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Original Research Article

Lymphocytopenia repercussions on stage III Non-small cell lung cancer (NSCLC) patients' tumour progression and their clinical results after chemoradiation

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ABSTRACT

Aim: According to earlier research, tumour response, Lymphocytopenia, and a system-wide immune-inflammatory indexes all affect the clinical results of Stage III NSCLC. We postulated that the tumour response to CRT would be related to hematologic parameters and could perhaps anticipate clinical results.
Materials and Methods: Retrospective evaluation of stage III NSCLC patients treated at a single facility between 2015 and 2020 was done. After receiving CRT, the pre-treatment gross tumour volume (GTV) was measured again. Full blood counts were taken before, during, and after treatment. Neutrophil platelet lymphocyte was used to define the systemic immune-inflammation index (SII). Kaplan-Meier estimates were used to compute overall survival (OS) and prognosis-free survival (PFS), which were then compared using Wilcoxon tests. Then, taking into account additional baseline parameters, pseudovalue regression was used to provide a multivariate study of hematopoietic factors affecting controlled average duration.
Results: There were 110 patients in total. The median PFS and OS were 20 and 35 months, respectively, after a median follow-up of 24 months. Baseline SII was correlated with OS ($p = 0.039$) but not PFS ($p = 0.10$), and baseline ALC was correlated with both PFS and OS ($p = 0.13$ and $p = 0.06$, respectively) in the multivariate model. The recovery SII, nadir ALC, and nadir SII were not connected to PFS or OS.
Conclusion: Baseline hematologic variables, such as baseline ALC, baseline SII, and recovery ALC, were related to clinical outcomes in this cohort of patients with stage III NSCLC. The relationship between disease response and hematologic variables or clinical outcomes was not strong.

1. Introduction

With 1.8 million deaths globally, or more than 18% of all cancer deaths, non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer-related death in an around the world. The 3-year overall survival rate (OS) is less than 60% despite recent improvements.[1] The gold standard for the final management of unresectable Stage III NSCLC is chemotherapy followed by radiation (CRT). Although the intricate interplay between oncologic therapy and the host immune system is not fully understood, it has the potential to change clinical outcomes. The immune system helps to prevent cancer, but it can also be blocked, which promotes the spread of the disease. By activating DNA damage and cellular stress pathways, radiotherapy can make cancer cells more immunogenic by exposing the immune system to immunogenic tumor-associated antigens.[2,3] In contrast, because lymphocytes are important mediators of the immunological response to cancer, multimodality radiation therapy can produce Lymphocytopenia.[4–6] and weaken the immune response.

Even at modest radiation exposures (less than 1 Gy), mature circulating lymphocytes show considerable DNA breakage due to their high radio-sensitivity.[7,8]

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While other research have been unable to demonstrate such a relationship, other investigations have linked Lymphocytopenia with a negative influence on clinical outcomes in specific cancer types.[5,6,9–11] In patients with Stage III NSCLC, it has been hypothesized that radiation exposure to the host immune system is linked to worse clinical outcomes.[12] The systemic immune-inflammatory index (SII) has been proposed to have predictive significance in patients treated for locally advanced NSCLC as well as other cancers. SII = neutrophil platelet lymphocyte.[13] Standard radiation for Stage III NSCLC generally contains additional margin for at-risk regions and treatment delivery issues in addition to the gross disease, which can have collateral effects on healthy tissue, including immune system tissue. Recent research reveals that the clinical outcome may be connected with tumour volume decrease as assessed by contemporary RT image guidance, such as cone beam computed tomography (CBCT) images.[14,15] In this retrospective investigation, we looked into the connections between Lymphocytopenia, SII, and the disease response seen on CT imaging after definitive chemoradiation (CRT) for stage III NSCLC. We postulated that the tumour response to CRT would be related to hematologic parameters and could serve as a clinical result predictor.

2. Materials and Methods

Patients with stage III NSCLC treated with definitive chemoradiation at a single facility between 2015 and 2020 were reviewed utilising an IRB-approved database using the electronic medical record (EPIC), accessible diagnostic imaging, and treatment planning system (Varian Eclipse). No patients had undergone any prior medical care. All patients who met the requirements below were included: (1) 20 years of age, (2) NSCLC with pathological confirmation, (3) readily accessible full blood counts before, during, and after treatment, and (4) CT-based imaging shortly before and 1 to 4 months after treatment. Patients without available blood counts, those without imaging, and those who stopped taking their medication were excluded. At the time of the most recent follow-up, patients were limited.

