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Transforming Growth Factor Beta-1 (TGF- β 1) is a Serum Biomarker of Radiation Induced Fibrosis in Patients Treated with Intracavitary Accelerated Partial Breast Irradiation (IBAPBI): Preliminary Results of a Prospective Study

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Abstract

Purpose—To examine a relationship between serum transforming growth factor beta-1 (TGF- β 1) values and radiation induced fibrosis (RIF).

Methods—We conducted a prospective analysis of development of RIF in 38 women with AJCC Stage 0-I breast cancer treated with lumpectomy and accelerated partial breast irradiation via interstitial brachytherapy (IBAPBI). An ELISA (Quantikine®, R&D, MN) immunoassay was used to measure serum TGF- β 1 pre-surgery, pre- IBAPBI, and during IBAPBI. Blood samples for TGF- β 1 were also collected from 15 healthy, non-treated women (controls). The previously validated tissue compliance meter (TCM) was used to objectively assess radiation-induced fibrosis (RIF).

Results—Median time to follow-up for 38 patients is 44 months (range, 5 – 59 months). RIF is graded by the TCM scale as 0, 1, 2 and 3 in 5/20 (25%), 6/20 (30%), 5/20 (25%) and 4/20 (20%) patients, respectively. TCM 6mm (moderate-to-severe RIF) is statistically different from TCM 3mm (none-to-mild RIF) ($p < 0.05$). Mean serum TGF- β 1 values are significantly higher in patients pre-surgery than disease-free controls in: a) all cancer patients ($30,201 \pm 5,889$ pg/ml, $p = 0.02$), b) patients with any type of RIF ($32,273 \pm 5,016$ pg/ml, $p < 0.0001$) and c) women with moderate-to-severe RIF ($34,462 \pm 4,713$ pg/ml, $p < 0.0001$). The post-IBAPBI mean serum TGF- β 1 is 21,915pg/ml in patients with TCM 6mm (moderate-severe RIF). This is significantly higher than the mean serum TGF- β 1, 14,940pg/ml, in patients with TCM 3mm ($p = 0.036$). In patients

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who develop moderate-to-severe RIF, pre-IAPBI mean TGF- β 1 values are also predictive of this sequela ($17,885 \pm 3,952$ pg/ml, $p=0.007$).

Conclusions—TGF- β 1 levels correlate with development of moderate-to-severe RIF. The pre-IBAPBI mean TGF- β 1 levels can serve as an early biomarker for development of moderate-to-severe RIF after IBAPBI

Keywords

transforming growth factor beta-1 (TGF- β 1); radiation induced fibrosis (RIF); tissue compliance meter (TCM); breast cancer; accelerated partial breast irradiation (APBI); radiation side effects

INTRODUCTION

Accelerated hypofractionated partial breast irradiation (APBI) condenses the standard 6 weeks of radiation treatment into 5 days, offering logistical and quality of life benefits (1, 2). A mode of APBI that has become increasingly popular is interstitial brachytherapy (IBAPBI) (3). Results from studies evaluating various interstitial brachytherapy systems have proven to yield local failure rates as low as 0–5.7% at up to 65 months, as well as good-to-excellent cosmetic results in 67 – 97% of patients (4, 5). Early and late normal tissue complications are thought to be comparable to other modes of APBI (6). In particular, a recent study evaluating rates of normal tissue toxicity for those treated with IBAPBI report grade I, II, and III radiation induced fibrosis (RIF) to occur at a rate of 26%, 2%, and 0%, respectively (7).

RIF is an unwanted normal tissue complication that occurs months to years following initial radiation exposure (8). RIF can be a painful and cosmetically undesirable condition seen clinically as skin retraction, atrophy, and decreased tissue compliance (9). Within tissue affected by RIF, there is an overproduction of extracellular matrix and a replacement of normal tissue by mesenchymal cells (10). These changes are the result of pro-inflammatory and pro-fibrotic cytokines such as transforming growth factor (TGF)- β 1 released during the initiating phase of RIF development (11, 12). During the chronic phase of RIF there is actually deregulation of fibrinolysis with diminished ECM break-down, resulting in the maintenance of the overabundant fibrous tissue (13). However, there is great variability in whether or not a patient experiences RIF following breast irradiation (14).

