The predictive value of G8 and the Cancer and Aging Research Group chemotherapy toxicity tool (CARG-tt) in treatment-related toxicity in older Chinese cancer patients

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Abstract

INTRODUCTION:

Older patients experience a higher risk of treatment-related toxicity (TRT). The G8 screening tool was developed to separate cancer older patients fit to receive standard treatment from those who are frail and experiencing functional decline due to reduced organ function and multiple comorbidities. The Cancer and Aging Research Group chemotherapy toxicity tool (CARG-tt) questionnaire was developed to predict chemotherapy toxicity in geriatric patients. This prospective observational study evaluated the performance of G8 and CARG-tt in predicting severe TRT in older Chinese cancer patients.

METHODS:

Chinese patients aged ≥65 with a diagnosis of solid malignancy and scheduled to receive anti-cancer treatment (chemotherapy or targeted therapy) were enrolled from March 2016 to July 2017 at the Department of Clinical Oncology at Queen Mary Hospital in Hong Kong. All patients completed the G8 and CARG-tt screening and pre-treatment assessments before starting treatment. Patients were monitored for any severe TRT, which was defined by grades 3–5 using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03 , treatment discontinuation, or unexpected hospitalization from starting to 30 days after treatment.

RESULTS:

A total of 259 patients (male: 154, 59.5%; median age: 73.4, age range: 65-93) were enrolled in the study. Two hundred and ten (81.1%) patients received chemotherapy while the rest (n=49, 18.9%) received targeted therapy. Overall, 146 patients (56.8%) experienced severe TRT.

The mean G8 score was 12.4 (SD: 2.8). The G8 score had a significant association with unexpected admission (cutoff: 14, 41.3% vs. 26.5%, p=0.03) but not significant in other types of TRTs. The mean CARG-tt score was 7.67 (SD: 3.7); it was not associated with severe TRTs.

CONCLUSIONS:

The G8 and CARG-tt demonstrated a weak prediction of severe TRT in older Chinese cancer patients. Future studies need to develop predictive tools for TRT in patients receiving novel antineoplastic therapies, with a focus on subgroup analysis for different populations.

Keywords: Treatment, prediction, toxicities, assessment, Chinese, screening

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Introduction

Cancer treatment in the older populations is challenging. Older patients with cancer are often under-represented in clinical trials. Less than 20% of patients enrolled in cancer therapeutic clinical trials were over 65 years old and less than 10% were over 75 years old.[1] Older patients are at a higher risk of toxicity from anti-cancer treatment due to comorbidities, nutritional status, preserved organ function and social support as compared to younger patients.[2,3,4,5] They form a very heterogeneous group in terms of their health condition, performance status, physical reserve and social support, making therapeutic decisions more complex and individualized.

In daily practice, treatment decisions rely mainly on clinical judgment and evaluating performance status, such as the Karnofsky Performance Scale Index, Eastern Cooperative Oncology Group (ECOG) Performance Status.[6,7] However, relying on age and performance status can easily lead to both under and overtreatment, causing inferior health outcomes. The International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) recommend comprehensive geriatric assessment (CGA) to develop individually tailored cancer care plans for older patients.[8,9] CGA is regarded as the gold standard in the assessment of frailty; it is a multidimensional and multidisciplinary evaluation of older patients' general health status and functional, cognitive, social and psychological parameters.[10] However, it is not widely implemented because it is time consuming and there is a shortage of trained staff.

Two tools combining geriatric assessment and oncologic parameters were developed to predict chemotherapy toxicity in older cancer patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score and the Cancer and Aging Research Group chemotherapy toxicity tool (CARG-tt).[11,12]

CRASH score involves eight variables and can be used to predict severe hematologic and non-hematologic toxicities separately. It seems to be comprehensive, but not that practical in clinical settings. It requires completion of the assessments of the Instrumental Activities of Daily Living (IADL), Mini Mental Status Score (MMS) and Mini Nutritional Assessment (MNA), which takes around 30 minutes to complete. Moreover, CRASH score requires a chemotherapy toxicity score calculated using the MAX2 index, which does not cover all chemotherapy regimens or targeted agents.

The CARG-tt was developed to predict chemotherapy-related toxicities in older cancer patients. The tool considers 11 items: patient, disease and treatment characteristics (age, type of cancer, number and dose of drugs used); laboratory findings (creatinine clearance and hemoglobulin); and geriatric variables (mobility, fall history, hearing, social activity/ support). Compared to CRASH, CARG-tt only considers the use of mono- and poly-chemotherapy. The tool divides patients into three risk categories: low (0-5 points), medium (6-9 points) and high (10-23 points). This questionnaire predicts chemotherapy toxicity better than the Karnofsky Performance Status Index.

