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* Category 1 is based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
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Gerson Regimen

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Barrie R. Cassileth, MS, PhD

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Practitioners of Gerson therapy believe that cancer is caused by an accumulation of toxic substances in the body. They recommend a special diet including high carbohydrate and potassium intake, no sodium or fat, low animal protein, supplementation with exogenous digestive enzymes, and coffee enemas aimed at detoxifying the body and stimulating metabolism. However, available scientific evidence does not support use of Gerson therapy.

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The strict dietary recommendations can cause severe nutritional deficiencies, and excessive use of coffee enemas can cause sepsis, dangerous electrolyte deficiencies, and death.

A recent trial of the closely related Gonzalez therapy found that pancreatic cancer patients on standard chemotherapy survived three times longer and had better quality of life than those who chose the Gonzalez regimen (pancreatic enzymes, nutritional supplements, detoxification, and organic diet).

-Barrie Cassileth, PhD

ALSO KNOWN AS: Gerson diet, Gerson therapy, Gerson method, Gerson program, Gerson treatment



SUMMARY: The Gerson regimen, developed by Max Gerson in the 1930s, is promoted as an alternative cancer treatment. It involves consuming fresh, raw fruit and vegetable juices, eliminating salt from the diet, taking supplements such as potassium, vitamin B12, thyroid hormone, pancreatic enzymes, and detoxifying liver with coffee enemas to stimulate metabolism.

Gerson therapy is based on the theory that cancer is caused by alteration of cell metabolism by toxic environmental substances and processed food, which changes its sodium and potassium content. It emphasizes increasing potassium intake and minimizing sodium consumption in an effort to correct the electrolyte imbalance, repair tissue, and detoxify the liver. The coffee enemas are believed to cause dilation of bile ducts and excretion of toxic breakdown products by the liver and through the colon wall. None of these theories has been substantiated by scientific research.[1,2]

Despite proponents' claims of recovery rates as high as 70% to 90%, case reviews by the National Cancer Institute (NCI) and the New York County Medical Society found no evidence of usefulness for the Gerson diet.[3]

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An NCI-sponsored study of Gonzalez therapy, which is similar to the Gerson diet, showed that patients with inoperable pancreatic adenocarcinoma who underwent standard chemotherapy with gemcitabine (Gemzar) survived three times longer and had better quality of life than those who chose enzyme treatment, which included pancreatic enzymes, nutritional supplements, detoxification, and an organic diet.[4]

TAKE HOME POINTS

- *Gerson and related regimens such as Gonzalez are unproven or disproved cancer treatments involving a special diet and harsh detoxification methods, which can have serious consequences.*
- *Cancer patients should be advised to avoid such “therapies.”*
- *Cancer patients should discuss use of alternative treatments with their physicians.*

For additional information, visit the Memorial Sloan-Kettering Cancer Center Integrative Medicine Service website, “About Herbs,” at <http://www.mskcc.org/AboutHerbs>.

ADVERSE REACTIONS: Adverse reactions to the Gerson regimen include flu-like symptoms, loss of appetite, perspiration with foul odor, weakness, dizziness, cold sores, fever blisters, high fever, tumor pain, intestinal cramping, diarrhea, and vomiting. (*The Gerson Therapy Handbook* claims that these adverse reactions are indicative of response.)[5] *Campylobacter fetus* sepsis caused by the liver injections was reported in 13 patients on Gerson therapy between 1980 and 1986. Coma from low serum sodium occurred in 5 of these patients.[6]

Coffee enemas cause electrolyte imbalance, which has resulted in serious infections, dehydration, colitis, constipation, and death.[7]

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The Prognostic Significance of Peripheral Blood Biomarkers in Patients With Advanced Non-Small Cell Lung Cancer Treated With Pembrolizumab: A Clinical Study

March 16, 2022

[Kira MacDougall, MD](#), [Muhammad Rafay Khan Niazi, MD](#), [Jeff Hosry MD](#), [Sylvester Homsy, MD](#),

[Alexander Bershadskiy, MD](#)

Oncology,



Kira MacDougall, MD, and co-investigators, research the importance of peripheral biomarkers in patients with advanced non-small cell lung cancer who are treated with pembrolizumab.

