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RESEARCH

Cancer-related fatigue among patients with advanced cancer receiving immune-checkpoint inhibitors: a prospective study

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Abstract

Purpose The aim of this study was to determine the frequency and factors associated with severity of cancer related fatigue (CRF) as assessed by Functional Assessment of Cancer Illness Therapy–Fatigue (FACIT-F), prior to, and during 12 weeks of immune-checkpoint inhibitors (ICIs). We also explored the effects of ICIs on fatigue dimensions and interference with daily activities (Multidimensional Functional Symptom Inventory, MFSI-SF, Patient-Related Outcome Symptom Measurement Information System Short form Fatigue 7a, PROMIS F-SF), QOL (Functional Assessment of Cancer Therapy-General, FACT-G), and cancer symptoms (Edmonton Symptom Assessment Scale, ESAS).

Methods In this prospective, longitudinal observational study, patients with a diagnosis of advanced cancer receiving ICIs were evaluated. Patient demographics, FACT-G, FACIT-F, MFSI-SF, PROMIS F-SF, and ESAS were collected prior to, and during 12 weeks of ICIs.

Results A total of 160 of the 212 enrolled patients were analyzed. The median age was 61 years, 60% were female, most common cancer was melanoma (73%), and most common ICI was nivolumab 46%. The frequency of clinically significant fatigue (defined as ≤ 34/52 on FACIT-F score) was 25.6% at baseline, 25.7% at week 8, and 19.5% at week 12. There was significant improvement in FACIT-F ($P = 0.016$), FACT-G physical well-being ($P = 0.041$), FACT-G emotional well-being ($P = 0.011$), ESAS anxiety ($P = 0.045$), and ESAS psychological distress ($P = 0.03$) scores from baseline to week 12 of ICIs. Multivariate analysis found significant association between clinically significant CRF and PROMIS F-SF ($P < 0.001$) and MFSI-SF global scores ($P < 0.001$).

Conclusions CRF is frequent prior to the initiation of ICI treatment. Over 12 weeks of ICI treatment, CRF significantly improved. FACT-G physical well-being, FACT-G emotional well-being, ESAS anxiety, and ESAS psychological distress scores improved overtime. Further studies are needed to validate these findings.

Keywords Fatigue · Cancer · Immunotherapy · Adverse event · Immune-checkpoint inhibitors

Introduction

Cancer-related fatigue (CRF) is the most frequently reported symptom associated with cancer and its treatment [1–4]. CRF is more severe and debilitating in patients with advanced cancer than in those with early cancer or in cancer survivors [1–3]. CRF may interfere with activities of daily living, affects the ability to continue to receive cancer therapy, and negatively affects quality of life (QOL). In advanced cancer patients receiving treatment, its frequency ranges from 60 to 90% [1–4]. Despite its high frequency and impact on patients' QOL, there are limited treatment options in patients with advanced cancer, a population which has been rapidly increasing and living longer as a result of advances in cancer treatments such as targeted therapy and immunotherapy.

Immunotherapy with immune-checkpoint inhibitors (ICIs) is fast emerging as an important component of cancer therapy. Recently, the frequency of ICI use has drastically increased with more than half of all patients with advanced cancer having received ICIs in several (neo)adjuvant and maintenance settings [1, 2]. ICIs are used as a single agent

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as well as combination regimens, including those involving other classes of ICIs, cytotoxic chemotherapy, radiotherapy, and biological and/or targeted therapies. There is growing importance of characterizing ICIs related adverse events such as CRF, its effective management in patients receiving ICIs, and implications on patients' QOL as recent studies have found ICIs improving progression free survival in patients with advanced cancer [3].

ICI-related adverse events usually occur within the first few months of the start of treatment but are known to occur any time, even after treatment discontinuation [3, 4]. CRF is reported as one of the more common adverse events in patients with advanced cancer receiving ICI immunotherapy [5, 6]. However, CRF frequency, severity, and aggravating factors are unclear as most studies evaluating CRF in patients treated with these agents have not used formal validated patient reported CRF instruments but used clinician reported assessment measures of toxicity such as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) [4–7]. As a result, there may be underreporting of CRF as well as its severity over the course of the ICI treatment and thereby limited research for ICI-related CRF treatment options [7]. Using adverse event assessments such as NCI CTCAE toxicities assessment, the prevalence of CRF was estimated to be 30–50% in patients receiving ICI immunotherapy [5–9].

The aim of this study was to determine the frequency and factors associated with CRF severity as assessed by Functional Assessment of Cancer Illness Therapy–Fatigue (FACIT-F), prior to, and during 12 weeks of ICIs. We also explored the effects of ICIs on fatigue dimensions and interference with daily activities using the Multidimensional Functional Symptom Inventory-Short form (MFSI-SF), and Patient-Related Outcome Symptom Measurement Information System Short form-Fatigue 7a (PROMIS F-SF); QOL using Functional Assessment of Cancer Therapy-General (FACT-G); anxiety and depression using Hospital Anxiety and Depression Scale (HADS); and additional cancer symptoms using Edmonton Symptom Assessment Scale (ESAS).

Methods

The University of Texas MD Anderson Cancer Center Institutional Review Board approved the protocol in accordance with the Declaration of Helsinki, and all patients were provided written informed consent for participation in the study.

