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Combining Physical and Biologic Parameters to Predict Radiation-Induced Lung Toxicity in Patients With Non-Small-Cell Lung Cancer Treated With Definitive Radiation Therapy

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Abstract

Purpose—To investigate the plasma dynamics of 5 proinflammatory/fibrogenic cytokines, including interleukin-1beta (IL-1β), IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and transforming growth factor beta1 (TGF-β1) to ascertain their value in predicting radiation-induced lung toxicity (RILT), both individually and in combination with physical dosimetric parameters.

Methods and Materials—Treatments of patients receiving definitive conventionally fractionated radiation therapy (RT) on clinical trial for inoperable stages I–III lung cancer were prospectively evaluated. Circulating cytokine levels were measured prior to and at weeks 2 and 4 during RT. The primary endpoint was symptomatic RILT, defined as grade 2 and higher radiation pneumonitis or symptomatic pulmonary fibrosis. Minimum follow-up was 18 months.

Results—Of 58 eligible patients, 10 (17.2%) patients developed RILT. Lower pretreatment IL-8 levels were significantly correlated with development of RILT, while radiation-induced elevations of TGF-β1 were weakly correlated with RILT. Significant correlations were not found for any of the remaining 3 cytokines or for any clinical or dosimetric parameters. Using receiver operator characteristic curves for predictive risk assessment modeling, we found both individual cytokines and dosimetric parameters were poor independent predictors of RILT. However, combining IL-8, TGF-β1, and mean lung dose into a single model yielded an improved predictive ability ($P < .001$) compared to either variable alone.

Conclusions—Combining inflammatory cytokines with physical dosimetric factors may provide a more accurate model for RILT prediction. Future study with a larger number of cases and events is needed to validate such findings.

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Introduction

Despite recent advances in radiation planning and delivery techniques, treatment of locally advanced and medically inoperable non-small-cell lung cancer (NSCLC) with concurrent chemoradiation therapy continues to be hindered by concerns of treatment-related toxicities, such as radiation-induced lung toxicity (RILT). The ability to predict RILT should facilitate individualized radiation dosing and potentially lead to a maximized therapeutic gain.

Accurate models for RILT prediction are lacking, and current risk assessment typically relies on physical dosimetric parameters, such as mean lung dose (MLD) and percentage of lung volume exposed to doses exceeding a threshold (V_{dose} ; eg, V_{20}) (1, 2). These parameters, however, are estimated on the basis of the sensitivity for a population of patients. Thus, their predictive accuracy for individual patients is limited.

In an attempt to more accurately assess individual patient's risks of developing RILT, recent research has focused on identifying biologic markers, namely plasma cytokines, involved in the molecular pathogenesis of lung damage. Presently, however, plasma cytokines have been inconsistently shown to serve as risk-predicting biomarkers. Transforming growth factor beta1 (TGF- β 1) is the cytokine most extensively studied for the prediction of RILT and has been reported to be independently predictive of RILT at the end of radiation therapy (RT) (3, 4), although other studies have failed to confirm this finding (5, 6). The utility of such prediction at the end of treatment has also been questioned, given that there is no longer the potential to alter therapy. More recent studies have shown a significant association between RILT and radiation-induced elevation of circulating levels of TGF- β 1 during therapy, suggesting that the TGF- β 1 ratio (ie, TGF- β 1 levels during RT divided by levels prior to RT) may be used as a predictor for RILT (7). In addition to TGF- β 1, circulating interleukins, such as interleukin-6 (IL-6) and IL-8, have been shown to be significantly correlated with the risk of RILT (6, 8).

Although recent insights into the pathogenesis of radiation-induced pulmonary injury have revealed the involvement of a number of proinflammatory and profibrogenic cytokines, such as IL-1 β , IL-6, IL-8, tumor necrosis factor alpha (TNF- α), and TGF- β 1, no clinically validated predictive model using plasma cytokines as risk-predicting biomarkers exists. Considering that the risk of RILT appears to be associated with radiation dosimetric parameters as well as individual heterogeneity in normal tissue response, an accurate predictive model should take all of these factors into consideration. Two studies have examined the utility of combining TGF- β 1 levels with a dosimetric factor (MLD and V_{30}) and have shown an improvement in the ability to stratify patients for their risk of RILT (7, 9). Given that multiple cytokines likely regulate RILT through different pathways, this study aimed to investigate the plasma dynamics of 5 cytokines biologically relevant to inflammation/fibrosis, including IL-1 β , IL-6, IL-8, TNF- α , and TGF- β 1 (10, 11), to ascertain their value in predicting RILT, both individually and in combination with dosimetric parameters.

