Cognitive and Other Predictors of Change in Quality of Life One Year After Treatment for Chronic Myelogenous Leukemia or Myelodysplastic Syndrome

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The role of cognitive function in quality of life is important among the growing numbers of survivors after cancer treatment. The authors conducted a prospective cohort study of 106 adults evaluated 5.6 months (median) after diagnosis and 77 of 83 (93%) survivors 12 months later with neuropsychological assessments yielding information about simple reaction time to stimuli and other aspects of cognitive function and with two quality of life measures. The two most consistent predictors of change in quality of life were baseline quality of life ratings and simple reaction time. This novel finding about simple reaction time warrants further confirmation.

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With nearly 12 million cancer survivors in the United States and more worldwide, quality of life is an increasingly important clinical endpoint for this growing cohort.[1,2] Both perceived cognitive function and objectively measured cognitive dysfunction have been shown to influence health related quality of life in patients with other types of medical problems, such as coronary artery disease.[3,4] Because cognitive functioning is closely connected with the core aspects of quality of life, their relationship in cancer survivors is an area of ongoing inquiry.[5]

Cognitive changes in cancer patients are complex and may reflect disease, treatment, and psychological responses, such as depression or anxiety.[6] Furthermore, cognitive impairment after cancer treatment may be subtle or occur intermittently, so that objective evidence may be difficult to obtain.[7] To date, much of the available literature on treatment-related cognitive dysfunction in

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non-central nervous systems cancers has focused on patients with breast cancer.[2]

The use of cognitive tests to evaluate changes is necessary to clarify cancer patients' complaints about memory and concentration problems because of the limited correlations reported between subjective and objective cognitive changes in cancer patients after treatment.[5,6,8] Yet, the amount of time and effort needed by the patient and examiner to complete the testing, the potential effect of practice on repeat testing by patients, and the influence of the patient's background such as education, age, or race on testing outcome have been raised as practical considerations.[6] In addition to these concerns about feasibility, others have suggested that the cost of cognitive testing is another potential barrier.[9] Hence, an efficient way to measure these changes is needed.[10]

Reaction time to a stimulus is a fundamental neuropsychological measure of the brain's information processing efficiency. Reaction time assessments offer some advantages over other psychometric tests because they are almost knowledge free, less likely to reflect an individual's educational and social background, and are quick to administer.[11] As such, they may have an important role in the pragmatic cognitive evaluation of cancer patients.

Several studies have demonstrated the promise of reaction time measurement in other settings. An innovative study of cognitive deficit and quality of life capitalized on the advantages of bedside measurement of simple and choice reaction times and found a statistically significant positive correlation between these measures and perfusion time in a sample of 50 patients who underwent open heart surgery.[12] Another study of 898 people showed that simple and choice reaction time variables measured at age 56 were significantly associated with mortality in the following 14 years.[11]

Because some malignancies involve the central nervous system (CNS), it is difficult to ascertain the contribution of treatment when the disease itself may account for mental status changes.[13,14] Hence, it is desirable to focus on malignancies that do not typically involve the CNS if the objective is to study the cognitive changes associated with treatment and their association with subsequent quality of life. Chronic myelogenous leukemia (CML) and myelodysplastic syndrome (MDS) are two such diseases without apparent CNS involvement. CML is considered to be a model in research and management among malignant disorders because of its linkage with a specific chromosomal abnormality.[15] MDS is a common, acquired, clinically challenging hematologic condition characterized by bone marrow failure and risk of progression to acute leukemia.[16] Their treatments can be similar, with allogeneic hematopoietic stem cell transplantation (HSCT) as a curative possibility; moreover, conventional chemotherapy with its possible cognitive effects is not a treatment option for either disease.

The purpose of this exploratory study was to evaluate the association of cognitive function to health-related quality of life 1 year after treatment for CML or MDS. Cognitive function was evaluated using a comprehensive battery of measures, including reaction time, and considered in the context of other demographic and clinical variables chosen because of their potential association with function after treatment in other studies.[17–20] We hypothesized that cognitive function, and in particular, simple reaction times would be predictive of health related quality of life after treatment.