Although differences in radiation delivery can influence RIF rates, increasing evidence suggests variation in patient response can be understood through genetic polymorphisms and gene expression (15). In particular, the TGF- β 1 gene has gained increased attention as a potential determinant of RIF occurrence (16). TGF- β 1 is a fibrosis promoting cytokine that stimulates fibroblast proliferation, while up-regulating ECM production (17). TGF- β 1 further contributes to fibrosis by diminishing epithelial repair, causing vascular damage that perpetuates tissue hypoxia (18). The effect of TGF- β 1 following tissue radiation is likely modulated by multiple factors including extracellular signaling, apoptosis, and inhibition of proliferation in response to DNA damage (19). In lung cancer, elevated TGF- β 1 levels were shown to positively associate with an elevated risk of radiation-induced pulmonary fibrosis (20). Among breast cancer patients, multiple SNPs associated with the TGF- β 1 gene have

been shown to correlate with RIF, though a recent meta-analysis has attempted to disprove this correlation (16, 21).

Previously, studies evaluating RIF in patients treated with external beam radiation have found a positive correlation between pre-treatment TGF- β 1 and radiation fibrosis (22). In this study, we prospectively assess TGF- β 1 as a serum marker of developing RIF in women treated with IBAPBI.

MATERIALS AND METHODS

Patients

Following approval by the institutional review board, patients scheduled to receive IBAPBI following lumpectomy were enrolled in a prospective trial assessing the relationship between TGF- β 1 levels with radiation-induced fibrosis (RIF). In total, 38 women with AJCC early-stage 0–1 breast cancer were enrolled. Prior to enrollment, all patients were informed of the risks and benefits of trial participation. All study participants signed informed consent. Enrollment criteria were based on publications by the American Brachytherapy Society (23), while consensus guidelines were used for the selection of patients for IBAPBI (24, 25). Patient, tumor, and dosimetric characteristics are described in Table 1. 15 healthy women were also recruited as control subjects for study participation. The following exclusion criteria were applied: any present or past history of breast or any other type of cancer, prior breast surgery, fibrocystic breast disease, current pregnancy or coagulopathy. Patients were assessed for RIF pre-treatment (baseline), 1 month following IBAPBI, and every subsequent 6 months.

Treatment

The MammoSite breast brachytherapy system (Hologic Inc, Bedford, Massachusetts) and Contura MLB (SenoRx, Inc., Aliso Viejo, California) balloons were used for the IBAPBI treatment. We used a prescribed dose of 34.0 Gy in 10 fractions of 3.4 Gy, given two times per day. A three-dimensional 1.0-cm expansion of the balloon cavity was used for the planning target volume (PTV), which was subsequently decreased by a 5 mm skin-to-balloon distance (SBD) to protect the skin from excess dose. Dose volume histogram (DVH) analysis confirmed 95% of prescribed dose covering 95% of the evaluable PTV (PTV-EVAL). The area of trapped air or fluid was accounted for by contouring the volume at each level, and subtracting the percentage of the PTV-EVAL displaced from the proposed dose coverage to ensure 95% dose coverage. Maximum skin and rib doses were limited to less than 125% and 145%, respectively. The V150 for breast tissue could not exceed 50 cc, while the V200 was reduced to not exceed 10 cc. Both volumes were set as low as possible while satisfying all other dose parameters.

Immunodetection of TGF- β 1

To quantify serum TGF- β 1 at pre-surgery, pre-treatment and post-treatment time points, an ELISA (Quantikine®, R&D, MN) immunoassay was used. All serum samples were harvested with a serum separator tube, allowing the sample to clot at room temperature for 30 minutes. Samples were incubated overnight at 5 °C. The samples were then centrifuged

at $1000 \times g$ for 15 minutes before serum was removed and stored at -70°C . The assay procedure was then carried out according to Quantikine® complete assay guidelines. Plates were read using a microplate reader set to 450 nm and measured values were converted into TGF- β 1 concentrations by reference to the standard curve.

