# Cognitive Impairment, Fatigue, and Cytokine Levels in Patients with Acute Myelogenous Leukemia or Myelodysplastic Syndrome

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**BACKGROUND.** The objective of the current study was to assess the correlations between cognitive function, fatigue, quality of life, and circulating cytokine levels in patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).

**METHODS.** Fifty-four patients with AML/MDS were seen for pretreatment evaluation of their cognitive function and symptoms. Fifty percent of the sample was reevaluated 1 month later, when response to protocol chemotherapy was assessed.

**RESULTS.** A significant proportion of patients had impaired cognitive function prior to the institution of chemotherapy. Sixty-five percent of patients also experienced significant fatigue. Levels of the circulating cytokines interleukin 1 (IL-1), IL-1 receptor antagonist (IL-1RA), IL-6, IL-8, and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) were elevated highly compared with normal controls. Higher IL-6 levels were associated with poorer executive function, whereas higher IL-8 levels were associated with better memory performance. IL-6, IL-1RA, and TNF-$\alpha$ levels were related to ratings of fatigue. Fatigue and cognitive dysfunction were unrelated. Hemoglobin levels were not associated significantly with either cognitive dysfunction or fatigue. Patients who obtained a complete response tended to have better fine motor control at baseline and lower circulating IL-1 levels. Treatment did not have a significant impact on cognition, although fatigue levels tended to increase.

**CONCLUSIONS.** Patients with AML/MDS are highly symptomatic and experience cognitive impairment and fatigue before the initiation of their treatment. The current results indicated a correlation between these symptoms and levels of circulating cytokines, providing some support to the hypothesis that cancer-related symptoms are related at least in part to cytokine-immunologic activation. Elucidation of immunologic correlates of symptoms will allow for targeted interventions. ***Cancer* 2005;104:788–93.** © *2005 American Cancer Society.*

**KEYWORDS: cytokines, cognition disorder, fatigue, leukemia**

Neurocognitive and neuropsychiatric symptoms are highly prevalent in patients with cancer and cause significant impairments in their ability to function and to tolerate their treatment. In previous studies, we found that a significant percentage of patients with various types of cancer had multiple symptoms, including impairments of memory, significant fatigue, and depression, before treatment is initiated.[1,2] Aggressive treatment for cancer often worsens these distressing symptoms in addition to causing the development of additional symptoms. These symptoms may not remit when treatment is discontinued, further disrupting patients' lives.[3] There is a growing suspicion that these symptoms may have an underlying biologic mechanism related to cytokine-immunologic activation.[4] This has


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been studied in animal models of "sickness behavior" that mimic many of the symptoms endured by cancer patients.

Cytokines have profound effects on brain function.[5] For example, it is known that interferon-$\alpha$ increases levels of interleukin 1 (IL-1), IL-6, and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and that these increases are associated with the impairments of memory, motor dexterity, executive functions, and mood that are suggestive of frontal-subcortical dysfunction.[6] IL-1 crosses the blood-brain barrier, with the highest rate of entry occurring in the hypothalamus.[7] The hypothalamus has rich connections with the brain stem, frontal cortex, and limbic system. IL-1 and its receptors are found in many areas of the brain. IL-1 mRNA is found in abundance in the hippocampus,[7] which is a critical structure for memory processes. IL-1 depresses the influx of calcium into hippocampal neurons, which may explain the preponderance of memory impairment in patients with IL-1-associated toxicity.[8] TNF-$\alpha$ also is neurotoxic and is associated with demyelination in the brain.[9] TNF-$\alpha$ and IL-1 are toxic synergistically[10] and are associated with the development of multiple sclerosis plaques and gliosis.[11] Patients with Alzheimer disease have elevated levels of IL-6.[12] We have observed that patients who have severe neurotoxicity after the administration of intraventricular IL-2 as treatment for leptomeningeal disease also have increased IL-6 levels in the cerebrospinal fluid compared with pretreatment levels.[13] In addition to their direct effects on brain function, these cytokines also provoke a stress hormone cascade that can affect mood and cognition as well as having discrete effects on brain neurotransmitter systems.[5,14] In sum, it appears that elevated cytokine levels may be associated with deficits in cognition and mood. These observations are of interest here, because it has been demonstrated that concentrations of IL-6 are higher on average in patients with large cell lymphoma and Hodgkin disease than in normal controls, with patients who have high levels more likely to have poor performance status and B symptoms (weight loss, fever, and night sweats) than patients who have lower levels.[15,16] Preclinical data suggest that IL-1, IL-6, and TNF-$\alpha$ similarly may be elevated in patients with leukemia and myelodysplastic syndrome (MDS).17–19

