Evaluation of the Chemotherapy Toxicity Risk Score (CTRS) for Treatment Decision in Elderly Cancer Patients

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A. SPECIFIC AIMS

The treatment of older adults with cancer is complicated by the heterogeneous aging process and the frequent presence of comorbidities. Although cancer patients over age 65 represent the fastest growing segment of the cancer population, a tremendous gap in knowledge exists regarding the optimal management of advanced cancer in these patients, including how to determine if a patient is fit or unfit to receive standard of care chemotherapy. A predictive model for chemotherapy toxicity in older adults -- the Chemotherapy Toxicity Risk Score (CTRS) -- was developed in a prospective study of 500 cancer patients ≥ 65 years. [1]

The CTRS score is derived from five measures included in a brief Geriatric Assessment (GA) (hearing, falls in the last 6 months, ability to take medications unassisted, ability to walk one block, engagement in social activity) and six non-GA measures (age, type of cancer, chemotherapy dose, polychemotherapy, hemoglobin level, creatinine clearance). The CTRS identified older adults at low (0 to 5 points; 30%), intermediate (6 to 9 points; 52%), or high risk (10 to 19 points; 83%) of chemotherapy toxicity, defined as percent incidence of grade 3 to 5 toxicity. In the study for the CTRS development, the dose and regimen were at the discretion of the treating oncologist. Notably, a planned dose reduction of chemotherapy at first cycle, designated as primary dose reduction (PDR), was documented in 26/179 (15%) and 81/321 (25%) of patients treated with curative and palliative intent, respectively. PDR was supposedly used by the treating oncologist in patients who were felt to be at high risk for chemotherapy toxicity. Gajra et al. reported age was independently associated with PDR in both sub-groups. Comorbidity (prior cancer or liver/kidney disease) was independently associated with PDR in the palliative subgroup alone while Karnofsky Performance Status was not associated with PDR in either subgroup.[2] The potential utility of the CTRS for chemotherapy decision making in older patients with advanced solid cancer has not been studied. And it has not been fully elucidated what factors may be associated with the clinical judgment to reduce chemotherapy. To address these research questions, we propose to conduct a secondary analysis of the prospective cohort study for the CTRS development. Specific aims of the study are:

AIM 1 (primary): To estimate agreement or disagreement in chemotherapy treatment decisions between clinical impression and CTRS. We will stratify the patients into curative and palliative intent groups.

Clinical impression based treatment decision:
This will be the actual treatment that the patient received. The patient is categorized into “standard” or “reduced” group based on type of cancer, treatment intent, line of therapy, chemotherapy regimen, and dosing for the first cycle. Detailed explanation for standard” and “reduced” therapy is described in B.2.

CTRS treatment decision:
For the same set of patients regardless of group assignment, CTRS scores will be calculated at baseline to determine whether the patient should have received “standard” or “reduced” therapy. If the patient is considered to be high risk for “standard” care (CTRS score is ≥10) then it will be expected that the patient should have received “reduced” therapy. If the patient is considered low or intermediate risk for chemotherapy toxicity (CTRS score is <10), then it will be expected that the patient should have received “standard” therapy.
**AIM 2 (secondary):** To evaluate the association between baseline renal and hepatic function and the clinical judgment to reduce chemotherapy. In the previous secondary analysis of this cohort study, chronic liver or kidney disease was independently associated with PDR in the palliative subgroup.[2] However, chronic liver or kidney disease was captured by the OARS subscale and may have been underestimated. Baseline renal and hepatic function may be more strongly associated with PDR.

**AIM 3 (secondary):** To describe the clinical circumstances (tumor type, chemotherapy regimen, sociodemographic factors, and geriatric assessment variables) in which clinical impression treatment decision does not align with the CTRS treatment decision stratified by treatment for curative or palliative intent. This could clarify clinical situations where patients may receive under- and over-treatment.

**B. APPROACH**

**B.1 Original Study Schema.**
This is a secondary analysis of the prospective cohort study for the CTRS development to estimate agreement or disagreement in chemotherapy treatment decisions between clinical impression and CTRS.

![Diagram](image)

**B.2 Clinical impression based treatment decision**
This will be the actual treatment that the patient received. For the *curative* intent group, if the patient receives combination therapy at standard dose, this patient will be categorized into the “standard” group. If the patient receives single agent or reduced dose, this patient will be categorized into the “reduced” group.

