VOLUME 36 · NUMBER 24 · AUGUST 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Do Patients With Advanced Cancer Have the Ability to Make Informed Decisions for Participation in Phase I Clinical Trials?

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Published at jco.org on July 9, 2018.

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0732-183X/18/3624w-2483w/$20.00

ABSTRACT

Purpose
Patients with advanced cancer (ACPs) participating in phase I clinical trials inadequately understand many elements of informed consent (IC); however, the prevalence and impact of cognitive impairment has not been described.

Patients and Methods
ACPs enrolled onto phase I trials underwent neuropsychological assessment to evaluate cognitive functioning (CF) covering the following domains: memory (Hopkins Verbal Learning Test), executive functioning (Trail Making Test B), language (Boston Naming Test-Short Version and Controlled Oral Word Association Test), attention (Trail Making Test A and Wechsler Adult Intelligenence Scale-IV Digit Span), comprehension (Wechsler Adult Intelligence Scale-IV), and quality of life (Functional Assessment of Cancer Therapy–Cognitive Function). Structured interviews evaluated IC and decisional capacity. Psychological measures included distress (Hospital Anxiety Depression Scale) and depression (Beck Depression Inventory-II).

Results
One hundred eighteen ACPs on phase I trials were evaluated, with CF ranging from mild impairment to superior performance. Only 45% of ACPs recalled physician disclosure of the phase I trial purpose. The 50% of ACPs who correctly identified the phase I research purpose had greater CF compared with ACPs who did not, as revealed by the mean T scores for memory (37.2 ± 5.6 *v* 32.5 ± 5.1, respectively; $P = .001$), attention (29 ± 2.7 *v* 26.9 ± 2.4, respectively; $P < .001$), visual attention (35.2 ± 6.6 *v* 31.5 ± 6.2, respectively; $P = .001$), and executive function (38.9 ± 7.5 *v* 34 ± 7.1, respectively; $P < .001$). Older ACPs (≥ 60 years) were less likely to recall physician disclosure of phase I purpose than younger ACPs (30% *v* 70%, respectively; $P = .02$) and had measurable deficits in total memory (34.2 ± 5.0 *v* 37.3 ± 5.6, respectively; $P = .002$), attention (24.5 ± 2.6 *v* 28 ± 2.8, respectively; $P < .001$), and executive function (32.8 ± 7.3 *v* 36.4 ± 7.6, respectively; $P = .01$). Older ACPs, compared with younger ACPs, also had greater depression scores (10.6 ± 9.2 *v* 8.1 ± 5.2, respectively; $P = .03$) and lower quality-of-life scores (152 ± 29.6 *v* 167 ± 20, respectively; $P = .03$). After adjustment by age, no psychological or neuropsychological variable was further significantly associated with likelihood of purpose identification.

Conclusion
CF seems to play a role in ACP recall and comprehension of IC for early-phase clinical trials, especially among older ACPs.

J Clin Oncol 36:2483-2491. © 2018 by American Society of Clinical Oncology

INTRODUCTION

In clinical research, the informed consent (IC) process is viewed as a means by which research participants are protected from harm.[1-5] An absolute requirement for adequate IC is intact decisional capacity, which includes the key element of comprehension of information provided during the IC process as well as appreciation, reasoning, and communication.[6-9] In general, the IC process for clinical research participation begins with disclosure of important elements (eg, nature of research, alternatives, and risks and benefits of participation). In addition to information disclosure that is mindful of potential

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.73.3592

DOI: https://doi.org/10.1200/JCO.2017.73.3592

participants' preferences for information, federal regulations governing human participant research require investigators to assist potential participants to understand this disclosed information to the greatest extent possible.[10]

In oncology, the IC process within the framework of phase I trials is especially significant because the primary scientific goal is to evaluate safety not efficacy, yet patients with advanced cancer (ACPs) often enroll onto trials with expectations of direct clinical benefit.[11] As a result, ethical and clinical concerns exist about the decisional capacity of this population required for adequate IC. Prior research overwhelmingly indicates that ACPs have an inadequate measured understanding of phase I IC elements, including phase I trial research purpose as dose and toxicity determination, likelihood of therapeutic benefit, and alternatives to trial participation.[4,11-30] Additional evidence suggests ACP understanding of phase I trials is influenced by overwhelming motivations for benefit and the IC process itself, including physician-investigator disclosure of the previously mentioned IC elements.[4,11-16,25-30]

