Editorial Commentary

Patient-focused insights: how emotional distress shapes immunotherapy response in non-small cell lung cancer

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A diagnosis of cancer does not impact only the physical status but also the mental health of patients, in terms of depression and anxiety. These two entities are often grouped under the definition of emotional distress (ED), which has been shown to be highly prevalent among patients with cancer and to negatively impact on quality of life (QoL), adherence to treatment, and survival after a cancer diagnosis (1).

The prevalence of depression (both minor and major) and anxiety in patients with cancer have been found to be approximately 15–40% and 10–45% respectively (2,3). Symptoms of ED vary according to cancer type depending on the prognosis, physical symptoms, and specific tumor- or treatment-related side effects (4).

In the setting of lung cancer, which represents the leading cause of cancer-related death in the US and worldwide (5), the incidence of any grade of depression and/or anxiety is around 30–70%; risk factors for developing ED have been identified in younger age, female sex, lower income, and lower educational level (6). Clinically, ED and cancer have been suggested to promote each other, giving rise to a vicious cycle.

Of note, the introduction of immune checkpoint inhibitors (ICIs) in clinical practice, alone or in combination with chemotherapy, have significantly improved clinical outcomes for lung cancer in recent years, particularly for non-small cell lung cancer (NSCLC). Looking at 5-year overall survival (OS) of ICIs-based clinical trials, in the KEYNOTE-024 the 5-year OS was 31.9% for pembrolizumab compared to 16.3% for chemotherapy, 19.4% versus 11.3% in the KEYNOTE-189 for pembrolizumab plus chemotherapy versus chemotherapy-alone, 18.4% versus 9.7% in the KEYNOTE-407 for pembrolizumab plus chemotherapy versus chemotherapy-alone, respectively (7-9). This means that, even if a percentage of patients derive long lasting benefit from ICIs, more research is needed to recognize mechanisms of resistance and tailored therapeutic approaches to prolong the response to ICIs and OS in a wide group of patients.

To date, several biomarkers have been discovered that support clinicians in predicting resistance or response to ICIs: higher expression of programmed death ligand 1 (PD-L1) tumor proportion score (TPS), higher levels of tumor mutational burden (TMB), and tumor infiltrating lymphocytes (TILs), all of which are related to higher benefit to ICIs; conversely co-mutations in *KRAS-KEAP1*,

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KRAS-STK11 or KRAS-SMARCA4, or high infiltration of T regulatory cells in the tumor microenvironment (TME) have been shown to predict resistance to immunotherapy (10). Beyond tumor-intrinsic factors, several hosts related biomarkers have been also suggested to impact the efficacy of ICIs, including sex, body mass index, and psychological factors (11). Regarding the latter, numerous retrospective and epidemiologic studies have been conducted, and prospective data are also emerging, suggesting a role for psychological status on clinical outcomes in patients with cancer (12). Zeng *et al.* now report the results from cohort 1 of the prospective observational STRESS-LUNG study, which studied the association between ED and efficacy of first-line ICIs in patients with advanced NSCLC (13).

The paper by Zeng *et al.* addresses a critical knowledge gap by assessing how pretreatment ED, commonly linked to depression and anxiety, may diminish the efficacy of ICIs. The cohort 1 of the STRESS-LUNG study included 227 patients, nearly half (48.9%, N=111/227) of whom showed signs of ED, assessed using validated tools. Among patients with ED symptoms, 53 patients (47.8%) exhibited depressive symptoms only, 10 patients (9.0%) showed anxiety symptoms only and 48 patients (43.2%) showed both depressive and anxiety symptoms synchronously. The primary endpoint was progression-free survival (PFS), while secondary endpoints included overall response rate (ORR) and OS. Additionally, the study explored the effects of ED on QoL and changes in distress biomarkers such as cortisol levels. In terms of baseline demographic and clinical characteristics, those patients experiencing ED (*vs*. no-ED) exhibited a significantly higher percentage of female patients, confirming previous observations that women with a diagnosis of cancer have higher risk of developing ED compared to men (6,14).

Overall, patients experiencing ED in the study were found to harbor significantly shorter PFS with ICIs (7.9 months) compared to those without ED [15.5 months, hazard ratio (HR) 1.73, P=0.002], and this association was maintained also after applying propensity score matching and inverse probability of treatment weighting to well balance baseline characteristics of the two groups of patients (ED *vs.* no-ED), but also in the multivariable analysis after correcting for confounding factors. The negative association of ED with PFS under ICIs was observed across key subgroups of patients.