METHODS

Participants were 106 adults with CML (86%) or primary MDS (14%), enrolled in a study with serial neuropsychological evaluations, first as they initiated treatment and then 12 months later. Seventy-seven of 83 (93%) potential participants completed the 12-month evaluation (23 individuals died and six withdrew or were lost). Eligibility criteria included reading and listening comprehension of English, and diagnosis within the past year or new treatment plan (e.g., for HSCT) for the next year. Exclusion criteria included history of significant head injury (resulting in loss of consciousness), stroke, epilepsy, or other CNS pathology requiring radiation, surgery, or intrathecal medication, and current alcohol or substance abuse or dependence. Subjects offered written, informed consent for this study which was reviewed and approved by the Institutional Review Board (Protocol 2000-P−002410). They received an honorarium of $50.00 for each evaluation. Additional details are available elsewhere.[21]

Initial Evaluation

Each participant completed an initial evaluation at a median of 5.6 months after the participants' diagnosis date. The initial evaluation included a participant profile with questions about age, racial and ethnic background, highest level of education achieved, marital status, and use of alcohol and drugs assessed by the Alcohol and

Drug Modules from the Structured Clinical Interview for DSM-IV.[22] They also completed measures of quality of life (QoL) and mood, and a neuropsychological assessment.

QoL and Mood Measures

These measures were completed at the time of initial evaluation and then 12 months later: 1) the Medical Outcomes Study 36-Item Short Form (SF−36), to evaluate their physical [physical component summary scale (PCS)] and mental health [mental component summary scale (MCS)][23]; 2) Functional Living Index–Cancer (FLIC), to measure the overall functional quality of the person's day to day life[24]; and 3) the Brief Profile of Mood States (Brief POMS) to summarize general distress or mood.[25] The Medical Outcomes Study SF−36 items and scales were scored as prescribed to generate the MCS and PCS. Each has a mean of 50 and a SD of 10; a higher score indicates higher function.[26] FLIC scores can range from 22 to 154, where higher scores are consistent with better daily function.[24] Scores for the Brief POMS range from 0 to 44, where higher scores are associated with more distress and depression.[25]

Neuropsychological Assessment

Neuropsychological assessments were completed at the time of the initial evaluation and then 12 months later. Neuropsychological test selection was based on previous research including patients with hematological malignancies, and incorporated measures of attention, executive function, language, memory, and motor speed.[10,27] The following measures were used: 1) Buschke Selective Reminding Test,[28,29] 2) Digit Span and Digit Symbol Coding subtests from the Wechsler Test of Adult Intelligence – III,[30] 3) Trail Making Test (Parts A and B),[31] 4) Verbal Fluency Test (both phonemic and animal fluency tasks),[32] 5) Stroop Color Word Test,[33] and 6) Grooved Pegboard Test.[34] The reliability and validity of these tests are well documented.[35] Experimental computer-based tests were also used and included a test of simple reaction time, which will be the focus of this evaluation. In order to mitigate possible learning effects on the neuropsychological testing, subjects were randomly assigned alternate forms of the Verbal Fluency Test, Trail Making Test, Buschke Selective Reminding Test, and computer tests.

The computer stimuli were presented on a MacIntosh computer using the PsyScope program.[36] In the simple reaction time task, subjects were presented with a box on the computer screen in which an asterisk (*) appeared to cue the subject that the target (an X) would appear. They were instructed to press the zero key on the external key pad as quickly as possible when the X appeared in the box. Sixty trails were presented, with presentation times varying randomly at 250 msec, 500 msec, 750 msec, 1000 msec, 1250 msec, and 1500 msec after the (*) appeared. Reaction times (msec) were obtained, as well as accuracy data. Because there were no differences between the reaction times at the different interstimulus intervals, an average reaction time was calculated for each subject at each assessment.

Neuropsychological tests were scored according to established protocols. Raw scores were converted to z scores from age, sex, and/or education corrected normative data.[37] A composite score for each domain was calculated by averaging the neuropsychological tests' z scores within their respective domains (e.g., attention, executive, language, memory, motor, and processing function). The Attentional domain included the Digit Span subtest from the Wechsler Adult Intelligence Scale-III and the Trail Making Test, Part A. Executive Functioning domain measures included the Trail Making Test, Part B, Verbal Fluency Test, and the Stroop Color Word (interference condition). The Language domain included the semantic fluency trial. Four measures from the Buschke were incorporated as the Memory domain. The Processing Speed domain included the WAIS-III Digit Symbol subtest, and the color and word conditions from the Stroop Color Word Test. The Motor domain included the Grooved Pegboard Test for both the dominant and non-dominant hands.

