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Determining Chemotherapy Tolerance in Older Patients With Cancer

Jerome Kim, MD^a and Arti Hurria, MD^b

^aHarbor UCLA Medical Center, Torrance, California

^bCity of Hope Comprehensive Cancer Center, Duarte, California

Abstract

Older adults with cancer constitute a heterogeneous group of patients who pose unique challenges for oncology care. One major concern is how to identify patients who are at a higher risk for chemotherapy intolerance, because a standard oncology workup may not always be able to distinguish an older individual's level of risk for treatment-related complications. Geriatric oncologists incorporate tools used in the field of geriatrics, and have developed the Comprehensive Geriatric Assessment to enhance the standard oncology workup. This assessment pinpoints problems with daily activities, comorbidities, medications, nutritional status, cognitive function, psychological state, and social support systems, all of which are risk factors for treatment vulnerability in older adults with cancer. Additional tools that also serve to predict chemotherapy toxicity in older patients with cancer are now available to identify patients at higher risk for morbidity and mortality. Together, these instruments complement the standard oncology workup by providing a global assessment, thereby guiding therapeutic interventions that may improve a patient's quality of life and clinical outcomes.

Oncologists face an immense challenge. As the US population ages, the number of patients with cancer is increasing. The annual incidence of cancer in the United States is 1.6 million new cases,¹ and patients aged 65 years or older constitute 61% of these newly diagnosed cases. It is projected that the US cancer incidence will increase to 2.3 million people by 2030, and that 70% of cases will occur in patients aged 65 years or older.² Although older adults represent most patients diagnosed with cancer, they constitute only 25% of the patients currently studied in clinical trials.³ Thus, the management of older patients with cancer continues to be based on skewed data derived from the youngest and strongest population.

The Importance of Determining Potential Toxicities

A major concern when treating geriatric patients with cancer is the risk for chemotherapy-related toxicities. Although trials show that chemotherapy is effective in patients with

Correspondence: Arti Hurria, MD, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010. ahurria@coh.org.

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“good” functional status, the same trials show that some older adults are at increased risk for chemotherapy toxicity.⁴ One could speculate from these studies that even older patients with “good” functional status are at a high risk for chemotherapy toxicity. However, an alternate explanation, given the large portion of older patients in the study who did not experience severe toxicity, is to recognize that the standard oncology tools are inadequate to distinguish which older adult is or is not at higher risk for chemotherapy-related complications.

The National Cancer Institute and the National Institute on Aging, recognizing the current knowledge gaps in geriatric oncology, have called for studies to identify patients at high risk for chemotherapy intolerance in order to facilitate treatment management.⁵ Geriatric oncology researchers have identified factors that predict chemotherapy toxicity, tolerance, and survival, and have developed tools to obtain this information. In addition, researchers have developed predictive models for chemotherapy toxicity in older adults with cancer. This article reviews these tools, along with practical ways for oncologists to use them, in order to assist in the care of this understudied population.

Going Beyond Chronologic Age

Chronologic age may be a convenient way to assess data, especially in epidemiologic studies, but older patients with cancer are a heterogeneous group that belies group identification based on numeric age alone. Studies have shown that overall health is more predictive for chemotherapy tolerance than chronologic age.⁶⁻¹⁰ Although decreased organ function is experienced universally with aging,^{11,12} the rate and degree of decline differs from person to person as a result of unique genetic and environmental factors. The standard oncology workup provides vital information to guide management of all patients with cancer, but it is not sufficient to identify those who are more vulnerable to treatment complications. This means that a practical way to characterize a patient’s global fitness is needed.^{13,14}

Comprehensive Geriatric Assessment

The Comprehensive Geriatric Assessment (CGA) includes an evaluation of a patient’s functional status, comorbidities, medications, nutritional status, cognitive function, psychological status, and social support system.¹⁵ Each domain of the CGA is independent yet interconnected (ie, a problem in one domain may not detect difficulties in another). Evaluating multiple domains provides a global perspective, thereby identifying potential areas of vulnerability.^{16,17}

