Assessment of Frailty and Risk of Chemotherapy Toxicity at a Geriatric-Oncology Multidisciplinary Clinic

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ABSTRACT

BACKGROUND: Multidisciplinary Geriatric-Oncology (GO-MDC) clinic performed comprehensive geriatric assessment (CGA) to determine frailty and chemotherapy toxicity risk.

METHOD: Retrospective cohort study of patients ≥65 years seen between April 2017 to March 2022. We compared Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) to CGA as a determinant of frailty and risk of toxicity from chemotherapy.

RESULTS: Mean age of the 66 patients was 79 years. Eighty-five percent were Caucasian. Predominant cancers were breast (30%), and gynecological (26%). One-third were stage 4. The CGA identified fit (35%), vulnerable (48%), and frail (17%) patients whereas ECOG-PS classified 80% as fit. CGA assessed 57% of ECOG-fit patients as vulnerable or frail ($p<0.001$). High chemotherapy toxicity risk using CGA was 41% and using ECOG was 17% ($p=0.002$).

CONCLUSION: At GO-MDC, CGA was a better predictor of frailty and toxicity risk than ECOG-PS. Treatment modification was recommended in one-third of patients.

KEYWORDS: aged; assessment; frailty; cancer; chemotherapy toxicity

INTRODUCTION

Older people are unique. In the process of aging, there is an individualized decline in organ system physiologic function. Combined with years of exposure and a constellation of comorbidities, each older person is a singular milieu of physiologic, cognitive, physical, and social function. When considering treatment for cancer, this individualized substrate needs to be considered.

Most cancers occur more commonly in older age. Cancer is the second leading cause of mortality.[1] The risk of malignancy peaks in the eighth decade[2] and 42% of the overall cancer population in the US is seventy years of age or older.[3-5] Despite the high incidence, older people are under-represented in cancer clinical trials.[6,7] As a result, the practice of cancer treatment in an aging population is evolving, with increasing consideration to the individualized physiology and performance measures as a marker of potential tolerability and toxicity of chemotherapy.

Oncologic societies recommend[8,9] comprehensive functional assessment prior to chemotherapy. The classic tools developed to assess functional status in cancer, such as the Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)[10] and the Karnofsky Performance Status (KPS)[11] lack validation in an older population. More recently, tools have been developed which focus on an older population. For example, the Cancer and Aging Research Group Toxicity Tool (CARG-TT)[12] and the Chemotherapy Risk Assessment Scale for High-age patients (CRASH)[13] score compile components of the Comprehensive Geriatric Assessment (CGA) to predict chemotoxicity. However, the elements of CGA require time and training to deliver.

Working together, oncology and geriatric co-management can bring CGA reliably to an older population to modify the outcomes. The CGA-based frailty status of patients evaluated at the Lifespan Geriatric Oncology Multidisciplinary Clinic (GO-MDC) was compared to ECOG-PS and the risk of moderate to severe chemotoxicity (grade 3-5) using the CARG-TT. We also compared ECOG-PS and the CARG-TT.

The primary outcome was to determine if CGA-based assessment would identify more people with frailty in comparison to ECOG-PS. The secondary outcome was to assess if CGA reveals high chemotherapy toxicity in greater number of older cancer patients when compared to ECOG, thereby resulting in treatment modification favoring lower toxicity.

