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


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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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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 years (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.

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

Bexarotene (Targretin®; Cephalon pharmaceuticals, Inc., Maisons-Alfort, France) is an X-receptor synthetic retinoid approved by the FDA in 1999 to treat CTCL in patients refractory to, at least, 1 prior systemic therapy. In Europe, 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. 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. 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. Hypertriglycerideremia 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. Adverse events require monitoring of laboratory parameters at the follow-up and are often well managed with concomitant drugs. All retinoids are teratogenic. The use of bexarotene for early- and advanced-stage disease is supported by 2 phase II/III clinical trials. 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.

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 TNM staging system was used for CTCL. The patients’ treatment was left to the physician’s criterion.

Patients received 75-mg bexarotene capsules with a varying dose of 150 mg/m² up to 300 mg/m² 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 ≥50% reductions in the area of skin lesions for, at least, 1 month, whereas progressive disease (PD) meant ≥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).

**Figure 1** Spanish hospitals participating in the study and no. of patients on bexarotene in each center.
Table 1  Patient characteristics and previous therapies.

<table>
<thead>
<tr>
<th>Sex, N (%)</th>
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<tbody>
<tr>
<td>Man</td>
<td>133 (61.6)</td>
<td></td>
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<tr>
<td>Woman</td>
<td>83 (38.4)</td>
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<tr>
<th>Age, years (min–max)</th>
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<tr>
<td>At bexarotene initiation</td>
<td>63.5 (27–95)</td>
<td></td>
</tr>
<tr>
<td>At CTCL diagnosis</td>
<td>55.22 (13–94)</td>
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<tr>
<th>Stage, N (%)</th>
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<tbody>
<tr>
<td>IA</td>
<td>41 (19.2)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>78 (36.4)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>40 (18.7)</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>16 (7.5)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>6 (2.8)</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>25 (11.7)</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>3 (1.4)</td>
<td></td>
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<tr>
<th>Previous therapies, N (%)</th>
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<tbody>
<tr>
<td>None</td>
<td>21 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>177 (81.9)</td>
<td></td>
</tr>
<tr>
<td>PUVA</td>
<td>113 (52.3)</td>
<td></td>
</tr>
<tr>
<td>NBUBV</td>
<td>29 (13.4)</td>
<td></td>
</tr>
<tr>
<td>IFN-α</td>
<td>53 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>36 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>22 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Topical chemotherapy</td>
<td>21 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Retinoids</td>
<td>20 (9.3)</td>
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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/m² up to 300 mg/m²) when study data were collected.

Adverse events (Table 6)

The most common adverse events reported were hypertriglyceridemia (79%), followed by hypercholesterolemia (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.

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.

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 complete 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 the median of 29.3 months (range: 4–47.2).

Discussion

The use of bexarotene was approved based on 2 phase II/III clinical trials 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, Vákevá et al. published their 10-year experience with bexarotene in 37 Finnish patients in 2012, while Quéréux 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).
Table 2  Bexarotene dosage and duration of therapy and treatment schedule (note that data of 12 patients are missing).

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>Body surface (m²)</td>
<td>1.81</td>
<td>1.38</td>
<td>2.36</td>
</tr>
<tr>
<td>Initial bexarotene dose (mg/day)</td>
<td>246.56</td>
<td>75</td>
<td>675</td>
</tr>
<tr>
<td>Maximal bexarotene dose (mg/day)</td>
<td>363.62</td>
<td>75</td>
<td>750</td>
</tr>
<tr>
<td>Period on bexarotene therapy (months)</td>
<td>20.78</td>
<td>1</td>
<td>114</td>
</tr>
<tr>
<td>Bexarotene monotherapy</td>
<td>92 (45.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing bexarotene therapy</td>
<td>44 (21.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other therapies plus bexarotene added later</td>
<td>27 (13.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined therapy</td>
<td>41 (20.1)</td>
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</table>

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%), Vákevá et al. of 75%, Quéréux 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 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 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. 13 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, Quéréux 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 Vákevá 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. 12,13 This might be due to the lower daily dose used in our study (364 mg/day, i.e. 200 mg/m²/day) vs 275 and 225 mg/m²/day used by Quéréux et al. and Abbott 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. Vákevá, Sokolowska-Wojdylo and Hamada’s results are consistent with ours, while Abbott obtained opposite results, and Quéréux 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 Quéréux 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...
In Lipid-lowering therapy, however, treatment 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,10,11 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/m² daily) for 2 to 4 weeks, and then up titrate to its full dose (300 mg/m² 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,4 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 Väkevää’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.

References


