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Innovative treatments: bexarotene

Introduction

There are now three FDA approved therapies for cutaneous T-cell lymphoma (CTCL) in the United States: denileukin diftitox (Ontak®, an interleukin (IL)-2 fusion protein, approved in 1998), bexarotene (Targretin®, the first retinoid-X receptor (RXR)-selective retinoid, approved in 1999), and vorinostat (a histone deacetylase inhibitor approved in 2006). These agents were approved based on Phase II clinical trials conducted in a limited number of CTCL patients. Treatment strategies in the management of MF are aimed at removal of the persistent antigen stimulus, reversal of the shift from Th2 to Th1 cytokine expression, inducing an increase in $CD8^+$ cells, avoidance of immunosuppression, and prophylaxis or treatment of associated infectious complications. How best to integrate the new agents with existing therapies will require additional well-designed, randomised trials. Our goal should be to produce rational combinations of drugs that can either induce a cure or prolonged complete responses in patients.

Retinoid therapy for cutaneous T-cell lymphoma

Retinoids, first used in 1983 for CTCL, remain the major biological response modifiers for first line systemic therapy for both mycosis fungoides (MF) or Sézary Syndrome (SS).[1-3] Retinoic acid receptor (RAR) agonists [isotretinoin (Accutane®), etretinate [Tegison®] have been demonstrated to produce an overall response rate of about 58%, but the complete response rate is low, at about 19% for the RAR retinoids.[2,4,5] Acetretin(Soriatane®) has replaced etretinate but has not been well studied for CTCL. In general, retinoids are more effective in patients with early disease than in those with advanced CTCL. RAR selective retinoids (etretinate, acitretin, and isotretoin) have consistently demonstrate response rates of about 50% as monotherapy for early patients, yet these agents have never been formally approved. In the USA, Retinoids have most often been combined with phototherapy or interferon safely to enhance responses to about 70%.[6] In the US, the I-Pledge program has made isotretoin difficult to administer even to elderly male MF patients.

Rexinoid therapy for cutaneous T-cell lymphoma

The RXR selective agonist, bexarotene (Targretin®, Ligand and Eisai Pharmaceuticals) was tested in two multi-center trials involving early and late CTCL patients. Oral bexarotene demonstrated dose related efficacy in both early and advanced CTCL patients. In early patients) Stage IA-IIA), a randomized multi-center trial compared an initial high dose of 650 mg/m^2 to a low dose of 6.5 mg/m^2. The lower dose was significantly worse (20% response rate) and was stopped in favour of the high dose arm. An initial starting dose of 650 mg/m^2 was subsequently reduced to 300 mg/m^2 due to the dose limiting hypertriglyceridemia with related pancreatitis.[7] In early patients the response rate was 54% at 300 mg/m^2 and 67% at higher doses. A second multi-center study in advanced MF/SS patients (Stages as > IIB) also showed an efficacy of 45% at 300 mg/m^2 or 55% at doses > 300 mg/m^2. Again, higher doses were reduced after pancreatitis was identified as a dose limiting toxicity when triglyceride levels were over 1000. This study also included patients with transformed MF and visceral disease, as well as patients who had failed poly chemotherapy.[8] Bexarotene was approved for the cutaneous manifestations of CTCL based on the best of either the physician's global assessment or the a composite index lesion assessment. Although bexarotene is selective for the RXR receptor, it also has RAR activity at highest doses. Toxicities identified with oral bexarotene therapy in the phase II studies included hyperlipidemia with triglycerides more affected than cholesterol, central hypothyroidism, transient headaches when starting drug, itching, and fatigue.

Retrospective studies of bexarotene oral therapy

We retrospectively evaluated 70 CTCL patients with all stages treated at MD Anderson Cancer Center. Fifty-four who received bexarotene monotherapy had an overall response rate of 48%, similar to the Phase II trial responses. A total of 16 patients received combination therapy of bexarotene with photopheresis, IFNα or PUVA, producing an overall response rate of 69%.[9] Tightly controlling hyperlipidaemia by adding the lipid-lowering agents fenofibrate (Lofibra®, TriCor®) and atorvastatin (Lipitor®) to the treatment regimen was shown to increase the response rate to 70%. Recently, we and others have added 1-4 grams per day of omega 3 fatty acid supplements to patients on bexarotene which may help to control their hyperlipidemia.[10]

