The Impact of Cancer-Specific Stress on Psychological, Physical, and Immunological Responses in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

DISSERTATION

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Abstract

Chronic lymphocytic leukemia (CLL) is the most prevalent form of adult leukemia and is considered incurable. While survival of patients has improved with newer therapies, all patients eventually relapse and continue to have poor outcomes with additional therapies. Ibrutinib is a new, targeted therapy for CLL that has demonstrated dramatic efficacy with little toxicity for those with relapsed/refractory CLL. Patients with CLL are understudied and little is known about their psychological and physical functioning, especially among those with relapsed/refractory disease. Furthermore, little is known about the impact of psychological factors on immunological factors that influence disease progression in hematologic malignancies. Research indicates that cytokine-driven processes of inflammation and angiogenesis influence disease progression. In particular, interleukin (IL)-6, tumor necrosis factor-alpha (TNF-alpha), and vascular endothelial growth factor (VEGF) are of interest. Understanding what factors may influence trajectories of psychological, physical, and immunological responses as patients undergo treatment for relapsed/refractory cancer is of utmost importance. According to the biobehavioral model of cancer, stress may be an individual difference variable that influences quality of life and immunity as patients undergo treatment. However, the relationship between stress and outcomes in patients with relapsed/refractory cancer is unclear. The current study examines the role of pre-treatment, cancer-specific stress on trajectories of psychological functioning, physical functioning, and selected cytokines as patients with relapsed/refractory CLL undergo treatment with ibrutinib. One-hundred fifty-one
patients were recruited for a phase II drug trial of ibrutinib. Patients completed self-report measures 4 times over the first 5 months of therapy. IL-6, TNF-alpha, and VEGF were analyzed at 3 time points over the first 2 months of therapy in a subset of patients (n=48). Regressions examined the concurrent relationship between cancer-specific stress and outcomes at baseline and hierarchical linear modeling examined the impact of baseline cancer-specific stress on psychological functioning, physical functioning, and cytokines over time. Improvements were noted in all psychological and physical outcomes, excepting mental health quality of life. Cancer-specific stress was related to depressive symptoms, mood disturbance, mental health quality of life, sleep disturbance, and fatigue interference at baseline. Furthermore, cancer-specific stress was related to trajectories of depressive symptoms, mood disturbance, mental health quality of life, sleep disturbance, and fatigue interference. Decreases in TNF-alpha, increases in VEGF, and no change in IL-6 were found. Cancer-specific stress was a predictor of baseline values of TNF-alpha and was predictive of trajectories of IL-6. Overall, these findings provide initial data to support improvements in quality of life and physical functioning in patients with relapsed/refractory CLL taking ibrutinib. Furthermore, cancer-specific stress is a predictor of psychological, physical, and immunological responses over time. Clinical implications and future directions are described.
Dedicated to my parents. This would not have been possible without your love and support over the years.
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Chapter 1: Introduction

In recent decades individuals with cancer are living longer and survival rates have increased. Furthermore, targeted treatments are advancing the state of current treatment for patients. Typically, endpoints for examining the impact of cancer treatments are objective response to the treatment as defined by remission and survival. However, the impact of cancer treatments on quality of life (QOL) and patient-reported outcomes has become increasingly important in clinical trials (Osoba, 2011). Quality of life is a multidimensional construct, but generally includes functional ability, psychological functioning, social adjustment, and disease and treatment related symptoms. Furthermore, changes in immunity, which affect disease progression, are also of interest during treatment.

A vast literature exists related to outcomes in patients with solid tumors (e.g., breast, lung, prostate), especially among those who are newly-diagnosed. However, less is known about the experiences of those with hematologic malignancies, and little about those with relapsed/refractory disease. The majority (90%) of individuals that are diagnosed with cancer have solid tumors (American Cancer Society, 2015a). Although a subset of these patients will develop recurrent disease, most will experience a period of time in which they are cancer-free. However, for hematologic cancers, a subset have chronic leukemia (i.e., chronic lymphocytic leukemia or chronic myeloid leukemia),
which tends to develop over a longer period of time and is generally harder to cure (American Cancer Society, 2015a). In particular, chronic lymphocytic leukemia (CLL) is considered incurable. While standard treatments have improved survival for CLL, they are not curative and patients have refractory disease or relapse and must undergo additional therapies that may not be as effective (Byrd et al., 2013). Understanding what factors may influence psychological, physical, and immunological responses is of utmost importance for patients with relapsed/refractory disease because they are faced with a chronic, incurable disease.

One factor that may influence outcomes is cancer-specific stress. The biobehavioral model of cancer stress and disease is a conceptual model that posits that cancer diagnosis and treatments are stressors (Andersen et al., 1998). According to the model, stress is an individual difference variable that can, over time, contribute to lower quality of life for cancer patients. Furthermore, stress can also have an impact on immunity, which can have ultimate consequences on disease progression. Although the treatment of relapsed/refractory cancer is considered a universally stressful experience, individuals may vary on the perceived stressfulness of the experience. This variability in the stress response may impact subsequent outcomes.

The present study will examine the role of cancer-specific stress on outcomes for those with relapsed/refractory CLL. Specifically, the study examines the impact of pre-treatment, cancer-specific stress on trajectories of psychological, physical, and immunological responses (i.e., proinflammatory and proangiogenic cytokines) in relapsed/refractory CLL patients participating in a phase II trial of ibrutinib. Ibrutinib is
a new, targeted therapy that has demonstrated dramatic efficacy with surprisingly little toxicity (Burger et al., 2014; Byrd et al., 2015; Byrd et al., 2013).

In this document, first, stress and the stress response will be reviewed. Second, a brief and general review will focus on the impact of perceived stress on psychological, physical, and immunological responses in non-cancer populations. Due to the chronic stress of relapsed/refractory cancer, emphasis will be placed on studies that examine the impact of differences in perceived stress among those experiencing a chronic stressor. This will be followed by a review of the role of cancer-specific stress on psychological, physical, and immunological responses in cancer patients. A description of CLL and the treatment patients in the current study will be receiving, ibrutinib, will be provided. Finally, the aims and hypotheses of the proposed research will be discussed.

**Defining Stress and the Stress Response**

Stressors and the stress response are related, but distinct concepts. According to the classic definition of stress from Lazarus and Folkman (1984), stress occurs when a person’s perceived resources do not meet environmental demands. An individual first appraises whether the environmental demand threatens their physical or psychological well-being (primary appraisal), as well as the resources available for meeting the environmental demand (secondary appraisal). Thus, the environmental demand (stressor) precedes the individual’s reaction to the demand (the stress response). Appraising the event as stressful also depends on factors that relate to the person (e.g., personality traits) and factors that relate to the situation (e.g., intensity of demand, proximity). Individual
stress responses can vary, even when a stressor is similar, depending upon one’s cognitive appraisal.

Stress has been studied and measured a number of different ways in the literature. Researchers have examined the role of both laboratory and “naturalistic” stressors on human health and immunity. Laboratory stressors (e.g., speech tasks) are usually short and of an experimental design. Naturalistic stressors include both acute (e.g., academic examinations) and chronic stressors (e.g., bereavement, caregiving of a dementia patient, job-related stress, traumatic events). Many studies of stress have examined stressors, and not the stress response, comparing groups of individuals that experienced a stressor versus those that did not (Thornton & Andersen, 2006). These contrasted group designs assume differences in perceived stress between the groups are due to the presence/absence of the stressor. However, these designs do not capture the variability in stress response among individuals experiencing a similar stressor.

The stressor to be studied here is relapsed/refractory cancer. It is likely that patients experience stress when they learn their disease has progressed and they are in need of further treatment. However, little is known about the stress response of those with relapsed/refractory cancer. Despite the differences described above between relapsed/refractory disease and recurrence in solid tumors, the literature on recurrent disease may be informative concerning the experience of having a chronic cancer. A diagnosis of recurrence is often associated with heightened psychological distress (Hotopf, Chidgey, Addington-Hall, & Ly, 2002), negative physical sequelae (Yang, Thornton, Shapiro, & Andersen, 2008) and poor prognosis. Compared to early stage patients, patients with recurrent disease report more physical symptoms that persist for a
longer time (Yang, Thornton, et al., 2008). Patients with recurrent disease also report high subjective stress. In an early study of patients with recurrent cancer of different malignancies, Mahon, Cella, and Donovan (1990) gave 40 patients a measure of cancer-specific stress, a measure of adjustment to illness, and interviewed the patients to ask about the differences between their recurrence and initial diagnosis. The patients described their recurrence diagnosis as highly stressful and harder to adjust to than their initial diagnosis. Recent studies have also reported that cancer-specific stress is high at the time of recurrence. In a longitudinal study, 30 breast cancer patients were followed from the time of their initial diagnosis until recurrence (Andersen, Shapiro, Farrar, Crespin, & Wells-Di Gregorio, 2005). Patient’s cancer-specific stress at the time of recurrence was as high as those they reported at initial diagnosis, and not surprisingly, were higher than that of disease-free survivors. Furthermore, in both studies, among individuals with recurrent cancer, the levels of cancer-specific stress varied, indicating that although a cancer diagnosis and its treatment are considered to be universally stressful, individuals can vary in the subjective stress response. Similarly, patients with relapsed/refractory disease also likely experience stress due to the chronicity of their disease, but may still vary in their subjective stress response.

In summary, stress and the stress response are related, but distinct concepts. Many studies examine the difference between those experiencing a stressor and those who are not. However, individuals experiencing the same chronic stressor may vary in their individual stress response. In this study, relapsed/refractory cancer is conceptualized as a chronic stressor. The perception of stress will vary amongst individuals, impacting psychological, physical, and immunological responses. The
following brief review will focus primarily on the role of perceived stress in non-cancer populations, especially among those experiencing a chronic stressor.

**Contributions of Perceived Stress to Psychological, Physical, and Immunological Responses in Non-Cancer Populations**

**Psychological functioning.** Although stress and distress are often used interchangeably, the extent to which an individual perceives an event as stressful can have an effect on their psychological functioning. It is well accepted in the general adult population that perceived stress and psychological distress, such as depression, are closely related (Cohen, Kamarck, & Mermelstein, 1983; Hewitt, Flett, & Mosher, 1992). For example, Hewitt, Flett, and Mosher (1992) found that among a clinical sample of depressed patients, greater perceived stress was associated with worse depression.

In the context of a chronic stressor, perceived stress has also been shown to impact concurrent and subsequent psychological functioning. Schulz and colleagues (1995) reported that poorer psychological functioning was related to greater perceived stress for dementia caregivers, an experience defined in the literature as a chronic stressor. Studies in parents of children with cancer have also demonstrated that greater levels of posttraumatic stress symptoms as a result of their child’s cancer diagnosis is predictive of poorer psychological functioning, even 18 months later (Barakat, Kazak, Gallagher, Meeske, & Stuber, 2000; M. J. Dunn et al., 2012). Furthermore, greater perceived stress has been found to be related to poorer psychological functioning in rheumatoid arthritis patients (Curtis, Groarke, Coughlan, & Gsel, 2005; Treharne, Lyons, Booth, & Kitas, 2007). Taken together, even in the context of a similar chronic stressor,
variations in the stress response have been related to differences in psychological functioning.

**Physical functioning.** Perceived stress is consistently related to a variety of negative health outcomes. It has been postulated that stressful events cause negative affective states (e.g., anxiety and depression), which then exert effects on biological processes or health behaviors that influence health (Cohen, Janicki-Deverts, & Miller, 2007). Studies have demonstrated that perceived stress is related to a greater risk of developing a cold and longer time for wound healing (Cohen, Tyrrell, & Smith, 1993; Ebrecht et al., 2004). Perceived stress has also been related to greater reports of physical symptoms. For example, in a recent study of 157 older adults, greater perceived stress was found to predict higher self-reported physical symptoms using a symptom checklist over the following 4 years, especially among those individuals who did not engage in physical activity (Rueggeberg, Wrosch, & Miller, 2012).

Perceived stress has also been related to the onset of chronic health problems, such as arthritis, heart disease, and chronic fatigue (Harris, Loxton, Sibbritt, & Byles, 2013; Kato, Sullivan, Evengard, & Pedersen, 2006; Richardson et al., 2012). In a recent study of 12,202 women participating in the Australian Longitudinal Study of Women’s Health, perceived stress predicted increased risk of developing arthritis three years later (Harris et al., 2013). Additionally, a recent meta-analysis found perceived stress is related to increased risk for incident coronary heart disease (Richardson et al., 2012).

Within those experiencing a chronic stressor, perceived stress has also been demonstrated to be related to poorer physical health reports. For example, in the context of traumatic stress, posttraumatic stress disorder (PTSD) and greater posttraumatic stress
symptoms have been shown to be related to poorer self-reported health (Rytwinski, Avena, Echiverri-Cohen, Zoellner, & Feeny, 2013; Schnurr & Jankowski, 1999; Schnurr & Spiro, 1999). It has been hypothesized that the development of PTSD mediates the association between the experience of a traumatic event and poorer physical health, with the underlying assumption that it is not the occurrence of the event, but rather the individual’s stress response that is related to poorer health (Green & Kimerling, 2004). In fact, in a sample of older veterans, more severe PTSD was associated with poorer QOL and the relationship between combat exposure and health had only an indirect effect, through PTSD (Schnurr & Spiro, 1999). In caregivers of dementia patients, caregivers’ feelings of overload (conceptualized as perceived stress) are also related to poorer self-reported health (Son et al., 2007). Taken together, varying levels of perceived stress in a chronic stress context are associated with physical functioning.

**Immunological responses.** The relationship between stress and markers of immunity, as a potential mediator of the relationship between stress and poorer health outcomes has been widely studied. Immune function is often measured as enumerative or functional analysis of immune cells (such as B and T cells) or other substances (such as cytokines). Meta-analyses have consistently demonstrated that healthy people demonstrate a down-regulation of immunity when experiencing acute or chronic, naturalistic stressors (Herbert & Cohen, 1993; Segerstrom & Miller, 2004; Zorrilla et al., 2001).

However, less research has examined the role that perceived stress has on immunity and findings have been inconsistent (Thornton & Andersen, 2006). A meta-analysis of 21 studies in which global perceived stress or intrusive thoughts related to the
stressor was measured found that perceived stress was not correlated with immunity in the general population (Segerstrom & Miller, 2004). However, of the 9 studies where participants were experiencing a common stressor, natural killer cell cytotoxicity was related to subjective stress, indicating that varying levels of perceived stress in the context of a similar stressor may be related to immune functioning.

Of particular interest for this study is the relationship of perceived stress to proinflammatory cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-alpha], C-reactive protein [CRP]) and proangiogenic cytokines (e.g., vascular endothelial growth factor [VEGF]). Cytokines are low-molecular weight proteins and glycoproteins that are secreted by white blood cells and other cell types (Jain, Bower, & Irwin, 2012). They are associated with the development and proliferation of immune cell subsets, promotion of inflammatory and non-inflammatory processes, and the alteration of neurochemical and neuroendocrine processes. Few studies have examined the relationship between stress, especially perceived stress, and cytokine production.

Perceived stress has been shown to be related to an increase in IL-6 production after being experimentally infected with an influenza A virus (Cohen, Doyle, & Skoner, 1999). In fact, IL-6 production mediated the relationship between perceived stress and subsequent symptoms of illness. Students with higher levels of perceived stress during an examination had significantly higher levels of inflammation (Maes et al., 1998). Furthermore, in a population-based sample of 188 middle-aged and older adults, perceived stress was found to be related to higher levels of CRP (McDade, Hawkley, & Cacioppo, 2006). Among pregnant women, greater perceived stress has been found to be related to greater IL-6 (Coussons-Read, Okun, & Nettles, 2007; Coussons-Read, Okun,
Schmitt, & Giese, 2005), though not all studies find this association (Christian, Franco, Glaser, & Iams, 2009).

Though studies indicate that chronic stressors are related to greater production of proinflammatory cytokines (Kiecolt-Glaser et al., 2003; Lutgendorf et al., 1999; Steptoe, Hamer, & Chida, 2007), fewer studies examine the variations in stress response and inflammation within the context of a similar chronic stressor. Individuals who develop PTSD after a traumatic event have been found to have higher IL-6 than those individuals who also experienced the same event but did not develop PTSD (Tucker, Jeon-Slaughter, Pfefferbaum, Khan, & Davis, 2010; von Kanel et al., 2010). Furthermore, greater posttraumatic stress symptoms have been found to be correlated with higher TNF-alpha (von Kanel et al., 2007). Thus, preliminary studies indicate that higher levels of the stress response may be related to increased inflammation, even within the context of a chronic stressor. The impact of perceived stress on proangiogenic cytokines in non-cancer populations is largely unstudied. Due to the dearth of literature on the impact of perceived stress on cytokine levels, further study is needed on the role of perceived stress on inflammation and angiogenesis.

