CTCL and shorter follow-ups. Therefore, our cohort seems to be the 2nd largest series ever reported of 216 patients with CTCLs (exclusively MF and SS) on bexarotene treated by the Spanish Working Group of Cutaneous Lymphomas. Data on real-life conditions are essential to assess the molecule long-term results and tolerability without the ideal conditions of clinical trials.

A total of 90% of our patients had already received other topical or systemic therapies prior to bexarotene, which is a similar rate compared to other studies. The rate of patients pretreated with systemic therapies was 44% (39% and 75% in the Finnish and French cohorts, respectively, and 52% in the Hamada series).

Our study confirms bexarotene is effective to treat both early and advanced-stage CTCL, with an OR of 70.3% (CR, 25.5%; PR, 44.8%). Abbott et al. reported an OR of 44% (CR, 9%; PR, 35%), Väkevä et al. of 75%, Quéreux et al. of 59% (CR, 13%; PR, 47%), and Sokolowska-Wojdylo et al. of 81%. Hamada et al. achieved the lowest OR of all (46.8%) with a CR of 11.5%. In our cohort, 12% of the patients achieved disease stabilization and 17% were not controlled and progressed despite the use of bexarotene.

In our study, the higher clinical response reported may be the result of over half of the population being treated with a combination therapy (55%) at some point while on bexarotene. In the French study fewer patients (44%) were co-treated with other systemic therapies, achieving a lower OR (59%). However, this hypothesis is not consistent with other studies: on one hand, in the British study, a similar

Table 5 CR, PR, SD and PD based on stage disease.

Stages	Complete response, *n* (%)	Partial response, *n* (%)	Stable disease, *n* (%)	Progression *N*° (%)	Total (%)
IA	18 (43.9)	13 (31.7)	5 (12.2)	5 (12.2)	41 (19.3)
IB	20 (25.7)	39 (50.0)	10 (12.8)	9 (11.5)	78 (36.6)
IIA	1 (20)	1 (20)	1 (20)	2 (40)	5 (2.3)
IIB	5 (12.8)	21 (53.8)	4 (10.3)	9 (23.1)	39 (18.3)
IIIA	4 (25.0)	6 (37.5)	1 (6.3)	5 (31.2)	16 (7.5)
IIIB	2 (33.3)	2 (33.3)	2 (33.3)	0	6 (2.8)
IVA	3 (12.0)	12 (48.0)	4 (16.0)	6 (24.0)	25 (11.8)
IVB	1 (33.3)	2 (66.7)	0	0	3 (1.4)
Total	54 (25.5)	95 (44.8)	27 (12.7)	36 (17)	212 (100)

Table 6 Adverse events associated with bexarotene therapy reported in our study.

	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Hypertriglyceridemia	170	74	47	32	17
Hypercholesterolemia	152	97	42	12	1
Hypothyroidism	108	72	29	6	1
Neutropenia	26	11	2	8	5
Hypertransaminasemia	26	12	9	5	0
Dermatologic adverse events	21	17	3	1	0
Myalgia	21	14	6	1	0
Glycemic disorders	20	8	5	7	0
GI disturbances	7	3	4	0	0
Pancreatitis	6	5	1	0	0
Impotence	3				
Anemia	2				
Asthenia	2				
Dizziness	2				
Photodermatitis	2				
Dysgeusia	1				
Ocular dryness	1				

rate of patients compared to those from our study (58%) were on 1 or more additional CTCL therapies, with a much lower OR (44%); on the other hand, fewer Finnish patients (41%) underwent combination therapy later in the course of bexarotene treatment, with better response rates (ORs were 75% and 73% in the monotherapy and concomitant therapy groups, respectively). Although the Polish study achieved the highest OR (81%), we should mention that they had a high mortality rate (53%). The lower OR achieved by Hamada et al. could be due to the presence of more patients in advanced stages vs other series.