Laboratory studies were consistent with cen-

Table 1. Combining bexarotene with other biological response agents or phototherapy increases the overall response rate.[9]

Bexarotene therapy group	*Number of patients*	*Overall response rate (%)*
Bexarotene monotherapy	54	48
Without lipid-lowering agents	12	25
With 1 lipid lowering agent	32	44
With 2 lipid lowering agents	10	90
Bexarotene combination therapy	116	69
With 1 lipid-lowering agent	12	66
With 2 lipid lowering agents	4	75

Lipid-lowering agents: fenofibrate and/or atorvastatin; combination therapies: psoralen plus ultraviolet A, extracorporeal photopheresis, interferon α.

tral hypothyroidism (low TSH and free T4 levels) in all treated patients. Supplementation with thyroxine was provided for all patients to keep their T4 in the normal range. Four patients had long term complete long lasting responses. After the patients were clear for a year, bexarotene was tapered slowly unless relapse occurred. The St. John's Institute of Dermatology recently reported the results of a retrospective analysis of 66 CTCL patients receiving bexarotene therapy prior to August 2007. There were 44 males and 22 females; 40 with mycosis fungoides and 26 with Sézary syndrome. Nineteen had early-stage (IB-IIA) refractory mycosis fungoides and 47 patients had advanced-stage CTCL (IIB-IVB). Only 52 of 66 patients (79%) patients completed > 1 month of bexarotene therapy for an intention-to-treat response of 44% (29/66). There were six (9%) complete responses, and 23 (35%) partial responses; fifteen (23%) had stable disease and eight (12%) had progressive disease. Median time to maximal response was 3 months (1-9 months). Median response duration was 8 months (1 to > 48 months). Median time to progression was 9 months (3-44 months). Responses occurred at all stages: 26% (five of 19) with early-stage and 51% (24/47) of advanced-stage disease. Responses were seen in skin, blood and lymph nodes. All patients had central hypothyroidism requiring thyroid replacement and hyperlipidaemia managed with lipid-lowering therapy +/- dose reduction). Twenty-eight out of 66 patients were treated with bexarotene monotherapy and the remainder were on one or more additional anti-CTCL therapies.[11] For patients with very early-stage disease (T1), topical retinoids including bexarotene[12] or tazarotene[13] cream are helpful for limited plaques disease.[14] Patients with more extensive skin involvement (T2) require oral retinoids (isotretoin or acitretin) or the rexinoid, bexarotene which are active as monotherapy. In addition, retinoids, when combined with UVB or psoralen plus ultraviolet A, are synergistic, allow clearing with lower doses of phototherapy, and boost overall response rates. Combined-modality therapy with oral retinoids, combined chemotherapy, electron-beam therapy and topical mustargen has also proved effective for patients at all stages. Retinoids are also used in combination with interferon alpha and photheresis in patients with Sézary Syndrome (SS).[14,15] For the treatment of advanced-stage disease, the targeted therapy denileukin diftitox provides a non-immunosuppressive alternative to conventional chemotherapy or radiation therapy and the addition of bexarotene may enhance its activity but inducing CD25 expression.[14,16] Gemcitabine as a monotherapy demonstrated fficacy in tumor stage MF[17] and we have added bexarotene in combination as a maintenance therapy.

Combination trials: interferon α and bexarotene

The obvious combination of oral bexarotene with IFNα-2b was tested in a Phase II, single-arm, multicenter study.[18] Twenty-two MF patients (stages IB to IV) were enrolled. Most had advanced disease, and all but one had failed prior therapy. Bexarotene was initiated at a dose of 300 mg/m^2 for 8 weeks. Three patients showed a complete response to this therapy and were not given interferon (IFN) alpha. In those who did not show a complete response, IFNα-2b, 3-5 MIU three days per week, was added for another 8 weeks. Seventeen of 22 patients completed the trial; 6/17 had partial responses and one had a complete response, giving an overall response rate of 41%. The mean duration of response in these advanced-stage patients, however, was low at 2.7 months (range 1-7.6 months). On this combination of full doses of IFN and bexarotene, the side-effects were more prevalent and the response rate was not different from that for either drug alone. Grade 3 or 4

toxicities recorded were high cholesterol and triglyceridaemia in five patients, neutropaenia in three, lymphopaenia in two and elevated aspartate aminotransferase in two; therefore, the trial was stopped early.

