Original Article

Cancer-Related Fatigue: Definitions and Clinical Subtypes

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Key Words

Cancer-related fatigue, definitions, case definitions, subtypes, genotypes, phenotypes, symptom clusters, cut scores

Abstract

Studies seeking to explain mechanisms associated with or causing fatigue are increasing; however, the underlying causes of fatigue remain largely unknown. Thus, identifying and predicting which patients may be at risk for developing fatigue, and tailoring interventions accordingly, are difficult. Whether fatigue experienced by patients with cancer can be classified into specific clinically significant subtypes would be useful to determine. These clinical subtypes might improve understanding of underlying mechanisms and help tailor treatment accordingly. This article refers to fatigue associated with cancer or its treatment as *cancer-related fatigue* (CRF). Given this broad designation, meant to encompass the array of causal mechanisms and treatment options, the authors recommend that meaningful clinical subtypes be articulated and differentiated. This article therefore reviews CRF definitions and proposes a nonexhaustive set of clinical subtypes that are intended to help sharpen thinking about causality and, ultimately, treatment recommendations. (*JNCCN* 2010;8:958–966)

Increasing attention is being given to exploring whether fatigue in patients with cancer experiencing similar symptoms can be classified or grouped into specific clinically significant subtypes. Various methods have been used to classify these patients according to subtype, including 1) definitional, 2) severity, 3) qualitative, 4) treatment-related, 5) disease-related, 6) symptom cluster, and 7) putative mechanisms.

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Definitional Subtypes

Subjective Perception and Impact on Functioning

How cancer-related fatigue (CRF) is defined can affect how specific subtypes are identified. The most commonly used definition is the one proposed by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Cancer-Related Fatigue (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). In these guidelines, CRF is defined as a distressing persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.[1] Both the subjective perception of CRF and its impact on function can be used to differentiate the clinical subtype of CRF from the usual sense of tiredness that healthy people experience.[2] Another characteristic, thought to distinguish the CRF subtype from the usual sense of tiredness but not included in the NCCN definition, is that CRF is not usually relieved by rest.[3]

Case Definitions

Consensus is emerging among clinicians and researchers regarding the need for development and use of a "case definition" for CRF. This case definition could better classify or subtype patients; enable comparisons across studies and populations;[4] identify clinically significant fatigue; and guide treatment planning.[5] No widely accepted case definition for CRF exists. In fact, more than one case definition for CRF may be needed to best capture and describe what constitutes clinically

significant fatigue in subgroups of patients who are undergoing active treatment, are disease-free and no longer receiving treatment (i.e., survivors), and have advanced disease or may be receiving palliative care.

Syndrome Criteria

In 1998, a group referred to as The Fatigue Coalition proposed the classification of patients with CRF into a specific clinical subtype that included a set of diagnostic criteria for the syndrome of CRF.[6] These consensus-based criteria were intended to differentiate clinically significant fatigue from increases in everyday tiredness. Prevalence rates (15%–30%) were far lower than expected when these criteria were used to classify CRF "cases."[2] Studies continue to evaluate the application of these CRF criteria in different cancer populations.[7–12]

Severity Subtypes

Severity Ratings

Clinicians often use severity ratings to decide whether a particular symptom is clinically significant and warrants treatment. Patients can be classified into severity subgroups according to their fatigue intensity ratings. The NCCN Guidelines on Cancer-Related Fatigue recommend that a simple 0 to 10 numeric rating scale (NRS) be used to assess CRF intensity during the past week (0 = no fatigue; 10 = worst fatigue you can imagine) in patients older than 12 years. Patients can be grouped by their severity responses into subtypes such as 0 = none; 1 to 3 = mild; 4 to 6 = moderate; and 7 to 10 = severe.[1,13–15] A CRF severity score of 4 or more can be used to indicate that further workup, referrals,[1] and treatment may be needed.[16] For children (7–12 years), a 1 (no fatigue) to 5 (worst fatigue) subtype assignment is recommended. For children aged 5 to 6 years, classification as tired or not tired is recommended.[1]

