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ORIGINAL RESEARCH

Effect of Lymphopenia on Tumor Response and Clinical Outcomes Following Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer

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Background: Prior studies suggest lymphopenia, systemic immune-inflammatory index, and tumor response all impact clinical outcomes in Stage III NSCLC. We hypothesized that tumor response after CRT would be associated with hematologic metrics and might predict clinical outcomes.

Materials and Methods: Patients with stage III NSCLC treated at a single institution between 2011 and 2018 were retrospectively reviewed. Pre-treatment gross tumor volume (GTV) was recorded then reassessed at 1–4 months post-CRT. Complete blood counts before, during and after treatment were recorded. Systemic immune-inflammation index (SII) was defined as neutrophil × platelet/lymphocyte. Overall survival (OS) and progression free survival (PFS) were calculated using Kaplan-Meier estimates, and compared with Wilcoxon tests. A multivariate analysis of hematologic factors impacting restricted mean survival was then performed using pseudovalue regression, accounting for other baseline factors.

Results: 106 patients were included. After median follow-up of 24 months, median PFS and OS were 16 and 40 months, respectively. Within the multivariate model, baseline SII was associated with OS ($p = 0.046$) but not PFS ($p = 0.09$), and baseline ALC correlated with both PFS and OS ($p = 0.03$ and $p = 0.02$, respectively). Nadir ALC, nadir SII, and recovery SII were not associated with PFS or OS.

Conclusion: In this cohort of patients with stage III NSCLC, baseline hematologic factors were associated with clinical outcomes including baseline ALC, baseline SII and recovery ALC. Disease response was not well correlated with hematologic factors or clinical outcomes.

Keywords: lymphopenia, myelosuppression, chemoradiation, tumor response

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death in the United States and worldwide with 1.7 million deaths globally, representing over 18% of all cancer deaths. Despite recent advances, 3-year overall-survival (OS) is less than 60%.[1] Chemoradiotherapy (CRT) followed by immunotherapy has become a standard for definitive management of unresectable Stage III NSCLC. Oncologic therapies interact with the host immune system potentially altering clinical outcomes, though the complex interplay is not fully understood. The immune system plays a role in suppression of malignancy, but can be inhibited, allowing for cancer progression. Radiotherapy can enhance cancer cell antigenicity by upregulating DNA damage and cellular stress pathways, exposing immunogenic tumor-associated antigens to the immune system.[2,3] Conversely, multimodality treatment with radiation can induce lymphopenia[4–6] and dampen the immune response, because lymphocytes are key mediators of the response to cancer. Mature circulating lymphocytes are highly radiosensitive and exhibit significant DNA fragmentation at even low radiation doses (<1Gy).[7,8] Multiple studies have associated lymphopenia with a detrimental impact on clinical outcomes in some cancer types[5,6,9–11] while others have failed to show such a relationship.[4] It has been proposed that radiation dose to the host immune system is associated with worse clinical outcomes in patients with Stage III NSCLC.[12] The systemic immune-inflammatory index (SII = neutrophil × platelet/lymphocyte) is

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a marker that has been suggested to have prognostic influence in patients treated with locally advanced NSCLC, as well as other malignancies.[13] Standard radiotherapy for Stage III NSCLC targets not only gross disease but often includes additional margin for at-risk regions as well as uncertainties in planning or treatment delivery, resulting in collateral effects on health tissue, including tissue involved in the immune response.

Recent evidence suggests tumor volume reduction as determined by modern RT image guidance such as cone beam computed tomography (CBCT) images may be correlated with clinical outcome.[14] In this retrospective study, we aimed to investigate the relationship between lymphopenia, SII, and disease response based on CT imaging following completion of definitive chemoradiation (CRT) in stage III NSCLC. We hypothesized that tumor response after CRT would be associated with hematologic metrics, and might ultimately predict for clinical outcomes.

Materials/Methods

Using an IRB approved database, patients with stage III NSCLC treated at a single institution with definitive chemoradiation between 2011 and 2018 were reviewed using electronic medical record (EPIC), available diagnostic imaging, and treatment planning system (Varian Eclipse). No patients had received prior treatment. All patients fulfilling the following criteria were included: (1) ≥18 years of age, (2) pathologically proven NSCLC, (3) available complete blood counts before, during and after treatment, and (4) CT-based imaging immediately prior to and 1 to 4 months following treatment. Patients without accessible blood counts, imaging, or patients who did not complete therapy, were excluded.

