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New lung cancer treatments (immunotherapy and targeted therapies) and their associations with depression and other psychological side effects as compared to chemotherapy

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A B S T R A C T

Objective: Lung cancer carries a high prevalence of distress, anxiety and depression. New treatments, targeted therapy and immunotherapy have changed the disease course for subsets of patients and confer longer survival, but their psychological associations and possible mechanisms (e.g., inflammation and physical symptoms) are not well described.

Method: Patients with metastatic lung cancer undergoing systemic treatment (n = 109) were evaluated for distress, self-endorsed problems using the Distress Thermometer and Problem List, and depression and anxiety using the Hospital Anxiety and Depression Scale. Demography, cancer-related information, and inflammation were evaluated for their associations with chemotherapy, targeted therapy, and immunotherapy. Inflammation was measured by C-reactive protein, albumin, and neutrophil to lymphocyte ratio.

Results: Chemotherapies were given most often followed by immunotherapy and targeted therapies. Depression and anxiety were endorsed by 23.9%, respectively, and 41.1% had significant distress. Chemotherapy was associated with depression ($p = .006$) and inflammation ($p < .001$). Physical symptoms were the same among treatment types. Targeted therapy and immunotherapy predicted for less depression ($p = .04$, $p = .04$ respectively) than chemotherapy when controlling for age, sex, and performance status however these predictors where not significant when controlled for inflammation.

Conclusion: New immunotherapy and targeted therapies are associated with less depression and inflammation among patients who are living longer while their physical symptoms are the same.

1. Introduction

1.1. Variables contributing to psychological outcomes in the lung cancer setting

Historically, metastatic lung cancer is known for its high rates of comorbid depression and other psychological associations as well as a high degree of related physical symptomatology [1,2]. For example, dyspnea, cachexia, and pain may be the result of progressive disease, sequelae of lung cancer such as pulmonary venothrombosis, or even from the lung cancer treatment itself causing anemia and anorexia. Distress, anxiety, and depression in the setting of metastatic lung cancer are exacerbated by progressive disability, loss of independence, unrelenting physical symptoms such as pain, or underlying mechanistic reasons such as systemic inflammation [3–5]. The prevalence of depression in lung cancer (16–29%) [6,7] exceeds the standard prevalence of major depression in cancer more generally, which is approximately 15% [2]. Distress and anxiety may also result from similar associations and are more closely attached to dyspnea and pain, for example [8]. Unfortunately, these physical and psychological symptoms (e.g., dyspnea and anxiety) co-exist in patients whose cancers, like lung cancer, have the poorest survival rate [9].

Systemic treatments affect all of these variables while additionally contributing to a variable side effect profile. However, paradigmatic shifts in systemic treatments for lung cancer have taken place over the last decade [10,11]. Ten years ago, limited targeted therapy drugs were available, such as the antiangiogenesis inhibitor, bevacizumab, and the Epidermal Growth Factor Receptor (EGFR) inhibitors erlotinib and gefitinib, but the vast majority of patients were treated with chemotherapy only [12]. Today, there are three primary classes of drugs for the treatment of systemic lung cancer: many forms of small molecule targeted therapies, immunotherapies, and traditional cytotoxic chemotherapies [13].

Understanding the psychological effects of the major classes of systemic lung cancer treatments is important since the rate of depression, in particular, is already elevated and leads to worse overall survival among those patients with depression [14]. Encouragingly, appropriately addressing and treating depression in the cancer setting eliminates the survival disadvantage seen in patients with depression [14]. Psychosocial resources are limited in most cancer treatment settings [15]. Therefore, it is important to know which patients are at a higher risk of psychological or psychiatric co-morbidity in order to best

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triage patient and allocate resources. This information will be helpful for psychiatric consultants who are evaluating patients with lung cancer and liaising with oncologic clinicians.