Cut Scores

Cut scores may vary according to how they are used to define a subgroup and by the CRF measure used. Based on a 0 to 10 CRF screening scale, one study identified a cut score of 5 as the optimal level for detecting cases of clinically significant fatigue defined by exceeding the established threshold for "caseness" on the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-F).[17] Other investigators have used a cut score of 2 or greater[16] or 4 or greater on a 0 to 10 NRS as eligibility criteria for entry into clinical studies.[14,15] One study documented that fatigue scores in cancer patients with and without anemia were significantly worse than fatigue scores found in the United States general population. A cut score of 43 or less on the FACIT-F (with lower scores representing worse fatigue) best distinguished the anemic cancer patients from those in the general population.[18] A cut score of 30 or less on the FACIT-F indicates clinically significant fatigue. Because this cut score is more than one standard deviation lower than the average fatigue score in the general population, it indicates a statistically and clinically significant score. A cut score of 12 or greater on the Fatigue Scale–Child effectively differentiated children who had high CRF from those who did not.[19] Reporting both average CRF severity scores and severity cut scores is recommended.[2] More studies are needed to validate CRF cut scores in other populations.[20]

Baseline Scores

Baseline CRF severity cut scores are predictive of severity scores over time in patients undergoing treatment.[21] It is important to assess CRF severity scores at baseline and to subgroup patients accordingly, because patients who have higher severity levels at baseline tend to experience higher severity scores over time.[1,22] Studies are needed to see if interventions targeted to those subtypes most at risk at baseline can break this severity pattern over time.

Interference-Based Scores

Because symptom severity may not always be linearly associated with the degree to which the symptom limits activity, assessment of both symptom severity and symptom limitations is recommended.[23] Because patients with cancer can respond differently when recording their level of fatigue on a simple 11-item NRS (0–10), anchoring a patient's fatigue severity score to its impact on activity may provide a useful indicator of clinical impact. Interference-based cut scores can be used to subtype patients into responder and nonresponder subgroups in intervention trials.[24] Given et al.[24] established fatigue interference–based severity cut scores for none, mild, moderate, and severe in patients with various tumor types undergoing chemotherapy.

In a subsequent longitudinal replication study, these investigators evaluated severity changes (0–10 NRS) in 16 symptoms, including fatigue with a

summed 4-item, 0 to 10 interference-based severity scale tailored to each symptom in patients with cancer (n = 589) undergoing chemotherapy.[16] These interference-based symptom severity cut scores were used to classify or subtype patients as responders or nonresponders and clearly differentiated moderate symptom severity levels from mild levels, and severe levels from moderate levels.[16] A shift of a patient's interference-based symptom severity score from severe to mild or from severe to moderate was considered to represent a clinically meaningful response.

Clinically Significant Scores

In CRF treatment trials, it is important to determine not only if a statistically significant change to an intervention occurs but also whether it constitutes a clinically meaningful change. Various methods have been used to determine clinically significant and meaningful changes to an intervention.[16,25,26] These have included calculating the percent of severity scores reduced by 20% to 50% over baseline scores; calculating difference scores based on patient reports of symptom relief attributed to a drug or procedure; observing a reduction of 2 or more points on a 10-point pain severity scale; and assigning patients who had more than a 30% reduction in mean of average and worse pain scores to a responder group.[16,27] In a range of studies, the minimum clinically important difference or change in score has tended to range from 0.3 to 0.5 standard deviation units.[25,26,28]

Qualitative Subtypes

Word Descriptors

The words that people use to describe their CRF experience and its behavioral impact can be culturally mediated, and may be useful in classifying fatigue experiences into unique and discrete subtypes. Qualitative studies in both adults and children have documented that the boundaries between descriptor subtypes may be somewhat fluid, because patients may describe shifting from one type of fatigue to another depending on their energy levels.[29,30] Tiredness, fatigue, and exhaustion subtypes are identified in adults,[29] and typical tiredness, treatment fatigue, and shutdown fatigue subtypes are reported in children and their parents.[30]

The words patients use to describe their fatigue experience and its impact can be used to differentiate disease-related fatigue subtypes, such as chronic fatigue syndrome, from CRF.[12] Different descriptor CRF subtypes are likely to be seen across the illness and treatment trajectories that require more study. Patients with advanced or incurable malignancies undergoing palliative care may use descriptors such as weakness more often to describe CRF experience.[31,32] These patients also may experience anorexia, weight loss, and loss of muscle mass, which can contribute to the sensation of weakness. In contrast, weakness may not be a common occurrence or CRF descriptor for patients in the earlier stages of disease.[2] More work is needed to analyze the words patients use to describe their fatigue experience to see if CRF descriptor subtypes can be identified to help tailor treatments accordingly.