Summary. Many studies examining the role of stress on health and immunity have examined the role of stressors, rather than the stress response. Studies indicate that variations in the stress response, or perceived stress, have consistently been linked to poorer psychological functioning. Perceived stress has also been linked to poorer self-reported health and the onset of chronic medical conditions. Furthermore, although studies indicate that perceived stress may be related to inflammatory and proangiogenic cytokines, less is known about this relationship. Of particular note is that among
individuals experiencing the same chronic stressor, perceived stress has been associated with psychological, physical, and immunological responses. Unfortunately, the impact of perceived stress has been less studied in cancer patients, especially those with relapsed/refractory cancer. The next section will detail what is known about the relationship between perceived stress, specifically cancer-specific stress, and physical, psychological, and immunological responses in cancer patients.

**Contributions of Cancer-Specific Stress to Psychological, Physical, and Immunological Responses**

Perceived stress has been measured in a variety of different ways in cancer. One of the most widely used measures of perceived stress is the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979; Weiss & Marmar, 1997), when used as a measure of cancer-specific stress. The experience of a cancer diagnosis and its treatments have been defined as a traumatic event that may be associated with symptoms consistent with PTSD (Cordova et al., 1995). These symptoms may manifest through avoidance and intrusive thoughts. Other measures of stress are the Perceived Stress Scale (PSS; Cohen et al., 1983), a measure of global perceived stress, and the Posttraumatic Checklist-Civilian Version (PCL-C; Cordova et al., 1995; Weathers, Huska, & Keane, 1991). For this review, emphasis will be placed on studies using the IES, but studies utilizing other measures of perceived stress will also be noted.

**Psychological functioning.** A number of studies have demonstrated a relationship between cancer-specific stress, and its components of avoidance and intrusions, and psychological functioning. These studies include a variety of cancers with solid tumor
patients at varying stages along the cancer continuum (e.g., newly diagnosed to long-term survivors). Cancer-specific stress and its component, intrusive thoughts, have been found to be related to psychological functioning, QOL, depression, and anxiety in breast cancer survivors (Anagnostopoulos, Slater, & Fitzsimmons, 2010; Epping-Jordan et al., 1999; Golden-Kreutz & Andersen, 2004; Lewis et al., 2001), metastatic breast cancer patients (Butler, Koopman, Classen, & Spiegel, 1999), prostate cancer survivors (Dirksen, Epstein, & Hoyt, 2009), and testicular cancer survivors (Mykletun et al., 2005) in cross-sectional studies. For example, our own research group examined the combined and independent influence of stressful life events, global perceived stress, and cancer-specific stress on depressive symptoms in newly diagnosed breast cancer survivors (Golden-Kreutz & Andersen, 2004). Stress predicted depressive symptoms, and cancer-specific stress was found to be a significant, independent predictor of depressive symptoms, even with the other stress variables in the model, indicating a strong relationship with depressive symptoms. Similarly, post-traumatic stress symptoms have been found to be related to poorer QOL and depressive symptoms in breast cancer survivors and mixed samples of cancer survivors (Cordova et al., 1995; Jacobsen et al., 1998; Morrill et al., 2008).

Longitudinal studies have also provided evidence that cancer-specific stress may predict subsequent psychological functioning. Primo and colleagues (2000) divided 85 women with newly diagnosed breast cancer into 4 groups using scores on the IES: high intrusions/high avoidance, high intrusions/low avoidance, high avoidance/low intrusions, and low avoidance/low intrusions. They found that those individuals with both high intrusions and high avoidance and those with only high levels of intrusions have the
poorest psychological functioning at the time of diagnosis, as well as 3 and 6 months later, as measured by anxiety and depression. Nordin, Berglund, Glimelius, & Sjoden (2001) were interested in predicting anxiety and depression 6 months after cancer diagnosis. They found that in 500 individuals with newly-diagnosed colorectal, gastric, breast, and prostate cancer, unsurprisingly, initial anxiety and depressive symptoms were the best predictor of later anxiety and depressive symptoms. However, intrusions were found to be an additional significant predictor of 6-month anxiety and depression as well. Furthermore, they found similar results in a sample of 159 patients with gastrointestinal cancer (Nordin & Glimelius, 1999). In another study, cancer-specific stress, social support, psychological distress, and QOL were assessed on the first day of treatment, on the final day of treatment, and 1 month after the end of treatment in 53 patients with either metastatic melanoma (n = 24) or metastatic renal cell cancer (n = 29) undergoing an experimental treatment (Devine, Parker, Fouladi, & Cohen, 2003). They found that increased cancer-specific stress on the final day of treatment predicted greater distress and worse mental health QOL 1 month after treatment end among those with low social support.

Our own research group has demonstrated that measures of stress at diagnosis are related to later QOL in newly diagnosed (Golden-Kreutz et al., 2005) and recurrent breast cancer patients (Yang, Brothers, & Andersen, 2008). Specifically, in a sample of 112 women with newly-diagnosed breast cancer, global perceived stress, stressful life events, and cancer-specific stress post-surgery were used to predict QOL at 4 and 12 months post-surgery, while controlling for baseline levels of QOL (Golden-Kreutz et al., 2005). Overall, stress was found to predict both mental and physical QOL at 4 and 12 months.
Furthermore, cancer-specific stress was found to independently predict mental and physical QOL at both time points. Of particular interest for the proposed study is that among 65 patients with breast recurrence, cancer-specific stress shortly after recurrence diagnosis was significantly related to poorer mental health QOL 4 months later (Yang, Brothers, et al., 2008).

In a recent study, intrusive thoughts measured approximately 4 weeks after treatment completion were used to predict trajectories of psychological and physical functioning (i.e., depression, negative affect, pain, sleep, fatigue, physical functioning, and QOL) in the following 12 months in 558 women with breast cancer enrolled in a psychoeducational intervention trial (Dupont, Bower, Stanton, & Ganz, 2014). Participants completed measures at 4 weeks post-treatment, 2 months later, 6 months later, and 12 months later. Intrusive thoughts were significantly related to all measures of psychological and physical functioning at the initial assessment. Furthermore, intrusive thoughts at the initial assessment predicted trajectories of pain, depressive symptoms, negative affect, and physical functioning over the following year. Individuals with higher intrusive thoughts started out with poorer physical and psychological functioning and improved over time, whereas those with lower intrusive thoughts stayed at a constant, low level. This provides evidence that a component of cancer-specific stress, intrusive thoughts, may influence trajectories of psychological and physical functioning in cancer survivors. However, this study focused exclusively on post-treatment breast cancer survivors. The role of cancer-specific stress on these trajectories in recurrent patients undergoing treatment is unknown.
Taken together, these studies indicate that perceived stress, specifically cancer-specific stress, is related to poorer concurrent and subsequent psychological functioning. However, most studies have examined this relationship in newly diagnosed patients or post-treatment survivors. Fewer studies have examined the role of cancer-specific stress in patients with recurrent cancer and no studies have examined it in patients with relapsed/refractory disease, though stress may be an important predictor for this population as well.

**Physical functioning.** Research examining the relationship between stress and physical functioning is rare. Studies described above also related cancer-specific stress to physical QOL (Lewis et al., 2001), insomnia severity (Dirksen et al., 2009), and testicular cancer-related side effects (Mykletun et al., 2005). Our own research group has reported relationships between cancer-specific stress and physical symptom burden in samples of gynecologic (Carpenter, Fowler, Maxwell, & Andersen, 2010) and untreated CLL patients (Morrison, 2013) in cross-sectional studies. Specifically in a sample of 260 gynecologic cancer survivors (mean time since diagnosis = 4.3 years), physical symptom burden (i.e., a composite of fatigue, vaginal change, sign/symptoms of treatment toxicities, and the physical components of general and disease-specific QOL measures) accounted for significant variance in cancer-specific stress, indicating a relationship between cancer-specific stress and physical health (Carpenter et al., 2010).

Two studies are of particular relevance to the proposed research. In an unpublished dissertation study, Morrison (2013) examined the relationship between physical symptom burden (i.e., a composite of CLL symptoms, fatigue, and pain) and psychological distress, including cancer-specific stress, in 112 early-stage, untreated CLL
patients. They reported a significant association between cancer-specific stress and physical symptom burden. Furthermore, in a recent study of 205 patients with acute leukemia that was a mixture of newly diagnosed, recently relapsed, or treatment failures, traumatic stress, as measured by the Stanford Acute Stress Reaction Questionnaire, was related to more physical symptoms and physical symptom distress (Rodin et al., 2013).

Few longitudinal studies have examined the role of cancer-specific stress on physical functioning over time. As described above, our research group has demonstrated that measures of stress at diagnosis significantly predicted physical QOL 4- and 12-months post-surgery (Golden-Kreutz et al., 2005) in newly diagnosed breast cancer patients. Interestingly, none of the stress variables were significant concurrent predictors of physical QOL at baseline. Also described above, intrusive thoughts 4 weeks post-treatment were related to changes in pain, fatigue and physical functioning in the year following treatment in breast cancer survivors (Dupont et al., 2014).

Taken together, these studies indicate that cancer-specific stress may impact physical functioning. However, the longitudinal studies included only women with breast cancer. Given the paucity of research, it is unclear the extent to which cancer-specific stress may impact subsequent physical functioning, especially longitudinally as patients undergo treatment for relapsed/refractory cancer. This relationship is of particular interest in those with relapsed/refractory cancer because similarly to those with recurrent cancer, they may experience greater physical symptom burden with few changes in physical functioning over time (Yang, Thornton, et al., 2008).

**Immunological responses.** One pathway through which stress may impact cancer progression is through the immune system. Adapted from Thornton and Andersen (2006)
and Lutgendorf and Sood (2011), the hypothesized pathway is shown in Figure 1. A stressor (e.g., relapsed/refractory cancer) leads to a stress response (e.g., cancer-specific stress), which could lead to changes in emotions, health behaviors, central nervous system activity, and endocrine activity. As described above, factors such as personality traits and stable characteristics influence this stress response. The stress response may then lead to an impaired cellular immune response [e.g., natural killer (NK) cell cytotoxicity and T-cell activity] and an increase in inflammation (e.g., IL-6 and TNF-alpha) and angiogenic factors (e.g., VEGF). This compromised immune system may then create an environment that promotes the growth and progression of the cancer (Andersen, Kiecolt-Glaser, & Glaser, 1994; Lutgendorf & Sood, 2011; Thornton & Andersen, 2006).

Of particular interest for this study is the role of proinflammatory and proangiogenic cytokines on disease progression. Inflammation is related to the incidence and progression of cancer. Specifically, inflammation has been linked to the onset of hematologic malignancies (e.g., multiple myeloma, non-Hodgkin’s lymphoma, CLL; Ershler & Keller, 2000). After the cancer has developed, inflammation also promotes tumor growth and spread. Specifically, inflammation contributes to the proliferation and survival of tumor cells, promotes metastasis, and impairs adaptive immunity (Mantovani, Allavena, Sica, & Balkwill, 2008). Thus, inflammation has been linked to poorer outcomes in cancer patients. Widely used markers of inflammation include the proinflammatory cytokines TNF-alpha and IL-6.

TNF-alpha activates and recruits neutrophils and monocytes to inflammatory sites. TNF-alpha, has been found to be elevated in many cancer types (i.e., non-small cell lung cancer, breast cancer, colorectal cancer, prostate cancer, malignant melanoma, non-
Hodgkin’s lymphoma, and gastric cancer), and of particular note in CLL (Lippitz, 2013). IL-6, another prominent proinflammatory cytokine, has been found to be increased in 13 cancer types (i.e., lung cancer, breast cancer, colorectal cancer, gastric cancer, malignant melanoma, pancreatic cancer, hepatocellular carcinoma, renal-cell carcinoma, neuroblastoma, non-Hodgkin’s lymphoma, nasopharyngeal carcinoma, head and neck squamos-cell carcinoma, and bladder cancer; Lippitz, 2013). Furthermore, higher serum concentrations of IL-6 are related to negative prognosis in a number of cancers, including CLL (Fayad et al., 2001; Lippitz, 2013).

In addition to markers of inflammation, another cytokine of interest that has been associated with tumor growth and spread is VEGF. VEGF is associated with angiogenesis. Angiogenesis is a vital process for tumor growth and metastatic spread because it stimulates the growth of new blood vessels that supply oxygen and nutrients for the tumors to grow (Carmeliet, 2005). Traditionally, VEGF has been known to play a vital role in solid tumor growth and metastatic spread. However, research has recently indicated that VEGF also plays a role in the spread of hematologic malignancies, including CLL (Letilovic, Vrhovac, Verstovsek, Jaksic, & Ferrajoli, 2006).

A number of studies have examined the association between psychosocial factors and immunity in cancer. However, it has been noted that although in the general psychology literature clear distinctions have been made between “stress”, “distress”, and “depression”, there have not been clear distinctions made in the biobehavioral oncology literature (Lutgendorf & Sood, 2011). Studies examining the relationship between immunity and cancer-specific stress are limited. Studies have demonstrated that cancer-specific stress is related to the downregulation of the cellular immune response. In an
early study of breast cancer patients that were post-surgery but had not yet begun adjuvant therapy, those with greater cancer-specific stress had poorer immune functioning even after controlling for relevant disease characteristics and time since surgery (Andersen et al., 1998). Specifically, greater cancer-specific stress was related to poorer NK cell cytotoxicity and T-cell blastogenesis. In a prospective study of 106 breast cancer patients, psychological data were collected one day before surgery and cell counts one day before surgery and seven days after surgery (Tjemsland, Soreide, Matre, & Malt, 1997). Pre-operatively those with higher cancer-specific stress had lower numbers of lymphocytes, B cells and T helper cells. Perceived stress has also been found to be related to lower NK cell activity and lower interferon-gamma among breast cancer patients (Von Ah, Kang, & Carpenter, 2007).

The relationship between cancer-specific stress and proinflammatory and proangiogenic cytokines has not been well studied. Instead, most studies have examined the role of distress and/or social support on these cytokines. For example, measures of depressive symptoms have been found to be related to higher levels of proinflammatory cytokines, including IL-6 and TNF-alpha, in cancer patients (Breitbart et al., 2014; Howren, Lamkin, & Suls, 2009). Of note, IL-6 gene expression was significantly elevated in depressed patients with acute leukemia compared to non-depressed patients with acute leukemia (El-Gohary, Azzam, Ahmed, & El-Shokry, 2008). VEGF has also been shown to be related to measures of psychosocial variables. In patients with ovarian cancer, lower social support was related to higher values of VEGF in serum (Lutgendorf et al., 2002) and in tumor tissue (Lutgendorf et al., 2008). VEGF has also been shown to be related to depressive symptoms, cancer-related concerns, and positive affect in
colorectal cancer patients pre-operatively and 6-8 weeks following surgery (Sharma, Greenman, Sharp, Walker, & Monson, 2008). Recently, VEGF was found to be associated with depressive symptoms, anxiety, and of note, perceived stress in a sample of head and neck cancer patients (Fang et al., 2013).

Taken together, these studies indicate that cancer-specific stress is related to suppression of the immune system. However, cancer-specific stress’s unique relationship with proinflammatory and proangiogenic cytokines is unknown. Furthermore, the majority of studies examining distress and cytokines have been cross-sectional; less is known about the impact over time. This relationship is of particular interest as patients undergo treatment, as their immune systems are actively combating the disease. Studies indicate that other psychosocial measures are related, but the specific role of cancer-specific stress is unknown. Additionally, the relationship between stress and immunity is largely unstudied in hematologic cancers. This relationship may differ as hematologic cancers are immunologically distinct from solid tumors. As cytokines play a role in disease progression, it is important to understand the unique role that cancer-specific stress may have as patients undergo treatment for relapsed/refractory cancer.

Focus of the Present Investigation

The choice of relapsed/refractory chronic lymphocytic leukemia. Hematologic malignancies are cancers that affect the blood, bone marrow, and lymph nodes. CLL is the most common adult leukemia and accounts for about one-quarter of the new cases of diagnosed leukemias in the United States (American Cancer Society, 2015b). In chronic leukemias, the cells only partially mature and do not function properly (i.e., do not fight
infection as well as normal white blood cells). In CLL, leukemia cells in the bone marrow invade the blood, build up and crowd out normal, functioning cells. With the growth of leukemia cells, the body cannot properly fight infections in the body (American Cancer Society, 2015b). CLL is a cancer that mainly affects older adults (i.e., the average age of diagnosis is 71 years old) with the risk slightly higher in men. Based on rates from 2008-2010, the lifetime risk of developing CLL is 0.52% (Howlader et al., 2013). The overall 5-year survival is 79.2% (Howlader et al., 2013).

Most individuals with CLL have no signs and symptoms of the cancer when diagnosed; it is often found during blood tests for an unrelated health problem or a routine checkup (American Cancer Society, 2015b). When symptoms occur they are often non-specific and can include weakness, feeling tired, weight loss, fever, night sweats, enlarged lymph nodes, and pain or a sense of fullness in the belly due to an enlarged spleen. Those with advanced disease may also experience anemia, increased risk of infection, and excessive bleeding or bruising.