ABSTRACT

Systemic inflammation has long been associated with poor outcomes in many types of solid tumors. Peripheral blood biomarkers, such as absolute lymphocyte count (ALC) and the ratio of absolute neutrophil count to absolute lymphocyte count (ANC/ALC), have been shown to be immune-inflammatory parameters highlighting an individual's immune status. The prognostic role of ALC and ANC/ALC on overall survival (OS) was examined in patients with advanced non-small cell lung carcinoma (NSCLC) receiving pembrolizumab. Of a total of 239 patients, 52% were male, with a median age of 67 years (interquartile range [IQR], 59-73). Most patients had a diagnosis of adenocarcinoma (76%), with stage IV disease (82%). PD-L1 expression was >50% in 44% of the patients. The median time on treatment with pembrolizumab was 5.8 months (IQR, 2.9-12.7). An ANC/ALC <5 was associated with improved OS at initiation of pembrolizumab ($P = .002$), whereas an ALC >1.4 deciliter (dL) trended toward improved OS compared with ALC <1.4 dL ($P = .053$). After adjusting for potential cofounders with a multivariate analysis, a baseline ANC/ALC of 5 or higher was associated with a significantly increased risk of death (HR, 1.93; 95% CI, 1.27-2.93; $P = .002$). An ANC/ALC <5 at the time of initiation of treatment with pembrolizumab was associated with improved OS in patients with advanced NSCLC. The median ALC and ANC/ALC were significantly lower after 6 weeks of treatment with pembrolizumab.

Keywords: pembrolizumab; non-small cell lung cancer; absolute lymphocyte count; absolute neutrophil count to absolute lymphocyte count ratio; immunotherapy; peripheral blood counts; anti-PD-1

Introduction

Lung cancer is the most common cause of cancer-related deaths, both in the United States and internationally.^{1,2} Non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of these cases. The discovery of immune checkpoint inhibitor therapy has led to significant improvement in both overall survival (OS) and progression-free survival (PFS) and represents a paradigm shift in treatment of NSCLC. In 2019, 2 anti-PD-1 antibodies, pembrolizumab (Keytruda) and nivolumab (Opdivo), and 1 anti-PD-L1 antibody, atezolizumab, were approved by the FDA for the treatment of metastatic NSCLC.³ PD-1 is an immune checkpoint transmembrane



protein that is expressed on macrophages, dendritic cells, and T and B lymphocytes. When PD-1 binds to one of its ligands that are expressed on human cancer cells—PD-L1 or PD-L2—it inhibits cytotoxic T-cell response and evades the body's immune surveillance system.^{4,5}

While PD-L1 receptor positivity in tumor cells has been shown to predict the responsiveness of the cancer to these agents, it has its limitations. Several small studies have been performed to assess the utility of hematologic biomarkers in predicting the effectiveness of immunotherapy. However, these studies have been small retrospective studies with small sample sizes.

These peripheral markers include absolute neutrophil count (ANC), absolute lymphocyte count (ALC), the ratio of absolute neutrophil count to absolute lymphocyte count (ANC/ALC), absolute eosinophil count, and absolute monocyte count (AMC). These biomarkers have been shown to be immune-inflammatory parameters highlighting an individual's immune status. Aggressive cancers are associated with an increased systemic inflammatory state, creating a microenvironment that promotes angiogenesis, survival of malignant cells, and metastasis. The response to immunotherapy in these cases is poor.⁶ Therefore, this question has arisen: Can these peripheral blood biomarkers predict patient outcomes in patients treated with immunotherapy?

The aim of this study is to investigate ALC and ANC/ALC in patients with advanced NSCLC receiving pembrolizumab and to determine if a correlation exists between these key biomarkers and OS. To our knowledge, of studies investigating this relationship, this is the largest in terms of number of patients with NSCLC treated with pembrolizumab.

Methods

Patient Selection

This retrospective observational study was approved by the Northwell Health Institutional Review Board, which waived the requirement for informed consent. Data for all patients with advanced NSCLC treated with pembrolizumab between September 2016 and May 2020 at Northwell Health hospital sites were collected by reviewing their electronic medical records. Patients treated with immunotherapy other than pembrolizumab were excluded. This helped to minimize heterogeneity related to different immunotherapy treatments.

Data Collection

All records were reviewed retrospectively and organized in the REDCap database. Parameters such as age at diagnosis, sex, histologic type, tumor PD-L1 status, stage of disease, line of treatment, history of radiation to the tumor, presence or absence of central nervous system (CNS) disease, and ECOG performance status were defined and adjusted for confounding. Peripheral blood counts including ALC, ANC, and AMC were examined at initiation of pembrolizumab and at 6 weeks on treatment. Patients without follow-up blood counts at 6 weeks were excluded.

Statistical Analysis

Based on literature review and previous studies that investigated this relationship, ANC/ALC cut-off values were ≥ 5 and < 5 , and ALC cut-off values were ≥ 1.4 dL and < 1.4 dL. The primary outcome was OS, as defined as date of first dose of pembrolizumab to death or last follow-up. Patients discontinued their immunotherapy due to disease progression or death, or because they experienced adverse events (AEs). Descriptive statistics were used to present patient characteristics. Chi-square or Fisher's exact test were used to compare categorical variables, and the Wilcoxon-Mann-Whitney test was used to compare continuous variables. OS rates were plotted on Kaplan-Meier curves and differences were evaluated with the log-rank test. A multivariable Cox regression model was used to determine the effect of baseline ANC/ALC on the risk of death after adjusting for potential confounders. All statistical tests were 2-sided and conducted using SPSS version 25.0 (IBM). $P < .05$ was considered statistically significant.

