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Elevated Circulating TNF-α and IFNγ may be correlated with Post-Radiation Fibrosis in Soft Tissue Sarcomas

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BACKGROUND: Fibrosis is a sequela of radiotherapy (RT) for the treatment of soft tissue sarcomas (STS) and is associated with functional deficits long term. Although approximately 30% of patients who receive a conventional course of pre-operative RT will develop fibrosis, much is unknown about the immune profile of this subset in relation to cytokine mediated events that occur post-RT.

A standard course of RT involves 5-weeks of treatment, however, there has been a shift towards pre-operative hypofractionation in STS given the abundant phase II data demonstrating excellent rates of local control and low incidence of acute toxicity. While there are many advantages to hypofractionated pre-operative RT, the long-term toxicity remains as does characterizing the population of patients at high risk for fibrosis.

QUESTIONS/PURPOSE: The goal of this study is to 1) assess the incidence and factors associated with fibrosis in patients enrolled on a prospective trial evaluating pre-operative hypofractionated RT for stage I-III extremity STS and 2) correlate pre-radiation circulating cytokine levels using enzyme-linked immune-assays to the development of long-term fibrosis.

PATIENTS AND METHODS: Preoperative hypofractionated RT was administered on a phase II prospective study to 35 Gy in 5 fractions every other day followed by resection 4 to 6 weeks later. Pre-RT whole blood samples were taken for each patient and bulk serum cytokine measurements were obtained using the Luminex apparatus. Cytokines associated with inflammation and tissue fibrosis (Table 1) were chosen and quantitative measurements of were obtained. Cytokine levels were evaluated using logistic regression and if significant, an ROC analysis was performed to assess the cutoff that was best associated with fibrosis.

RESULTS: Of the 32 patients were enrolled on trial, 23 had evaluable fibrosis at 2 years. In this subset, grade 1, 2 and 3 fibrosis occurred in 34.7% (8/23), 21.7% (5/23) and 13.0% (3/23), respectively. Age, tumor size and location, administration of chemotherapy, acute dermatitis, and postoperative wound complications were not significantly associated with the development of grade ≥2 fibrosis. Of the inflammatory cytokines evaluated, TNF-α ($p=0.02$, ROC 29.87 pg/mL) and IFNγ ($p<0.001$, ROC cutoff: 47.7 pg/mL) was associated with the development of fibrosis. 71% of patients with a TNF-α >29.87 pg/mL developed fibrosis compared to 10% of patients with a TNF-α ≤29.87. Similarly, 86% of patients with IFNγ > 47.7 pg/mL developed fibrosis vs. 6% with IFNγ ≤47.7 pg/mL.

CONCLUSIONS: TNF-α and IFNγ are known mediators of soft tissue fibrosis and are responsible for a diverse range of signaling events within cells post-injury. In this study, 71% of patients who had circulating levels of TNF-α > 29.87 pg/mL and 86% of patients with IFNγ levels > 47.7 pg/mL developed long term tissue fibrosis. Future studies in larger populations and a cohort of conventional dose/fractionation schemes in STS are warranted to corroborate these findings.

Inflammatory Cytokine	Median
IL-1b	12.96 pg/ml
IL-4	0.47 ng/mL
IL-6	27.16 pg/ml
IL-10	16.01 pg/ml
IL—17A	0.06 ng/ml
IL-25	0.06 ng/mL
IL-31	0.12 ng/mL
IL-32	10.35 pg/ml
IL-33	69.77 pg/ml
MIP1a	47.33 pg/ml
TNF-α	24.72 pg/ml
TNF-β	0.22 g/mL
TGFβ1	3878.73 pg/ml
TGFβ2	211.07 pg/ml
IFNγ	37.08 pg/ml

Table 1: Pro-Inflammatory Cytokines