CLL is considered incurable. It is heterogeneous, with some individuals having indolent disease for years and others rapidly progressing. Although the leukemia cells look alike for these individuals, lab tests may reveal differences in proteins or genetic factors that indicate poorer prognosis. For example, those with a deletion of part of chromosome 17 (i.e., del17p) often have a poorer prognosis and poorer response to treatment (Stephens & Byrd, 2012).

Patients diagnosed with early stage CLL (i.e., stages 0 to II) do not receive treatment since it has not been shown to offer a survival advantage (American Cancer Society, 2015b). Instead, patients are continually monitored, a process that has been
termed “watchful waiting.” For those who initially are or become symptomatic, treatment is recommended. Currently, the first line of treatment is chemotherapeutic agents. Furthermore, the addition of monoclonal antibodies to chemotherapy have resulted in higher response rates, extended remission, and improved overall survival (Hallek et al., 2010). However, chemoimmunotherapy is not curative, and treatment options for individuals that relapse have reduced effectiveness and possibly greater toxicity (Byrd et al., 2013). Patients with relapsed/refractory CLL likely have greater physical symptom burden and are facing a poorer prognosis. Furthermore, they have undergone and continue to undergo multiple rounds of treatment. The process of undergoing repeated treatments may contribute to increased stress, yet little is known about the psychological and physical impact of this experience.

Inflammation and angiogenesis are also of interest in CLL because studies have shown they contribute to disease progression. In CLL, TNF-alpha is independently associated with adverse disease features (e.g., higher stage) and poorer survival above and beyond other clinical features (e.g., white blood cell count, disease stage; Ferrucci et al., 1999). IL-6 has also been found to be related to adverse disease features (e.g., higher stage) and worse median and 3-year survival in CLL patients (Fayad et al., 2001). Furthermore, increased serum levels of VEGF in patients with early stage CLL have been associated with earlier disease progression (Molica, Vitelli, Levato, Gandolfo, & Liso, 1999). Taken together, inflammation and angiogenesis are vital processes that contribute to disease progression in this population.

Despite CLL being the most common adult leukemia in the US, few studies (n=17) have examined psychosocial functioning and QOL in this population (see Table
1). Conducted studies have focused mainly on patients receiving treatment for the first time or mixed samples of treated and untreated patients. To our knowledge there have been only two studies that have specifically examined the psychosocial functioning of those with relapsed/refractory CLL (Burger et al., 2014; Robak, Lech-Maranda, & Robak, 2010). Furthermore, hematologic malignancies are immunologically distinct from solid tumors, and the impact of stress on immunity in this population has been rarely studied (Lutgendorf & Sood, 2011). In particular, no biobehavioral studies could be found that examined the relationship between psychosocial factors and immunity in CLL.

Eichhorst and colleagues (2007) examined QOL in 249 previously untreated and younger (<66 years old) German CLL patients receiving chemotherapy and concluded that patients had lower QOL compared to the general population and that women had worse physical functioning than men. Else and colleagues (Else et al., 2012; 2008) examined QOL prior to active treatment and after 5 years of treatment in previously untreated patients. They found that prior to starting treatment patients had impaired QOL compared to population norms. In their longitudinal study, they found that for some treatments, impairments in QOL were seen during active treatment. Patients who had complete or partial remission had QOL scores closer to the general population, while patients whose disease progressed had clinically worse QOL compared to the general population. Shanafelt and colleagues (2007) conducted a web-based survey of 1482 CLL patients, of which 40% had been treated at some point in the past. They found that lower QOL was related to older age, greater fatigue, greater severity of co-morbid health conditions, and current treatment. In a study conducted by Holzner and colleagues
(2004), 76 patients with CLL not actively receiving treatment (43% previously treated) were assessed four times over the period of one year and compared to 152 age-and gender-matched healthy controls. Compared with healthy controls, CLL patients reported lower QOL in all domains, and no differences were found between those who had already received treatment and those who had not. In a recent study from our research group, distress and physical symptom burden were studied in 112 early stage, untreated CLL patients (Morrison, 2013). Not surprisingly, higher levels of distress were related to higher levels of physical symptom burden. Furthermore, history of pharmacotherapy use, history of psychotherapy, and low social support were found to moderate this relationship. Interestingly, when making comparisons of those who are on active treatment versus “watching and waiting” in a sample of 105 CLL patients, depression, anxiety and QOL were similar (Levin, Li, Riskind, & Rai, 2007). However, younger patients had worse depression, anxiety, and emotional and social QOL. For those diagnosed longer than 6 years, their emotional QOL was similar to those newly diagnosed, but their physical QOL was worse. In one study in those with relapsed disease, patients who had previously had one type of treatment were found to not experience any changes in QOL while undergoing a second treatment (Robak et al., 2010). In the second study, patients with relapsed/refractory disease participating in a phase II drug trial for ibrutinib with rituximab experienced improvements in QOL after 6 and 12 months, as well as improvements in symptoms such as fatigue (Burger et al., 2014).

Taken together, these studies indicate that both treated and untreated CLL patients have poorer QOL compared to the general population. As patients undergo treatment,
their QOL declines, but as patients respond to treatment, their QOL becomes comparable to those in the general population. However, those patients who have disease progression are at particular risk for worse physical QOL. As those patients with relapsed/refractory disease are experiencing disease progression, it is likely they have poorer physical health. However, the unique experience of this population is in need of further study.

**Ibrutinib: targeted cancer therapy for CLL.** Advancing research in CLL has found that B-cell receptor signaling is a driving force for CLL tumor-cell survival (Herman et al., 2011). Specifically, Bruton tyrosine kinase (BTK) is downstream of the B-cell receptor and is important in activating pathways that promote CLL tumor-cell survival. Ibrutinib, a BTK inhibitor, has been implicated as a potent drug that is successful in the treatment of CLL (Herman et al., 2011; Sanford, Wierda, Burger, Keating, & O'Brien, 2015).

In a recent phase Ib/II trial with ibrutinib, the estimated progression-free survival rate was 75% and the rate of overall survival was 83% at a median of 26 months of follow-up in relapsed or refractory CLL patients (Byrd et al., 2013). Individuals with clinical and genomic risk factors (i.e., del17p) also responded equally as well to the treatment. Furthermore, ibrutinib was found to have minimal toxic effects in patients with relapsed/refractory CLL. In a recent study, after 3 years, longer treatment with ibrutinib was associated with improvements in response and durable remissions, and diminished likelihood of toxicities in treatment-naïve and previously treated patients (Byrd et al., 2015). Given the promising results in trials, in February 2014, ibrutinib received accelerated approval for the treatment of CLL by the US Food and Drug Administration (Sanford et al., 2015). Thus, there is indication that ibrutinib is a
promising, targeted agent for relapsed/refractory CLL that will be used extensively in the treatment of this disease.

The impact of ibrutinib on inflammation and angiogenic factors is largely unknown. In a recent study, patients taking ibrutinib plus rituximab were found to have decreases in TNF-alpha after 1 month (Burger et al., 2014). Furthermore, lab studies have demonstrated that T-cells treated with ibrutinib produce less proinflammatory cytokines, such as IL-6 and TNF-alpha (Herman et al., 2011). Thus, preliminary findings indicate that ibrutinib may contribute to lowered levels of inflammation. The impact of ibrutinib on QOL is also unknown, though with the low toxicity profile, results are promising. Unlike chemotherapy and radiation, which often result in an increase in physical symptoms (e.g., fatigue, pain) during active treatment, ibrutinib may actually lead to the stability or improvement of physical health. As noted above, the only trial measuring QOL in patients taking ibrutinib showed an improvement in overall QOL (Burger et al., 2014).

**Overall summary.** The diagnosis and treatment of cancer is a negative, stressful experience. Evidence suggests that cancer patients experience considerable stress, but individuals vary in their stress response. According to the biobehavioral model of cancer, differences in the stress response prior to cancer treatment may impact QOL during treatment and/or recovery. Furthermore, differences in the stress response may also impact inflammation and angiogenesis, which may affect cancer progression. Examining QOL, specifically psychological and physical outcomes, and immunological responses in relapsed/refractory cancer patients is important because they are faced with a more
chronic, physically burdensome disease compared to the newly diagnosed and cancer survivors.

There is evidence to suggest that perceptions of stress modulate the impact of the stressor on psychological, physical, and immunological responses in non-cancer populations, even within those experiencing a chronic stressor. Furthermore, evidence suggests that cancer-specific stress is related to poorer psychological, physical, and immunological functioning. However, there is a paucity of longitudinal studies, especially examining the impact of cancer-specific stress on subsequent physical health and immunity, outcomes particularly relevant to patients with relapsed/refractory disease. Identifying those who may be at risk for poorer functioning at pre-treatment may serve as an indicator of those to target for stress-reduction interventions prior or concurrent to treatment.

Furthermore, these relationship have been rarely studied among those with hematologic malignancies. In particular, most studies examining physical health and immunity have been conducted in solid tumor patients (e.g., breast, ovarian, prostate). Less is known about the impact of cancer-specific stress on these outcomes in individuals with hematologic malignancies, an immunologically distinct disease. Patients with CLL are also understudied. Specifically, patients with relapsed/refractory CLL may experience high levels of cancer-specific stress because they are living with an incurable chronic disease that has not responded to treatment. Since CLL patients know their disease will progress, it is especially important to understand their physical and psychological functioning as they undergo treatment. Furthermore, since cytokine-driven processes of inflammation and angiogenesis influence disease progression in CLL, it is
also important to understand what factors influence cytokines. Most studies examining QOL enroll cancer patients receiving different types of treatments, a source of variability that may impact outcomes. Examining the role of stress as all patients receive the same treatment (e.g., ibrutinib) provides a more stringent test of the role that cancer-specific stress has on functioning in patients with CLL.

**Study Design and Aims**

The role of pre-treatment cancer-specific stress on concurrent and subsequent psychological functioning, physical functioning, and proinflammatory and proangiogenic cytokines is studied. Repeated measures data from patients with relapsed/refractory CLL participating in a phase II clinical trial of ibrutinib is utilized. Psychological functioning is conceptualized as depressive symptoms, general mood disturbance, and mental health QOL. Physical functioning will be assessed using a measure of physical QOL, as well as measures of pain, fatigue and sleep disturbance, as these physical symptoms are common in cancer patients.

The research has three aims (see Figure 2). The first is to test the concurrent relationship between cancer-specific stress and physical and psychological functioning in relapsed/refractory CLL patients using hierarchical multiple regression. It is hypothesized that at pre-treatment, higher levels of cancer-specific stress will be associated with poorer psychological and physical functioning.

The second aim of the study is to test pre-treatment cancer-specific stress as a predictor of psychological and physical functioning across 5-month trajectories. Hierarchical linear modeling will model change in outcomes measured at baseline, 1
month, 2 months, and 5 months with cancer-specific stress at baseline as a predictor. It is hypothesized that higher levels of pre-treatment cancer-specific stress will be associated with a slower improvement in psychological and physical functioning over 5 months.

The third aim of the study is exploratory. The relationship between pre-treatment cancer-specific stress and 2-month change in proinflammatory (IL-6, TNF-alpha) and proangiogenic (VEGF) cytokines will be studied. Hierarchical linear modeling will model change in cytokines measured at baseline, 1 month, and 2 months, with cancer-specific stress at baseline as a predictor. It is hypothesized that higher levels of pre-treatment cancer-specific stress will be associated with higher levels of pre-treatment cytokines and a slower decline over 2 months.
Chapter 2: Method

Participants

One-hundred fifty patients with relapsed or refractory CLL participated (see Table 2). The majority were males (71%), Caucasian (97%; 3% African-American), and with a mean age of 64.0 years (SD = 10.78 years; range = 26-91). The majority were also retired (53%), had greater than a high school degree (69%), had an income greater than $50,000 (55%), and were in a relationship with a significant other (87%).

Medical and treatment history indicated that 51% had disease with del17p. On average patients had received 3.47 (SD = 2.61; range = 1-16) prior treatments. The unadjusted Charlson Comorbidity Index mean was 2.53 (SD = 0.99; range = 2-9), with all participants receiving 2 points for having CLL.

Procedures

Individuals with a confirmed diagnosis of relapsed or refractory chronic lymphocytic leukemia who required treatment and had failed at least one prior therapy were sought for a phase II clinical drug trial for ibrutinib at the Ohio State University Comprehensive Cancer Center- Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. The primary aim of the clinical trial is to determine the 2-year progression-free survival of single agent ibrutinib in relapsed and refractory CLL.
patients. All potential participants were initially screened. Eligibility criteria were as follows:

- Older than 18 years of age
- ECOG performance status ≤ 2
- Life expectancy greater than 2 months
- Normal organ function as clinically defined
- If sexually active and able to bear children, patient had to use contraception during the study and 30 days after the last dose of treatment
- Ability to understand and willingness to sign written informed consent

Exclusion criteria were as follows:

- Patients who had chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to the first dose of the drug.
- Patients who had not recovered from an adverse event of a ≥ Grade 3 toxicity due to agents administered more than 4 weeks prior.
- Patients receiving any other investigational agent.
- Patients with known secondary malignancies that limit survival to less than two years
- Patients with malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
• Patients with a life-threatening illness, medical condition, or organ system
dysfunction, which could compromise the patient’s safety or interfere with the
absorption or metabolism of ibrutinib.

• Patients with uncontrolled or active infection requiring antibiotic treatment.
Patients with controlled infections who were receiving extended antibiotics or
prophylactic therapy were still eligible.

• Patients with significant cardiovascular disease such as uncontrolled or
symptomatic arrhythmias, congestive heart failure, or myocardial infarction
within the previous 6 months, or any Class 3 or 4 cardiac disease.

• Patients with lymphoma of the central nervous system.

• Patients who were pregnant or breastfeeding.

Patients were enrolled from May 2012 to April 2014. One hundred fifty-one
participants were enrolled in the trial and began treatment. However, one individual did
not complete a baseline assessment and was excluded from these analyses.

Within 10 days of enrollment, participants began ibrutinib therapy at a dose of
420 mg orally once a day for 28-day cycles and continued until disease progression or
unacceptable toxicity. Other reasons for study removal were intercurrent illness that
prevented ibrutinib administration, changes in condition that rendered them unacceptable
to continue further as judged by the investigator, noncompliance with study procedures
and/or evaluations, receipt of prohibited concomitant medications, pregnancy, or patient
withdrawal from the study. Furthermore, if participants became eligible for stem cell
transplantation, they were also removed from the trial.
Participants independently completed self-report questionnaires measuring cancer-specific stress, psychological functioning, and physical functioning at study visits on the first day of treatment (day 1 of cycle 1), after 1 month (day 1 of cycle 2), after 2 months (day 1 of cycle 3), and after 5 months (day 1 of cycle 6). Routinely, blood was drawn at trial visits. For this study, samples provided on pre-dose on the first day of treatment, after 1 month, and after 2 months were used.

**Measures**

**Predictor.**

*Cancer-specific stress.* The Impact of Events Scale-Revised (IES-R; Horowitz et al., 1979; Weiss & Marmar, 1997) was utilized to measure cancer-specific stress. This is a 22-item self-report questionnaire that measures reaction to cancer diagnosis and treatment. According to factor analytic studies this measure examines three factors: intrusive thoughts (e.g., “Any reminders brought back feelings about having CLL”), avoidant thoughts/behaviors (e.g., “I stayed away from reminders about CLL”), and hyperarousal (e.g., “I was jumpy and easily startled”). Participants rate the frequency of these feelings or events in the past week, using a five-point Likert scale ranging from 0=not at all to 4=extremely. Only the intrusive thoughts and avoidant behaviors/thoughts items were used and summed for a total score (range 0-64), as the hyperarousal scale assesses many physical reactions and was also not included in the original IES, which is often used in cancer studies (Andersen et al., 1998; Horowitz et al., 1979). The Cronbach’s alpha for the sum of the intrusions and avoidance subscales at baseline was 0.86.
Psychological Outcomes.

Depressive symptoms. The Beck Depression Inventory-2nd edition (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item inventory that was used to measure the severity of depressive symptoms. Participants were asked to rate their symptoms in the past month on a scale from 0 to 3. Items are summed, with higher scores indicating more depressive symptoms. The BDI-II has been previously used in cancer patients (Brothers, Yang, Strunk, & Andersen, 2011). Additionally, two different scores may be calculated representing the cognitive-affective symptoms of depression (Items 1-14) and the somatic symptoms often associated with depression (e.g., fatigue, insomnia; items 15-21; Beck, Steer, & Garbin, 1988). Since the somatic symptoms are likely confounded with the physical symptoms experienced by cancer patients, analyses were conducted using only the cognitive-affective subscale (Wedding et al., 2007). The scores on the cognitive-affective subscale can range from 0 to 42. The Cronbach’s alpha for this subscale in the sample ranges from 0.80 to 0.89 across assessments.

