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Associations of inflammation with symptom burden in patients with acute myeloid leukemia

Tamara E. Lacourt[a], Annemieke Kavelaars[a], Jessica R. Galloway-Peña[b], Pranoti V. Sahasrabhojane[b], Nina D. Shah[c,1], Andrew Futreal[d], Dimitrios P. Kontoyiannis[b], Samuel A. Shelburne[b,d], Cobi J. Heijnen[a,*]

[a] Neuroimmunology Laboratory, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Infectious Disease, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Department of Stem Cell Transplantation, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

The aim of the study was to assess the association inflammation with symptom burden in patients with acute myeloid leukemia (AML), assessed before and during remission induction chemotherapy (IC). Patients with AML (n = 95) were followed from baseline (before IC) to the third week of IC for severity of self-reported somatic symptoms (assessed with the MD Anderson Symptom Inventory) and plasma levels of 13 inflammation-related biomarkers (n = 64). A composite symptom burden severity score was computed as the average score of the six most severe somatic symptoms i.e., fatigue, disturbed sleep, drowsiness, dry mouth, lack of appetite, and pain. Results from cross-sectional analyses showed that inflammation was weakly associated with symptom burden before IC (multiple regression model, explained variance = 10%) but this association grew stronger during IC (week 3 explained variance = 35%). About half of the sample showed a change over time in symptom severity. These changes were not reflected in similar changes over time in inflammatory markers, suggesting that it is the absolute concentration of a given inflammatory marker at a given time point rather than its relative change over time that is of importance. In conclusion, inflammation was strongly associated with symptom burden only during IC, possibly because expression of cytokines only then becomes relevant for regulation of symptom burden. While the current study does not allow for determination of causality, the results suggest that AML patients might benefit from anti-inflammatory interventions during treatment to alleviate somatic symptom experience.

1. Introduction

Acute myeloid leukemia (AML) is a hematological cancer in which myeloid blasts do not develop into mature white blood cells. This leads to an accumulation of immature (and thus, dysfunctional) white blood cells in the bone marrow and circulation, resulting in a reduction of effector cells such as platelets and immune cells. About 21,380 new cases of AML in the US alone are estimated for 2017 (www.cancer.org, 2017). The first line of treatment for AML generally involves high intensity remission induction chemotherapy (IC) aimed at reducing the number of myeloid blasts. Not surprisingly, both AML and its treatment are associated with a range of symptoms affecting health-related quality of life (Mohamedali et al., 2012; Redaelli et al., 2004). Reduced quality of life is associated with less-favorable cancer treatment outcomes (Oliva et al., 2011), emphasizing the importance of understanding the characteristics and mechanisms of symptom burden. However, the mechanisms of the relation between symptoms and treatment of AML are largely unknown.

Mechanisms of AML-related symptoms have mostly focused on fatigue (Fung et al., 2013; Meyers et al., 2005; Panju et al., 2009; Wang et al., 2002). For example, Wang et al. reported associations between fatigue and low serum albumin in patients with acute leukemia at different stages of their treatment (Wang et al., 2002). Meyers et al. found associations between fatigue and cognitive functioning with several inflammatory markers assessed in patients before the start of chemotherapy (Meyers et al., 2005). Fung et al. (2013) reported associations between fatigue and inflammatory markers in patients 1–3 days after starting IC. They further reported an association between changes

* Corresponding author at: 1515 Holcombe Blvd Unit 1450, Houston, TX, 77030, USA.
E-mail address: CJHeijnen@MDAnderson.org (C.J. Heijnen).
[1] Present address: Department of Medicine, University of California San Francisco, San Francisco, California, USA.

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in fatigue and changes in the pro-inflammatory marker TNF-α over 1 month. Whether different factors contribute to symptom burden at the various time points (e.g., before vs. during IC) has not been addressed yet. Also, although it is clear that fatigue is a prominent symptom of AML and its treatment, additional symptoms contributing to the overall symptom burden of the patient have not been reported on in previous studies.

In the literature it has been suggested that inflammation is a likely contributor of symptom burden both before and during treatment (e.g., Panju et al., 2009). Pre-clinical research has firmly established that inflammatory cytokines can induce symptoms such as fatigue and pain (Benson et al., 2012; Larson and Dunn, 2001). In AML, myeloid blasts can induce an array of inflammatory mediators, including lipids, chemokines, cytokines, and growth factors (Fiancette et al., 2011; Reikvam et al., 2015). Chemotherapy may induce inflammation as well through organ and tissue damage. IC regimes for AML also induce alterations in leukocyte subpopulations and lymphopenia that trigger an upregulation of homeostatic cytokines, including interleukin (IL)-7 (Wendelbo et al., 2002), a cytokine with pro-inflammatory properties. Thus, in AML a pro-inflammatory state may well induce symptom experience both before and during IC although the inducer of inflammation may change over the course of the disease and the treatment (i.e., from myeloid blast-related to chemotherapy-induced).