Patients were censored at time of last follow up. Local recurrence was defined as failure within high dose radiation field. CT scans 1–4 months after completion of CRT were evaluated for initial response. Pre- and post-treatment CT scans were analyzed and contours were generated manually, allowing for calculation of tumor volume both before and after treatment. Lymphopenia, defined as an absolute lymphocyte count (ALC) <1.0 $x10^3/\mu L$, was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. Overall survival (OS) and progression free survival (PFS) were calculated using Kaplan-Meier estimates from the date of diagnosis for the entire cohort and also based on histology.

Since the assumption of proportional hazards does not hold, commonly used Log rank test and Cox model were not used. Instead, Wilcoxon tests were used to compare the survival times. A multivariate analysis of hematologic factors impacting restricted mean survival up to 60 months was then performed using pseudovalue regression, accounting for other baseline factors,[15] including age, AJCC, T stage, N stage, histology, consolidation, GTV initial and GTV response. All analyses were performed using SAS© 9.4 and statistical tests with p values less than 0.05 were considered as statistically significant.

Results

Patient and Treatment Characteristics

Overall, 106 patients were included in the study. Median age was 62 years (range: 47–85) and 56% were female. Current, former, and never smokers represented 63%, 33%, and 4% of the patients, respectively. Patients had a median of 40 pack-years smoking history. 59% were stage IIIA (AJCC 7th Ed). Histologically, 42% had adenocarcinoma, 50% had squamous cell carcinoma, and 8% were poorly differentiated. At diagnosis, 89% were ECOG 0–1. Baseline demographic, tumor, and treatment characteristics are summarized in Table 1. All patients were treated with definitive concurrent chemoradiotherapy, and weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) was the most common chemotherapy regimen. Thoracic radiotherapy was given to a median dose of 60 Gy in 30 fractions, and 22 (20.8%) received a simultaneous integrated boost.

Myelosuppression

Prior to starting treatment, the median baseline absolute lymphocyte count (bALC) was 1.49 $x10^3/\mu L$, the median absolute baseline neutrophil count (bANC) was 6.4 $x10^3/\mu L$, the median absolute baseline platelet count was 299 $x10^9/L$, and the median absolute baseline albumin was 4.0 g/dL. Median drop in ALC (dALC) during treatment was 1.13$x10^3/\mu L$. ALC typically declined precipitously following initiation of CRT, reaching its nadir by week 6–7, and recovered

Table 1 Baseline Clinical, Treatment, and Response Factors of 106 Patients with Stage III NSCLC

N=106	N = 106	%
T stage		
T0	2	1.9
T1	14	13
T2	21	20
T3	32	30
T4	37	35
N Stage		
N0	8	7.5
N1	8	7.5
N2	63	59.4
N3	27	25.5
Stage (7th edition)		
IIIA	62	58.5
IIIB	44	41.5
Median age (range)	62 (47–85)	
<50	8	8
50–60	36	34
60–70	34	32
70–80	23	22
80+	5	5
Sex		
Male	47	44
Female	59	56
Smoking Status		
Current	67	63.2
Former (Quit 1–15 years ago)	14	13.2
Former (Quit >15 years ago)	21	19.8
Never	4	3.8
Histology		
Adenocarcinoma	44	41.5
Squamous	53	50.0
Other/Poorly Diff	9	8.5

(*Continued*)

Table 1 (Continued).

Prescription Dose		
Median Prescription (Gy)	60 (21% SIB)	
Median DPF (Gy)	2	
Concurrent Chemotherapy		
Platinum/taxane	96	90.5
Platinum/etopiside	4	3.7
Platinum/gemcitabine	3	2.8
Platinum/pemetrexed	3	2.8
Consolidation/Maintenance		
No	34	32
Yes - Cytotoxic	64	60.3
Yes - Durvalumab	8	7.5
Tumor Volumetrics		
25th-50th-75th Initial GTV (cc)	59–110-226 cc	
25th-50th-75th % Response	61–74-85%	

following the completion of CRT, although not to baseline (Figure 1). Patients reached approximately 50% of their pre-treatment lymphocyte count by two months post-treatment. Median drop in neutrophils, platelets and albumin were, 4.8 $x10^3/\mu L$, 173 $x10^3/\mu L$, and 0.4 g/dL, respectively. 54.7% and 32.1% of patients experienced Grade 3 and Grade 4 lymphopenia, respectively. 29.2% of patients experienced ≥ grade 3 leukopenia.