Components of the CGA

Functional Status—Patients with Karnofsky performance status greater than 70 or ECOG performance status less than 2 are often considered to have “good” performance status. However, a study of older patients with cancer noted that 38% of patients with good performance status still had difficulties with instrumental activities of daily living (IADLs), which include tasks necessary to live independently in the community (eg, shopping, housekeeping, accessing transportation, doing laundry, using the telephone, managing finances, and taking medications),¹⁸ whereas 9% needed assistance with activities of daily

living (ADLs), which include basic tasks needed to live at home (eg, bathing, dressing, grooming, feeding, toileting, maintaining continence, and transferring from bed to chair).^{17,19} This is important because problems performing IADLs are prognostic for severe chemotherapy toxicity⁶⁻⁸ and poorer survival in older patients with cancer,^{20,21} whereas needing assistance with ADLs has been linked to increased health care use and shorter survival in geriatric patients.²²

Screening a spectrum of activities improves the sensitivity to detect problems, because each activity relies on a unique skill set. If problems exist within or between body systems (ie, central nervous system, peripheral nervous system, musculoskeletal system), these deficits will manifest in a variety of ways based on the severity of the underlying problem and any compensatory adaptations that a patient has learned to perform. Functional deficits signal a breakdown of some component in this interplay. Parallels can be made between surveying older adults based on daily activities and screening pediatric patients based on tasks that mark functional milestones. In both situations, impairments signal an underlying problem, and in older adults with cancer this may be an indication of an increased risk for chemotherapy toxicity.

Comorbidities—Although comorbidities are routinely assessed during a standard oncology workup, the CGA uses validated tools that account for the type and severity of each medical problem.²³ Comorbidities predict early mortality in patients with cancer, independent of age and functional status.^{24,25} The number of comorbidities increases with age, leading to a situation in which the risks and benefits of cancer treatment must be weighed against contending causes of morbidity and mortality.²⁶ Medical problems such as diabetes mellitus are associated with an increased risk of mortality in older adults with cancer,^{27,28} whereas organ dysfunction such as renal insufficiency is a risk factor for chemotherapy toxicity.^{7,8}

Medications—Close to one-third of patients with cancer take a combination of medications that are known to interact.²⁹ Polypharmacy (ie, an increased number of medications, unnecessary medications, potentially inappropriate medications, over/underuse of medications, or drug–drug interactions)^{30,31} is an independent risk factor for overall survival in older patients with ovarian cancer.⁹ Physicians should assess for polypharmacy using tools such as the Beers criteria,³² Medication Appropriateness Index (MAI),³³ Screening Tool of Older Persons' Prescriptions (STOPP), and Screening Tool to Alert doctors to Right Treatment (START) criteria.³⁴

Nutrition—Prospective studies have identified malnutrition as a risk factor for chemotherapy intolerance^{7,10} and decreased survival^{10,35,36} in older patients with cancer. Weight loss is a poor prognostic sign that has been linked to shorter median survival compared with patients without weight loss across tumor types in this population.³⁷ A body mass index of less than 22 kg/m² has also been associated with shorter survival in older patients.³⁸

Cognition—Cognitive problems are associated with chemotherapy intolerance^{6,7,10} and hospitalization⁶ in older adults with cancer. The prevalence of dementia will continue to

increase as the population ages.³⁹ Therefore, identifying patients with impaired cognitive function is imperative, because multiple aspects of oncology care rely on the patient's ability to recall and understand complex tasks, including taking medications and navigating the complicated health care system.⁴⁰ In addition, older patients with lower baseline cognitive reserve may be at higher risk for further cognitive decline with chemotherapy.⁴¹

Psychological Status—Studies have linked depression to hospitalizations,⁶ chemotherapy toxicity, and decreased survival in older adults with cancer.⁹ Studies have noted loss of independence and fatigue as leading causes of patient distress, which leads to a reduced ability to adapt to life with cancer.^{42,43}

Social Support—Social isolation has been linked to increased chemotherapy toxicity⁸ and decreased survival in patients with cancer.^{44,45} Identifying a patient's social network (or lack thereof) involves understanding their support system and identifying who is present for emotional and tangible support (ie, someone to assist in daily activities).

