Symptom Biomarkers for Children Receiving Treatment for Cancer: State of the Science

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Abstract

The Children's Oncology Group Nursing Discipline has identified the most concerning symptoms during childhood cancer treatment and the need for continued symptom assessment and intervention during treatment trajectory. To develop appropriate interventions, symptom science strategies must explore the biological mechanisms associated with symptoms of cancer and cancer treatment. To explore the associated biological mechanisms, biomarkers have been recommended for inclusion in symptom science studies, when applicable. The biomarker assessed, as well as the method of collection and storage, can affect the reliability and validity of the study results and clinical implication. This review will describe biomarkers that have been described in pediatric oncology symptom science research and provides special considerations for specimen collection and processing.

Keywords

bimarkers, oxidative stress, cytokines, cortisol

Symptom assessment and management is a priority in pediatric cancer nursing and nursing science and is foundational to the work of the Children's Oncology Group (COG) Nursing Discipline, which has focused its research aims on key knowledge gaps that include understanding illness-related distress (Landier, Leonard, & Ruccione, 2013). In October 2018, a State of the Science Symposium, "Symptom Assessment During Childhood Cancer Treatment" (R13CA232442 Rodgers/Hockenberry), was convened by the COG Nursing Discipline to develop expert consensus regarding the major symptoms experienced during childhood cancer treatment, to explore what is known about the appropriate observational and biological measures to assess these symptoms, and to identify the key strategies necessary for consistent symptom assessment throughout the illness trajectory.

The symptoms of pain, nausea and vomiting, fatigue, sleep disturbance, and sadness have been identified by the COG Nursing Discipline as contributing to symptom distress for patients with pediatric cancer. Here, we summarize the evidence presented at the October 2018 State of the Science Symposium regarding what is known about the biological mechanism driving symptoms, and specific biomarkers that have been found to be associated with these symptoms.

Background

Biomarkers are utilized in health care to objectively measure and evaluate normal biological processes, pathogenic

processes, and pharmacologic responses (Biomarkers Definition Working Group, 2001). In cancer care, biomarkers are used to determine the appropriate treatment, measure the efficacy of cancer treatment, as well as identify markers of symptoms. For example, α fetoprotein and human chorionic gonadotropin are biomarkers for germ cell tumors, while minimal residual disease is a biomarker for tumor burden quantification. Other examples of biomarkers include pulse and blood pressure, as well as biomarkers of inflammation and stress measured in biological samples (e.g., blood, urine, saliva, hair).

Many of the symptoms experienced during cancer therapy are related to the activation of innate immune inflammatory processes and dysregulation of neuroendocrine pathways (Cleeland et al., 2003; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Reyes-Gibby et al., 2008). An understanding of the relevant biomarkers associated with inflammation and neuroendocrine dysfunction may assist in identifying patients at greatest risk for severe symptoms and poorer health-related quality of life. Along with identifying those at greatest risk, biomarkers may be

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Table 1. Biomarkers of Oxidative Stress Described in Pediatric Cancer.

Biomarker	Symptom
3-nitro-tyrosine (3NT) ^a	<ul style="list-style-type: none"> • Nitrosative stress marker • Increased in response to toxicants and inflammation resulting in symptoms of fatigue, depression, pain, muscle aches, memory, and concentration impairment.
F2 isoprostane ^b	<ul style="list-style-type: none"> • Higher CSF levels of 3NT were associated with higher fatigue early in treatment. • Prostaglandin-like compounds formed from peroxidation of arachidonic acid. • CSF levels of F2-IsoP were higher in children receiving more than six doses of intrathecal methotrexate.
Oxidized Phosphatidylcholine (PC) ^c	<ul style="list-style-type: none"> • May contribute to neurocognitive function. • Predominant glycerophospholipid in the brain and cell membranes. • CSF levels of PC were higher in children reporting more frequent and severe symptoms.
Glutathione (GSH) ^d	<ul style="list-style-type: none"> • Antioxidant
Reduced/oxidized glutathione ratio (GSH/GSSG) ^d	<ul style="list-style-type: none"> • Antioxidant • Low CSF levels demonstrated oxidative stress, with low ratios associated with fatigue early in treatment.

Note. CSF = cerebrospinal fluid.

^aHockenberry et al. (2018). ^bHockenberry et al. (2014). ^cHockenberry et al. (2014). ^dRodgers et al. (2016).

used to monitor the efficacy of symptom interventions. The purpose of this article is to review biomarkers including oxidative stress, cytokines, melatonin, and cortisol that have been associated with symptoms of pain, nausea, fatigue, sleep disturbance, and sadness. These symptoms have been identified by the COG Nursing Discipline as most bothersome for children with cancer during treatment and into survivorship. Along with describing the biomarker and symptom association, the article will describe methods for biomarker collection.

