

INVESTIGATIVE REPORT

Ten-year Experience of Bexarotene Therapy for Cutaneous T-cell Lymphoma in Finland

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Bexarotene is an oral retinoid shown to be active against the cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). Literature on the efficacy, dosing and side-effects of bexarotene is sparse. We present here data on 37 Finnish patients with CTCL treated with bexarotene during the last 10 years. Bexarotene was equally effective as monotherapy or when combined with other treatment modalities, resulting in overall responses of approximately 75%. Early-stage CTCL responded better than advanced-stage CTCL (83% vs. 33%). The mean time to observable response was 3 months and the mean duration of the response was 21 months. The dose of bexarotene was generally lower than recommended due to side-effects. Abrupt elevation of liver transaminases, resulting in cessation of treatment, was observed in 4 (11%) patients. We conclude that the dose of bexarotene should be titrated individually to achieve optimal results. Maintenance therapy with low-dose bexarotene is a feasible alternative. Key words: cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome; bexarotene; Finland.

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Primary cutaneous T-cell lymphomas (CTCL) define a heterogeneous group of T-cell lymphoproliferative disorders originating in the skin. Mycosis fungoides (MF) is the most common form, comprising almost half of all primary cutaneous lymphomas. MF typically affects older adults (median age at diagnosis 57.5 years), and the male:female ratio is 1.8:1 (1). Sézary syndrome (SS) is the leukaemic form of CTCL with distinct molecular pathogenesis of MF (2). The treatment algorithm of CTCL is based on the stage of the disease (3, 4). The tumour-node-metastasis-blood (TNMB)-based staging criteria were revised in 2007 (5).

MF has an indolent clinical course and the disease progresses slowly. The estimated 5-year survival rate is 88% (1). However, in SS the prognosis is poor, the

5-year survival rate being only 24%. Skin-directed therapy (e.g. topical steroids) usually leads to long remissions in the early stages (IA–IIA). MF confined to the skin is treated with photo-(chemo)-therapy, ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA), whereas combination chemotherapy is recommended for systemic CTCL (stage IV). SS is treated with extracorporeal photopheresis (ECP), either alone or in combination with, e.g. interferon (IFN)- α , or with IFN- α alone or in combination with PUVA. Other novel treatment modalities for MF and SS include CD52 antibody alemtuzumab, histone deacetylase inhibitors vorinostat, romidepsin; recombinant fusion protein denileukin diftitox, and selective retinoid bexarotene, as discussed further in this article (3, 6–9). In highly selected cases of MF or SS, bone marrow transplantation may be an option (10).

Retinoids belong to the steroid hormone family of molecules. They have long been used alone or in combination with other therapies for CTCL (11, 12). The advantage of retinoids is that they do not have the side-effects of immunosuppressive drugs and can be administered orally. The biological effects of retinoids have been shown to be mediated by the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Bexarotene is the first synthetic highly (RXR) selective retinoid "rexinoid" that has proven effective, safe and well tolerated in refractory CTCL (13). Bexarotene was approved by the Food and Drug Administration (FDA) in 1999 and was licensed in Europe in 2002 for the treatment of advanced stages of CTCL. In Finland, we have used bexarotene as a second-line therapy since 2002. The exact mechanism of action of bexarotene is unknown, but it binds to RXR and induces dose-dependent apoptosis of malignant T lymphocytes (14). It does not affect T-regulatory cells, keratinocytes or Langerhans' cells of the skin (15–17). The well-known side-effects of bexarotene include hypertriglyceridaemia, which requires individual dosing of this drug and often a preventative usage of lipid-lowering therapy and thyroid hormone replacement, followed by monitoring of laboratory parameters. There are only a few reports concerning the optimal duration and guidance for bexarotene treatment (8, 18, 19).

The aim of this study was to evaluate 10-year bexarotene treatment results and observed unexpected side-

effects in CTCL patients treated in our hospital district, to determine the optimal schedule for bexarotene treatment, tapering of the dose, and duration of therapy. Also, we report on the difference in response rates between bexarotene monotherapy and combination with other treatment modalities.