Despite this evidence, ACP cognitive functioning (CF) and its effect on IC comprehension have never been formally evaluated. This is notwithstanding growing research demonstrating that patients with cancer experience mild, yet potentially clinically significant, cognitive impairment (CI) that is undetected without formal testing.[5,8,9,31-33] Prior research reveals that CI in patients with cancer may be a result of several underlying factors.[34-58] Since the early 1970s, CI has been associated with prior treatment effects (eg, chemotherapy, radiation). In patients with solid tumors, neuropsychological testing has revealed cognitive deficits involving attention, concentration, verbal and visual memory, and executive function.[35-37] Multiple cognitive tasks (and neuropsychological measures) are associated with specific decisional capacity domains.[39] For example, comprehension and understanding are associated with tasks of conceptualization and confrontation naming, executive functions, memory, and comprehension.[39] Additional contributors strongly associated with CI known to impair decisional capacity include psychological distress, fatigue, sleep disturbances, opiate and other medication use, and biochemical manifestations of cancer (eg, hormonal fluctuations, cytokine deregulation).[35-37,44,50,55-57] Moreover, as the incidence of CI increases with age, age-related impairments, and other comorbidities including working memory decline, concerns about CI and decisional capacity are further heightened in older ACPs.[5,8,9,31-33,58,59]

Given these concerns, our primary study objective was to formally describe CF related to decisional capacity in ACPs enrolling onto phase I trials. This study was designed to assess CF in ACPs on phase I trials using formal neuropsychological testing, including health-related quality of life (QOL) and ACP distress (depression and anxiety) impairing decision making, and to explore potential associations between age and ACP CF related to decisional capacity. We hypothesized that ACPs would report mild CI, diminished QOL, and mild distress as evaluated by formal neuropsychological and psychosocial assessment. We also hypothesized that poor CF, which may vary by age, would adversely impact and interfere with ACP IC understanding and reasoning related to phase I clinical trial decisions.

PATIENTS AND METHODS

Patients

Potential ACP participants recently providing IC for phase I trial participation were recruited from University of Chicago's Developmental Therapeutics Clinic. Eligibility requirements for phase I trial enrollment included ACP ability to give IC as determined by phase I investigators, age $\geq$ 18 years, survival prognosis of $\leq$ 3 months, Karnofsky performance status $\geq$ 60%, and a documented diagnosis of advanced cancer proven to be refractory to standard therapy or for which no identifiable standard therapy exists.

Procedure

Institutional review board approval was obtained before study initiation. This prospective, original report of a consecutive ACP sample included neuropsychological assessments completed at one time point—10 days after ACP provision of consent for phase I trial participation (before receipt of investigational agent[s]). Once consent for this IC study was obtained, ACPs completed neuropsychological tests and the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-COG), and IC and decisional capacity structured interview, and quantitative psychological measures (Hospital Anxiety and Depression Scale [HADS] and Beck Depression Inventory-II) in the clinic or infusion suite. One investigator (F.J.H.) trained in standardized administration of neuropsychological and psychological assessment, under the guidance of a neuropsychologist (E.R.L.), conducted testing and interviews. Neuropsychological testing assessed specific ACP cognitive tasks. Table 1 lists associations between ACP decisional capacity domains, cognitive tasks, and neuropsychological measures.[39]

Measures

Sociodemographic and clinical information was recorded per ACP self-report.

Neuropsychological tests. **Memory.** The Hopkins Verbal Learning Test–Revised (HVLT-R)[60] is a test of immediate and delayed learning assessing episodic memory, learning, and retention. The task required ACPs to recall 12 words after examiner presentation over three trials. Raw score is the sum of words recalled over three trials. A second delayed recall score is the number of words recalled 20 to 25 minutes after the initial task.

Executive functioning. The Trail Making Test B[61] is a test of executive function, set shifting, inhibitory control, and flexibility. ACPs connected randomly distributed numbers and letters, alternating sequentially between both. Raw score was number of seconds needed for task completion.

Language. The Boston Naming Test–Short[62-65] is a picture test of confrontation naming and word retrieval in individuals with aphasia or language disturbance as a result of neurologic deficits. The test contains 15 line drawings graded in difficulty for ACPs to name the picture.

The Controlled Oral Word Association Test[61,62,66,67] is an executive control measure assessing semantic and phonetic cues (eg, word retrieval, verbal initiation and fluency). ACPs recalled words beginning with the letter A within 60 seconds. Raw scores reflect number of all acceptable words.