Biomarkers

Oxidative Stress

Measuring oxidative stress has increasingly become more common in research, as the clinical implications of this biomarker have been established. Oxidative stress occurs when there is an imbalance between oxidants and antioxidants, with greater oxidants leading to disruption of the redox signaling process and resulting in molecular damage (Sies, Berndt, & Jones, 2017). Under oxidative stress, reactive nitrosative species (RNS) and reactive oxygen species (ROS) damage cellular biomolecules, including lipids, sugars, proteins, and polynucleotides (Roberts et al., 2010). RNS/ROS are produced as byproducts of cellular metabolism and at low levels function in cell signaling and serve as a line of defense against environmental attacks. In the presence of cancer or cancer treatment, RNS/ROS are produced at higher levels (Moloney & Cotter, 2018). Normally, the balance between production and destruction of RNS/ROS is governed by antioxidants and enzymes. An imbalance of oxidative stress can cause damage to DNA and RNA, producing alterations in cell signaling, and triggering cell apoptosis (Frijhoff et al., 2015).

Oxidative stress has been implicated in multiple pathophysiological processes associated with aging and chronic diseases such as cardiovascular disease (Sack, Fyhrquist, Saijonmaa, Fuster, & Kovacic, 2017), diabetes (Rehman & Akash, 2017), and obesity (Manna & Jain, 2015); as well as in fatigue, depression, pain, memory, and concentration (Maes, 2011). In pediatric oncology, higher levels of oxidative stress have been associated with the presence and severity of patient-reported fatigue (Hockenberry et al., 2018; Hockenberry, Taylor, Gundy, et al., 2014; Hockenberry, Taylor, Pasvogel, et al., 2014; Rodgers et al., 2016).

Multiple methods exist for measuring oxidative stress (Marrocco, Altieri, & Peluso, 2017), and because of the instability of oxygen species, it is difficult to measure oxidative stress directly. This issue can be overcome by measuring oxidative stress indirectly through molecular damage caused by RNS/ROS, such as the byproducts of damaged lipids, nucleic acids, or other cell targets. Table 1 describes biomarkers of oxidative stress measured in patients with pediatric cancer (Hockenberry et al., 2018; Hockenberry, Taylor, Gundy, et al., 2014; Hockenberry, Taylor, Pasvogel, et al., 2014; Rodgers et al., 2016). Enzyme-linked immunosorbent assay methods are commercially available for oxidative stress biomarkers, although they are generally considered less accurate than measurements performed through gas chromatography-mass spectrometry (Frijhoff et al., 2015).

The selection of a measurement method for oxidative stress will determine how the specimens should be collected and processed. Some protocols for oxidative stress biomarkers mandate minimal time between specimen collection, processing, and freezer storage. These types of issues should be carefully considered when specimens are collected in a setting that is physically distant from a

lab. When collecting urine for biomarker measurements, it is common to quantify urine creatinine levels, during processing, in order to standardize the dilution of the samples (Barr et al., 2005).

Cytokines

Cytokines are another category of biomarkers often explored in oncology-related symptom research due to their association with immune system response and inflammation (Lippitz, 2013). Cytokines is a broad term, which encompasses interleukins, interferons, tumor necrosis factors, adipokines, chemokines, and mesenchymal growth factors (Dinarello, 2007).

It is important to note that there is currently conflicting evidence related to specific cytokines and associated diseases or symptoms. However, cytokines are included in research related to cancer development, cancer metastasis, prognostication, and symptom science. Related symptoms include pain, fatigue, cognition, depression, and sleep, with associated cytokines, including interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), and IL-10. In adult oncology, these selected biomarkers have relevance to symptoms experienced during cancer therapy. IL-6 has been linked to cancer-related fatigue and depression (Barsevick et al., 2010; Jehn et al., 2015; Saligan et al., 2015). Proinflammatory cytokines, such as TNF- α , have also been linked with major depression (Ma, Zhang, & Baloch, 2016). IL-1 β is another proinflammatory cytokine that is instrumental in immune system response to infection, cell signaling, and inflammation. In contrast, IL-10 is an anti-inflammatory cytokine that serves to keep inflammation in check by inhibiting the expression of proinflammatory cytokines, such as TNF- α or IL-1 β . Limited research has been conducted in children, especially children with cancer, to explore specific cytokines associated with patient symptoms. Among children and adolescents with acute lymphoblastic leukemia, the IL-6 and TNF genotype has been found associated with sleep disruption. The IL-6 promoter (-174G>C) C allele was associated with fewer sleep minutes, and patients with the TNF (-308G>A) genotype AA had more minutes of wake after sleep onset and a 5% lower sleep efficiency rate than their GA genotype counterparts (Vallance et al., 2011).