Data Analysis

All analyses were carried out using the SAS statistical package (version 9.1). Simple descriptive statistics were calculated and are reported as percentages, means, SDs, and ranges, as appropriate. Participant characteristics at enrollment, considered to be the baseline, and then 12 months later, were compared using chi-square and t tests of significance.

Longitudinal analyses were restricted to the 77 participants who had completed the 12-month evaluations to avoid projecting quality of life for patients who were unavailable for the follow-up evaluation. Univariate associations of change in QoL between enrollment and 12 months were evaluated using the GENMOD procedure, adjusting for initial QoL. Multivariate regression models were built for each QoL outcome, adjusting for initial baseline QoL, diagnosis, and treatment. To adjust

for confounding, initial Brief POMS as well as any initial demographic and/or cognitive measures were included in the multivariate model if the univariate association was less than $p<0.10$. No further variables were added to or removed from the final multivariate models.

Additional analyses are described in the data supplement that accompanies the online edition of this article. (To view the Appendix, also see the data supplement.)

RESULTS

Table 1 summarizes the demographic and clinical characteristics at enrollment for all subjects and among the 77 for whom longitudinal data were available. Both groups were similar in terms of mean age (~48 years), sex (>50% male), marital status (~62% married), and educational attainment (~50% with at least a 4-year college degree). Most were of white, non-Hispanic (~88%) background. None satisfied diagnostic criteria for current alcohol or substance use disorders, and both groups had similar rates of lifetime substance use disorders. However, the groups did differ in other ways, primarily related to attrition because of mortality. Higher proportions of those able to provide longitudinal data had stable phase CML (p=0.002), had treatments other than HSCT (p=0.008), and higher hemoglobin values at study enrollment (p=0.0013). More people with CML received HSCT than those with MDS (47% versus 20%, p=0.053); 94% of the HSCT recipients received total body irradiation (total dose 14 Gy, in seven fractions). Among those with CML treated in other ways, the majority received imatinib mesylate (84.5%); other treatments included hydroxyurea (10.4%) or interferon (4.2%). Treatment other than HSCT for those with MDS included hydroxyurea (17%), supportive treatment (25%), erythropoietin (33%), and azacitidine (42%), with some individuals receiving more than one of the treatments simultaneously.

With regards to cognitive measures, both the baseline and follow-up samples had similar performances on executive function, language, memory, and motor domains at the time of study enrollment. However, among those who provided longitudinal data, better attention (p=0.02), and less impaired processing speed (p=0.03) were observed. Please refer to the data supplement for more details.

QoL Measures

Predictors of changes in quality of life between enrollment and 12 months are summarized in Table 2 and Table 3. Table 2 summarizes the univariate baseline predictors of change. Table 3 summarizes the multivariate models for predictors of change.

The FLIC

The FLIC provides a summary measure of an individual's overall functional day to day life. With a possible range in values from 22 to 154, higher values indicated higher function. The mean FLIC at enrollment was 119.2 (SD=22.3) and increased to 126.1 (SD=23.7) 12 months later (p=0.06). While adjusting for the initial FLIC, two univariate baseline predictors of FLIC change at 12 months were identified. Greater age (p=0.10) and increased reaction times (p=0.01) were both negatively associated with improved FLIC scores at 12 months. Each additional year of age was associated with a decrease of 0.25 (SE=0.15) in FLIC change at 12 months. For each unit increase in reaction time, there was a decrease of 0.01 (SE=0.004) in FLIC change at 12 months.