Mood disturbance. The Profile of Mood States –Short Form (POMS-SF; Shacham, 1983) is a 37-item questionnaire that was used to assess patient mood. Participants rated how much they felt a certain emotion (e.g., tense, angry) in the past week on a 5-point Likert scale (0 = not at all, 1 = a little, 2=moderately, 3=quite a bit, 4=extremely). Six mood subscales are obtained: Anxiety, Depression, Anger, Vigor, Fatigue, and Confusion. The total mood disturbance (TMD) score is the sum of the subscale scores (with the Vigor scale subtracted from the total) and ranges from -24 to 124, with higher scores indicating greater mood disturbance. The POMS-SF shows significant correlations with the original POMS and similar internal consistencies in a
sample of breast cancer patients undergoing chemotherapy (DiLorenzo, Bovbjerg, Montgomery, Valdimarsdottir, & Jacobsen, 1999). Due to researcher error, one question from the Confusion subscale (i.e., unable to concentrate) on the POMS-SF was incorrectly specified on the questionnaire. Therefore, this item was removed for analyses, and the possible range on the POMS-TMD was -24 to 120. The Cronbach’s alpha for the POMS-TMD is 0.95 to 0.96 across assessments in this sample.

_Mental Health Related Quality of Life._ The Mental Component Summary (MCS) score of the Medical Outcomes Study- Short Form Health Survey (SF-12; Ware, Kosinski, & Keller, 1996; Ware, Kosinski, Turner-Bowker, & Gandek, 2002) was used to assess mental health QOL. The SF-12 assesses eight aspects of QOL including physical functioning, role functioning-physical, bodily pain, general health perceptions, vitality, social functioning, role functioning-emotional, and mental health. Higher scores reflect better QOL. The eight primary subscales are summarized into two component scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS). The SF-12 demonstrates reliability and validity comparable to other measures of QOL (Ware et al., 1996). Internal consistency, test-retest reliability, and convergent and discriminant validity coefficients for the SF-12 are similar to those of the SF-36 (Ware et al., 2002). The SF-12 discriminates between healthy and illness groups and between high and low psychological distress in community samples (Schofield & Mishra, 1998). The SF-12 is used in many chronic illness populations such as cardiac patients (Bennett et al., 2002; Dempster & Donnelly, 2001), migraine patients (Lipton, Hamelsky, Kolodner, Steiner, & Stewart, 2000), and psychiatric inpatients (Salyers, Bosworth, Swanson, Lamb-Pagone,
& Osher, 2000). Internal consistency ranged from .81 to .83 for the MCS across assessments.

**Physical outcomes.**

*Fatigue Interference.* The Fatigue Symptom Inventory (FSI; Hann et al., 1998) is an 11-item questionnaire used to measure the frequency, severity, and daily pattern of fatigue, as well as its impact on quality of life in the past week. A 7-item subset of the FSI, the Total Disruption Index, was used in this study and measures the degree of interference of fatigue on multiple aspects of life in the past week (e.g., enjoyment of life, ability to concentrate, relations with other people). Items are rated on an 11-point Likert scale from 0 = no interference to 10=extreme interference. Total scores can range from 0 to 70, with higher scores indicating greater fatigue interference. The Cronbach’s alpha is 0.93 to 0.95 across assessments in this sample.

*Pain.* The Medical Outcomes Study SF-36 Bodily Pain Scale (Ware & Sherbourne, 1992) is a 2-item measure used to measure bodily pain. The first item assesses the amount of bodily pain or discomfort in the past 4 weeks on a 6-point Likert scale. The second item assesses the extent to which pain interferes with normal activities in the past 4 weeks on a 5-point Likert scale. Scores are transformed into a 0-100 scale. Higher scores indicate lower pain. In this study sample, Cronbach’s alpha ranged from 0.80 to 0.86 across assessments.

*Sleep Disturbance.* The Medical Outcomes Study- Sleep Scale (MOS-Sleep; Hays, Martin, Sesti, & Spritzer, 2005) is a 12-item measure that was used to assess sleep disturbance. Participants reported how long it usually took them to fall asleep in the past 4 weeks and on average how many hours of sleep they got each night in the last 4 weeks.
They also reported how often they experienced 10 specific difficulties with sleep (e.g., awaken during your sleep and have trouble falling asleep again) on a 6-point Likert scale (1=All of the time to 6=None of the time). The six-item sleep problem index II was utilized in this study. Scores are transformed into a 0-100 scale with higher scores on the index indicating greater levels of sleep disturbance. In this study sample, Cronbach’s alpha ranged from 0.72 to 0.75 across assessments.

*Physical Health Related Quality of Life.* As described above, the SF-12 was used as a measure of overall QOL (Ware et al., 1996). The Physical Component Summary (PCS) was used as a measure of physical QOL. Internal consistency ranged from 0.90 to 0.91 for the PCS across assessments.

*Cytokine outcomes.*

IL-6, TNF-alpha, and VEGF were measured using the Quantikine ELISAs (R&D Systems). Following the blood draw, plasma was isolated by centrifugation and frozen at -80C. Later, plasma samples were thawed, batched by participant, and spun down to remove debris. ELISAs were run in batches according to the manufacturer’s instructions. Cytokine assay plates contained 96 wells, 24 for control assays and 72 for processing study samples.

The cytokine assays had lower limits of 0.70 pg/ml for IL-6, 9.0 pg/ml for VEGF and 1.6 pg/ml for TNF-alpha. All study samples were processed in triplicate and values of each assay per participant at each time point were averaged. If a participant’s value was too low to detect, half the lower limit of detection for each cytokine was imputed, consistent with previous studies (Lengacher et al., 2013; Sepah & Bower, 2009).
Control variables.

Sociodemographic characteristics. Data for age, gender, race, highest level of education, income, employment status, and partner status were obtained from self-report.

Disease and treatment variables. Information on disease and treatment variables were collected via chart review. This included information regarding number of prior therapies and del17p status. The Charlson Comorbidity Index was used to estimate the prevalence of health comorbidities. It is a measure of risk of death from comorbid conditions (CCI; Charlson, Pompei, Ales, & MacKenzie, 1987). The index is comprised of 19 conditions, with each weighted from 1-6 depending on the severity of the condition and its relation to mortality. Total scores can range from 0-37. The CCI has been validated for use in chronically ill populations, including breast cancer (Charlson et al., 1987). All participants in this sample received 2 points for having CLL.

Analytic Strategy

Descriptive statistics were used to characterize the sample and scores on cancer-specific stress and outcome variables. Correlations between IES and the outcome variables were also examined at baseline using Spearman’s rank correlation. The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for all preliminary and main analyses.

Hypothesis 1: At pre-treatment, higher levels of cancer-specific stress will be associated with poorer psychological and physical functioning. Hierarchical multiple regression was utilized to examine the concurrent relationship between cancer-specific stress and the seven physical and psychological outcomes at baseline. Variables were
entered as follows: (a) sociodemographic; (b) medical/treatment-related variables; and (c) cancer-specific stress (IES). The following were considered as controls: age (continuous, mean-centered), gender (0=female), del17p status (0=absent), number of prior therapies (continuous, mean-centered), and comorbidity index (with 2 subtracted to make the lowest value 0). Only those potential control variables that were significantly associated (p < 0.10 using Spearman’s rank correlation) with the outcome variable of interest were included in each model. For all analyses, residuals were examined to determine if they were non-normal, an assumption of hierarchical multiple regression. If this was the case, the variable was either square-root transformed (if positively skewed) or reflected and then square-root transformed (if negatively skewed). Outliers were also analyzed. Outcomes of interest did not change as a result of transformation or outlier removal, therefore, the non-transformed data is presented for ease of interpretation.

**Hypothesis II:** Higher levels of pre-treatment cancer-specific stress will be associated with a slower improvement in psychological and physical outcomes over 5 months. Hierarchical linear modeling (HLM) was utilized to test the effect of baseline cancer-specific stress on the trajectories of psychological and physical outcomes during the first 5 months of treatment. HLM is advantageous to other repeated-measures analyses because it utilizes all available data, while producing consistent, efficient estimates (Raudenbush & Bryk, 2002). Important for this study, HLM can handle data that is unbalanced (i.e., missing data). Thus, all individuals who completed a baseline assessment were included in analyses even if subsequent data were missing.

Each outcome variable was modeled for data collected at baseline, month 1, month 2, and month 5. Baseline IES was independently analyzed with each outcome
variable of physical and psychological functioning; thus, seven models were tested. Both fixed and random effects were tested. Fixed effects for baseline IES, Time, and the IES x Time interaction were included in all models. The baseline IES effect tests the relationship between IES and the outcome of interest at baseline. The Time effect tests whether the outcome changes during the follow-up period. The baseline IES x Time interaction determines if the rate of change on the outcome varies by the baseline IES value.

Initially, a first-order autoregressive error covariance structure was assumed. Then, each model was constructed in 4 general steps. (1) An unconditional growth model containing only fixed effects using linear and quadratic trajectories as the only predictors was conducted for the outcome of interest. The quadratic model was retained if the quadratic slope was significant (p < 0.05). (2) Intercept (baseline), linear change, and quadratic change (if needed) were tested as random effects for all models to determine if including any of these random effects and their covariances would improve model fit by examination of the Akaike Information Criterion (AIC) and negative 2 log likelihood (−2LL). A significant random intercept, linear slope, and quadratic slope indicates there is significant variability among participants at baseline, in their linear slope, and in their quadratic slope, respectively. (3) All possible controls and baseline IES were added to the models. The best fitting covariance structure was then determined. Homogeneous, diagonal, first-order autoregressive, and unstructured covariance structures were examined and the best fitting was determined using the AIC and the −2LL. The following were considered as controls: age (continuous, mean-centered), gender (0 = female), del17p status (0 = absent), number of prior therapies (continuous, mean-centered), and
comorbidity index (with 2 subtracted to make the lowest value 0). All main effects and two-way interactions with Linear and Quadratic (if needed) functions were entered into the model. Due to the small sample size, all non-significant controls (p > 0.20) were eliminated one by one in a backwards step fashion to create a more parsimonious final model. If a higher-order interaction was significant, its lower order interaction factor was retained in the analyses, even if not significant. For example if del17p x Quadratic was significant, del17p x Linear and del17p were retained in the analyses. These analyses show the overall trajectory of each outcome and the impact of baseline IES on this trajectory. In all models, IES was retained as a continuous variable, but for illustrative purposes the figures represent a median split at baseline.

For all analyses, residuals were examined to determine if they were non-normal, an assumption of HLM. If this was the case, the variable was either square-root or log-transformed if positively skewed or reflected and then square-root transformed if negatively skewed. Outliers in the residual plots were also analyzed. Outcomes of interest did not change as a result of transformation, therefore, the non-transformed data is presented for ease of interpretation. However, any differences of note are indicated.

**Hypothesis III: Higher levels of pre-treatment cancer-specific stress will be associated with higher levels of pre-treatment cytokines and a slower decline in cytokines over 2 months.** Hierarchical linear modeling was also utilized to test the effect of baseline cancer-specific stress on the trajectory of the cytokines (IL-6, TNF-alpha, and VEGF) during the first two months. Cancer-specific stress was independently analyzed with each outcome variable; thus, 3 models were tested. Cytokine data were modeled for data collected at baseline, month 1, and month 2. Each model was
constructed using 4 general steps as described above, excepting that only a linear trajectory was tested, as there were only 3 time points, and initially a homogeneous covariance structure was assumed due to the smaller sample size. These analyses show the overall trajectory of each cytokine and the impact of baseline IES on this trajectory. All cytokines were log-transformed, as they were all positively skewed. Analyses are presented on the log-transformed data, as this is often done in the literature (Breitbart et al., 2014; Sepah & Bower, 2009). In all models, IES was retained as a continuous variable, but for illustrative purposes the figures represent a median split at baseline.
Chapter 3: Results

Data Availability

All 150 participants were utilized for Aim I and Aim II analyses. Of the 150, 10 participants died and 8 were taken off the study by 5 months (See Figure 3). Of the 150, 141 (94%) completed a 1-month assessment, 137 (92%) completed a 2-month assessment, and 124 (83%) completed a 5-month assessment. Furthermore, if a participant did not complete more than 75% of a scale and/or subscale their score on that scale was not included in analyses. If individuals missed an item (no more than 25%), then the scales were calculated by averaging across the number they did complete and multiplying that by the possible number of items.

For Aim III, 48 participants were studied. The first 24 participants were chosen by rank ordering the accrued participants by that time by the measure of their IES on the initial day of treatment within their gender, as it is unknown if there are differences in immunity and distress by gender in this population. Using this strategy, every third participant was chosen to attain 12 females and 12 males with a distribution of IES scores. The second group of 24 participants were randomly chosen from participants who had been accrued and had samples at each time point (see Table 2 for sociodemographic characteristics).
Preliminary Analyses

Descriptive statistics of variables are presented in Tables 3-4. At baseline, BDI-II cognitive-affective scale (ρ = .547; p < .001), POMS-TMD (ρ = .594; p < .001), SF-12 MCS (ρ = -.404; p < .001), sleep disturbance (ρ = .318; p < .001), and fatigue interference (ρ = .305; p < .001) were significantly correlated with IES. SF-36 bodily pain (ρ = -.101; p = ns) and SF-12 PCS (ρ = -.042; p = ns) were not significantly correlated with IES at baseline. Cytokines were not significantly correlated with IES at baseline (ρ’s = -.042 - .245)

Aim I: Regression Analyses at Baseline of Psychological and Physical Outcomes

All residual plots were skewed, and therefore analyses were conducted on square root (if positively skewed) or reflected and then square root (if negatively skewed) transformed variables. However, as substantive results did not change after transformation and for ease of interpretation, the untransformed results are presented. The results of the regressions examining the relationship between IES and outcomes at baseline are summarized in Table 5. Based on Spearman Rho correlations (ρ < 0.10) the following controls were included in the following models: age was significantly correlated with BDI-II cognitive-affective scale, SF-12 MCS, and SF-12 PCS; Charlson Comorbidity Index with SF-36 bodily pain; del17p with BDI-II cognitive-affective scale, POMS-TMD, sleep disturbance, SF-36 bodily pain, fatigue interference, and SF-12 PCS; and prior number of therapies with sleep disturbance, SF-36 bodily pain, fatigue interference, and SF-12 PCS. When IES was added to each model after inclusion of significant covariates, it was a significant unique predictor of BDI-II cognitive-affective
scale (β = 0.492; p < .001), POMS-TMD (β = 0.601; p < .001), SF-12 MCS (β = -0.418; p < .001), sleep disturbance (β = 0.314; p < .001), and fatigue interference (β = 0.348; p < .001) in the expected directions. IES accounted for 10% to 36% of the variance in these outcomes, as measured by change in R². IES did not covary with SF-36 bodily pain (β = -0.088; p = .258) and the SF-12 PCS (β = -0.041; p = .595).

**Aim II: HLM Analyses of Psychological and Physical Outcomes**

All residual plots indicated non-normality, and therefore analyses were conducted on transformed variables. However, as substantive results did not change after transformation and for ease of interpretation, the untransformed results are presented. The results of the unconditional HLM models of physical and psychological outcomes with only fixed and random effects of intercept and time are summarized in Table 6. In the unconditional growth models with fixed effects, the quadratic rate of change was significant for all variables, except SF-12 MCS (See Figures 4-11). For the BDI-II cognitive-affective scale, POMS-TMD, fatigue interference, and sleep disturbance the variables decline in the first 1-2 months and then level off or slightly rise. For the SF-12 PCS, on average there is an increase (indicative of improvement) in the first 2 months, which then levels off. With the SF-36 bodily pain, on average it initially goes up (indicative of improvement) and then almost returns back to the baseline level by 5 months. For the SF-12 MCS, neither the quadratic nor linear rate of change was significant.

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1 Analyses were also conducted removing those 18 participants who died or were taken off study. The only difference noted was that baseline IES was a predictor of linear and quadratic slope for bodily pain, but this did not impact final interpretations. Analyses are only presented including the entire sample (N=150).
Random effects were also examined. Intercept, linear, and quadratic random effects with an unstructured covariance matrix was the best fitting model for all outcomes except the SF-12 MCS and the SF-36 bodily pain scale, which included only random intercepts. With regards to the error covariance structure, a homogeneous variance structure fit best for the BDI-II cognitive-affective scale, sleep disturbance, fatigue interference, and the SF-12 PCS, a diagonal covariance structure fit best for the SF-12 MCS, and a first-order regressive fit best for the POMS-TMD and SF-36 bodily pain.

