Bexarotene: a novel retinoid in cutaneous T-cell lymphomas (CTCL) treatment

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ABSTRACT

The present paper is an exhaustive review on an active pharmaceutical ingredient-Bexarotene (rexinoids) that specifically enact retinoid X receptors (RXRs), which used for the management of cutaneous T-cell lymphomas (CTCL). It is available in the form of topical gel and oral drug product. The earlier one having a high efficacy in the patients with settle and plaque organizes CTCL. Its preeminent toxicities are neighborhood erythema at the area of application. This review article focuses about its chemistry, mechanism of action, uses and side effects.

KEYWORDS

Bexarotene, rexinoids, retinoid X receptors, Cutaneous T-cell lymphoma

INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are the special types of cancers that begin within the T-cell lymphocytes. Mycosis fungoides (MF) and Sezary Syndrome (SS) are two types of lymphomas of skin. It can emerge in other parts of the body as well such as lymph hubs, membrane of GIT, or the spleen. [1,2,3]

CTCLs also include cutaneous CD30+ T-cell lymph proliferative disarranges, subcutaneous panniculitis-like T cell lymphoma (SPTL), and fringe T cell lymphoma.[4]

In early, gentle, and gradually dynamic stages, treatment is basically focused on at decreasing side effects and topical treatments (corticosteroids, BXT), topical chemotherapy (nitrogen mustard), radiation or electron bar treatment, phototherapy and topical imiquimod.[5]

CTCL is an indolent, extra nodal non-Hodgkin's T-cell lymphoma.[6,7] The most common and sluggish shape of CTCL is MF.[8] Diagnostically, single-cell epidermatropism of lymphocyte along the cellar layer are more commonly famous than the normal intraepithelial collections called pautrier's smaller scale abscesses.[9, 10,11]

Patients with organize IA (T1, patches and/or plaques), arrange IB (T2, patches and/or plaque, no lymphadenopathy), organize IIA (clinically unusual lymph hubs), prominent arrange III (T4, generalised erythroderma),and long time in patients with arrange IV (pathologically included lymph hubs or visceral involvement) disease.[12]

HISTORY OF BXT

Retinoids are immunomodulating operators as vitamin A, its metabolites and engineered analogs.[13,14] It cause concentration dependent apoptosis of CTCL cells and in patients with SS cause fringe blood T-cells.[15, 16] It has impacts on cell separation and apoptosis conjointly.[17,18] The natural impacts of retinoids are actuated by the nearness of retinoic corrosive receptors (RARs) and RXRs.[19] Retinoids can increment antigen introduction in Langerhans cells, as well as the surface expression of HLA-DR and CD11 particles, included in T-cell actuation. [20,21] It has been surveyed for potential utilize in strong tumors as well like breast cancer [22, 23] and non-small cell lung cancer.[24,25] RAR can homodimerise or heterodimerize with RXR to influence separation and cell growth.[26-28] Retinoic acids have been considered utilized as antitumor or tumor preventive agents.[29,30,31]

Rexinoids influence cancer by suppressing prolifiration, inducing terminal separation and advancing apoptosis. [32,33,34]

Retionoids having natural impacts through action by retinoic acid (RA) on retinoid X(RX) receptors.[35-38] The common retinoids, such as all-trans retinoic corrosive (ATRA) and its 9-and 13-cis isomers, are non particular agonists related with a range of well characterized toxicities.[39-42]

PROPERTIES OF BXT

The poisonous quality profile of characteristic retinoic acids, consisting essentially of dryness of the skin and mucous membranes, arthralgia, myalgia, osteoarthropathy, hair misfortune and hyperlipidaemia.[43] **BXT** is 4-(1-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-napthalenyl]benzoic acid. [44]

