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Geriatric Oncology

Estimating the Risk of Chemotherapy Toxicity in Indian Geriatric Patient Population and Utility of Chemotherapy Risk Assessment Scale for High Age Patients (CRASH) Score

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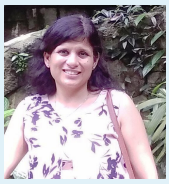
Abstract



Aditi Mittal

Background Aging is a heterogeneous process, and elderly population is diverse in health status and functional reserve. The present study was undertaken to predict severe chemotherapy toxicity using the Chemotherapy Risk Assessment Scale for High-Age Patients' (CRASH) score.

Materials and Methods Elderly patients (age ≥65 years) with malignancy, who were planned to be treated with a new course of cytotoxic chemotherapy, were enrolled. The CRASH score was calculated, and patients were stratified into four categories, that is, low (0–3), intermediate (Int)-low (4–6), Int-high (7–9), and high (<9). Patients developing grade 3/4/5 nonhematologic (NH) or grade 4/5 hematologic (H) toxicity were taken as the development of severe toxicity.

Results Of 100 enrolled patients, 64 (64%) were able to complete their prescribed treatment. Forty-four percent of patients (44 patients) of our study cohort experienced grade-4 H or grade 3/4 NH toxicity. The highest score in each category (heme/nonheme/CRASH) predicts nearly 100% toxicity risk. At a critical value of CRASH ≥ 6.5, the sensitivity is calculated as 100%, while specificity is 89.09%. The accuracy of prediction is 93.88%. The median time taken to develop toxicity was 39.5 days.

Conclusion CRASH score utilizes clinical assessment and basic laboratory values. Yet, it accurately predicts severe chemotherapy toxicity above a critical value of 6.5. Based on the above study, the first 30 days are crucial as 45% of patients experienced toxicity in this time frame. With the help of these clinical predictive markers, the care of elderly will be optimized.

Keywords
- chemotherapy
- elderly
- risk assessment
- toxicity

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Introduction

The field of geriatrics is gradually being recognized as the need of the century. Throughout the world, all populations are seeing the burgeoning numbers of elderly. As per the latest census of 2011 in India, the population aged above 65 years comprises 5% (4.8% urban and 5.1% rural).[1] Cancer is a disease of aging, with the majority falling in the age group above 65 years.[2]

Data from earlier trials and meta-analysis provide conflicting results regarding the benefit of chemotherapy in elderly.[3-5] An Indian study[6] noted an increased dropout rate or discontinuation of treatment in elderly compared with younger population.

As a standard oncology evaluation cannot recognize those with the likelihood of toxicity due to treatment, objective and measurable factors are needed for rational decision-making. Few predictive scores are available to assess the individual risk of severe toxicity, namely, the Cancer and Aging Research Group (CARG),[7] Chemotherapy Risk Assessment Scale for High-Age Patients' (CRASH) score,[8] and Get up and Go test.[9] CRASH is a more comprehensive, detailed, and informative score. CRASH utilizes the MAX2 index[10] for estimating the chemotherapy toxicity. The MAX2 index is a convenient and reproducible way of comparing the average per patient risk for toxicity from chemotherapy across several regimens.

Hence, this exploratory study was undertaken if we can predict severe chemotherapy toxicity using the CRASH score as a model at a tertiary health care center. It is perhaps the first study quoting predictive factors for chemotherapy toxicity in the Indian geriatric population.

Materials and Methods

The present study was a single-institution prospective observational cohort study conducted in the Department of Medical Oncology at Dr. B.L. Kapur Hospital, Pusa Road, New Delhi, from October 2014 to 2016. Patients were enrolled as per the type-1 progressive censoring scheme. As per the institution load, it was decided to conduct a pilot study, and 100 consecutive patients were enrolled as per the following inclusion and exclusion criteria. Patients with (1) age ≥65 years, (2) histologic documentation of malignancy, (3) planned for new course of cytotoxic chemotherapy, (4) able to answer questions, (5) willing to give consent, (6) received radiation >3 months before or after the completion of chemotherapy were included in the study. Patients (1) undergoing radiation therapy <3 months, (2) have complaints of dementia and are in altered behavior or sensorium, (3) undergoing chemotherapy for bone marrow transplant, and (4) unwilling to give consent were excluded from the study.