Attention. Wechsler Adult Intelligence Scale-IV Digit Span[66] is a test of verbal working memory, sustained attention, and encoding. ACPs were read a number sequence and asked to recall it in exact order. Next, ACPs were read a number sequence and asked to recall it in reverse order. Raw score is the longest digit span recalled.

The Trail Making Test A[61] is a test of visual scanning, graphomotor speed, and attention. ACPs were instructed to connect numbers, randomly distributed across the page, in sequence. Raw score was number of seconds needed for task completion.

Verbal comprehension. Wechsler Adult Intelligence Scale-IV Comprehension[61,62,66,67] is a measure of verbal comprehension, reasoning, and judgment. ACPs responded to questions based on understanding of general principles and social situations. Raw score was the number of questions answered correctly.

Table 1. Associations Between ACP Decisional Capacity Domains, Cognitive Tasks, and Neuropsychological Measures

Decisional Capacity Domain	Cognitive Function Tasks	Neuropsychological Measures
Comprehension/understanding: ability to comprehend clinical trial and treatment-related information, including the risks or benefits of proposed treatments[39]	Conceptualization and confrontation naming	Boston Naming Test–Short
	Executive functioning	Trail Making Test B
	Memory	Hopkins Verbal Learning Test
	Comprehension	WAIS-IV Comprehension
Appreciation: ability to relate trial/treatment information and related consequences to one's own personal situation[39]	Verbal fluency	COWAT
	Visual attention	Trail Making Test A
	Conceptualization	Boston Naming Test–Short
Reasoning: ability to rationally evaluate and compare treatment alternatives[39]	Verbal fluency	COWAT
	Executive functioning	Trail Making Test B
	Mental flexibility	Trail Making Test B
	Attention	WAIS-IV Digit Span
	Delayed memory	Hopkins Verbal Learning Test
Expression of choice: ability to convey a relatively consistent treatment choice[39]	Auditory comprehension	WAIS-IV Comprehension
	Comprehension	WAIS-IV Comprehension
	Confrontation naming	Boston Naming Test–Short
	Memory	Hopkins Verbal Learning Test
	Attention	WAIS-IV Digit Span

Abbreviations: ACP, patient with advanced cancer; COWAT, Controlled Oral Word Association Test; WAIS-IV, Wechsler Adult Intelligence Scale-IV.

QOL. The FACT-COG Version 2[35,68-72] is a health-related QOL measure with CF domains (perceived CI, cognition, QOL impact, and concerns from others), yielding the following four summary scores: CF, Impact on functional domain/interferences (IOF), impact on quality of life (QOL), and total. Responses rated on 5-point Likert scale (0 = never to 4 = several times a day) the frequency with which each statement occurred in the past week. Low scores indicate poor overall QOL.

Table 2. Demographic Characteristics of the Total Phase I ACP Population and According to Age

	Total Phase I ACP Population (N = 118)		ACPs < 60 Years Old (n = 47)		ACPs ≥ 60 Years Old (n = 71)	
Characteristic	No.	%*	No.	%*	No.	%*
Total	118	100	47	39.8	71	60.2
Age, years						
Median	60		48.5		64	
Range	23-83		23-59		60-83	
Sex						
Male	83	70	32	68	51	72
Female	35	30	15	32	20	28
Race						
White	108	92	42	89	66	93
African American	7	6	4	9	3	4
Hispanic	1	1	—	—	1	2
Asian	—	—	—	—	—	—
Other	2	1	1	2	1	2
Marital status						
Single	11	9	3	6	8	12
Married	69	59	31	66	38	53
Divorced	4	3	3	6	1	1
Widow	9	8	4	9	5	7
Other	25	21	6	13	19	27
Education						
Some high school	1	1	—	—	1	1
High school	35	30	19	40	16	23
Some college	38	32	13	28	25	35
College graduate	27	23	7	15	20	28
Some postgraduate	6	5	3	6	3	4
Professional degree	11	9	5	11	6	9
Diagnosis						
GI	71	60	29	62	42	59
Lung/esophageal	22	19	6	12	16	22
Genitourinary	11	9	5	11	6	9
Other†	14	12	7	15	7	10

Abbreviations: ACP, patient with advanced cancer.
*Percentages are based on column percentages calculated.
†Includes sarcomas and breast and ovarian malignancies.