Frailty—Frailty is a clinical syndrome defined by at least 3 of the following characteristics: unintentional weight loss, poor endurance, weakness, slow gait, and low physical activity.⁴⁶ Frail patients are more vulnerable because of decreased physiologic reserve. In a study of community-dwelling older adults, frailty was associated with increased incidences of falls, hospitalizations, and death.⁴⁶

Delivering the CGA

Geriatric oncologists recognize the limited health care resources and time constraints that are faced in practice. For this reason, research efforts have been directed at self-administered surveys that patients could perform before visits. A study conducted in a cohort of oncology patients seen at a Veterans Affairs Medical Center found that 76% of patients returned a self-reported survey that was mailed before a clinic visit.⁴⁷ A separate study noted that patients took a median of 22 minutes to complete a primarily self-administered CGA.⁴⁸ Current studies using computer technology, such as touchscreen devices, are ongoing as a means of improving efficiency, accessibility, and delivery of the CGA to patients, and to provide oncologists with a real-time summary of a patient's strengths and vulnerabilities.⁴⁹

The question of who should be assessed with a CGA is a matter of debate. Some geriatric oncologists advocate that the CGA should be performed on every older adult with cancer before the start of a new chemotherapy regimen to identify patients who are at higher risk for chemotherapy toxicity. Other experts in the field have proposed prescreening tests, such as the Vulnerable Elders Survey (VES-13)⁵⁰ or the abbreviated CGA,⁵¹ that take a fraction of the time to complete and would potentially identify vulnerable patients who would then undergo further evaluation with a full CGA.⁵¹⁻⁵³ Performing a full CGA on all older patients with cancer would improve detection of those who are at higher risk for chemotherapy toxicity, but at the cost of screening a group of patients without vulnerability. Using a prescreening test would decrease the resources needed for screening, but has the potential to miss some vulnerable patients. The balance between the time and resources needed to administer these tests versus the level of sensitivity for detecting patients with a higher risk

of toxicity is the central focus when considering each viewpoint, and research is underway to provide evidence to guide the optimal approach.

Potential time points to administer the CGA include times of transition. This includes during initial consultation, when changing therapy, or when clinically significant events occur (ie, hospitalization). The CGA is a tool to detect vulnerabilities, thereby guiding interventions that may improve outcomes. Although each patient's situation is unique, research to define which interventions are most effective, efficient, and feasible for individual problems identified by the CGA is imperative.

Although some may argue that the information gained by a CGA can be parsed out during a detailed standard oncology workup, identifying risk factors for chemotherapy intolerance is critical given that therapy-related toxicity is a major concern when treating this population. A study in older adults with cancer has demonstrated the inability of a physician-assigned functional status assessment to predict chemotherapy toxicity in older adults.⁸ Severe chemotherapy toxicity is associated with decreased quality of life,⁵⁴ increased health care use,⁵⁵ and compromised cancer care,⁵⁶ and may lead to earlier death⁵⁷ in this population. Patient treatment preferences also often change with age, with studies noting that many older adults value quality of life over length of survival.^{58,59} Therefore, predicting severe chemotherapy toxicity is a key step in improving cancer care in older adults.