PATIENTS AND METHODS

Thirty-seven patients with CTCL treated with bexarotene in Helsinki University Central Hospital (HUCH, the Skin and Allergy Hospital for the years 2002 to 2012) were examined retrospectively. Six patients (16%) were followed up in other dermatological clinics after initiation of bexarotene therapy in HUCH. The median age of the patients was 60 years (range 23–87 years). Twenty-one patients (57%) were male and 16 (43%) female. The diagnosis of CTCL was based on the clinical picture, histopathological characteristics of multiple skin biopsies, computed tomography analysis, and T-cell receptor gene rearrangement analysis (1, 20). The patients were mainly evaluated clinically, but occasionally skin biopsy histology was also performed. All patients were classified according to the TNMB classification for CTCL staging and the International Society for Cutaneous Lymphomas (ISCL)/European Organization of Research and Treatment of Cancer (EORTC) classification (5), according to which 26 of the patients (70%) had an early-stage MF (stages IA–IIA). Of these early cases, 8 (31%) were folliculotropic type. Three MF patients (8%) had advanced stage disease (stages IIB–IVB), 4 (11%) had Sézary syndrome (SS), 1 (3%) had peripheral T-cell lymphoma and 2 (5%) had subcutaneous panniculitis-like T-cell lymphoma. The majority of patients had received other therapies before bexarotene administration. Twenty-two patients (59%) received UV therapy, mainly PUVA. Eight patients (22%) received radiation therapy, and 14 (39%) received systemic therapy, for example interferon (IFN), doxorubicin, methotrexate, aciclovir, and chlorambucil. Twenty-three patients (64%) had a pre-existing chronic illness, typically a cardiovascular disease requiring regular medication. On the other hand, 13 patients (36%) were otherwise healthy with no regular medication. Ten patients (28%) developed another primary malignancy after CTCL diagnosis, mainly squamous cell carcinomas of the skin and carcinomas of the prostate, mammary glands, and lungs. These secondary malignancies were recorded randomly before or after bexarotene therapy.

Before starting therapy, the patients were evaluated carefully for past medical history, clinical examination, skin biopsy (if not taken recently), computed tomography (CT) scan (if not performed within the past 12 months), and wide laboratory examinations, including full blood cell count, Sézary cell count, renal and liver function tests, infection parameters, lipid profile and thyroid hormone levels. When starting bexarotene therapy, the patients were hospitalized for a short period and monitored for the immediate side-effects of bexarotene. The essential laboratory parameters were assessed weekly at the beginning of the treatment for 4 weeks and monthly thereafter. Clinical follow-up was every 2–3 months, and later, in a stable phase of the treatment, every 4–6 months.

The daily starting dosage of bexarotene was 300 mg/m² in the earliest years of our bexarotene experience. Since only a few patients tolerated it without considerable side-effects, we changed to more individual dosing, starting with approximately 150 mg/m² daily dose. The dosage is individually altered in relation to clinical response and manageable side-effects. In the first years of bexarotene use, the patients were followed up for laboratory side-effects and a thyroid hormone supplement

and lipid-lowering agents were started only when needed. Thereafter, upon the establishment of bexarotene usage guidelines (8), all the patients have been placed on thyroid hormone supplement and 2 different lipid-lowering agents, atorvastatin and fenofibrate, simultaneously with bexarotene.

In this retrospective study it was not possible to use the tumour burden index (TBI) to determine the degree of cutaneous involvement. A complete response (CR) to bexarotene therapy was defined as no evidence of disease in the skin or extracutaneous organs for a minimum of one month. A partial response (PR) was defined as a 50% reduction in the area of skin lesions for a minimum of one month. The overall response category included both PR and CR patients. The patient had stable disease (SD), when no significant change in the skin or extracutaneous manifestations occurred. Progressive disease (PD) was defined as a 50% area increase in skin lesions, and/or appearance of lymph node, blood, or visceral involvement. The time to achieve the response was determined from the time of starting bexarotene to the first documentation of either CR or PR. The duration of response was determined from the first documentation of achieving CR or PR to the subsequent documentation of PD.