Patients

This prospective, longitudinal, observational study was conducted from May 2018 to June 15, 2022. Patients with the following eligibility criteria were included in the study: diagnosis of metastatic or recurrent cancer, scheduled to be treated with ICI immunotherapy, aged 18 years or older, hemoglobin level of ≥ 8 g/dL within 2 weeks of study enrollment, be able to read, write, and speak English, be able to understand the description of the study, and give an informed consent. Patients were excluded if they had cognitive failure as evidenced by Memorial Delirium Assessment Scale (MDAS) score of ≥ 13 out of 30 at baseline.

Study assessments

After obtaining consent, the research coordinator collected patient demographics including age, sex, cancer diagnosis, race, marital status, any cancer treatments within the study period, hemoglobin level, neutrophil lymphocyte ratio, and thyroid stimulating hormone levels. CRF and related symptoms were prior to, and during first 12 weeks of ICIs treatment using validated assessments measures including FACIT-F, FACT-G, HADS, ESAS, MFSI-SF, and PROMIS F-SF.

FACIT-F scale

The FACIT-F was the primary outcome of the study and was used to assess fatigue over time during the study [8–11]. It is a 13-item scale in which the patient rates the intensity of their fatigue and its related symptoms on a scale of 0 to 4. The total score can range between 0 and 52, with higher scores denoting less fatigue. Prior studies by Cella et al. suggested one standard deviation (SD) below the general population mean of 43 to denote the threshold for fatigue impairment [9]. Previous studies defined patients as having clinically significant fatigue if their scores were 34 or less [10]. The rationale for the use of FACIT-F is that this scale is brief 13-item scale, easy to administer and places minimal burden to the patient. FACIT-F has been extensively validated to measure fatigue in various types of cancer patients [8–11]. It has excellent internal consistency and reliability with test–retest reliability coefficients of 0.84–0.90, and internal consistency of $\alpha = 0.93–0.95$ [8, 11].

FACT–G

The FACT-G survey was used to assess QOL over time during the study. It consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional) on a scale of 0–4 (0 = not at all, 4 = very much) over the past 1 week. Test–retest reliability coefficients are 0.84–0.90 [8].

HADS

Depression and anxiety symptoms were assessed by using the 14-item HADS questionnaire. This validated questionnaire has 14 items with 7-item subscale for anxiety and depression [12, 13]. The responses for each item ranges from 0 (no problem) to 3 (high level of problem). The score in each subscale is summed up to a maximum of 21 units. Higher scores indicate greater anxiety, depression, or distress. In cancer patients, optimal cut-off for clinically relevant anxiety was 10 or 11 for the HADS anxiety subscale (sensitivity 0.63; specificity 0.83), and 7 for the HADS depression subscale (sensitivity 0.86; specificity 0.81) [13]. The reliability (Cronbach's alpha) of HADS-A and HADS-D sub-scales was 0.79 and 0.87 respectively [14].

ESAS

ESAS was used to measure common cancer-related symptoms during the past 24 h. The symptoms included pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feeling of well-being and other symptoms (sleep, cough, blurry vision, pain due to mouth sores/ulcers, rash, diarrhea, headaches, fever chills, joint/muscle aches, itching, night sweats, swelling/ tingling, and numbness of hands and feet) [15]. For the purpose of "post-hoc" analysis [16–18], we categorized the ESAS as follows: ESAS symptom distress, sum of pain, dyspnea, appetite, nausea, fatigue, drowsiness, anxiety, depression, and well-being scores; ESAS physical, sum of pain, shortness of breath, appetite, nausea, fatigue, and drowsiness scores; and ESAS psychological, sum of anxiety, and depression scores.

MFSI-SF

MFSI-SF is a 30 items valid questionnaire, designed to assess the multidimensional nature of fatigue [19, 20]. Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor). The first four MFSI-SF subscales (general, physical, emotional, and mental fatigue) were summed, and the vigor scale was subtracted to create a fatigue total score. The total MFSI-SF score ranges from − 24 to 96, with a higher score indicating a higher fatigue level.

The PROMIS SF v1.0–Fatigue 7a

The PROMIS SF v1.0–Fatigue 7a (PROMIS F-SF) consists of seven items that measure both the experience of fatigue and the interference of fatigue on daily activities over the past week [21]. Response options are on a 5-point Likert scale, ranging from 1 = never to 5 = always. PROMIS F-SF scores were on a *T* score metric (mean = 50, standard deviation, SD = 10), to compare the score to the national norm (e.g., 50 referred as the mean *T* score of the United States general population). A higher score indicates greater fatigue [21].

MDAS

Patients' cognition for eligibility to participate in the study was assessed using the Memorial Delirium Assessment Scale (MDAS) [22]. It has been validated in advanced cancer with a sensitivity 98% and specificity of 96%. MDAS score of ≥ 13 out of 30 is considered as a cut-off for cognitive failure or delirium with a sensitivity of 70.59% and a specificity of 93.75%. MDAS score of < 13 at baseline was used to considered for eligibility for this study [23].

Statistical considerations

Before performing inferential procedures, we conducted extensive descriptive statistical analyses of the outcome and predictor variables. Standard descriptive statistics, including means, standard deviations, ranges, and frequencies, were computed. If the data did not appear to be approximately normally distributed, transformations were made to the data, or appropriate nonparametric methods were used.