The multivariate model for the change in FLIC at 12 months (Table 3) identified three baseline correlates that had effects on the extent of change: 1) FLIC, whereby those with higher baseline scores had less change (Effect=−0.23 (SE=0.09), p=0.01); 2) treatment, whereby those receiving HSCT experienced more improvement in quality of life [Effect=11.22 (SE=4.8), p=0.02] and 3) simple average computer reaction time, [Effect=−0.01 (SE=0.004), p=0.0009]. Quicker reaction time at enrollment was the only significant cognitive correlate of subsequent improvement in quality of life as measured by the FLIC.

MCS

The MCS is standardized to have a mean of 50 and SD of 10. The median MCS established for the general US population with cancer (except skin cancer) is 48.54 (SD=11.24), with an expected range between 20 and 67.[26] Participants in this study began with a mean MCS of 46.5 (SD=11.0) and experienced improvement on this measure to 49.0 (SD=10.6) at 12 months (p=0.16).

Four univariate baseline predictors of change in MCS at 12 months (Table 2) were identified: 1) treatment, whereby HSCT compared with other treatment was associated with greater improvement [Estimate (SE)=3.94 (2.01), p=0.05]; 2) language, so that those with those with higher semantic fluency scores also had better MCS scores [Estimate (SE) =1.69 (0.96), p=0.08]; 3) reaction time, where slower reaction times were associated with less MCS change [Estimate (SE)=−0.005 (0.002),p=0.0006]; and 4)

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Sample

Variable	All (N=106)	Longitudinal Sample (N=77)	p
Mean age (SD)	47.9 (13.5)	48.6 (13.7)	0.40
Sex			
Male	55%	52%	0.35
Female	45%	48%	
Marital status			
Single	22.7%	20.8%	0.43
Married	61.3%	63.6%	
Divorced	11.3%	9.1%	
Widowed	2.8%	3.9%	
Other	1.9%	2.6%	
Race			
White, non-Hispanic	87.6%	88.2%	0.63
Black, non-Hispanic	6.7%	6.6%	
Asian/Pacific Islander	2.9%	1.3%	
Native American	1.0%	1.3%	
Other	2.0%	1.3%	
Education			
Graduate or professional	20.8%	20.8%	0.87
College, 4-year	28.3%	28.6%	
Partial college	26.4%	27.3%	
High school	22.6%	20. 8%	
Other	1.9%	2.6%	
Disease			
CML, stable	67%	77%	**0.0017**
CML, accelerated	19%	12%	
MDS	14%	11%	
Treatment			
HSCT	42%	34%	**0.0084**
Other treatment	58%	66%	
Baseline Hg (mean, SD)	11.77 (1.84)	12.18 (1.52)	**0.0013**
Lifetime Substance Abuse or Dependence			
Alcohol	28%	27.3%	0.70
Cocaine	9%	6.5%	0.23
Marijuana	12%	13%	0.71
Cognitive Measures[a]			
Attention	0.31 (0.86)	0.43 (0.86)	**0.021**
Executive function	–0.39 (1.2)	–0.26 (1.2)	0.09
Language	0.067 (1.1)	0.105 (0.99)	0.60
Memory	–0.95 (1.3)	–0.88 (1.3)	0.37
Motor	–0.94 (1.7)	–0.85 (1.6)	0.42
Processing	–0.29 (0.68)	–0.20 (0.65)	**0.03**
Reaction time, msec	479.5 (503.9)	481.9 (555.4)[b]	0.91
Psychological Mood			
Brief POMS (mean, SD)	9.06 (8.8)	8.35 (8.71)	0.17

[a]Results for the Cognitive Test Domains (except for Reaction Time) are presented as mean z scores with (SD).
[b]Based on N=72.

the Brief POMS, where a higher Brief POMS score (or more depressive symptoms) was associated with less MCS change [Estimate (SE)=−0.48 (0.20), p=0.015].

The multivariate model for MCS change at 12 months (Table 3) identified two factors that predicted more change and three factors that predicted less change. Greater MCS change was associated with HSCT treatment [Effect (SE) =5.42 (1.76), p=0.002] and better language function [Effect (SE) =1.67 (0.80), p=0.03]. Higher baseline MCS was associated with less MCS change at 12 months [Effect (SE) =−0.65 (0.13), p<0.0001]; as were higher reaction times [Effect (SE) =−0.007 (0.001), p<0.0001] and a higher Brief POMS score [Effect (SE) =−0.46 (0.16), p=0.004].