Denileukin diftitoxin and Bexarotene

A small Phase I trial was conducted at one center combining escalating doses of oral bexarotene given prior to initiating treatment with denileukin diftitox. There was an increase in the expression of CD25 on lymphocytes, as determined by flow cytometry, following treatment even with low doses of bexarotene (at least 150 mg/day). Thus, there may be some synergism between these two drugs and the response rate was higher with bexarotene pretreatment.[16] Clinically, we have found that treating tumours with denileukin diftitox can be followed by oral bexarotene maintenance with the addition of skin-directed therapies as needed to achieve near-complete and durable responses in patients with advanced, difficult-to-treat disease.

Gemcitabine plus bexarotene

The obvious agent for combination with gemcitabine is bexarotene. While gemcitabine is highly effective against tumours, bexarotene will clear patches and plaques of MF. It is possible to use a combination of low-dose bexarotene and low-dose gemcitabine in elderly patients for whom chemotherapy would not be tolerated. Lower doses of gemcitabine (500-750 mg/m^2) are given by infusion twice a month as long as tumours persist, and bexarotene, 150-300 mg/m^2, have maintained patients for more than one year. Bexarotene is given continuously, whereas gemcitabine is infused initially to gain a response and then only when required to treat new tumours. The patients have been well, treated at home, with no infections and no need for intravenous lines. We find the treatment to be well tolerated and it seems to be a safe alternative to combined chemotherapy in elderly patients. Patients may experience mild myelosuppression and anaemia, but no nausea, vomiting or alopecia. Stem-cell factor support is rarely needed.

Bexarotene: mechanism of action

Retinoids are ligands for RAR receptors and while bexarotene is selective for the RXR receptors, it also is able to activate RARs at higher doses. It is not known which RAR or RXR receptors are most important for CTCL activity. In general, RAR receptors cause differentiation and RXRs induce apoptosis. Bexarotene binds to RXR receptors which partner with other steroids hormone receptors to modulate gene transcripton. Thus, bexarotene's action might be enhanced by co-administration of vitamin D which activates VDRs, of peroxisome proliferator-activated receptor (PPAR) agonists, or by other retinoids that bind RARs. We have shown that bexarotene will induce T-cell apoptosis *in vitro* as a single agent[19] and demonstrated increased activity when bexarotene is combined with 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO), a PPAR agonist.[20] Another possible combined therapy would be with agents such as the histone deacetylase (HDAC) inhibitors that change levels of transcription factors including retinoid receptors at the level of the promoter.[21] In clinical study, bexarotene was noted to increase the number of circulating CD8$^+$ T-cells among responders.[22] Among 33 patients with MF and four with other lymphomas, 32 had high CD4:CD8 ratios at baseline. Following treatment with bexarotene, 150-300 mg/m^2/day for 13 months (range 4-18 months), a total of 26 patients showed normalisation of CD8$^+$ cell counts after 6.5 weeks (range 3.5-12 weeks). The patients who responded to bexarotene therapy had higher numbers of CD8$^+$ cells than those who did not (975 *vs.* 221/mm^3) (p=0.002) and lower

CD4:CD8 ratios (0.8 *vs.* 2.5) (p=0.005). In addition, a subsequent reduction in $CD8^+$ cell count was associated with relapse. As an increase in $CD8^+$ cells is a desirable outcome in the treatment of CTCL, this provides a rationale for the use of bexarotene in combination with a number of other agents that augment CD8 cytotoxicity.

Conclusions

Bexarotene is highly active as a single agent with response rates of 45-55% even in patients with advanced CTCL who have failed prior systemic therapies. Bexarotene is frequently used with phototherapy to reduce the amount of light given and is combined with IFNα and photopheresis for SS patients. In addition, combinations of bexarotene with PPAR agonists or HDAC inhibitors is an attractive idea for evaluation in clinical trials. Bexarotene may enhance the action of denileukin diftitox by increasing CD25 expression. It may be given to maintain a response following chemo or other therapy. Optimal combinations of existing and future therapies may allow us to achieve complete, lasting responses in CTCL.

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