The G8 questionnaire is an accurate and easy-to-use screening tool to evaluate frailty.[13] It consists of eight items: nutritional status, weight loss, body mass index, motor skills, psychological status, number of medications, self-perception of health and age of the patient. A score of $\leq$14 corresponds to abnormal screening and requires CGA. Previous studies also demonstrated the survival prediction of G8 in older cancer patients.[14,15,16] Some studies investigated the predictive value of G8 for chemotherapy toxicity but showed conflicting results.

Both CARG-tt and G8 scores take roughly 5-10 minutes to calculate. With advancements in medical technology, more novel chemotherapies, targeted agents and immunotherapies were developed and became standard treatment for many different types of cancer. It is not known if CARG-tt and G8 scores can be used to predict treatment-related toxicity (TRT) for new antineoplastic agents like targeted therapy and immunotherapy. In addition, both tools were validated using the U.S. population, leaving a gap regarding their effectiveness for Asian population.

In this study, we aim to evaluate the potential predictive performance of G8 and CARG-tt in older Chinese cancer patients undergoing chemotherapy or targeted therapy.

Materials and Methods:

This is a prospective, single-centre observational study. Patients were recruited in the out-patient clinics and in-patient ward at the Department of Clinical Oncology in Queen Mary Hospital, Hong Kong from March 2016 to July 2017. Chinese patients aged ≥65 with a diagnosis of solid malignancy and scheduled to receive anti-cancer treatment using chemotherapy or targeted therapy, in curative or palliative intent, were eligible to participate. We excluded patients diagnosed with hematological malignancy, scheduled for systemic treatment concomitant with radiotherapy or hormonal therapy alone, and with dementia as well as those mentally unfit to provide

consent.

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB).

Study design

Eligible patients completed both the G8 and CARG-tt questionnaires, as well as baseline assessments, with the help of the research team. Treating physicians were blinded to the score results and therefore were not influenced by them when estimating risk or determining treatment path. Physicians selected treatment regimens and doses based on institutional treatment guidelines.

Tumour characteristics (e.g., type of cancer, stage of the disease and sites of metastasis), clinical variables (e.g., body weight, body height, body mass index, ECOG performance status), and treatment details with regimen, dose (standard or reduced dose), line of treatment and intent were recorded.

Toxicity assessment:

Patients were monitored for any severe TRT from starting of treatment until 30 days after treatment. If treatment continued beyond 6 months, the follow-up period ended at 6 months to avoid skewing data through long treatment durations. In this study, severe TRT was defined as grades 3-5 toxicity using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, treatment discontinuation due to treatment-related adverse events and unexpected hospitalization. All medical records of the participants were checked for any hematologic and non-hematologic toxicity, by screening blood tests results: hematologic parameters, serum electrolytes, and liver and renal function tests. To ensure that identical procedures were followed in data collection, a standardized form with CTCAE criteria was used.

Statistical analysis

Descriptive analyses were performed to summarize patient, tumour and treatment characteristics, as well as geriatric assessment results. The incidence and types of TRT were calculated.

G8 (normal/abnormal) and CARG-tt (low, intermediate, high) scores were calculated to determine the proportion of patients at risk of severe toxicity in each group. Associations between risk groups and severe toxicity were determined using chi-

square or Fisher's exact tests whenever appropriate. The G8 score was evaluated as a dichotomous predictor according to the cutoff value of the tool, and the CARG-tt score was evaluated according to the three risk categories. The area under the receiver operating characteristic curve (AUC) was calculated to determine the predictive value of the two tools. A p-value of <0.05 was considered statistically significant and corresponding 95% confidence intervals were calculated.

All statistics analyses were performed using SPSS Statistics v25.

