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Doc, I Feel Tired … Oh Really, So How's Your Mucositis?

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Precis:

Cancer-related fatigue is common in head and neck cancer patients. This complex, multidimensional patient-reported outcome has quality of life and cancer treatment implications.

Lay Summary:

Cancer-related fatigue is common in head and neck cancer patients. This complex, multidimensional patient-reported outcome has quality of life and cancer treatment implications.

Keywords

Head and neck cancer; Cancer-related fatigue; Inflammation; Radiation therapy; Cisplatin chemotherapy

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The very first step towards success in any occupation is to become interested in it. - William Osler, *Aequanimitas, With Other Addresses to Medical Students, Nurses and Practitioners of Medicine*. Chapter XVIII. The Master-Word in Medicine. 1914:376.

For the past 40 years,[1] cancer-related fatigue (CRF) has been the subject of intense but sequestered investigation. CRF is commonly 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 interferes with usual functioning".[2] Excess CRF is known to occur in virtually all head and neck cancer (HNC) patients receiving chemoradiation[3] and half of these patients have sustained elevations in fatigue as long as two years later.[4] CRF has significant impacts in terms of lost productivity, lost days from work, and decreased quality of life (QOL).[5] In addition, CRF may be associated with decreased survival.[6] However, despite its high prevalence rate and negative effects on patients and society,[5] limited progress has been made in clinical assessment and treatment.

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In the day-to-day whirlwind of clinical oncology practice, the assessment of CRF is not often perceived as a priority, particularly among HNC patients. Patients' frequent reporting of this symptom is simply lost in the busy shuffle of handling HNC patients' many other severe and complex medical problems. The reasons for this lack of attention are likely multifactorial. They may include a de-prioritization of what is perceived as a primarily subjective concern, a generally poor medical and clinical understanding of CRF in the oncology community, a lack of training in standardized assessment or treatment options for CRF, or a perception that CRF has little meaningful bearing on patients' oncologic outcomes. Additionally, a comprehensive treatment plan for CRF may require multidimensional assessment and multiple routes of intervention, with no rapidly delivered "magic bullet." For these reasons, CRF has been called "the forgotten symptom" in oncology.[7]

It is fair to say that the underlying mechanisms for CRF remain under investigation.[8] The most commonly cited of these include interacting alterations in: immune function or inflammation, energy metabolism, neurotransmission, anemia, and circadian rhythm. Variations in genotype, gene expression levels, and methylation patterns related to inflammatory mechanisms are associated with CRF severity in patients treated with chemotherapy and radiation.[5] However, the lack of a clinically applicable risk prediction model is a barrier hindering any impetus to develop more effective management procedures.[9] A widely accepted and accurate risk prediction model could assist clinicians in identifying high risk patients who could be targeted for interventions to prevent or reduce CRF.

The study by Xiao et al. in this issue provides a clinically accessible demonstration of the importance of assessing and treating CRF in the context of treating HNC. This research maps out the relative contributions of chemotherapy and/or radiation to CRF and CRF's associations with elevated measures of epigenetic aging and chronic inflammation in this specific population of HNC patients. The direct application to HNC patients being treated with curative intent makes clear the physiologic significance and health consequences of this often-neglected patient-reported outcome. These findings could be the basis for a renewed communication around this issue that is very important to patients' quality of life and may also affect their cancer treatment outcomes.

Xiao et al. assessed 133 HNC patients receiving curative-intent radiation therapy, 80% of whom also received concurrent chemotherapy, mostly cisplatin. DNA methylation was used to estimate epigenetic age (predominantly although not exclusively employing the DNAmPhenoAge method). This epigenetic age was compared to patients' chronologic age at four timepoints: before radiotherapy, at the end of radiotherapy, and 6 and 12 months after finishing radiotherapy. As complementary assessments, the Multidimensional Fatigue Inventory was used to record patients' self-reported fatigue at these same time points, and inflammatory cytokines and cytokine receptors were measured before and after radiotherapy and at 12 months later.

Half of the patients experienced severe fatigue at some point during the study period. Other major findings, in models accounting for patient and disease covariates, were that

epigenetic age acceleration (EAA) changes over time of about 4.9 years occurred at the end of radiotherapy. Post hoc analysis found that increased changes in EAA at this timepoint were significant among those receiving chemotherapy and were not significant among those who did not have chemotherapy. Effects at one year, suggestive but not statistically significant, pointed toward a continued higher change in EAA of 2.54 years among the patients who had received cisplatin as compared to those who received carboplatin and paclitaxel. Furthermore, those patients who reported severe fatigue had higher changes in EAA by 3.1 years than those who did not, and at 12 months, among these severely fatigued patients, EAA change was 5.63 years higher in those with human papillomavirus (HPV)-negative cancers. Finally, elevated inflammatory cytokines (e.g., CRP, Il-6, IL-1ra, IL-10, and sTNFR2) were associated with higher levels of EAA changes, and high CRP or IL-6 put patients at a higher risk for EAA changes of 4.6 to 5.9 years at completion of radiotherapy as compared to patients with low CRP or IL-6 with a continuing EAA effect at 1 year. Models adjusting for CRP, IL-6, and IL-1ra removed the effect of EAA on fatigue, but the inflammatory factors themselves remained associated with fatigue. In additional modeling EAA was found to mediate fatigue through CRP, IL-6, and IL-1ra separately.

