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Geriatric assessment and treatment outcomes in older adults with cancer receiving immune checkpoint inhibitors

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Abstract

Objectives—Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer, but outcomes in older adults are not well defined. We evaluated the associations of geriatric assessment (GA) domains with treatment-related outcomes in older adults with solid tumors receiving ICIs.

Methods: We performed a single-center, retrospective study of patients age ≥ 65 years diagnosed with solid tumors who received ICIs and were evaluated with a GA from January 2011 to April 2017. Using Wilcoxon rank sum test, we examined the associations of GA domains and treatment-related outcomes, including the number of ICI cycles received, best response, immune-related adverse events (irAEs), and hospitalizations during ICI treatment.

Results: We identified 28 patients (median age at ICI treatment=78 years, range 66–93); 60% had Eastern Cooperative Oncology Group (ECOG) Performance Status of ≥ 2; 39% had lung cancer; 89% had stage IV cancer; and 50% received pembrolizumab. Seventy-five percent had at least one GA domain impairment. Patients with any instrumental activities of daily living (IADL) impairment received fewer cycles of ICI (median: 2.0 vs. 7.0 cycles, $p=0.02$). In this small sample, neither age nor GA domain measures were associated with best response, irAEs, or hospitalization during ICI treatment.

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Conclusions: Older adults treated with ICIs had a high prevalence of impairments in GA domains, and IADL impairments were associated with shorter duration of ICI treatment. Future prospective studies are needed to evaluate the role of the GA further in this vulnerable patient population in the immunotherapy era.

Keywords

older adults; cancer; geriatric assessment; immune checkpoint inhibitors; immunotherapy

1. Introduction

Approximately 53% of new cancer cases and 70% of cancer-related mortality occur in patients age ≥ 65 years.¹ Nonetheless, older adults with cancer are under-represented in clinical trials.² As a result, there is less evidence to support their treatment decisions. To assist with treatment decision-making, a geriatric assessment (GA) can be helpful and is recommended by several guidelines.^{3, 4}

Immune checkpoint inhibitors (ICIs) are agents that exert their antitumor activity by disabling the “brakes” on the immune system.⁵ In recent years, ICIs have revolutionized the treatment of multiple cancer subtypes including lung cancer and others.^{6–9} ICIs have been shown to have higher or similar efficacy and better tolerability than chemotherapy.^{6, 10} The efficacy of ICIs in older adults, however, is less well-defined. While most landmark trials included older adults, those age ≥ 75 years constitute <10% of the study sample.¹¹ In clinical practice, approximately 70% of patients are ≥ 65 years, and 36% are ≥ 75 years.¹² In addition, those who were included had relatively good performance status (PS) and organ function and may not reflect a “real-world” population of older adults with cancer.¹³

To the authors’ knowledge, no studies have evaluated the associations of GA domains with the efficacy and toxicity of ICIs. In this study, we evaluated the associations of GA measures with treatment-related outcomes in older adults age ≥ 65 years with advanced solid tumors receiving ICIs.

2. Methods

2.1 Study Design, Setting, and Population:

We conducted a single-center, retrospective study at the University of Rochester Wilmot Cancer Institute. Patients were recruited from the Specialized Oncology Care and Research in the Elderly (SOCARE) clinic. The SOCARE clinic primarily provides consultative geriatric oncology services for older adults with cancer.¹⁴ Referral to the SOCARE clinic is at the discretion of the primary treating physician. For the purpose of this study, adults age ≥ 65 years diagnosed with any solid tumor who completed a GA and received ICI treatment between January 1, 2011 and April 30, 2017 were included. After informed consent was obtained, patient information was entered into an ongoing data registry. For this study, the data cut-off was on January 15, 2018. The project was approved by the local institutional review board.