Thorough characterization of these symptoms, correlation of these symptoms with clinical laboratory data, and providing mechanism-based interventions for these symptoms are important directions for clinical research. Herein, we report our study of patients with acute myelogenous leukemia (AML) and MDS (AML/MDS), a population at considerable risk for neuropsychiatric and neurocognitive symptoms. These patients have elevated levels of cytokines at presentation and are treated aggressively with multiagent chemotherapy that also may induce cytokine production. Preliminary data also indicate a significant prevalence of symptomatology in this patient population. Therefore, these patients provide a useful model system for understanding the biologic and neural substrates for these symptoms and for testing rational, mechanism-based interventions to ameliorate them.

**TABLE 1**
**Demographic Characteristics**

| Characteristic | Mean (range) | No. of patients (%) |
|---|---|---|
| Age (yrs) | 60.2 (21–84) | |
| Education (yrs) | 13.0 (5–18) | |
| Gender | | |
| Male | | 30 (56) |
| Female | | 24 (44) |
| Diagnosis | | |
| Myelodysplastic syndrome | | 35 (65) |
| Acute myelogenous leukemia | | 19 (35) |
| Response at 1 month (total sample = 54 patients) | | |
| Complete response | | 19 (35) |
| Partial or no response | | 23 (43) |
| Not evaluated | | 12 (22) |
| Response at 1 month (patients seen at follow-up = 26 patients) | | |
| Complete response | | 14 (54) |
| Partial or no response | | 8 (31) |
| Not evaluated | | 4 (15) |

## MATERIALS AND METHODS

In total, 54 of 60 patients with newly diagnosed AML/MDS were seen for baseline evaluation of their cognitive function and symptoms before undergoing protocol therapy with lipodaunocin plus cytoxan or topotecan, plus or minus thalidomide, representing a 90% participation rate. All patients signed informed consent to participate. Demographic characteristics are listed in Table 1. Patients underwent a baseline evaluation of their cognitive function and symptoms, and a subset of patients was seen after 1 month of therapy, when response was assessed. The following tests were selected because they are widely used, standardized psychometric instruments that have demonstrated sensitivity to the neurotoxic effects of cancer treatment in other clinical trials. The tests have published normative data that take into account age and education. The tests also were selected to minimize the effects of repeated administration. Standard devi-

ations from the normative mean were calculated for each test (mean = 0; standard deviation = 1). The tests were 1) Digit Span to measure attention span[20]; 2) Digit Symbol to measure graphomotor speed[20]; 3) Hopkins Verbal Learning Test for memory, including Total Recall, Immediate Recognition, and Delayed Recall[21]; 4) Controlled Oral Word Association for verbal fluency[22]; 5) Trail Making Test Part A for visual-motor scanning speed[23]; 6) Trail Making Test Part B for executive function[23]; and 7) Grooved Pegboard for fine motor dexterity.[23] Impairment on a test was defined as $\leq$ 1.5 standard deviations from the normative mean, because only 6.7% of the general population would be expected to score in this range. Binomial tests were conducted to determine whether the frequency of impairment on each test observed in our study group differed from normative expectations. Changes in test performance in the subset of patients seen at follow-up were analyzed by Student *t* tests for paired samples with two-tailed tests of significance. The difference in cognitive performance, symptoms, and cytokine levels in those patients who achieved an early complete response versus those who did not were analyzed by Student *t* tests for independent samples with two-tailed tests of significance.

