Tumor Infiltrating Lymphocytes as a Predictive Biomarker for Response to CTLA-4 and PDL-1 Therapies

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Abstract

Recently approved immunotherapies capitalize on antitumor mechanisms of the patient's immune system by inhibiting CTLA-4 and PD-1 pathways. Studies have shown better overall survival with increased tumor infiltrating lymphocyte (TIL) across multiple cancer. Recent trials with anti-PDL-1 has shown better response with high PDL-1 expression. However, studies have not evaluated whether TIL level would correlate with anti-PDL-1 or anti-CTLA-4 responses. The aim of this study is to determine if the level of TIL in metastatic melanoma and lung cancer correlates with patient response to modern immunotherapies. We identified 10 patients with melanoma or lung cancer treated with an immune checkpoint inhibitor. The biopsy samples were stratified according to level of TIL. The TIL categories ranged from 0 to 3, with 0 indicating no TIL detected and 3 indicating 67-100% TIL infiltration. Survival analysis was achieved with Kaplan-Meier curve, and tumor size change was evaluated with linear mixed model analysis. Overall survival was significantly longer in patients who had TIL (TIL0-0.3 yr; TIL1-2-2.4 yr; TIL3-1.6 yr, p=0.024). Tumor size also dramatically decreased at first follow up based on TIL level (TIL 1-2: 371% greater decrease than TIL 0, p < 0.01; TIL 3: 406%; p<0.01). Decrease in tumor size for TIL0 was 0.12cm^2 at first follow-up. Baseline tumor size for TIL0 was 41.9cm^2; TIL1-2 0.4 cm^2; TIL3 1.4cm^2. Our study shows that TIL level may serve as a biomarker to predict tumor response to immunotherapy, without specific histochemical staining. This study is limited by the low number; a larger review is currently taking place.

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Introduction

- Traditionally, cancer treatment has largely relied upon cytotoxic chemotherapies and radiation.
  - Limitations
    - Large side effect profile
    - Development of resistance to drugs
    - Radiation therapy is localized
- Immunotherapy was pioneered by Dr. William Coley (19th century)
  - Deliberately provoked an immune response in cancer patients by injecting streptococcus, causing tumors to shrink
- Immune checkpoints
  - Inhibitory proteins that prevent active immune response to certain stimuli
  - Important in preventing tissue injury and autoimmunity
  - Cancer cells capitalize on this mechanism for immune evasion
- Two immune checkpoint proteins have become of interest
  - Programmed cell death-1 **(PD-1)** and cytotoxic T-lymphocyte antigen 4 **(CTLA4)**
  - Bind to their ligands, **PD-L1** and **B7**, respectively
  - These receptors on the T cell bind to antigen presenting cells and tumor cells to inhibit an active T cell response
  - Blocking this pathway can lead to an active immune response
- Studies have shown that immune checkpoint inhibitor treatment response correlated with ligand expression (PD-L1 and B7)
- Ligand expression correlated with T-cell infiltration in tumors
- **TIL associated with longer survival**

We hypothesize that the level of TIL in samples of melanoma or lung cancer patients who received immune checkpoint inhibitor treatment will positively correlate with overall survival and response to therapy.

Methods

Study design: Retrospective chart review
Study setting: Banner MD Anderson Cancer Center (BMDACC), Gilbert, AZ
Inclusion Criteria
- Melanoma or lung cancer patients treated with immune checkpoint inhibitors between January 1, 2012 and December 31, 2015.
- Patients who have biopsy slides available to be analyzed by pathologist
- Age Range: 18-89 yrs

TIL Data
TIL density categorized into a 4-tiered system[4]
0: absence of TILs
1: low TILs (<33%)
2: moderate (34-67%)
3: marked increase in TIL (>80%)

Data Analysis
- Kaplan-Meier survival analysis for each TIL level
- Linear mixed model of tumor size over time