2.2 Data Collection:

As part of the SOCARE registry, demographic data including age, gender, race/ethnicity, educational level, and living situation were collected. Clinical data included cancer type, cancer stage, Eastern Cooperative Oncology Group (ECOG) PS, prior chemotherapy, type of ICI treatment, line of ICI, and timing of GA [whether GA was performed immediately prior to ICI or immediately prior to first-line chemotherapy (i.e., second-line ICI)] were collected from the electronic medical record. As part of the GA, all patients underwent a geriatric screening tool - Vulnerable Elders Survey (VES)-13.¹⁵ GA domains included functional status [activities of daily living (ADL), instrumental ADL (IADL), self-reported falls in the previous year]; physical performance (Short Physical Performance Battery); comorbidity [Older American Resources and Services (OARS) Comorbidity, hearing impairment, and visual impairment]; cognition (BLESSED Orientation-Memory-Concentration); nutrition (self-reported weight loss and patient-reported sarcopenia using the SARC-F questionnaire)¹⁶; social support (OARS Medical Social Support); and psychological state (Geriatric Depression Scale-15) (see Appendix A).

2.3 Study End-Points:

The primary aim of this study was to examine the associations of GA domains and treatment-related outcomes, including the number of ICI cycles received, best response, immune-related adverse events (irAEs), and hospitalizations during ICI treatment. Data were obtained from the electronic medical record. Best response was assessed by consensus of the study investigators based on radiographic and clinical findings, given the retrospective nature of the study. For irAEs, the frequency, type, supportive treatment and severity were examined. Severity of irAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3.¹⁷

2.4 Statistical Analyses:

We used descriptive analyses to summarize patient demographics and the prevalence of GA domain impairment. The associations of age and GA domain impairments with number of ICI cycles received, best response, incidence of irAEs, and hospitalization during ICI treatment were evaluated with the Wilcoxon rank sum test. All analyses were carried out using SAS/STAT[®] software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Patients and Treatment Characteristics:

Twenty-eight patients were included in this study. Baseline characteristics are shown in Table 1. The median age at initiation of ICI was 78 years (range, 66–93). The majority of patients were male (69%) and had stage IV disease (89%; 3 patients had inoperable stage III disease and received palliative treatment); 60% of the patients had an ECOG PS 2–3. Lung cancer was the most common cancer diagnosis (39%). Half of the cohort received pembrolizumab, and 43% received ICI first-line.

3.2 Geriatric Assessment Domains:

The median age at the time of GA was 77 years (range, 66–91). Over half of the patients (54%) underwent GA immediately prior to ICI treatment while the remaining (46%) underwent GA earlier (i.e. immediately prior to first-line chemotherapy; ICI was given second-line). Twenty-five percent of the patients had 1 deficit in ADL, while 43% had 1 deficit in IADL. More than one-third (39%) had at least 5% weight loss (N=11), while 32% had 1 fall in the year prior to the GA (N=9). Impairments in other GA domains are shown in Table 2.

3.3 Immune Checkpoint Inhibitors Treatment Duration and Response:

The median number of ICI cycles received was 3.5 (range, 1–39). At the time of data cut-off, three patients were still on ICI treatment. Patients with any IADL impairment were more likely to receive fewer cycles of ICI (median: 2.0 vs. 7.0 cycles, $p=0.02$; Table 3). Reasons for discontinuation of therapy in patients with any IADL impairment were toxicities (N=4), disease progression (N=2), patient's choice (N=2) and worsening performance status (N=4). Patients with 5% weight loss and without any ADL impairment tended to receive more cycles of ICI, but these associations did not reach statistical significance ($p=0.06$ and 0.14 , respectively).

In our study cohort, one patient attained a complete response, six patients had a partial response, five patients had stable disease, and nine patients had progressive disease. Response was not able to be assessed in seven patients who had died prior to restaging scans.