Since CRF (FACIT-F) scores were obtained at baseline (prior to ICI treatment), weekly for 12 weeks, we analyzed the data by using repeated analysis of variance (ANOVA) in patients with complete assessments at baseline, and during 12 weeks of ICIs. We performed exploratory data analyses to assess treatment effects for other continuous outcome variables including PROMIS F-SF, FACT-G, MFSI-SF, and HADS scores using the same statistical methods described above. We conducted exploratory analysis of the ESAS data using univariate mixed effects modeling. We included significant univariate variables in the final multivariable generalized estimating equation models to determine the factors associated with severity of clinically significant fatigue during ICI immunotherapy or its combinations. All statistical analyses were performed using Stata/MP v17.0 (College Station, TX).

Results

A total of 160 of 212 enrolled were analyzed. Figure 1 shows the study flow including the reasons for exclusion from the study ($N = 52$) and dropouts ($N = 78$).

Table 1 shows the demographics and clinical factors of the total study patients analyzed and the complete cases (patients with complete CRF assessments from baseline to week 12). The median age was 61 years, 60% were female, 91% were white, and the most common cancer was

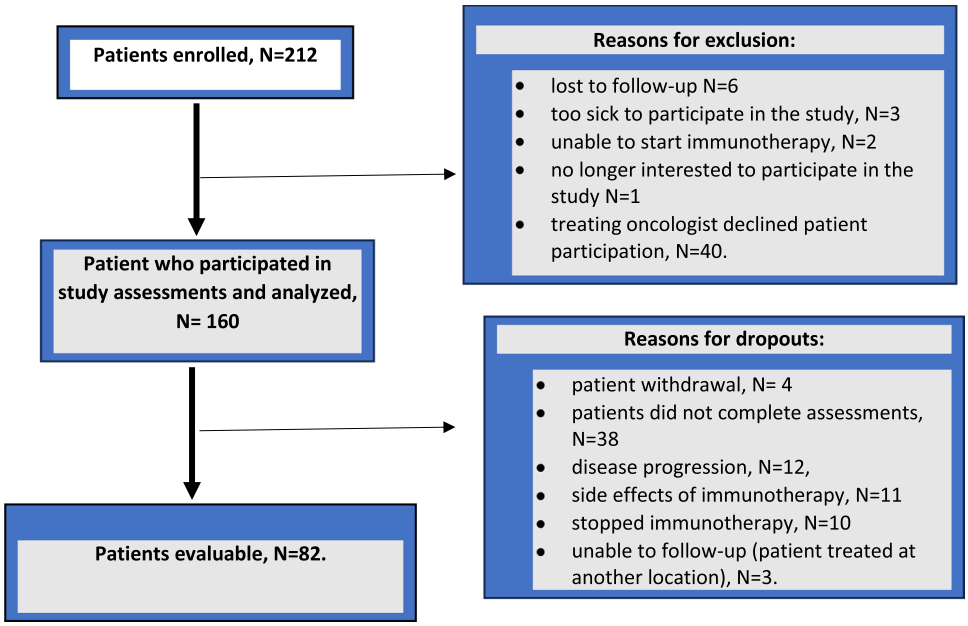

Fig. 1 Study flow chart

melanoma (73%). The most common ICI immunotherapy was nivolumab [46% ($N=72$)]. Two ICI agent immunotherapy was given to 26% ($N=41$). The cancer treatments commonly used with ICI were chemotherapy (6.3%), and chemotherapy plus radiation therapy (5.6%).

Table 2 shows that the frequency of clinically significant fatigue (defined as ≤ 34/52 on FACIT-F) was 25.6% at baseline, 21.9% at week 4, 25.7% week 8, and 19.5% at week 12. There was significant improvement of FACIT-F scores from baseline to week 12 ($P=0.016$). There was no significant difference in the baseline FACIT-F scores in patients with missing assessments ($N=159$), and in the patients with complete assessments from baseline to week 12 ($N=82$), [40.03 vs. 41.03, $P=0.54$].

There was improvement in FACT-G physical well-being ($P=0.041$), FACT-G emotional well-being ($P=0.011$) over time from baseline to week 12. There was no significant change in the severity of symptoms as assessed using PROMIS F-SF, MSFI-SF, FACT-G total, and HADS scores.

Table 3 shows ESAS symptoms from baseline to week 12. The severity of cancer-related symptoms as assessed by ESAS were mild with no significant change from baseline to week 12 except for anxiety ($P=0.045$), and psychological distress scores ($P=0.03$).

Table 4 shows spearman's correlations between severity of CRF and other cancer treatment related symptoms at baseline and week 12 of ICI immunotherapy.

Table 5 shows unadjusted univariate models suggest significant association between female patients ($P<0.001$), immunotherapy treatment combinations ($P=0.004$), immunotherapy with other cancer treatments ($P<0.001$) treatment duration ($P=0.02$) treatment cycles ($P=0.03$), hemoglobin levels ($P=0.01$), PROMIS F-SF ($P<0.001$), MFSI-SF global ($P<0.001$), FACT-G total ($P=0.004$), HADS anxiety ($P<0.001$), and HADS depression ($P<0.001$) scores and clinically significant CRF. Adjusted multivariate model suggests significant association between CRF (FACIT-F), PROMIS F-SF ($P<0.001$), and MFSI-SF global scores ($P<0.001$).