Failure within a radiation area with a high dosage was referred to as local recurrence. Initial response was assessed using CT scans performed one to four months after CRT was finished. The tumour volume could be calculated both before and after therapy by analyzing and manually creating outlines from pre- and post-treatment CT scans. According to Common Terminology Criteria for Adverse Events (CTCAE) version 5, Lymphocytopenia was classified as an absolute lymphocyte count (ALC) less than 1.0 x 103/μL. Based on histology and Kaplan-Meier estimates from the date of diagnosis for the complete cohorts overall survival (OS) and progression-free survival (PFS) were estimated.

The widely used Log rank test and Cox model were not applied since the assumption of proportional risks is false. The survival times were instead contrasted using Wilcoxon tests. Then, using pseudovalue regression, a multivariate analysis of hematologic determinants affecting restricted mean survival up to 60 months was carried out, taking other baseline factors (15) into consideration, such as age, AJCC, T stage, N stage, histology, consolidation, GTV initial, and GTV response. SAS 9.4 was used for all analyses, and statistical tests with p values under 0.05 were regarded as statistically significant.

3. Results

3.1. Patient and treatment characteristics

110 patients in total were enrolled in the study. 56% of the population was female, with a median age of 65 years (range: 47-85). A total of 64%, 35%, and 6% of the patients were current, former, or never smokers, respectively. Patients had smoked for a median of 40 pack-years. (AJCC, 7th Ed) 60% were in stage IIIA. According to histology, 6% were poorly differentiated, 45% had adenocarcinoma, and 50% had squamous cell carcinoma. 92% of patients had an ECOG score of 0 or 1 at the time of diagnosis.

Table 1 summarized the demographic,tumour, and treatment characteristics at baseline. All patients received definitive concomitant chemoradiotherapy, with the most popular chemotherapy regimen being weekly carboplatin (AUC 2) and paclitaxel (50 mg/m2). A simultaneous integrated boost was administered to 22 (21.8%) patients who got thoracic radiation with a median dosage of 60 Gy over the course of 30 fractions.

3.2. Myelosuppression

Immediately before commencing treatment, the median comparative baseline blood platelet count was 299 x109/L, the median absolute baseline albumin was 4.0 g/dL, the median absolute baseline neutrophil count (bANC) was 8.4 x103/μL, and the median absolute baseline lymphocyte count (bALC) was 3.49 x103/μL. The median ALC (dALC) decrease throughout therapy was 2.13 x 103/μL. Following the start of CRT, ALC generally fell rapidly, reaching its lowest point by weeks 6–7, and then rebounded after CRT was finished, though not to baseline (Figure 1). By two months after therapy, patients' lymphocyte counts had returned to about 50% of their pre-treatment levels. Neutrophils, platelets, and albumin all experienced median declines of 5.8 x 103/μL, 183 x 103/μL, and 0.4 g/dL, respectively. Grade 3 and Grade 4 Lymphocytopenia were present in 54.7% and 32.1% of patients, respectively. In 32.2% of patients, leukopenia in $\geq$ grade 3 was present.

Table 1: Baseline clinical, treatment, and response factors of 110 patients with stage III NSCLC

N = 110	**N = 110**	**%**
T Stage		
T0	2	1.8
T1	12	14
T2	14	22
T3	22	18
T4	35	29
N Stage		
N0	9	8.4
N1	8	8.9
N2	65	55.3
N3	30	28.3
Stage (VIIth)		
IIIA	65	60.0
IIIB	45	43.2
Median age 65 (35-45)		
<50	9	9
50-65	35	33
65-75	32	30
75-85	24	20
85+	8	8
Sex		
Male	48	45
Female	60	57
Smoking Status		
Current	70	65.3
Former (Quit 1-10 Years)	18	15.2
Former (Quit >10 Years ago)	23	18.1
Never	5	2.4
Histology		
Adenocarcinoma	45	42.4
Squamous	54	49.5
Other	10	7.5
Prescription Dose		
Median Prescription (Gy)	70 (25% SIB)	
Median DPF (Gy)	5	
Concurrent Chemotherapy		
Platinum / Taxane	98	95.5
Platinum / Etopiside	5	3.5
Platinum / Gemcitabine	4	1.5
Platinum / Pemetrexed	4	1.5
Consolidation/ Maintenance		
No	35	30
Yes - Cytotoxic	65	62.2
Yes - Durvalumab	9	6.5
Tumor Volumetrics		
20 -25- 50-70-75th Initial GTV (cc)	60-120-130 cc	
20-25-50-70-75th % Responses	62-75-90 %	

