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TNF-blockade in Patients with Advanced Hormone Refractory Prostate Cancer

Luis A. Diaz Jr^{1,2}, Wells Messersmith³, Lori Sokoll⁵, Vicki Sinibaldi², Sandy Moore², Michael Carducci², and Mario Eisenberger²

¹The Ludwig Center for Cancer Genetics & Therapeutics at Johns Hopkins, Baltimore, Maryland 21231

²Department of Medical Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD 21231

³Division of Medical Oncology, University of Colorado Cancer Center, Denver, CO 80010

⁵Department of Pathology, Johns Hopkins Medical Institutes, Baltimore, Maryland 21231

Interleukin-6 (IL-6) levels are universally elevated in advanced prostate cancer and these levels increase in proportion to tumor burden and decrease with therapeutic response [1–4]. Despite this intriguing relationship, a role for IL-6 in prostate cancer progression is unclear. Several preclinical studies suggest that IL-6 may be an anti-apoptotic agent and a key growth factor in hormone-refractory prostate cancer (HRPC) [5–7]. Furthermore, anti-IL-6 antibodies can induce apoptosis and tumor regression in mice bearing human hormone-refractory prostate cancer xenografts [8–10].

We hypothesized that TNF α -inhibition may block IL-6 production and result in a measurable clinical response in patients with bone metastases and HRPC. A pilot study was initiated to examine the effects of TNF α -blockade (infliximab, Centocor) in patients with treatment-refractory HRPC and painful bone metastases. Six patients with HRPC and painful bone metastases were enrolled and treated with infliximab 5 mg/kg at 0, 2, 6 and 12 weeks. Two of the six patients had a transient but complete response in pain that lasted between 2–5 days. Biochemically, IL-6 levels declined with pain resolution. The clinical or biochemical effect of TNF α -blockade was transient and could not be reproduced after 3–4 weeks of treatment and IL-6 levels increased thereafter. The remaining patients' were refractory to any clinical benefit in pain from infliximab and all showed an increase in IL-6 throughout the course of treatment. (Table 1) All patients withdrew from the study after there was radiographic evidence of disease progression. No treatment-related adverse events were reported.

The observations from this study were unexpected but may allow us to distinguish the source of IL-6 in these patients. It remains unclear whether IL-6 is directly produced by the classic inflammatory cascade (TNF α dependent) within a bone metastasis, or if the tumor cells produce the majority of the IL-6 in HRPC. TNF α -blockade should at least, in part, inhibit IL-6 production and alleviate pain related to such inflammation. In our patients, we only witnessed pain relief in two subjects. Although this clinical benefit was associated with a drop in IL-6 levels, both the clinical and IL-6 responses were transient. In addition, those patients without a clinical benefit demonstrated an increase in IL-6 levels when treated with infliximab. From these results, it is clear that IL-6 expression in HRPC is not TNF α -dependent. (figure 1)

The pain response and concomitant IL-6 suppression does suggest that there was an initial, albeit transient, TNF α -dependent component in two patients. This rapid development of resistance in these two patients and the reactive increase in IL-6 levels in the remaining patients suggest an alternative pathway of IL-6 expression that is not TNF α -dependent. Supporting the concept that IL-6 expression in HRPC may be tumor in origin rather than a purely reactive inflammatory process. Its function as an autocrine growth factor in hormone-refractory disease has been postulated [8,11] and blocking the IL-6 signal does lead to apoptotic death and growth suppression in pre-clinical models [8–10]. Addiction to growth factor signals is not a novel concept in Oncology and dependence on IL-6 could clearly play a role in prostate cancer growth, metastasis and progression [12].

In summary, we have observed that IL-6 expression is not TNF α -dependent in patients with painful bone metastases in HRPC. While it appears that pain is associated with fluctuations in IL-6 levels and TNF α -blockade with infliximab is safe in HRPC, it is not a useful therapeutic option. Direct blockade of IL-6 may be needed for therapeutic efficacy.

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Figure 1. Representative subjects and IL-6 (pg/mL) levels in patients with a clinical response (pain resolution) and without a clinical response.

Table 1

Patient characteristics

Subject	Age	Testosterone	Week	TX	CRP	IL-6 (pg/mL)	% Change Inflammatory Marker	PSA
1	73	<20	Baseline	X	3	15.5		72.2
			Day 2			10.4	-33%	
			Week 2	X	5.3	29.7	92%	
			Week 4					96.6
			Week 6	X	1.9	6.4	-59%	
2	62	<20	Week 8		3.9	10	-35%	124
			Week 12		3.2	11.9	-23%	195
			Baseline	X	1.1	5.9		0.2
			Day 2			3.2	-46%	
			Week 2	X	1	3.5		
3	48	<20	Week 4					
			Week 6	X	1.4	4.1	-31%	0.2
			Week 8		2.3			
			Week 12		2.3	5.0	-15%	
			Baseline	X	5.9	11.2		0.1
4	52	<20	Day 2		6.7	9	-20%	
			Week 2	X				
			Week 4		5.1	18.5	65%	0.1
			Week 6	NT				
			Baseline	X	0.3	2.1		15.1
5	64	<20	Week 2	X	1.7	7.9	276%	
			Week 4		0.3			39.1
			Week 6	X		18.8	795%	
			Baseline	X	3.1	17.6		974
			Day 2					
			Week 2	X	6	ND	94%	
			Week 4					
			Week 6	NT	0.3	ND	-90%	442

Subject	Age	Testosterone	Week	TX	CRP	IL-6 (pg/mL)	% Change Inflammatory Marker	PSA
6	51	<20	Week 8					115
			Baseline	X	1.3	4.1		7.1
			Day 2		3.3	3.7	-10%	
			Week 2	X	3.9	4.3	5%	29.1
			Week 4			9.3	127%	50.7
			Week 6	X	ND	ND		393
			Week 8					
			Week 12	NT	ND	ND		