Discussion

Our study is one of the first to longitudinally evaluate frequency and characteristics of CRF in patients prior to, and during 12 weeks of ICI immunotherapy using validated assessment tools for evaluation of CRF in patients with advanced cancer. We found that CRF was more frequent and severe prior to the start of ICI treatment and CRF becomes less frequent and severe during ICI treatment over 12 weeks. CRF during treatment of ICIs is significantly associated with FACT-G physical well-being, FACT-G emotional well-being, ESAS psychological distress, and ESAS anxiety scores.

A study by Abdel-Rehman et al. [6] evaluating the risk for CRF due to ICI treatment found that the overall incidence of treatment-associated CRF varied from 14 to 42%; whereas the incidence of high-grade treatment-associated CRF varied from 1 to 11%. The absolute incidences of CRF in individual studies varied based on the dosing of the specific ICI, the schedule (every 2 weeks versus every 3 weeks) as well as the use of combination regimens versus single agent ICIs [6]. The reported data suggests that CTLA-4 inhibitors (ipilimumab 10 mg/kg and tremelimumab) were

Table 1 Demographics and clinical factors of the study patients

Characteristics	*N* = 160 (total patients analyzed)	*N* = 82 (complete cases)[#]
Age, years, mean (SD)	61 (12)	63 (11)
Sex, *N* (%)		
Female	60 (37.5)	32 (39)
Race, *N* (%)		
American Indian or Alaska Native	1 (0.6)	0
Asian or Pacific Islander	2 (1.3)	0
Black or African American	5 (3.1)	4 (4.9)
White	152 (94.1)	78 (95.1)
Marital status, *N* (%)		
Divorced or separated	13 (8.1)	7 (8.5)
Married	128 (80.0)	64 (78)
Single* or widowed	19 (11.9)	11 (13.4)
Cancer diagnosis, *N* (%)		
Gastrointestinal	2 (1.3)	1 (1.2)
Genitourinary	30 (18.8)	19 (23.2)
Melanoma	116 (72.5)	52 (63.4)
Sarcoma	2 (1.3)	1 (1.2)
Thoracic	10 (6.3)	9 (11)
Immune-checkpoint inhibitors agents, *N* (%)		
Atezolizumab	3 (2)	3 (3.7)
Avelumab	4 (2.5)	2 (2.4)
Ipilimumab	2 (1)	0
Ipilimumab, nivolumab	49 (31)	21 (25.6)
Nivolumab	72 (46)	37 (45.1)
Pembrolizumab	28 (18)	19 (23.2)
Any cancer treatments within the study period, *N* (%)		
Chemotherapy	10 (6.3)	6 (7.3)
Radiation	5 (3.1)	3 (3.7)
Surgery	7 (4.3)	3 (3.7)
Chemotherapy, radiation	2 (5.6)	1 (1.2)
Radiation, surgery	2 (1.2)	1 (1.2)
Other therapy	4 (2.5)	2 (2.4)
Others^	6 (3.7)	6 (7.3)
Hemoglobin, g/dL, mean (SD)	13.5 (2.1)	13.3 (1.7)
Neutrophil lymphocyte ratio, mean (SD)	3.4 (1.6)	2.69 (4.0)
Thyroid-stimulating hormone, mIU/L, mean (SD)	2.1 (1.9)	2.1 (2.3)

[#]Complete cases—cohort with no missing fatigue data over 12 weeks. *SD* standard deviation. *Single/lives with partner or never married. ^Chemotherapy and other therapy, chemotherapy and target therapy, target therapy, surgery and other therapy, chemotherapy and radiation and surgery, radiation and target therapy. Normal level of hemoglobin: 14–18 g/dl for men and 12–16 g/dl for women. Neutrophil lymphocyte ratio: 0.78–3.53. Thyroid-stimulating hormone: 0.4 to 4.0 mIU/L

linked to a higher risk of all- and high-grade CRF compared with control regimens, whereas PD-1 inhibitors (nivolumab and pembrolizumab) are linked to a lower risk of all- and high-grade CRF compared with control regimens [6, 24, 25]. Moreover, a subgroup difference based on the cancer treated could not be detected [6]. A recent study by Hodi et al. reported fatigue as an adverse event in up to 42% of patients being treated in a therapeutic clinical trial [26]. Jim et al. found that among participants in their GO2 Foundation for Lung Cancer registry treated with ICIs, 85% retrospectively reported CRF, with 41% experiencing moderate to severe fatigue [27]. Zhou et al. found that CRF occurred in 31% of patients receiving ICI with chemotherapy, 34% of patients treated with an ICI/targeted therapy combination,

Table 2 Cancer-related fatigue and related symptoms from baseline to week twelve of immune-checkpoint inhibitors