PCS

The PCS is standardized to have a mean of 50 and a SD of 10; the mean for the general US population with cancer (except skin cancer) is 41.1 (SD=11.5), with an expected range from 17 to 61.[26] The mean PCS at enrollment 46.8 (SD=8.5) and did not change significantly by 12 months when there was a mean of 46.7 (SD=10.3).

TABLE 2. Univariate Models for Predictors of Change in Quality of Life Measures between Enrollment and 12 Months

	FLIC Change[a]		MCS Change[b]		PCS Change[c]	
Demographic Variables	**Estimate (SE)**	**p**	**Estimate (SE)**	**p**	**Estimate (SE)**	**p**
Age	**–0.25 (0.15)**	**0.10**	–0.08 (0.07)	0.25	–0.08 (0.07)	0.28
Sex	–2.39 (4.21)	0.57	–0.76 (1.97)	0.70	–2.28 (2.05)	0.27
Marital status	3.25 (4.26)	0.45	–0.11 (2.02)	0.96	–1.26 (2.25)	0.58
Race	0.04 (2.16)	0.98	0.93 (1.46)	0.52	–0.72 (1.55)	0.64
Education	5.49 (4.77)	0.25	–0.16 (2.31)	0.94	**6.54 (2.35)**	**0.01**
Clinical Variables						
Disease	4.94 (6.27)	0.43	0.48 (2.96)	0.87	**5.29 (3.06)**	**0.08**
Treatment	7.00 (4.42)	0.11	**3.94 (2.01)**	**0.05**	–2.95 (2.14)	0.17
Baseline Hg	0.53 (1.40)	0.70	0.20 (0.66)	0.76	0.72 (0.69)	0.30
Lifetime Substance Abuse or Dependence						
Alcohol	1.44 (4.63)	0.76	–0.01 (2.19)	0.99	–0.15 (2.32)	0.95
Cocaine	3.86 (8.96)	0.67	1.59 (4.21)	0.70	3.30 (4.49)	0.46
Marijuana	–1.60 (6.20)	0.80	0.15 (2.92)	0.96	–0.50 (3.10)	0.87
Cognitive Measures						
Attention	1.73 (2.41)	0.47	0.33 (1.12)	0.77	**2.11 (1.22)**	**0.08**
Executive function	2.54 (1.75)	0.15	0.91 (0.83)	0.27	0.29 (0.90)	0.75
Language	0.70 (2.08)	0.74	**1.69 (0.96)**	**0.08**	–0.64 (1.04)	0.54
Memory	–0.07 (1.63)	0.97	0.16 (0.77)	0.83	0.45 (0.79)	0.57
Motor	–0.53 (1.25)	0.68	–0.34 (0.59)	0.57	–0.15 (0.63)	0.81
Processing	3.67 (3.15)	0.24	–0.03 (1.49)	0.98	2.52 (1.57)	0.11
Reaction Time	**–0.01 (0.004)**	**0.01**	**–0.005 (0.002)**	**0.00**	**–0.005 (0.002)**	**0.00**
Psychological Mood						
Brief POMS	–0.51 (0.40)	0.20	**–0.48 (0.20)**	**0.02**	**–0.34 (0.12)**	**0.00**

[a]Models adjusted for initial FLIC.
[b]Models adjusted for initial MCS.
[c]Models adjusted for initial PCS.

TABLE 3. Multivariate Models of Predictors of Change in Quality of Life Measures between Enrollment and 12 Months

	Adjusted Full Models	
FLIC Change	**Effect (SE)**	**p**
Baseline FLIC	–0.23 (0.09)	**0.01**
Disease	1.44 (6.46)	0.82
Treatment	11.22 (4.8)	**0.02**
Age	–0.13 (0.17)	0.47
Reaction time	–0.01 (0.004)	**0.0009**
MCS Change	**Effect (SE)**	**p**
Baseline MCS	–0.65 (0.13)	**<0.0001**
Disease	0.30 (2.31)	0.9
Treatment	5.42 (1.76)	**0.002**
Language	1.67 (0.80)	**0.03**
Reaction Time	–0.007 (0.001)	**<0.0001**
Brief POMS	–0.46 (0.16)	**0.004**
PCS Change	**Effect (SE)**	**p**
Baseline PCS	–0.61 (0.11)	**<0.0001**
Disease	8.33 (2.59)	**0.0013**
Treatment	–1.04 (1.89)	0.62
Education	2.54 (2.13)	0.23
Attention average	0.28 (1.10)	0.80
Reaction time	–0.006 (0.002)	**0.0003**
Brief POMS	–0.41 (0.10)	**<0.0001**