Results:

Patient characteristics:

From March 2016 to July 2017, a total of 272 patients were invited to join the study. 13 patients refused to participate or were excluded for incomplete baseline assessment. The remaining 259 patients (response rate 95.2%; male: 153, 59.3%) were enrolled for final analysis. Patient characteristics are summarized in Table 1. The median age was 73.4 years old (age range: 65-93). Most patients had good performance status (ECOG 0-1: 88.8%). Of the total patients, 180 (69.5%) started systemic treatment in the out-patient clinic. The most frequent tumour types were colorectal cancer (30.1%) and lung cancer (27.8%). Two hundred and ten (81.1%) patients received chemotherapy while 49 (18.9%) patients received targeted therapy alone. For patients receiving chemotherapy, 130 (61.9%) patients received poly-chemotherapy and 98 patients (46.7%) had dose reduction at initial diagnosis. Ninety three (35.9%) patients were receiving treatment in adjuvant/curative intent while 166 patients (64.1%) were in palliative intent. The list of systemic treatments used is provided in Table 2.

Serious adverse events

A total of 146 patients (56.3%) experienced at least one severe TRT, and 91 (35.1%) had grade $\geq$3 hematological toxicity. The three most common hematological toxicities were neutropenia (44, 17.0%), anemia (27, 10.4%) and thrombocytopenia (23, 8.9%). Sixty three (24.3%) patients had grade $\geq$3 non-hematological toxicity. The three most common non-hematological toxicities were infection (26, 10.0%), diarrhea (16, 6.2%) and nausea/vomiting (12, 4.6%).

More hematological toxicities were seen in participants receiving chemotherapy-containing regimens (chemotherapy vs. targeted agent: neutropenia 18.2% vs. 10.2%, anemia: 11.0% vs. 8.2%, thrombocytopenia: 9.2% vs. 8.2%) than those on targeted agents alone. On the other hand, more non-hematologic toxicities were seen in

participants on targeted agents alone (mucositis: 7.1% vs. 16.3%, diarrhea: 5.2% vs. 10.2%).

Fifty-nine patients (22.8%) discontinued treatment due to TRT (chemotherapy-containing regimen: 50, 23.8%; targeted therapy alone: 9, 18.4%).

Ninety-six patients (37.1%) had unexpected hospital admissions, with 59 (61.5%) due to TRT (chemotherapy-containing regimen: 49, 23.3%; targeted therapy alone: 10, 20.4%) and the remaining 37 (38.5%) due to disease progression or complications (e.g., ascites, pleural effusion, bowel perforation, intestinal obstruction and cord compression), co-morbidities (e.g., heart failure, ischemic heart disease and atrial fibrillation) and accidents (e.g. slipped and fell, hip fracture).

Table 3 shows the different types of TRT in both chemotherapy-containing regimens and targeted agents.

Risk predictions

The mean G8 score of the whole sample was 12.4 (SD: 2.8). 189 patients (73.0%) had an impaired G8 score. Severe TRT was seen in 102 patients (54.0%) with abnormal G8 and in 44 patients (62.9%) with normal G8. There was no significant association between G8 and TRT (p=0.13). Using the standard cut-off of 14, G8 was significantly associated with overall unexpected hospital admission (41.3% vs. 26.5%, p=0.03). The predictive performance was fair, with an AUC of 0.50 (95% CI: 0.40-0.59) for the whole population; an AUC of 0.43 (95% CI: 0.35-0.51) for patients treated with chemotherapy and an AUC of 0.57 (95% CI: 0.42-0.74) for patients treated with targeted agents. G8 was not significantly associated with hospital admission due to TRTs. Results of the univariable analysis of TRT are shown in Table 4, and the predictive performance of G8 with AUCs, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) is shown in table 5a.

The mean CARG-tt score was 7.7 (SD: 3.7). CARG-tt stratified participants into three risk groups: low- (87, 33.6%), medium- (96, 37.1%) and high-risk (76, 29.3%). Severe TRT was seen in 48 patients (75.0%) considered low-risk, 58 patients (60.4%) considered medium-risk, and 40 patients (52.6%) in the high-risk category (Table 4). The predictive performance of CARG-tt is shown in Table 5b; it suggests that CARG-tt risk categories were not associated with the total number of TRTs nor any specific type of TRT.

Discussion

Our study evaluated the potential effectiveness of G8 and CARG-tt in predicting TRT in older Chinese patients undergoing treatment with chemotherapies or targeted agents. Although G8 and CARG-tt were not significantly associated with the TRTs, there are several valuable findings. Targeted agents are generally thought to have fewer side effects compared with chemotherapy and are preferred in treating older populations. However, in our cohort, the incidence rates of severe TRT among patients undergoing chemotherapy-containing regimens (56.7%) and those on targeted therapies alone (55.1%) were similar. Targeted agents were usually used in palliative intent. Majority of the patients with advanced malignancy were frailer and had a lower tolerance towards antineoplastic treatment. Patients on targeted agents experienced fewer hematologic toxicities but more agent-specific non-hematologic toxicities. The two most common types of severe TRT with targeted agents were diarrhoea and mucositis. These types of TRT can cause severe complications or decompensation in older patients. For example, one patient developed diarrhea and poor appetite after targeted therapy. This might cause dehydration and consequently impaired renal function. In our study, 9 patients (10.9%) on targeted agents alone required treatment discontinuation due to TRT. Treatment discontinuation will increase the risk of disease progression in metastatic disease and risk of recurrence in adjuvant setting. Physicians need to keep a close eye on the specific complications of each targeted agent and treat them in a timely fashion.