Supplementing the Standard Oncology Workup

Prospective studies have combined information from a standard oncology workup with data obtained from the CGA in an attempt to determine which combination of factors best predicts chemotherapy intolerance and decreased survival in older adults with cancer (Table 1). Poor nutrition and cognition predicted the inability to tolerate 4 cycles of chemotherapy,¹⁰ whereas poor nutrition and frailty were associated with decreased survival in a study of older patients with a variety of tumor types.¹⁰ Similarly, poor nutrition and cognition were risk factors for decreased survival in a separate study of older women with advanced breast cancer.³⁵ A study of older patients with metastatic colon cancer noted that poor cognition, limitations in IADLs, or receipt of irinotecan with fluorouracil was associated with an increased incidence of severe chemotherapy toxicity.⁶ The same study found that the addition of irinotecan and an elevated alkaline phosphatase were associated with decreased chemotherapy dose-intensity, whereas depression and poor cognition predicted the need for hospitalization. A separate study in older women with advanced ovarian cancer found depression, lack of autonomy, and a performance status of 2 or more predicted severe chemotherapy toxicity, whereas depression, taking more than 6 medications per day, and stage IV disease predicted worse survival.⁹ Male sex, metastatic disease, poor nutrition, and longer timed Get Up and Go (an objective performance measure) were independent risk factors that predicted death within 6 months after initiation of chemotherapy.³⁶

The combinations of predictive risk factors for chemotherapy intolerance differ from one study to another. Differences may be explained by variability between study populations and measurement tools. Overall, the patterns from these prospective studies support the idea that

a global assessment integrating data from a standard oncology workup and a CGA is necessary to identify the subpopulation of older adults who are most vulnerable to chemotherapy toxicity.

Measuring Chemotherapy Toxicity Risk in Older Patients With Cancer

Predictive tools provide physicians with a means to categorize patients based on the presence of high-risk clinical characteristics.^{60,61} Two independent studies have successfully formulated instruments that predict severe chemotherapy toxicity in older adults with cancer.^{7,8}

The Cancer and Aging Research Group Chemotoxicity Assessment

The Cancer and Aging Research Group (CARG) toxicity tool (Table 2, Figure 1)⁸ was formulated in a study in which baseline characteristics were collected from 500 patients aged 65 years or older before the initiation of a chemotherapy regimen as prescribed by their primary oncologist. The information included variables from a standard oncology workup, including host (ie, age, sex, Karnofsky performance status), tumor, laboratory, and treatment factors, along with variables from a CGA.¹⁵

The CARG tool identified risk factors that were combined to formulate a predictive model for severe chemotherapy toxicity that included 1) host factor: age 72 years or older; 2) tumor factors: genitourinary or gastrointestinal primary site; 3) laboratory studies: hemoglobin (men, <11 g/dL; women, <10 g/dL), creatinine clearance of (<34 mL/min); 4) treatment factors: standard treatment dosing, multiple chemotherapy agents; and 5) CGA factors: any fall in the past 6 months, hearing impairment, limited in walking one block, inability to take medications independently, decreased social activities because of physical or emotional problems. Each factor was assigned a risk score based on its association with toxicity, and the combined score provided an estimate of an individual's risk for severe chemotherapy toxicity. The CARG toxicity tool estimated risk of chemotherapy toxicity ranging from 25% in the lowest-risk groups to 89% in the highest-risk groups. The CARG toxicity tool has been internally validated, and an external validation study is nearing completion in an independent cohort of older patients with cancer.

The Chemotherapy Risk Assessment Scale for High-Age Patients

The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) toxicity tool (Table 3, Figure 2)⁷ was formulated in a study evaluating 518 patients aged 70 years or older before the initiation of a new chemotherapy regimen. The patients were randomly assigned to the derivation cohort or the validation cohort in a 2:1 ratio. Baseline factors, including host, tumor, laboratory, treatment, and CGA factors, were collected before initiation of chemotherapy. The CRASH tool used the MAX2 index⁶² to account for differences in relative risk of severe toxicity among chemotherapy regimens. The CRASH study was designed to formulate separate tools to predict grade 3 or greater nonhematologic toxicity and grade 4 or greater hematologic toxicity. Independent risk factors for chemotherapy toxicity were combined to formulate the final risk model.