The results of the conditional HLM models of baseline IES and covariates predicting the physical and psychological outcomes are summarized in Table 7. Parameter estimates for random effects and covariates were not included in this table for clarity, but Appendix C provides an example of a full HLM model with all parameter estimates for the BDI-II cognitive-affective scale. For the psychological outcomes, IES at baseline was significantly related to intercept, linear slope, and quadratic slope for the BDI-II cognitive-affective scale and the POMS-TMD (see Figures 11-12). That is, higher baseline levels of IES were associated with greater baseline BDI-II cognitive-affective scores ($\gamma_{\text{IES}} = 0.216, p < .001$) and baseline POMS-TMD ($\gamma_{\text{IES}} = 1.349, p < .001$). Furthermore, higher baseline IES was related to a faster decline, indicated by a more negative linear slope, in the BDI-II cognitive affective score ($\gamma_{\text{IES}*\text{Linear}} = -0.075, p < .001$) and POMS-TMD ($\gamma_{\text{IES}*\text{Linear}} = -0.639, p < .001$). Higher IES at baseline was also related to a more positive quadratic slope, indicating a greater leveling out of the BDI-II cognitive affective score ($\gamma_{\text{IES}*\text{Quadratic}} = 0.010, p = .003$) and POMS-TMD ($\gamma_{\text{IES}*\text{Quadratic}} = 0.092, p < .001$). With regards to the SF-12 MCS, IES at baseline was significantly related to both intercept and linear slope. Higher baseline IES was related to lower SF-12 MCS scores at
baseline ($\beta_{\text{IES}} = -0.386 \ p < .001$) and a more rapid improvement over time, as indicated by a more positive linear slope ($\beta_{\text{IES} \times \text{Linear}} = 0.055, \ p = .001$; see Figure 13). In summary, higher IES at baseline was related to poorer psychological functioning at baseline, with a more rapid rate of improvement over time in these outcomes.

For the physical outcomes, IES at baseline was related to intercept, linear slope, and quadratic slope for fatigue interference (see Figure 16). That is, higher baseline levels of IES were associated with greater baseline fatigue interference ($\beta_{\text{IES}} = 0.664, \ p < .001$), a faster decline, indicated by a more negative linear slope ($\beta_{\text{IES} \times \text{Linear}} = -0.375, \ p < .001$), and a more positive quadratic slope ($\beta_{\text{IES} \times \text{Quadratic}} = 0.055, \ p = .004$), indicating a greater leveling out of this outcome. IES was related to only the intercept for sleep disturbance ($\beta_{\text{IES}} = 0.673, \ p < .001$), indicating that higher IES at baseline was related to greater sleep disturbance but not linear or quadratic rate of change (see Figure 14). However, in follow-up analyses, when the non-significant IES x quadratic term was removed, IES became a significant predictor of linear slope ($\beta_{\text{IES} \times \text{Linear}} = -0.144; \ p < .001$), indicating that individuals with higher IES at baseline had a steeper linear rate of improvement in sleep disturbance. IES was not a predictor of intercept, linear slope, or quadratic slope for SF-36 bodily pain or SF-12 PCS (all p’s > 0.05; see Figures 15 & 17). In follow-up analyses, when the non-significant IES x quadratic term was removed, the IES was still not a predictor of linear slope for SF-36 bodily pain or SF-12 PCS. In summary, higher IES at baseline was related to greater fatigue interference and sleep

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2 When fatigue was log-transformed, IES was no longer predictive of linear or quadratic slope. However, when the IES x quadratic term was removed, baseline IES was a significant predictor of linear slope.
disturbance at baseline and more rapid rates of improvements on these outcomes. IES was not related to SF-12 PCS or SF-36 bodily pain.

In follow-up analyses to determine whether IES at baseline was still predictive of the outcomes at month 5, correlations were conducted between the predicted values from each hierarchical linear model at month 5 from each outcome and raw IES scores at baseline. These analyses indicated, that individuals with higher baseline IES still had higher BDI-II cognitive-affective (r = .292; p < .001) and POMS-TMD scores (r = .211; p < .05), and lower SF-12 MCS (r = -.165; p < .05) scores at 5 months. However, there was not a significant relationship between baseline IES and predicted values of sleep disturbance (r = -.032; p = .700), SF-36 bodily pain (r = .138; p = .093), fatigue interference (r = .132; p = .107), or SF-12 PCS (r = .135; p = .101) at 5 months, indicating that all individuals came to similar levels on the physical outcomes over time regardless of any differences at baseline.

**Aim III: HLM Analyses of Cytokines**

For all cytokines, the log-transformation was applied because the distributions were positively skewed. For TNF-alpha, 22% of the values were imputed with half the minimal detectable level (0.8 pg/ml). For VEGF, only 1 value (0.1%) was imputed with half the minimum detectable level (4.50 pg/ml). No values were imputed for IL-6.

The results of the unconditional HLM models of cytokine outcomes with only fixed and random effects of intercept and time are summarized in Table 8. In the unconditional growth curves, IL-6 did not have a significant linear slope, VEGF had a significant positive slope, and TNF-alpha had a significant negative slope.
In the unconditional growth curves, a random intercept and random slope improved model fit for IL-6, but allowing these random effects to covary did not improve fit. Only a random intercept improved model fit for TNF-alpha and VEGF. The best fitting error covariance structure was a homogeneous structure for IL-6 and TNF-alpha, whereas the diagonal structure was best fitting for VEGF.

The results of the conditional HLM models of IES and covariates predicting the cytokine outcomes are summarized in Table 9. For IL-6, baseline IES significantly impacted the rate of change of IL-6 ($\gamma_{\text{IES}*\text{Linear}} = -0.006, p = .051$), but not the baseline value ($\gamma_{\text{IES}} = -0.006, p = .396$), such that higher baseline IES was related to a faster decline (see Figure 18). Baseline IES significantly impacted initial TNF-alpha ($\gamma_{\text{IES}} = 0.022, p = .046$), but not rate of change ($\gamma_{\text{IES}*\text{Linear}} = -0.001, p = .820$), such that individuals with higher IES at baseline had higher levels of TNF-alpha at baseline which remained elevated over time (see Figure 19). Baseline IES was neither related to the intercept nor rate of change of VEGF ($p$’s > 0.05; see Figure 20).
Chapter 4: Discussion

The present study examined the role of baseline cancer-specific stress on psychological, physical, and immunological responses in patients with relapsed/refractory CLL undergoing treatment with ibrutinib. Results show favorable changes in psychological and physical functioning over time with depressive symptoms, mood disturbance, fatigue interference, sleep disturbance, and physical QOL improving during the first 5 months of treatment. At baseline, cancer-specific stress covaried with depressive symptoms, mood disturbance, mental health QOL, fatigue interference, and sleep disturbance. Results also revealed an interaction between baseline cancer-specific stress and trajectories of depressive symptoms, mood disturbance, mental health QOL, sleep disturbance, and fatigue interference. Those patients with higher baseline cancer-specific stress started out with poorer psychological and physical functioning, but demonstrated more rapid rates of improvement over time. However, they remained elevated on psychological outcomes but not physical outcomes at 5 months. Cytokine analyses demonstrated a decrease in TNF-alpha, increase in VEGF, and stability of IL-6 over the first 2 months of treatment. Furthermore, baseline cancer-specific stress at baseline covaried with baseline TNF-alpha and interacted with IL-6 slope, such that individuals with higher baseline cancer-specific stress demonstrated higher TNF-alpha and a more rapid decline in IL-6 over time.
As predicted, on the first day of treatment, there was significant variability in cancer-specific stress. Thus, despite individuals experiencing the same chronic stressor, progression of CLL, there were individual differences in their stress response.

Participants, on average, reported similar levels of intrusions ($M = 4.79$) as 558 breast cancer survivors who recently completed treatment ($M = 4.59$; Dupont et al., 2014) and similar levels of overall cancer-specific stress, including the hyperarousal scale ($M = 11.66$), as 112 “watchful waiting” CLL patients ($M = 13.7$; Morrison, 2013)$^3$. On the first day of treatment, participants, on average, also reported minimal cognitive-affective depressive symptoms, low mood disturbance, and good mental health QOL. Their mean scores ($M = 52.33$) on the SF-12 MCS were comparable to published norms for the U.S. population ($M = 50.04$) and greater than cancer patients ($M = 47.12$; Ware et al., 2002).

In a validation sample, 479 patients awaiting bone marrow transplant, the average POMS-TMD score was 25.1$^4$, whereas in this sample it was only 7.9 (Baker, et al., 2002). The majority of participants had a zero on the BDI-II cognitive-affective scale, with a mean of 2.85, similar to the mean in a sample of 213 hospitalized cancer patients ($M = 2.9$; Wedding, et al., 2007). Overall, these results suggest that even with the necessity of experimental therapy, the CLL patients who are considered to have the severest disease are not reporting elevated levels of psychological distress at treatment initiation.

In contrast, patients reported significant physical impairment. Physical health-related QOL (SF-12 PCS) scores ($M = 39.50$) were comparable to norms reported for cancer patients ($M = 40.76$) and worse than the average U.S. population ($M = 50.12$;

$^3$ This author could not find a reference in which the intrusions, avoidance, and hyperarousal subscale means were independently reported for the IES-R. Therefore, direct comparisons with other studies of the sum of intrusions + avoidance scale utilized in this study could not be done.

$^4$ They report a mean of 49.1, but it appears they added 24 to the score to make the lowest value 0.
Ware, et al., 2002). These patients reported more fatigue interference (M = 16.36) compared to “watchful-waiting” CLL patients (M = 11.4; Morrison, 2013), but less (M = 20.93) compared to 62 chronic myeloid leukemia patients treated with tyrosine kinase inhibitors for a mean of 4 years (Phillips et al., 2012). For CLL patients who are “watchful waiting” or in active treatment, the SF-36 bodily pain ranged from 53.47-58.21, whereas in this sample it was 68.41 indicating less pain than reported in other CLL patients (Levin et al., 2007), but similar to a sample of 488 patients with chronic myeloid leukemia treated with long-term tyrosine kinase inhibitors (M = 70.4; Efficace et al., 2011). Their mean scores on sleep disturbance (M = 29.88) were also comparable to published norms of 3,445 individuals with chronic illness (M = 28.31; Spritzer & Hays, 2003). Therefore, relapsed/refractory CLL patients have overall poor physical QOL, have greater fatigue interference than “watchful waiting” CLL patients, but are not reporting significant sleep disturbance or pain.

As hypothesized, there was a significant relationship between cancer-specific stress and psychological outcomes at baseline with higher stress related to more depressive symptoms, greater mood disturbance, and poorer mental health QOL. These results are consistent with the cancer literature, in which cancer-specific stress and its components, avoidance and intrusions, have been reliably associated with measures of psychological functioning, QOL, depression, and anxiety in numerous cancer populations from diagnosis to long-term survivorship (Butler et al., 1999; Dirksen et al., 2009; Epping-Jordan et al., 1999; Golden-Kreutz & Andersen, 2004; Lewis et al., 2001). This study adds onto the existing literature by determining that this relationship between the
subjective stress response and psychological distress also exists among individuals with relapsed/refractory disease.

In contrast, the relationship between cancer-specific stress and physical outcomes was more variable. Cancer-specific stress covaried with sleep disturbance and fatigue interference, but not pain and overall physical QOL. Previous studies have shown that both intrusions (Wright, Schnur, Montgomery, & Bovbjerg, 2010) and avoidance (Hoyt, Thomas, Epstein, & Dirksen, 2009) are related to sleep difficulties in cancer populations. Furthermore, with increased stress there may be heightened sensitivity to physical symptoms or activation of biological pathways that lead to symptoms such as fatigue (Bower, Crosswell, & Slavich, 2014). Surprisingly, cancer-specific stress was not found to be related to pain, even though fatigue, pain, depression and sleep problems often co-occur in cancer patients and are believed to have common underlying biological mechanisms (Bower, 2008; Cleeland et al., 2003; Thornton, Andersen, & Blakely, 2010). However, these patients reported little pain, and thus there may have been insufficient power to detect any relationship. The non-significant relationship with concurrent physical QOL is also consistent with findings in newly diagnosed breast cancer patients (Golden-Kreutz & Andersen, 2004).

Importantly, the study provides insight into trajectories of physical and psychological functioning of these patients. The data show significant improvements in all outcomes excepting mental health QOL. Furthermore, bodily pain seemed to improve, but then almost return back to the baseline value. Improvements in outcomes were typically seen early--the first 1-2 months--after treatment initiation. This suggests that ibrutinib may not only have a positive impact on disease progression, but also on
various aspects of psychological and physical functioning. This is in contrast to the majority of CLL clinical trials, which typically do not indicate an improvement in QOL during treatment (Andersen et al., in prep). This is also in contrast to solid tumor patients undergoing traditional therapies, such as chemotherapy or radiation, who often experience an increase in symptoms such as fatigue during active treatment, which may then remit or persist long after treatment completion (Donovan et al., 2004; Rosenthal et al., 2014; Thornton, Carson, Shapiro, Farrar, & Andersen, 2008). Targeted therapies, such as ibrutinib, are known to have fatigue and pain as common side effects. However, in the only other known study to examine QOL in patients with CLL taking ibrutinib (with rituximab), overall QOL, pain, and fatigue were improved when assessed after 6 and 12 months (Burger et al., 2014). This study expands these findings to depressive symptoms, mood disturbance, and sleep disturbance. Future studies need to replicate these findings and examine trajectories as treatment cycles continue.

Although improvements were seen, on average, there was still significant inter-individual variability in the trajectories. In fact, numerous studies in cancer patients have found that there is a great heterogeneity of responses with regards to trajectories of psychological and physical functioning (L. B. Dunn et al., 2011; Van Onselen et al., 2012). Current guidelines for cancer care emphasize the need for detecting cancer patients with increased distress in order to target and provide interventions for those who need it most (Andersen, Rowland, & Somerfield, 2014). Therefore, investigating factors at diagnosis that predict poorer outcomes would help to identify those in need of psychological treatment and to determine the best time to intervene, if at all.
In patients with relapsed/refractory CLL, cancer-specific stress at baseline is one such predictor. Higher cancer-specific stress at baseline was related to poorer initial levels and greater improvements in depressive symptoms, mood disturbance, and mental health QOL, whereas lower cancer-specific stress at baseline seemed to be related to constant, low levels of these same outcomes over time. Furthermore, follow-up analyses indicated that individuals with higher cancer-specific stress at baseline continued to have higher levels of depressive symptoms, mood disturbance, and worse mental health QOL at 5 months. Results from breast cancer survivors indicate a similar pattern with intrusive thoughts after treatment completion predicting more depressive symptoms, more negative affect, and poorer mental health QOL over the following year (Dupont et al., 2014). Therefore, this study provides more evidence that cancer-specific stress is a consistent predictor of poorer psychological functioning, even among those with relapsed/refractory disease.

Whereas individuals with higher cancer-specific stress at baseline continued to have poorer psychological functioning, any differences at baseline in physical outcomes became null after 5 months. As described above, higher cancer-specific stress at baseline was related to greater fatigue interference and sleep disturbance at baseline, but was also related to a larger improvement of these symptoms over time. For pain and physical QOL, no differences were noted initially and over time by baseline cancer-specific stress. As a result, at 5 months those individuals with higher cancer-specific stress at baseline had similar levels of physical QOL, sleep disturbance, fatigue interference and pain compared to those with lower stress at baseline. Overall, stress appears to predict concurrent fatigue and sleep, but not levels thereafter. These findings are in contrast to
breast cancer survivors, which demonstrated that women with higher levels of intrusive thoughts at baseline stayed worse on fatigue, sleep quality, and pain after a year (Dupont et al., 2014). It may be possible that due to the potency and efficacy of ibrutinib, regardless of one’s stress level at baseline, physical symptoms improve drastically for everyone.

When examining the cytokines, trajectories differed. Despite both IL-6 and TNF-alpha being related to poorer prognosis in CLL, only TNF-alpha significantly declined. This is consistent with findings in a previous study, which demonstrated a significant decline in TNF-alpha after 1 month in 40 patients with relapsed/refractory CLL taking ibrutinib and rituximab (Burger et al., 2014). These findings also support in vitro evidence for ibrutinib-associated declines in TNF-alpha in T cells (Herman et al., 2011). Contrary to hypotheses, VEGF increased over time in the sample. Previous clinical trials in CLL patients using ibrutinib have demonstrated that there is increased lymphocytosis, or increased lymphocytes in the blood, after starting the drug (Woyach et al., 2014). Interestingly, this lymphocytosis is not associated with adverse progression-free survival (Woyach et al., 2014). Previous research has also shown that in patients with CLL, serum levels of VEGF are significantly related to peripheral blood lymphocytosis (Molica et al., 1999). While the exact relationship between CLL and VEGF is unknown, there may be a possible relationship between the increased lymphocytosis and increased VEGF. Therefore, the relationship between VEGF levels in blood and the efficacy of ibrutinib may be more complex than initially hypothesized and needs further study.

When examining the impact of cancer-specific stress on trajectories, those with higher baseline stress remained higher on TNF-alpha than those with lower stress. On
the contrary, cancer-specific stress was not related to baseline IL-6, but did interact with slope, such that those with higher stress at baseline had a greater decline in IL-6 over time. Although one would expect IL-6 and TNF-alpha to demonstrate similar patterns, previous research in CLL has indicated that whereas TNF-alpha is related to the survival and proliferation of B-CLL lymphocytes, IL-6 inhibits the proliferation of B-CLL cells that are induced by TNF-alpha (Aderka et al., 1993). Furthermore, a previous study in prostate and breast cancer patients found that greater positive affect was related to higher levels of IL-6 during radiation treatment (Sepah & Bower, 2009). This result was also considered to be counterintuitive, and the authors hypothesized that IL-6 production may be beneficial in the short-term during treatment, but may be harmful if too large, occurs too frequently, or remains elevated over time. (Sepah & Bower, 2009). Therefore, the elevated IL-6 in patients with low cancer-specific stress at baseline may not have adverse effects on CLL cell proliferation.