Table 3. Psychosocial Characteristics of Perceived Cognitive Impairment and Distress for the Total Phase I ACP Population and by Age Group

Psychosocial Measure	Score			*P*
	Total Phase I ACP Population (N = 118)	ACPs < 60 Years Old (n = 47)	ACPs ≥ 60 Years Old (n = 71)	
QOL				
FACT-COG perceived CI				
Mean (SD)	100.8 (20.6)	106 (17.3)	97.7 (22)	.06
Range	40-123	62-123	40-122	
FACT-COG impact on QOL				
Mean (SD)	26.5 (6.9)	27 (5.8)	26 (6.8)	.04
Range	13-32	14-32	13-32	
FACT-COG total				
Mean (SD)	158 (27)	167 (20)	152 (29.6)	.03
Range	90-194	115-194	90-190	
Anxiety				
HADS anxiety				
Mean (SD)	8.8 (2.5)	9.3 (2.9)	8.6 (2.3)	.26
Range	5-18	6-18	5-16	
Depression				
HADS depression				
Mean (SD)	11.5 (2.7)	11.5 (3.3)	11.5 (2.3)	.92
Range	4-16	4-16	5-16	
BDI-II				
Mean (SD)	9.8 (8.1)	8.1 (5.2)	10.6 (9.2)	.03
Range	1-47	1-42	1-47	

Abbreviations: ACP, patient with advanced cancer; BDI-II, Beck Depression Inventory-II; CI, cognitive impairment; FACT-COG, Functional Assessment of Cancer Therapy–Cognitive Function; HADS, Hospital Anxiety and Depression Scale; QOL, quality of life; SD, standard deviation.

Psychological measures. The HADS[73] is a 14-item distress scale with the following two subscales: seven items measure anxiety (eg, "Worrying thoughts go through my mind") and seven items measure depression (eg, "I feel cheerful"). Responses are scored from 0 to 3 points, with subscale total scores of 0 to 21 points (score ranges: normal, 0 to 7; mild, 8 to 10; moderate, 11 to 14; and severe, 15 to 21).

The Beck Depression Inventory-II[74] is a 21-item depression inventory measuring affective (eg, "I do not feel sad") and somatic symptoms (eg, "My appetite is no worse than normal"). Responses are scored from 0 to 3 points (score ranges: minimal depression, 0 to 13; mild depression, 14 to 19; moderate depression, 20 to 28; and severe depression, 29 to 63).

Phase I IC structured interview. Decisional capacity of the phase I clinical trial IC elements was assessed, as previously reported,[14-16,75-78] including research purpose, trial alternatives, risk and benefits, and expectations of benefit. The interview included demographic, structured (yes or no), and open-ended questions. Two questions related to ACP recall and comprehension of the phase I research purpose were posed. First, ACPs were asked to recall physician disclosure of the phase I trial purpose ("When you enrolled, what did the physician tell you was the purpose of the investigational study?"). Second, ACP comprehension gained regarding phase I IC was evaluated ("As far as you know, what are the doctors and researchers trying to find out in the experimental study in which you are participating?"; Appendix, online only).

Statistical Analysis

All data were analyzed using Stata 13.0 statistical software (Stata, College Station, TX).[79] Demographics were summarized using frequencies, percentages, medians and means, ranges, and standard deviations. To examine age differences as a result of expected increase in CI with advancing age, summary statistics were tabulated for the total population and dichotomized on the basis of population median into two groups (age < 60 and age ≥ 60 years), and characteristics were compared between groups using the *t* test, Fisher's exact test, or χ^2 test. Distinct multivariable logistic regression models were applied for each psychological and neuropsychological measure adjusted by demographic variables. For neuropsychological tests, T scores were calculated using mean raw score, with overall mean T scores, standard deviations, and ranges. *t* tests were completed to detect differences between group scores. T scores range from 20 (profound deficit) to 80 (very superior performance) with CF classifications as follows: very superior, 70 to 80; superior, 64 to 69; high average, 58 to 63; average, 43 to 57; low average 37 to 42; borderline, 30 to 36; impaired, 28 to 29; mild, 27.2 to 27.9; moderate, 26 to 27; severe, 24 to 25; and profound, < 24. The statistical significance threshold was set at $P < .05$.

