The Role of Systemic Retinoids in the Treatment of Cutaneous T-Cell Lymphoma

Auris O. Huen, PharmD, MD, Ellen J. Kim, MD*

KEYWORDS

• Retinoids • Rexinoids • Bexarotene • Isotretinoin • Acitretin • Cutaneous T-cell lymphoma • Mycosis fungoides • Sézary syndrome

KEY POINTS

- Mycosis fungoides and Sézary syndrome subtypes of cutaneous T-cell lymphoma (CTCL) have a variable clinical course, ranging from indolent disease that does not alter life expectancy to aggressive, rapidly progressive disease.
- Goals of treatment, especially in patients with early-stage disease, are to induce remission with agents that have a low toxicity profile. The systemic retinoids are an important component of the treatment options for all stages of this disease because of the ease of administration and relatively low toxicity profile.
- Bexarotene is the only systemic retinoid approved by the Food and Drug Administration specifically for CTCL but does require additional medications to treat the associated hyperlipidemia and hypothyroidism during the duration of bexarotene treatment.
- Combination treatment with retinoids and other agents with activity against mycosis fungoides/Sézary syndrome appear to be well tolerated and associated with high response rates in relapsed or treatment refractory patients in small studies and series.

INTRODUCTION

Retinoids are signaling molecules that are structural and functional derivatives of vitamin A (retinol). The term collectively describes naturally occurring retinol and its metabolites, as well as synthetic analogs. Retinoid receptors are found ubiquitously in virtually all organ systems, and they regulate important functions in the body, including embryonic development, vision, immune and neural function, as well as cell proliferation, differentiation, and apoptosis.[1,2] These compounds exert their effects through control of gene expression. In the treatment of cancer, the retinoids are considered "biologic response modifiers" (BRMs) in that they are dissimilar to traditional cytotoxic chemotherapy, inducing response without immune suppression, and often augmenting the immune response.[3–5] Although there have been a number of clinical studies using retinoids for treatment of breast, ovarian, renal, head and neck, melanoma, and prostate cancers, they are most prominently used in the treatment of hematologic malignancies. In the case of acute promyelocytic leukemia, retinoids in the form of all-*trans* retinoic acid are used as first-line treatment to restore normal myeloid

Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Boulevard, Suite 330S, Philadelphia, PA 19104, USA
* Corresponding author. Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 1 Dulles Building, 3400 Spruce Street, Philadelphia, PA 19104.
E-mail address: Ellen.Kim@uphs.upenn.edu

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differentiation to leukemic cells, inducing the formation of mature granulocytes.[6] In T-cell lymphoma cells, retinoids are thought to induce apoptosis and DNA fragmentation in affected T lymphocytes.[7,8]

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of uncommon primarily mature T-helper lymphoproliferative disorders. The most common form is mycosis fungoides (MF), which accounts for approximately 60% of all cases.[9] It typically displays indolent behavior, although disease progression to higher stages or transformation to large-cell lymphoma can occur. Sézary syndrome (SS) is a related subtype of CTCL presenting as erythroderma, with a significant population of circulating atypical T-lymphocytes and typically has a more aggressive course than MF. Patients with the earliest stages of MF do not have decreased survival due to their disease, and skin-directed therapy, such as phototherapy or topical medications, are the mainstays of treatment.[10] Additionally, treatment with BRMs, such as interferons or retinoids, also are commonly used in these patients, although systemic treatment is generally reserved for patients with MF who have failed local or skin-directed therapy or have more extensive disease.[5,10] The anecdotal use of retinoids for treatment of MF was first reported in the 1980s, both as monotherapy or in combination with chemotherapy.[3,11,12] Currently, topical and systemic retinoids are an integral part of the treatment armamentarium for CTCL. This article focuses primarily on systemic retinoids in MF and SS.

RETINOIDS AND MECHANISM OF ACTION

All retinoids have similar molecular structure, containing a benzene ring, a polyene chain, and a carboxylic end group. In the body, retinol is metabolized to all-*trans* retinoic acid and then further isomerizes to 13-*cis* retinoic acid (isotretinoin) and 9-*cis* retinoic acid in the liver.[2] Subsequently, synthetic retinoids have been derived from retinol, including mono-aromatic second-generation retinoids (eg, etretinate, acitretin) followed by polyaromatic third-generation compounds called arotenoids (eg, bexarotene).[13] More recently, alitretinoin, which is a synthetic analog of 9-*cis* retinoic acid, has been developed with efficacy in atopic dermatitis and a few reports showing effects in MF/SS.

Retinoids bind to 2 distinct families of nuclear receptors regulating gene transcription called retinoic acid receptors (RARs) and retinoic X receptors (RXRs). Each receptor is associated with 3 subtypes, α, β, and, γ, which bind to specific ligands.[1,14] These receptors are part of a larger superfamily of nuclear receptors, including thyroid hormone receptor, vitamin D3 receptor, and glucocorticoid receptor (**Table 1**).[1] Transactivation of some of these other nuclear receptors is believed to be linked to some of the side effects seen with the retinoids.[1]

Despite significant progress in elucidating the mechanism by which retinoids exert their activity, their effect on tumorigenesis and cancer biology remains poorly understood. The RAR receptors

Table 1
Human nuclear receptors and ligands

Receptor	Ligand(s)
Retinoic acid receptor (RAR) α, β, γ	All-*trans* retinoic acid, 9-*cis* retinoic acid, isotretinoin, etretinate, acitretin
Retinoic X receptor (RXR) α, β, γ	9-*cis* retinoic acid, bexarotene
Thyroid hormone receptor (TR)	Thyroid hormone
Vitamin D3 receptor (VDR)	Vitamin D, calcitriol
Peroxisome proliferator-activated receptor (PPAR) α, β, γ	Fatty acids, fibrates, leukotriene B4, thiazolidinediones
Pregnane X receptor	Xenobiotics
Liver X receptor α, β (LXR)	Oxysterols
Estrogen receptor α, β	Estradiol
Progesterone receptor	Progesterone
Glucocorticoid receptor	Cortisol, corticosteroids
Mineralocorticoid receptor	Aldosterone, spironolactone
Androgen receptor	Testosterone

Data from Sokołowska-Wojdyło M, Ługowska-Umer H, Maciejewska-Radomska A. Oral retinoids and rexinoids in cutaneous T-cell lymphomas. Postepy Dermatol Alergol 2013;30:19–29.