Methods and Materials

Study population

This work was part of 3 prospective Institutional Review Board-approved NSCLC studies conducted at the University of Michigan Cancer Center and the Veterans Affairs Medical Center, Ann Arbor, MI: (1) a phase 1/2 study of RT dose escalation (limited to a lung normal tissue complication probability [NTCP] value of <15%) with concurrent chemotherapy and 2 consecutive studies using (2) functional imaging and (3) biomarkers to assess outcome. Eligible subjects included patients with stages I–III NSCLC undergoing

definitive RT. All clinical data, including grading of RILT and blood samples, were prospectively collected. Plasma samples were available for 58 patients who were willing to participate in the biomarker portion of the studies. No restrictions were placed on the degree of weight loss or pulmonary compromise. Exclusion criteria included life expectancy of <6 months, malignant pleural or pericardial effusion, and noncontiguous involvement of the parietal pleura.

Treatment regimen

All patients received conventionally fractionated RT with or without sequential or concurrent chemotherapy. Radiation was delivered using a 3-dimensional (3D) conformal technique, as previously described (12). Gross tumor volume included the primary tumor and any involved hilar or mediastinal lymph nodes. Uninvolved lymph node regions were not included in the clinical target volume. Normal lung dose volume histograms (DVHs) were generated in the exhale state, with inclusion of both lungs and exclusion of the gross tumor volume. Tissue inhomogeneity corrections were applied for all plans. Our planning constraints attempted to confine MLD to <20 Gy and total lung V₂₀ 35%.

Cytokine analysis

Cytokine measurements were performed in platelet-poor plasma samples at 3 time points: at baseline (within 2 weeks before the start of RT) and at 2 and 4 weeks during RT. Plasma samples were collected and prepared as previously described (7). A commercial cytokine panel kit (xMAP plasma assay; Luminex, St. Charles, MO) was used to measure levels of IL-1 β , IL-6, IL-8, and TNF- α , while TGF- β 1 level was measured by molecule-specific enzyme-linked immunosorbent assay. All sample tests were run in duplicate.

Follow-up and toxicity evaluation

Patients were evaluated weekly during RT, with follow-up evaluation at 1 month after completion of RT, and then every 3 months for 2 years. At each follow-up, patients underwent a history and physical examination as well as a chest computed tomography scan. Treatment-related toxicity was evaluated and graded according to Common Terminology Criteria for Adverse Events version 3.0.

The primary endpoint in this study was RILT grade 2. Details of diagnosis and grading systems for RILT have been described previously (2). Briefly, RILT was prospectively assessed according to a system modified from Radiation Therapy Oncology Group/Southwest Oncology Group/National Cancer Institute Common Toxicity Criteria for acute radiation pneumonitis and fibrosis. RILT was diagnosed on the basis of worsening symptoms by at least 1 grade from baseline levels during or after RT, without evidence of tumor recurrence or other specific cause. Radiologic change alone was scored as grade 1 and, thereby, was insufficient for the diagnosis of RILT in this study.

Statistical considerations

Individual markers were assessed using 2-sample mean comparisons between the RILT and non-RILT subgroups, with adjustments made for multiple comparisons using the Bonferroni method corrected for 17 tests. Statistical analysis was performed on the log₂ scale to account for abundance levels that tend to be right skewed. A *P* value of .05 was considered significant. Receiver operating characteristics (ROC) analysis was used to assess the predictive ability of single-marker and multimarker signatures of RILT. For each set of markers, logistic regression was used to form a linear combination of the quantitative levels of the markers in the set that best predicted the outcome (presence of RILT). A ROC curve was then generated from that signature. Leave-one-out cross-validation was used to provide

unbiased estimates of the population ROC curve. The area under the curve (AUC) was used to summarize the predictive ability shown in the ROC curve. Nonparametric bootstrapping was then used to construct standard errors and 95% confidence intervals (CI) for the AUC values.