The wide variability in results of cytokine and associated symptoms may be due, in part, to inconsistent sample collection and processing. Biomarker development overall has been hindered by variability in pre-analytical methods (Agrawal, Engel, Greytak, & Moore, 2018). To facilitate reliable and valid associated cytokine biomarkers and symptoms, special consideration should be undertaken during study planning and implementation. For example, the necessary infrastructure must be in place for

sample processing, storage, and assays. Informed decisions should be made upfront related to the biomarker of interest and the planned assay, as this helps determine the appropriate specimen type (whole blood, plasma, and/or serum). The type of blood specimen analyzed, collection method (in tubes with or without anticoagulants), and time of day collected may affect cytokine levels (Biancotto, Feng, Langweiler, Young, & McCoy, 2012). If whole blood is collected, cytokine analysis is improved by storing the samples at 4°C and/or rapid processing of the specimens after collection (Thavasu, Longhurst, Joel, Slevin, & Balkwill, 1992). Prior to freezer storage, samples should be aliquotted in small volumes to minimize the number of times that samples are later thawed and refrozen (known as “freeze–thaw”), as repeated freeze–thaw cycles can lead to interassay variability. The length of time that cytokine samples are stored at –80°C can also affect findings. Some frozen cytokine specimens exhibit degradation within 1 year, while others have been shown to remain stable for 3 years (de Jager, Bourcier, Rijkers, Prakken, & Seyfert-Margolis, 2009). Last, it is important to consider available expertise for processing samples. Core lab facilities, if available, may provide a standardized platform for specimen processing. It is also recommended that medications be considered when planning cytokine collection, as some medications (i.e., glucocorticoids, opioids) may modulate cytokine levels (Brattsand & Linden, 1996).

Melatonin

Melatonin is a neuromodulator with synthesis in the pineal gland and, to a lesser extent, all mitochondria containing cells in the body. As a biomarker, inadequate or absent melatonin secretion may be associated with disruptions in circadian rhythm and the sleep–wake cycle. Melatonin is regulated by the central circadian pacemaker (biological clock) in the suprachiasmatic nuclei of the anterior hypothalamus. Environmental light controls melatonin synthesis, as light perceived by the retina is transmitted to the retinohypothalamic tract to the suprachiasmatic nuclei, which conveys the signal via the dorsomedial hypothalamic nucleus; the upper thoracic cell columns of the spinal cord, the superior cervical ganglia, and the postganglionic adrenergic fibers innervate the pineal gland (Korf, 1999; Korf, Schomerus, & Stehle, 1998). This illustrates the importance of intact light perception and spinal cord integrity for melatonin synthesis. Therefore, patients with loss of vision, with spinal cord injury/tumor, or with central nervous system tumors involving the hypothalamic–pituitary axis are at risk for inadequate melatonin secretion and disorders of the sleep–wake cycle and circadian rhythm disorders. Melatonin also produces adaptive changes in reproduction, immune response, energy

balance, and behavior (Carrillo-Vico et al., 2006; Lewy, Emens, Jackman, & Yuhas, 2006). Additionally, there is evidence that melatonin can counteract the effects of reactive oxygen and nitrogen species and may be neuroprotective (Reiter, Tan, Manchester, & Tamura, 2007).

Pineal gland secretion and rise in melatonin occurs 2 hours prior to habitual bedtime and is referred to as dim light melatonin onset. Melatonin is released into the cerebrospinal fluid and circulation, exerting biological actions on melatonin receptor target tissues. Once melatonin is released into circulation, levels can be assessed through examination of blood, urine, and saliva. Melatonin continues to rise within the biological night and declines to pre-dim light melatonin onset near habitual wake time.

Urine and salivary assessment of melatonin are most feasible, with blood sampling costly and a burden to the research participant. To assess melatonin, a urine sample is collected after the first morning void and a 5-mL sample is transferred to a date- and time-labeled vial for storage in the freezer. This is repeated with each void over 48 hours. (Bojkowski, Arendt, Shih, & Markey, 1987). Serum melatonin levels are 10 times higher than those in saliva; however, salivary melatonin has the advantage of being less invasive to collect (Benloucif et al., 2008). While there is no consensus on the best method for collecting salivary melatonin, in-home collection has been found to be acceptable and feasible in children and adolescents (Mandrell et al., 2018).