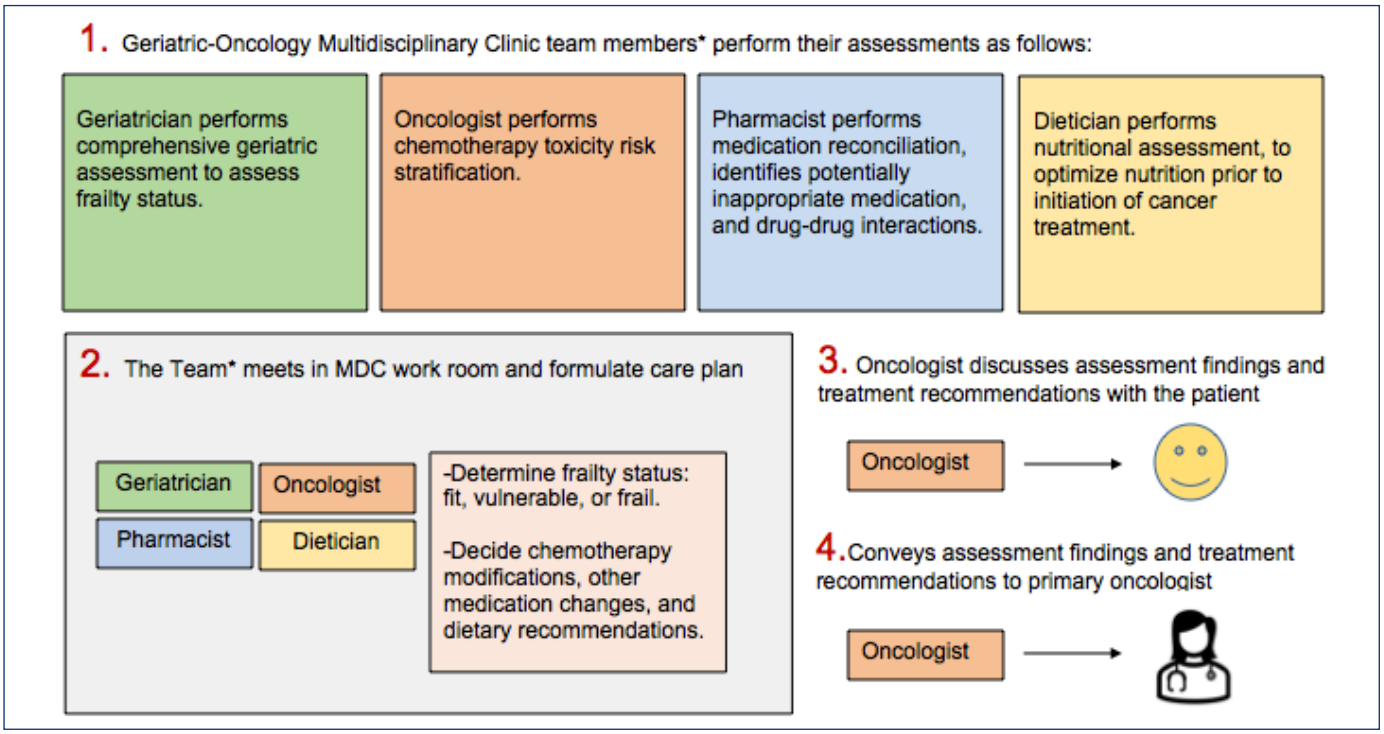
Using the clinical patient population of the GO-MDC, we performed a retrospective cohort analysis to determine these associations.

METHODS

Cohort

The retrospective cohort consists of patients seen between April 2017–March 2022 at the Lifespan Cancer Institute, affiliated with The Warren Alpert Medical School of Brown University. The members of the GO-MDC team include an oncologist, a geriatrician, a pharmacist, and a dietitian. This is a one-time consultative evaluation prior to initiation of chemotherapy in newly diagnosed or recurrent cancer patients, 65 years or older in age. The in-person assessment is ideally conducted within 7 days of referral made by the primary oncologist. This analysis was approved by the Lifespan IRB.

Figure 1.



Comprehensive Geriatric Assessment

The CGA was performed during the clinic visit and consisted of medical, oncologic, and social histories, cognitive and mood screening, polypharmacy, functional and nutritional assessment.

At the conclusion of the in-person visit, the team members met to review each case and formulated a comprehensive treatment plan based on the expertise from each discipline. A description of the contributions of each member of the inter-professional evaluation team is included in (**Figure 1**).

(CGA) Assessment Instruments

Specific tools in the CGA are detailed in **Table 1** and include Katz and Lawton Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) scale;[14,15] Timed Up & Go (TUG) test[16], the Mini-Cog assessment tool,[17] the PHQ-9[18], and Mini Nutrition Assessment (MNA).[19]

ECOG-PS

ECOG-PS indicates an increasing level of disability. A score of 0 indicating fully active, 1- restricted in strenuous activity, 2- restricted in work activity but ambulatory and capable of self-care, 3- capable of limited self-care, 4- completely disabled, and 5- dead.[10]

Chemotherapy Toxicity Risk

CARG-TT is a pre-chemotherapy assessment tool to predict moderate to severe chemotherapy toxicity. It is calculated from demographics, tumor and treatment variables, laboratory test results and CGA variables (function, comorbidity,