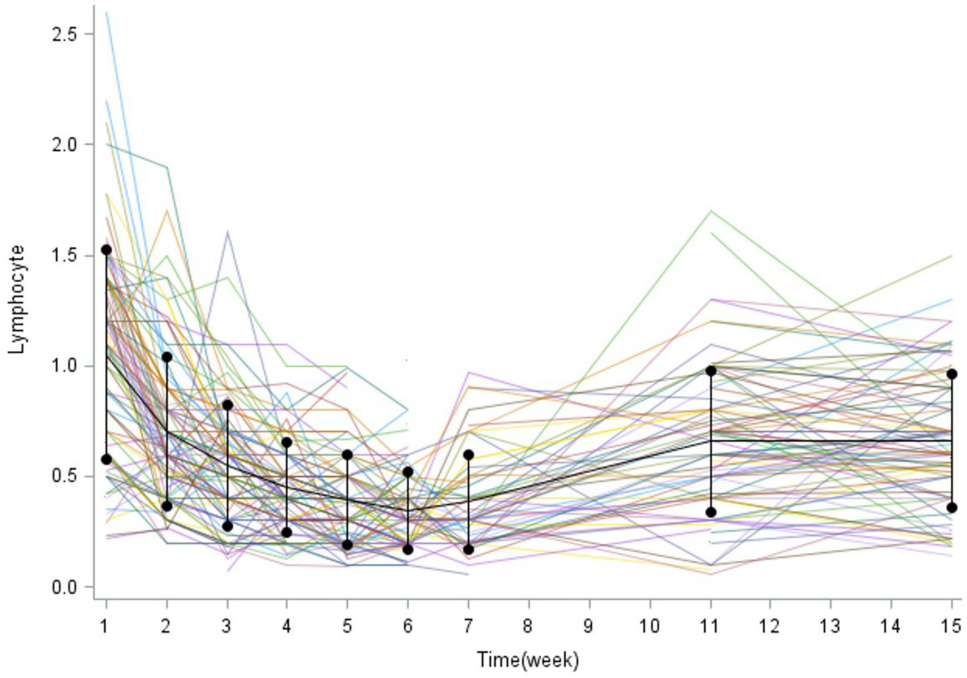

Figure 1 Absolute Lymphocyte Count ($x10^3/\mu L$) for each patient during and following completion of chemoradiation.

Clinical Outcomes

After median follow-up of 24 months (range: 4–97 months), median PFS (95% CI, 14–36) and OS (95% CI, 24–52) were 16 and 40 months, respectively. Local tumor recurrence (LR) was noted in 13.2% with a median time to LR of 26 months, and 27.4% of patients failed distally with a median time to distant recurrence of 17 months. Local recurrence occurred in 18.2% of patients with adenocarcinoma compared with 9.4% of patients with squamous cell carcinoma (p=0.104). Larger GTV (> 120 cc) was negatively associated with PFS (p=0.048) and OS (p=0.032). AJCC 7th edition stage grouping as well as T and N categories were highly associated with OS and PFS.

Estimates for OS and PFS based on baseline absolute lymphocyte count (ALC), baseline SII, and recovery ALC, dichotomized by median split and compared with Wilcoxon tests, are summarized in Figure 2. On univariate analysis, baseline ALC >1.5 x10^3/μL was associated with improved PFS (p=0.009) and improved OS (p=0.001). Additionally, baseline SII <1200 was associated with improved PFS (p=0.01) and OS (p=0.005). Neither ALC nor SII during nadir phase (weeks 5–7) were associated with PFS or OS. Recovery ALC (1–2 months post-CRT) was associated with improved PFS (p=0.01) but not OS (p=0.09). SII was not associated with PFS or OS during the recovery phase. When stratified by histology, squamous cell carcinoma baseline ALC >1.5 x10^3/μL was associated with improved PFS (p=0.05) and OS (p=0.003). Squamous cell carcinoma baseline SII <1200 was also associated with improved OS. Baseline ALC, baseline SII and recovery ALC were not statistically significant in the adenocarcinoma subset (Table 2). Within the multivariate model over restricted mean survival time up to 60 months, baseline SII remained significant for OS (p = 0.046) but not PFS (p = 0.09), and bALC remained associated with both PFS and OS (p = 0.03 and p = 0.02,