All patients were evaluated with a detailed history and physical examination. The staging was performed as per routine clinical practice. Standard chemotherapy was planned by the treating physician. Biochemical, hematological, and radiological tests were done before recruitment and on follow-up.

The Eastern Cooperative Oncology Group (ECOG) performance status (PS), Lawton nine-item Instrumental Activities of Daily Living (IADL), Mini Nutritional Assessment (MNA), and Folstein Mini-Mental Status Examination (MMSE) were administered by principal investigator verbally, and results were recorded. The risk of severe chemotherapy toxicity was computed using the MAX2 index.[10] Briefly, the MAX2 index is average of the highest frequency of both grade-4 hematologic (H) and grade 3/4 nonhematologic (NH) toxicity. It is reproducible across cancer types and is sensitive to toxicity differences. The component of CRASH score[8] and its variables are shown in ►Table 1. The CRASH score varies from 0 to 12. Patients were stratified into four categories, that is, low (0–3), intermediate (Int)-low (4–6), Int-high (7–9), and high (<9). All procedures followed were in accordance with the ethical standard of the responsible committee on human experiments (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008.[5] Written informed consent was obtained from all patients before the enrollment.

Toxicity was graded as per CTCAE (Common Terminology Criteria for Adverse Events) adverse events criteria version 4.0, published on May 28, 2009. Patients developing grade 3/4/5 NH or grade 4/5 H toxicity were taken as the development of severe toxicity.

Statistical Analysis

The quantitative variables were expressed as mean ± standard deviation (SD) and compared using unpaired *t*-test. Data grouped in contingency tables, wherein the Chi-square test was used to assess the associations. Receiver operating characteristic (ROC) curves were made to identify the critical values, and, hence, odds ratio, sensitivity, and specificity were calculated. Kaplan–Meier product limit estimator is used to calculate the expected median survival time. A *p*-value of <0.05 is considered as statistically significant. (SPSS, International Business Machines Corporation, Armonk, New York, United States) version 16.0 software is used for statistical analysis.

Table 1 Components of the chemotherapy risk assessment scale for high-age patients score

Chemotherapy risk (chemotox score) as per MAX2 index	0–0.44 (score 0)
	0.45–0.57 (score 1)
	>0.57 (score 2)
Hematologic risk factors and scoring	Diastolic blood pressure (>72 mm Hg = 1)
	IADL (<26 = 1)
	LDH (>459 = 2)
Nonhematologic risk factors and scoring	ECOG PS (1–2 = 1; 3–4 = 2)
	MMSE (<30 = 2)
	MNA (<28 = 2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MMSE, Mini-Mental Status Examination; MNA, Mini Nutritional assessment; PS, performance status.

Results

Patient, disease, and treatment characteristics are shown in ►Table 2. Most of the patients had one or more comorbidity (61%), the most common being diabetes mellitus (41%). Chemotherapy-related toxicity was 51.2, 27.5, and 50% in patients with zero, one, more than one comorbidity (p = 0.107). No association could be deduced between chemotherapy toxicity and carcinoma site due to a small sample size and varied histopathology. In total, 29 different chemotherapy regimens and schedules were used. Weekly paclitaxel and carboplatin were most commonly used regimens (26%) followed by nab-paclitaxel (11%). Among patients with metastatic setting, 67% of them received first-line chemotherapy. A subset of patients (8) was receiving third-line chemotherapy and they experienced maximum toxicity (six out of eight patients) (p = 0.234). Although p-value was not statistically significant, still this points toward the role of cumulative chemotherapy toxicity.

Geriatric assessment variables were a critical part of the predictive model. Three-fourth of the patients had ECOG PS ≤2 (76 out of 100), as shown in ►Table 2. More than 90% of patients with PS-3 developed toxicity in comparison to 23.3% in patients with PS-1 (p < 0.05). The mean score on IADL was 23.03 (SD = 4.02, range: 13–29), with 68% of them having a score <26, and functionally disabled in one or more IADL. The mean MMSE score was 28.47 (SD = 2.72, range: 16–30); 49 with normal cognition. The mean score of MNA was 20.7 (range: 12–28.5). Twenty percent of the patient population was found to be severely malnourished (MNA score <17), and 53% was at risk. The incidence of toxicity was the highest in the malnourished group (55.5%). Body mass index alone was not a good tool for evaluating nutritional status in an individual (p = 0.61).