1.2. Targeted therapies

Targeted therapies have emerged as a result of understanding the interplay of 'driver' mutations and their susceptibilities to small molecule drugs that work intracellularly (within the cancer cell) or on the cell surface [16]. Standard of practice has resulted in a proliferation of accepted 'targetable' mutations for which appropriate therapies exist [17]. These treatments have grown from small molecule inhibitors that treat mutations in the EGFR gene (~20%) and the Anaplastic lymphoma kinase (ALK) gene (~4%) to an array of possible driver mutations (e.g., BRAF, HER2, NTRK, ROS1) thanks to advances in molecular testing [18]. Now, molecular testing has become accepted practice and targetable mutations are identified and incorporated into standard treatments for most cancers and also for non-small cell lung cancer (NSCLC) [19]. These drugs come in oral form and are generally well tolerated with expected side effects which are most commonly rash, diarrhea, and fatigue [20]. These side effects may be responsive to dose reductions as well. These small molecule inhibitors can cause thyroid dysfunction and generally are effective at crossing the blood brain barrier to treat brain lesions. Despite their therapeutic efficacy on lung cancers, their actual associations with psychological/psychiatric phenomena are not fully appreciated. While not every patient experiences predictable side effects, they can be severe and interfere with quality of life significantly, which would have distinct ramifications for psychological wellbeing.

1.3. Immunotherapy

The next newest class is immunotherapy [21]. Different forms of immunotherapy have been used to treat various cancers such as Interleukin-2 (IL-2) for the treatment of melanoma or Bacillus Calmette-Guerin (BCG) vaccine in the treatment of superficial bladder cancers. However, these are older forms of immunotherapy that manipulate the innate immune system to elicit a general inflammatory response. New, more elegantly designed 'immunotherapy' treatments are known as 'checkpoint inhibitors' since they inhibit certain checkpoints in the inflammatory cascade that tell the adaptive immune system to stop proliferating [22]. These checkpoint inhibitors work by stopping the inherent inhibition of the immune system that normally protects the body from excessive inflammation or from developing autoimmune type of physiology or disease, in other words. It acts by taking the brakes off the immune system and inducing an autoimmune-like state relying on an immune response directed at the cancer. Checkpoint inhibitors are monoclonal antibodies directed at specific sites on the surface of inflammatory cells such as T lymphocytes called Program Cell Death Protein 1 (PD-1), or directed to the surface of other inflammatory cells (e.g., macrophages) called Programmed Death-ligand 1 (PDL-1) or on the surface of regulatory T cells called Cytotoxic T-Lymphocyte-associated Protein 4 (CTLA-4) that signal for the immune system to turn itself off when activated by a cancer cell and actually turn the immune system on when inhibited by one of these checkpoint inhibitors. In the lung cancer setting, the PD-1 (nivolumab, pembrolizumab) and PDL-1 (atezolizumab, avelumab, durvalumab) checkpoint inhibitors were used as second line treatment but could be used as a first line treatment if the cancer cells expression of PD-L1 protein was high because this infers a higher response rate to immunotherapy over traditional chemotherapy. In 2017, immunotherapy was approved to be used with chemotherapy as a first line treatment. In addition, the PD-1 inhibitor, nivolumab is used in combination with another class of checkpoint inhibitor called CTLA-4 inhibitor (e.g., ipilumamab) with small cell lung cancer. This combination allows for an increased immune response. Surprisingly the overall response rate is not typically that much better than chemotherapy but the impressive quality of immunotherapy is the duration of response which can be for years once a response is obtained. It is also thought to change the trajectory of disease even if the disease does not become appreciably smaller (stable disease). Side effects are not predictable, but mimic autoimmune disease and most commonly cause fatigue, diarrhea, rash, thyroid dysfunction.

1.4. Chemotherapy

Chemotherapies are drugs that are directly toxic to the cancer DNA and take advantage of the fact that cancer cells are exposing their DNA by dividing faster than normal healthy cells. They incur side effects by indiscriminate killing of replicating cells (healthy or cancerous). Most patients will be exposed to chemotherapy at some point in their treatment trajectory [23]. Side effects from chemotherapy are more predictable generally with higher prevalence of fatigue, diarrhea, neuropathy, and cytopenias, for example [24].

1.5. Possible psychological associations with lung cancer-related physical symptoms and inflammation

While these broad categories of anticancer treatments may differentially influence psychological wellbeing, the effects may be related to physical symptoms or treatment or cancer-related inflammation [25,26]. Both physical symptoms and cancer-related inflammation are associated with depression and other psychological symptoms seen in patients with lung cancer [27]. Inflammation has been associated with depression in multiple clinical settings including medically healthy and chronically ill patients, but is particularly relevant for lung cancer where there are high rates of both depression and inflammation that are both associated with worse survival outcomes [28–30]. Inflammation may play a role in treatment refractory depression as well [31,32]. Peripheral biomarkers of inflammation are being studied in population-based and case controlled studies [33–38]. However, the role of systemic lung cancer therapies (e.g., targeted therapy and immunotherapy) in influencing inflammation and depression has not been studied previously.