Adverse effects occurring during bexarotene therapy were determined and graded according to National Cancer Institute common terminology criteria for adverse events.

RESULTS

Management of bexarotene therapy

The mean age at starting bexarotene treatment was 65 years (range 37–88 years). All but 3 patients started bexarotene treatment as monotherapy. Those 3 patients started bexarotene therapy simultaneously with PUVA therapy. Nine patients underwent several periods of bexarotene treatment because of initial termination of the therapy due to side-effects or CR. The dose of bexarotene was first determined based on the body surface area, but as experience with the drug increased, the dosage was adjusted individually, and it was generally lower than the recommended dose. The bexarotene doses varied between 75 and 675 mg/day. Patients were treated with bexarotene from 2 to 107 months (mean 26 months). The overall experience of bexarotene treatment studied is thus 68 patient years.

Majority of cutaneous T-cell lymphoma patients respond to bexarotene

A total of 33 patients (75%) achieved an overall response (either CR or PR; Figs 1 and 2). On the other hand, 11 patients (25%) did not respond to bexarotene (stable or progressive disease). Of the early-stage patients (stages IA–IIA), 25 (83%) were responders and 5 (17%) were non-responders. Of the advanced-stage patients (stages IIB–IVB) only 1 (33%) was a responder and 2 (67%) were non-responders. All 4 patients with SS responded to bexarotene therapy completely or partially. The 2 patients with subcutaneous panniculitis-like T-cell lymphoma (SPTL) responded partially to bexarotene. The mean time to achieve the response to bexarotene



Fig. 1. Stage IA mycosis fungoides (a) before and (b) after bexarotene treatment (complete response). The time-interval between (a) and (b) is 3 months in patient No. 17.

treatment was 3 months (range 1–11 months). The mean duration of response to therapy was 21 months, ranging from 1 to 74 months. Thirteen patients (35%) remained on low-dose bexarotene maintenance therapy (Figs 3 and 4).

In total, 15 patients (41%) underwent combination therapy later in the course of bexarotene treatment. The duration of combination therapy was short compared with the overall duration of bexarotene therapy. The most common concurrent therapy was PUVA for 8 patients (53%), followed by IFN (6 patients, 40%). Local electron beam (EB) and extracorporeal photopheresis (ECP) were combined with bexarotene therapy in 2 and 1 cases, respectively. PUVA therapy was given for a 2-month period, and IFN for a period of 1 to 9 months (mean 3 months). Eleven patients (73%) receiving concurrent therapy with bexarotene responded well to the combination.

The most common reasons for withdrawal of bexarotene were inefficiency (41%) or side-effects (20%). Three patients stopped taking bexarotene after achieving CR and one patient after becoming pregnant despite precautions. Table SI (available from: [http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-](http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1359)

1359) shows in detail the different CTCL subgroups and their response, duration of response, combination therapy and percentage of maintenance therapy.

Side-effects of bexarotene therapy

In the early phases of bexarotene use in our clinic, all patients developed hypertriglyceridaemia and hypothyroidism. With increasing clinical experience, lipid-lowering therapy and thyroid supplementation were routinely administered to patients undergoing bexarotene therapy, and, thus, the incidence of these side-effects was reduced. Nine patients (24%) reported no side-effects when undergoing bexarotene therapy. The most common side-effect remained hypertriglyceridaemia, with 19 patients (51%) affected (Table SII; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1359>). The grade of hypertriglyceridaemia varied between II and IV, the highest value being 37 mmol/l. Hypertriglyceridaemia was manageable with lipid-lowering therapy and for only one patient was it the reason for cessation of bexarotene treatment. Hypercholesterolaemia was evident in 7 patients (19%), usually manageable with



Fig. 2. Stage IIA mycosis fungoides (a) before and (b) after bexarotene treatment (partial response). The time-interval between (a) and (b) is 6 months in patient No. 26.