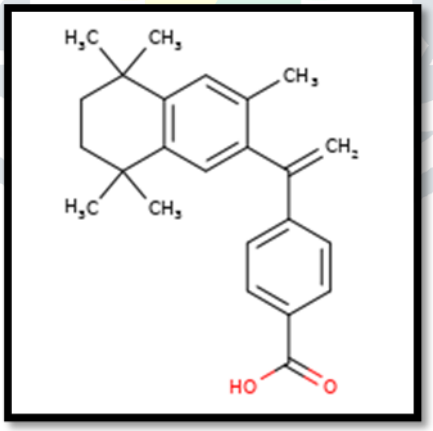

Figure 1: Chemical structure of BXT

BXT was found to initiate anticancer movement in a assortment of preclinical *in vitro* and *in vivo* rat cancer models, including human tumor xenografts.[45,46] In 1999,bexarotene was endorsed for the treatment CTCL as a capsule dosage form, and in 2000 it was affirmed for the early stages as a topical gel formulation. More recently, peripheral blood from patients with CTCL was dissected for *in vivo* and *in vitro* apoptosis taking after BXT treatment. [47-49]

BXT MECHANISM OF ACTION

Retinoids are ligands for RAR receptors and whereas bexarotene is specific for the RXR receptors, it moreover is able to enact RARs at higher dosages.[50]

Table 1: BXT dose regimen for the treatment of CTCL

Dosage/Administration Form	Dose
Oral-Tablet/Capsule	Initial Dose: 300mg/m² daily single time with food. Maintenance dosage: 400 mg/m^2/day if no tumor response after 56 days.
Topical gel	Application for single time per day for a week

PHARMACOKINETICS AND METABOLISM

BXT is highly protein bound (99%) and eliminated primary through the hepatobiliary system. It is metabolized by the CYP3A4 isozyme.[51] It having plasma half-life t1/2 (7-9h) and dose relative Cmax and AUC values. [45,52]

SIDE EFFECTS

Lipid variations and most commonly hypertriglyceridemia is widespread. To combat this fenofibrate is prescribed. Leucopenia and anemia also observed in some cases. Some of side-effects and their management listed in table 2. [53,54]

Table 2: BXT side effects and their management

Side effects	Treatment
Increase lipid content	Fibrate therapy
Decrease activity of thyroid	Thyroxin replacement
Leucopenia (High dose)	Start of granulocyte - colony stimulating factor with reduction of dose
Drug-drug interactions	Inducers of CYP3A4(reduce efficacy) Inhibitors of CYP34A (increase toxicity)
Increased CK	antilipidemic therapy (combination therapy stopped) Statin monotherapy (recommended)
Teratogenicity	Contraindication (pregnancy)

BXT IN CTCL OTHER THAN MF AND SS

There are a couple of literature found on BXT in the treatment of CD30+ expansive T-cell lymphoma and lymphomatoid papulosis. A combination treatment of subcutaneously connected IFN-α 3 MU 3-times week by week and oral BXT 150 mg/day was illustrated to result in a total reaction taking after 12 months of treatment. Bexarotene appeared restorative adequacy indeed in patients with subcutaneous panniculitis-like T-cell lymphoma. [55-58]

CLINICAL APPLICATIONS

BXT was administered at three different dose levels 6.5, 300 and 650 mg/m^2/day. It has been utilized in combination with IFN-a, extracorporeal photo chemotherapy, denileukin diftox, accomplishing a clinical reaction rate extending from 50 to 100% in progressed CTCL patients**.** [59-62]

FUTURE PROSPECTUS

As per our study, BXT to be a successful and provocative unused course of action to control CTCL. When patients come up short to have satisfactory reaction to combination treatment and bexarotene, systemic chemotherapy is used. Retinoic corrosive plays a vital part within the intracellular pathways and can be capable specialists.

EXPERT OPINION

BXT may be considered as the best treatment of CTCL, with lesser side effects as compared with other therapy. It is accessible in both forms as topical and oral dosage form. The earlier one features a wide use in patients with fix and plaque arrange CTCL.

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