The predictive performance of a screening tool is determined by discrimination, which is assessed by AUC. An AUC value over 0.7 is suggestive of good discrimination, meaning a strong ability to predict TRT. In the current study, the AUCs of TRT in G8 and CARG-tt were all less than 0.7, suggesting weak predictive performance. We propose several potential explanations for this weak predictive performance: first, 56.3% of the patients in our study had severe TRT. The differences in patient cohort (no hematologic malignancies, more patients received treatment with dose reduction and monotherapies) might explain why overall incidence in our study was lower compared with similar studies with incidence of 61-81%.[17,18] In our daily practice, the systemic treatment and regimen doses were decided on and modified according to physicians' judgments. A significant proportion of our patients receiving chemotherapy (46.7%) had a dose reduction to start with. Because of the lack of data on the tolerability of anti-cancer treatment or a standard guideline on doses of systemic treatment in geriatric populations, combined with the fear of inducing unwanted toxicities, our physicians commonly prescribe less aggressive antineoplastic treatments to the older patients, including either dose reduction or use of monotherapies. Some even reduce

the treatment dose solely based on patient's age even if the patient is fit with minimal comorbidities. A similar situation has also been observed in other studies. Up to 50% of older cancer patients have had their treatment schemes modified by administering suboptimal dose, omitting drugs or prescribing monotherapies, and even a higher percentage has been observed among patients undergoing treatment in palliative intent.[19,20]

Second, Chinese cancer patients usually take a passive role in doctor-patient communication. Patients seldom ask many questions, as doing so is perceived to challenge doctor's authority role.[21,22] Some patients even do not dare to tell their physicians about their discomfort until the situation becomes severe. This may delay the detection of early signs or symptoms of the disease complications and toxicity.

Third, more preventive and supportive measures were prophylactically provided for our geriatric patients compared with the younger patients. To avoid potential side effects of the antineoplastic agents, our physicians tend to be more liberal in giving supportive measures, including more frequent use of granulocyte colony-stimulating factors (G-CSF) to prevent neutropenia, a higher class of anti-emetics for nausea and vomiting and more frequent follow-ups after starting treatment. In our cohort, 32 patients (15.2%) receiving chemotherapy had prophylactic G-CSF while only 6 patients received chemotherapy with 20% or higher risk of febrile neutropenia. Moreover, all patients were given prophylactic antiemetics when they started antineoplastic treatment and had weekly follow-up till the second cycle.

All of these reasons might contribute to the lower incidences of TRT in our study and hence affect the predictive performances of the two tools.

In our study, G8 was less likely to predict TRT in older cancer patients. This finding concurs with results in other studies. A recent systematic review studied the association of G8 with the course of treatment.[23] Five out of eight studies which reported on anticancer treatment-related complications failed to show any associations between G8 and chemotherapy-related toxicities. Three studies, separately reporting toxicity rates among fit and frail patients based on the G8, found significantly higher rates of chemotherapy- and/or radiotherapy-related toxicity in the latter, with relative risks varying from 1.4 to 11.3. However, they did not specify whether the toxicity was due to chemotherapy or radiotherapy. Another recently published study on 40 advanced pancreatic cancer patients aged over 70 who were treated with palliative chemotherapy gemcitabine and nab-paclitaxel also found no

association between G8 and all types of severe grade 3/4 toxicity, delays or dose reductions (chi-square statistic 0.2427 with a p-value of 0.622).[24]

G8 was significantly associated with unexpected admission in our study. Patients with G8 score ≤14 were generally frailer with worse performance status and multiple co-morbidities (e.g. heart failure and fall risk), which likely increase the risk of hospitalization. Schulkes et al.'s study, which included 142 lung cancer patients aged over 70 in the Netherlands, showed that a low G8 score could significantly predict hospitalization and mortality.[25] Future studies with a larger sample size and number of confounding variables are warranted to confirm the association of G8 with TRT and hospital admission.