Amidst the various laboratory variables, mean hemoglobin, albumin, and serum lactic dehydrogenase values were 11.3, 3.65, and 322 g/dL, respectively. The value of serum lactate dehydrogenase (LDH) was greater than twice the normal in 13% of patients (range: 106–3,224).

Overall, 64 (64%) patients were able to complete their prescribed treatment. Twelve patients stopped or changed to another chemotherapy regimen due to disease progression. Twenty-four patients (24%) stopped the treatment due to toxicity. Among patients who stopped treatment , most of them had advanced disease (22 out of 24) and poor PS. More than half of them (54%)received polychemotherapy. Two patients were lost to follow-up and their data were censored till the last follow-up.

Forty-four percent of patients (44 patients) of our study cohort experienced grade-4 H or grade 3/4 NH toxicity, 13% (13) had grade-4 H toxicity, and 42% (42 patients) had grade 3/4 NH toxicity. Three patients (3%) died within 1 month of starting treatment. Maximum events (45.4%) occurred in the first month of starting chemotherapy.

►Fig. 1 shows the four groups as per the CRASH score and the occurrence of chemotherapy-related toxicity. The highest score in each category (heme/nonheme/CRASH) predicts nearly 100% toxicity risk. The association between CRASH score and toxicity (Chi-square p < 0.001) is found to

Table 2 Baseline demographic and clinical characteristics of elderly patients

Variable	*n*
Age (y)	65–80
Mean ± SD	68.46 ± 4.3
65–74 (young old)	90
75–84 (old-old)	10
>85 (oldest old)	0
Sex	
Female	44
Male	56
Comorbidities	
0–1	68
>1	32
Tumor site	
GI	27
Carcinoma ovary (including PPC)	21
Breast carcinoma	14
Carcinoma lung	13
NHL (DLBCL)	8
Genitourinary cancer	8
Head and neck cancer	7
Synovial sarcoma	2
Disease extent, stage wise	
1	3
2	11
3	17
4	69
Intent of chemotherapy	
Definitive (adjuvant/curative/ neoadjuvant)	35
Palliative	65
ECOG PS	
0–1	32
>1	68
Serum lactic dehydrogenase (IU/L)	
Score 2 (>459)	13
Score 0 (<459)	87
Chemotherapy	
Monochemotherapy	31
Polychemotherapy (>1 drug)	69
Chemotherapy regimens (most common)	
Weekly paclitaxel + carboplatin	26
Weekly nab-paclitaxel	11
FOLFOX/CAPOX	10
Use of G-CSF	
Yes	77
No	23

Abbreviations: DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FOLFOX (folinic acid, fluorouracil, and oxaliplatin) CAPOX (capecitabine, oxaliplatin); G-CSF, growth colony-stimulating factor; GI, gastrointestinal; NHL, non-Hodgkin's lymphoma; PPC, primary peritoneal cancer; PS, performance status; SD, standard deviation.

be statistically significant. The mean CRASH score among patients who developed toxicity was 8.52 ± 1.19 versus 5.15 ± 1.33 ($p < 0.001$). Similar observations were made for heme and nonheme scores.

The ROC of the CRASH model with chemotherapy toxicity produces area under the curve as 97% ($p < 0.001$) which has a high statistical significance value. Choosing a critical value of CRASH score of ≥6.5 for predicting toxicity, the sensitivity is calculated as 100%, while specificity is 89.09%. The accuracy of prediction is 93.88%. The area under the ROC curve is 94.3% ($p < 0.001$) and 90.7% for heme and nonheme score, respectively. The accuracy of prediction is around 90% for both models.

The mean survival time was 540 days for patients who did not develop toxicity versus 264 days for those who developed toxicity. The difference between the groups is statistically significant ($p < 0.005$). The Kaplan–Meier curves are shown in ►Fig. 2. Overall, 37% of our study patients died during the study.