3.4 Safety and Toxicity:

Eleven patients (39%) had at least one irAE of any grade, and five patients (18%) experienced at least one grade 3–5 irAE (Table 4). The most frequently reported irAE was dermatitis, which occurred in five patients (18%); one was grade 3 one was grade 2, and the remaining three were grade 1. Corticosteroids were administered to nine patients experiencing an irAE; six of those (67%) required systemic corticosteroids. None of the irAEs observed required other immunosuppressive agents. Treatment was interrupted in eight patients (29%), and 14 patients (50%) were hospitalized during ICI treatment, 3 of whom were hospitalized twice. The most common reason for hospitalization were: infection (N=7 admissions); symptoms from disease progression; (N=6); irAEs (colitis, pneumonitis, and inflammatory arthritis) (N=3); non-immune-related acute kidney injury (N=1). Three patients were admitted to the intensive care unit, and one patient died from treatment-related pneumonitis. Ten patients (36%) discontinued treatment due to irAEs. On bivariate analyses, neither age nor any of the GA domains was associated with the frequency of irAEs regardless of grade or risk of hospitalization (data not shown).

4. Discussion

In this retrospective study, we found that older adults who were referred for a GA receiving ICIs are vulnerable, with 75% having impairment in at least one of the GA domains. On unadjusted analysis, IADL impairment was associated with shorter ICI treatment duration.

ADL impairment and weight loss may be associated with ICI treatment duration, but these associations did not reach statistical significance, likely due to our small sample size. To the authors' knowledge, this is the first study to evaluate the role of GA in older adults with cancer receiving ICI therapy.

A number of studies have demonstrated the association of IADL impairment with treatment duration/outcome.^{18, 19} Consistent with these studies, we found that IADL impairment was associated with treatment duration in the setting of ICI treatment. This suggests that IADL should be performed in older patients with cancer receiving ICI as well. In our study, no correlation was found between the duration of treatment and age, ECOG PS, and other GA domain impairments, which indicates that age may not be the sole predictor of treatment tolerability and may not accurately reflect the "true" physiologic or functional status of older adults with cancer.

ICIs are generally perceived to be more tolerable than systemic chemotherapy, especially in older adults. Cross-comparison across trials is challenging given differences in regimen. In our study, ten patients (36%) discontinued treatment because of irAEs (five were grade 3–5), while nine patients (32%) required immunomodulatory therapy. This highlights the impact of grade 1–2 grade AEs on older adults with cancer. Findings on the association of age and toxicity are mixed. In the CheckMate-069 study that compared nivolumab plus ipilimumab versus ipilimumab in advanced melanoma, patients >65 years who received the nivolumab plus ipilimumab combination had similar rates of grade 3–4 toxicities as those <65 years (52% vs. 54%, respectively).²⁰ In a pooled analysis of clinical trials for renal cell carcinoma (RCC), melanoma and NSCLC, Singh *et al* reported that the frequency of grade 3–5 adverse events was similar in patients age <65 and ≥65 years (58% vs 63%, respectively). However, in the subgroup of patients ≥70 years, the frequency of grade 3–5 adverse events was higher (72%). Patients age ≥70 years also had a higher rate of nivolumab discontinuation (19.8%) than patients age <65 years (14.4%) as well as higher rates of adverse events requiring immunomodulatory medications (51.9% vs. 41.5%).²¹ Another single institutional study evaluating the toxicities and outcomes of ICI in older patients showed similar rates of irAEs and similar outcomes in patients ≥75 years compared to patients <75 years.²² Sabatier *et al* looked at the efficacy and toxicity of nivolumab in "real-world" older patients with advanced NSCLC, the rate of higher grade irAEs was almost doubled (20%) compared to the previously reported rates in the landmark clinical trials.²³

Numerous studies have confirmed the role of the GA in predicting chemotherapy-related adverse events but its association with ICI-related adverse events is lacking. In a retrospective study, Sabatier *et al* did not find any association of the Geriatric 8 (G8) screening tool,²⁴ Charlson's comorbidity index²⁵ and polypharmacy with toxicities or outcomes.²³ Similarly, we did not find any associations between impairment in GA domains and adverse outcomes including irAEs and hospitalizations; nevertheless, the lack of significant associations could be related to the small sample size of our study.

