Prospective Phase II Study Evaluating the Relationship Between Fatigue And Plasma Inflammatory Cytokine Levels In Prostate Cancer (PC) Patients Undergoing External Beam Radiation Therapy (EBRT)

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Background

Cancer patients undergoing EBRT experience significant fatigue during treatment that negatively impacts physical functioning and quality of life (QOL). Our hypothesis was that EBRT-induced increases in inflammatory cytokines resulting from tissue toxicity play an important mechanistic role in treatment-related fatigue. We undertook a prospective, longitudinal, single arm, Phase II study with specific aims to evaluate the relationship between cytokines, patient activity levels, and self-reported fatigue-related symptoms during a standard course of EBRT for PC.

Methods:

28 men undergoing EBRT for low to intermediate risk PC without androgen therapy (ADT) were accrued onto an IRBapproved prospective clinical trial. Participants used an Actiwatch Score (MiniMitter/Respironics Inc.) to record their daily fatigue level, on a 1-10 scale (1= no fatigue, 10= worst fatigue) , prior to and during EBRT to 78 Gy at 2 Gy/fraction. Peripheral blood was collected immediately prior to the 1st treatment and then after the 5th, 15th, 25th, and 39th treatment. Cytokine analysis was performed using a bead based immunofluorescene assay (Luminex Inc.) for serum IL-1alplha, IL-1beta, TNF-alpha, IL-6, IL-8, IL-10 and VEGF. Area under the curve analysis with respect to total (AUCt) across the repeated measures was computed for fatigue and serum cytokine response measures. Multiple regressions were used to test the relationship between the serum cytokine response and fatigue measures.

Results:

Participants were 96% Caucasian with an average age of 66.8 yrs (range 58-81). Gleason Score = 6-7, clinical stage = T1c - T2b, and initial average PSA = 7.7 ng/mL (Table 1). Average pre-treatment levels of fatigue were 2.05 ± 1.06 (Table 2). We observed a substantial inter-individual difference in fatigue trajectories (Figure 1). A significant correlation between pre-treatment levels of fatigue and serum levels of IL-6 (r= 0.42, p= 0.026), IL-1alpha (r=0.408, p= 0.031), and VEGF (r=0.42, p=0.023) was evident (Table 3). The average change in fatigue level by the end of treatment was 1.4 ± 1.8. The only significant correlation identified was between total IL-6 (IL-6AUCt) and total fatigue response (Fatigue(AUCt) during treatment (Table 4; r= 0.387, p= 0.046) .

Table 1: Demographics	
Race/Ethnicity	96% Caucasian
Mean Age (range)	66.8 years (58-81)
Mean Gleason Score (range)	6.5 (6-7)
Mean iPSA	7.7ng/mL
Mean BMI	31.5

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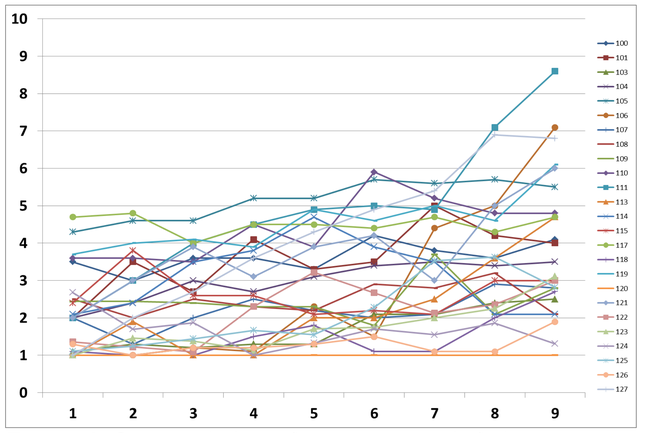

Figure 1. Spaghetti plots of average weekly fatigue scores (y-axis) for 28 men 1 week prior to and during each of 8-weeks (x-axis) of EBRT to 78 Gy at 2 Gy/fraction. Note the substantial inter-individual differences in the trajectories of weekly fatigue.