Results

Patient characteristics and radiation-induced lung toxicity

Table 1 lists the characteristics of the 58 patients included in this study. Fifty-one patients were male and 7 were female and the median age was 69 years. Forty-four patients (76%) were treated with a combination of chemotherapy and RT. Forty-two patients received concurrent chemotherapy with the following regimens: carboplatin and paclitaxel (n=38), cisplatin and etoposide (n=2), pemetrexed (n=1), and erlotinib (n=1). The remaining 2 patients received sequential chemotherapy with carboplatin and paclitaxel, followed by thoracic radiation. The median prescribed radiation dose was 66 Gy (interquartile range [IQR], 64.2–70.0) with 96% of patients receiving radiation doses $\geq$ 60 Gy. The median MLD was 15.6 Gy (IQR, 12.3–18.0), and the median V_{20} was 25.1% (IQR, 17.7–31.2). Over a minimum follow-up period of 18 months for surviving patients, we observed clinically significant grade $\geq$ 2 RILT in 10 of 58 patients (17.2%), with all events occurring within 12 months of RT. Of note, no patient received adjuvant docetaxel, which is known to increase the risk of pneumonitis, within the first year of completing RT.

Clinical and dosimetric parameters

On univariate analysis, no significant correlation was detected between the incidence of RILT and any of the following clinical or dosimetric parameters: age, gender, smoking status, baseline pulmonary function, administration of concurrent chemotherapy, dosimetric factors (V_{20} and MLD), or total radiation dose (Table 1).

Cytokine levels and RILT

A summary of the 5 cytokines evaluated prior to treatment and at weeks 2 and 4 during RT is displayed in Table 2. Statistically significant differences were observed in the absolute levels of IL-8 both prior to and during RT among patients who did and did not develop RILT, while the ratio of TGF- β 1 levels (ie, levels during RT divided by levels prior to RT) was weakly associated with development of RILT. Of the 3 remaining cytokines, IL-1 β , IL-6, and TNF- α , neither the absolute levels nor the ratios demonstrated any significant association with the development of RILT.

For the entire cohort of 58 patients, lower levels of IL-8 at pretreatment and at weeks 2 and 4 during radiation were found to be significantly associated with RILT ($P < .01$). Patients who did not develop RILT had a mean $\pm$ SD pre-RT IL-8 level (23.6 ± 3.6 pg/mL) that was approximately 3 times higher than the mean pre-RT IL-8 level in patients who developed RILT (7.2 ± 1.6 pg/mL). This ratio remained consistent throughout the course of treatment, as the level of IL-8 exhibited minimal variation at weeks 2 and 4 during radiation (Fig. 1).

During RT, the absolute levels of TGF- β 1 increased in patients who developed RILT, resulting in an elevation of the TGF- β 1 ratio at weeks 2 (2.6 ± 0.7 vs. 1.0 ± 0.01) and 4 (2.0 ± 0.5 vs. 0.8 ± 0.1) (Fig. 1). Prior to adjustments for multiple comparisons, this radiation-induced elevation of TGF- β 1 was significantly associated with RILT ($P = .02$ and $P = .01$ for TGF- β 1 ratios at 2 and 4 weeks during RT, respectively). However, after adjusting for multiple comparisons, the ratio was no longer significant at weeks 2 and 4 ($P = .41$ and $P = .26$, respectively).

Predictive risk assessment models

To predict the risk of RILT, we generated unbiased cross-validated ROC curves based on the quantitative levels of single and multiple cytokine signatures with and without dosimetric parameters. Both the individual cytokines and the dosimetric parameters alone were found to be poor independent predictors of RILT. AUC values for pre-RT IL-8 levels alone, TGF- β 1 ratio at week 2, and MLD were 0.69 (95% CI, 0.45–0.93, $P=.16$), 0.57 (95% CI, 0.23–0.91, $P=.67$), and 0.54 (95% CI, 0.22–0.86, $P=.85$), respectively (Fig. 2). However, combining all 3 parameters into a single model improved the predictive ability compared to either of the variables alone, producing an AUC of 0.80 (95% CI, 0.66–0.94, $P<.001$). A model incorporating all 5 cytokines of interest in conjunction with MLD did not appear to yield further gains (AUC, 0.81; 95% CI, 0.65–0.97).