There are several strengths in our study. First, to the authors' knowledge, this is the first study that describes GA in the context of immunotherapy treatment. Second, our study represents a cohort of older adults treated with ICI outside the context of a clinical trial.

Several limitations should be noted. First, this was a single center study and we included patients who were referred to a specialized geriatric oncology clinic (based on the primary oncologist's preference), which may introduce selection bias and limit the generalizability of the findings. Second, the timing of the GA was not immediately prior to ICI treatment in all patients. Third, the small sample size limits the ability to detect associations between GA impairments and clinical outcomes. More specifically, with such a small sample size, normality-based tests have little power to detect whether the sample was drawn from a normally distributed population. Our choice of non-parametric tests may have resulted in p-values that were non-significant. Forth, given the retrospective nature of the study, missing data were present. In addition, we did not collect biomarkers of efficacy and toxicities (e.g., PD-L1 expression). Fifth, adverse events were determined based on chart reviews and may be underestimated. Finally, it is important to note that all analyses were unadjusted given our small sample size and larger prospective studies are needed to confirm our findings.

In summary, our study suggested that older adults referred for GA and treated with ICI have a high prevalence of impairments in several GA domains. IADL impairment may be associated with shorter duration of ICI treatment. Future prospective studies are needed to evaluate the role of the GA and its impact on toxicity, efficacy, and patient-reported outcomes among older adults with cancer receiving ICI treatment alone or in combination with chemotherapy or other treatment modalities.

5.: Appendix

Appendix A:

Geriatric assessment domains and definitions of impairment

	Tools	Descriptions	Definitions of impairment
Functional status	Activities of Daily Living (ADL)	Assess difficulty with the following 6 activities: bathing, dressing, eating, getting in and out of bed/chairs, walking, toileting (options: yes/no/doesn't do)	Any deficit (yes)
	Instrumental ADLs	Assess independence in the following 7 activities: using the telephone, transportation, shopping, preparing meals, doing housework, taking medicine, managing money (options: without help, with some help, completely unable to)	Any deficit (with some help or completely unable to)
	Falls history	Assess the number of falls	Any history of falls in the previous year
Physical performance	Short Physical Performance Battery	Assess balance, gait speed, and strength; higher score indicates better performance (range 0–12 points)	9 points
Comorbidity	OARS Comorbidity	Assess the presence of 13 illnesses (e.g. other cancer or leukemia, arthritis, glaucoma) and how much each problem interferes with his/her activities (options: not at all, somewhat, a great deal)	Patient answered "yes" to 3 illnesses OR answered that 1 illness interferes "a great deal"
	Hearing impairment	Assess hearing impairment by asking "How is your hearing?" (options: excellent, good, fair, poor and totally deaf)	Patients answered "fair", "poor", or "totally deaf"
	Vision impairment	Assess visual impairment by asking "How is your eyesight?" (options: excellent, good, fair, poor and totally blind)	Patients answered "fair", "poor", or "totally blind"

	Tools	Descriptions	Definitions of impairment
Cognition	Blessed Orientation-Memory-Concentration	Assess orientation, memory, and concentration using 6 items and scores are weighted; higher score indicates worse performance (range 0–28 points)	11 points
Nutrition	Weight loss	Assess change in weight over 6 months	> 10% change in weight from 6 months ago
	Sarcopenia	Assess self-reported sarcopenia using the SARC-F questionnaire which includes five components (score of 0–2 for each): strength, assistance walking, rise from a chair, climb stairs, and falls; higher score indicates worse sarcopenia (range 0–10)	4 points
Social Support	OARS Medical Social Support	Assess the presence of social support using 4 items (“someone to help if you were confined to bed, someone to take you to the doctor if needed, someone to prepare your meals if you were unable to do it yourself, someone to help you with daily chores if you were sick.” options: none of the time, a little of the time, some of the time, most of the time, all of the time)	Patient answers any one of questions as “some of the time, a little of time, none of the time”
Psychological health	Geriatric Depression Scale	Assess depression using 15 items; higher score is worse (range 0–15 points)	5 points