Main outcomes, mean (SD)	Baseline ($n=82$)	Week 4 ($n=82$)	Week 8 ($n=82$)	Week 12 ($n=82$)	P^a
FACIT fatigue	41.03 (10.97)	41.25 (11.40)	42.04 (10.85)	43.45 (10.31)	**0.016**
Clinically significant CRF[^], *N* (%)	21 (25.6)	16 (21.9)	19 (25.7)	16 (19.5)	0.76
Presence of CRF impairment [#], N (%)	35 (42.7)	27 (37)	26 (35.1)	28 (34.1)	0.68
PROMIS F-SF					
Fatigue	47.22 (8.21)	46.57 (8.031)	46.15 (9.34)	45.67 (9.52)	0.96
MFSI-SF					
Global	7.52 (14.55)	4.30 (14.73)	3.68 (11.6)	4.86 (13.13)	0.86
General fatigue	6.95 (6.89)	5.95 (7.09)	5.40 (6.92)	5.53 (7.23)	0.94
Physical fatigue	2.94 (4.43)	3.0 (4.66)	2.33 (3.19)	2.72 (3.99)	0.73
Emotional fatigue	3.70 (4.6)	2.21 (3.19)	2.0 (2.45)	2.50 (2.82)	0.10
Mental fatigue	2.9 (4.28)	1.95 (3.09)	1.83 (2.95)	2.08 (2.83)	0.96
Vigor	8.85 (3.54)	9.38 (3.31)	8.50 (3.29)	8.36 (3.47)	0.53
FACT-G total	59.03 (8.08)	57.06 (8.5)	57.31 (8.05)	58.70 (7.25)	0.93
Physical wellbeing	4.19 (4.40)	3.33 (4.25)	3.15 (4.19)	3.17 (4.16)	**0.041**
Social/family wellbeing	25.22 (4.40)	24.71(5.10)	25.19 (5.34)	25.73 (5.06)	0.23
Emotional wellbeing	6.59 (3.69)	5.41 (3.04)	5.76 (2.80)	5.75 (2.63)	**0.011**
Functional wellbeing	23.15 (5.18)	23.61 (4.34)	23.22 (3.93)	24.06 (4.21)	0.78
HADS					
Anxiety	2.80 (3.05)	2.53 (2.93)	2.71 (2.75)	2.73 (3.01)	0.65
Depression	2.74 (3.51)	2.39 (3.13)	2.29 (3.15)	1.88 (3.19)	0.65

CRF Cancer-related fatigue, *SD* standard deviation, *FACIT-F* Functional Assessment of Chronic Illness Therapy–Fatigue, mild fatigue: 35–52. [^]Clinically significant fatigue, FACIT-F values equal to or lower than 34. [#]Presence of cancer related fatigue impairment was defined as FACIT-F values equal to or lower than 42. PROMIS F-SF: measured by Patient Reported Outcome Measurement Information System Fatigue-Short Form (PROMIS F-SF) and converted to PROMIS-T scores, higher scores indicating greater fatigue including normal limits: < 55, mild: 55–60, moderate: 60–70, severe: > 80. ESAS, Edmonton Symptom Assessment Scale. *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *FACT-G*, Functional Assessment of Cancer Therapy-General, mild fatigue for FACT-G total score: 80–108, mild fatigue for physical wellbeing: 26–28, mild fatigue for social/family wellbeing: 20–28, mild fatigue for emotional wellbeing: 22–28; mild fatigue for functional wellbeing: 21–28. *HADS*, Hospital Anxiety Depression Scale, mild anxiety, or depression: 0–7. a. repeated ANOVA. *P* values lower than 0.05 were considered statistically significant. Bold *P* values indicated that there were statistically significant differences across multiple visits

24% of patients with concurrent immunotherapy and radiotherapy, and 26% of patients treated with immunotherapy combinations [5]. There are no published longitudinal studies evaluating the frequency and severity of CRF over the course of 12 weeks of ICI treatment using validated tools [6, 7]. A prior study by Cortellini et al. found that 19% of patients experienced CRF of any severity (assessed using NCI-CTCAE v. 4) within one month of commencement of ICI immunotherapy, and 38.9% of patients experienced any CRF one month after commencement of ICI immunotherapy [25]. Miaskowski et al. and others examined the trajectories of CRF from the time of simulation to completion of radiotherapy and beyond [28, 29]. They found that the severity of CRF increased during radiotherapy, but although CRF did decrease from its maximum after completion of radiotherapy, it persisted in the post-therapy period. In patients receiving chemotherapy, higher frequency of CRF over treatment was found especially in patients with psychological symptoms and comorbidities [30, 31].

Our study confirms prior studies that assessed CRF as a part of adverse event reporting (NCI CTCAE) that frequency of fatigue was lower than seen after chemotherapy or radiotherapy or combination therapy. The possible reasons could be that the molecular and biochemical pathways may be different in comparison to other therapy such as chemotherapy and or radiotherapy [7, 32, 33]. Also, the differential risk of fatigue among patients receiving ICIs in our analysis suggests varying role of type, and combination of immunotherapy in the causation of clinically significant fatigue. Recent studies by our group and others suggest a multifactorial origin for CRF, with a significant role of dysregulation of hypothalamus–pituitary–adrenal axis, inflammatory cytokines such as IL-6, IL-1RA, TNF-α, and cancer-related physical and psychological symptoms [33]. The exact etiology of CRF in patients receiving immunotherapy may be multifactorial (patient, malignancy, or treatment associated). Some patients may be of higher risk; however, not all presentations of CRF during ICI treatment are due to an immune mechanism [6, 34]. Also some placebo-controlled immunotherapy studies showed significant fatigue in placebo groups suggesting disease-related fatigue [35, 36]. Immune-related gastrointestinal (e.g., diarrhea and colitis),