Energy, Vigor, and Vitality

Lack of energy, vigor, or vitality may be synonymous with fatigue. In fact, energy is considered to be a core concept in CRF descriptions by parents and children with cancer.[30] Several adult studies have validated classifying breast cancer survivors as having significant fatigue when their scores on the SF-36 vitality subscale are below 50.[15,33–35] One study validated this vitality subscale score (< 50) against a cut score of 4 on the Piper Fatigue Scale total score to classify women as being fatigued.[15] In contrast, some authors caution that it may be premature to conclude that CRF, energy, vigor, and vitality are identical constructs that share the same meanings, because their individual effect sizes differed when they were measured in the same CRF intervention trial. More study is needed to clarify whether these distinctions matter in intervention trials and practice settings.[4]

Acute Fatigue

Although not well characterized, some patients with cancer describe a sudden and unexpected onset of acute fatigue. This rapid-onset fatigue can compel them to discontinue activities suddenly and can be accompanied with considerable distress. This phenomenon suggests that some patients are vulnerable to an acute CRF subtype.

Treatment-Related Subtypes

Some characteristic patterns of CRF that occur over time and are related to treatment can be used to identify CRF subtypes. Most of what is known about these

characteristic subtype patterns is derived from studies conducted in patients undergoing active treatment with chemotherapy and radiation therapy (RT). Less is known about specific fatigue subtype patterns that occur over time associated with other forms of treatment, and that occur during survivorship and palliative care.

Chemotherapy

In patients undergoing chemotherapy, 80% to 90% report CRF, and its prevalence rates and subtype patterns over time are thought to vary according to the specific chemotherapy agent, its route of administration, and the frequency and density of treatment cycles.[36] A "roller-coaster" subtype pattern of CRF over time is observed in women with early-stage breast cancer receiving 3- to 4-week chemotherapy cycles.[37] A recent study found that fatigue increased significantly over time, irrespective of the adjuvant chemotherapy regimen, from mild at baseline to moderate at treatments 4 and 8, and falling back to mild 30 days after the last chemotherapy treatment.[38] Subtype data conflict as to whether women with breast cancer experience more fatigue on dose–dense chemotherapy regimens versus dose–standard (21-day cycle) regimens[38] and at nadirs. Also not well known are the CRF subtype patterns that exist prediagnosis[22] and in patients receiving oral or targeted chemotherapy agents.[2]

RT

During RT, a different CRF subtype pattern is seen over time. Approximately 70% to 100% of patients experience a gradually increasing, cumulative pattern of CRF over time that peaks and plateaus, usually at 4 to 6 weeks, and gradually declines thereafter. Patients undergoing RT must be forewarned about the possibility that they will experience this pattern over time.[1]

Diurnal and Interindividual Variability Over Time

Limited information is available on CRF trajectories and predictors of CRF interindividual variability over time during RT,[39] chemotherapy, and other forms of cancer treatment. Miaskowski et al.[40] used hierarchical linear modeling (HLM) to determine how morning and evening fatigue levels diurnally changed over time in men with prostate cancer. Younger men with higher baseline (simulation) fatigue levels were at increased risk for higher levels of morning and evening fatigue over time. Younger age and higher baseline depression and sleep scores predicted higher evening fatigue scores over time, whereas higher baseline depression scores predicted higher morning fatigue scores at baseline and over time.

In a subsequent study using HLM, baseline (simulation) morning and evening fatigue levels were higher[41] in women undergoing RT for breast cancer than in men undergoing RT for prostate cancer.[40] Predictors of baseline evening fatigue in these women included having children at home and having higher depression scores. Women who were employed were at higher risk for higher evening fatigue levels over time. Predictors of higher baseline morning fatigue levels were younger age, higher levels of sleep disturbance, trait anxiety, and lower body mass index.[41] The authors concluded that HLM may be a useful statistical procedure to identify subgroups of patients who are at higher risk for CRF over time, and who may require different types of CRF interventions based on their baseline symptom severity and diurnal fatigue patterns.[40]

Disease-Related Subtypes

Advanced Cancer and Comorbidities

In one study, CRF was universally experienced in patients with advanced cancer who were referred to a palliative care service. CRF was associated with impairment in daily activities and poor quality of life.[42] One systematic review evaluated symptom prevalence in patients with incurable cancer. Increased levels of CRF were reported by patients with advanced malignancies[31] and in those with other illnesses or comorbidities.[43] Therefore, patients with advanced cancer in addition to other comorbidities may represent an at-risk CRF subtype. Increased CRF levels are also reported in other cancer patients and are associated with an increased number of comorbidities. The relationships among malignancies, specific types of comorbidities, such as diabetes, and CRF have not been well studied.[43,44]

