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Correlation between cytokine levels and changes in fatigue and quality of life in patients with acute myeloid leukemia

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ABSTRACT

Cancer-related fatigue (CRF) is a major problem in patients with acute myeloid leukemia (AML) and may be mediated by circulating cytokines. We examined this relationship in 74 adult AML patients before and after the first cycle of induction chemotherapy. Plasma levels of 13 cytokines were measured via electrochemiluminescence. At baseline, potentially clinically important ($r > 0.30$) correlations were seen between tumor necrosis factor (TNF)-α and fatigue ($r = -0.336$, $p = 0.017$). Over time, correlations with fatigue were noted with TNF-α ($r = -0.341$, $p = 0.006$) and interferon-inducible protein (IP)-10 ($r = 0.353$, $p = 0.005$). The link between IP-10 and fatigue is novel, implicating CXC chemokine pathways for CRF in hematologic malignancies.

1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematological malignancy with an incidence of 3.5 per 100,000 people in the United States; its incidence increases with age [1]. Initial treatment of AML consists of 4–5 weeks of in-hospital induction chemotherapy (IC) followed by several cycles of consolidation chemotherapy after complete remission has been achieved. In addition to the significant toxicities and mortality risk from chemotherapy [2], cancer-related fatigue (CRF) is one of the most common symptoms and negatively impacts on quality of life (QOL) [3–5]. Compared to usual fatigue, CRF is a more severe and enduring fatigue that may persist for months to years after cancer treatment and is not alleviated by rest or adequate sleep [6,7].

A previous study of AML patients age 60 or older revealed that over 90% of patients reported fatigue at every time point between baseline (time of diagnosis) and 6 months (the end of intensive chemotherapy), which only mildly improved by one year post-diagnosis [8,9]. Increasing fatigue was associated with both worse QOL and worse daily function [8]. Furthermore, unlike CRF associated with solid tumors [7,10], AML-related fatigue does not appear to be related to anemia or improve with achievement of complete remission [3,8]. Therefore, AML-related fatigue may be due to different mechanisms than fatigue associated with solid tumors.

Although the etiology of CRF is complex and treatment approaches to date remain limited [11,12], changes in the immune system may contribute to the initiation and persistence of CRF. In particular, the "sickness behavior model" suggests that non-specific behavioral symptoms such as fatigue, sleep disturbance, and cognitive changes are due to inflammation associated with chronic medical conditions such as cancer [6,13]. Sickness behaviors are thought to arise from increased expression of pro-inflammatory cytokines, associated with Th1 cell-mediated immunity.

Three studies have examined cytokines in the AML and/or myelodysplastic syndrome (MDS) population [14–16]. The first and largest of these was by Meyers et al., and included 54 patients with AML or MDS prior to chemotherapy. They reported statistically significant correlations between interleukin (IL)-6, IL-1 receptor

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antagonist (IL-1ra), and tumor necrosis factor (TNF)-α with fatigue (Spearman correlations ranging from 0.41 to 0.62) [14]. El-Gohary et al. enrolled 28 patients with either AML ($n = 7$) or acute lymphoblastic leukemia ($n = 21$). Patients with depressive symptoms were statistically significantly more likely to be fatigued and have elevated IL-6 levels, but direct correlations between cytokines and fatigue were not reported [15].

The current longitudinal study expands upon a previous pilot study we conducted of 34 AML patients age 50 and older that showed potential correlations between fatigue scores, global QOL scores, and changes in several cytokines over 4 weeks [16]. In that study, we found statistically significant or borderline significant relationships between global QOL and interferon (IFN)-γ ($p = -0.031$), IL-2 ($p = -0.053$), IL-5 ($p = 0.035$), IL-8 ($p = 0.077$), and TNF-α ($p = 0.064$). Only IL-6 showed a borderline correlation with fatigue ($p = 0.059$) at baseline. Looking at changes over 4 weeks, both changes in IL-5 ($p = 0.073$) and IL-10 ($p = 0.091$) had borderline correlations with change in fatigue scores [16].

As far as we know, the present study is the largest observational longitudinal study of cytokines and patient-reported outcomes in AML patients to date. The objective is to identify specific cytokines that contribute to baseline (pre-treatment) fatigue and identify correlations between changes in specific cytokine levels and changes in fatigue and QOL measures in AML patients undergoing IC.

2. Methods

The cytokine study is part of a larger longitudinal study of QOL in adult patients with AML. Consecutive newly diagnosed AML patients were recruited between May 2008 and June 2010 from the Princess Margaret Hospital, an academic tertiary cancer referral center for ~75% of AML patients in the Greater Toronto Area (catchment area of 5 million). Patients 18 years and older were enrolled within 3 days of starting IC and were assessed at two points: at baseline (i.e., Visit A: after AML diagnosis) and one month later (i.e., Visit B: after IC and prior to any consolidation chemotherapy). For the cytokine study, blood samples were only collected if Visit A occurred before the start of any chemotherapy.

Exclusion criteria were another active malignancy, life expectancy of less than one month, or a lack of fluency in reading/writing English unless a validated translation of the questionnaires was available in the patient's language and a translator was available for the visit assessments. The study protocol was approved by the institutional Research Ethics Board.

Questionnaires were administered and blood samples were collected at each visit. AML diagnosis was determined by bone marrow aspirate and cytogenetic risk group was assigned based on karyotypic analysis using the Medical Research Council classification [17]. White blood cell count (WBC) was recorded at baseline. Infection status (yes/no) was recorded at each time point. Remission status was determined after IC using standard criteria [18]. All patients were treated as inpatients during induction, and received daunorubicin 60 mg/m^2/day for 3 days plus cytosine arabinoside (Ara-C) 200 mg/m^2/day (100 mg/m^2/day for patients aged ≥60) as a continuous infusion for 7 days, as detailed in a recent publication [19].