Hematologic Toxicity—Risk factors for nonhematologic toxicity included 1) host factor: diastolic blood pressure greater than 72 mm Hg; 2) laboratory value: lactate dehydrogenase greater than 0.74 times the upper limit of normal; 3) treatment factor: MAX2 score; and 4) CGA factor: impaired IADLs.

Nonhematologic Toxicity—Risk factors for hematologic toxicity included 1) host factor: ECOG PS; 2) treatment factor: MAX2 score; and 3) CGA factors: impaired cognition and decreased nutrition.

The estimated risk for hematologic toxicity ranged from 7% in the lowest-risk group to 100% in the highest-risk group. Similarly, nonhematologic toxicity ranged from 33% in the lowest-risk group to 93% in the highest-risk group.

The CARG and CRASH toxicity tools provide user-friendly, efficient means of estimating the risk of severe chemotherapy toxicity in an individual patient. Providing a personalized risk evaluation can improve communication when discussing the risks and benefits of chemotherapy with older patients. However, although the tools are able to discriminate chemotherapy toxicity risk, they do not replace the information gained from a CGA.

Future Directions

Up to this point, many studies using the CGA and predictive models for chemotherapy toxicity have studied cohorts of patients with mixed tumor types and stages, thereby identifying risk factors for vulnerability shared among patients across tumor types. Studies using the CGA to characterize participants with specific tumor types and chemotherapy regimens are beginning to be reported, and represent critical steps in learning how to use the CGA to improve the management of older patients with particular cancers.^{6,35,64}

So far the CGA has been used primarily to evaluate an older patient's strengths and vulnerabilities before the start of a new chemotherapy regimen. This provides a snapshot of how a person is doing at one point in time. Future directions may examine longitudinal evaluations that could assess changes in CGA domains over time, and test the efficacy of CGA-guided interventions to improve or maintain an older adult's length and quality of survival.

There are still many avenues to explore that may improve outcomes for the older patient with cancer. The ultimate goal of ongoing research is to evaluate how the CGA and toxicity tools can be used to tailor chemotherapy to decrease toxicity, maximize dose intensity, minimize health care resources and cost, improve quality of life, and extend overall survival in older patients with cancer. Unification and coordination of research will put geriatric oncology on a forward path by improving study design, and will lead to trials that will provide a broad pool of evidence that can be used in treating older patients with cancer more effectively.

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Figure 1.

The Cancer and Aging Research Group toxicity tool. Risk of grade 3–5 chemotherapy toxicity based on total risk score. An individual's total risk score is calculated using Table 2. From Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002;20:494–502; with permission.

Figure 2.

The Chemotherapy Risk Assessment Scale for High-Age Patients score. Risk of (A) grade 3 or higher nonhematologic toxicity, (B) grade 4 or higher hematologic toxicity, and (C) combined risk for chemotherapy toxicity. An individual's total risk score is calculated using Table 3.

Table 1
Studies Evaluating Risk Factors That Predict Chemotherapy Toxicity/Tolerance and Overall Survival in Older Adults With Cancer

Research Studies									
Risk Factors			Toxicity/Tolerance			Survival			
	Aaldriks et al ¹⁰	Aparicio et al ⁶	Extermann et al ⁷	Freyer et al ⁹	Hurria et al ⁸	Aaldriks et al ¹⁰	Aaldriks et al ³⁵	Freyer et al ⁹	Soubeyran et al ³⁶
Standard Workup	Sex								x
	Age				x				
	PS		x		x				
	Vital signs		x ^a						
	Laboratory results	x ^b	x ^c		x ^{d,e}				
	Cancer type				x ^f				
	Stage						x		x
	Chemotherapy	x ^g	x ^h		x ⁱ				
CGA Workup	Daily activity ^j	x	x		x				
	Comorbidity					x ^k			
	Polypharmacy						x		
	Nutrition	x ^l		x		x		x	x
	Cognition	x ^l	x	x					
	Psychological state		x ^m		x			x	
	Social support					x			
	Objective test ⁿ								x