Tissue compliance meter (TCM)

To assess compliance of the irradiated breast we employed the tissue compliance meter (TCM), a previously validated hand-held mechanical device (9, 16). Tissue compliance is a measurement of the device's penetration in relation to the force applied (Figure 1). The tissue compliance is measured by a millimeter (mm) scale. The detailed protocol and validation of the TCM as a superior objective quantitative assessment of RIF has been published by Wernicke et al previously (26). TCM (mm) is the difference between the values of the index and control areas. The TCM classification of RIF is graded as follows: 0=none, 1=mild, 2=moderate, and 3=severe, corresponding to a change in TCM (TCM) between the index and control breasts of 2.9, 3.0–5.9, 6.0–8.9, 9.0mm, respectively.

Statistical analysis

Descriptive statistics (including mean, median, range, proportion) were calculated for demographic and clinical variables of interest. Mean TGF- β 1 (pg/ml) and TCM (mm) values reflected the mean difference between the index and control breasts and none-to-mild versus moderate-to-severe RIF. The paired *t* test and Pearson correlation coefficient (*r*) were used to assess TGF- β 1 and RIF. All *p* values were two-sided and statistical significance was set at the 0.05 alpha level. All analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL).

RESULTS

A total of 38 women were evaluated in the study. Median age was 69 years (range, 47 – 82 years). Median follow-up time after completion of IBAPBI was 44 months (range, 5 – 59 months). The majority of patients had tumors that were well or moderately differentiated (90%), and estrogen receptor positive (78%). Most tumors (90%) were situated in the outer quadrants of the breast. Most patients (85%) were treated with Mammosite, and the remaining (15%) received Contura. Hormonal therapy was administered to (51%) of the patients. Complete patient and tumor characteristics can be found in table 1.

RIF, graded by TCM scale as 0, 1, 2, and 3, occurred in 5/20(25%), 6/20 (30%), 5/20(25%), and 4/20 (20%) of patients (Figure 2). A TCM of >6mm (moderate-to-severe RIF) was statistically different from a TCM $\leq$ 3mm (none-to-mild RIF) ($p<0.05$) (figure 3). Post-IBAPBI, the mean serum TGF- β 1 was 21,915pg/ml in patients with TCM $\geq$ 6mm (moderate-severe RIF). This is significantly higher than the mean serum TGF- β 1 of 14,940pg/ml in patients with TCM $\leq$ 3mm (none-mild RIF) ($p=0.036$) (Figure 4). Furthermore, Pearson's correlation analysis demonstrated that TGF- β 1 is positively correlated with occurrence of breast RIF ($r=0.61$, $p=0.0001$).

The mean TGF- β 1 value of the post-menopausal controls was $23,692 \pm 3,956$ pg/ml, significantly lower than values prior to lumpectomy in all cancer patients ($30,201 \pm 5,889$

pg/ml, $p=0.02$). TGF- β 1 levels drawn prior to surgery were predictive of any type of RIF ($32,273 \pm 5,016$ pg/ml, $p<0.0001$) and moderate-to-severe RIF ($34,462 \pm 4,713$ pg/ml, $p<0.0001$). TGF- β 1 values were also predictive of moderate-to-severe RIF prior to IBAPBI ($17,886 \pm 3,953$ pg/ml, $p<0.007$). Patients with none-to-mild RIF were not significantly associated with TGF- β 1 values prior-to-surgery ($p=0.14$) or prior-to-IBAPBI ($p=0.77$). In addition, no TGF- β 1 values drawn during IBAPBI were significantly different from controls (Table 2).

DISCUSSION

Radiation treatment planning is guided by the known dose tolerances of normal tissues (27). By minimizing dose to normal tissue, the theoretical risk of early or late complications or treatment are decreased (28). A potential normal tissue complication of breast irradiation is RIF. Knowing clinical risk factors for RIF could be a valuable tool in determining the intensity of treatment regimen, thereby individualizing treatment and preventing unnecessary complications.