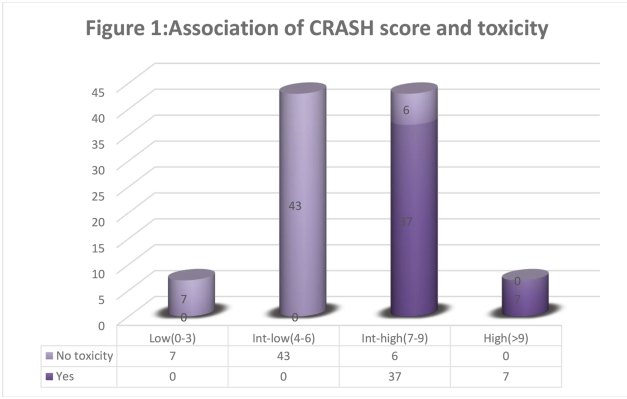

Fig. 1 Association of the Chemotherapy Risk Assessment Scale for High-Age Patients' (CRASH) score and severe chemotherapy toxicity. This figure shows that patients with the low Chemotherapy Risk Assessment Scale for High-Age Patients score are at 0% risk of toxicity versus patients at other end with high score have 100% toxicity. Int, intermediate.

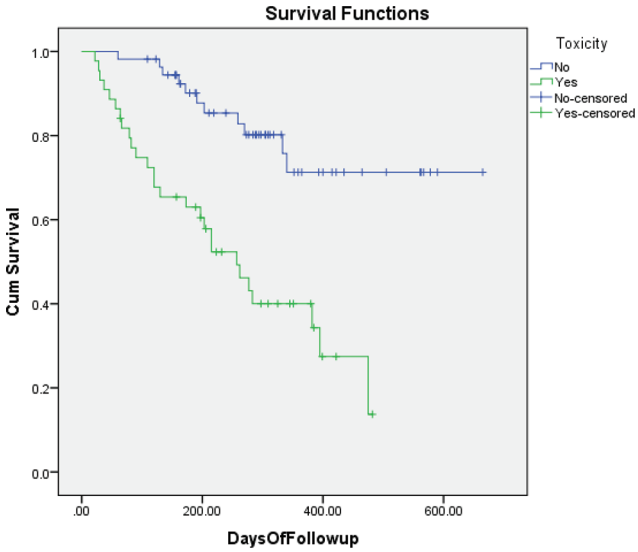

Fig. 2 Kaplan–Meier curves of those who developed toxicity versus who do not. Kaplan–Meier curves of patients those who developed toxicity versus who do not. The figure depicts the rapidly falling curve for the patients who develop toxicity and hence decreased median survival.

Discussion

This prospective, observational, single hospital–based study evaluated risk factors for the prediction of chemotherapy toxicity in elderly population (≥65 years) with the usage of the CRASH score. In this study, CRASH was found to be a good predictive tool above a value of 6.5 to anticipate chemotherapy-related severe toxicity ►Table 3 (accuracy 93.88%). More than half (64%) of patients completed treatment, and 44% experienced severe chemotherapy-related toxicity.

Approximately 11 lakh new cancer patients are being diagnosed in India yearly (GLOBOCAN 2018).[11] About 12 to 23% of all cancer occurs in elderly (≥65 years).[12] Thus, in years to come, treating physician/oncologist will face a huge number of older patients with cancer. Chemotherapy works not only for improving the quantity of life but also to improve the quality of life. Effective management of chemotherapy-related toxicity with appropriate supportive care is crucial. The International Society of Geriatric Oncology and National Comprehensive Cancer Network advise performing some form of geriatric assessments in all older patients with cancer.[13] As suggested by the previous studies, geriatric assessment can lead to modification in treatment planning in 20 to 50% of patients.[14] CRASH[8] is one such tool with high sensitivity and specificity. It utilizes various patients, diseases, and chemotherapy-related variables and creates a comprehensive landscape for the clinician. Among others, the CARG model[7] distributes patients into three groups with the occurrence of toxicity as 36.7, 62.4, and 70.2% in low-, medium-, and high-risk groups, respectively ($p < 0.001$). The notable difference between these models is that CRASH is exhaustive, and in addition, it defines H and NH toxicities separately.