In our study, CARG-tt was not associated with severe TRTs, even in the chemotherapy-containing subgroup. There are other studies similarly showing no association between CARG-tt and chemotherapy-related toxicity. A Canadian study tested CARG-tt score in a cohort of 46 patients receiving docetaxel for metastatic prostate cancer. The percentages of toxicity across different risk groups were not significantly different (p=0.65).[26] Another study on 126 cancer patients aged $\geq$65 in Australia also showed that CARG-tt could not predict severe chemotherapy toxicity (odds-ratio 1.04, 95% CI 0.92–1.18, p=0.54; AUC 0.52).[27]

We should be aware that the prediction of chemotherapy toxicity may be inaccurate in 30% of patients in the original CARG-tt validation study (AUC: 0.72). In addition, CARG-tt was validated in patients using traditional chemotherapies.[12] Novel antineoplastic agents generally have fewer side effects than the traditional ones, likely resulting in the insignificant predictive performance.

The ethnic variability of clinical outcomes among patients receiving antineoplastic treatment is well known, in terms of both efficacy and adverse events. Factors suggested to contribute to this variability in outcomes include ethnic diversity in pharmacogenomics and pharmacokinetics, variability in pharmacodynamics and drug metabolisms, tumour biology or profiles differences, as well as differences in lifestyles, culture and body build. Previous studies revealed that Asian cancer patients who received capecitabine or 5FU had fewer serious adverse events, including hand-foot syndrome, compared with other populations (relative risk: 1.21–2.83, p-value=0.013).[28] In our study, more than one-third of our participants received capecitabine/5FU regimens. This may explain the relatively lower percentage of serious TRT in our cohort. Other examples of ethnic differences in terms of anti-cancer

treatment toxicity include the following: more Asian patients had hematological toxicities and febrile neutropenia than Caucasian patients when using docetaxel and carboplatin to treat lung cancer;[29] Japanese patients experienced more grade 3/4 hematological toxicities than North American patients when treated with irinotecan/cisplatin or etoposide/cisplatin for small cell lung cancer[30]; Asian breast cancer patients experienced more grade 4 neutropenia and chemotherapy-induced nausea/vomiting than Caucasian patients on doxorubicin/cyclophosphamide;[31] and Asian patients had more adverse events than Caucasian patients when taking regorafenib for refractory colorectal cancer.[32,33] It should be noted that only 5% of the participants were Asian in the CARG-tt validation study. Taken together with the ethnic differences in clinical outcomes, it is uncertain whether CARG-tt can be applied in Asian older cancer patients in the same way as Caucasians.

Despite the negative results of both G8 and CARG-tt, this study has a number of strengths, including prospective design, well-balanced cancer types, inclusion of chemotherapies and targeted therapies, and large sample size. Nevertheless, there are some limitations. Most of the participants were recruited in our out-patient clinic, where patients were usually fitter than those in the in-patient setting; this could account for the lower incidence of TRT compared with other studies. The majority of our participants received chemotherapy-containing regimens and only 18.9% received targeted agents alone. For a more accurate evaluation of these tools' predictive performance on targeted agent-related toxicities, a larger study population using targeted agents is needed. In addition, the chemotherapy-containing group also included patients who used both chemotherapy and targeted agents. Thus, the results in the chemotherapy-containing group could be affected by adverse events from the targeted agents. Our study also did not collect patient-reported outcomes. It is unknown whether the baseline G8 or CARG-tt score can predict any functional or cognitive decline due to antineoplastic treatment.

Our findings indicated that both CARG-tt and G8 scores did not effectively predict severe TRTs; this is consistent with results from other studies. There is a need for researchers to develop a predictive tool on TRTs in patients receiving novel antineoplastic therapies and special focus on the Chinese/ Asian older cancer patients.

Conclusion:

The potential predictive performance of both G8 and CARG-tt in TRT in older Chinese cancer patients was generally weak. However, G8 score was associated with unexpected admission. Community assessments or out-of-hours care should be

implemented for patients with abnormal G8 to provide more out-patient support and early detection of complications of the disease or toxicities from systemic treatment to avoid hospitalisation. Future studies should also focus on developing new tools that can effectively predict TRT in older cancer patients, especially those receiving newer anti-cancer treatments such as targeted agents or immunotherapies as they are increasingly used in the cancer treatment pathway. Planned subgroup analysis on different population is also highly recommended.

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