Our objective was to determine the associations of inflammation with somatic symptom burden both before and during IC. We monitored patient-reported symptoms from diagnosis (pre-IC) to the third week of IC and determined associations of symptom burden with inflammatory biomarker levels at each time point. In addition, we investigated if changes in symptom burden during IC were associated with changes in inflammatory markers. The inclusion of several time points during IC and a sample size that allows for assessment of associations both at baseline and during IC sets this study apart from previous studies on mechanisms of symptom burden in AML patients.

2. Methods

2.1. Study population

Adult patients (≥18 years of age) were recruited in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas, between September 2013 and August 2015. Patients with a confirmed diagnosis of AML or myelodysplastic syndrome, admitted or planned to be admitted to receive IC within two weeks, were considered eligible. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2, a calcium phosphorus product ≤4.0 $mmol^2/L^2$ (50 mg^2/dL^2), and adequate organ function. Patients were excluded if they had another concurrent malignancy or had received any chemotherapeutic or investigational anticancer drug within the previous two weeks, had been exposed to a mitogen-activated protein kinase inhibitor, were predisposed to or had a history of retinal vein occlusion or central serous retinopathy, had any cardiac risk factor, or had any unresolved grade 1+ toxicity from previous therapy. This protocol also had the aim of studying the role of gastrointestinal microbiome in infectious complications during IC, the results of which have been published elsewhere (Galloway-Pena et al., 2016). For this aim, patients with an active bacterial infection at baseline – defined as current receipt of therapeutic (not prophylactic) antibiotics – were excluded.

2.2. Design

Assessments were done at baseline (prior to or within 8 h after start of IC) and during IC until neutrophil count recovery (an absolute neutrophil count > 500 cells/μL), which generally occurred at the start of the fourth week of IC. At study completion, it became clear that for the majority of patients this criterion was reached in week 3, which meant that only a marginal subset of patients was followed beyond week 3. Thus, for the here reported analyses, we decided to focus on data collected up to week 3 (four time points: baseline and weeks 1, 2, and 3 during IC). Symptom reports were obtained twice weekly if possible, and blood samples were collected weekly. The study (protocol PA13-0339) was approved by The University of Texas MD Anderson Cancer Center Internal Review Board. All participants provided written informed consent.

2.3. Patient-reported symptoms

Symptom severity was assessed with the MD Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000), a 13-item questionnaire that asks patients to rate the severity of 11 somatic and 2 psychological symptoms at their worst in the last 24 h on a scale of 0 (“not present”) to 10 (“as bad as you can imagine”). The MDASI was designed to assess a core set of symptoms common to most cancers. Although this set of symptoms is expected to be relevant for most cancer patients, the MDASI was not designed to assess an underlying symptom structure universal for all cancer patients. Previous reports on the MDASI have incorporated both single-item analyses as well as selection of most severe symptoms for one symptom burden score (e.g., Rosenthal et al., 2014; Wang et al., 2014) in line with the MDASI user guide (Cleeland, 2016). The twice-weekly assessments during therapy were averaged to create a weekly score; if one of the assessments during a week was missed, the single assessment score was used. The somatic symptoms that were scored as most severe across all time points were combined in an average symptom burden score. We decided to cluster relevant symptoms rather than analyze them separately as the current sample size was not adequate for the multitude of tests and subsequent adjustment of significance thresholds that would have been necessary to assess the associations per symptom.

2.4. Inflammation

Peripheral blood (3–4 mL) was collected in EDTA-anticoagulating tubes and put on ice. Samples were spun down at 3000 rpm for 10 min and plasma was then stored at −80 °C until batchwise analysis could be performed. Plasma concentrations of proinflammatory and anti-inflammatory cytokines (IL-6, IL-7, IL-36β, IL-1 receptor antagonist (IL-1Ra), tumor necrosis factor (TNF)-α, and soluble TNF receptor I (sTNF-RI)) and adhesion molecules (E-selectin, P-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1) were assessed with Magnetic Luminex Screening Assays (R&D Systems, Minneapolis, MN). Plasma concentrations of damage-associated molecular patterns DAMPs, including heat-shock protein (HSP) 70, high-mobility group box (HMGB)1, and soluble form of receptor for advanced glycation (sRAGE), were assessed with enzyme immunoassays (ENZ-KIT-101, ENZO Life Sciences, Farmingdale, NY; ST51011, IBL International, Hamburg, Germany; and DRG00, R&D Systems). Biomarkers with plasma concentrations below detection levels were imputed with the [lowest detectable concentration/SQRT(2)]. Biomarkers with concentrations higher than the highest value of the standard curve were imputed with the highest value obtained from the standard curve.

2.5. Demographic and clinical laboratory factors

Demographic and clinical laboratory values were obtained from electronic medical records. Hemoglobin and albumin concentrations were obtained for each time point. Percentage of myeloid blasts in blood and in bone marrow was obtained for baseline and week 3.

2.6. Statistical analyses

IBM SPSS Statistics version 24 (IBM Corporation, 1989) was used