We also evaluated current symptoms and the ability to perform activities of daily living. The patient filled out the Brief Fatigue Inventory,[24] in which the worst level of fatigue in the past 24 hours and the degree that fatigue interfered with the patients' daily routine are reported (scores $\geq$ 4 on a scale of 0–10 indicate moderate to severe fatigue). The Functional Assessment of Cancer Therapy was administered to measure quality of life, and z-scores were calculated from the general cancer population norms reported by Cella et al.[25] The Barthel Activities of Daily Living Index was administered, with scores less than the maximum of 20 indicating that the patient needed some assistance with activities of daily living.[26]

Serum levels of multiple cytokines were measured by commercially available, standard enzyme-linked immunoadsorbent assays. Circulating levels of IL-1, IL-1 receptor antagonist (IL-1RA), IL-6, IL-8, and TNF-$\alpha$ were obtained. Elevations were determined by calculating the standard deviation of the mean value obtained for each cytokine compared with laboratory normative controls. Hemoglobin levels were also recorded. Spearmen correlations with two-tailed tests of significance were used to determine the relation between these biologic markers and tests of cognitive function and symptoms. Given the multiple correlations performed, $\rho$ values $\geq$ 0.35 were considered significant to control for Type I error (moderate to large effect size).[27]

## RESULTS

The means and standard deviations of raw scores at baseline on all study measures are presented in Table 2. The proportions of patients who were impaired at baseline and at follow-up are presented in Table 3. Figure 1 displays the average z-score for each test at baseline, and Figure 2 displays the average z-score for baseline serum cytokine levels. The figures show that, as a whole, the patients performed well below expectation on tests of memory, verbal fluency, cognitive processing speed, executive function, and fine motor dexterity. In addition, the group as a whole reported significant fatigue, and 20% required some assistance with their activities of daily living. However, the overall quality of life was fairly positive (Table 4). There was an expected association between education and cognitive test performance as well as an association between age and the ability to perform activities of daily living. There were no apparent associations between diagnosis (AML vs. MDS) or age on cognitive test performance.

Compared with normal controls, circulating levels of cytokines were elevated highly. Table 5 displays the correlations between cytokine levels, cognitive function, and symptoms. Levels of IL-6, IL-1RA, and TNF-$\alpha$ were related significantly to fatigue and overall quality-of-life ratings. Higher IL-6 levels also were associated with worse performance on the Trail Making Test Part B for executive function. In contrast, higher IL-8 levels were related to better memory performance. There were no correlations $\geq$ 0.35 between hemoglobin level, fatigue, or cognitive test performance at baseline. There were no associations between these biologic markers and age, education, or diagnosis.

Only 26 patients were reassessed after 1 month of treatment due to logistic problems (follow-up appointments were not made by the primary service at random). Only fine motor control and fatigue worsened significantly. Unfortunately, not enough individuals had follow-up cytokine levels obtained to allow for analyses.

The baseline performance of patients who achieved a complete response was compared with that of patients who did not achieve a complete response. The only difference was found in baseline fine motor control, with better performance observed in complete responders compared with nonresponders ($P = 0.037$). In addition, there was a trend for patients who achieved a complete response to have lower circulating IL-1 levels at baseline ($P = 0.052$).

## DISCUSSION

The current findings suggest that patients with AML/MDS, in general, do not have difficulty with tests of

**TABLE 2**
**Means and Standard Deviations of Study Measures at Baseline**

| Measure | Mean ± SD score | Units | Possible range |
|---|---|---|---|
| Digit Span | 12.35 ± 3.58 | Raw score | 0–28 |
| Digit Symbol | 41.30 ± 15.38 | Raw score | 0–93 |
| Hopkins Verbal Learning Test | | | |
| Total recall | 21.43 ± 6.68 | Raw score | 0–36 |
| Recognition | 10.78 ± 1.37 | Raw score | −12–12 |
| Delayed recall | 7.30 ± 3.11 | Raw score | 0–12 |
| COWA | 29.37 ± 11.48 | Words/3 minutes | |
| Trails A | 49.04 ± 32.26 | Seconds to complete | |
| Trails B | 118.85 ± 84.48 | Seconds to complete | |
| Pegboard Dominant | 101.58 ± 58.96 | Seconds to complete | |
| Pegboard Nondominant | 109.35 ± 73.08 | Seconds to complete | |
| FACT-G | 76.81 ± 15.75 | Raw score | 0–108 |
| BFI Worst | 5.26 ± 2.92 | Raw score | 0–10 |
| BFI Interference | 3.78 ± 2.73 | Raw score | 0–10 |
| Barthel | 19.35 ± 2.20 | Raw score | 0–20 |
| Hemoglobin | 9.08 ± 1.37 | g/dL | |
| TNF-$\alpha$ | 12.52 ± 5.3 | pg/mL | |
| IL-6 | 30.58 ± 90.57 | pg/mL | |
| IL-8 | 72.34 ± 149.55 | pg/mL | |
| IL-1RA | 1224.07 ± 2448.17 | pg/mL | |
| IL-1$\beta$ | 3.72 ± 0.61 | pg/mL | |