Phase I IC Content Analysis

This was an iterative process of qualitative analysis of ACP response to structured interview inquiry as recorded within each decisional capacity domain for phase I IC. Responses were read by investigators (F.J.H. and H.S.N.) and coded using a consensus process of whether ACPs understood phase I IC and purpose. Responses involving dosage, toxicity, or dosage and toxicity were considered correct. Other responses (eg, cure) were considered incorrect. One investigator (C.K.D.) resolved discrepancies. Investigators systematically identified recurrent themes and generated a category list for responses using the constant comparison method to confirm conceptual development. Coded responses were summarized as proportions to specific questions, enabling subsequent quantitative analyses to identify associations between variables of interest.

RESULTS

A consecutive sample of 251 ACPs enrolled onto phase I trials from the University of Chicago's Developmental Therapeutics Clinic were approached for study participation. A total of 133 patients did not complete full assessment with survey as a result of unexpected toxicity or fatigue. No significant differences in demographics were found between noncompleters and completers with the exception of ACP age (56 ± 11.4 years *v* 61 ± 9.7, respectively; $P = .02$). Noncompleters were younger and disenrolled early from trial participation. No ACP refused study participation. A final sample of 118 ACPs (47%) consented and completed full assessment with survey. Table 2 lists the demographics for the total population and the age groups. In the total population, the median age was 60 years (range,

Table 4. Neuropsychological Characteristics for the Total Phase I ACP Population and by Age

Neuropsychological Measure	T Score			P
	Total Phase I ACP Population (N = 118)	ACPs < 60 Years Old (n = 47)	ACPs ≥ 60 Years Old (n = 71)	
HVLT-R Trial 1				
Mean (SD)	41.6 (7.6)	41.6 (7.4)	41.6 (7.6)	.50
Range	20-69	20-69	21.5-63	
HVLT-R Total				
Mean (SD)	35 (5.2)	37.3 (5.6)	34.2 (5.0)	.002
Range	20-65	20-65	20-61.4	
HVLT-R Delay				
Mean (SD)	35.1 (5.4)	36.4 (5.7)	32.5 (5.9)	< .001
Range	20-68	36-68	20-60	
HVLT-R Recognition				
Mean (SD)	32.7 (5.8)	37.3 (5.9)	30.1 (5.1)	< .001
Range	20-62	20.1-60.7	20-62	
WAIS-IV Digit Span Total				
Mean (SD)	27.5 (2.8)	28 (2.8)	24.5 (2.6)	< .001
Range	23-33	23-33	23-27	
Trail Making Test A				
Mean (SD)	41.9 (6.5)	41.9 (6.3)	41.8 (6.4)	.93
Range	20-71.5	20-71.5	20-71.5	
Trail Making Test B				
Mean (SD)	34.6 (7.5)	36.4 (7.6)	32.8 (7.3)	.01
Range	20-64.4	20-62	20-64.4	
COWAT Verbal Fluency–Animals				
Mean (SD)	35.6 (5.7)	36.4 (5.7)	30.1 (5.2)	< .001
Range	21-50	21-50	21-49.2	
Boston Naming Test–Short				
Mean (SD)	55.5 (4.6)	55.9 (4.7)	55.5 (4.6)	.64
Range	24.6-65	25-64	24.6-65	
WAIS-IV Comprehension				
Mean (SD)	63.6 (6.2)	63.5 (6.2)	63.6 (6.2)	.93
Range	37-80	37-80	43-80	

Abbreviations: ACP, patient with advanced cancer; COWAT, Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test–Revised; SD, standard deviation; WAIS-IV, Wechsler Adult Intelligence Scale-IV.

23 to 83 years), 70% were male, 92% were white, 37% were college or professional graduates, and 60% had a GI malignancy. ACPs reported mild anxiety, moderate depression (HADS), and poor total FACT-COG QOL (Table 3).

Neuropsychological Outcomes

ACP neuropsychological T scores for CF are listed in Table 4. Overall, phase I ACP CF ranged from mild impairment to superior performance (27.5 ± 2.8 to 63.6 ± 6.2). ACPs experienced borderline impairment in CF for memory, executive function, and verbal fluency. ACPs exhibited low average attention, average language, and superior comprehension.

ACP Phase I IC Recall and Comprehension

Table 5 lists ACP IC understanding of phase I trials according to age. Only 45% of ACPs recalled disclosure of dosage or toxicity as the primary phase I research purpose. In total, 50% of ACPs correctly identified dosage as the phase I purpose.