Results

Patient Characteristics

A total of 239 patients with advanced NSCLC treated with pembrolizumab at Northwell Health hospital centers were included. Baseline characteristics are presented in **Table 1**. Median age at diagnosis was 67 years (interquartile range [IQR], 59-73). Of all patients, 52% were male and most (76%) had a diagnosis of adenocarcinoma, with stage IV disease (82%). The majority (52%) of the included patients were former smokers. PD-L1 expression was $> 50\%$ in 44% of the patients. ECOG performance status was 0 or 1 in 70% of patients. Radiographic evidence of CNS disease at the time of pembrolizumab therapy was present in 28% of patients, and 20% had



received radiation therapy to the tumor prior to the initiation of pembrolizumab. Pembrolizumab was first-line therapy in 65% of patients. Pembrolizumab monotherapy was being used for treatment in 119 patients (50%), whereas 120 patients (50%) received a combination of pembrolizumab plus platinum-based chemotherapy.

TABLE 1. Baseline Characteristics

Comparison of Peripheral Blood Biomarkers at Baseline and at 6 Weeks of Treatment

The median ALC and ANC/ALC ratio were significantly lower after 6 weeks of pembrolizumab therapy compared with the start date of treatment (1.3 dL [IQR, 0.9-1.7] vs 1.4 dL [IQR, 1.0-2.0]; $P < .001$, and 3.6 [IQR, 2.1-6.1] vs 4.6 [IQR, 2.8-7.0] respectively; $P = .002$).

Comparison of OS Based on Baseline Peripheral Blood Biomarkers

Median OS was 10.8 months (IQR, 4.9-17.4) and overall time on treatment was 5.8 months (IQR, 2.9-12.7). An ALC of ≥ 1.4 dL trended toward improved OS compared with ALC < 1.4 dL ($P = .053$) (**Figure A**). Patients with a baseline ANC/ALC of ≥ 5 had a worse median OS rate compared with those with ANC/ALC < 5 , at 8.8 months (IQR, 3.98-15.65) vs 11.75 months (IQR, 6.68-20.51; $P = .02$) (**Figure B**), and after adjusting for potential cofounders in multivariate analysis (HR, 1.93; 95% CI, 1.27-2.93; $P = .002$) (**Table 2**). There was no difference in OS in patients who received pembrolizumab monotherapy compared with those who received pembrolizumab plus platinum-based chemotherapy (HR, 1.51; 95% CI, 0.92-2.47; $P = .11$).

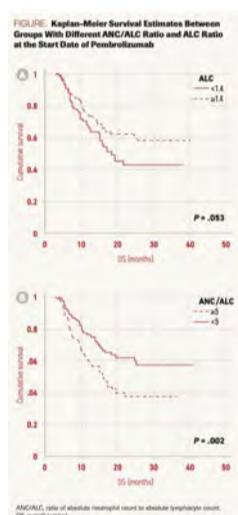


FIGURE. Kaplan-Meier Survival

Discussion

This is the largest study analyzing the effect of the baseline serum levels of ANC and ALC, and of the ANC/ALC ratio, on the OS of patients treated with pembrolizumab for NSCLC. We show here that patients with an ALC of ≥ 1.4 dL and an ANC/ALC ratio < 5 at the initiation of pembrolizumab therapy had an improved OS compared with their respective counterparts. After adjusting for potential cofounders, we found that patients with baseline ANC/ALC ratio of ≥ 5 treated with pembrolizumab had almost 2 times increased risk of death (all-cause mortality) (HR, 1.93; 95% CI, 1.27-2.93), compared with those with a baseline ANC/ALC < 5 .

Meier Survival
Estimates
Between Groups
With Different
ANC/ALC Ratio
and ALC Ratio at
the Start Date of
Pembrolizumab

	HR	WHR	P
Age > 60 years	1.00	1.00	.99
Adenocarcinoma vs other histology	0.64	0.69-0.60	.90
GFR performance status (0.0 vs 1.0)	2.11	2.00-1.00	1.03
NET Adjuvant Chemotherapy (Yes)†	0.29	0.20-0.19	.29
CNS metastasis, yes (n = 11)	1.00	0.60-1.00	.99

TABLE 2.