*All Models adjusted for diagnosis and treatment, regardless of significance in univariate tests

Five baseline predictors of PCS change at 12 months (Table 2) were identified when change was adjusted for baseline PCS value. Three predictors associated with more PCS change were 1) education, whereby those with more education had more change on the PCS [Effect (SE) =6.54 (2.35), p=0.01] 2) disease, whereby those with stable phase CML had the most change compared with other diseases [Effect (SE) =5.29 (3.06) p=0.08]; and 3) attention, whereby those with higher attention domain scores had more change on the PCS [Effect (SE) =2.11 (1.22), p=0.08]. Two predictors associated with less PCS change were 1) reaction time [Effect (SE) =−0.005 (0.002), p=0.003] and 2) the brief Brief POMS score [Effect (SE) =−0.34 (0.12) p=0.003]. For both of these predictors, higher reaction time and more depressive symptoms were associated with less change on the PCS.

Results from the multivariate model for PCS change at 12 months (Table 3) included several of the univariate predictors. Disease (stable phase CML compared with the other diseases) had a positive effect [Effect (SE) =8.33 (2.59), p=0.0013], but baseline PCS [Effect (SE)=−0.61 (0.11), p<0.0001], reaction time [Effect (SE)=−0.006 (SE=0.002), p<0.005], and the Brief POMS score [Effect

(SE) = −0.41 (0.10), $p<0.0001$] all had negative effects on PCS change.

DISCUSSION

Quality of life after cancer treatment is complex and changes over time. In general, patients did not enjoy large improvements in quality of life 1 year after treatment. Nonetheless, the two most consistent predictors of change in 12-month quality of life in this sample were the initial quality of life results and simple reaction time. Participants with higher baseline quality of life measures had less improvement at follow-up. Those with faster initial reaction times were the most likely to show improvements in the quality of life measures used in the study. Semantic fluency was the only other cognitive measure associated with change in the quality of life aspect measured by the mental component summary scale of the Medical Outcomes Study SF−36.

The lack of association between other cognitive measures and change in quality of life is noted and may reflect the general challenges when evaluating cognitive changes in cancer patients. These challenges include the lack of a consistent, widely accepted definition of cognitive impairment and variation in the types of neuropsychological tests used in this population.[7] Some subgroups of patients may be more vulnerable to treatment induced cognitive changes than others.[38] Another explanation includes the limited correlations reported between objective and subjective measures of cognitive changes in cancer patients after treatment, where patients may sense more subtle changes that are not captured by the standard neuropsychological tests.[5,6,8] Thus, simple reaction time may be a more sensitive but less specific measure of cognitive processing. This novel finding from our study will require replication and further investigation by other investigators.

Other clinical predictors of changes in quality of life were important, depending on the aspect of quality of life studied. For example, the Brief POMS score, a measure of affective distress, was associated with change in the two summary scales of the SF−36, but not the FLIC. Type of treatment had an effect on changes for the FLIC and MCS, whereby those who received HSCT had the greatest improvements on these measures. Disease was associated with the PCS change, so that those with stable phase CML had the greatest improvement. Demographic variables such as marital status or race, and history of past substance use disorders were not predictive of quality of life changes at 12 months. These results are supported by other researchers who have reported that psychosocial factors account for change in mental health, and clinical factors account for change in physical well- being after treatment such as hematopoietic stem cell transplantation.[39]