Associations Between Neuropsychological Outcomes, ACP Phase I IC Recall, and Comprehension

ACPs who recalled the physician disclosure of the trial purpose as dosage had better CF than ACPs who failed to recall purpose, as measured by HVLT-R delayed memory (41 ± 6.7 *v* 32.1 ± 5.4, respectively; $P = .01$), recognition (38.5 ± 5.7 *v* 21 ± 4.1, respectively; $P = .001$), and digit span attention (31 ± 2.8 *v* 27.9 ± 2.4, respectively; $P < .001$). Regarding trial comprehension, ACPs who identified purpose had better CF than ACPs who failed to identify purpose, as assessed by HVLT-R delayed memory (37.2 ± 5.6 *v* 32.5 ± 5.1, respectively; $P = .001$); digit span attention (29 ± 2.7 *v* 26.9 ± 2.4, respectively; $P < .001$), Trail Making Test A visual attention (35.2 ± 6.6 *v* 31.5 ± 6.2, respectively; $P = .001$), and Trail Making Test B mental flexibility (38.9 ± 7.5 *v* 34 ± 7.1, respectively; $P < .001$).

Highly educated ACPs were more likely to identify trial purpose compared with less educated ACPs (53% *v* 27%, respectively; $P = .03$). Female sex was associated with greater likelihood of purpose identification (70% *v* 47% for men; $P = .04$). After adjustment by age, no psychological or neuropsychological variable was further significantly associated with likelihood of purpose identification (Table 6).

Neuropsychological Outcomes and ACP Comprehension of Phase I IC According to Age

Age is well known to affect performance on neuropsychological measures. As expected, several, but not all, measures indicate significant differences between age groups. Older ACPs performed poorly compared with younger ACPs on memory, attention, executive function, and verbal fluency tasks (Table 4). They also had

Table 5. Phase I Informed Consent Understanding in the Total ACP Population and According to Age

Phase I Informed Consent	Total Phase I ACP Population (N = 118)		ACPs < 60 Years Old (n = 47)		ACPs ≥ 60 Years Old (n = 71)		
	No.	%	No.	%	No.	%	P
Recall phase I purpose	54	45	33	70	21	30	.02
Correct identification of purpose (comprehension)	59	50	12	26	47	66	.03
Benefit–efficacy	69	58	26	55	43	60	.23
Benefit to future patients	6	5	1	2	5	7	.99
Risk–general	114	97	46	98	68	96	.77
Risk of death	17	14	5	10	12	17	.62
No risk	10	8	3	6	7	10	.67
Alternatives to phase I trial presented	100	85	40	85	60	84	.75
Phase I was only option	67	57	26	55	41	58	.80
Denial of hospice or palliative care as options	63	53	12	25	51	72	.01

Abbreviation: ACP, patient with advanced cancer.

greater depression and poorer total QOL (Table 3). Older ACPs were less likely to recall purpose compared with younger ACPs (30% *v* 70%, respectively; $P = .02$), yet more likely to correctly identify trial purpose (66% *v* 26%, respectively; $P = .03$) and to deny that supportive care was presented (72% *v* 25%, respectively; $P = .01$; Table 5).

DISCUSSION

The key foundation of IC is the presence of intact decisional capacity. This study examined the essential IC elements for phase I trials and their relationship to ACP decisional capacity and CF using formal neuropsychological testing. On the basis of tests of memory (recall and recognition), verbal fluency, and executive functioning, we found evidence of borderline CI in ACPs enrolled onto phase I trials. Our data reveal that CF may play a role in ACP recall and comprehension of IC for phase I clinical trials. Other factors, including demographics, psychological distress, and QOL, may also be associated with this recall and comprehension.

Neuropsychological testing detected evidence of CI in ACPs involving encoding, retrieval, and recognition of consent information, as well as attention and executive functioning required for decision making. These data suggest that some ACPs may not be fully equipped to process information necessary to provide adequate IC. CI is prevalent in ACPs[59] but was particularly salient in older ACPs, who experienced more significant deficits in memory, language, attention, and executive functioning and were less likely to recall physician disclosure of trial purpose. This is consistent with research revealing that recall decreases with age, yet is dependent on quantity of information provided; when more information is discussed, older ACPs experience significant challenges remembering this information.[80] Therefore, physician communication of phase I IC should be tailored to engage visual and cognitive abilities of older ACPs in order to enhance understanding

