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/
## 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 $\chi^2$ test); (ii) efficacy of BXR is not impaired by using lower doses than recommended (148 mg/m²/day vs 300 mg/m²/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.

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### Table I. Population, bexarotene prescription and adverse events characteristics

| Characteristics | Population (n = 64) | BXR prescription | Adverse events (n) |
|-----------------|-------------------|-------------------|-------------------|
| Age at diagnosis, years, mean ± SD | 64.0 ± 14.7 |  |  |
| Age at BXR introduction, years, mean ± SD | 67.9 ± 13.3 |  |  |
| Sex (male), n (%) | 38 (59.8) |  |  |
| Time for BXR 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) |  |  |
| Total steroids | 62/62 (100.0) |  |  |
| Chloromethine | 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) |  |  |
| 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] |  |  |
| Hypercholesterolaemia | 30 (46.9) |  |  |
| Hypertriglyceridaemia | 59 (92.2) |  |  |
| Hypothyroidism | 45 (70.3) |  |  |
| Hyperkeratosis | 30 (46.9) |  |  |
| Depression symptoms | 9 (14.1) |  |  |
| Anemia | 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) |  |  |
| BXR discontinuation due to AE, n (%) | 17 (26.6) |  |  |
| Depression symptoms | 5/19 (25.9) |  |  |
| Anemia | 3/17 (17.6) |  |  |
| Neutropaenia | 3/17 (17.6) |  |  |
| Anemia | 1/17 (5.9) |  |  |
| Diarrhoea | 1/17 (5.9) |  |  |
| Abnormal INR | 1/17 (5.9) |  |  |

SD: standard deviation; IQR: interquartile range; AE: adverse events; BXR: 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.
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