Multivariable Cox Regression Analysis for Association of Baseline Peripheral Blood Biomarkers With Overall Survival

Our findings are consistent with those of previous studies on peripheral blood biomarkers in patients being treated with anti-PD-1 antibodies. In a metanalysis of 16 studies that included 1700 patients, a high blood neutrophil-to-lymphocyte ratio (NLR) or ANC/ALC was found to be associated with shorter OS and PFS in patients getting treatment with PD-1/PD-L1 inhibitors for NSCLC.⁷ In a retrospective study of 22 patients with NSCLC treated with nivolumab, baseline ALC levels and ANC/ALC ratios were positively and negatively correlated, respectively, with OS on nivolumab.⁸ Another study of 109 patients with advanced NSCLC treated with nivolumab found that posttreatment ANC/ALC ≥ 5 after 2 cycles of nivolumab was associated with poor OS.⁹ Soyano et al studied this effect in patients treated with nivolumab ($n = 146$) and pembrolizumab ($n = 11$), finding that a baseline ANC/ALC ratio of 5.9 or more was associated with a significantly increased risk of death (HR, 1.94; 95% CI, 1.24-3.03; $P = .004$).¹⁰ Hasegawa et al demonstrated that high NLR (>4.55) at the pretreatment stage was significantly associated with shorter PFS and OS in a study of 51 patients with NSCLC who had a tumor proportion score $>49\%.$ ¹¹ Unlike our study, this was studied solely in patients who received pembrolizumab monotherapy. Zer et al studied these peripheral biomarkers in correlation with OS, disease control rate, and time to progression, and they found improved outcomes in patients with NLR of ≤ 4 , in the patients with NSCLC who were under treatment

The results of several studies have shown that tumor-related neutrophils are predictive of a poor prognosis in patients with malignancies. These neutrophils are attracted by cytokines such as interleukin-8 (IL-8), which further promotes the angiogenesis, local invasion of vessels, and metastasis.

One study demonstrated that lung carcinomas release IL-6 and granulocyte colony-stimulating factor that leads to increased peripheral leukocyte count, predicting ominous outcomes.¹⁵ PD-1/PD-L1 inhibitors act by blocking the interaction of negative regulators of T-cells that increase the antitumor immunity and decreases the antitumor immune tolerance, and it is plausible that these changes alter the count of peripheral neutrophils and lymphocytes. Increased peripheral neutrophil count correlates with reduced CD8-positive T-lymphocyte counts in NSCLC, and lymphopenia reflects impaired cellular immune response.^{16,17} Conversely, high lymphocyte counts have been considered a positive prognostic factor due to an improved antigen-driven immune response. The exact mechanism by which NLR affects immunotherapy or checkpoint blockade is not known, but it has been repeatedly shown to be associated with better outcomes in malignancies and other systemic diseases.

The use of PD-1 and PD-L1 inhibitors have revolutionized cancer immunotherapy and have led to improvement in patient outcomes. Their effect, however, seems to be limited to certain patient subgroups. Given the significant immune-related AEs that can occur with these drugs, along with their financial toxicity, there is a need to individualize treatment for every single patient. Tumor PD-L1 immunohistochemical testing is often used as a predictor of response, but it has limitations. Complete blood count measures and differential testing are inexpensive and routinely performed before the initiation of immunotherapy and before every treatment cycle.

Limitations

This study sought to determine the usefulness of hematologic biomarkers in predicting patient outcomes. However, it did have limitations due to its retrospective study design. Concurrent inflammatory states and use of immunomodulatory agents or steroids could not be ruled out; these could alter the cell counts. Furthermore, the ANC/ALC could not be assessed separately at the tumor site and could differ from that of the peripheral blood. Future studies should be designed to address these issues.

Conclusions

An ANC/ALC <5 at the time of initiation of treatment with pembrolizumab was associated with improved OS in patients with advanced NSCLC. However, further prospective studies are warranted to establish if ANC/ALC can be reliably used as a predictive biomarker in patients with advanced NSCLC who are treated with immunotherapy.

Author Affiliations:

Kira MacDougall, MD¹; Muhammad rafay Khan Niazi, MD²; Jeff hosry MD,²; Sylvester homsy, MD³; alexander Bershadskiy,MD⁴

¹Department of Hematology & Medical Oncology, Oklahoma University of Health Sciences, Oklahoma City, OK, USA

²Department of Internal Medicine, Zucker School of Medicine at Hofstra/Northwell at Staten Island University Hospital, Staten Island, NY, USA

³Department of Hematology & Medical Oncology, SUNY Downstate Medical Center, Brooklyn, NY, USA

⁴Division of Hematology & Medical Oncology, Zucker School of Medicine at Hofstra/Northwell at Staten Island University Hospital, New York, NY, USA

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