The association of EAA with an HPV-negative tumor status is intriguing and for many experienced HNC clinicians, feels like a recognizable phenomenon. Why would HPV status have a relationship to EAA or CRF? One possibility is the concept of a chronically proinflammatory state, which may reflect a fundamental biology and could even be causally related to the development of aggressive HNC.[10] Conversely, it could be also possible that addressing aspects of the cytokine signaling cascades associated with nonresponsiveness to radiation and/or chemotherapy could be both oncologically effective and work against a dysfunctionally inflammatory background.[11] If validated, this would be an exciting new strategic direction for HPV-negative HNC patients, whose cancer outcomes and quality of life remain significantly inferior to those of HPV-positive patients.

Progress in the assessment of CRF will be challenging due to the heterogeneity of instruments.[12] For example, in a recent systematic review of unidimensional and multidimensional scales used to assess CRF,[12] 25 different instruments were evaluated. Future research could focus on the development of a “universally-defined tool kit for the assessment of CRF [which] may help to clarify the concept of fatigue and promote a systematic approach to fatigue measurement.”[12] Smaller item lists could be used to assess CRF in the clinic. For instance, findings of a recent study using machine learning approaches to develop predictive models of CRF severity suggest that oncology clinicians can ask patients two simple questions focused on the words ‘exhaustion’ and ‘worn-out’ to better predict patients’ evening CRF severity across cycles of chemotherapy.[13]

In addition, future research could more comprehensively evaluate the molecular mechanisms associated with CRF severity. CRF occurs as a result of complex interactions among a patient’s demographic and molecular characteristics, environmental influences, and disease and treatment states. Given this complexity, the application of a variety of omics approaches (e.g., genomics, epigenomics, transcriptomics, proteomics, metabolomics) could increase understanding of the molecular mechanisms that underlie CRF.[14, 15] To date, studies of associations between CRF and molecular mechanisms have focused on a single

type of omics data in their analysis. Although useful, these studies are limited by the characteristic of the biological material under scrutiny. By evaluating for multiple molecular characteristics simultaneously (e.g., using a data-integrated multi-omics approach[15]) and incorporating these data with in-depth clinical characterizations, a systems biology approach might offer a more comprehensive picture of CRF.[15, 16]

In the meanwhile, what can clinicians do? Although much effort has been expended in developing nonpharmacologic and pharmacologic interventions for CRF, current treatments have limited efficacy. In part, this may be due to the complicated etiology of CRF. Best practices advise that potentially contributing factors should first be addressed, such as anemia, pain, excess opioid or medication loads, emotional distress or depression, sleep disturbance, nutritional and fluid deficits, infection, and endocrinopathies or other unaddressed medical conditions.[17] Once this type of overall approach to CRF has been organized, then the treatments that have shown the most consistent efficacy among HNC and cancer patients are exercise programs,[1819] with only uncertain benefits attributable to psychological interventions[20] or integrative approaches.[21] In regards to HNC patients receiving radiation therapy, specific distributions of the radiation doses may predispose to CRF, especially when directed towards neural tissues (e.g., brain and brainstem).[222324] Increasingly conformal radiation technologies such as particle therapies appear to be capable of reducing neural tissue doses but require more testing for evidence of benefit in specific clinical scenarios.[25]

In a separate recent publication, this group of authors has provided additional analyses demonstrating an association of EAA with overall survival in these HNC patients.[26] Although an assessment of CRF was not included in this analysis, HPV-negative status, comorbidities, severe symptom clusters, and body mass index were each associated with increased changes in EAA. Also, a dose-dependent effect was seen in association with smoking, with reduced change in EAA associated with a greater number of years since smoking cessation. It is logical that in addition to CRF, other modifiable causes of EAA should be addressed, if the ultimate goal is to mitigate the effects of aging and increase survival in our cancer patients. Activity modification, smoking cessation, and prevention or mitigation of severe treatment-related symptoms are highly commonsensical measures that should be part of the standard of care and have positive health effects on multiple levels.

In summary, CRF is an underrecognized problem that may play an important role in influencing patients' treatment outcomes as well as their experiences and QOL. Developing useable, efficient, systematized assessments of CRF should be prioritized as this would lead to increased clinical familiarity and a stronger foundation for developing and implementing effective treatment algorithms for patients at high risk. Furthermore, the weight of the evidence seems to indicate that CRF is not just an ancillary symptom but a meaningful physiologic phenomenon reflecting a dangerous biology at work in these patients. Could a chronic inflammatory state that predisposes to the fatigue and premature aging we so often see in our HNC patients also be a contributing cause of their poor outcomes? If there are possibilities that we might be able to combine advances in oncologic aims with improving the overall health and quality of life of our patients who are at highest risk in all of these domains, these deserve concentrated and serious exploration. It is possible that fatigue has

been a hidden biomarker that, as Osler said, if we would only become interested in it, would be the first step towards success.

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