SHORT COMMUNICATION

Real-life Use of Bexarotene for T-cell Cutaneous Lymphoma Management: Efficacy and Tolerance with Low Doses

Jacques ROUANET[1,2], Inès JOULIE[1], Céline LAMBERT[3] and Michel D'INCAN[1]
[1]Dermatology and Oncodermatology Department, CHU Clermont-Ferrand, Université Clermont Auvergne, FR-63000 Clermont-Ferrand, [2]Université Clermont Auvergne, INSERM, U1240 Imagerie Moléculaire et Stratégies Théranostiques and, [3]DRCI, Biostatistics Unit, CHU Clermont-Ferrand, Clermont-Ferrand, France. E-mail: jrouanet@chu-clermontferrand.fr
Accepted Feb 17, 2022; Epub ahead of print xx
Acta Derm Venereol 2022; 102: adv00746. DOI: 10.2340/actadv.v102.718

Mycosis fungoides (MF) and erythrodermic cutaneous T-cell lymphomas (E-CTCL) represent approximately 50% of primary cutaneous lymphomas (1). In 2001, bexarotene (BXR) has obtained a European marketing authorization (EMA) for treatment of skin manifestations of advanced-stage CTCL in patients refractory to at least 1 systemic treatment (2). However, BXR seems to be widely prescribed in early-stage CTCL (3–8) or as a first-line therapy (5) outside these recommendations. In addition, the recommended dose (300 mg/m²/day) leads frequently to treatment discontinuation (2, 4) due to dose-dependent adverse events (AE). Therefore, some authors suggest the use of BXR at lower doses (5). These data all show clear disparity between EMA recommendations and practical use of BXR.

METHODS AND RESULTS

The use of BXR was assessed in real-life conditions, considering effectiveness and tolerance, in 64 patients with MF and E-CTCL (**Fig. 1**, **Table I**) treated between 2006 and 2020 in a reference centre. All cases were reviewed by the French Cutaneous Lymphoma Study Group. Patients were staged according to the 2007 tumour-node-metastasis (TNM) classification proposal by the International Society for Cutaneous Lymphomas - European Organization of Research and Treatment of Cancer (ISCL-EORTC). Early-stage mycosis fungoides corresponded to stage I mycosis fungoides ($n=13$). Advanced-stage mycosis fungoides corresponded to stage II mycosis fungoides ($n=22$). ECTCL regrouped T4 CTCL (stage III, $n=15$, and stage IV, $n=14$), including 6 erythrodermic mycosis fungoides (T4, B0), 9 intermediate stage (T4, B1) and 14 Sézary syndrome (SS) (T4, B2).

In 70.3% of patients, BXR was prescribed according to the EMA. In other cases, BXR was prescribed for early-stage CTCL (4.7% or as a first-line (17.2%) or both (7.8%). BXR was prescribed as a first-line systemic therapy in older patients (74.9 ± 12.2 years vs 64.9 ± 12.9 years; $p=0.009$, 2-sided Student's t-test) because of concerns regarding methotrexate AE in ageing patients. BXR was used in monotherapy in 78% of cases.

The BXR starting dose was between 150 and 450 mg/day, with a median [interquartile range; IQR] of 225 mg/day [150; 225], corresponding to a BSA median dose of 117 mg/m²/day [100; 133]. The median of mean daily doses was 259 mg/day [223; 297], corresponding to a median of BSA mean daily doses of 135 mg/m²/