Serum Cytokine Level Pre-Treatment

	Mean	SD	N
Fatigue	2.0571	1.06520	28
IL1beta	14.7866	23.44254	28
IL6	159.2329	186.61035	28
IL8	70.4421	63.21411	28
IL10	31.2804	58.93729	28
IL1alpha	377.4609	520.25166	28
TNFalpha	23.3021	25.03306	28
VEGF	606.9982	476.36836	28

Table 2. Levels of self reported fatigue and serum cytokine levels before the start of treatment.

Correlations

		Fatigue	IL1beta	IL6	IL8	IL10	IL1alpha	TNFalpha	VEGF
Fatigue	Pearson Correlation	1	.305	.420*	.364	.281	.408*	-.041	.429*
	Sig. (2-tailed)		.114	.026	.057	.148	.031	.837	.023
	N	28	28	28	28	28	28	28	28
IL1beta	Pearson Correlation	.305	1	.541**	.642**	.365	.792**	.112	.527**
	Sig. (2-tailed)	.114		.003	.000	.056	.000	.570	.004
	N	28	28	28	28	28	28	28	28
IL6	Pearson Correlation	.420*	.541**	1	.823**	.643**	.765**	.205	.856**
	Sig. (2-tailed)	.026	.003		.000	.000	.000	.295	.000
	N	28	28	28	28	28	28	28	28
IL8	Pearson Correlation	.364	.642**	.823**	1	.559**	.783**	.148	.742**
	Sig. (2-tailed)	.057	.000	.000		.002	.000	.451	.000
	N	28	28	28	28	28	28	28	28
IL10	Pearson Correlation	.281	.365	.643**	.559**	1	.407*	-.109	.437*
	Sig. (2-tailed)	.148	.056	.000	.002		.032	.582	.020
	N	28	28	28	28	28	28	28	28
IL1alpha	Pearson Correlation	.408*	.792**	.765**	.783**	.407*	1	.248	.751**
	Sig. (2-tailed)	.031	.000	.000	.000	.032		.204	.000
	N	28	28	28	28	28	28	28	28
TNFalpha	Pearson Correlation	-.041	.112	.205	.148	-.109	.248	1	.384*
	Sig. (2-tailed)	.837	.570	.295	.451	.582	.204		.043
	N	28	28	28	28	28	28	28	28
VEGF	Pearson Correlation	.429*	.527**	.856**	.742**	.437*	.751**	.384*	1
	Sig. (2-tailed)	.023	.004	.000	.000	.020	.000	.043	
	N	28	28	28	28	28	28	28	28

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Table 3. Correlation table showing relationship between pre-treatment fatigue levels and serum cytokine levels. Note the signiofocant correlation between fatigue levels and serum IL-6, IL-1alpha, and VEGF levels.

Correlations

		IL6AUCT	Fatigue AUCT
IL6AUCT	Pearson Correlation	1	.387*
	Sig. (2-tailed)		.046
	N	27	27
FatigueAUCT	Pearson Correlation	.387*	1
	Sig. (2-tailed)	.046	
	N	27	28

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4. Correlation table showing the relationship between total IL-6 (IL-6AUCt) and total fatigue response (Fatigue(AUCt) during treatment.

Conclusions:

The observed relationship between serum IL-6 levels and fatigue is consistent with existing studies in cancer patients. None of the other inflammatory cytokines analyzed were associated with fatigue response during treatment. This lack of an association may be related to small sample size or the relatively small average increase in fatigue level during treatment Our study establishes a feasible model for prospectively evaluating activity, symptoms, and cytokines related to fatigue that serves as a standard for future protocols. Given the substantial inter-individual differences in fatigue trajectories, further examination of the inter-individual differences in the individual change parameters will be warranted.

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