Symptom Cluster Subtypes

Fatigue-Containing Symptom Clusters

Fatigue is rarely the only symptom a patient with cancer experiences. It often co-occurs with other symptoms such as pain, depression, and insomnia.[1,45–49] More study is warranted to determine if

subtypes can be defined when CRF occurs by itself or co-occurs with other symptoms. In one study that required eligible cancer outpatients to have fatigue or pain scores that were 4 or greater on a 0 to 10 NRS, more patients at study entry had fatigue alone (56.2%; n = 105), followed by pain and fatigue co-occurring (33.2%; n = 62), followed by pain alone (10.7%; n = 20).[14] Miaskowski et al.[28] documented 2 distinct subgroups, showing that for some patients with cancer, fatigue and pain can occur independently.

In addition, pain co-occurring with CRF may be more common in certain subgroups of patients. One study of patients (n = 841) aged 65 years or older diagnosed with breast, colon, lung, or prostate cancer found that women, patients with late-stage cancer, patients with lung cancer, or patients with 3 or more comorbidities were more likely to experience pain and fatigue concurrently.[43] In women who were survivors of early-stage breast cancer, the 3 strongest CRF correlates were pain, depressed mood, and sleep disturbance.[49] These and other studies have stimulated research to investigate whether clinical subtypes of CRF can be determined through identifying the symptoms with which CRF most commonly co-occurs or "clusters," and evaluating what effects these fatigue-containing symptom clusters or subtypes have on patient outcomes, such as functional status.[16]

Developmental Symptom Clusters

In one of the first studies to examine CRF symptom clusters in children and adolescents (age, 7–18 years) undergoing the same chemotherapy regimen,[50] CRF severity levels increased over time in adolescents and, when clustered with sleep disturbance over time, were a significant predictor of depression and behavioral change. In contrast, CRF did not increase over time or cluster with sleep disturbance in children (≤ 12 years), but children who had higher CRF levels had more depression and behavioral changes. Study findings, along with others,[51] suggest that unique age-related developmental subtypes of CRF may exist in children and adolescents.[50] These fatigue-containing symptom clusters or subtypes also may share a common underlying pathway or mechanism,[52–55] which would mean that treatment of one or more of these symptoms might beneficially affect the other symptoms.[1,56]

Consensus is emerging that a symptom cluster is defined as a grouping of at least 2 related co-occurring symptoms that are stable (reproducible) and independent of other groupings.[57] Because the relationships among co-occurring symptoms can be complex, multivariate statistical procedures are used to classify patients and their symptoms into subgroups based on empirical data.[45,58–64] Although some longitudinal studies have investigated how fatigue clusters with other symptoms at baseline, and how these symptom clusters may remain stable or change over time,[17,65–68] most symptom cluster studies have used cross-sectional designs[58] with heterogeneous samples to validate symptom inventories. Discussion of design issues related to symptom cluster research[64] and the types of multivariate statistical procedures and their indications can be found in published reviews[58,59,64] and specific studies.[63]

Patient Clusters

Statistical procedures such as cluster analysis also can be used to classify patients into specific subtypes who have similar symptom intensity profiles.[45] Miaskowski et al.[28] clustered outpatients undergoing active cancer treatment (n = 191) who were experiencing 4 common symptoms: fatigue, pain, insomnia, and depression. Patients were subtyped into 4 cluster subtypes: those who reported low levels of all 4 symptoms (35%), those who reported high levels of all 4 symptoms (15%), those who reported high levels of fatigue and low levels of pain (35%), and those who reported low levels of fatigue and high levels of pain (15%). This study was replicated cross-culturally in an Israeli group of cancer outpatients (n = 228) with similar patient subtypes classified.[68] These authors concluded that using cluster analyses to classify patients into low-, moderate-, and high-risk subgroups and then analyzing phenotypic or genetic determinants may help advance understanding about underlying fatigue mechanisms and the development of targeted symptom management techniques.[28,68]