Table 6. Series of Multivariable Logistic Regression Models and Analyses: Age and Psychological and Neuropsychological Factors—Likelihood of Correct Identification of the Phase I Trial Research Purpose

Factor	Unadjusted OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
Age	1.05 (1.00 to 1.10)	.03		
BDI-II	0.98 (0.91 to 1.05)	.48	0.99 (0.90 to 1.09)	.90
HADS Anxiety	0.94 (0.78 to 1.15)	.55	0.98 (0.78 to 1.21)	.82
HADS Depression	1.25 (1.02 to 1.53)	.03	1.21 (0.97 to 1.53)	.11
Digit Span, total score	1.02 (0.92 to 1.13)	.03	1.02 (0.90 to 1.16)	.72
Trail Making Test B	1.01 (0.99 to 1.02)	.04	1.01 (0.99 to 1.03)	.19
WAIS Comprehension	1.25 (1.05 to 1.48)	.01	1.18 (0.96 to 1.44)	.11
HVLT-R Total	1.01 (0.94 to 1.09)	.76	0.99 (0.90 to 1.09)	.88
HVLT-R Delay	1.15 (0.98 to 1.36)	.08	1.12 (0.91 to 1.38)	.29
HVLT-R Discrimination Index	1.09 (0.90 to 1.31)	.37	1.19 (0.93 to 1.52)	.17
FACT-COG Negative	1.01 (0.98 to 1.03)	.53	1.00 (0.98 to 1.03)	.75
FACT-COG QOL	0.98 (0.90 to 1.06)	.59	0.95 (0.85 to 1.07)	.42
FACT-COG QOL + Negative	1.00 (0.98 to 1.02)	.96	1.00 (0.97 to 1.02)	.74
FACT-COG Positive	1.01 (0.95 to 1.06)	.86	0.99 (0.93 to 1.07)	.87
FACT-COG Total	1.00 (0.98 to 1.02)	.85	1.00 (0.98 to 1.02)	.83

Abbreviations: BDI-II, Beck Depression Inventory-II; FACT-COG, Functional Assessment of Cancer Therapy–Cognitive Function; HADS, Hospital Anxiety and Depression Scale; HVLT-R, Hopkins Verbal Learning Test–Revised; OR, odds ratio; QOL, quality of life.
*Adjusted for age.

given that many ACPs cognitively receive and process trial content differently. Oncologists must enhance this IC process using communication practices including corrected feedback (repetition of information and categorizing complex information), provision of pictorial representations, and teachback (checking understanding; eg, "We discussed a great deal today. Can you tell me in your own words what is the purpose of a Phase I clinical trial?") where ACPs engage in cognitive tasks (eg, naming, executive function, memory, comprehension). Indeed, it is not quantity of information alone but also quality of IC that is critical in this communication.

ACP CI may be further exacerbated by underlying psychological distress, as older ACPs tended to report more depressive symptoms. In addition, in the older and total ACP groups, depression may have impacted appropriate recall and comprehension of the phase I trial purpose. These results support prior evidence indicating that ACPs' realistic expectations of outcome are associated with psychological morbidity.[14,81,82] Also, older ACPs had significantly poorer QOL, as indicated by FACT-COG. Given the terminal status of phase I ACPs, cognitive-related issues coupled with disease progression suggest this is a vulnerable population whose ability to provide IC is questionable in many cases, particularly among older patients. The CI discovered could further be expected to worsen ACP emotional, social, and physical well-being in the long term.[35,36] ACPs who are neurologically robust are more likely to recall and understand IC information as provided by a physician-investigator during trial discussions.