Our study is underpowered to compare the effectiveness of bexarotene monotherapy vs its combination with other therapies, as regimens, duration and schedule of combined treatments are heterogeneous. According to a randomized prospective controlled trial, a combination of PUVA plus bexarotene is safe and well tolerated, although no significant differences in the clinical response rates were reported.[18] Same as we did, Hamada et al. found a difference in OR between the 2 patient groups with and without adding PUVA (57.6% vs 25.5%).

Response rates also seem to be related to duration and doses of treatment. The longer the duration of the therapy, the better the clinical outcomes: Abbott et al. reported an OR of 44% with a mean course of treatment of 11 months, Quéreux et al. reported an OR of 59% with 17 months of therapy, our study reported an OR of 70% with 21 months of therapy, and Väkevä et al. reported an OR of 75% with 26 months of therapy. Once again, Sokolowska-Wojdylo et al.'s study seems to be the exception to the rule, as they achieved an OR of 81% with a 15-month course of therapy. The longest duration of the therapy in a patient was recorded in our study (114 months) and the shortest one in the study conducted by Hamada et al. (0.3 months with a median of 9.1 months). Regarding doses, their results indicated that patients on higher mean dose of bexarotene tended to show better response rates. However, patients in advanced stages received lower doses to avoid adverse side effects.

In our study, time to response was longer than in previous studies (initial, partial and complete responses were achieved at 8, 21 and 27 months respectively), with a mean time to response of nearly 2–4 months.[12–15] This might be due to the lower daily dose used in our study (364 mg/day, i.e. 200 mg/m^2/day) vs 275 and 225 mg/m^2/day used by Quéreux et al. and Abbot et al., respectively. Indeed, clinical response has been shown to be dose related in clinical trials,[9,10] as Hamada et al. also confirmed.

In our study, earlier cases seem to have better outcomes than the advanced ones, which is controversial in the scientific medical literature currently available. Väkevä, Sokolowska-Wojdylo and Hamada's results are consistent with ours, while Abbot obtained opposite results, and Quéreux cohort shows a similar OR between early and advanced disease. Abbott et al. hypothesize that higher response rates in their advanced stage-disease patients may be due to a role-increased bexarotene side effect tolerance in this group. Interestingly, clinical response in our cohort seems to be faster in advanced stages.

According to the scientific medical literature currently available, bexarotene can maintain long-lasting responses (median response duration of 16 months in the Quéreux cohort), and once clinical response is achieved, progression is rare.[14] Recent guidelines state that bexarotene should be continued as maintenance therapy with a minimal effective dose until loss of response, as CTCL tend to progress slowly and have no curative treatment, being the sole aim of therapy to achieve most durable remission.[5,13]

Our work also confirms bexarotene was well tolerated, as only 24 patients (11%) experienced drug-related grade 4 adverse events, and 0 experienced grade 5 adverse events. As previously reported, most frequent side effects were hyperlipidemia and hypothyroidism, which seemed to be dose-related.[17]

Hypertriglyceridemia was the most widely reported side effect in 79% of the patients, and over two-thirds of such patients were low-grade (grades 1 or 2). Other cohorts

reported[14] similar rates (78%), and so did the initial clinical trial[9,10] (64% and 79%). Nevertheless, the simultaneous administration of lipid-lowering agents usually controls lipid levels, and only 6 cases of pancreatitis were noted in our series, all of them low-grade reactions (1 grade 5, and another grade 2). Hypercholesterolemia was also frequent (70%) and mainly mild. Almost all patients received lipid-lowering drugs, although a quarter of them received it after bexarotene initiation. As a matter of fact, the new clinical guidelines recommend pre-treating patients with a fibrate 1 week prior to starting bexarotene therapy, preferably with fenofibrate 150–300 mg daily.[11,19,20] Lipid levels should then be monitored, and if needed, other agents such as statins can be added to fibrates if high triglyceride and low-density lipoprotein cholesterol persist. Nonetheless, such combination increases the risk of inducing myopathy, rhabdomyolisis, and acute kidney failure, which is why extreme caution is advised. Additionally, fibrates are associated with several adverse events, such as muscle pain, elevated creatine kinase levels and hypertransaminasemia, which would require treatment discontinuation. If fibrate-related side effects occur or a statin is needed to control hypercholesterolaemia, Musolino et al. demonstrated that omega-3 fatty acids are a good alternative to fenofibrate as they are effective and well tolerated.