Cancer-specific stress had no relationship with VEGF, despite previous studies indicating that psychosocial variables, such as social support and depressive symptoms, are associated in solid tumor cancer patients (Fang et al., 2013; Sharma et al., 2008). However, this finding may be due to a small effect size in this relationship that could not be detected in the small sample size. Furthermore, all known studies examining the relationship between VEGF and psychosocial variables have been done in patients with solid tumors. Although VEGF is now considered to play a crucial role in hematologic cancers, the relationship between VEGF and psychosocial variables may be different in this population.
Strengths and Limitations

The present study adds to the current literature on psychological and biobehavioral outcomes in an understudied population, patients with CLL. This is the first known study to examine the relationship between behavioral and biological variables in CLL. The longitudinal design allowed for the examination of trajectories of outcomes for the first 5 months in patients receiving ibrutinib, a treatment increasingly used for this disease. Furthermore, other studies used only general QOL scales (e.g., SF-36, EORTC, FACT-G) with only two exceptions (Levin et al., 2007; Morrison, 2013). Using specific measures allowed for the detection of psychological and physical change, compared with the null effects on mental health QOL which mirrors the findings in many other studies of CLL patients. Furthermore, the use of HLM allowed the explicit modeling of individual differences in initial levels and changes in outcomes using all available data, with baseline cancer-specific stress considered as a predictor of these variables.

An additional strength of the study is that all participants were homogeneous in the treatment they were receiving. In many studies, cancer patients are receiving different types of treatment, and this must often be statistically controlled and results in a decrease in power. In this sample, the homogeneity of treatment is not a source of variability and provides a more stringent examination of the role of cancer-specific stress in patients as they undergo treatment.

However, the findings must also be interpreted in the context of the limitations of the study. First, the generalizability of the findings to more diverse populations may be limited. In general, in clinical trials with cancer patients, minorities (Heller et al., 2014) and older adults (Eichhorst et al., 2009) are underrepresented. Therefore, compared to the
average CLL patient ($M = 69.6$ years old; 88.9% Caucasian, 6.8% African-American, 1.4% Hispanic; 59% male) as estimated from the National Cancer Data Base (Diehl, Karnell, & Menck, 1999), participants in this trial were younger ($M = 64.0$), more likely to be Caucasian (97%), and more likely to be male (71%). Thus, findings may not be generalizable to older, minority populations of lower socioeconomic status.

Secondly, although longitudinal, the data is observational and does not allow for causal or temporal inferences to be made on the relationship between stress and psychological, physical, and immunological responses. Cancer-specific stress was conceptually chosen as the predictor in this study, however, the relationship between stress and the outcomes is likely to be bidirectional.

**Implications and Future Directions**

In summary, this study provides new data of biobehavioral aspects of CLL. The context of the research is important, as ibrutinib was recently FDA-approved and will likely become a frontline therapy (Aalipour & Advani, 2014). Findings provide support for the hypothesis that biobehavioral relationships hold true not only in solid tumors, but are also of relevance to hematologic cancers. Therefore, future studies are needed to determine the reliability of these findings, as well as to examine other biological variables of interest specific to hematologic cancers. Studies examining stress as a predictor of clinical and functional outcomes, such as number of hospitalizations, experienced toxicities, disease progression, and survival are also warranted. For example, in animal models chronic stress has been shown to accelerate progression of hematologic cancers,
such as acute lymphoblastic leukemia (Lamkin et al., 2012). In vivo studies of such findings are needed.

Second, examining the trajectories of symptoms over time provides additional support for not only the efficacy of ibrutinib on clinical outcomes, but also psychological and physical functioning. Unlike other treatments, which are accompanied with fatigue, gastrointestinal toxicity, neuropathy, and other effects, these data suggest ibrutinib has minimal toxicities and adverse side effects. Given that ibrutinib is likely to become a widely used treatment for CLL, these results are promising for patients’ QOL as they undergo treatment. The longitudinal interval studied here is a strength, but longer trajectories are needed. Unlike other cancer treatments which are often time-limited, at present ibrutinib is being used until disease progression or unacceptable toxicity arises. Until the dosage regimen changes, understanding the long-term implications of this drug is important.

Additionally, cancer-specific stress as an indicator of individuals who start out with poorer psychological functioning and continue to have higher levels of distress provides insight into patients at risk for poorer psychological functioning. On average, patients reported minimal distress at the beginning of treatment, indicating that most patients are likely not in need of intervention. However, those patients experiencing greater levels of intrusions and avoidance may be at risk for continued difficulties with psychological functioning. Overall mental health QOL, depressive symptoms, and mood might be improved if psychological interventions are offered to patients with high stress at the time of beginning treatment. However, based on this current study, such an intervention would likely not have an effect on physical outcomes, as all individuals
came down to similar levels of physical health after 5 months, regardless of their stress levels at the beginning of treatment. Yet due to the variation in intercepts and slopes in all of the outcomes, it is likely that a subset of patients may also demonstrate poor physical functioning over time. Therefore, one possible future direction is to look at other variables of interest (e.g., social support) to determine what else might moderate psychological and physical trajectory outcomes. Identifying risk factors for poorer functioning will allow for greater sensitivity in determining who might be helped with psychological or behavioral interventions.
References


previously untreated patients with chronic lymphocytic leukemia. Journal of Clinical Oncology, 22(7), 1260-1267. doi: 10.1200/JCO.2004.05.012


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Appendix A: Tables
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Aim(s)</th>
<th>Sample</th>
<th>Baseline Sample Description</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holzner, et al., 2001</td>
<td>Cross-sectional study</td>
<td>1) Compare two measures of QOL in cancer patients</td>
<td>381 cancer patients (118 patients with breast cancer, 126 with Hodgkin’s disease, 81 with CLL, and 56 bone marrow transplant [BMT] patients)</td>
<td>CLL: mean age = 67.1 years; 59% male; mean time since diagnosis = 4.8 years; 44% had chemotherapy at some point</td>
<td>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-30); Functional Assessment of Cancer Therapy-General Scale (FACT-G)</td>
<td>Patients with CLL had worse physical and role functioning compared to BMT patients, but better social functioning using the EORTC QLQ-30. BMT patients had worse emotional functioning compared to CLL using the FACT-G. Patient age influenced scores on the EORTC but not on the FACT-G.</td>
</tr>
<tr>
<td>Osterborg, et al., 2002</td>
<td>Randomized clinical trial (epoetin beta vs. placebo); Assessments completed at baseline and after 4,8,12, and 16 weeks.</td>
<td>1) Investigate the effect of epoetin beta on anemia and transfusion need in severely anemic patients 2) Investigate the effect of epoetin beta on QOL</td>
<td>343 hematologic cancer patients (125 with CLL, 102 with non-Hodgkin’s lymphoma, 116 with Multiple Myeloma)</td>
<td>All patients: 50% male; median age = 63.5 years</td>
<td>FACT-G; FACT-AN (Anemia); FACT-F(Fatigue)</td>
<td>There was higher transfusion free survival for epoetin beta vs. placebo. Greater improvements in FACT-G, FACT-AN, and multiple subscales at 12 and 16 weeks for epoetin vs. placebo. However, there were no differences in FACT-AN or FACT-F by treatment group at any point.</td>
</tr>
</tbody>
</table>

Table 1. Quality of Life Studies in Patients with CLL
### Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Aim(s)</th>
<th>Sample</th>
<th>Baseline Sample Description</th>
<th>Measures</th>
<th>Findings</th>
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</thead>
</table>
| Holzner, et al., 2004 | Longitudinal study; Assessments completed at baseline, and after 3, 6, and 12 months | 1) Determine long-term QOL of patients with CLL  
2) Investigate the relationship between QOL and sociodemographic and clinical parameters | 76 patients with CLL and 152 age-and-gender matched controls          | CLL: median age= 68 years; 59% male; Mean time since diagnosis = 4.8 years; 43% had chemotherapy before baseline, but 0% in active treatment at baseline  
Controls: Median age =66.5 years; 59% male | EORTC QLQ-30 | Significant differences in QOL between patients and healthy controls. Female CLL patients had worse emotional and social functioning than male patients. No differences in QOL observed between CLL patients who had already received treatments and those who had not.  
There was a 71.6% response rate, with a median of 841 days to progression.  
Improvements were seen in mean emotional scores and insomnia.  
There were no significant differences in survival between treatments. QOL was better for responders vs. non-responders, but no significant differences between treatments at any time point. |
| Rossi, et al., 2004       | Phase II trial (oral fludarabine); Assessments completed at baseline, 3 months, and post-treatment Randomized clinical trial (fludarabine alone or fludarabine + cyclophosphamide) Assessments completed at baseline, and 3, 6, 12, 24, 36, 48, and 60 months | 1) Assess oral fludarabine phosphate in terms of safety, efficacy, and QOL. | 81 patients with untreated CLL | Mean age = 61 years; 63% male; 0% treated | EORTC QLQ-C30 |                                                                   |
| Catovsky, et al., 2007    | Randomized clinical trial (fludarabine alone or fludarabine + cyclophosphamide) Assessments completed at baseline, and 3, 6, 12, 24, 36, 48, and 60 months | 1) Compare overall survival between treatments  
2) Compare QOL between treatments | 387 patients with untreated CLL | Median age = 65 years; 74% male; 0% treated | EORTC QLQ-C30 |                                                                   |
<table>
<thead>
<tr>
<th>Study</th>
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</thead>
</table>
| Eichhorst, et al., 2007   | Randomized clinical trial                   | 1) Compare QOL of untreated CLL patients undergoing treatment to normative data.  
2) Compare QOL changes between treatments  | 321 patients under 66 years old with advanced, untreated CLL           | Mean age= 56.6 years; 73% male; 0% treated         | EORTC QLQ-C30               | Significant differences in QOL between full sample and normative German population data at baseline. No significant differences in QOL between patients receiving different treatments. |
| Levin, et al., 2007       | Cross-sectional, group-comparison           | 1) Compare anxiety, depression, and quality of life in “watch and wait” patients vs. those in active treatment | 105 patients classified into “watch and wait” (n=57) or active treatment (n = 48) | “Watch and wait”: Mean age= 59.1 years; 61% male; 0% treated; Mean time since diagnosis = 4.12 years  
“Active treatment”: Mean age = 58.9 years; 65% male; 100% treated; mean time since diagnosis = 5.62 years | BDI-II; Beck Anxiety Inventory; FACT-Lymphoma; SF-36: Patient Health Questionnaire | No significant differences in depression, anxiety, and QOL between groups. Patients ≤ 60 years old had greater depressive symptoms and poorer QOL. Poorer physical QOL related to longer time since diagnosis. |
<p>| Shanafelt, et al., 2007   | Cross-sectional, web-based study            | 1) Examine QOL in CLL patients                                           | 1482 CLL patients                                   | Median age= 59 years; 57% male; median time since diagnosis= 3.4 years; 40% treated some point in past and 9% on active therapy | Brief Fatigue Inventory; FACT-G                                   | No significant differences between published norms and patients on physical, social/family, functional, and overall QOL scores. Poorer emotional well-being in CLL patients compared to published norms. Poorer QOL among individuals with advanced stage, older age, greater fatigue, severity of co-morbid health conditions, and being currently treated. |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Else, et al., 2008</td>
<td>Randomized clinical trial; baseline data</td>
<td>1) Examine effects of active, untreated CLL on QOL compared to population norms</td>
<td>777 untreated CLL patients (only 431 had valid baseline data)</td>
<td>Median age= 64 years; 74% male; median time since diagnosis= 8 months; 0% treated</td>
<td>EORTC-QLQ-C30</td>
<td>Compared to population norms, patients had QOL impairments in 13/15 possible domains. The largest difference was in fatigue, sleep disturbance, role functioning, and overall QOL. Older age was associated with poorer physical functioning. Fifty-six percent thought about their diagnosis daily. Greater than 90% felt their doctor understood how their disease was progressing, but less than 70% believed their physician understood CLL’s impact on QOL. Satisfaction with physicians in various areas, as well as phrases physicians used to describe CLL, were related to patient’s emotional and overall QOL.</td>
</tr>
<tr>
<td>Shanafelt, et al., 2009</td>
<td>Cross-sectional; web-based study</td>
<td>1) Evaluate patients’ satisfaction with physicians caring for them</td>
<td>1482 CLL patients</td>
<td>Median age= 59 years; 57% male; Median time since diagnosis= 3.4 years; 40% treated some point in past and 9% on active therapy</td>
<td>Brief Fatigue Inventory; FACT-G; Patient Satisfaction with Physician</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Aim(s)</td>
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<td>Baseline Sample Description</td>
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<tr>
<td>Else, et al., 2012</td>
<td>Randomized clinical trial (chlorambucil, fludarabine, or fludarabine+ cyclophosphamide [FC]); Assessments completed at baseline and after 3, 6, 12, 24, 36, 48, and 60 months</td>
<td>1) Compare changes in QOL between treatments</td>
<td>777 untreated CLL patients (only 409 included in main analyses)</td>
<td>Median age= 64 years; 74% male; median time since diagnosis= 8 months; 0% treated</td>
<td>EORTC-QLQ-C30</td>
<td>Greater QOL impairments at 3 months for those receiving fludarabine and FC compared to chlorambucil. QOL was similar between treatment groups. Those with complete or partial remission had QOL similar to general population, whereas those with disease progression had worse QOL, despite subsequent treatment. Rituximab significantly improved treatment response. QOL did not substantially change over the study period and differences between groups were small.</td>
</tr>
</tbody>
</table>
| Robak, et al., 2010   | Randomized clinical trial (rituximab plus fludarabine and cyclophosphamide [R-FC] or fludarabine + cyclophosphamide [FC]); Assessments completed at baseline, and at 3, 6, and 12 months. | 1) Compare responses to different treatment regimens  
2) Compare QOL between treatments | 552 CLL patients previously treated once | R-FC group: median age = 62.0 years; 66% male; median time since diagnosis = 3.69 years; 100% previously treated  
FC group: median age = 63.0 years; 68% male; median time since diagnosis = 3.79 years; 100% previously treated | FACT-G                           |                                                                                                    |
<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Aim(s)</th>
<th>Sample</th>
<th>Baseline Sample Description</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans, et al., 2012</td>
<td>Cross-sectional, qualitative</td>
<td>1) To better understand the effects of “watchful waiting”</td>
<td>12 CLL patients initially managed with “watch and wait”</td>
<td>Mean age = 68 years; 33% male; mean time since diagnosis = 6.6 years; 50% previously treated at time of interview</td>
<td>Qualitative interview</td>
<td>Some people reported distress over being diagnosed with an incurable condition without getting treatment. The invisibility of the condition contributed to some not disclosing their condition to others. As symptoms increased, patients made lifestyle changes even before treatment was recommended. Physical symptom burden and emotional distress were bidirectionally related. History of pharmacotherapy use, history of psychotherapy, and low social support moderated the relationship between physical symptom burden and distress.</td>
</tr>
<tr>
<td>Morrison, 2013</td>
<td>Cross-sectional</td>
<td>1) To examine the association between physical symptom burden and emotional distress 2) To examine the moderating role of history of pharmacotherapy, history of psychotherapy, social support, socioeconomic status, relationship satisfaction, and psychiatric history on the relationship between physical symptom burden and emotional distress</td>
<td>112 “watch and wait” CLL patients</td>
<td>Mean age=61 years old; 55% male; mean time since diagnosis= 4.6 years; 0% treated</td>
<td>Psychiatric history; Dyadic Adjustment Scale; FSI; Interpersonal Support Evaluations List; Center for Epidemiological Studies Depression Scale; Generalized Anxiety Disorder Questionnaire-IV; IES-R; Health Anxiety Questionnaire; CLL Signs and Symptoms; Brief Pain Inventory</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Aim(s)</td>
<td>Sample</td>
<td>Baseline Sample Description</td>
<td>Measures</td>
<td>Findings</td>
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</tr>
<tr>
<td>Pashos, et al., 2013</td>
<td>Cross-sectional</td>
<td>1) To examine the association between gender and QOL as CLL patients initiate therapy outside the clinical trial setting</td>
<td>1,140 CLL patients prior to starting a new treatment (first or subsequent treatment)</td>
<td>Mean age = 69 years; 62% male; 58% were initiating first-line therapy, 18% second-line therapy, and 23% a higher line of therapy</td>
<td>Brief Fatigue Inventory; FACT-Leukemia; EQ-5D</td>
<td>Women reported worse fatigue, pain, anxiety, and depression compared to men. Women reported overall worse QOL.</td>
</tr>
<tr>
<td>Burger, et al., 2014</td>
<td>Phase II trial (Ibrutinib + Rituximab); Assessments completed at 2nd week, 1 month, 3 months, 6 months, and 12 months</td>
<td>1) To examine progression-free survival (PFS) 2) To examine QOL over time during treatment</td>
<td>40 “high risk” CLL patients with relapsed CLL with del11q (n=13), a PFS &lt; 36 months after front-line therapy (n=7), or 17p deletion or TP53 mutation (n=20)</td>
<td>Median age = 63.2; 65% male; 90% previously treated</td>
<td>EORTC-QLQ-C30</td>
<td>At 18 months, PFS was 78%. Patients reported improvements in overall QOL, as well as in all the functioning, symptom, and item scales, except constipation.</td>
</tr>
<tr>
<td>De Wrede, et al., 2014</td>
<td>Randomized clinical trial (autologous stem cell transplantation + chemotherapy vs. observation only); Assessments completed at baseline and after 4, 8, 12, 24, 36, and 48 months</td>
<td>1) Assess impact of treatment on QOL over time.</td>
<td>186 CLL patients</td>
<td>Median age = 55; 73% male; 100% previously treated</td>
<td>EORTC-QLQ-C30</td>
<td>There is a negative impact of ASCT on QOL for the first year and comparable QOL in the following 2 years. For those patients who relapsed, QOL of life was worse and worsened over time.</td>
</tr>
</tbody>
</table>
### Sociodemographics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=150)</th>
<th>Patients for Cytokine Analyses (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years), M (SD)</td>
<td>64.0 (10.78)</td>
<td>64.3 (10.06)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School/Technical School or Below</td>
<td>44 (29%)</td>
<td>16 (33%)</td>
</tr>
<tr>
<td>Some College/College Graduate</td>
<td>57 (38%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Some Graduate School/Graduate Degree</td>
<td>46 (31%)</td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Household income (K)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>40 (27%)</td>
<td>15 (31%)</td>
</tr>
<tr>
<td>51-100</td>
<td>36 (24%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>46 (31%)</td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Prefers Not to Answer</td>
<td>23 (15%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Unknown to Participant</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>146 (97%)</td>
<td>48 (100%)</td>
</tr>
<tr>
<td>African-American</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Employment Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed Full or Part-time</td>
<td>44 (29%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Retired</td>
<td>79 (53%)</td>
<td>23 (48%)</td>
</tr>
<tr>
<td>Other (Disabled, Unemployed, Homemaker)</td>
<td>27 (18%)</td>
<td>13 (27%)</td>
</tr>
<tr>
<td>Married/Partnered (Yes)</td>
<td>130 (87%)</td>
<td>41 (85%)</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>107 (71%)</td>
<td>34 (71%)</td>
</tr>
<tr>
<td>Disease Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prior therapies, M (SD)</td>
<td>3.47 (2.61)</td>
<td>4.29 (2.72)</td>
</tr>
<tr>
<td>Deletion of 17p (Yes)</td>
<td>77 (51%)</td>
<td>23 (48%)</td>
</tr>
<tr>
<td>Unadjusted Charlson Comorbidity Index&lt;sup&gt;a&lt;/sup&gt;, M(SD)</td>
<td>2.53 (0.99)</td>
<td>2.63 (0.96)</td>
</tr>
</tbody>
</table>