C-reactive protein (CRP) is an acute phase reactant and biomarker produced by the liver in response to multiple pro-inflammatory cytokines, especially IL-6, and increases by at least 25% with general inflammation [39,40]. Peripheral blood CRP has also recently been shown to correlate strongly with CRP in the cerebrospinal fluid (CSF) along with other inflammatory markers in the CSF [41]. Albumin is the most common protein in the blood. It is produced by the liver and it decreases as a negative acute phase reactant in response to inflammation, similar to CRP and other acute phase reactants [42]. Albumin has been associated with depression in limited settings (e.g., with HIV) and has been studied most as a prognostic marker of survival in cancer settings [43–45]. While albumin level can be affected by nutrition, prealbumin is a better indicator nutritional status. In the cancer population, inflammation and nutritional status may overlap. CRP and albumin have long half-lives and therefore less diurnal/circadian fluctuation than pro-inflammatory cytokines and provide a good measure of general inflammation that may correspond with total number or individual physical symptoms. Neutrophil to Lymphocyte Ratio (NLR) is another marker of general inflammation that measures both the innate (neutrophil) and adaptive (lymphocyte) forms of the immune system [46,47]. NLR has been used as a prognostic marker in lung cancer. In addition, it is a very broad measure of lymphocyte activity which can decrease in the setting of depression and may be relevant for those patients receiving immunotherapy (i.e., checkpoint therapy inhibits T regulatory cells) [48,49].

Given that targeted therapy and immunotherapy are relatively new drugs with variable side effect profiles, their associations with psychological symptoms have not been fully appreciated. We hypothesize that the predictability and higher percentage of physical symptoms and

inflammation associated with the cell destruction of chemotherapy will create higher levels of psychological outcomes, specifically depression, in patients with metastatic lung cancer receiving chemotherapy over other systemic drugs such as targeted therapies and immunotherapy.

2. Methods

The Memorial Sloan Kettering Cancer Center Institutional Review Board (IRB) approved this study May 2018. Surveys and routine blood work (CRP, albumin, NLR) were collected as standard of care practice from May 2017 to November 2017.

2.1. Participants

Men and women with histologically confirmed stage IV lung cancer who were undergoing active treatment, spoke English, and had a performance status of Eastern Collaborative Oncology Group (ECOG) 0–2 were included. Participants with other cancers or not undergoing treatment for stage IV lung cancer were excluded. Participants had to be on active treatment for at least one month and had to be more than one month from receiving the diagnosis of lung cancer to be included.

2.2. Procedure

Patients were asked to complete a one-time survey by a treating staff member (e.g., nurse practitioner, medical oncologist). They filled out the questionnaire containing standardized survey questions, and laboratory values (CRP, albumin, NLR) were obtained the same day that the questionnaires were completed. Available psychological services were provided in the survey, and patients were asked to raise any concerns with clinic staff and, in particular, to tell a staff member if they felt significantly depressed or had suicidal ideation. The surveys were collected as routine standard of care screening as per distress screening guidelines.

3. Materials

3.1. Patient demographic and medical characteristics

Patient demographic information was obtained from the medical record and included age, race/ethnicity, sex, marital status, body mass index (BMI), length of time since diagnosis, type of treatment (e.g., chemotherapy, immunotherapy, targeted therapy), line of treatment (i.e., 1st, 2nd, 3rd or beyond), and whether they were taking an antidepressant medication.

3.2. Biological characteristics of inflammation

A CRP value was obtained by turbidimetric immunoassay in a Clinical Laboratory Improvement Amendments (CLIA) certified lab [50]. Inter- and intra-assay coefficient of variation is reliably $< 5\%$. A CRP > 1 mg/L has been used in studies to identify patients with generalized inflammation and to evaluate preferential antidepressant responses [51,52]. A cut-point of CRP > 3 mg/L reveals dopamine depletion on fMRI [34]. An albumin bromocresol green (BCG) assay is used for the quantification of albumin in human serum or plasma [53]. Standard laboratory procedures were used to obtain neutrophil and lymphocyte values from the standard complete blood counts in the clinical lab at MSKCC.