Chemotherapy-related toxicities in elderly vary across studies ranging from 28 to 64%.[7,8,15,16] Sparse data are available from India concerning this problem. Sarkar and Shahi[6] reported treatment (radiation, surgery, and chemotherapy)-related grade 3/4 toxicity in elderly as 10.2% (4/39 patients). We sought to identify lone chemotherapy-related toxicity in this cohort. H and NH toxicities were experienced by 13 and 42 patients, respectively. Older adults seem to be susceptible to increased myelosuppression due to limited hematopoietic reserve.[17] Balducci and Corcoran[17] mentioned that myelosuppression can be reduced with the use of growth factors. We observed limited H toxicity (13%) due to the liberal use of growth factors (77%) and the exclusion of leukemia and high-dose therapy (►Table 3).

Patients with PS-3 developed toxicity in 91% patients in comparison with 23.3% in PS-1 ($p < 0.05$). In addition, patients with stage-4 disease has higher toxicity (49.2 vs. 32.2%) but statistically insignificant. Similarly, Freyer et al[15] deduced depression ($p = 0.006$), PS ≥2 ($p = 0.026$), and dependence ($p = 0.048$); FIOGO (The International Federation of Gynecology

Table 3 Statistical parameters of the Chemotherapy Risk Assessment Scale for High-Age Patients' score

Toxicity CRASH score	Yes *n* (%)	No *n* (%)	*p*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
<6.5	0 (0.00)	50 (89.28)	<0.001	100.00	89.09	87.76	100.00	93.88
≥6.5	44 (100.00)	6 (10.71)						
Total	44 (100)	56 (100)						

Abbreviations: CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients' score; NPV, negative predictive value; PPV, positive predictive value.

and Obstetrics) stage IV ($p = 0.075$) as risk factors for developing toxicity.

The components of the CRASH score are equally useful. The odds of developing H toxicity were found to be 125 times more when heme score >3.5. This information can be utilized to categorize patients in whom either dose modification or the use of growth factors is warranted. Akin to this, NH score of >5.5 entails an individual 40 times prone for adverse events.

Crawford et al[18] and Lyman et al[19] stated the maximum occurrence of H toxicity after the first cycle of chemotherapy. In our cohort, the maximum number of events (45.4%) occurred in first month of starting chemotherapy. To infer, one should carry close and frequent monitoring during this period.

Authors have employed 10 to 45 minutes to conduct abbreviated comprehensive geriatric assessment (aCGA).[8,20,21] In a resource-strained country like India, it is a daunting process to allot around one and half to conduct this score. The feasibility in day-to-day practice is matter of concern.

The aCGA predicts mortality as shown by Fried's operational criteria for frailty,[22] functional status,[23] cognitive impairment,[24] nutrition,[25] and depression.[25] On the other hand, Puts et al[21] failed to find a correlation between frailty markers and mortality. The mean time of survival was significantly worse for those who developed toxicity ($p < 0.005$). The CRASH score was associated with the development of toxicity, and latter is a risk factor for decreased survival. Consequently, CRASH may also serve as an indirect measure of survival.

Limitations

The limitations of the study are as follows: the study was conducted in a single center with small ($n = 100$) and heterogeneous cancer population. We reported only grades 3 to 5 toxicity, although grade-2 toxicities (diarrhea and neuropathy) may also be pertinent to the geriatric population. The aCGA was done once; however, longitudinal evaluation would be more informative. CRASH is still not validated for targeted, oral, and immunotherapy. However, our results show that some simple parameters can be systematically assessed to guide the physicians to choose the best therapeutic strategy.

Conclusion

We reported the incidence of lone chemotherapy-related toxicity, perhaps for the first time in the Indian context. Although the CRASH score is time consuming and exhaustive, it correlated well with anticipation of toxicity. For frail elderly, the first 30 days are most crucial. The mean survival and number of chemotherapy cycles received are adversely affected with the development of toxicity. Large-scale disease-specific studies are needed to identify clinical and laboratory factors affecting the development of toxicity.

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Conflict of Interest
There are no conflicts of interest to declare.

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