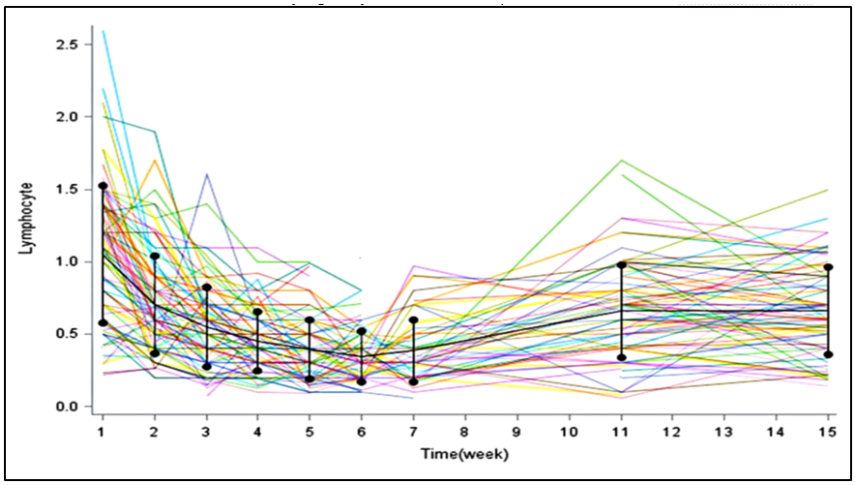

Fig. 1: Illustrates the absolute amount of lymphocyte count (x103/μL) before and afterchemoradiation for each patient.

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

		Adenocarcionoma	Squamous	Entire Cohort
Baseline ALC	OS	p=0.06	p=0.004	p=0.002
	PFS	p=0.59	p=0.06	p=0.08
Baseline SII	OS	p=0.53	p=0.007	p=0.001
	PFS	p=0.60	p=0.55	p=0,03
Recovery ALC	OS	p=0.08	p=0.48	p=0.06
	PFS	p=0.38	p=0.12	p=0.02