3.3. Distress and associated self-reported problems

The Distress Thermometer and Problem List (DT&PL) is a one-item measure of distress, ranging from 0 (Not at all distressed) to 10 (Extremely distressed). A cut-off of ≥ 4 has been accepted by the National Comprehensive Cancer Network to indicate clinically meaningful distress [54]. The DT&PL has been validated among international cancer populations [55]. Problem list categories include Practical (0–6), Familial (0–4), Emotional (0–6), Spiritual (0–1), and Physical Problems ($0-22$).

3.4. Anxiety and depression

Anxiety and depression severity was measured by the Hospital Anxiety and Depression scale (HADS), which has been validated in the lung cancer setting [56,57]. The HADS is a 14-item symptom rating scale that was developed to identify clinically significant cases of anxiety and depressive disorders among medically ill patients [56]. Unlike most symptom rating scales, physical symptoms are excluded from the HADS due to the potential confounding effects of illness on symptoms such as sleep, appetite disturbance, and fatigue. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D). Responses are rated 0 to 3 points such that total scores on the HADS-A and HADS-D may range from 0 to 21 points. A cut-off of 8 on the HADS-A and HADS-D subscales is most commonly used to identify clinically significant depression, with an average sensitivity and specificity of 0.80 [56,58].

4. Statistical analysis

The primary outcome of this study is the psychological outcomes associated with the three primary types of systemic anticancer treatments in patients with metastatic lung cancer. Secondarily, this study will assess their associations with markers of systemic inflammation, physical symptoms, and other demographic and treatment related variables. Because CRP and NLR data are not normally distributed (see below), CRP and NLR values were log transformed prior to data analysis; however, untransformed values are also reported for ease of interpretation. Univariate associations between patient demographic (age, BMI, time with disease), inflammatory (CRP, albumin, NLR) and psychological characteristics (distress, anxiety, depression) and treatment type (chemotherapy, immunotherapy, and targeted therapy) were assessed using ANOVA. Categorical variables (line of treatment, disease type, race, sex, married/partnered status, antidepressant use) were evaluated for their association with treatment type using chi square analyses. Univariate associations between continuous variables and depression were assessed using rank-order correlations for age, BMI, time since diagnosis, CRP, albumin, NLR, and ANOVAs were used for ordinal variables (line of treatment, treatment type, and disease type) and categorical variables (type of treatment, disease status). Statistically significant covariates were selected for inclusion in multiple regression analysis. For multi-level categorical variables, dummy-coding was used to assess the contribution of treatment type (i.e., immunotherapy and targeted therapies; chemotherapy was set as the reference variable) and disease type (i.e., squamous cell and small cell lung cancer; adenocarcinoma was set as the reference variable). Statistical procedures were performed using the SPSS version 24 software (SPSS, Chicago, IL 2013), and all statistical tests were two-tailed with a 5% significance level.

5. Results

Out of 140 potential participants, 109 returned survey information (77.9% response rate). Sample characteristics are presented in Table 1. The average age was 65.9 years old and the majority of the sample was female (62.4%), white (85.2%), and married (69.7%). Most patients had adenocarcinoma non-small cell lung cancer (71.8%), followed by small cell lung cancer (16.5%) and squamous cell carcinoma (6.4%) and 4.6% were unspecified type of lung cancer. Forty-seven participants were receiving chemotherapy (45.2%), 35 were receiving immunotherapy (33.7%), 22 were receiving targeted therapies (21.2%), and 6 were on a treatment that didn't fit into one of the three main

Table 1
Clinical and demographic characteristics of the sample.