Table 1. Assessment tools used in Comprehensive Geriatrics Assessment

CGA Tools	Tool Description
Katz Index of Activities of Daily Living (ADL)	Includes self-reported measures of 6 basic self-care activities: feeding, dressing, bathing, transfer, continence, and toileting. One point is scored for independence in each activity. Score range is 0–6 with higher scores representing better function.
Lawton-Brody Instrumental Activities of Daily Living (I.A.D.L.)	Includes seven more complex activities: finances, medication management, driving, housekeeping, food preparation, shopping, laundry, and ability to use the telephone.1 point is scored for independence in each activity. Score ranges 0–8 with higher scores representing more independence
Patient Health Questionnaire – 9 (PHQ-9)	Assesses nine depressive emotional distress symptoms. Score range is 0–27. Normal mood: 1–4, Mild depression: 5-9, moderate depression: 10–14, moderately severe: 15–19, severe depression: 20–27
Mini Cog	It includes 3-word recall and a clock-draw test. Score ranges 0–5. 1 point for each correct word-recall and 2 points for a correctly drawn clock. A score of < 4 is considered abnormal.
Timed Up and Go Test (TUG)	Is used to assess risk for falls. The time it takes to walk 3 meters from a seated position and back without a break is measured. Increased risk of falls is associated with time >14s
Mini Nutritional Assessment tool (MNA)	Assesses nutritional status. It is scored from 0–14. Normal nutritional status is a score of 12–14, at risk of malnutrition is scored 8–11, and malnutrition has a score of 0–7

cognition, psychological state, social activity/support, and nutritional status). The CARG-TT score ranges from 0–19. Each risk category is associated with percentage likelihood of developing moderate to severe toxicity. Low risk is a score of 0–5 (<30%), intermediate risk, 6–9 (40–60%), and high risk, 10–19 (>70%).[20,21]

STATISTICAL ANALYSIS

All data was abstracted from the Electronic Medical Record (EMR) into a REDCap database,[22] a web-based chart review tool, and the analysis were conducted using SAS© software (Version 9.4, SAS Institute Inc., Cary, NC). The characteristics of the population are summarized with means (±SD) for continuous variables and number (%) for dichotomous variables. For the assessment instruments, we calculated literature-based cutoffs and present the number and percent. ECOG-PS was compared with CGA-based frailty and with CARG-TT moderate to severe chemotherapy risk using Chi-Square.

Table 2. Patient demographic and Clinical Data

Patient Characteristics/Demographics	Patients (n=66) (n%)
Age, years, range and mean	66–94 years, mean age:79 ± 6.9 years
Gender: Female	50 (76%)
Male	16 (24%)
Race: White	56 (85%)
Black	6 (9%)
Other/Mixed/Unknown	4 (6%)
Body Mass Index (BMI) range and mean	15–49, 29 ± 6.7
Carlson Comorbidity Index range and mean	3–20, 10.6 ± 4.3
Residence: Home	59 (89%)
Residence: ALF or Nursing home	7 (11%)
Cancer Risk Factors	
Family history of cancer	39 (59%)
History of smoking	34 (51%)
History of alcohol use	40 (61%)
New cancer diagnosis	55 (83%)
Recurrent Cancer	11 (17%)
Type of Cancer: Breast	20 (30%)
Gynecological	17 (26%)
Lung	14 (21%)
Other	15 (23%)
Stage of Cancer: Stage 1	14 (21%)
Stage 2	8 (12%)
Stage 3	17 (26%)
Stage 4	22 (33%)
Unknown	5 (8%)
Treatment received: 1st line	54 (82%)

RESULTS

The characteristics of the population (N=66) are described in **Table 2**. Consistent with the older population of Rhode Island, the cohort was older (mean age 79: range: 66-94 years), female (n=50; 76%), and racially heterogeneous (White n=56, 85%, Black n=6, 9%). Malignancies were varied with breast (n=20, 30%) gynecological (n=17, 26%) and lung (n=14, 21%) cancer represented. Most patients were newly diagnosed with cancer (83%) and had advanced cancer, stage 3 (n=17, 26%) or stage 4 (n=22, 33%).