Research Studies										
	Toxicity/Tolerance			Survival						
Risk Factors	Aaldriks et al ¹⁰	Aparicio et al ⁶	Extermann et al ⁷	Freyer et al ⁹	Hurria et al ⁸	Aaldriks et al ¹⁰	Freyer et al ⁹	Aaldriks et al ¹⁰	Soubeyran et al ²⁵	Kim et al ²⁶
Frailty ^o						x		x		

Abbreviations: PS, Karnofsky performance status or ECOG performance status; CGA, Comprehensive Geriatric Assessment.

- ^aVital signs, diastolic blood pressure greater than 72 mm Hg.
- ^bAlkaline phosphatase greater than twice the upper limit of normal.
- ^cLactate dehydrogenase greater than 0.74 times the upper limit of normal.
- ^dHemoglobin less than 11 g/dL for men and less than 10 g/dL for women.
- ^eCreatinine clearance less than 34 mL/min (calculated by Jelliffe formula with ideal weight).
- ^fGastrointestinal or genitourinary primary tumor.
- ^gIrinotecan-based chemotherapy.
- ^hMAX2 score, chemotherapy regimen-based toxicity risk score.⁶²
- ⁱChemotherapy given at standard dose or chemotherapy regimen containing more than 1 drug.
- ^jDaily activity: activities of daily living and instrumental activities of daily living.
- ^kHearing problems self-evaluated as fair or worse.
- ^lRisk factor for chemotherapy tolerance.
- ^mRisk factor for hospitalization.
- ⁿObjective test, Timed Get Up and Go.⁶³
- ^oFrailty, Groningen Frailty Indicator.

Table 2CARG Scoring Tool to Calculate Chemotherapy Toxicity Risk^a

Risk Factor	Score
Age ≥ 72 y	2
GI or GU cancer	2
Standard chemotherapy dosing	2
>1 chemotherapy drug	2
Anemia ^b	3
Creatinine clearance ^c	3
Any fall in the past 6 months	3
Hearing, fair or worse	2
Limited in walking 1 block	2
Inability to take medications independently	1
Decreased socialization because of physical/emotional health	1

Abbreviations: CARG, Cancer and Aging Research Group; GI, gastrointestinal; GU, genitourinary.

^a Risk score based on association with grade 3–5 chemotherapy-related toxicity.

^b Hemoglobin less than 11 g/dL for men and less than 10 g/dL for women.

^c Creatinine clearance (Jelliffe, ideal weight) less than 34 mL/min.

Table 3

Chemotherapy Risk Assessment Scale for High-Age Patients Toxicity Tool for Estimating Chemotherapy Toxicity Risk^a

	Risk Factor	Score
Hematologic toxicity	DBP >72	1
	IADL <26	1
	LDH ^b	2
	Chemotoxicity ^c	1–2
Nonhematologic toxicity	ECOG PS ^d	1–2
	MMS <30	2
	MNA <28	2
	Chemotoxicity ^c	1–2
Combined toxicity	Total score ^e	0–12

Abbreviations: CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; DBP, diastolic blood pressure; ECOG PS, Eastern Cooperative Oncology Group performance status; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MMS, Mini Mental Health Status; MNA, Mini Nutritional Assessment.

^a Risk score based on association with grade 4 or higher hematologic toxicity and grade 3 or higher nonhematologic chemotherapy-related toxicity.

^b LDH greater than 0.74 times the upper limit of normal.

^c Chemotoxicity score: low = 0; medium = 1; high = 2.^{7,62}

^d ECOG PS: 0 = 0; 1–2 = 1; 3–4 = 2.

^e Chemotoxicity scored only once.