The benefit of combining biologic and physical parameters was explored further by using threshold values for pretreatment IL-8 expression (7.6 pg/mL), TGF- β 1 ratio at week 2 (0.5), and MLD (14.0 Gy), determined from the individual ROC curves based on a sensitivity of 80% for RILT prediction. Using threshold values for IL-8 and MLD, patients were initially risk stratified into 1 of 4 subgroups: high pretreatment IL-8 and low MLD (group 1), high IL-8 and high MLD (group 2), low IL-8 and low MLD (group 3), and low IL-8 and high MLD (group 4). The incidence of RILT was 6%, 4%, 20%, and 70% in groups 1–4, respectively, with elevated levels of IL-8 exhibiting a protective effect in patients with unfavorable dosimetry (Table 3). The addition of TGF- β 1 provided further stratification with patients assigned to 1 of 4 subgroups based on the presence of risk factors: IL-8 <7.6 pg/mL, TGF- β 1 ratio <0.5, and MLD <14.0 Gy. The incidences of RILT were 0%, 5%, 12%, and 75% in patients with zero ($n=5$), 1 ($n=19$), 2 ($n=26$), and 3 ($n=8$) risk factors, respectively (Table 4).

Discussion

Data from our study demonstrate that reduced pretreatment levels of IL-8 are significantly correlated with development of RILT in patients with NSCLC, while radiation-induced elevations of TGF- β 1 are weakly correlated with RILT. More importantly, a model combining pretreatment levels of multiple circulating cytokines and MLD may more accurately predict RILT. Because these parameters can be obtained within the early course of RT, this model has the potential to serve as a predictive tool to prescribe personalized RT.

Interestingly, IL-8 is associated with protection against RILT. This result is in accordance with the findings of Hart et al (6) demonstrating that lower pretreatment plasma levels of IL-8 are an independent risk factor for the development of RILT. Moreover, we showed that IL-8 levels exhibit minimal variation during the course of treatment and continue to serve as a predictive biomarker at weeks 2 and 4 during RT. The reasons that a proinflammatory cytokine might be protective against RILT in the setting of NSCLC are not entirely clear. Numerous observations have established IL-8 as a key mediator in neutrophil-mediated acute lung inflammation (13). Chronic overexpression of IL-8, however, has been shown to lead to long-term impaired neutrophil migration in response to acute inflammation (14). Thus, it is possible that NSCLC patients with elevated levels of circulating IL-8 might exhibit an impaired inflammatory response to sites of tissue injury.

Differences observed in the ratio of circulating TGF- β 1 between patients with and those without RILT confirm our previous finding that radiation-induced elevation of TGF- β 1 during RT correlates with development of RILT (7). In other studies, the efficacy of TGF- β 1 in predicting RILT has been inconsistent. Investigators at Duke University reported TGF- β 1 was independently predictive of RILT at the end of RT (3, 4), whereas others have failed to confirm this finding (5, 6). The reasons for these conflicting results are unclear, as numerous

factors may confound the predictive value of TGF- β 1, including differences in assay/sample handling methods (TGF- β 1 is richly stored in platelets), tumor-confounding effect, and statistical under-powering by limited cases and toxicity events. In particular sample handling, processing, and storage can greatly affect the adequacy and reliability of cytokine measurements in clinical specimens due to degradation, absorption, and/or cellular production of cytokines through processes such as platelet degradation (leading to the release of various cytokines including TGF- β 1 and IL) as well as the binding and release of cytokines to inflammatory mediators secreted from other cellular elements. As such, great care must be taken to ensure standardization of sample collection protocols in order to minimize interassay variations and provide comparable and meaningful values.