<sup>a</sup>CCI includes the 2 points every participant would get for having leukemia

Table 2. Participant Characteristics
<table>
<thead>
<tr>
<th></th>
<th>Baseline (N = 150)</th>
<th>Month 1 (n = 141)</th>
<th>Month 2 (n = 137)</th>
<th>Month 5 (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IES - Total (Intrusions + Avoidance)</td>
<td>9.21 (8.37)</td>
<td>5.52 (6.61)</td>
<td>5.25 (6.02)</td>
<td>5.23 (5.93)</td>
</tr>
<tr>
<td>BDI-II, Cognitive- Affective Subscale</td>
<td>2.85 (3.67)</td>
<td>1.87 (2.89)</td>
<td>1.69 (2.50)</td>
<td>1.93 (3.16)</td>
</tr>
<tr>
<td>POMS-TMD</td>
<td>7.87 (20.07)</td>
<td>-1.45 (15.20)</td>
<td>-0.86 (16.46)</td>
<td>-0.62 (18.36)</td>
</tr>
<tr>
<td>SF-12 MCS</td>
<td>52.33 (8.88)</td>
<td>54.21 (8.44)</td>
<td>53.88 (8.47)</td>
<td>54.14 (8.65)</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>29.88 (18.30)</td>
<td>24.03 (16.49)</td>
<td>24.32 (16.91)</td>
<td>24.33 (17.46)</td>
</tr>
<tr>
<td>SF-36 Bodily Pain</td>
<td>68.47 (24.95)</td>
<td>75.42 (23.35)</td>
<td>74.69 (23.62)</td>
<td>71.37 (25.87)</td>
</tr>
<tr>
<td>Fatigue Interference</td>
<td>16.36 (15.58)</td>
<td>12.07 (15.20)</td>
<td>10.98 (13.55)</td>
<td>9.82 (13.28)</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>39.50 (11.83)</td>
<td>42.91 (11.18)</td>
<td>43.55 (11.15)</td>
<td>44.17 (11.44)</td>
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</table>

Note. IES = Impact of Events Scale; BDI-II = Beck Depression Inventory- 2nd Edition; POMS-TMD = Profile of Moods Total Mood Disturbance; MCS = Mental Component Summary; PCS = Physical Component Summary

Table 3. Descriptive Statistics for the Psychological and Physical Outcomes at Baseline, 1 month, 2 months, and 5 months for Aim II (N = 150)
<table>
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<tr>
<th>Cytokine</th>
<th>Baseline Mean (SD)</th>
<th>Month 1 Mean (SD)</th>
<th>Month 2 Mean (SD)</th>
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<tr>
<td>IL-6</td>
<td>12.06 (10.87)</td>
<td>10.85 (10.19)</td>
<td>12.80 (12.25)</td>
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<td>TNF-alpha</td>
<td>29.79 (34.71)</td>
<td>12.34 (25.25)</td>
<td>16.75 (45.08)</td>
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<td>VEGF</td>
<td>93.32 (85.02)</td>
<td>98.87 (92.75)</td>
<td>131.65 (113.07)</td>
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*Note. IL-6 = Interleukin-6; TNF-alpha = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor. All variables are in pg/ml.*

Table 4. Descriptive Statistics for the Cytokines at Baseline, 1 month, and 2 months for Aim III (n =48)
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<th>Δ R²</th>
<th>B</th>
<th>S.E.</th>
<th>95% CI</th>
<th>β</th>
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<td>.011</td>
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<tr>
<td>2. Del17p</td>
<td>.042</td>
<td>.031</td>
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<td>.163</td>
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<td>.016</td>
<td>4.748</td>
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<td>.119</td>
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<td>.008</td>
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<td><strong>Fatigue Interference (n = 149)</strong></td>
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<td>.047</td>
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<td>3. Prior Therapies</td>
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<td>-0.533</td>
<td>.595</td>
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</table>

*Note.* BDI-II = Beck Depression Inventory - 2nd edition; IES = Impact of Events Scale-Intrusions+Avoidance; Prior Therapies = Prior Number of Therapies

Table 5. Hierarchical Multiple Regressions of Cancer-Specific Stress Predicting Psychological and Physical Outcomes at Baseline
<table>
<thead>
<tr>
<th>Effect</th>
<th>Parameter estimate</th>
<th>Confidence interval</th>
<th>Wald $z$</th>
<th>df</th>
<th>t</th>
<th>p</th>
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<tr>
<td><strong>BDI-II Cognitive- Affective Scale</strong></td>
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<td>-0.653, -0.265</td>
<td>-4.637</td>
<td>&lt;.001</td>
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<td><strong>POMS-TMD: Mood Disturbance</strong></td>
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<td>Fixed Effects</td>
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<tr>
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Table 6. Hierarchical Linear Modeling of Unconditional Models (No Covariates) of Psychological and Physical Outcomes Predicted by Time with Fixed and Random Effects (N = 150)
Table 6 continued

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<th>SF-36 Bodily Pain</th>
<th>Effect</th>
<th>Parameter estimate</th>
<th>Confidence interval</th>
<th>Wald z</th>
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<th>p</th>
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<td>153.843, 376.187</td>
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</tbody>
</table>

Fatigue Interference

| Fixed Effects | Intercept       | 16.312             | 13.791, 18.832      | 147    | 12.790 | <.001 |
| Linear Slope  | -3.817          | -5.579, -2.056     | 143                | -4.284 | <.001 |
| Quadratic Slope | 0.522         | 0.209, 0.835       | 141                | 3.299  | .001  |
| Random Effects | Intercept variance | 185.780          | 136.286, 253.249    | 6.326  | <.001 |
| Linear variance | 38.192         | 16.342, 89.257     | 2.309              | .021   |
| Quadratic Variance | 0.971         | 0.332, 2.843       | 1.824              | .068   |
| Intercept-Linear Covariance | -37.621       | -70.399, -4.843    | -2.250             | .024   |
| Intercept-Quadratic Covariance | 4.596        | -0.914, 10.106     | 1.635              | .102   |
| Linear-Quadratic Covariance | -5.958        | -11.653, -0.263    | -2.051             | .040   |

SF-12 PCS: Physical Quality of Life

| Fixed Effects | Intercept       | 39.747             | 37.861, 41.633      | 150    | 41.639 | <.001 |
| Linear Slope  | 2.841           | 1.558, 4.124       | 134                | 4.379  | <.001 |
| Quadratic Slope | -0.412       | -0.634, -0.190     | 132                | -3.674 | <.001 |
| Random Effects | Intercept variance | 118.105          | 90.649, 153.876    | 7.408  | <.001 |
| Linear variance | 35.654         | 22.733, 55.919     | 4.355              | <.001  |
| Quadratic Variance | 0.925         | 0.547, 1.563       | 3.732              | <.001  |
| Intercept-Linear Covariance | -24.616       | -41.621, -7.611    | -2.837             | .005   |
| Intercept-Quadratic Covariance | 3.130        | 0.279, 5.980       | 2.152              | .031   |
| Linear-Quadratic Covariance | -5.556        | -8.294, -2.817     | -3.976             | <.001  |

Note. BDI-II = Beck Depression Inventory-2nd edition

* N=149 for analyses with Mood Disturbance
### Table 7. Hierarchical Linear Modeling of Conditional Models of Psychological and Physical Outcomes Predicted by Time with the Effects of Baseline Cancer-Specific Stress and Covariates (N = 150). Random Effects Are Not Included for Clarity.

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<th>p</th>
<th>Covariates Included</th>
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*a* Continued
Table 7 continued

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*Note. BDI-II = Beck Depression Inventory -2nd edition; IES = Impact of Events Scale-Intrusions + Avoidance Scale; CCI = Charlson Comorbidity Index; Prior Therapies = Prior Number of Therapies

aN=149 for analyses with Mood Disturbance
bThe IES*Linear variable is significant (IES*Linear Parameter Estimate = -.144; p < .001), if the IES*Quadratic term is removed from analyses for Sleep Disturbance.
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*Note.* IL-6 = Interleukin-6; TNF-alpha = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor

Table 8. Hierarchical Linear Modeling of Unconditional Models (No Covariates) of Cytokines Predicted by Time with Fixed and Random Effects ($n = 48$)
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<td>-0.005</td>
<td>-0.018, 0.008</td>
<td>49</td>
<td>-0.740</td>
<td>.463</td>
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<tr>
<td>IES*Linear</td>
<td>-0.001</td>
<td>-0.008, 0.004</td>
<td>53</td>
<td>-0.479</td>
<td>.634</td>
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</tbody>
</table>

*Note: IES= Impact of Events Scale- Intrusions + Avoidance Scale; CCI = Charlson Comorbidity Index; Prior Therapies = Prior Number of Therapies*

Table 9. Hierarchical Linear Modeling of Conditional Models of Cytokines Predicted by Time with the Effects of Baseline Cancer-Specific Stress and Covariates (n = 48). Random Effects Are Not Included for Clarity.
Figure 1. Hypothesized pathway by which stress affects disease progression adapted from Thornton & Andersen (2006) and Lutgendorf & Sood (2011)
Note. BDI-II = Beck Depression Inventory-2nd edition; SF-12 = Medical Outcomes Study- Short Form Health Survey; MCS = Mental Component Summary; PCS = Physical Component Summary; POMS-SF = Profile of Moods – Short Form; FSI = Fatigue Symptom Inventory; MOS = Medical Outcomes Study.

Figure 2. Diagram of aims for study
Figure 3. Flow diagram of study participants at each time point

Total in Study = 151

Completed Screening or Baseline Questionnaire N=150

Completed Month 1 Questionnaire N=141

Completed Month 2 Questionnaire N=137

Completed Month 5 Questionnaire N=124

Not included in analyses N=1 (Did not complete a baseline questionnaire)

Died = 2
Taken Off Study = 1
Missing/Incomplete = 6

Died = 3
Taken Off Study = 3
Missing/Incomplete = 7

Died = 10
Missing = 6
Taken Off Study = 8
Not Yet Collected = 2

(Did not complete a baseline questionnaire)
Figure 4. Beck depression inventory- 2nd edition (BDI-II) cognitive-affective scale predicted by time with no covariates. A significant curvilinear decrease in symptoms is demonstrated (N= 150).
Figure 5. Mood disturbance (POMS-TMD) predicted by time with no covariates. A significant curvilinear decrease in symptoms is demonstrated (N=149).
Note. Higher scores indicate better quality of life.

*Figure 6.* Mental health quality of life (SF-12 Mental Component Summary) predicted by time with no covariates. There is no significant change over time (N = 150).
Figure 7. Sleep disturbance predicted by time with no covariates. A significant curvilinear decrease in symptoms is demonstrated (N= 150).
Note. Higher scores indicate less pain.

Figure 8. Bodily pain predicted by time with no covariates. A significant curvilinear change in symptoms is demonstrated (N= 150).
Figure 9. Fatigue interference predicted by time with no covariates. A significant curvilinear decrease in symptoms is demonstrated (N= 150).
**Note.** Higher scores indicate better quality of life

*Figure 10.* Physical quality of life (SF-12 Physical Component Summary) predicted by time with no covariates. A significant curvilinear improvement in QOL is demonstrated (N= 150).
Figure 11. Beck depression inventory -2nd edition (BDI-II) cognitive-affective scale predicted by time, categorized by IES at baseline. Individuals with higher IES at baseline had a higher intercept, steeper linear slope, and more positive quadratic slope. (N =150)
Figure 12. Mood disturbance (POMS-TMD) predicted by time, categorized by IES at baseline. Individuals with higher IES at baseline had a higher intercept, steeper linear slope, and more positive quadratic slope. (N =149)
Note. Higher scores indicate better quality of life

Figure 13. Mental health quality of life (SF-12 Mental Component Summary) predicted by time, categorized by IES at baseline. Individuals with higher IES had a lower intercept and a steeper linear improvement. (N =150)
Figure 14. Sleep disturbance predicted by time, categorized by IES at baseline. Individuals with higher IES had a higher intercept and a steeper linear decline. (N = 150)
Note. Higher scores indicate less pain.

