Original Article

Different Phenotyping Approaches Lead to Dissimilar Biologic Profiles in Men With Chronic Fatigue After Radiation Therapy

Li Rebekah Feng, PhD, Kristin Dickinson, PhD, RN, Neila Kline, BA, and Leorey N. Saligan, PhD, RN, CRNP, FAAN

National Institute of Nursing Research (L.R.F., K.D., L.N.S.), National Institutes of Health, Bethesda, Maryland; and Vassar College (N.K.), Poughkeepsie, New York, USA

Abstract

Context. Cancer-related fatigue (CRF) persists months after treatment completion. Although a CRF biomarker has not yet been identified, validated self-report questionnaires are used to define and phenotype CRF in the discovery of potential biomarkers.

Objectives. The purposes of this study are to identify CRF subjects using three well-known CRF phenotyping approaches using validated self-report questionnaires and to compare the biologic profiles that are associated with each CRF phenotype.

Methods. Fatigue in men with nonmetastatic prostate cancer receiving external beam radiation therapy was measured at baseline (T1), midpoint (T2), end point (T3), and one-year post–external beam radiation therapy (T4) using the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) and Patient Reported Outcomes Measurement Information System–Fatigue. Chronic fatigue (CF) and nonfatigue subjects were grouped based on three commonly used phenotyping approaches: 1) T4 FACT-F <43; 2) T1–T4 decline in FACT-F score ≥ 3 points; 3) T4 Patient Reported Outcomes Measurement Information System–Fatigue T-score >50. Differential gene expressions using whole-genome microarray analysis were compared in each of the phenotyping criterion.

Results. The study enrolled 43 men, where 34%–38% had CF based on the three phenotyping approaches. Distinct gene expression patterns were observed between CF and nonfatigue subjects in each of the three CRF phenotyping approaches: 1) Approach 1 had the largest number of differentially expressed genes and 2) Approaches 2 and 3 had 40 and 21 differentially expressed genes between the fatigue groups, respectively.

Conclusion. The variation in genetic profiles for CRF suggests that phenotypic profiling for CRF should be carefully considered because it directly influences biomarker discovery investigations. J Pain Symptom Manage 2016;■:■–■. © *2016 Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine.*

Key Words

Cancer-related fatigue, radiation therapy, prostate cancer, transcriptome profiles, fatigue phenotypes

Introduction

Cancer-related fatigue (CRF) is often the most commonly reported distressing side effect of cancer and cancer therapy, affecting anywhere from 50% to 90% of oncology patients.[1] CRF negatively reduces health-related quality of life and increases mortality among cancer patients.[2] The management of CRF is challenging for health care clinicians because the concept is poorly defined and its etiology is unknown.

Efforts to understand the etiology of CRF remain challenging because the CRF phenotype has not been well characterized. This lack of a

Address correspondence to: Leorey N. Saligan, PhD, RN, CRNP, FAAN, National Institute of Nursing Research, National Institutes of Health, 9000 Rockville Pike, Building 3, Room 5E14, Bethesda, MD 20892, USA. E-mail: saliganl@mail.nih.gov

Accepted for publication: July 29, 2016.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2016.07.007

well-characterized CRF phenotype stems from the lack of a consistent definition and a standard phenotyping approach.[3] In a recent review of 47 articles exploring the biology of CRF, the lack of consensus among researchers in defining CRF was confirmed because CRF was measured using multiple approaches.[3] Although most researchers operationally defined CRF using a variety of multi-item and single-item self-report questionnaires, a number defined CRF using clinical guidelines (e.g., National Cancer Institute Common Toxicity Criteria) or conducting diagnostic clinical interviews. Furthermore, studies in these reviewed articles used various scoring rubrics and cutoff scores to determine the presence or absence of CRF when attempting to phenotype CRF for biomarker discovery.[3] This lack of consistency and consensus in defining CRF and in characterizing the CRF phenotype creates confusion among researchers who are trying to advance the science of CRF to understand its biologic underpinnings. To advance our science in CRF, the authors would like to refocus the conversation on the need for a clear, well-defined CRF phenotype by presenting three commonly used CRF phenotyping approaches and highlighting the strengths of each phenotyping approach, with the hope of provoking further discussion on the issue.

A clear, well-defined phenotyping approach has been successful with other symptoms, notably pain and depression. For example, a well-characterized pain phenotype led to the development of better therapeutic strategies using effective antinociceptive therapies.[4,5] Moreover, a well-described phenotype for depression led to the inclusion of new depressive disorder classifications in the Diagnostic and Statistical Manual, fifth edition and an array of effective personalized and targeted treatments.[6] A well-characterized CRF phenotype is an essential step in the process of identifying biologically relevant therapeutic targets and developing precise and effective personalized management. Therefore, the purposes of this study are to identify subjects with persistent fatigue after cancer therapy. Considering that there is no gold standard approach to phenotype CRF, we used three well-known CRF phenotyping approaches using validated self-report questionnaires to categorize subjects with persistent fatigue and compared the biologic profiles that are associated with each phenotyping approach. Instead of identifying specific genes associated with CRF, the main goal of the study was to demonstrate that different approaches to phenotype CRF are associated with different transcriptome profiles. In addition, we aimed to determine biological pathways associated with these distinct transcriptome profiles generated by different phenotyping approaches.

Methods

Subjects

Men with nonmetastatic prostate cancer, who were receiving androgen deprivation therapy and scheduled to receive external beam radiation therapy (EBRT), were enrolled under a National Institutes of Health (NIH) institutional review board–approved study (NCT00852111). Patients were enrolled from the radiation oncology clinic of the Hatfield Clinical Research Center, NIH, Bethesda, Maryland, from May 2009 to December 2010. Fatigue was measured and blood was drawn at four time points: baseline or before EBRT (T1), midpoint (T2), end point (T3), and one-year post-EBRT (T4). Subjects were excluded from the study if they had progressive disease causing significant fatigue; experienced major psychiatric illness within five years; had uncorrected hypothyroidism or anemia; took sedatives, steroids, or nonsteroidal anti-inflammatory agents; or had a second malignancy. After obtaining informed consent, demographic information and medical history were obtained by patient interview and medical records review.

Fatigue Questionnaires

Fatigue was measured by the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale and the Patient Reported Outcomes Measurement Information System–Fatigue (PROMIS-F) subscale. FACT-F is a 13-item measure with scores that range from 0 to 4 for each item (0 = the worst; 4 = the best) with 52 as the maximum possible score. The lower the FACT-F score, the higher the fatigue intensity.[7] FACT-F has good test-retest reliability ($r = 0.90$) and internal consistency reliability ($\alpha = 0.93$ and 0.95) on initial and test-retest administration, suggesting that it can be administered as an independent, unidimensional measure of fatigue; it has been used extensively in individuals with cancer.[7] In addition, a FACT-F score of 43 best divides fatigue scores of cancer patients and the general population.[8] PROMIS-F is a seven-item questionnaire that was developed from more than 1000 data sets from multiple disease populations including cancer, heart disease, rheumatoid and osteoarthritis, psychiatric conditions, spinal cord injury, and chronic obstructive pulmonary disease. Initial testing of psychometric properties showed an internal consistency reliability coefficient of 0.81.[9] The PROMIS measures are reported on a T-score metric that is anchored to the mean score of a healthy American general population.[10] The T-score metric has a mean of 50 and an SD of 10, which improves the interpretability of scores.[11] A higher PROMIS T-score represents more of the concept being measured or greater fatigue. We selected to use both FACT-F and PROMIS-F because