Potential limitations to the ability to generalize study results include the study sample, which was restricted to those with either CML or MDS. It was impossible to randomize participants to cancer treatment for both clinical and ethical reasons. While health related quality of life was measured by the widely used Medical Outcomes Study SF−36 and FLIC, the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog) has since become available.[40] The Brief POMS was selected because of its concision, but a more comprehensive assessment of affective state using the Symptom Checklist−90 Revised (SCL−90-R), may result in a broader range of psychological concerns for future studies.[41] Reaction time was measured using the experimental PsyScope program which was available to the research team at the time of the study. Given these promising study results, other commercially available measures of reaction time could be used in clinical practice, such as the Conners' Continuous Performance Test-II or the Test of Variables Attention (TOVA). However the administration time for many of these measures are usually longer than the experimental measure we used. Reaction time findings were based on 94% (72 of 77) participants; results for five (6%) were unavailable for a variety of reasons inconsistent with systematic bias (participant preference, time constraints, data storage loss). The data supplement that accompanies the online edition of this article has additional information about reaction time analyses. As with most longitudinal studies of cognitive changes in cancer patients, a true baseline was not possible because information about cognitive function before the cancer diagnosis is unavailable.[6] Finally, participants reported on quality of life 1 year after treatment, and so the full extent of improvement is unknown for subsequent periods. These potential limitations notwithstanding, strengths of this study include a longitudinal assessment of a cohort with a 93% rate of participation of survivors 1 year after treatment for hematological malignancy with no known CNS involvement, and administration of

a comprehensive cognitive battery that included both standard and novel components.

CONCLUSIONS

Although pending further confirmation, it appears that use of simple reaction times may be an efficient and sensitive measure of cognitive function that is also predictive of quality of life change in the year after treatment for CML and MDS. The advantages of simple reaction time have already been noted, but this straightforward measure of the brain's information processing efficiency may also be more sensitive to changes that other psychometric tests of cognition do not capture.[7] Many other measures of processing speed involve more complex integration of brain systems as opposed to the simple reaction time task. Appreciation of the contribution of cognitive changes to quality of life is important, particularly since they are distinct from affective changes that also may exert an impact. Assessing reaction times prior to treatment might help to identify which patients will have better functional outcomes and which patients might benefit from anticipatory efforts such as psychoeducation regarding the disease and treatment processes to improve and strengthen existing support systems.

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References

1. Centers for Disease Control and Prevention (CDC): Cancer survivors—United States, 2007. MMWR Morb Mortal Wkly Rep 2011; 60:269–272
2. Wefel JS, Witgert ME, Meyers CA: Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. Neuropsychol Rev 2008; 18:121–131
3. Kiessling A, Henriksson P: Perceived cognitive function is a major determinant of health related quality of life in a non-selected population of patients with coronary artery disease—a principal components analysis. Qual Life Res 2004; 13:1621–1631
4. Phillips-Bute B, Mathew JP, Blumenthal JA, et al: Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006; 68:369–375
5. Poppelreuter M, Weis J, Külz AK, et al: Cognitive dysfunction and subjective complaints of cancer patients. a cross-sectional study in a cancer rehabilitation centre. Eur J Cancer 2004; 40:43–49
6. Nail LM: Cognitive changes in cancer survivors. Cancer and cancer treatment often cause cognitive deficits, but no guidelines exist for screening or treatment. Am J Nurs 2006; 106 (Suppl):48–54
7. Vardy J, Rourke S, Tannock IF: Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 2007; 25:2455–2463
8. Cull A, Hay C, Love SB, et al: What do cancer patients mean when they complain of concentration and memory problems? Br J Cancer 1996; 74:1674–1679
9. Lai JS, Butt Z, Wagner L, et al: Evaluating the dimensionality of perceived cognitive function. J Pain Symptom Manage 2009; 37:982–995
10. Harder H, Cornelissen JJ, Van Gool AR, et al: Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer 2002; 95:183–192
11. Deary IJ, Der G: Reaction time explains IQ's association with death. Psychol Sci 2005; 16:64–69
12. Ajtay Z, Kellényi L, Hejjel L, et al: Simple and choice reaction times are prolonged following extracorporeal circulation: a potential method for the assessment of acute neurocognitive deficit. Med Sci Monit 2009; 15:CR470–CR476
13. Juergens A, Pels H, Rogowski S, et al: Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. Ann Neurol 2010; 67:182–189
14. Klein M, Taphoorn MJB, Heimans JJ, et al: Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. J Clin Oncol 2001; 19:4037–4047
15. Quintás-Cardama A, Cortes JE: Chronic myeloid leukemia: diagnosis and treatment. Mayo Clin Proc 2006; 81:973–988
16. Steensma DP, Bennett JM: The myelodysplastic syndromes: diagnosis and treatment. Mayo Clin Proc 2006; 81:104–130
17. Caro JJ, Salas M, Ward A, et al: Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001; 91:2214–2221
18. Heinonen H, Volin L, Uutela A, et al: Quality of life and factors related to perceived satisfaction with quality of life after allogeneic bone marrow transplantation. Ann Hematol 2001; 80:137–143
19. Heinonen H, Volin L, Uutela A, et al: Gender-associated differences in the quality of life after allogeneic BMT. Bone Marrow Transplant 2001; 28:503–509
20. Chiodi S, Spinelli S, Ravera G, et al: Quality of life in 244 recipients of allogeneic bone marrow transplantation. Br J Haematol 2000; 110:614–619
21. Chang G, Meadows ME, Orav EJ, et al: Mental status changes after hematopoietic stem cell transplantation. Cancer 2009; 115:4625–4635
22. First MB, Spitzer RL, Gibbon M, et al: Structured clinical interview for axis I DSM-IV disorders. Patient edition (SCID-I/P,