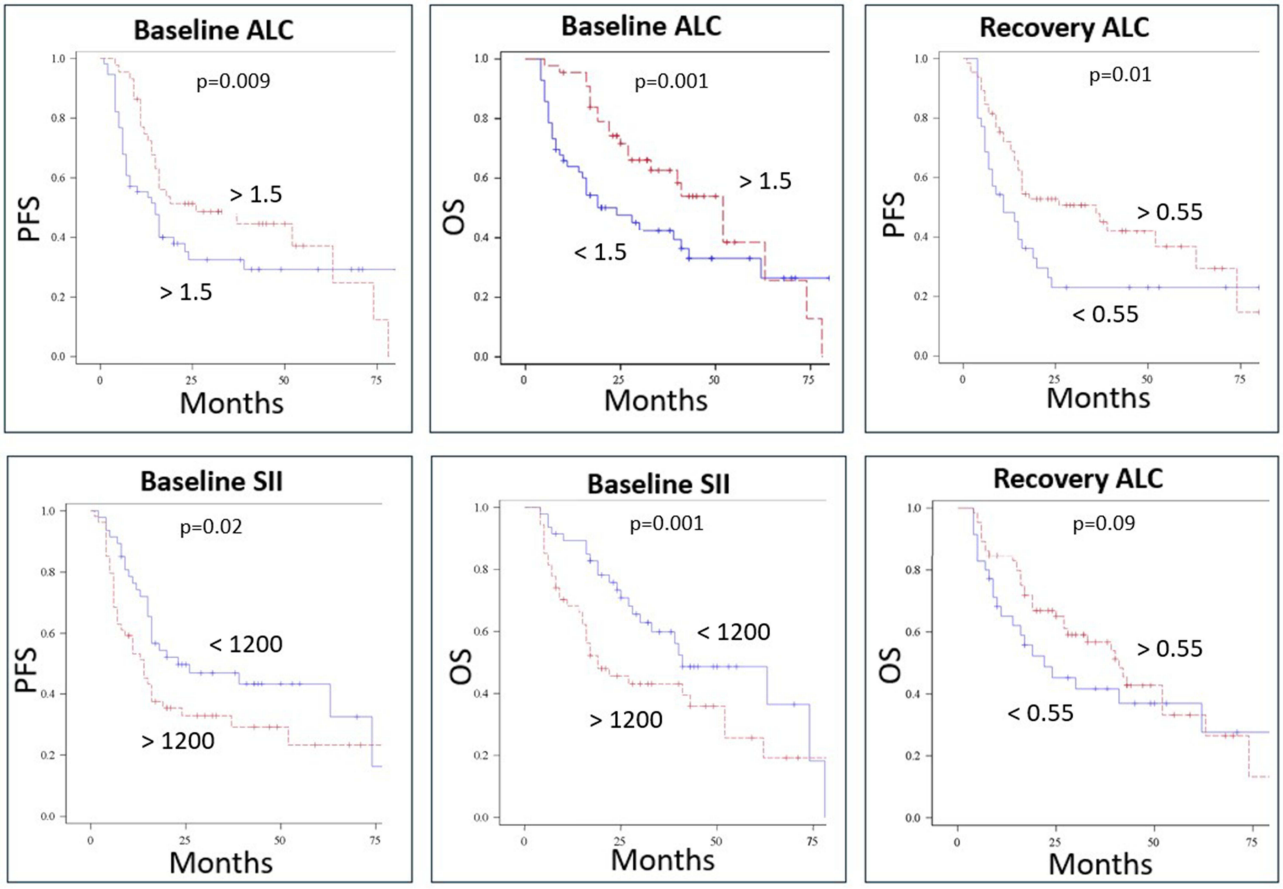

Figure 2 Estimates for OS and PFS based on baseline absolute lymphocyte count (ALC), baseline SII, and recovery ALC, dichotomized by median split.

Table 2 Statistical Significance of Kaplan-Meier Estimates for OS and PFS Based on Baseline Absolute Lymphocyte Count (ALC), Baseline SII, and Recovery ALC, Dichotomized by Median Split and Compared with Wilcoxon Tests

		Adenocarcinoma	Squamous	Entire Cohort
Baseline ALC	OS	p=0.07	p=0.003	p=0.001
	PFS	p=0.58	p=0.05	p=0.09
Baseline SII	OS	p=0.52	p=0.006	p=0.001
	PFS	p=0.58	p=0.54	p=0.02
Recovery ALC	OS	p=0.07	p=0.47	p=0.09
	PFS	p=0.39	p=0.17	p=0.01

respectively), after accounting for the confounding effects from age, AJCC, T stage, N stage, histology, consolidation, GTV initial and GTV response.

Tumor and Response

Median pre- and post-GTV were 110 cc and 23 cc, respectively, with a median 74.3% median response (GTVres) from pre-treatment simulation scan to post-treatment imaging. Neither baseline nor nadir hematologic values were associated with magnitude of tumor response. Percent tumor response was not associated with PFS (p=0.258) or OS (p=0.185).