	Total (n = 109)
	M (SD)
Age (years)	65.9 (9.3)
Body mass index	26.1 (5.0)
Time with disease (months)	15.4 (17.3)
C reactive protein (mg/L)	1.79 (2.5)
Albumin (2.8–4.6)	3.81 (0.377)
NLR (0.68–24.33)	6.04 (5.27)
Depression score (HADS-D) (0 − 21)	4.9 (3.7)
Anxiety (HADS-A) (0–21)	5.39 (3.94)
Distress (0 − 10)	3.91 (2.96)
Practical problems (0–3)	0.38 (0.63)
Familial problems (0–3)	0.22 (0.56)
Emotional problems (0–6)	2.19 (2.02)
Spiritual problems (0–1)	0.04 (0.19)
Physical problems (0–15)	4.8 (3.46)
	N (%)
Meets criteria screen	
•Depression (HADS-D ≥ 8)	26 (23.6%)
•Anxiety (HADS-A ≥ 8)	26 (23.6%)
•Distress (DT&PL ≥ 4)	39 (41.1%)
Gender	
•Male	41 (37.6%)
•Female	68 (62.4%)
Disease type	
•Adenocarcinoma	79 (71.8%)
•Squamous cell carcinoma	7 (6.4%)
•Small cell lung cancer	18 (16.5%)
•Unspecified	5 (4.6%)
Performance status (ECOG)	
•0	47 (43.1%)
•1	51 (46.8%)
•2	11 (10.1%)
Treatment type	
•Chemotherapy	47 (45.2%)
•Immunotherapy	35 (33.7%)
•Targeted therapy	22 (21.2%)
•Missing	6 (5.5%)
Line of treatment	
•1st	56 (53.3%)
•2nd	34 (32.4%)
•3rd or beyond	15 (14.3%)
•Missing	5 (4.5%)
Race/ethnicity	
•Black	7 (6.4%)
•White	93 (85.2%)
•Latino	7 (6.4%)
•Asian	2 (1.8%)
Married	
•Yes	76 (69.7%)
•No	33 (30.3%)
Antidepressant	
•Yes	18 (16.5%)
•No	91 (83.5%)

Abbreviations: DT&PL, Distress Thermometer and Problem List; ECOG, Eastern Cooperative Oncology Group; HADS, Hospital Anxiety Depression Scale; NLR, Neutrophil to Lymphocyte Ratio.

categories (5.5%). The majority of participants were in the 1st line of treatment (53.3%), followed by 2nd line (32.4%), and 3rd line and beyond treatments (14.3%), and 4.5% were not on known treatments. Participants were fairly evenly divided between ECOG performance status of 0 and 1 with 11 (10.1%) with an ECOG of 2.

Patients had their lung cancer for an average of 15.4 months and had an average of 2.19 emotional problems (from 0 to 6 possible) and 4.8 physical problems (from 0 to 22 possible) among other issues listed in Table 1. Twenty-six of the 109 participants endorsed clinically significant symptoms of depression (HADS-D ≥ 8) (23.9%) while 26 endorsed clinically significant anxiety (HADS-A ≥ 8) (23.9%), and 39 endorsed clinically significant distress (DT&PL ≥ 4) (41.1%). Eighteen participants reported that they were taking antidepressant medication (16.5%), including only seven out of the 26 participants with clinically significant depression (26.9%).

Table 2
Univariate analysis of demographic and disease characteristic factors and treatment types (chemotherapy, immunotherapy, and targeted therapy).

	Chemo	Immune	Targeted	F	P
Age	–	–	–	0.53	.59
BMI	–	–	–	0.32	.73
Time with disease (months)	8.9 (11.4)	17.3 (12.9)	23.2 (26.6)	6.465	.002
Performance status (ECOG)	–	–	–	1.692	.19
CRP (mg/L)	2.45 (3.3)	1.73 (1.7)	0.3 (0.3)	9.332	< .001
Albumin (g/dL)	–	–	–	1.078	.34
NLR	6.2 (5.2)	7.5 (6.1)	3.6 (3.3)	3.431	.04
Distress (DT&PL)	–	–	–	2.976	.06
Practical problems	–	–	–	0.064	.94
Family problems	0.2 (0.5)	0.1 (0.3)	0.5 (0.9)	4.425	.02
Emotional problems	–	–	–	2.126	.13
Spiritual problems	–	–	–	0.212	.81
Physical problems	–	–	–	0.249	.78
Anxiety (HADS-A)	–	–	–	1.539	.22
Depression (HADS-D)	6.0 (3.7)	4.9 (3.7)	2.9 (3.3)	5.425	.006

	Chemo	Immune	Targeted	χ^2	p
Line of treatment				26.124	< .001
1st	36	9	11		
2nd	4	20	7		
3rd and beyond	6	5	4		
Disease type				10.548	.03
Adenocarcinoma	29	26	22		
Squamous cell	4	3	0		
Small cell	11	4	0		
Race					
Non-White	42	27	19	2.366	.31
White	5	8	3		
Sex					
Male	15	18	5	5.590	.06
Female	32	17	17		
Married					
Yes	34	24	17	0.511	.78
No	13	11	5		
Antidepressant					
Yes	8	5	5	0.663	.72
No	37	30	17		

Abbreviations: BMI, Body Mass Index; CRP, C-reactive Protein; DT&PL, Distress Thermometer and Problem List; ECOG, Eastern Cooperative Oncology Group; HADS, Hospital Anxiety Depression Scale; NLR, Neutrophil to Lymphocyte Ratio.