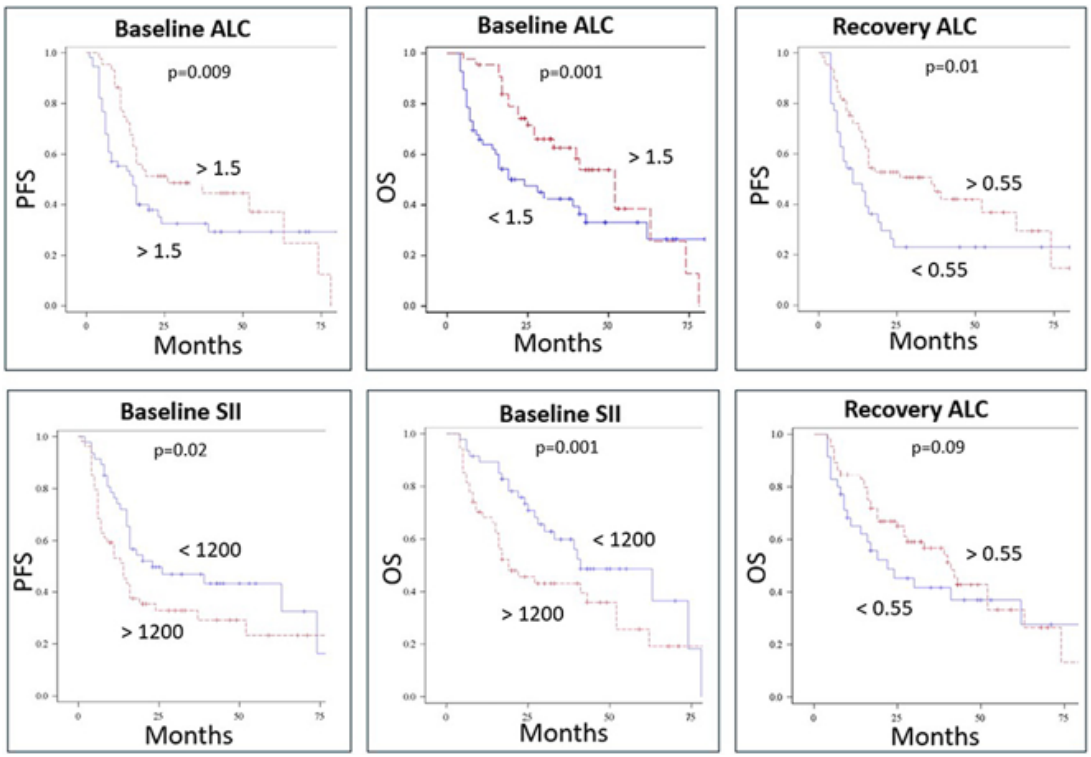

Fig. 2: Estimates for OS and PFS based on baseline absolute lymphocyte count (ALC), baseline SII, and recovery ALC, dichotomized by median split.

3.3. Clinical results

The median PFS (95% CI, 14-36) and OS (95% CI, 24-52) were 16 and 40 months, respectively, after a median follow-up of 24 months (range: 4-97 months). 13.2% of patients experienced a local tumour recurrence (LR), with a median time to LR of 26 months, and 27.4% of patients experienced a distant tumour recurrence, with a median time to distant recurrence of 17 months. In contrast to 9.4% of patients with squamous cell carcinoma, 18.2% of patients with adenocarcinoma experienced local recurrence (p=0.104). PFS (p=0.048) and OS (p=0.032) were negatively correlated with larger GTV (> 120 cc). T and N categories, as well as stage groupings from the AJCC 7th edition, were strongly related to OS and PFS. Figure 2 provides an overview of the estimates for OS and PFS depending on baseline absolute lymphocyte count (ALC), baseline SII, and recovery ALC. These estimates were dichotomized by median split and compared using Wilcoxon tests. Baseline ALC >1.5 x 103/μL was linked to better PFS (p=0.009) and OS (p=0.001) on a univariate analysis. Additionally, PFS (p=0.01) and OS (p=0.005) were also improved with baseline SII <1200. Neither ALC nor SII were related to PFS or OS during the nadir phase (weeks 5-7). Recovery ALC (1-2 months post-CRT) was not associated with OS (p=0.09) but was associated with better PFS (p=0.01). PFS or OS were not connected to SII throughout the recovery stage. Squamous cell carcinoma baseline ALC >1.5 x 103/μL was linked with better PFS (p=0.05) and OS (p=0.003) when stratified by histology. A lower baseline SII < 1200 for squamous cell carcinoma was likewise linked to a better overall survival rate. In the adenocarcinoma sample, baseline ALC, baseline SII, and recovery ALC were not statistically significant (Table 2). After adjusting for the confounding effects of age, AJCC, T stage, N stage, histology, consolidation, GTV initial, and GTV response, baseline SII remained significant for OS (p = 0.046) but not PFS (p = 0.09) in the multivariate model over the restricted mean survival time up to 60 months, and bALC remained associated with both PFS and OS (p = 0.03 and p = 0.02, respectively).

3.4. 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).

4. Discussion

In patients with stage III NSCLC, the development of Lymphocytopenia after chemoradiation is anticipated. The new study confirms prior findings in a variety of cancer types that a relationship exists between the initial lymphocyte count and clinical outcomes.[16–19] According to Tong et al. and our investigation, pre-treatment SII could serve as a separate predictive biomarker for OS.[13] Our search for a significant correlation between the degree of myelosuppression and the size of the tumour response came up empty. This is the first evaluation of this potential association that we are aware of. Furthermore, in our patient cohort, the depth of the immunologic nadir caused by the medication was not linked to the clinical result. This is in line with data from a recent study by Ng et al. on patients receiving CRT for oropharyngeal cancer, in which they discovered no connection between the emergence of G3/G4 Lymphocytopenia and overall survival.4 In contrast, grade 4 ALC nadir was linked to lower OS and disease-specific survival outcomes in studies of individuals with esophageal cancer.[20] Recent research suggests that early response to treatment can predict post-CRT survival.[14,21] These results were not confirmed in our series, and we were unable to explain the size of the response using baseline or treatment-induced Lymphocytopenia. It is possible that a relationship does in fact exist but was missed by our research strategy. Notably, proper disease-response volumetric evaluation is fraught with difficulties.