Abbreviations: ADL, Activity of Daily Living; OARS, Older American Resources and Services;

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Table 1.Baseline patient and treatment characteristics (N=28)^a

Characteristics	N (%) ^b
Age at ICI treatment - years	
Median (range)	78 years (66–93)
Sex	
Male	19 (69)
Females	9 (31)
Race/ethnicity	
Caucasian	26 (93)
African American	2 (7)
Household composition	
Lives alone	9 (32)
Lives with spouse, partner or child	13 (46)
Unknown	6 (21)
ECOG performance status	
0–1	11 (39)
2–3	17 (60)
Cancer Type	
Lung	11 (39)
Melanoma	5 (18)
GU	8 (28)
GI	2 (7)
Other	2 (7)
Stage	
III	3 (11)
IV	25 (89)
Prior chemotherapy	
No	12 (43)
Yes	16 (57)
ICI Agent	
Pembrolizumab	14 (50)
Nivolumab	9 (32)
Atezolizumab	3 (10)
Ipilimumab	2 (7)
Line of therapy (ICI)	
First line	12 (43)
Second line	10 (36)
Third line	3 (11)
Fourth line	3 (11)

Abbreviations: ECOG, Eastern Collaborative Oncology Group; GI, gastrointestinal; GU, genitourinary

^aData expressed as N (%) unless otherwise specified.

^bDue to rounding, percentages may not always add up to 100%

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Table 2.Baseline geriatric assessment domains (N=28)^a (Impairments defined in Appendix A)

Characteristics (N=28)	N (%) ^b
Age at GA - Median (range)	77 (66–91)
76 years	15 (54)
>76 years	13 (46)
Timing of CGA	
Immediately prior to ICI	15 (54)
Immediately prior to chemotherapy but prior to ICI	13 (46)
ADL impairment	
No	7 (25)
Yes	7 (25)
Unknown	14 (50)
IADL impairment	
No	12 (43)
Yes	12 (43)
Unknown	4 (14)
Falls in the past year	
No	19 (68)
Yes	9 (32)
SPPB impairment	
No	3 (11)
Yes	21 (75)
Unknown	4 (14)
Comorbidities	
4	8 (28)
>4	12 (43)
Unknown	8 (28)
Hearing impairment	
No	16 (57)
Yes	9 (32)
Unknown	3 (11)
Vision impairment	
No	18 (64)
Yes	7 (25)
Unknown	3 (11)
BOMC Score impairment	
No	17 (61)
Yes	10 (36)
Unknown	1 (3)
Weight loss ^c	

Characteristics (N=28)	N (%) ^b
No	12 (43)
Yes	11 (39)
Unknown	5 (18)
Sarcopenia (Patient-Reported) ^d	
No	10 (36)
Yes	8 (28)
Unknown	10 (36)
OARS social support impairment	
No	14 (50)
Yes	9 (32)
Unknown	5 (18)
GDS Score impairment	
No	21 (75)
Yes	7 (25)
VES-13 scale impairment	
No	8 (28)
Yes	13 (46)
Unknown	7 (25)

Abbreviations: ADL, Activities of Daily Living; BOMC, BLESSED Orientation-Memory-Concentration Test; GA, geriatric assessment; IADL, Instrumental Activities of Daily Living; OARS, Older American Resources and Services; SPPB, Short Physical Performance Battery Test; VES-13, Vulnerable Elders Survey-13

^aData expressed as N (%) unless otherwise specified.