The CGA findings are presented in **Table 2**. The population described functional limitations, with dependence in at least one ADL (n=28, 42%) and IADL (n=33, 50%). Cognitive deficits were detected on Mini Cog (n=32, 51%) and moderate to severe depressive symptoms were identified (n=26, 41%). Polypharmacy was documented in 60 patients (92%). On nutritional assessment, 26 patients (41%) were classified as at risk for malnutrition and 17 (26%) as malnourished.

The comparison of ECOG and CGA are presented in **Table 3**. CGA determined 23 patients to be fit (35%), 32 patients to be vulnerable (48%) and 11 patients to be frail (17%).

ECOG-PS was classified as non-fit (ECOG-PS ≥ 2) in 13 patients (20%) and fit (ECOG-PS: 0-1) in 53 patients (80%).

Table 3. Findings of Comprehensive Geriatric Assessment Domains and Aging Research Group (CARG) Chemo-Toxicity Classification

CGA Parameters	Patient population N= 66 (%)
Physical Function	
ADL dependence (requiring help in ≥ 1 ADL)	28 (42%)
IADL dependence (requiring help in ≥ 1 IADL)	33 (50%)
Normal TUG (time <14s)[a,b]	49 (74%)
Abnormal TUG (time ≥ 14s)	6 (9%)
Brain Function	
Mini Cog abnormal score of 0–3[c]	32 (51%)
PHQ 9 scale indicating moderate depression[d,e]	24 (38%)
PHQ 9 score indicating severe depression	2 (3%)
Other Assessments	
Polypharmacy (greater than 3 medication)	60(92%)
Nutrition: Normal	21
At risk for malnutrition	26 (41%)
Malnutrition	17 (26%)
CARG- TT[f]	
Low-risk toxicity	3 (5%)
Intermediate toxicity	36(54%)
High toxicity	27(41%)

a. Timed Up and Go test (TUG)
b. 9 patients did not participate in due to gait instability.
c. 2 patients unable to do Mini Cog due to cognitive decline.
d. PHQ-9 Patient Health Questionnaire-9
e. 3 patients were unable to participate in depression screen.
f. CARG-TT Cancer Aging and Research Group Toxicity Tool

Table 4. Comparison of ECOG-PS scores with CGA

ECOG score	CGA Assessment n=66 (n%)			
	Fit	Vulnerable	Frail	Total
0 to 1 (normal)	23 (35%)	26 (39%)	4 (6%)	53
>2 (restricted activity)	0	6 (9%)	7 (11%)	13
Total	23 (35%)	32 (48%)	11 (17%)	66

Table 5. Comparison of ECOG-PS with Cancer and Aging Research Group (CARG) Tool

ECOG score	Chemotoxicity risk calculated by CARG Tool (n)(%)		
	Low	Intermediate	High
0 –1 (normal)	3 (5%)	34 (52%)	16 (24%)
>2 (restricted activity)	0	2 (3%)	11 (17%)

Importantly, of ECOG-fit patients, CGA determined 30 (45%) to be vulnerable or frail. CARG-TT risk was intermediate in 34 patients (52%) and high in 16 patients (24%) of the patients who were classified as ECOG-fit (**Tables 4** and **5**).

CGA results correlated more closely with the chemotoxicity risk calculated by the CARG-TT, (p-value=0.0015). None of the patients who were deemed fit by CGA had a high chemotoxicity risk per CARG-TT. Treatment change to downgrade was recommended in 23 patients (37%). No treatment change was recommended in 44% of patients. Treatment modification recommendations, made by GO-MDC, were accepted by the primary oncologist in over 95% of the patients.

DISCUSSION

Older patients are a heterogeneous population and tailoring cancer treatment to the individual requires weighing risks against benefit in the context of frailty that is best assessed by CGA.[23,24] Past literature supports CGA to assist with prognostication in the scenario of adjuvant therapy[25] and risk stratification in the case of chemotherapy[26] or surgery.[27] By understanding the individualized risks and benefits, patients and oncologists can provide patient-centered treatment options.