Insomnia-like CRF is also a serious issue because it is associated with other symptoms during and after cancer treatment, such as CRF and pain. The co-occurrence of the symptom cluster of pain, fatigue, and insomnia in elderly patients was associated with an increased risk of death during the first year after diagnosis.[69] In another study, women survivors of breast cancer without evidence of disease who had insomnia could be subtyped into 3 groups based on their fatigue scores, measured by the 7-item Profile of Mood States Fatigue–Inertia subscale (POMS-F/I):

all high scores indicated exhausted (35%), all average scores indicated tired (41%), and all low scores indicated restored (24%).[70]

One study followed 76 women with newly diagnosed stage I to III breast cancer undergoing at least 4 cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy who had a symptom cluster that included sleep disturbance, fatigue, and depression.[71] Before the start of chemotherapy, these women were subdivided into 3 groups based on the frequency and number of symptoms (achieving symptom scores above the cut scores for standard fatigue, sleep, and depression scales). A symptom cluster index was computed for each group. Women, regardless of subgroup, experienced worse sleep, more fatigue, and more depression during treatment than at baseline. However, the baseline subgroup differences remained consistent over time. Thus, pretreatment baseline assessment of CRF and these other symptoms may identify at-risk subtypes for maintaining above-threshold severity ratings of symptoms over time during chemotherapy.[71] Future studies are needed to determine how these patient subtypes differ according to specific demographics, disease, treatment,[48,57] and underlying mechanisms.

Research into patient and symptom clusters including CRF is growing, and more work is needed to better define what constitutes a definable and reproducible symptom cluster. Associated questions relate to identifying relevant subgroups of patients, optimal statistical procedures to elucidate the phenomenon in a meaningful way, and how best to determine inter- and intraindividual variability over time.[57] It will take some time before the concept of grouping symptoms together with fatigue into definable and treatable symptom clusters or subtypes becomes a clinical reality.[45]

Putative Mechanism Subtypes

Although much speculation exists about biologic or molecular factors involved in CRF, the empirical data are limited. Experts have proposed that the interindividual variability in fatigue-severity patterns, at baseline and over time, might be attributable partly to differences in patients' abilities to respond to different stressors with changes in proinflammatory cytokines[72] that might be caused by specific genetic variations or cytokine gene polymorphisms.[35,73,74] In the future, patients with cancer experiencing CRF may be classified into specific subtypes based on specific genetic polymorphisms and genome-wide association studies.[74,75]

Phenotypes/Genotypes

Several molecular-genetic studies have examined genome-wide expression analyses[75] and single nucleotide polymorphisms (SNPs; gene variants) and their associations with CRF,[76] pain, depression, and insomnia phenotypes.[35,73] Several promising but preliminary studies suggest that an inflammatory process might be involved with the CRF phenotype.

One preliminary study performed genome-wide expression analyses on whole blood samples from breast cancer survivors classified as chronically fatigued 2 to 6 years after diagnosis (n = 49).[75] Nonfatigued survivors (n = 88) served as controls. Study findings suggest that the CRF phenotype in breast cancer survivors may be associated with 5 gene sets involved in plasma- and B-cell pathways, suggesting that a B-cell-mediated inflammatory process might underlie chronic fatigue in these women.[75] Other teams are suggesting that SNPs or gene variants in proinflammatory cytokine genes may be associated with the CRF phenotype. Polymorphisms in the promoter gene sequence of IL-1B may underpin specific CRF phenotypes in breast cancer survivors, even after controlling for demographic, biobehavioral, and treatment-related factors.[35]

In a study investigating SNPs over time in patients with breast, prostate, lung, or brain cancer undergoing RT and in their family caregivers,[73] an association among a functional promoter SNP in the tumor necrosis factor-ß gene was associated with morning fatigue and severity of sleep disturbance. If study findings can be replicated, future evidence may indicate treatments that are finally targeted to the specific underlying genetic variants and pathways producing the CRF phenotype.

Summary and Future Directions

CRF is a complex, multicausal, and multidimensional sensation.[77,78] Current evidence seems to suggest that determining baseline severity scores,[21,71] age-related descriptors in children and adolescents,[50,51] and impact on functioning[1] may offer some of the best methods to clinically subtype patients experiencing CRF who may also be at risk for higher CRF levels over time. Earlier intervention in pa-

tients who have moderate to high CRF cut scores at baseline must be studied.[71] In the future, it may be possible to subtype high-risk patients according to CRF severity, its associations and clustering with other symptoms, and its underlying genotypes and pathways.[79] Specific CRF interventions might then finally be able to be targeted with more precision to treat patients at most risk.

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