^bDue to rounding, percentages may not always add up to 100%

^cDefined as more than 5%

^dUsing the SARC-F questionnaire

Table 3:

Association of demographics and GA domains with number of ICI cycles received

Variable		ICI Cycles Received		
		# of observations	Median (IQR limits)	Test * p-value
Age at GA (years)	76	13	2.0 (2.0–6.0)	0.80
	>76	15	5.0 (1.0–15.0)	
Timing of GA	Immediately prior to ICI	15	2.0 (1.0–7.0)	0.44
	Immediately prior to chemotherapy but prior to ICI	13	6.0 (1.0–15.0)	
ECOG Performance Status	0–1	11	3.0 (2.0–19.0)	0.55
	2–3	17	4.0 (1.0–7.0)	
Any ADL impairment	No	7	7.0 (2.0–19.0)	0.14
	Yes	7	2.0 (1.0–15.0)	
	Unknown	14		
Any IADL impairment	No	12	7.0 (2.5–25.5)	0.02
	Yes	12	2.0 (1.0–5.0)	
	Unknown	4		
Falls (in past year)	No	19	3.0 (1.0–7.0)	0.75
	Yes	9	5.0 (2.0–15.0)	
SPPB impairment	No	3	4.0 (2.0–7.0)	1.00
	Yes	21	5.0 (1.0–16.0)	
	Unknown	4		
Comorbidities	4	8	7.0 (3.5–16.0)	0.27
	>4	12	2.0 (1.5–6.0)	
	Unknown	8		
Hearing impairment	Excellent/Good	16	6.0 (1.5–15.5)	0.84
	Fair/Poor	9	3.0 (2.0–6.0)	
	Unknown	3		
Vision impairment	Excellent/Good	18	4.0 (1.0–7.0)	0.34
	Fair/Poor	7	6.0 (2.0–32.0)	
	Unknown	3		
BOMC impairment	No	17	4.0 (2.0–7.0)	0.98
	Yes	10	3.5 (1.0–17.0)	
	Unknown	1		
Presence of weight loss ^a	No	12	6.0 (2.0–16.5)	0.06
	Yes	11	2.0 (1.0–6.0)	
	Unknown	5		
Patient-reported sarcopenia	No	10	7.0 (3.0–17.0)	0.13
	Yes	8	2.0 (1.0–10.0)	
	Unknown	10		

		ICI Cycles Received		
Variable		# of observations	Median (IQR limits)	Test* p-value
GDS Score impairment	No	21	4.0 (2.0–7.0)	0.71
	Yes	7	2.0 (1.0–15.0)	
VES-13 impairment	No	8	5.5 (1.5–13.0)	0.80
	Yes	13	3.0 (2.0–15.0)	
	Unknown	7		

* Wilcoxon Rank Sum Test

Abbreviations: ADL, Activities of Daily Living; BOMC, Blessed Orientation-Memory-Concentration Test; CR, complete response; ECOG, Eastern Collaborative Oncology Group; GA, geriatric assessment; IADL, Instrumental Activities of Daily Living; SPPB, Short Physical Performance Battery Test; VES-13, Vulnerable Elders Survey-13

^a Defined as more than 5%

Table 4:

Immune-related adverse events

Immune-related Adverse Events Characteristics (N=28)	N (%)
irAE	
Yes	11 (39)
No	17 (60)
Grade	
1	5 (18)
2	1 (3)
3	3 (11)
4	1 (3)
5	1(3)
Event	
Colitis/Diarrhea	1(3)
Thyroiditis	1 (3)
Dermatitis	5 (18)
Musculoskeletal	2 (7)
Pneumonitis	1 (3)
Uveitis	1 (3)
Immunomodulatory therapy	
Systemic	6 (21)
Local	3 (11)
Not needed	2 (7)
ICI Treatment Discontinuation	25 (89)
Reason for discontinuation	
Toxicity	10 (36)
Disease progression	8 (28)
Other	7 (25)

Abbreviations: irAE; Immune-related Adverse Events, ICI; Immune Checkpoint inhibitors.