SD: standard deviation; COWA: Controlled Oral Word Association for verbal fluency; Trails A: Trail Making Test Part A for visual-motor scanning speed; Trails B: Trail Making Test Part B for executive function; FACT-G: Functional Assessment of Cancer Therapy-General; BFI: Brief Fatigue Inventory; TNF-$\alpha$: tumor necrosis factor-$\alpha$; IL: interleukin; RA: receptor antagonist.

**TABLE 3**
**Percent of Patients Impaired[a]**

| Test | Baseline ($n$ = 54) | Follow-up ($n$ = 26) |
|---|---|---|
| Attention | 7 | 8 |
| Psychomotor speed | 8 | 13 |
| Total recall | 44[b] | 58 |
| Immediate recognition | 7 | 25 |
| Delayed recall | 41[b] | 58 |
| Verbal fluency | 17[c] | 25 |
| Visual scanning | 28[b] | 38 |
| Executive | 29[b] | 46 |
| Dexterity | 37[b] | 54[d] |

[a] Impairment was defined as ≥ 1.5 standard deviation below the normative mean.
[b] $P < 0.001$ (binomial test).
[c] $P < 0.05$ (binomial test).
[d] $P < 0.05$ (Student $t$ test).

attention span or psychomotor speed. However, > 40% of patients had impairments in learning new information, ≈ 33% had impaired fine motor coordination, and 25% had difficulties with executive function or visual-motor scanning speed prior to treatment. In addition, a large percentage of individuals reported experiencing significant fatigue that interfered with their ability to function in their daily routine. These results afford preliminary support for our hypothesis that patients with AML/MDS are at risk for cognitive dysfunction as a consequence of their disease per se. In addition, the cognitive dysfunction is not global, but rather follows a frontal-subcortical pattern.[28] The cognitive impairments observed in this study were not related to fatigue or to anemia.

Although follow-up testing was limited to 50% of the sample, making comparisons between the pretreatment and posttreatment evaluations difficult, it appears that treatment had no adverse effects on cognitive function, although fatigue did worsen. However, a larger, better powered sample will be needed to address fully the treatment-related effects on cognition.

There appears to be a relatively strong correlation between symptoms and levels of circulating cytokines, with highly significant correlations in the large effect size range. There was a weaker correlation reported between IL-6 levels and poorer executive function and a positive correlation reported between IL-8 levels and memory function. It is noteworthy that IL-8 reportedly enhances the survival of hippocampal cells in vitro, suggesting that not all cytokines contribute to adverse symptoms.[29] Future studies with larger sample sizes will be needed to determine whether disease type (MDS vs. AML), demographic variables, or affective distress mediate the correlations between symptom burden and cytokine levels.