Given the large doses per fraction and accelerated treatment time with APBI, there is a theoretically elevated risk of RIF with this mode of treatment (29). However, the effects of IBAPBI on acute and late toxicity are still being investigated. Wallace et al. conducted a Phase I/II trial evaluating long-term toxicity in patients treated with IBAPBI for early-stage breast cancer. Among the patients with short-term follow-up (<6 months), Grade I, II and III toxicities occurred at a RIF frequency of 25%, 2%, and 0%, respectively, while long-term follow-up patients (≥ 6 months) had Grade I, II and III RIF frequency of 26%, 2%, and 0%, respectively. However, median follow-up was only 11.4 months (range, 5.4–48 months) (7). Unfortunately, there are no published studies comparing IBAPBI versus other forms of ABPI, such as external beam ABPI. However, the rates of fibrosis determined by other fractionation schedules and modes of ABPI do appear to be comparable (30).

TGF- β 1 is a pro-fibrotic cytokine that has been proposed as a genetic and serum marker for radiation fibrosis (17). TGF- β 1 is known to stimulate fibroblast differentiation and ECM production, while contributing to endothelial dysfunction thought to underlie fibrosis development (18). The clinical evidence for TGF- β 1 in radiation fibrosis pathogenesis is most reliably shown in radiation pneumonitis in lung patients. One of the early studies by Anscher et al revealed that among the 73 patients treated for lung cancer, a return of plasma TGF- β 1 to normal following radiation had a sensitivity and positive predictive value of 90% for not developing symptomatic radiation pneumonitis (20). Further studies revealed that normal post-radiation TGF- β 1 levels could be used to determine eligibility for dose escalation, potentially improving local control and survival in patients with non-small cell lung cancer (31, 32). Unfortunately, not all subsequent studies supported these conclusions and the relative small patient number and differences in toxicity definitions limit conclusions made (10).

Researchers have also begun to investigate the role of TGF- β 1 in RIF among breast cancer patients. Li et al evaluated pre-radiotherapy serum of 91 patients with early stage breast cancer, finding TGF- β 1 levels to be significantly elevated in patients with moderate-to-

severe RIF of the breast when compared those with none-to-mild RFI. Using 96.0 pg/ml as a cut-off value, an elevated TGF- β 1 level had a 76% sensitivity and 74% specificity for predicting moderate-to-severe RIF. Further studies have focused on genetic and molecular expression (33). Quarmby et al studied multiple TGF- β 1 gene polymorphisms within DNA collected from 103 breast cancer patients post-radiation treatment. In particular alleles -509T and +869C were found to be significantly associated with patients who developed severe RIF, contributing up to a 15-fold increase in risk of breast RIF development (16). Multiple subsequent studies supported these findings (32). However, a recent meta-analysis evaluated 2782 patients from 11 different cohorts and concluded that patients with the -509T allele had an odds ratio (OR) of 0.95% (Confidence Interval (CI) 0.85–1.11) (21). Interestingly, Reuther et al. discovered that the potential elevated risk of carrying -509T allele had no effect on gene expression, protein secretion, or cellular radiosensitivity (34).

In this study, we attempted to investigate the impact of serum TGF- β 1 values pre-surgery, post-surgery and pre-IBAPBI, and during-IBAPBI and after IBAPBI treatment. Like Li et al (22), we found pre-radiation therapy levels of TGF- β 1 to be significantly elevated in breast cancer patients who developed RIF. We were also able to determine that elevated serum TGF- β 1 levels are a significant biomarker for severe-to-moderate prior to *both* IBAPBI and surgery. Therefore, serum TGF- β 1 levels could theoretically be drawn soon after diagnosis to assist in risk assessment for treatment planning. Those with low pre-surgery TGF- β 1 levels, and therefore a decreased risk of RIF, could be eligible for dose escalation, while those with elevated levels could be treated more conservatively. Should there be a viable treatment to prevent RIF, TGF- β 1 levels could be the determinant of eligibility for such treatment. Also, given the lack of consensus on the utility of genes predictive of RIF, using serum TGF- β 1 levels could be a simple alternative for RIF risk-assessment.