Table 3 Edmonton symptom assessment scale from baseline to week twelve of immune-checkpoint inhibitors treatment

Mean (standard deviation)	Baseline ($n=153$)	Week 2 ($n=104$)	Week 4 ($n=63$)	Week 6 ($n=68$)	Week 8 ($n=45$)	Week 10 ($n=52$)	Week 12 ($n=35$)	P^a
ESAS								
Pain	1.69 (2.39)	1.53 (2.20)	1.59 (2.01)	1.24 (2.12)	1.29 (1.95)	1.67 (2.31)	1.63 (2.21)	0.83
Fatigue	2.35 (2.45)	2.36 (2.46)	2.79 (2.75)	3.15 (3.01)	2.18 (2.81)	2.21 (2.63)	2.43 (2.80)	0.33
Nausea	0.73 (1.87)	0.52 (1.47)	0.30 (0.91)	0.66 (1.62)	0.33 (1.15)	0.21 (0.50)	0.14 (0.49)	0.09
Depression	0.75 (1.55)	0.73 (1.58)	0.55 (1.17)	0.56 (1.15)	0.27 (0.72)	0.29 (0.78)	0.29 (0.89)	0.10
Anxiety	1.14 (1.81)	1.11 (1.98)	0.73 (1.37)	0.81 (1.54)	0.51 (1.06)	0.49 (1.03)	0.60 (1.22)	**0.045**
Drowsiness	1.20 (2.03)	1.27 (2.03)	1.34 (2.13)	1.46 (2.41)	1.04 (2.34)	1.02 (1.90)	1.23 (2.20)	0.93
Appetite	1.86 (2.57)	1.57 (2.25)	1.45 (1.78)	1.88 (2.20)	1.36 (1.88)	1.25 (1.91)	0.86 (1.54)	0.16
Wellbeing	2.14 (2.27)	2.26 (2.42)	2.02 (2.14)	1.93 (2.21)	1.71 (1.87)	1.40 (1.75)	1.20 (1.73)	0.08
Dyspnea	0.78 (1.77)	0.88 (2.09)	0.75 (1.65)	0.88 (1.78)	0.49 (1.60)	0.56 (1.54)	0.60 (1.70)	0.83
Sleep	2.39 (2.64)	2.62 (2.58)	2.41 (2.67)	2.79 (3.00)	2.09 (2.60)	2.00 (2.55)	2.09 (2.82)	0.63
Other symptoms								
Dry mouth	1.40 (2.50)	1.22 (2.34)	0.92 (2.19)	1.35 (2.31)	1.27 (2.56)	1.31 (2.50)	1.29 (2.60)	0.96
Rash	0.63 (1.87)	0.82 (1.87)	0.83 (2.03)	0.71 (1.91)	0.33 (0.87)	0.37 (1.15)	0.51 (1.27)	0.61
Diarrhea	0.65 (1.79)	0.57 (1.72)	0.31 (1.01)	0.50 (1.66)	0.54 (1.57)	0.27 (1.22)	0.12 (0.54)	0.50
Headache	0.87 (1.83)	0.66 (1.65)	0.54 (1.38)	0.94 (1.71)	0.71 (1.63)	0.59 (1.49)	0.22 (0.66)	0.38
Fever	0.30 (1.28)	0.24 (0.93)	0.22 (0.74)	0.22 (0.81)	0.21 (0.87)	0.22 (0.86)	0.40 (1.33)	0.98
Joint pain	1.81 (2.66)	1.33 (2.20)	1.17 (2.27)	1.59 (2.32)	1.52 (2.43)	1.47 (2.43)	1.49 (2.61)	0.75
Itchy	1.19 (2.27)	1.38 (2.30)	1.70 (2.54)	1.25 (2.19)	0.93 (1.52)	1.04 (1.82)	1.20 (1.76)	0.65
Night sweats	0.93 (1.94)	0.55 (1.68)	0.35 (1.53)	0.38 (1.31)	0.31 (0.84)	0.39 (1.08)	0.29 (0.83)	0.06
Swelling	1.09 (2.33)	0.66 (1.59)	0.76 (1.70)	1.11 (2.41)	0.95 (2.17)	0.82 (2.22)	0.66 (1.80)	0.74
ESAS composite variables								
Physical distress‡	8.64 (9.10)	8.19 (8.61)	8.15 (7.70)	9.27 (9.25)	6.69 (8.11)	6.92 (7.64)	6.89 (7.54)	0.59
Psychological distress	1.89 (3.11)	1.84 (3.24)	1.28 (2.26)	1.37 (2.39)	0.78 (1.69)	0.78 (1.68)	0.89 (1.99)	**0.03**
Symptom distress§	12.68 (12.29)	12.28 (12.10)	11.45 (10.16)	12.56 (12.03)	9.18 (10.79)	9.13 (10.31)	8.97 (10.69)	0.28

ESAS, Edmonton Symptom Assessment Scale. ‡Sum scores of pain, fatigue, nausea, drowsiness,,dyspnea and appetite. ¶Sum scores of depression and anxiety. §Sum scores of pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, appetite, and feeling of wellbeing. a. univariate mixed effects modeling. *P* values lower than 0.05 were considered as statistically significant. Bold *P* values indicated that there were statistically significant differences across multiple visits

hepatic (e.g., elevated transaminases), renal (presenting as nephritic or nephrotic syndrome), and pulmonary toxicities may have an important role in the development of fatigue with these agents [3, 5, 22]. The mechanism of fatigue commonly seen during cancer treatment may be absent during ICI treatment, for example, mitochondrial dysfunction due to cisplatin, and hence the possible reason for lack of severity of CRF [33, 37].