Inflammatory indices included a mean CRP concentration of 1.79 mg/L (SD 2.5; Median 0.75 mg/L) with a range of < 0.05 to 18.51 mg/L. As expected, CRP values were highly skewed and kurtotic (skew = 2.45, kurtosis = 6.78); the distribution approximated a normal distribution following log transformation (skew = −0.78, kurtosis = 0.85). The average albumin was 3.81 g/dL (SD 0.37) (range 2.8–4.6 g/dL) and NLR was 6.04 (SD 5.28) (range 0.68–24.3). Participants reported an average of 4.8 (SD 3.46) physical problems with a range of 0 to 15 (max is 22). While number of physical symptoms was highly correlated to distress (r = 0.342, p = .001), anxiety (r = 0.452, p < .001), and depression (r = 0.625, p < .001), number of physical symptoms was not significantly different between chemotherapy (5.1 [SD 4.0]), immunotherapy (4.9 [SD 3.6], and targeted therapy (4.4 [SD 3.5]) (F = 0.249, p = .78).

Table 2 demonstrates that chemotherapy was associated with greater levels of depression (HADS-D 6.00) than immunotherapy (HADS-D 4.9) or targeted therapy (HADS-D 2.91) (p = .006) and higher CRP levels (2.45 mg/L) than immunotherapy (CRP 1.73 mg/L) or targeted therapy (CRP 0.33 mg/L). At the same time, NLR was higher in immunotherapy (NLR 7.48) versus chemotherapy (NLR 6.15) or targeted therapy (NLR 3.58). The elevated NLR in the immunotherapy

group is based on the higher neutrophil counts in the chemotherapy group (5.4 × 10^9/L) and immunotherapy group (6.2 × 10^9/L) over the targeted therapy group (3.6 × 10^9/L) (F = 3.499, p = .03) because the lymphocyte counts did not vary across groups (F = 0.567, p = .57). Albumin did not vary significantly between treatment types (p = .3). Length of time with disease was shorter in the chemotherapy group (8.91 months) and significantly longer in the immunotherapy group (17.29 months) and targeted therapy group (23.23 months) (F = 6.465, p = .002).

There is an uneven distribution of treatment types (chemotherapy, immunotherapy, and targeted therapy) among lines of treatment (p < .001) with a greater amount of immunotherapy in the second line and disease type (p = .03) and targeted therapies only being used on adenocarcinoma NSCLC (Table 2).

In addition to treatment type, other significant associations with depression (HADS-D) include disease type, inflammatory markers, and performance status. A greater amount of depression was seen in patients with small cell lung cancer (HADS-D 6.72) over adenocarcinoma NSCLC (HADS-D 4.32) and squamous cell NSCLC (HADS-D 5.71). Depression was also associated with inflammatory markers CRP (r = 0.47, p < .001), albumin (r = −0.35, p < .001), and NLR (r = 0.2, p = .05) (Table 3). Worsening performance status was associated with worsening depression (p < .001).

Multivariate analyses evaluating predictors of depression (Table 4) found that immunotherapy and targeted therapy predicted less depression (p = .04 and p = .04 respectively) than chemotherapy and worsening performance status predicted for more depression (p < .001) when controlling for age and sex but that treatment types (e.g., chemotherapy, immunotherapy or targeted therapies) where not significant when controlling for inflammatory markers (CRP, albumin, and NLR). Performance status and CRP predict for depression when taking into account age and sex control variables, treatment and disease types, and other inflammatory markers.

Table 3
Univariate analysis of demographic and disease characteristic factors, treatment types (chemotherapy, immunotherapy, and targeted therapy) and depression.

Depression (HADS-D)			
Variable		Univariate analysis	
		r	P
Age		0.12	.38
BMI		0.08	.32
Time with disease		−0.06	.75
CRP		0.47	< .001
Albumin		−0.35	< .001
NLR		0.20	.05
		F	P
Line of treatment		2.18	.12
1st			
2nd			
3rd and beyond			
Treatment type		5.42	.006
Chemo	6.00 (3.7)		
Immuno	4.9 (3.7)		
Targeted	2.91 (3.3)		
Disease type		3.37	.02
Adeno	4.32 (3.8)		
Squamous	5.71 (3.1)		
Small cell	6.72 (3.1)		
Performance status (ECOG)		3.626	< .001
0	2.94 (2.6)		
1	6.13 (3.5)		
2	8.25 (4.4)		
		t	p
Race		−0.330	.74
Non-White	5.25 (3.3)		
White	4.91 (3.8)		
Sex		−1.624	.11
Male	5.71 (3.9)		
Female	4.51 (3.6)		
Married		0.902	.37
Yes	4.75 (3.6)		
No	5.45 (4.0)		
Antidepressant		−1.126	.26
Yes	5.83 (3.7)		
No	4.74 (3.7)		