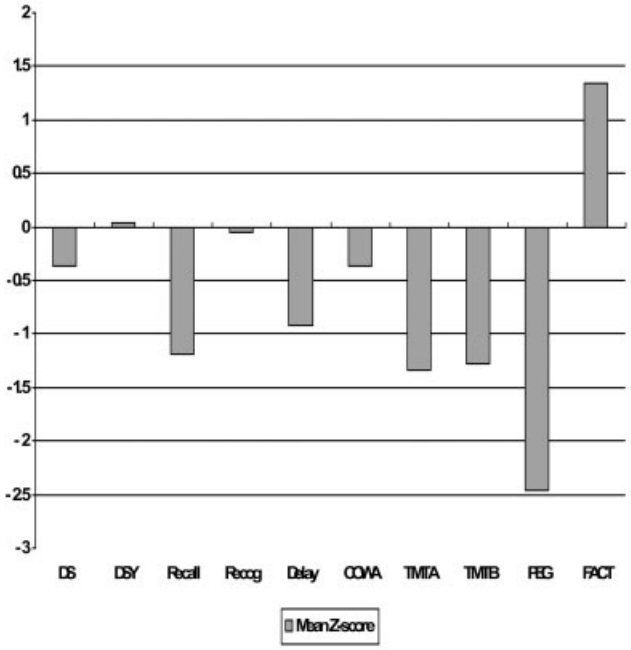


**FIGURE 1.** This chart illustrates the mean z-scores of cognitive tests. DS: Digit Span to measure attention span; DSY: Digit Symbol to measure graphomotor speed; Recall: Hopkins Verbal Learning Test for Memory, Total Recall; Recog: Hopkins Verbal Learning Test for Memory, Immediate Recognition; Delay: Hopkins Verbal Learning Test for Memory, Delayed Recall; COWA: Controlled Oral Word Association for verbal fluency; TMTA: Trail Making Test Part A for visual-motor scanning speed; TMTB: Trail Making Test Part B for executive function; PEG: Grooved Pegboard for fine motor dexterity; FACT: Functional Assessment of Cancer Therapy.

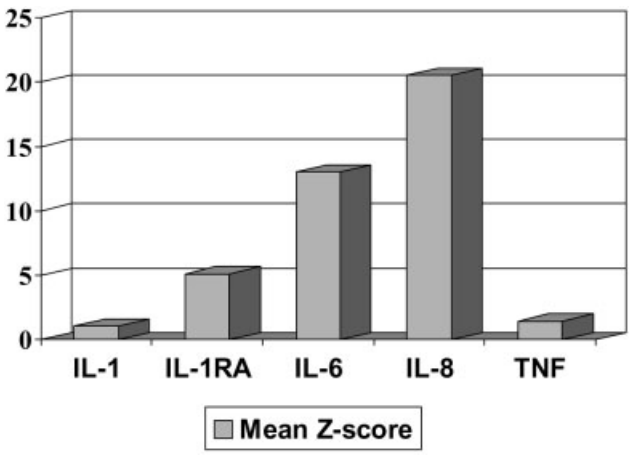


**FIGURE 2.** This chart illustrates the mean z-scores of circulating cytokine levels. IL-1: interleukin 1: IL-1RA: IL-1 receptor antagonist; TNF: tumor necrosis factor-$\alpha$.

**TABLE 4**
**Percent of Patients with Significant Symptoms**

| Measure | Baseline | Follow-up |
|---|---|---|
| Quality of life | 13 | 17 |
| Fatigue | 65 | 79[a] |
| Interference | 48 | 50 |
| Activities of daily living | 20 | 21 |

[a] $P < 0.05$ (Student $t$ test).

**TABLE 5**
**Correlation of Cytokine Levels and Symptoms at Baseline**

| Cytokine/symptom | Spearman *r* |
|---|---|
| Interleukin-6 | |
| Executive | −0.36 |
| Fatigue | 0.62 |
| Interference | 0.60 |
| QOL | −0.42 |
| Interleukin-8 | |
| Total recall | 0.38 |
| Recognition | 0.37 |
| Interleukin-1 receptor antagonist | |
| Fatigue | 0.52 |
| Interference | 0.62 |
| QOL | −0.49 |
| Tumor necrosis factor | |
| Fatigue | 0.41 |
| Interference | 0.40 |
| QOL | −0.39 |
| Interleukin-1 | |
| QOL | −0.49 |

Spearman *r*: Spearman correlation coefficient; QOL: quality of life.

The current findings provide provocative insight into the potential effect of physiologic changes on cognition and symptoms. We previously reported a case study showing that anemia and fatigue alone did not necessarily affect cognitive functioning, because worsening of both during chemotherapy treatment was seen in the context of cognitive improvement and resolution of leukocytosis and reduction of circulating TNF-$\alpha$ levels.[30] Identification of the physiologic mechanisms for disease-related symptoms will allow for the development of targeted interventions. Optimizing the quality of life of cancer patients is possible, essential, and should be on equal footing with anticancer therapy.

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