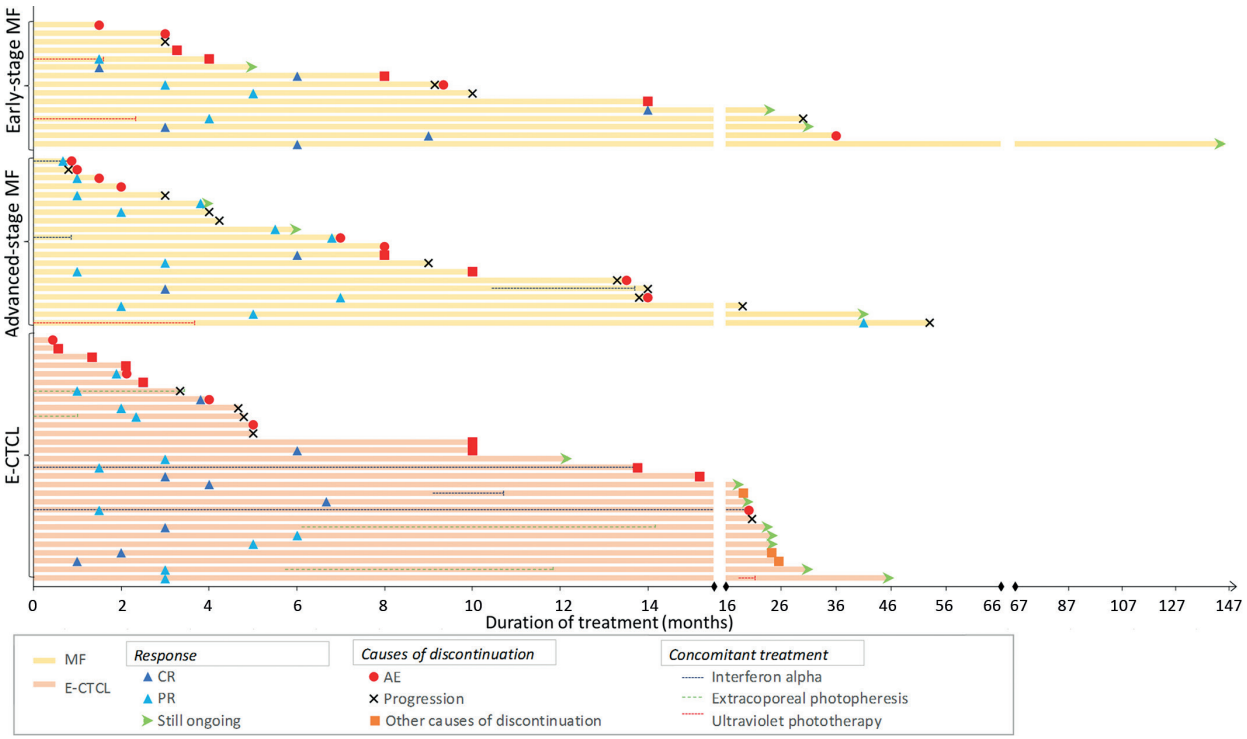

Fig. 1. Clinical response, duration of treatment and outcomes. AE: adverse event; CR: complete response; E-CTCL: erythrodermic cutaneous T-cell lymphoma; MF: mycosis fungoides; PR: partial response.

Table I. Population, bexarotene prescription and adverse events characteristics

Characteristics of the population ($n=64$)	
Age at diagnosis, years, mean±SD	64.0±14.7
Age at BXT introduction, years, mean±SD	67.9±13.3
Sex (male), *n* (%)	38 (59.4)
Time for BXT introduction since CTCL diagnosis, years, median [IQR]	2.0 [0.5; 5.8]
Pathology), *n* (%)	
MF, including:	35 (54.7)
Early-stage MF	13 (20.3)
Advanced-stage MF	22 (34.4)
E-CTCL, including:	29 (45.3)
Erythrodermic MF	6 (9.4)
Intermediate stage	9 (14.0)
SS	14 (21.9)
Stages, *n* (%)	
Early	15 (23.4)
Advanced	49 (76.6)
Previous local treatments), *n* (%)	62 (96.9)
Topical steroids	62/62 (100.0)
Chlormethine	16/62 (25.8)
Carmustine	19/62 (30.6)
Previous systemic treatments), *n* (%)	48 (75.0)
Ultraviolet phototherapy (UVB or PUVA)	23/48 (47.9)
Interferon alpha	16/48 (33.3)
Methotrexate	26/48 (54.2)
Total skin electron beam therapy	5/48 (10.4)
Extra corporeal photopheresis	10/48 (20.8)
Others	21/48 (43.8)
BXT prescription	
Prescription according to the EMA indications), *n* (%)	45 (70.3)
Starting dose, mg/day, median [IQR]	225 [150; 225]
Dose at BCR, mg/day, median [IQR]	300 [225; 375]
Concomitant treatment, *n* (%)	14 (21.9)
Ultraviolet phototherapy (UVB or PUVA)	4/14 (28.6)
Interferon alpha	6/14 (42.9)
Extra corporeal photopheresis	4/14 (28.6)
Overall response, *n* (%)	46 (71.9)
Complete response	16 (25.0)
Partial response	30 (46.9)
Stable disease, *n* (%)	14 (21.9)
Progressive disease, *n* (%)	4 (6.2)
Time to response, months, median [IQR]	3.0 [2.0; 5.4]
Duration of response, months, median [IQR]	16.8 [8.0;37.8]
Duration of treatment, months, median [IQR]	9.0 [3.6; 19.8]
Adverse events, *n* (%)	
Hypothyroidism	59 (92.2)
Hypertriglyceridaemia	45 (70.3)
Hypercholesterolaemia	30 (46.9)
Asthenia	13 (20.3)
Depression symptoms	9 (14.1)
Lymphopaenia	8 (12.5)
Anaemia	4 (6.2)
Neutropaenia	2 (3.1)
Liver toxicity	1 (1.6)
Myalgia	1 (1.6)
Diarrhoea	1 (1.6)
Abnormal INR	1 (1.6)
BXT discontinuation due to AE, *n* (%)	17 (26.6)
Depression symptoms	5/17 (29.4)
Asthenia	3/17 (17.5)
Hypertriglyceridaemia	2/17 (11.8)
Neutropaenia	2/17 (11.8)
Anaemia	1/17 (5.9)
Liver toxicity	1/17 (5.9)
Myalgia	1/17 (5.9)
Diarrhoea	1/17 (5.9)
Abnormal INR	1/17 (5.9)