Abbreviations: BMI, Body Mass Index; CRP, C-reactive Protein; DT&PL, Distress Thermometer and Problem List; ECOG, Eastern Cooperative Oncology Group; HADS, Hospital Anxiety Depression Scale; NLR, Neutrophil to Lymphocyte Ratio.

6. Discussion

New systemic treatment options for patients with lung cancer, targeted therapies and immunotherapy, are associated with less depression and also with less inflammation than chemotherapy, but there were no differences for levels of distress or anxiety. Initially, targeted therapies such as tyrosine kinase inhibitors and immunotherapy were thought to increase the risk of depression through thyroid dysfunction or other mechanisms [59,60]. While depression may be precipitated via small molecular inhibitor mechanisms, depression was less common in patients on targeted therapies and immunotherapy than for patients on chemotherapy in this study. These findings are consistent with a limited number of other studies that found patients with driver mutation associated lung cancer (e.g., Epidermal Growth Factor Receptor mutant) NSCLC on targeted therapies such as erlotininb were less likely to have depressive symptoms [61,62]. This study builds on these previous studies and further describes its relationship with inflammation. In contradistinction to the Jacobs et al. study that found elevated Tumor Necrosis Factor α was associated with EGFR mutant NSCLC and decreasing depression [62], this study found that CRP was also lower in patients with EGFR mutant NSCLC consistent with the inflammatory hypothesis of depression.

While a multivariate analysis revealed that treatment type (chemotherapy) was associated with depression, the association was not significant when controlling for inflammation and performance status. Inflammation may be mediating the relationship between treatment type and depression. The rates of distress, anxiety, and depression are consistent with historical rates [63,64]. Also, the distribution of systemic treatment types is consistent with what would be expected in a cohort of stage IV lung cancer that included both NSCLC and small cell lung cancer types [65]. Performance status was the greatest predictor for depression independently of treatment type, inflammation and other demographic variables. This is not a surprising however among patients with advanced metastatic lung cancer with high morbidity since performance status is intimately related to quality of life and advancing disease approaching that approaches the end of life is also associated with depression [6,66].

The relationship between chemotherapy and depression may be due to cell lyses causing inflammation versus other potential depression-causing mechanisms. Patients receiving chemotherapy had lung cancer for a shorter period of time. Although the majority of chemotherapy was given in the 1st line setting, receiving chemotherapy may also correspond with more advanced or aggressive disease or disease and patient medical situations in which immunotherapy or targeted therapies could not be offered. In other words, patients receiving chemotherapy may have actually been closer to the end of life since their diseases were more advanced or treatment options were more limited and advanced disease was responsible for greater depression rates. However, the number of physical symptoms reported was the same between each treatment group. Although physical symptoms and depression are related in many clinical scenarios, this finding suggests that the difference in rates of depression between treatment groups was independent of physical symptoms and therefore would not be responsible for greater depression in the chemotherapy group.

Table 4
Multivariate regression of significant demographic and treatment variables on depression as measured by the Hospital Anxiety and Depression scale.

Variable	Depression (HADS-D)			Depression (HADS-D)		
	Regression coefficient	*t* value	P	Regression coefficient	*t* value	P
Age	−0.07 (0.04)	−0.837	.40	−0.08 (0.04)	−0.882	.38
Sex	0.05 (0.70)	0.517	.61	0.03 (0.78)	0.281	.78
Performance status (ECOG)	0.43 (0.52)	4.767	< .001	0.43 (0.63)	3.928	< .001
C reactive protein (log transformed)	–	–	–	0.25 (0.74)	2.007	.05
Albumin	–	–	–	−0.03 (1.15)	−0.223	.82
NLR (log transformed)	–	–	–	−0.09 (1.03)	−0.963	.34
Treatment type						
Chemotherapy		Ref			Ref	
Immunotherapy	−0.19 (0.78)	−2.069	.04	−0.15 (0.82)	−1.568	.12
Targeted therapy	−0.19 (0.87)	−2.034	.04	−0.08 (1.06)	−0.698	.49
Disease type						
Adenocarcinoma		Ref			Ref	
Squamous cell	−0.05 (1.12)	–	.59	0.02 (1.23)	−0.240	.81
Small cell	0.07 (0.98)	0.541.806	.42	0.09 (0.98)	0.981	.33
	F 5.223 Adjusted R2 0.200			F 4.808 Adjusted R2 0.280		