2.1. QOL questionnaires

Questionnaires were administered at both Visits A and B. At Visit B where possible, questionnaires were completed before the patient had their appointment with their hematologist and was made aware of their remission status, minimizing possible confounding bias. Fatigue was assessed using two questionnaires: the Functional Assessment of Cancer Therapy – Fatigue subscale (FACT-F) [20] and the Fatigue Visual Analog Scale (VAS). FACT-F is a questionnaire that asks a patient to rate their level of fatigue on 13 different items. A score out of 52 is generated, with higher scores representing less fatigue. The Fatigue VAS is a single-item scale from the Edmonton Symptom Assessment Scale [21] and is used to assess global fatigue severity on a scale of 0–10. Scores of 1–3, 4–6, and 7–10 represent mild, moderate, and severe levels of fatigue, respectively.

QOL was assessed with the European Organisation for the Research and Treatment of Cancer core 30-item (EORTC QLQ-C30) questionnaire [22]. The EORTC QLQ-C30 includes a global QOL index, five functional scales, and nine symptom scales. Our study focused on the global QOL index and the five functional scales (physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF)). These items are scored from 0 to 100, with higher scores representing better QOL.

Both the FACT-F and the EORTC QLQ-C30 are well-validated in cancer populations and have been used in leukemia patients [5,14,16,23–25]. A minimum clinically significant difference (MCID) in FACT-F, Fatigue VAS, and EORTC QLQ-C30 is a 3-, 1-, and 10-point difference, respectively [26–28].

2.2. Cytokine measurement

Based on findings in previous studies in AML [14–16] and other malignancies [24,25,29–31] suggesting relationships with global QOL and/or fatigue, a panel of 13 cytokines were selected for the current study. Specifically these were a Th1/Th2 standard 10-plex panel consisting of IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12 p70, IL-13, and TNF-α, in addition to custom kits including IL-6, IFN-inducible protein (IP)-10, and IL-1ra. Of these cytokines, only IL-13 was not a pre-specified cytokine in our protocol but was included in the standard Th1/Th2 kit we purchased.

Blood samples were drawn in EDTA test tubes on the morning of the assessment visit, usually between 0700 and 0900 h. All samples were centrifuged, aliquotted and frozen at −70 °C within 30 min of collection. Cytokine immunoassays tests were performed in batches on singly thawed plasma samples. Multiplexed electrochemiluminescence cytokine immunoassays from Meso Scale Discovery (Gaithersburg, MD), all from a single lot number, were read on a SECTOR® Imager 2400. The detection range was 20–100,000 pg/ml. Due to fiscal restraints, IL-6, IP-10, and IL-1ra assays were run in duplicate, whereas the other cytokines were run singly once an initial duplicate run of 40 samples demonstrated acceptable calibration and variability (data not shown).

2.3. Statistical analysis

Our primary outcomes were FACT-F for fatigue and global QOL from the QLQ-C30. The distributions of cytokine data were graphically inspected and log-transformed to create normalized distributions. Three sets of analyses were performed. First, Spearman correlations were performed between cytokines and fatigue/QOL at baseline and change scores of both cytokines and fatigue/QOL scores from Visit A to Visit B. Second, patients were categorized into three groups based on clinically significant change in fatigue and global QOL (worse, unchanged, or improved) based on MCIDs for each outcome. Kruskal–Wallis tests were performed against changes in cytokine concentration for each group. Finally, linear regression models were performed to observe the individual effects of each cytokine on fatigue and QOL outcomes when adjusted for age, gender, baseline WBC, and remission status.

Aside from our previous study [16], there is currently insufficient data to suggest strong relationships between specific cytokines and either fatigue or QOL in the AML population. Therefore, our study was exploratory in nature. To balance the risk of false positives (due to a moderate sample size, multiple cytokines, and multiple significance testing) against the risk of missing potentially important relationships, we chose a Spearman's rho correlation coefficient of 0.30 and above as potentially clinically significant [32] and chose 2 primary outcomes. All statistical analyses were two-sided and done using SAS version 9.1 (SAS Institute, Research Triangle, NC). A p-value of 0.05 was used to denote statistical significance. No correction for multiple significance testing was performed.

3. Results

3.1. Patient characteristics

Baseline patient characteristics are listed in Table 1. A total of 74 patients with a mean age of 54.8 years (range 22–81 years) met inclusion criteria and were enrolled. At baseline, 92% of patients experienced at least mild fatigue (i.e., Fatigue VAS of 1 or more), of whom 52% experienced moderate to severe levels of fatigue (i.e., Fatigue VAS of 4 or more).

3.2. Clinical outcomes

Of 74 patients, 55 (76%) had achieved complete remission at the end of the first cycle of IC (i.e., at Visit B). One patient died before the completion of IC (i.e., before Visit B) and was excluded from analysis of remission status. An additional eight patients did not have cytokines measured at Visit B due to being too sick ($n = 1$), missing the visit ($n = 1$), or administrative error ($n = 6$), leaving 65 patients with cytokines at both time points for analyses of change scores.

3.3. Correlations of cytokines with fatigue, QOL, and other variables at baseline

Potentially clinically important correlations were noted for our primary outcomes with TNF-α for both FACT-F ($r = -0.366$, $p = 0.017$) and global QOL ($r = -0.313$, $p = 0.008$) at baseline. Among