Figure 15. Bodily pain predicted by time, categorized by IES at baseline. There was no significant effect of IES on intercept or slope. (N = 150)
Figure 16. Fatigue interference predicted by time, categorized by IES at baseline. Individuals with higher IES at baseline had a higher intercept, steeper linear slope, and more positive quadratic slope. (N = 150)
Note. Higher scores indicate better quality of life

*Figure 17.* Physical quality of life (SF-12 Physical Component Summary) predicted by time, categorized by IES at baseline. There is no significant effect of IES on intercept or slope. (N =150)
Figure 18. Log(IL-6) predicted by time, categorized by IES at baseline. IES does not predict baseline IL-6, but higher baseline IES is related to a steeper decline. (N = 48)
Figure 19. Log(TNF-alpha) predicted by time, categorized by IES at baseline. Higher IES at baseline is related to higher TNF-alpha. The rate of decline is similar between groups. (N = 48)
Figure 20. Log(VEGF) predicted by time, categorized by IES at baseline. IES is not related to intercept or slope. (N = 48)
Appendix C: Example Table of Full Hierarchical Linear Model for the Beck Depression Inventory –II Cognitive Affective Scale with All Covariate, Random Effect, and Residual Variance Parameter Estimates
<table>
<thead>
<tr>
<th>Effect</th>
<th>Parameter estimate</th>
<th>Confidence interval</th>
<th>Wald z</th>
<th>df</th>
<th>t</th>
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<td>Fixed Effects</td>
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<td></td>
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<tr>
<td>Intercept</td>
<td>1.240</td>
<td>0.312, 2.169</td>
<td>156</td>
<td>2.638</td>
<td>.009</td>
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<tr>
<td>Linear Slope</td>
<td>-0.341</td>
<td>-0.935, 0.252</td>
<td>150</td>
<td>-1.137</td>
<td>.258</td>
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<tr>
<td>Quadratic Slope</td>
<td>0.084</td>
<td>-0.017, 0.184</td>
<td>145</td>
<td>1.640</td>
<td>.103</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.036</td>
<td>-0.083, 0.011</td>
<td>151</td>
<td>-1.503</td>
<td>.135</td>
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<tr>
<td>Age*Linear</td>
<td>0.048</td>
<td>0.017, 0.078</td>
<td>146</td>
<td>3.093</td>
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<tr>
<td>Age*Quadratic</td>
<td>-0.008</td>
<td>-0.013, -0.003</td>
<td>144</td>
<td>-3.136</td>
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<td>CCI</td>
<td>0.223</td>
<td>-0.209, 0.656</td>
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<td>1.021</td>
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<td>CCI*Linear</td>
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<td>-0.156, 0.018</td>
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<tr>
<td>Del17p (absent)</td>
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<td>-2.134, -0.132</td>
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<td>-2.235</td>
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<td>Del17p*Linear</td>
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<td>1.560</td>
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<td>Del17p*Quadratic</td>
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<td>IES</td>
<td>0.216</td>
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<td>150</td>
<td>7.234</td>
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<td>IES*Linear</td>
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<td>2.973</td>
<td>.003</td>
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<td>Random Effects</td>
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<tr>
<td>Intercept variance</td>
<td>8.021</td>
<td>6.155, 10.453</td>
<td>7.401</td>
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<td>Linear variance</td>
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<td>1.456, 3.496</td>
<td>4.476</td>
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<td>Quadratic Variance</td>
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<td>0.033, 0.095</td>
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<td>Intercept-Linear Covariance</td>
<td>-2.383</td>
<td>-3.548, -1.219</td>
<td>-4.013</td>
<td>&lt;.001</td>
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<td>Intercept-Quadratic Covariance</td>
<td>0.380</td>
<td>0.185, 0.576</td>
<td>3.809</td>
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<tr>
<td>Linear-Quadratic Covariance</td>
<td>-0.348</td>
<td>-0.515, -0.181</td>
<td>-4.074</td>
<td>&lt;.001</td>
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<td>Residual Error</td>
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<td>Homogeneous Variance</td>
<td>1.385</td>
<td>1.089, 1.759</td>
<td>8.181</td>
<td>&lt;.001</td>
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</table>

Appendix C. Example of a full hierarchical linear model for the BDI-II cognitive affective scale predicted by baseline IES, covariates, random effects, and residual error.
Appendix D: Measures
Sociodemographics
CLL II Study
Page 1 of 2

Current date: / / Birth year: 

Home zip code: 

Gender:
○ Male ○ Female

What is your ethnicity?
○ Latina/Latino/Hispanic ancestry ○ Not Hispanic

What is your racial/ethnic group? (Choose yes or no for each; you may choose yes for more than one.)
- Caucasian/White ○ Yes ○ No
- African-American/Black ○ Yes ○ No
- Asian ○ Yes ○ No
- American Indian/Alaskan Native ○ Yes ○ No
- Native Hawaiian/Other Pacific Islander ○ Yes ○ No
- Other: ○ Yes ○ No

Have you ever been or are you currently married?
○ Single, never married
○ Currently married
○ Not married, but in a relationship with significant other
○ Separated or divorced
○ Widowed

Are you currently living with a romantic partner?
○ Yes ○ No

How long have you been married? If you are living with a romantic partner, how long have you been living together? (Code XX if not applicable; data code 99999).

How many individuals are living in your household?

How many children under the age of 18 are living in your home?

What is the highest level of formal education that you have completed?
○ 8th grade or less
○ Some high school
○ Completed high school/GED
○ Technical, vocational, or certificate program
○ Some college (no degree)
○ Associate's degree
○ Bachelor's degree
○ Some graduate school
○ Master's degree
○ Doctoral degree (MD, PhD, JD)

What is your current job status?
○ Employed full-time
○ Employed part-time
○ Homemaker, raising children, care of others
○ Disabled
○ Temporarily unemployed, seeking employment
○ Retired
○ Retired, working part or full time
○ Other ____________________
Sociodemographics
CLL II Study
Page 2 of 2

On average, how many hours per week did you work for pay in the last month? (Code XX if not employed; data code 99999).

____ hours/week

If you work for pay, how many days did you take sick days or time off because of physical health problems since your cancer diagnosis? (Code XXXX if not employed; data code 99999.)

____ days

If you work for pay, how many days did you take sick days or time off because of emotional health problems since your cancer diagnosis? (Code XX if not employed; data code 99999.)

____ days

What is your occupation? If not currently employed, what was your occupation at your last full time job?

- Homemaker
- Major professional, executive or proprietor (e.g., MD or PhD level)
- Lesser professional, manager or proprietors of medium-sized concern (MA or MS level)
- Administrative personnel of large concern, owner of small business (e.g., teacher, nurse)
- Assistant manager, owner of little business
- Technician (high tech type)
- Clerical or sales person
- Skilled crafts person
- Semi-skilled operative (e.g., school bus driver)
- Unskilled labor

How important is your occupation or continuing to work to your well-being? If retired, disabled, or unemployed, how important was your occupation or continuing to work to your well-being?

- Not at all important
- Not very important
- Somewhat important
- Moderately important
- Very important

What are/were your household (family) gross wages or income last year (pre-tax)?

- Less than $15,000
- $15,001 - $25,000
- $25,001 - $35,000
- $35,001 - $50,000
- $50,001 - $75,000
- $75,001 - $100,000
- $100,001 - $150,000
- $150,001 - $200,000
- $200,001 - $250,000
- More than $250,000
- I don't know.
- I prefer not to answer.
Impact of Events
CLL II Study - IES-R

Indicate how frequently these comments have been true in describing your feelings about having CLL in the past seven days. If they did not occur during that time, please indicate "not at all."

1. Any reminder brought back feelings about having CLL. o o o o o
2. I had trouble staying asleep. o o o o o
3. Other things kept making me think about CLL. o o o o o
4. I felt irritable and angry. o o o o o
5. I avoided letting myself get upset when I thought about or was reminded of CLL. o o o o o
6. I thought about CLL when I didn't mean to. o o o o o
7. I felt as if my diagnosis hadn't happened or wasn't real. o o o o o
8. I stayed away from reminders about CLL. o o o o o
9. Pictures about CLL popped into my mind. o o o o o
10. I was jumpy and easily startled. o o o o o
11. I tried not to think about CLL. o o o o o
12. I was aware that I still had a lot of feelings about CLL, but I didn't deal with them. o o o o o
13. My feelings about CLL were kind of numb. o o o o o
14. I found myself acting or feeling like I was back at that time. o o o o o
15. I had trouble falling asleep. o o o o o
16. I had waves of strong feelings about CLL. o o o o o
17. I tried to remove CLL from my memory. o o o o o
18. I had trouble concentrating. o o o o o

Subject ID

Assessment

16666
<p>| | | | |</p>
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<th></th>
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<td>CLL II Study - IES-R</td>
<td>Page 2 of 2</td>
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<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. Reminders of CLL caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>20. I had dreams about CLL.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>21. I felt watchful or on-guard.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>22. I tried not to talk about CLL.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
1. Sadness
   ○ (0) I do not feel sad.
   ○ (1) I feel sad much of the time.
   ○ (2) I am sad all the time.
   ○ (3) I am so sad or unhappy that I can't stand it.

2. Pessimism
   ○ (0) I am not discouraged about my future.
   ○ (1) I feel more discouraged about my future than I used to be.
   ○ (2) I do not expect things to work out for me.
   ○ (3) I feel my future is hopeless and will only get worse.

3. Past Failure
   ○ (0) I do not feel like a failure.
   ○ (1) I have failed more than I should have.
   ○ (2) As I look back, I see a lot of failures.
   ○ (3) I feel I am a total failure as a person.

4. Loss of Pleasure
   ○ (0) I get as much pleasure as I ever did from things I enjoy.
   ○ (1) I don't enjoy things as much as I used to.
   ○ (2) I get very little pleasure from the things I used to enjoy.
   ○ (3) I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
   ○ (0) I don't feel particularly guilty.
   ○ (1) I feel guilty over many things I have done or should have done.
   ○ (2) I feel quite guilty most of the time.
   ○ (3) I feel guilty all of the time.

6. Punishment Feelings
   ○ (0) I don't feel I am being punished.
   ○ (1) I feel I may be punished.
   ○ (2) I expect to be punished.
   ○ (3) I feel I am being punished.

7. Self-Dislike
   ○ (0) I feel the same about myself as ever.
   ○ (1) I have lost confidence in myself.
   ○ (2) I am disappointed in myself.
   ○ (3) I dislike myself.

8. Self-Criticalness
   ○ (0) I don't criticize or blame myself more than usual.
   ○ (1) I am more critical of myself than I used to be.
   ○ (2) I criticize myself for all of my faults.
   ○ (3) I blame myself for everything bad that happens.
Feelings in the Past Month
CLL II Study - BDI-II
Page 2 of 3

9. Suicidal Thoughts or Wishes
○ (0) I don't have any thoughts of killing myself.
○ (1) I have thoughts of killing myself, but I would not carry them out.
○ (2) I would like to kill myself.
○ (3) I would kill myself if I had the chance.

10. Crying
○ (0) I don't cry anymore than I used to.
○ (1) I cry more than I used to.
○ (2) I cry over every little thing.
○ (3) I feel like crying, but I can't.

11. Agitation
○ (0) I am no more restless or wound up than usual.
○ (1) I feel more restless or wound up than usual.
○ (2) I am so restless or agitated that it's hard to stay still.
○ (3) I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
○ (0) I have not lost interest in other people or activities.
○ (1) I am less interested in other people or things than before.
○ (2) I have lost most of my interest in other people or things.
○ (3) It's hard to get interested in anything.

13. Indecisiveness
○ (0) I make decisions as well as ever.
○ (1) I find it more difficult to make decisions than before.
○ (2) I have much greater difficulty in making decisions than I used to.
○ (3) I have trouble making any decisions.

14. Worthlessness
○ (0) I do not feel I am worthless.
○ (1) I don't consider myself as worthwhile and useful as I used to.
○ (2) I feel more worthless as compared to other people.
○ (3) I feel utterly worthless.

15. Loss of Energy
○ (0) I have as much energy as ever.
○ (1) I have less energy than I used to have.
○ (2) I don't have enough energy to do very much.
○ (3) I don't have enough energy to do anything.

16. Changes in Sleeping Pattern
○ (0) I have not experienced any change in my sleeping pattern.
○ (1a) I sleep somewhat more than usual.
○ (1b) I sleep somewhat less than usual.
○ (2a) I sleep a lot more than usual.
○ (2b) I sleep a lot less than usual.
○ (3a) I sleep most of the day.
○ (3b) I wake up 1-2 hours early and can't get back to sleep.
17. Irritability
○ (0) I am no more irritable than usual.
○ (1) I am more irritable than usual.
○ (2) I am much more irritable than usual.
○ (3) I am irritable all the time.

18. Changes in Appetite
○ (0) I have not experienced any change in my appetite.
○ (1a) My appetite is somewhat less than usual.
○ (1b) My appetite is somewhat greater than usual.
○ (2a) My appetite is much less than before.
○ (2b) My appetite is much greater than usual.
○ (3a) I have no appetite at all.
○ (3b) I crave food all the time.

19. Concentration Difficulty
○ (0) I can concentrate as well as ever.
○ (1) I can't concentrate as well as usual.
○ (2) It's hard to keep my mind on anything for very long.
○ (3) I find I can't concentrate on anything.

20. Tiredness or Fatigue
○ (0) I am no more tired or fatigued than usual.
○ (1) I get more tired or fatigued more easily than usual.
○ (2) I am too tired or fatigued to do a lot of things I used to do.
○ (3) I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
○ (0) I have not noticed any recent change in my interest in sex.
○ (1) I am less interested in sex than I used to be.
○ (2) I am much less interested in sex now.
○ (3) I have lost interest in sex completely.

22. Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes?
○ (0) N/A
○ (1) No
○ (2) Yes

23. If you answered "yes" to item 22, have you felt depressed or sad much of the time in the past year?
○ (0) N/A
○ (1) No
○ (2) Yes
Instructions: Indicate how you have been feeling in THE LAST WEEK, INCLUDING TODAY.

Tense  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Angry  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Worn out  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Unhappy  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely

Lively  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Confused  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Peeved  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Sad  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely

Active  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
On edge  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Grouchy  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Blue  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely

Energetic  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Hopeless  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Uneasy  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Restless  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely

Unable to concentrate  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Fatigued  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Annoyed  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
Discouraged  ○ Not at all  ○ A little  ○ Moderately  ○ Quite a bit  ○ Extremely
### MOODS

*Indicate how you have been feeling in **the last week, including today.***

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<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
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<tbody>
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<td>Resentful</td>
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<td>Cheerful</td>
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<td>Bitter</td>
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<td>Weary</td>
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<td>Bewildered</td>
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<td>Furious</td>
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<tr>
<td>Full of Pep</td>
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<td>Worthless</td>
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<td>Forgetful</td>
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<td>Vigorous</td>
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<td>Uncertain about things</td>
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<tr>
<td>Bushed</td>
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Feelings in the Past Month
CLL II Study - SF-12
Page 1 of 2

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to conduct your daily activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. Fill in the circle that best describes your answer.

1. In general, would you say your health is: ○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

2. Does your health limit you now in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
   ○ Yes, limited a lot ○ Yes, limited a little ○ No, not limited at all

3. Does your health limit you now in climbing several flights of stairs?
   ○ Yes, limited a lot ○ Yes, limited a little ○ No, not limited at all

4a. How much bodily pain have you had during the last month?
   ○ None ○ Very mild ○ Mild ○ Moderate ○ Severe ○ Very severe

4b. During the past month, how much did pain interfere with your normal work (including both outside the home and housework)?
   ○ Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely
Feelings in the Past Month
CLL II Study - SF-12
Page 2 of 2

These questions are about how you feel things have been going for you during the past month. For each question, give the one answer that comes closest to the way you have been feeling.

During the PAST MONTH, how much of the time have you.....

5. Accomplished less than you would like at work or other regular daily activities as a result of your physical health?  
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time
   -  

6. Been limited in the kind of work or other activities you could do as a result of your physical health?  
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time
   -  

7. Accomplished less than you would like at work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?  
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time
   -  

8. Done your work or activities less carefully than usual at work or home as a result of emotional problems (such as feeling depressed or anxious)?  
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time
   -  

9. Have you felt calm and peaceful?  
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time
   -  

10. Did you have a lot of energy?  
    - All of the time
    - Most of the time
    - Some of the time
    - A little of the time
    - None of the time
    -  

11. Have you felt downhearted and depressed?  
    - All of the time
    - Most of the time
    - Some of the time
    - A little of the time
    - None of the time
    -  

12. Has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?  
    - All of the time
    - Most of the time
    - Some of the time
    - A little of the time
    - None of the time
    -  

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For each of the following, fill in the one number that best indicates how that item applies to you.

1. Rate how much, in the past week, fatigue interfered with your enjoyment of life:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

2. Rate how much, in the past week, fatigue interfered with your general level of activity:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

3. Rate how much, in the past week, fatigue interfered with your ability to bathe and dress yourself:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

4. Rate how much, in the past week, fatigue interfered with your normal work activity (includes both work outside the home and housework):
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

5. Rate how much, in the past week, fatigue interfered with your ability to concentrate:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

6. Rate how much, in the past week, fatigue interfered with your relations with other people:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference

7. Rate how much, in the past week, fatigue interfered with your mood:
   - 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
   - No interference
   - Extreme interference
**Your Sleep**

CLL II Study - MOS Sleep subscale

Please answer the following questions about your sleep patterns over the PAST 4 WEEKS.

1. How long did it usually take you to fall asleep during the PAST 4 WEEKS?
   - 0-15 minutes
   - 16-30 minutes
   - 31-45 minutes
   - 46-60 minutes
   - More than 60 minutes

2. On average, how many hours did you sleep EACH NIGHT during the PAST 4 WEEKS? [ ] hours per night

How often during the PAST 4 WEEKS did you...

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little bit of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Feel that your sleep was not quiet (e.g., moving restlessly, feeling tense, speaking, etc. while sleeping)?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>4. Get enough sleep to feel rested upon waking in the morning?</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>5. Awaken short of breath or with a headache?</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>6. Feel drowsy or sleepy during the day?</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<td>7. Have trouble falling asleep?</td>
<td>○</td>
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<tr>
<td>8. Awaken during your sleep and have trouble falling asleep again?</td>
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<td>○</td>
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<tr>
<td>9. Have trouble staying awake during the day?</td>
<td>○</td>
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<tr>
<td>10. Snore during your sleep?</td>
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<tr>
<td>11. Take naps (5 minutes or longer) during the day?</td>
<td>○</td>
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<tr>
<td>12. Get the amount of sleep you needed?</td>
<td>○</td>
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<td>○</td>
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<td>○</td>
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