Note: ECOG, Eastern Cooperative Oncology Group; HADS-D, Hospital Anxiety and Depression Scale-Depression; NLR, Neutrophil to Lymphocyte Ratio.

Immunotherapy and targeted therapies incurred as many physical symptoms as chemotherapy. This is consistent with the notion that these therapies are also associated with significant physical symptom side effects even though they are generally thought of as more tolerable [67]. It is possible that although the number of physical symptoms were similar that the severity was less, for example.

6.1. Limitations

This observational study was limited by the number of observations at a single institution and therefore would need to be repeated in order to be verified. This study was cross-sectional at a cancer referral center. Therefore, the average age was about 6 years younger than the average patient with lung cancer and also adenocarcinoma was more heavily represented as these patients may have been seeking novel treatment options. Symptom trajectories during different treatments (chemotherapy, targeted therapies and immunotherapy) would be helpful to understand psychological associations with these three main treatment types. Information on previous treatments were not collected but may have influenced inflammatory profiles for instance. Also, the study only evaluated a limited number of possible mechanisms to explain psychological associations and used limited measures. For example, number of physical symptoms was obtained using the DT&PL which does not account for symptom severity and there are more sensitive measures for physical symptoms. In addition, a future study could account for the effect of socioeconomic status (SES) on the psychological association of treatment types since SES is known to effect cancer outcomes [68]. Smoking status was not available but is also associated with psychological outcomes and should be controlled for, especially because there is a complicated relationship between smoking, inflammation and immunotherapy [69]. Another limitation is that while these treatment categories are not going to change, many treatments in these categories will continue to develop and evolve into combinations for example, which have already come into use. This complicates the simple categorical division of treatment options presented in this study. Also, survey results may more accurately reflect psychopathology if delivered by a neutral third party.

6.2. Implications for consult-liaison psychiatry

Historically, lung cancer has been a cancer type that has many physical and emotional symptoms and patient face end of life issues quickly in their disease trajectory. These new treatments have changed the landscape of lung cancer over the last decade such that there is a more varied clinical presentation among patients with stage IV lung cancer. This means that while certain subsets of patients, perhaps receiving targeted and/or immunotherapy, may be able to maintain a good quality of life or even thrive under the diagnosis of lung cancer, other patients continue to have greater symptom difficulties, like depression, that require a greater amount of attention and care. This study highlights some of these differences in patient profiles as determined by their current treatment types. Understanding the relationship between lung cancer treatment type and psychological variables can help the consulting psychiatrist to conceptualize the patient trajectory and risk of developing depression or depression recurrence, for example. This information may also help determine allocation of resources that may translate into frequency of follow up visits, coordinated care, etc.. Also, the study highlights how quickly paradigmatic shifts in treatment can fundamentally change the symptomatic care required for groups of patients. It would be interesting to follow these patients longitudinally in order to understand if there are other treatment-specific psychological outcomes that develop in patients taking targeted and immunotherapy over time.

6.3. Future directions

This study is hypothesis-generating but the findings warrant a further and deeper evaluation into the psychological symptom differences in patients with lung and other cancers based on new paradigmatic shifts in anti-cancer treatments. Future studies should evaluate these symptoms in a longitudinal manner, with a greater number of participants. Inflammatory markers should be measured over time and evaluated for mediation/moderation of psychological symptoms. The specific relationship between chemotherapy and depression should be further explored. These differences in depression among treatment types may translate into targeted psychological treatments for depression in the setting of chemotherapy, for example.

6.4. Summary

This study highlights the interplay between treatment type, which is really a life altering event, and psychological states while trying to understand what may be responsible for the differences. Chemotherapy is associated with depression and greater inflammation than either immunotherapy or targeted therapies. Targeted therapy and immunotherapy are associated with longer life span and may offer a reprieve from depressive symptoms in patients with metastatic lung cancer.

Conflict of interest

No conflict of interest reported by the author.

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