Looking at response, ORR was also found to be significantly lower in patients with ED compared to those without ED (46.8% *vs.* 62.1%). Moreover, even if the median OS in the overall population was immature, patients with ED patients exhibited a reduced 2-year survival rate (46.5%) compared to those without ED (64.9%).

An exploratory analysis was conducted on 187 patients with completed baseline and on-treatment ED assessment, and remission of ED seemed to have a positive impact on ICIs efficacy, with longer median PFS in the remission group compared to persistent group (12.7 *vs.* 6.5 months, P=0.03). Notably, higher events of death were observed among those patients with the onset of ED on-treatment compared to those that never developed ED (HR 2.42, 95% CI: 1.01–5.80, P=0.48). The authors also showed that patients with ED reported worse QoL, in terms of global health, and more symptoms, impacting significantly on the overall well-being of patients.

Lastly, the blood concentration of cortisol and adrenocorticotropic hormone (ACTH) was assessed at baseline before ICIs start: patients experiencing ED had higher levels of serum cortisol compared to those in the no ED group and serum cortisol levels impacted on clinical outcomes with a shorter median PFS in patients with higher serum cortisol (above the median) compared to those with low serum cortisol (below the median).

The worse outcomes with ICIs observed in the ED group of the STRESS-Lung study emphasizes the need for comprehensive patient care that includes psychological health. This is also true for mild cases of depression or anxiety, which were found to negatively impact outcomes with ICIs in the study. The negative impact of ED on ICIs efficacy was also observed in both subgroups of patients with different levels of ED, mild ED and moderate-to-severe ED, with mild ED referring to mild depression and/or anxiety symptoms (either PHQ-9 or GAD-7 scores were 5 to 9) and moderate-to-severe ED refers to moderate-to-severe depression and/or anxiety symptoms (either PHQ-9 or GAD-7 scores #10) suggesting that, even a mild depressing or anxious state should be recognized and manage promptly. ED not only impacted on ICIs efficacy but also on QoL of patients. QoL, assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), is increasingly being recognized as a crucial endpoint in clinical trials, also in those that changed clinical practice for NSCLC, such as KEYNOTE-024, KEYNOTE 189 and KEYNOTE 407, underlining a more patient-centered approach to research, looking not only at the disease itself, but also at the overall well-being of the patient (15-17).

The findings from the study by Zeng *et al.* highlight the

importance to assess the psychological status of patients, not only at baseline before starting ICIs but also during treatment; moreover, they suggest that an improvement in the psychological status during treatment can impact overall on survival, supporting the importance of routinely assessing the patient's overall well-being in clinical practice.

It is also important to notice the negative association of ED with PFS observed even in those subgroups of patients with well-established negative prognostic factors: patients with squamous histology and negative PD-L1 TPS <1% are known to derive less benefit from immunotherapy compared to those with adenocarcinoma or high PD-L1 expression (≥50%), having shorter PFS and OS under ICIs-based therapy. Therefore, data from this study suggest that ED could exacerbate this poor prognosis by further compromising the immune response. Furthermore, comorbidities burden seems to impact negatively on outcomes of patients with cancer treated with ICIs (18). A recent study showed that patients with type 2 diabetes mellitus (T2DM) with higher pretreatment glycemia had higher NLR, a well-known negative prognostic biomarker, and exploratory tumoral transcriptomic profiling in a subset of patients revealed differential regulation of innate and adaptive immune pathways in patients with T2DM that may explain their worse clinical outcomes under ICIs (19). The activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system by ED might exacerbate hypertension and diabetes mellitus, highlighting the need for a comprehensive approach to patient care (20). By addressing ED alongside the management of these comorbidities in patients with chronic conditions, these results suggest that overall patient outcomes under ICIs might be optimized.

The positive correlation between ED and cortisol underlines the strong interconnection between psychological condition of ED and the stress response system: prolonged ED, through HPA and sympathetic nervous system, leads to the secretion of stress hormones, including glucocorticoids, and adrenergic mediators that have an impact on systemic inflammation and immune cells function (13). Glucocorticoids are potent immunomodulators and immunosuppressors, that promote T cell apoptosis and tumor progression, providing a mechanistic explanation for the clinical observations of this trial (21).

