Optimizing bexarotene therapy for cutaneous T-cell lymphoma

Bexarotene (Targretin® oral capsules) is the first RXR selective retinoid, approved for all stages of cutaneous T-cell lymphoma (CTCL). Two phase II clinical trials were conducted in early and advanced patients with CTCL (Mycosis Fungoides (MF) and Sezary Syndrome (SS)). The overall response rate RR was 45% at an optimal dose of 300 mg/m²/day. Higher response rates were seen in earlier patients (54%) and at higher doses 300 mg/m²/day. Hypertriglyceridemia was reported in 79% of the patients and therefore we always administer lipid lowering agents (LLA) to optimize the clinical response. Statins (inhibitors of HMG-CoA reductase) may modulate class II MHC expression and T-cell responses.

We prospectively evaluated 70 CTCL patients treated with oral bexarotene as monotherapy or in combination with other active agents. Fifty-four patients receiving bexarotene monotherapy achieved an overall response rate (RR) of 48%. Thirteen were stage IA-IIA (RR=53%, 1 CR); 41 were stage IIB-IVB (RR=46%, 2 CR). Forty-two (77%) of these also required one or more lipid lowering agents (LLA): atorvastatin (n=29, RR 43%), atorvastatin plus fenofibrate (n=10, RR 90%) or gemfibrozil (n=3, RR 33%). Gemfibrozil was never used as it increased bexarotene levels and triglycerides. Patients on two LLA had a significantly higher response rate (90%) on monotherapy, than those on 0 or 1 LLA agent ($p<.0001$). Forty of 54 patients received thyroid hormone replacement to normalize T4 levels and to increase lipid clearance to control hypertriglyceridemia. Four patients on monotherapy have achieved CCRs of >3 years duration. Sixteen advanced patients took bexarotene (225-750 mg/day) in combination with other ongoing CTCL therapies and achieved an overall RR of 69% (11/16) with concomitant statin therapy. Bexarotene was safely combined with PUVA plus interferon alpha (IFN) (n=2, RR=50%), with photopheresis (ECP) (n=8, RR=75%, 1 CR), with ECP/IFN (n=4, RR =50%), with ECP/IFN/PUVA (n=1, RR=100%), and with IFN/PUVA/plus HN2 (n=1, RR=100%). Two patients on IFN had slight leukopenia as a side effect. No patients developed rhabdomyalgias associated with multiple LLA.

Conclusions
This single center study supports the multiconor efficacy and safety of bexarotene monotherapy and confirmed the results of the two Phase II studies. Long durable CCRs may be achieved with oral monotherapy. Statins and fibrates may improve response rates by allowing higher and uninterrupted bexarotene administration, by modulating the immune response or both. Bexarotene can be combined with other active CTCL therapies including interferon, photopheresis, PUVA, denileukin diftitox, and gemcitabine to induce higher response rates achieved even in advanced patients, without unacceptable side effects.

References