For the *palliative* intent group, if the patient receives combination therapy at standard dose as a first line therapy for their advanced cancer for which combination chemotherapy is the standard (Lung, GI, GYN and bladder cancers), this patient will be categorized into the “standard” group. The definition of the “reduced” group for these cancers is the same as the curative intent group. For patients with advanced cancer for which single agent is the standard first-line chemotherapy (e.g. breast and prostate cancer) and patients receiving a second line therapy for their advanced cancer, single agent chemotherapy at standard dose is designated as “standard”. If the patient receives single agent at reduced dose, this patient will be categorized into the “reduced” group.

**B.3 Chemotherapy Toxicity Risk Score (CTRS) based treatment decision:**
The CTRS uses five brief GA variables (hearing, falls in the last 6 months, ability to take medications unassisted, ability to walk one block, engagement in social activity) and six non-GA measures (age, type of cancer, chemotherapy dose, polychemotherapy, hemoglobin level, creatinine clearance).[1] We will calculate a baseline CTRS score for all patients, making the assumption that all of them received “standard” therapy. For the *curative* intent group, the “standard” therapy is defined as combination therapy at standard dose and the patient gets 2 points from polychemotherapy and 2 points from standard dose.

For the *palliative* intent group, combination therapy at standard dose is the “standard” therapy for patients
receiving a first line therapy for their advanced lung, GI, GYN and bladder cancers. For patients with advanced breast and prostate cancer and patients receiving a second line therapy for their advanced cancer, the “standard” therapy is designated as single agent chemotherapy at standard dose. The CTRS will then be used to determine whether the patient should have received “standard” or “reduced” therapy. If the patient’s CTRS score is ≥10, that patient will be considered high risk for “standard” therapy and should have received “reduced” therapy. If the patient’s score is <10, that patient will be considered low or intermediate risk and should have received “standard” therapy. For Aim 1, the CTRS treatment decision will be compared for agreement or disagreement with the treatment decision actually made by the treating oncologist who was not aware of the CTRS result.

**Example results table:**

<table>
<thead>
<tr>
<th>Chemotherapy Choice based on CTRS</th>
<th>Standard (score &lt;10)</th>
<th>Reduced (score ≥10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Choice based on Clinical Impression</td>
<td>Standard (Combo/standard dose, Single/standard dose)</td>
<td>Agree</td>
</tr>
<tr>
<td>Reduced (Single/standard dose, Combo/reduced dose, Single/reduced dose)</td>
<td>Disagree</td>
<td>Agree</td>
</tr>
</tbody>
</table>

**B.4 Evaluation of renal and hepatic function**

Renal function will be calculated with Cockcroft-Gault equation (CG) based on the recent report that decreased creatinine clearance as measured by CG with actual body weight was associated with increased risks of chemotherapy-related toxicity.[3] Hepatic function will be assessed with total bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase (ALP). When using these variables as categorical variables, abnormal creatinine clearance will be defined as <60 mL/min and abnormal liver function tests are as follows; bilirubin>1 mg/dL, AST>35 U/L, and ALP>120 U/L.[4]

**B.5 Statistical Considerations**

The original study cohort consisted of 500 patients age ≥ 65 years. Recently, additional 250 patients were studied in the validation cohort. In total, 750 patients will be available for this study. All analyses will be conducted separately in the curative intent and palliative intent chemotherapy groups. For Aim 1, we will use a kappa statistic with a 95% confidence interval to estimate the agreement between clinical impression and CTRS. The kappa statistic determines the proportion of agreement that occurs after random chance is subtracted from the actual proportion of agreement seen. Kappa coefficients range in value from 1 to -1. According to Landis and Koch et al [Biometrics. 1977 Mar;33(1):159-74.], the following interpretations are suggested kappa coefficients of 0.81 -1.00; almost perfect, 0.61 -0.80; substantial, 0.41 -0.60; moderate, 0.21 -0.40; fair, 0.01 -0.20; slight and 0.0 or less; poor agreement. For Aim 2, association between baseline renal and hepatic function and the clinical judgment to reduce chemotherapy will be evaluated by multivariable logistic regression. For Aim 3, descriptive analyses will be performed to determine mean, median, standard deviation (SD), ranges for continuous variables, and frequencies for categorical variables.
REFERENCES