Assigning a residual tumour volume after a significant response that is confounded with post-treatment alterations, for instance, is probably vulnerable to a significant amount of inter-observer variability. Recovery The fact that ALC was linked to increased OS and PFS suggests that the immune system's capacity to recover may be useful in predicting clinical outcome. Others have demonstrated a correlation between decreased hematologic immunosuppression and lower radiation doses to the heart, lymphoid organs, and circulating blood pool.[22,23] The detrimental clinical effects of chemoradiation-induced Lymphocytopenia that persisted after treatment imply that creative strategies to reduce radiation dosage to organs connected to lymphocytes that are at risk while preserving target coverage merit further research. It has been suggested that radiation procedures, such as dosage rate and target size, may be connected to Lymphocytopenia brought on by treatment. Even when the overall radiation dose was held constant, Lymphocytopenia was found to be inversely proportional to fraction number in the 1970s.[24]

The lymphotoxic effects may be lessened by methods including stereotactic body radiotherapy (SBRT), hypofractionation, proton therapy, ultra-high dose rate (FLASH) RT, and de-intensification through dose, volume, or systemic therapy.[18,25] Given the extreme sensitivity of lymphocytes to low doses of radiation, recent findings suggest that decreasing lung V5-V10 may be crucial for optimizing immune response, particularly in patients with XRCC1 rs25487 genotype.[26,27] When the dose was

increased from 60 Gy to 74 Gy in RTOG 0617, there was an unanticipated trend towards worse local control 61.8 → 54.3%(p=0.07) and OS 32.1 → 23% (p=0.06).[28] The host immune response may be inhibited by dose escalation by lowering lymphocyte populations, according to one theory.[29] The immune system could be avoided as an organ at risk, potentially affecting clinical results, according to Colton et al. and Ladbury et al.[12,30]

Durvalumab is already considered standard of care in the adjuvant situation (e.g. ECOG-ACRIN 5181), and researchers are also looking into its potential use in the concurrent setting. However, participants in this study did not receive immunotherapy. Although anti-PDL1 therapy has been adopted under current guidelines, its use is nevertheless restricted by a number of real-world issues, with recently documented immunotherapy initiation rates as low as 65%.[31] Although the implications of Lymphocytopenia in immunotherapy patients are not fully understood, it has been hypothesized that peri-immunotherapy Lymphocytopenia may indicate poorer clinical outcomes.[18,32] The need to comprehend the interactions between radiation therapy, systemic therapy, and the host immune system is growing along with the function of immunotherapy. Clinical outcomes may be further improved by using techniques and timing for radiation that are adjusted to reduce Lymphocytopenia. This study has limitations that are common to all retrospective studies from a single institution with a modest sample size, particularly when stratifying by histology. Additionally, there was considerable variation in the number and timing of imaging and blood draws in relation to radiation treatments since these were not standardised. Finally, it is difficult to evaluate tumour response while looking for associations with hematologic markers. Therefore, care should be taken when interpreting these findings, and bigger validation studies are probably necessary to more fully assess or confirm any potential relationship.

5. Conclusion

Several baseline and recovery hematologic variables, including baseline ALC, baseline SII, and recovery ALC, were linked to clinical outcomes in this cohort of patients with stage III NSCLC treated with final chemoradiation. Hematologic nadir caused by treatment were not linked to a positive clinical outcome. We still need to learn more about the interactions between the immune system, hematologic toxicity, and clinical outcomes after CRT.

6. Human Ethics Statement

The Institutional Review Board for the Protection of Human Subjects at Lugansk State Medical University acquired ethical permission before the study could begin. The information accessible comply with all applicable privacy and data protection laws.

7. 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 and 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.

8. Conflicts of Interest

None.

9. Source of Funding

None.

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