Hypothyroidism was observed in over half of the patients, and almost all cases were mild (93% were grade 1 or 2). Other series reported higher rates of this side effect (74% and 93% in Abbott and Quéreux's studies, respectively, and 85.8% in Hamada's trial), while the 2 initial clinical trials[9,10] reported lower rates (40% and 39%), probably underestimating its actual incidence rate. Nonetheless, there are usually no severe cases of hypothyroidism, and when they occur, they are always controlled with low-dose thyroxine, meaning it is not a worrisome reaction. Recent clinical guidelines recommend thyroid hormone supplementation routinely added since day 1 of bexarotene therapy, starting at 50 μg of levothyroxine daily and individually titrating it based on serum levels of T4.[11,19] In our study, 95% of the patients received thyroid supplementation, but over half of them initiated it after starting their bexarotene regimen. Thus, adding levothyroxine to bexarotene might prevent some of these adverse events from happening. Additionally, correcting hypothyroidism helps control hyperlipidemia by increasing lipid clearance, which is reduced in the presence of a low thyroid function.[20] Lipid-lowering agents and thyroid hormone supplementation should be continued while on treatment to maintain stable lipid and T4 levels, and their levels should be monitored while on treatment too.

The aforementioned adverse events seem to be dose-related,[10,17] so dosage can be individualized to achieve maximum clinical benefit with minimal adverse reactions. Some guidelines recommend initially to start bexarotene at half doses (150 mg/m^2 daily) for 2 to 4 weeks, and then up-titrate to its full dose (300 mg/m^2 daily) in patients without toxicity,[20] while Hamada et al. recommend starting with the full dose to achieve better responses.

Overall, bexarotene is well tolerated, and holds the advantage of being less immunosuppressive than other drugs,[8] thus preventing the occurrence of more infectious diseases in these patients (we did not observe infections in our cohort, and neither did Quéreux' trial). Furthermore, it is orally administered, which really helps.

Regarding other side effects, hypertransaminasemia occurred in 12% of our patients, which was reported in Väkevä's trial (10%) for the first time in 2012 and then by Quéreux's trial (3%; only 1 patient developed it), and Hamada's series (15%).

Interestingly, 3 patients developed impotence, in which statins may play a role. It has been reported that statins may reduce testosterone levels, favoring erectile dysfunction.[21,22] However, this is controversial in the literature, as there are studies supporting that these lipid-lowering drugs might have positive effects on erectile function, especially for non-responders to phosphodiesterase type 5 inhibitors.[23] Hence, further studies are needed to investigate the role of statins in this symptom.

We are aware that our study carries some limitations. First, it has the main drawbacks of retrospective studies, including selection bias, with a heterogeneous population holding different prognostic features based on different comorbidities, previous treatments and different combination therapies, and information bias, as recorded data depends on the availability and accuracy of health records. Second, solid conclusions cannot be drawn from retrospective studies, which can only generate new hypotheses to be confirmed in further controlled prospective trials. And finally, as in the previously published cohorts, we could not use a standardized scoring system for assessing tumor burden, using a global assessment for patient responses instead.[24]

Conclusions

Bexarotene seems to be effective, safe, and well tolerated to treat early and advanced CTCL and should be continued as maintenance therapy after CR has been achieved. It can be used as monotherapy or combined with other therapies. Dosage should be individualized to achieve maximum benefit with manageable side effects. Moreover, routine laboratory tests are needed to carefully monitor the most widely reported adverse events (hyperlipidemia and hypothyroidism), which are usually preventable and/or manageable with concomitant drugs.

Authors' contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for its content, including participation in the concept, design, analysis, drafting, or revision of the manuscript. Furthermore, each author certifies that this material, or similar material has not been and will not be submitted to or published in any other publication.

Conflicts of interest

None declared.

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