In this analysis, no significant association was observed between the incidence of RILT and individual levels of IL-1 β , IL-6, or TNF- α . As part of their plasma cytokine profile analysis, Hart et al (6) examined plasma levels of IL-1 β , IL-6, and TNF- α prior to RT, while Rube et al (15) measured the levels of these 3 cytokines before, during, and after RT. In concert with our findings, those studies found no association between plasma concentrations of IL-1 β , IL-6, and TNF- α and RILT in patients irradiated for advanced NSCLC. In contrast, Chen et al (16) and Arpin et al (8) reported significantly higher circulating levels of IL-6 before and during RT, respectively, in patients who developed RILT. These discrepancies in IL-6 measurements again highlight the difficulties encountered in measuring cytokines in clinical samples, as discussed above, with TGF- β 1. Furthermore, in patients with advanced NSCLC, IL-6 and TGF- β 1 plasma levels have been shown to depend on the local tumor production of these cytokines (15). Thus, the release of IL-6 or TGF- β 1 as a result of radiation-induced lung injury may be superimposed by the variable cytokine production of the tumor.

While biomarkers continue to undergo evaluation, radiation dosimetric parameters such as MLD, V₂₀, and NTCP models have been extensively studied in relation to RILT and are commonly used as predictive factors in practice (1, 12). DVH parameters, however, are based on the risk of RILT for populations of patients rather than individuals. For instance, parameters are useful in designing treatments that limit the rate of RILT to 10%, but they do not predict which 10 of 100 patients will develop complications. Given that DVH parameters are associated with RILT in populations of patients but lack optimal predictive ability for individuals, we hypothesized that the addition of biologic parameters to the model should improve the prediction of post-treatment RILT for individual patients.

This study, using single- and multiple-cytokine signatures in conjunction with MLD, supports the notion that a model incorporating both biologic and dosimetric parameters may improve RILT prediction. Although we observed that lower levels of IL-8 were significantly correlated with the development RILT, IL-8 showed limited predictive ability when used as the sole variable in the model (AUC 0.69, $P=.16$). Combining IL-8, TGF- β 1, and MLD into a single model improved the predictive ability (AUC 0.80, $P<.001$) compared to that with either of the variables alone. Importantly, these parameters were obtained within the first 2 weeks of treatment and, thus, may afford the opportunity to individualize therapy.

Conclusions

Overall, these data appear to be promising, albeit very preliminary, in the search for pretreatment predictive risk assessment parameters for RILT. This study is notably limited by the small number of events for modeling. Thus, validation in a prospective multicenter study is essential prior to clinical incorporation of these predictive models. If confirmed, this approach has the potential to lead to individualized RT based on each patient's risk profile.

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Summary

Although radiation-induced lung toxicity (RILT) is associated with dosimetric parameters as well as individual heterogeneity in normal tissue response, current risk assessment models typically rely on dosimetric parameters alone. This study demonstrates RILT prediction in patients with non-small-cell lung cancer were improved by combining an inflammatory plasma cytokine signature with standard dosimetric parameters. Importantly, all parameters were obtained within the first 2 weeks of treatment, thereby, affording the opportunity to individualize therapy.

Fig. 1. The kinetics of plasma cytokines prior to and during 3D conformal RT for patients who did and did not develop RILT. (A) IL-8 plasma levels; (B) TGF-β1 plasma levels; (C) TGF-β1 ratio. Data are means $\pm$ standard error of the means.

Fig. 2.
ROC curve based on the sensitivity and specificity of pretreatment IL-8 alone, week 2 ratio of TGF-β1 alone, MLD alone, and all 3 parameters combined to predict RILT.