The results of the study suggests that the patients report higher levels of symptoms including and CRF and emotional distress at the time of initiation of the ICIs, and therefore, it may be an appropriate time to refer these patients to supportive/palliative care service so as to optimize the symptoms and provide support to these patients. Our findings in the study (Tables 4 and 5) show that the other validated fatigue tools such as PROMIS F-SF and MFSI SF global correlated well with FACIT-F scores in patients receiving ICIs. In the multivariate model, we did not find major independent predictors of FACIT-F fatigue score changes during ICI treatment, and more research is needed to better characterize the factors associated with CRF.

Management of fatigue due to immunotherapy

The NCCN guidelines on ICI suggest that patients experiencing CRF should be first evaluated for an underlying immune-related adverse event, such as hypothyroidism or endocrinopathy [38]. If no treatable underlying immune-related adverse event is found, clinicians may consider adding low-dose steroids for treatment of moderate CRF. If CRF

Table 4 Association between cancer-related fatigue severity and other symptoms at baseline and week twelve of immune-checkpoint inhibitors treatment

Assessments	FACIT fatigue subscale		Cancer-related clinically significant fatigue^	
	Baseline (*N* = 155)	**Week 12 (*N* = 35)**	**Baseline (*N* = 155)**	**Week 12 (*N* = 35)**
FACT-G total	−0.261**	−0.344*	0.230**	0.332*
Physical wellbeing	−0.844**	−0.794**	0.687**	0.540**
Social/family wellbeing	0.168*	0.157	−0.172*	−0.158
Emotional wellbeing	−0.367**	−0.607**	0.273**	0.515**
Functional wellbeing	0.559**	0.562**	−0.473**	−0.344*
HADS				
Anxiety	−0.421**	−0.529**	0.276**	0.555**
Depression	−0.750**	−0.666**	0.618**	0.671**
PROMIS F-SF	−0.815**	−0.811**	0.658**	0.645**
MFSI-SF global	−0.809**	−0.694**	0.675**	0.628**
ESAS				
Pain	−0.473**	−0.402*	0.357**	0.081
Fatigue	−0.812**	−0.805**	0.630**	0.723**
Nausea	−0.470**	−0.410*	0.455**	0.297
Depression	−0.375**	−0.459**	0.267**	0.395*
Anxiety	−0.337**	−0.552**	0.268**	0.451**
Drowsiness	−0.526**	−0.473**	0.401**	0.330
Appetite	−0.559**	−0.385*	0.505**	0.247
Wellbeing	−0.534**	−0.563**	0.480**	0.264
Dyspnea	−0.266**	−0.282	0.224**	0.154
Sleep	−0.400**	−0.391*	0.299**	0.299
Other symptoms				
Dry mouth	−0.334**	−0.464**	0.327**	0.315
Rash	−0.152	0.483**	0.101	−0.303
Diarrhea	−0.133	−0.184	0.018	0.138
Headache	−0.305**	−0.216	0.170	0.402*
Fever	−0.309**	−0.159	0.294**	−0.018
Joint pain	−0.319**	−0.261	0.166	0.152
Itchy	−0.255**	0.198	0.093	−0.217
Night sweats	−0.233**	−0.048	0.133	−0.055
Swelling	−0.260**	−0.198	0.191*	0.102
ESAS composite variables				
Physical distress‡	−0.794**	−0.858**	0.642**	0.595**
Psychological distress	−0.397**	−0.546**	0.294**	0.429*
Symptom distress§	−0.786**	−0.851**	0.646**	0.574**

FACIT-F Functional Assessment of Chronic Illness Therapy–Fatigue, *FACT-G* Functional Assessment of Cancer Therapy-General, *HADS* Hospital Anxiety Depression Scale, *PROMIS F-SF* Patient Reported Outcome Measurement Information System Fatigue-Short Form v1.0–Fatigue 7a (PROMIS F-SF), *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *ESAS* Edmonton Symptom Assessment Scale. ‡Sum scores of pain, fatigue, nausea, drowsiness, dyspnea, and appetite. ¶Sum scores of depression and anxiety. §Sum scores of pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, appetite, and feeling of wellbeing. Spearman's correlation test was used. *Correlation is significant at 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed). ^FACIT-F values equal to or lower than 34

is severe, however, withholding or discontinuing ICI treatment should be considered [38]. Short-term corticosteroid therapy may be helpful and would probably also suppress the cytokine-mediated mechanisms of ICI-related fatigue.

It is currently unclear how the results of QOL tools compare with the adverse events collected during randomized trials, however, at least baseline symptoms may be reported more commonly by patients than by clinician [38, 39].