Another study published in 2023 by Fraterman *et al.* investigated the impact of pretreatment ED on clinical outcomes of patients with melanoma that received neoadjuvant ICIs in the phase 2 PRADO trial (NCT02977052) (22). In this trial, where ED assessment differed from STRESS-Lung (i.e., used the EORTC QLQ C30 questionnaire), ED was found to be associated with lower recurrence-free survival (RFS) and distant metastasis-free survival (DMFS): the 2-year RFS and 2-year DMFS were lower in the group of patients with ED compared to those without ED (2-year RFS: 74% *vs.* 91%); patients with ED showed a significantly reduced 2-year DMFS (78% *vs.* 95%). Moreover, patients with baseline ED had reduced rate of major pathological response (MPR) compared to those without ED (46% *vs.* 65%), underlining the impact of psychological status on clinical and pathological outcomes also in melanoma patients.

The different methods currently used to assess ED underscore the need for additional research to standardize the evaluation of patients' psychological status in clinical practice. Recognizing ED as a potential biomarker for treatment efficacy aligns with the holistic approach of treating the patient as a whole entity, encompassing both body and mind. Standardizing these assessments will enhance the consistency and reliability of psychological evaluations, ultimately leading to improved patient's care and outcomes. The STRESS-Lung study emphasizes the importance of integrating psychological assessment into the cancer treatment pathway, starting at the time of diagnosis. It suggests that in addition to an active oncology treatment plan, a tailored psychological care plan should be developed in line with a holistic approach to cancer care. This integrated model recognizes the patient as a whole person, addressing both the physical and psychological dimensions of the disease to improve overall well-being and outcomes. A well-structured psycho-oncological (PO) program was established in Germany between 2018 and 2022 (German Clinical Trials Register No. DRKS00015326), aiming to create a high-quality PO care program that can be implemented as an integrated, cross-sectoral approach for patients with cancer, with the potential for adoption into national standard care practices. The patients' perspectives data, published in 2023, reported high satisfaction with the PO care, with a significant improvement of patient-reported outcomes (anxiety and depression, health status, and work ability), supporting the need of the integration of a structured collaborative PO care programs into oncologic departments (23). A randomized controlled trial is ongoing in Germany (German Clinical Trials Register DRKS00030077) to evaluate the impact of a well-structured PO approach on anxiety, depressive symptoms, distress, supportive care needs, and QoL in patients with a diagnosis of lung cancer.

Although STRESS-Lung is a single-center cohort in

China, which may limit the generalizability of the results to more diverse populations, and although there is an imbalance between male and female populations that may influence the results because of the difference on the immune system, response to therapy, and gender-related psychological status, it points to an important area of research that needs further investigation, especially in clinical trials, integrating psychological factors such as ED with biological markers to predict treatment outcomes.

Future research, ideally in the setting of clinical trials, should explore the impact of ED on outcomes and appropriate studies should be designed to investigate whether addressing ED through interventions like psychological counseling or pharmacological treatments, can enhance ICIs efficacy.

The STRESS-Lung study also promotes the integration of the well-known biomarkers, such as PD-L1, NLR, with the psychological state of the patients, introducing the concept of 'psycho-biomarker', and suggesting that the incorporation of ED screening into routine clinical practice could enhance survival predictions and support early intervention programs for mental health since start of therapy.

Finally, the impact of ED on clinical outcomes highlights the need for a well-structured, multidisciplinary approach to patient care, involving the integration of a PO team from the time of diagnosis, conducting a baseline evaluation and, when necessary, developing a tailored PO plan to address the patient's specific needs. The European Society of Medical Oncology (ESMO) developed clinical practice guidelines for anxiety and depression in adult patients with cancer encouraging a regular screening and assessment of patients for psychological distress along with timely interventions when necessary (2). Moreover, the ESMO guidelines discuss the critical issue of awareness about psychological distress in patients with cancer, emphasizing that it is often underrecognized or denied by the patients themselves. In this context, oncologists, both in clinical practice and research contexts, should actively collaborate with psycho-oncology experts to develop comprehensive projects and structured programs aimed at raising awareness, assessing, and supporting patients' mental health. Such efforts are essential given the arising evidence of the profound impact of mental health on clinical outcomes and QoL of patients with cancer.

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