Table 1

Association between patient- and treatment-related characteristics and RILT

Characteristics	All patients (n=58) (%)	No RILT (n=48) (%)	RILT (n=10) (%)	P value*
Age (y)				.66
Median	69	68	70	
Interquartile range	60–76	60–75	63–76	
Gender				.82
Male	51 (88)	42 (88)	9 (90)	
Female	7 (12)	6 (13)	1 (10)	
Smoking status				.08
Current	29 (50)	27 (56)	2 (20)	
Former	28 (48)	20 (42)	8 (80)	
Never	1 (2)	1 (2)		
FEV ₁ (L)				.56
Median	1.6	1.6	1.5	
Interquartile range	1.4–2.3	1.3–2.3	1.4–2.4	
DLCO (mL/min/mm Hg)				.46
Median	12.4	11.8	13.0	
Interquartile range	9.9–15.2	9.6–15.6	12.1–13.8	
Concurrent chemotherapy				.74
Yes	42 (72)	35 (73)	7 (70)	
No	16 (28)	13 (27)	3 (30)	
Radiation dose (Gy)				.56
Median	66.9	68.8	64.1	
Interquartile range	64.2–70.0	64.2–70.0	63.9–69.0	
Mean lung dose (Gy)				.16
Median	15.6	15.0	17.9	
Interquartile range	12.3–18.0	10.8–17.7	15.2–18.0	
V ₂₀ (%)				.13
Median	25.1	24.0	29.0	
Interquartile range	17.7–31.2	17.4–30.1	27.0–32.0	
RILT				
0–1	48 (83)	-	-	-
2	10 (17)	-	-	-

Abbreviations: DLCO = diffusion capacity for carbon monoxide; FEV₁ = forced expiratory volume in 1 sec; RILT = radiation-induced lung toxicity; V₂₀ = volume of normal lung receiving 20 Gy or more.

* Logistic regression.

Table 2

Correlation between cytokines and RILT

Cytokine (concentration)	No RILT		RILT		P value*
	Mean	SD	Mean	SD	
IL-1 β (pg/mL)					
Baseline	40.7	20.8	16.8	7.1	1.00
W 2	49.1	33.7	14.1	4.9	1.00
W 4	33.6	19.7	11.4	3.1	1.00
IL-6 (pg/mL)					
Baseline	65.1	18.7	22.8	5.6	1.00
W 2	66.9	19.7	22.0	4.7	1.00
W 4	61.1	19.4	23.5	2.5	1.00
IL-8 (pg/mL)					
Baseline	23.6	3.6	7.2	1.6	<.01
W 2	20.5	3.3	6.7	1.6	<.01
W 4	20.0	3.1	6.6	1.6	<.01
TNF- α (pg/mL)					
Baseline	14.7	2.2	18.6	7.2	1.00
W 2	13.6	2.7	13.1	4.2	1.00
W 4	13.8	2.7	16.4	3.5	1.00
TGF- β 1 (ng/mL)					
Baseline	10.4	1.3	5.6	1.0	.85
W 2	8.4	1.3	10.4	2.1	1.00
W 4	6.4	0.9	9.1	1.7	1.00
TGF- β 1 ratio					
W 2/baseline	1.0	0.01	2.6	0.7	.41
W 4/baseline	0.8	0.1	2.0	0.5	.26

Abbreviations: RILT = radiation-induced lung toxicity; SD = standard deviation.

* Two sample comparison of the mean, Bonferroni corrected for 17 tests, performed on log₂ scale.

Table 3

Incidence of RILT based on the presence of MLD and pretreatment IL-8

		<u>No RILT</u>	<u>RILT</u>	
Pretreatment		No. of patients	No. of patients	Incidence of RILT (%)
IL-8 7.6, MLD <14.0		16	1	6
IL-8 7.6, MLD 14.0		25	1	4
IL-8 <7.6, MLD <14.0		4	1	20
IL-8 <7.6, MLD 14.0		3	7	70

Abbreviations: IL-8 = interleukin 8 (pg/mL); MLD = mean lung dose (Gy); RILT = radiation-induced lung toxicity.

Table 4

Incidence of RILT in subgroups

Risk factor	No RILT	RILT	Incidence of RILT (%)
	No. of patients	No. of patients	
0	5	0	0
1	18	1	5
2	23	3	12
3	2	6	75

Abbreviations: IL-8 = interleukin 8 (pg/mL); MLD = mean lung dose (Gy); RILT = radiation-induced lung toxicity; TGF- β 1 = transforming growth factor beta1.

Table shows the incidence of RILT in subgroups based on the presence of risk factors: MLD (≥ 14 Gy), pretreatment IL-8 <7.6 pg/mL, and 2-week TGF- β 1 ratio ≥ 0.5 .