Version 2.0). New York, Biometrics Research Department, New York State Psychiatric Institute, 1994
23. McHorney CA, Ware JE Jr, Raczek AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31:247–263
24. Schipper H, Clinch J, McMurray A, et al: Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. J Clin Oncol 1984; 2:472–483
25. Cella DF, Jacobsen PB, Orav EJ, et al: A brief POMS measure of distress for cancer patients. J Chronic Dis 1987; 40:939–942
26. Ware JE, Kosinski M: SF-36 physical and mental health summary scales: A manual for users of version 1, 2nd ed. Lincoln, RI, Quality Metric Incorporated, 2001
27. Andrykowski MA, Schmitt FA, Gregg ME, et al: Neuropsychologic impairment in adult bone marrow transplant candidates. Cancer 1992; 70:2288–2297
28. Buschke H, Fuld PA: Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974; 24:1019–1025
29. Masur DM, Fuld PA, Blau AD, et al: Distinguishing normal and demented elderly with the selective reminding test. J Clin Exp Neuropsychol 1989; 11:615–630
30. Wechsler D: Wechsler Adult Intelligence Scale, 3rd ed. San Antonio, TX, Psychological Corporation, 1997
31. Reitan RM: The relation of the trail making test to organic brain damage. J Consult Psychol 1955; 19:393–394
32. Benton AL, Hamsher Kde S: Multilingual Aphasia Examination. Iowa City, IA, AJA Associates, 1989
33. Golden CJ, Freshwater SM: Stroop color and word test. Los Angeles, CA, Western Psychological Services, 1998
34. Grooved Pegboard. Lutz, FL, Psychological Assessment Resources, Inc., 2000
35. Lezak MD, Howieson DB, Loring DW: Neuropsychological Assessment, 4th ed. New York, Oxford University Press, 2004
36. Cohen JD, MacWhinney B, Flatt M, et al: PsyScope: A new graphic interactive environment for designing psychology experiments. Behav Res Methods Instrum Comput 1993; 25: 257–271
37. Strauss E, Sherman EMS, Spree O: A compendium of neuropsychological tests: administration, norms, commentary, 3rd ed. New York, Oxford University Press, 2006
38. Ahles TA, Saykin AJ, McDonald BC, et al: Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol 2010; 28:4434–4440
39. Wingard JR, Huang IC, Sobocinski KA, et al: Factors associated with self-reported physical and mental health after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2010; 16:1682–1692
40. Kuenstner S, Langelotz C, Budach V, et al: The comparability of quality of life scores. a multitrait multimethod analysis of the EORTC QLQ-C30, SF-36 and FLIC questionnaires. Eur J Cancer 2002; 38:339–348
41. Pedersen G, Karterud S: Is SCL-90R helpful for the clinician in assessing DSM-IV symptom disorders? Acta Psychiatr Scand 2004; 110:215–224