Oncologists struggle with estimation of life expectancy, and without a reasonable estimate of life expectancy there is a risk for under- or over-treatment of patients.[28] Widely used validated prognostication tools that estimate life expectancy,[29,30,31] such as Walter-Covinsky Life tables, Lee Index and Schonberg's tool, require assessment of mobility, ADLS, IADLS, etc. These functional parameters are not routinely assessed in oncologic care but are known components of CGA. These tools estimate life expectancy independent of cancer. This becomes especially relevant in curative intent treatment, when an older patient may have a competing co-morbid condition that affects overall survival. For example, an 80-year-old woman in the top quartile of health would have a life expectancy of 13 years versus 4.6 years in the bottom quartile.[32]

For risk stratification, there are two validated tools that predict for moderate to severe chemotherapy toxicity: CARG-TT and CRASH score.[12,13,20] These tools are specifically designed and more accurate in predicting moderate to severe chemotherapy toxicity when compared to other oncologic measures of functional assessment like ECOG. The clear advantage of CARG-TT (that we utilized) over ECOG-PS was also evident. A total of 46 patients deemed fit by ECOG-PS were 'frail' based on CGA, highlighting a significant limitation of this tool. Our analysis showed that ECOG-PS can potentially miss frailty and may result in enhanced toxicity of cancer treatment.

The GO-MDC is built on literature-based models incorporating geriatric assessment into the management of older adults with cancer. CGA has a two-fold role in this clinic.

Firstly, CGA prior to cancer treatment allows for tailoring treatment based on patients' vulnerabilities, rather than at the time of occurrence of toxicity.[33] This results in better communication, patient-caregiver satisfaction, and advance care planning.

Secondly, CGA findings and subsequent use of CARG-TT leads to potential modification in treatment to minimize toxicity. This role of CGA has been well established in literature. A systematic review of 11 trials showed a change in initial treatment plan after CGA in 5–54% of patients (median 28%), mostly for less intensive therapy.[34] Similarly, the GO-MDC, change in treatment was recommended in 37% of patients also for less intensive treatment.

At GOMDC, our data analysis supports the established role of CGA as a more sensitive method for detecting frailty and CARG-TT as a better screener for unmasking chemotherapy toxicity risk. The high number of ECOG-PS 'fit' patients who subsequently scored as frail or having high chemotherapy toxicity risk highlights the importance of the more comprehensive CGA assessment.

A randomized control trial, comparing a cohort receiving CGA with one receiving ECOG evaluation-only would be a reliable means of further establishing the sensitivity of CGA and CART-TT in detecting frailty and chemotherapy toxicity risk in older cancer patients.

Additionally, CGA-based assessment also gives guidance on non-oncologic interventions that have direct impact on patients' quality of life and cancer treatment tolerance.[35,36,37] They fall into seven main categories: medication, co-morbidity optimization, mobility/fall risk assessment, cognitive screen, psychologic screen, nutritional, and social interventions.

At the GO-MDC, we identified notable cognitive, psychological, and nutritional deficits that are not routinely assessed in oncologic evaluation. None of these geriatric syndromes were uncovered by ECOG assessment.

There is limited data in literature looking at allocation of

chemotherapy based on CGA in randomized fashion. There is only one randomized control trial, in lung cancer, showing better quality of life, less toxicity, and similar survival, even though more patients had best supportive care in the CGA-based allocation of cancer treatment.[38]

Limitations

This study is a descriptive analysis and definitive conclusions regarding benefits of CGA cannot be drawn from our data analysis. Also, being a retrospective analysis, this study has an inherent patient-selection bias. The referral system to GO-MDC is entirely dependent upon the discretion of the primary oncologist. This directly impacts the diversity of patients, in terms of ethnicity, race, and cancer-type. Consequently, the referrals sent to GO-MDC were primarily breast and gynecological cancer patients.

Additionally, the primary oncologists, making triaging decisions for referrals, can potentially miss patients who otherwise may benefit from the GO-MDC evaluation.

Since the GO-MDC requires an additional clinic visit, patients may choose to forgo it, despite the referral.

GO-MDC is a one-time consultative evaluation and subsequent follow-ups are with the primary oncologist. By design, the clinic is limited in assessing the influence on treatment tolerability, patients' quality of life, and cancer outcomes.

CONCLUSION

GO-MDC provides a platform for CGA-based assessment of cancer patients and the information obtained from CGA was able to identify frailty status and chemotherapy toxicity risk. These findings are supported by the literature demonstrating that GO-MDC is able to identify frailty status for cancer treatment and implementation of CGA in routine oncology practice remains challenging.

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