Results

- N=10; 4 males and 6 females
- Mean age: 62.8 (SD=12.6)
- N for each TIL level:
  - TIL 0: 4
  - TIL 1: 2
  - TIL 2: 1
  - TIL 3: 3

Patient	Sex	Cancer type	Age at tx start	TIL level	Location of mass	OS (in days)
A	M	Melanoma	50	1	Brain	1015
B	M	Melanoma	54	3	Femur	895
C	M	Melanoma	48	3	Nose	777
D	F	Melanoma	70	0	Liver	179
E	F	Melanoma	54	1	Parietal scalp	594
F	M	Melanoma	88	2	Temporal scalp	1175
G	F	Lung Cancer	63	0	Mainstem bronchus	168
H	F	Lung Cancer	73	0	Lung	50
I	F	Lung Cancer	57	0	Vertebral body	41
J	F	Lung Cancer	71	3	Lung	35

Table 1. Characteristics of patients included in this study.

- Baseline tumor size for TIL 0: 41.9cm^2 (SD=35.0); TIL 1-2: 0.4 cm^2 (SD=0.6); TIL 3: 1.4cm^2 (SD=0.8)
- Overall survival was significantly longer in patients who had TIL (TIL 0: 0.3 yr; TIL 1: 2-2.4 yr; TIL 3: 1.6 yr, p=0.024)

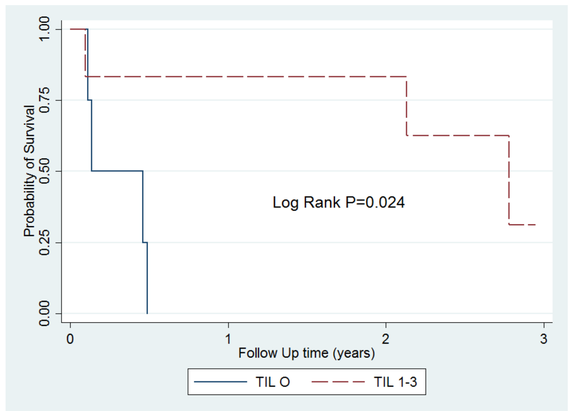

Figure 1. Kaplan-Meier curve for probability for survival by TIL 0 vs 1-3. Time=0 is the treatment start date.

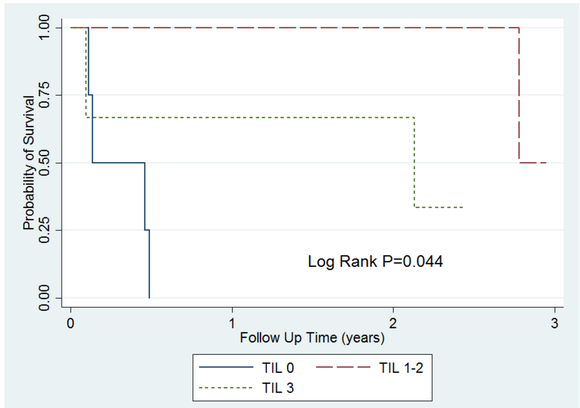

Figure 2. Kaplan-Meier curve for probability for survival by TIL 0 vs 1-2 vs 3. Time=0 is the treatment start date.

- Decrease in tumor size for TIL 0 was 0.12cm^2 at first follow-up.
- Tumor size also dramatically decreased at first follow up based on TIL level
  - TIL 1-2: 371% greater decrease than TIL 0, p<0.01
  - TIL 3: 406% greater decrease than TIL 0, p<0.01

Discussion and Conclusions

- Our study shows that TIL level is associated with overall survival.
  - Support for the concept of using TIL as a biomarker for predicting response to immune checkpoint inhibitor therapy.
- Novel findings showing TIL correlates with decrease in tumor size.
- This study is limited by the low number of subjects available for analysis; a larger review is currently taking place.
- Analyze further radiological characteristics of tumors to assess potential differences with TIL level.

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