Discussion

The development of lymphopenia during chemoradiation is expected in patients with stage III NSCLC. The current study supports an association between baseline lymphocyte count and clinical outcomes, previously suggested by others in a range of cancer types.[16–19] Our study was in agreement with Tong et al in suggesting that pre-treatment SII as an independent prognostic biomarker for OS.[13]

Our search for a signal of association between degree of myelosuppression and magnitude of tumor response did not yield significance. To our knowledge, this is the first attempt to evaluate this potential relationship. Moreover, depth of treatment-related immunologic nadir was not associated with clinical outcome in our patient population. This is consistent with findings in a recent study of patients undergoing CRT in oropharyngeal cancer from Ng et al where no association between the development of G3/G4 lymphopenia and overall survival was found.[4] A contrary result was published regarding patients with esophageal cancer where grade 4 ALC nadir was associated with worse OS and disease-specific survival outcomes.[20]

Early response to treatment has recently been posited to predict for post-CRT survival.[14,21] These findings were not replicated in this series, and our attempt to explain magnitude of response by baseline or treatment-induced lymphopenia was not fruitful. It is possible that a relationship does indeed exist, but could not be uncovered by our method of study. Notably, there are significant challenges associated with accurate disease-response volumetric assessment. For example, assigning a residual tumor volume following substantial response conflated with post-treatment changes is likely subject to significant inter-observer variability.

Recovery ALC was associated with improved PFS and a trend towards improved OS, suggesting that the immune system's ability to rebound might be helpful in anticipating clinical outcome. Others have shown that lower radiation doses to the circulating blood pool, lymphoid organs, and heart are associated with reduced hematologic immunosuppression.[22,23] The negative clinical outcomes associated with persistent chemoradiation induced lymphopenia following treatment suggest novel approaches to minimize radiation dose to lymphocyte-related organs at risk while maintaining target coverage deserve further consideration.

It has been postulated that treatment-related lymphopenia may be related to radiation techniques including dose rate and target size. As early as the 1970s, lymphopenia was noted to be inversely proportional to fraction number, even when

total radiation dose was held constant.[24] Techniques such as stereotactic body radiotherapy (SBRT), hypofractionation, proton therapy, ultra-high dose rate (FLASH) RT and de-intensification through reduction of dose, volume, or systemic therapy may reduce the lymphotoxic effects.[18,25] Recent studies suggest that reducing lung V5-V10 may be important for optimization of immune response given the high sensitivity of lymphocytes to low levels of radiation, especially in patients with XRCC1 rs25487 genotype.[26,27] In RTOG 0617, dose escalation to 74 Gy compared to 60 Gy resulted in an unexpected trend towards inferior local control 61.8 → 54.3% (p=0.07) and OS 32.1 → 23% (p=0.06).[28] One potential explanation suggests that dose escalation may inhibit the host immune response by reducing populations of lymphocytes.[29] Indeed, Colton et al, and Ladbury et al suggested that the immune system could be avoided as an organ at risk, potentially impacting clinical outcomes.[12,30]

Although most patients in this study did not receive immunotherapy, durvalumab is now standard of care in the adjuvant setting and studies are ongoing (eg ECOG-ACRIN 5181) investigating its role in the concurrent setting. Despite adoption of anti-PDL1 therapy within contemporary guidelines, multiple real-world factors limit its utilization, with recent published immunotherapy initiation rates as low as 65%.[31] The effects of lymphopenia in patients receiving immunotherapy is not well established, but it has been suggested that peri-immunotherapy lymphopenia may predict for worse clinical outcomes.[18,32] As the role of immunotherapy grows, so does the need to better understand the interplay between the host immune system, radiation therapy, and systemic therapy. Strategies for adapting radiotherapy timing and technique to minimize lymphopenia may offer an opportunity to further advance clinical outcomes.

Limitations to this study include those inherent to any retrospective study from a single institution with a relatively small sample size, especially when stratifying by histology. Additionally, blood draws and imaging were not standardized so there was some heterogeneity in their frequency and timing relative to radiation treatments. Finally, evaluation of tumor response while seeking association with hematologic parameters is complex. Thus, caution is advised in interpreting these results, and larger validation studies are likely required to more thoroughly evaluate or corroborate any potential interaction.

Conclusions

In this cohort of patients with stage III NSCLC treated with definitive chemoradiation, several baseline and recovery hematologic factors were associated with clinical outcomes including baseline ALC, baseline SII and recovery ALC. Treatment related hematologic nadir were not associated with clinical outcome. Further understanding of the interplay between the immune system, hematologic toxicity, and clinical outcomes following CRT is needed.

Human Ethics Statement

Prior to starting the study, ethical approval was obtained by Upstate Medical University Institutional Review Board for the Protection of Human Subjects and project was determined to be EXEMPT FROM IRB REVIEW according to federal regulations. The data accessed complied with all relevant data protection and privacy regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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