Fig. 3. Patient No. 32 with Sézary syndrome (SS) (a) before and (b) after treatment with bexarotene. The patient is now on maintenance treatment with 75 mg/day (stable disease). This patient was initially treated for ultraviolet B (UVB)-photosensitivity (and actinic reticuloid), which still persists in the neck and face area.

lipid-lowering drugs. Five patients (14%) developed reversible leucopaenia, usually neutropaenia. Four patients (11%) were diagnosed with elevated liver transaminases while undergoing bexarotene therapy. The transaminases (AST and ALT) were at least 5-fold, even over 20-fold elevated, and resulted in termination of bexarotene therapy. The levels of liver enzymes returned to normal after termination of bexarotene, and no hepatitis virus infection or any other known cause was involved. For 2 patients, bexarotene was re-administered with a lowering dose, but rapidly resulted in elevation of liver transaminases in one patient.

Since the management algorithm was different at the beginning of bexarotene treatment, hypothyroidism was diagnosed in only 4 patients (11%). Three of these

patients had preventatively administered thyroid supplementation and in one patient thyroid supplementation was added after starting bexarotene. Anaemia and rash (e.g. flush reaction during the first days of bexarotene) was observed in 3 patients (8%). Hypoglycaemia (2 patients), thrombocytopenia (1 patient) and gastrointestinal nausea (1 patient) were rare side-effects. One patient developed erysipelas of the lower leg 3 times during bexarotene treatment (Table SII).

DISCUSSION

This article summarizes our 10-year experience of using bexarotene for treatment of CTCL in Finland. Bexarotene is a well-tolerated and effective systemic therapy in advanced stages of CTCL. For patients bexarotene is user-friendly, convenient and easy to administer. It can be used as monotherapy or in combination with other therapies. Our results show that bexarotene was equally effective as monotherapy or when combined with other treatment modalities. The overall response rate as monotherapy was 75% and as combination therapy 73%. The response rates are higher than previously reported (13, 21, 22), probably due to the larger number of early-stage patients included in our series. Of the early-stage CTCL, 83% responded to bexarotene, while 17% did not. Of the advanced-stage CTCL, 33% responded and 67% did not. In a previous British study (22) the response rates were higher in advanced-stage disease than in early-stage disease. The authors speculate the role-increased tolerance of bexarotene side-effects in patients with advanced disease. Interestingly, all 4 of our patients with SS responded well to bexarotene. Similarly, Abbott et al. (22) reported the best response for bexarotene therapy

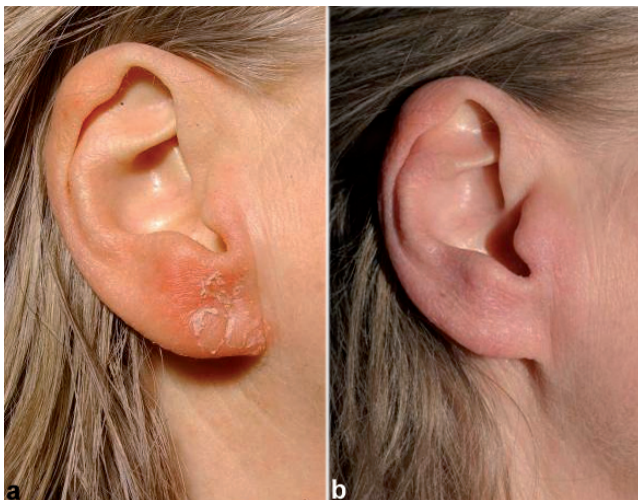


Fig. 4. Follicular mycosis fungoides (a) before and (b) after treatment. This patient was treated with bexarotene 225 mg and 300 mg on alternating days for 17 months (complete response) in patient No. 1. This patient was nickel patch test negative.