Cortisol

Cortisol, a glucocorticoid, is frequently used in psychobiological studies as a biological marker of stress, aging, anxiety, depression, and circadian rhythm. Cortisol is the most important glucocorticoid and is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. When stimulated, the hypothalamus secretes corticotrophin-releasing hormone (CRH), triggering pituitary secretion of adrenocorticotrophic hormone (ACTH), and then stimulating the adrenal gland cortex for secretion of cortisol. The HPA axis is regulated via negative feedback, with high cortisol levels suppressing the secretion of CRH and ACTH. Any dysregulation of the HPA axis will subsequently disrupt cortisol secretion. Cortisol circulates both unbound and bound to corticosteroid-binding globulin and albumin, with a half-life of 80 minutes. Serum cortisol is a total measurement of both bound and unbound cortisol.

As a master hormone, cortisol regulates the 24-hour physiological function around the light/dark cycle. On awakening, light stimulates the suprachiasmatic nucleus (circadian pacemaker), which begins the upregulation of CRH, ACTH, and then cortisol. The highest cortisol secretion occurs with the cortisol awakening response, increasing cortisol in circulation by 20% to 100% and

peaking within 30 to 45 minutes (Pruessner et al., 1997). After peaking, cortisol declines throughout the day and reaches the lowest level at early sleep onset, thus providing a circadian signal to downstream physiological function. Thus, cortisol may be altered with fatigue and sleep disturbance.

Cortisol as a biomarker can be collected from blood, urine, saliva, and hair. Measurement of cortisol in blood, urine, and saliva can assist in establishing the diurnal profile of cortisol and variability of diurnal cortisol patterns in disease (Wosu, Valdimarsdottir, Shields, Williams, & Williams, 2013), with a single sample only informing of short-term cortisol concentrations. Additionally, the cortisol measurement may be affected by factors specific to the time of collection (Adam, Hawkley, Kudielka, & Cacioppo, 2006). Numerous disadvantages are described in the measurement of cortisol in blood, urine, and saliva. The most significant disadvantage is invasive collection, time-consuming collection procedures, and the necessity of numerous samples to be collected per day over several days in establishing chronic cortisol measurements. Repeated measures are expensive and burdensome to the participants, resulting in risk for incomplete sampling and loss of participants (Wosu et al., 2013).

While blood, urine, and saliva measure acute or short-term activity of the HPA axis, hair reflects chronic or long-term activity (Russell, Koren, Rieder, & Van Uum, 2012). Scalp hair cortisol is relatively easy and less expensive to collect as compared with blood, urine, and saliva. The hair sample is best taken from the posterior vertex and cut closely at the scalp. The posterior vertex is preferred, as this region has less cortisol variability than other scalp areas (Cooper, Kronstrand, & Kintz, 2012). Hair grows approximately 1 cm per month; therefore, 1 cm of hair, measured from the end closest to the scalp, is proxy for HPA axis activity from the previous month. The typical hair sample is 3 centimeters and is proxy for HPA axis activity from the previous 3 months. Another advantage of hair is cost, with the cost of blood, urine, and saliva cortisol averaging \$20.00 dollars per sample, with multiple samples costing hundreds of dollars per day. The estimated cost for hair cortisol is less than \$50.00, with only one sample needed (Sauve, Koren, Walsh, Tokmakejian, & Van Uum, 2007). The use of hair products and hair dye may result in lower cortisol expression than nontreated hair and should be considered in the analysis (Wosu et al., 2013).

Recently, cortisol expression has been obtained from fingernail samples. The average rate of fingernail growth is 1 mm per 10 days; therefore, the nail must grow several months to fully extend from the nail matrix (de Berker, Andre, & Baran, 2007). For collection, nail samples are clipped from every digit. Once the nail is clipped, the samples reflect cortisol levels several months prior to collection (Izawa, Miki, Tsuchiya, Yamada, & Nagayama, 2019).

Conclusion

Biomarkers for detecting and monitoring subjective patient symptoms, such as fatigue and sleep, have clinical applicability, as their use would allow accurate data to be captured from those unable to provide self-report, such as very young children or children who are critically ill. Proven biomarkers would also allow for measuring the effectiveness of interventions provided to treat symptoms.

Inclusion of biomarkers for symptom assessment, however, are currently not part of routine care. More research is needed to standardize data collection methods and to clearly identify and confirm biomarkers for specific symptoms. The development of common data elements biomarker databases would help build needed evidence to address symptom science research questions. In addition to common biomarkers, there is also a need for uniform data collection related to patient symptoms. This would entail that patient symptoms be consistently and similarly assessed, around the time of specimen collection.

The use of biomarkers in symptom science research is imperative to further unravel the biological foundations of symptoms and/or disease. This article provided an overview of biomarkers of interest and special considerations that are needed when planning and implementing biomarker studies. Additional symptom science research is needed to expand our knowledge of biomarkers that could be used for identifying and managing symptoms associated with childhood cancer and its therapy.

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