Our study has several limitations. These include the study was conducted as a single cancer center, the lack of diversity in our study sample as our study mainly represented white and females, limited sample size, and lack of assessment

Table 5 Factors associated with clinically significant cancer-related fatigue in patients during treatment of immune-checkpoint inhibitors

Demographic and clinical factors		Unadjusted univariate[a]		Adjusted multivariable[a]	
Covariates		**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, years		0.98 (0.96, 1.01)	0.20	-	-
Gender	*Female vs. male*	2.83 (1.55, 5.19)	**< 0.001**	2.27 (0.76, 6.74)	0.14
Race	*Non-White or Caucasian^ vs. White or Caucasian*	0.52 (0.18, 1.54)	0.24	-	**-**
Cancer type	*Genitourinary vs. melanoma*	0.61 (0.29, 1.29)	0.20	-	-
	Others # vs. melanoma	1.52 (0.61, 3.82)	0.37	-	
Treatment combination*	*Two immunotherapy agents vs. one immunotherapy agent*	2.95 (1.41, 6.17)	**0.004**	3.05 (0.78, 11.95)	0.11
	Immunotherapy with other treatments vs. one immunotherapy agent	3.87 (1.83, 8.20)	**< 0.001**	2.16 (0.57, 8.20)	0.26
Immunotherapy cycles, cycles		0.85 (0.73, 0.98)	**0.03**	0.99 (0.59, 1.67)	0.98
Immunotherapy duration, days		0.99 (0.98, 1.00)	**0.02**	0.99 (0.97, 1.02)	0.61
Hemoglobin, g/dl		0.55 (0.35, 0.87)	**0.01**	-	-
PROMIS F-SF		1.41 (1.31, 1.52)	**< 0.001**	1.27 (1.14, 1.41)	**< 0.001**
MFSI-SF global		1.19 (1.14, 1.24)	**< 0.001**	1.13 (1.08, 1.19)	**< 0.001**
FACT-G total		1.07 (1.02, 1.12)	**0.004**	-	-
HADS anxiety		1.22 (1.12, 1.33)	**< 0.001**	-	-
HADS Depression		1.69 (1.38, 2.08)	**< 0.001**	-	-

^American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, and Hispanic. #Gastrointestinal, sarcoma, and thoracic. *One immunotherapy: avelumab, ipilmumab, nivolumab, and pembrolizumab. Two immunotherapy agents: ipilimumab and nivolumab. Immunotherapy with other treatments: pembrolizumab, chemotherapy; ipilimumab, nivolumab, surgery; nivolumab, radiation, ipilimumab, nivolumab, radiation; nivolumab, surgery; pembrolizumab, other therapy; atezolizumab, chemotherapy; atezolizumab, chemotherapy, other therapy; atezolizumab, chemotherapy, radiation; avelumab, surgery; ipilimumab, nivolumab, chemotherapy; ipilimumab, nivolumab, other therapy; ipilimumab, nivolumab, radiation, surgery; nivolumab, chemotherapy; nivolumab, chemotherapy, radiation, surgery; nivolumab, chemotherapy, target therapy; nivolumab, other therapy; nivolumab, radiation, surgery; nivolumab, radiation, target therapy; nivolumab, surgery, other therapy; pembrolizumab, chemotherapy, radiation; pembrolizumab, surgery; pembrolizumab, target therapy. *ORs* Odds ratios; *CI*: confidence intervals. Generalized estimating equations modeling were used. P values lower than 0.05 (bold) were considered as statistically significant. Significant cancer induced fatigue was defined as FACIT-F values equal to or lower than 34 PROMIS F-SF: Patient Reported Outcome Measurement Information System Fatigue-Short Form v1.0–Fatigue 7a (PROMIS F-SF). *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *FACT-G* Functional Assessment of Cancer Therapy-General, *HADS* Hospital Anxiety Depression Scale. a. Variables with significant *P* values and clinical significance from univariate modeling were included in the final multivariable generalized estimating equations model

of various markers associated with CRF such as thyroid function tests, inflammatory (neutrophil/ lymphocyte ratio, c-reactive proteins and cytokines) over the 12-week study period. The improvement in the CRF over 12 weeks of ICI treatment found in our study should be interpreted cautiously due to missing assessments. However, the analysis of baseline FACIT-F scores was similar in the dataset of patients who had missing assessments and in the cohort with complete cases. Further studies are needed to validate the findings of this study and to determine (a) whether there are any racial/ethnic variation in reporting of CRF related to ICIs, and (b) whether thyroid function tests and inflammatory markers are associated with CRF related to ICIs.

Conclusions

CRF is frequent prior to the initiation of ICI treatment. Over 12 weeks of ICI treatment, CRF significantly improved. FACT-G physical well-being, FACT-G emotional well-being, ESAS anxiety, and ESAS psychological distress scores also improved overtime. Further studies are needed to validate these finding.

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Declarations During the preparation of this work the authors have not used any AI or AI-assisted technologies.

Ethics approval The University of Texas MD Anderson Cancer Center Institutional Review Board approved the protocol in accordance with the Declaration of Helsinki, and all patients were provided written informed consent for participation of the study.

Competing interests Sriram Yennurajalingam, Pfizer (research funding for Cachexia study); Pfizer (Consultation for Cachexia study). The rest of the authors declare no conflict of interest.

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