Our study emphasizes the importance in timing TGF- β 1 level assessment. Interestingly, TGF- β 1 levels *during* IBAPBI were statistically insignificant. Also, TGF- β 1 levels drawn between radiation and surgery were actually lower than the comparative controls. This may appear to be contradictory; however, it is known that TGF- β 1 levels undergo a regulated decrease in cancer patients post-operatively (35). Although post-treatment TGF- β 1 levels are also predictive of RIF, we suggest drawing pre-treatment TGF- β 1 levels as the superior approach. By doing so, one may not only inform the patient of the inherent risk, but modify treatment accordingly.

CONCLUSION

The current data suggest that pre-surgery and pre-IAPBI mean TGF- β 1 levels can serve as an early biomarker for development of moderate-to-severe RIF after IAPBI. Furthermore, a simple TGF- β 1 blood test may render a potentially easy and accurate pre-treatment diagnosis of RIF, much earlier than its detection with TCM or TGF- β 1 in follow-up. In this way, we can potentially predict which patients are at increased risk for developing RIF after IBAPBI. This will allow customizing radiation treatments accordingly and may render standard fractionation regimens as an option to patients at-risk of moderate-to severe RIF.

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SUMMARY

Radiation induced fibrosis (RIF) is a painful and cosmetically undesirable complication of radiation treatment to the breast. This study evaluates TGF- β 1 as a serum biomarker for predicting RIF in patients treated with accelerated partial breast irradiation (IBAPBI). Our data reveals pre-surgery and pre-IBAPBI TGF- β 1 levels positively correlate with the development of moderate-to-severe RIF.

Figure 1.
Distribution of radiation-induced fibrosis among patients.

Figure 2. Comparison of TGF- β 1 levels in none to mild and in moderate to severe radiation-induced fibrosis (RIF). RT = radiation therapy; TGF- β 1 = transforming growth factor.

Figure 3.

Receiver operator characteristic (ROC) curve for serum TGF- β 1 levels *ROC curves were generated using the state variable of moderate to severe radiation-induced fibrosis. AUC = area under the curve

Table 1Baseline Patient, Tumor, and Dosimetric Characteristics ($n = 39$)

Characteristics	<i>n</i> (%)
Age	
Median	69
Range	47 – 82
Breast treated	
Left	25 (64)
Right	14 (36)
Breast (cup) size	
A	0 (0)
B	8 (20)
C	17 (44)
D+	14 (36)
T stage	
Tis	9 (23)
T1a	5 (13)
T1b	16 (41)
T1c	9 (23)
Stage	
0	5 (13)
I	26 (67)
II	8 (20)
Device	
Mammosite	33 (85)
Contura	6 (15)
Chemotherapy	
Yes	2 (5)
No	33 (85)
Unknown	4 (10)
Median balloon size (range), cc	41.2 (37.6 – 50.0)
Median SBD (range), cm	1.4 (0.2 – 5.5)

Abbreviations: SBD = skin-to-balloon distance

Table 2TGF- β 1 levels before and during radiation treatment

RIF	Time	TGF-β1 Value	P-value
Any	Prior to surgery	32,273 $\pm$ 5,016	< 0.0001
	Prior to APBI	20,339 $\pm$ 6,775	0.22
	During APBI	29,178 $\pm$ 5,113	0.52
None-to-Mild RIF	Prior to surgery	26,715 $\pm$ 4,291	0.14
	Prior to APBI	20,261 $\pm$ 8,415	0.30
	During APBI	27,638 $\pm$ 4,059	0.77
Severe RIF	Prior to surgery	34,468 $\pm$ 4,713	< 0.0001
	Prior to APBI	17,886 $\pm$ 3,953	0.007
	During APBI	23,411 $\pm$ 3,030	0.87

Abbreviations: TGF- β 1 = transforming growth factor; RIF = radiation induced fibrosis; APBI: acceleration partial breast irradiation