among patients with SS. Bexarotene is known to inhibit malignant T-cell chemotaxis in SS, which may be a possible explanation for a better response (23). Of cases of follicular MF, 63% (5/8) responded to bexarotene, while 37% (3/8) did not. Previously, a good response to bexarotene has been reported in some cases of folliculotropic MF (24). Our 2 SPTL cases first responded partially to bexarotene. However, after 3–7 months of clinical response, the disease progressed, resulting in cessation of bexarotene therapy. Recently, 82% overall response rates have been reported for bexarotene in SPTL (25). The mean time to achieve a response to bexarotene treatment was 3 months in our CTCL patients. A large majority of the patients achieved the response to bexarotene early, 73% within 3 months. For only 27% of patients, the response was achieved after 3 months of bexarotene therapy. Similar results have been reported previously (22). The duration of the response to therapy was a mean of 21 months, ranging from 1 to 74 months. This is significantly longer than reported previously (22, 26).

CTCL is a group of diseases that has no curative treatment. The aim of different therapies is to achieve the most durable remission. CTCL patients usually survive for many decades, especially those in early-stage disease. Thus, maintenance treatment must be convenient, with minimal side-effects, and it should also prolong remission and survival. After targeted therapy, we need tools to keep the disease in a non-progressive and stable stage (27). Previous studies have shown that bexarotene is able to induce and maintain long-lasting responses (19). One of our patients with SS has been in complete remission with bexarotene monotherapy for 74 months, i.e. for longer than 6 years. Ten patients (32%) have been in remission for longer than 24 months and 22 patients (71%) for longer than 12 months. Our experience shows that, after reaching response, bexarotene should be continued for an extended time with a minimal effective dose as maintenance therapy. Our current practice is to individually titrate the dose to the lowest dose that will maintain the response. For the SS patient mentioned previously we have been able to keep the disease under control with only 75 mg of bexarotene/day (approximately 45 mg/m²).

In our study we first used higher dosages of bexarotene (300 mg/m² daily), but with experience and due to side-effects, we began with approximately 150 mg/m² daily and aimed at individual dosing. This is in line with previous reports, in which the dose of bexarotene was titrated to 2–4 tablets (150–300 mg) per day (19). We have also found alternate dosing (e.g. 3 and 4 capsules on alternate days) to be most optimal for several patients.

The most common side-effects in the early years of using bexarotene were hypertriglyceridaemia and hypothyroidism, which were seen in all our patients. We

did not pre-treat patients with fenofibrate, which may have explained the increased levels of triglycerides. Also, at the beginning thyroid supplementation was not added simultaneously with bexarotene. With increasing clinical experience, lipid-lowering therapy and thyroid supplementation were administered routinely to patients undergoing bexarotene therapy, and thus the incidence of these side-effects was lowered. Hypertriglyceridaemia, however, remained the most common side-effect (51%) of bexarotene treatment. We reported 4 patients with elevated liver transaminases during bexarotene therapy. In one patient the increase was detected 2 years after the start of therapy. We ruled out all other possible reasons (hepatitis, other drugs and toxins) for the increase. The levels of liver enzymes returned to normal level after termination of bexarotene. To our knowledge, this is the first clinical study reporting elevated liver enzymes in CTCL patients treated with bexarotene. In one previous report elevated liver transaminases were detected, but this was in combination with methotrexate (28).

Bexarotene has been used in Finland for 10 years. In our experience, it is a safe, effective and reasonably well-tolerated drug. This retrospective study revealed somewhat higher response rates than previous studies. Specific subgroups of CTCL, e.g. SS and follicular MF, responded well to bexarotene therapy.

In conclusion, the dose of bexarotene should be determined individually in order to achieve maximum benefit with manageable side-effects. Bexarotene therapy should be continued for long periods as a maintenance therapy after achieving CR. Side-effects should be monitored carefully with routine laboratory tests. We reported notable and recurrent elevation of liver enzymes resulting in cessation of therapy.

The authors declare no conflicts of interest.

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