SD: standard deviation; IQR: interquartile range; AE: adverse events; BCR: best clinical response; BXT: bexarotene; CTCL: cutaneous T cell lymphoma; E-CTCL: erythrodermic cutaneous T cell lymphoma; EMA: European marketing authorization; INR: international normalized ratio; MF: mycosis fungoides; PUVA: psoralen and ultraviolet A; SS: Sézary syndrome; UVB: ultraviolet B.

day [107; 181], representing less than half the EMA-recommended dose. The median dose for best clinical response (BCR) was 300 mg/day [225; 375], corresponding to 148 mg/m^2/day [121; 208]. Sixteen, 30 and 14 patients achieved complete response (CR), partial response (PR) and stable disease (SD), respectively. Overall response (OR=CR+PR) and overall control rate (CR+PR+SD) were 71.9% and 93.8%, respectively.

As expected, the most common drug-related AE were hypothyroidism (92.2%), hypertriglyceridaemia (70.3%) requiring fibrate treatment (when exceeding 5 g/l) in two-thirds of cases and hypercholesterolaemia (46.9%) requiring statin treatment in only one-third of cases. Seventeen patients (26.6%) had to stop BXR treatment due to AE. Interestingly, 9 patients reported several associated mild to moderate depression symptoms (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] criteria). These symptoms were: abulia, asthenia, sleep disorders (hypersomnia/insomnia), sadness, concentration disorders and weight variations without others causes. None of the patients meet the DSM-5 criteria to define a major depressive episode. However, in 5 cases, depression symptoms were responsible for BXR discontinuation and have improved after withdrawal of BXR. Only 2/9 patients received a co-treatment with interferon alpha, which could have aggravated those symptoms. Seven of these depressed patients had hypothyroidism, but all were supplemented and had a normalized fT4 level.

DISCUSSION

This work raises several points of interest: (*i*) BXR seems to be more efficient when used as first systemic treatment (CR: 43.8% in first-line BXR patients vs 19% in previously-treated patients ($p=0.09$, 2-sided χ^2 test); (*ii*) efficacy of BXR is not impaired by using lower doses than recommended (148 mg/m^2/day vs 300 mg/m^2/day) as we report BXR response rate (OR 71.9%) and a median time to achieve BCR (3 months) similar to most series using higher doses (3–6); (*iii*) in contrast to EORTC recommendations (9), when using low-doses of BXR, adding a lipid-lowering drug could not be systematically necessary at BXR initiation, in order to limit drug-related iatrogeny, but should be used as soon as dyslipidaemia appears, as, in our series, only two-thirds of patients with hypertriglyceridaemia and one-third of patients with hypercholesterolaemia needed a lipid-lowering drug treatment; however, a larger sample is mandatory to confirm this suggestion; (*iv*) depression symptoms are an underestimated specific AE of BXR: depression symptoms were reported as AE in 9/64 patients, responsible for BXR discontinuation in 5 of them.

Considering the cost-effectiveness of BXR and the occurrence of severe AE, these data suggest that low doses of BXR may be reasonably used in patients with CTCL. In addition, physicians should be attentive to the risk of depression symptoms, which may lead to discontinuation of treatment.

The authors have no conflicts of interest to declare.

REFERENCES

1. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019; 133: 1703–1714.
2. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. J Clin Oncol 2001; 19: 2456–2471.
3. Sokolowska-Wojdylo M, Florek A, Zaucha JM, Chmielowska E, Giza A, Knopinska-Posluszny W, et al. Polish Lymphoma Research Group experience with bexarotene in the treatment of cutaneous t-cell lymphoma. Am J Ther 2016; 23: e749–756.

4. Quereux G, Saint-Jean M, Peuvrel L, Brocard A, Knol AC, Dreno B. Bexarotene in cutaneous T-cell lymphoma: third retrospective study of long-term cohort and review of the literature. Expert Opin Pharmacother 2013; 14: 1711–1721.
5. Väkevä L, Ranki A, Hahtola S. Ten-year experience of bexarotene therapy for cutaneous T-cell lymphoma in Finland. Acta Derm Venereol 2012; 92: 258–263.
6. Abbott RA, Whittaker SJ, Morris SL, Russell-Jones R, Hung T, Bashir SJ, et al. Bexarotene therapy for mycosis fungoides and Sezary syndrome. Br J Dermatol 2009; 160: 1299–1307.
7. Roche Gamon E, Perez Ferriols A, Vilata Corell JJ, Alegre de Miquel V. [Mycosis fungoid treated with oral bexarotene: study of 13 cases]. Med Clin (Barc) 2007; 129: 677 (in Spanish).
8. Fujimura T, Sato Y, Tanita K, Amagai R, Shimauchi T, Ogata D, et al. Case series of cutaneous T-cell lymphomas treated with bexarotene-based therapy. J Dermatol 2020; 47: 636–640.
9. Gniadecki R, Assaf C, Bagot M, Dummer R, Duvic M, Knobler R, et al. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol 2007; 157: 433–440.