Several limitations of our study should be noted. It is statistically difficult to control for individual differences in consent forms from multiple trials. However, although the phase I consent form is standardized to include key IC elements as mandated by the institutional review board and federal regulations, the consent form is only one piece of a complicated, rigorous IC process involving, first, formal oncologist's disclosure of key phase I IC elements to the ACP, followed by oncologist-ACP dialogue involving the nature of IC, concluded by stringent review and signing of the form with an opportunity for the ACP to gain clarity. Our goal was not to analyze the impact of the consent form only but all aspects related to the IC process, such as understanding and communication, as defined by multiple cognitive tasks, potentially affected by potential CI. Next, formal control groups were not included. Healthy, age-matched people or ACPs receiving outpatient chemotherapy should be considered. We desired to describe whether CI was present in this selected ACP group and to examine its effect on phase I IC recall and comprehension. A second limitation involved the one-time CF assessment at initiation of phase I trial enrollment. Longitudinal study assessing ACP CF during the trial would provide meaningful data. An additional limitation includes significant selection bias (118 of 251 ACPs enrolled onto phase I trials completed assessment). It may be that ACPs who completed the study were healthier with better CF compared with those unable to complete the study. Finally, reporting on only two outcomes strongly reduces the impact of study results. However, we examined all four domains of decisional capacity, finding only comprehension to be associated with demographic variables of interest. Data were skewed for additional domains (eg, appreciation ["Do you feel you had the option to refuse study?"; 100% responded "yes"]). Similar results were found for choice and reasoning. We focused on recall, although not a capacity domain, as a significant cognitive task specific to memory and representative in all domains. In addition, any differences in neuropsychological performance are only limited to statistical significance. With regard to any associations, especially between phase I IC decisional capacity and neuropsychological outcomes, we recognize that any explanation is speculative. However, these associations do provide hypotheses for further study.

Future research must determine the significance of CI and the impact of comorbidities on ACP IC comprehension for phase I clinical trials. The underlying causes of CI and contributors (eg, distress) are likely multifactoral.[34-59,83,84] Educators and caregivers should become involved in the IC process. Potential ACP barriers to understanding accurate information involve studying oncologists and patients during the IC process. Brief cognitive measures (eg, Montreal Cognitive Assessment) might provide options for determining which ACPs need additional IC communication. Moreover, longitudinal study of ACPs throughout phase I trial enrollment and beyond (hospice) should assess decisional capacity. Finally, application of pharmacologic (eg, modafinil, methylphenidate), clinical (eg, cognitive rehabilitation, biofeedback, brief cognitive-behavioral therapy), and communication support tools and/or interventions (corrected feedback or teachback) should be considered to address CI.[85-101] Such interventions will assist ACPs with coping, QOL, and decision making.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by National Institutes of Health Grant No. RO1 CA 087605-01A1 (C.K.D.) and the Greenwall Foundation Program for Bioethics (C.K.D. and G.A.S.)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Do Patients With Advanced Cancer Have the Ability to Make Informed Decisions for Participation in Phase I Clinical Trials?

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No relationship to disclose

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Research Funding: Novartis (Inst), Genentech (Inst), Ipsen (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: GlaxoSmithKline, Bayer

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Research Funding: AbbVie (Inst), Dicerna (Inst)
Patents, Royalties, Other Intellectual Property: Royalties related to *UGT1A1* genotyping for irinotecan, royalties related to *UGT1A1* genotyping for irinotecan (Inst), pending patent related to a genomic prescribing system, pending patent related to a genomic prescribing system (Inst)
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Appendix

Structured Interview Questions Assessing Comprehension of Elements of Informed Consent by Patients With Advanced Cancer

Understanding and comprehension.

- What is the purpose of this investigational study? (When you enrolled, what did the physician tell you the purpose of the study was?)
- What alternatives were present to you in addition to joining the investigational study?
- Can you recall the side effects that were presented to you during the explanation of this experimental protocol? Can you name a couple?

Appreciation.

- Why do you think the physician talked to you about joining the study today?
- Did you feel like you had the option to refuse to be in the investigational study?
- If no, why did you feel like you did not have the option to refuse to be in the investigational study?
- Do you feel like you can withdraw at any time?

Interview Questions Assessing Elements of Informed Consent

Reasoning.

- What were the benefits of choosing to participate in this study?
- What were the risks of participating in this study?

Communication.

- Did you have the opportunity to ask the physician questions?
- What questions did you ask that were not answered?
- What information did you receive about the drug trial you are in that you didn't understand?

Interview Questions Assessing Elements of Informed Consent

- Was any nonexperimental therapy discussed with you before you made a decision to participate in the study at the University of Chicago?
  –If yes, what kind of therapy was discussed?
- Was the possibility of no chemotherapy discussed with you as an option?
- Was the possibility of care that would only relieve symptoms but would not have any chance of destroying your cancer discussed with you?
- As far as you know, what are the doctors and researchers trying to find out in the experimental study in which you are participating?
- Of the following choices, which one best states the research purpose of the investigational drug study you are in?

  A. I don't know the purpose
  B. To determine the side effects and the right dose of the drug
  C. To determine if the drug can cure my cancer
  D. To determine if the drug can destroy or shrink my cancer