Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study


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A brief, comprehensive measure is needed that identifies the seemingly fit older individual at risk for chemotherapy toxicity.
Conceptual Model

Labs
1) Renal function
   -Creatinine clearance
2) Hepatic function
   -Liver function tests
3) Hematologic function
   -WBC
   -Hemoglobin

Sociodemographic
1) Age
2) Gender
3) Race/ethnicity
4) Education
5) Marital status
6) Living companion

Chemotherapy Toxicity

Geriatric Assessment
1) Functional status
2) Comorbidity
3) Cognition
4) Psychological state
5) Social support
6) Nutritional status

Tumor & Treatment
1) Tumor type
2) Tumor stage
3) Chemotherapy
   -Mono- vs Poly- chemo
   -Dosage
4) Growth Factor Use
Objective

1. Develop a predictive model for chemotherapy toxicity in older adults
   - Sociodemographic characteristics
   - Tumor characteristics
   - Treatment characteristics
   - Laboratory values
   - Geriatric assessment parameters

2. Internally validate the model
**Study Schema**

**Eligibility criteria**
- Age 65 or older
- Diagnosis of cancer
- To start a new chemotherapy regimen

**Pre-chemo Assessment**

**End chemo**

**Chemotherapy toxicity grading (2 MDs)**

NCI CTCAE v3.0

- Sample size: 500 patients
- 7 participating institutions (Cancer and Aging Research Group)
Geriatric Assessment

- **Functional Status:**
  - Activities of Daily Living
  - Instrumental Activities of Daily Living
  - Karnofsky Performance Rating Scale
  - Timed Up & Go
  - Number of Falls in Last 6 Months

- **Comorbidity:** Physical Health Section

- **Cognition:** Blessed Orientation-Memory-Concentration Test

- **Psychological:** Hospital Anxiety and Depression Scale

- **Social Functioning:** MOS Social Activity Limitations Measure

- **Social Support:**
  - MOS Social Support Survey: Emotional and Tangible Subscales
  - Seeman and Berkman Social Ties

- **Nutrition:**
  - % Unintentional Weight Loss in the Last 6 Months
  - Body Mass Index

*Hurria et al. Cancer 2005, JCO 2011*
1. **Bivariate analysis:**
   - Youden Index: cut-off point for toxicity
   - Chi-square test: association of variables with toxicity

2. **Multivariate Logistic Regression:**
   - Variables: \( p < 0.1 \) in bivariate analysis or clinically relevant
   - Predictive model development
     - Individual items in the GA measures
       - Best-subsets selection method
     - Goodness of fit & Receiver operating characteristics

3. **Internal Validation**
   - 10-fold Cross-Validation
Results
Patient Characteristics

# of Patients  500

Mean age  73 years
(Range)  (65-91)

Education (college educated)  61%

Employment (retired)  83%

Race (white)  85%

Gender

Female  56%
Male  44%
Cancer Stage: 61% stage IV  
Treatment: 70% polychemotherapy  
18% WBC growth factor with cycle 1
Geriatric Assessment Results

- 43% require assistance with IADL
- 18% fallen in last 6 months
- 44% with > 2 co-morbidities
- 6% with cognitive impairment (B-OMC > 10)
- 16% with anxiety/depression (HADS > 14)
- 38% with weight loss ≥ 5%
- 12% have a BMI < 22
Toxicity Summary

Incidence

- Grade 3-5: 53%
- Grade 4: 39%
- Grade 3: 18%
- Grade 5: 5%

All Types

- Grade 3-5: 43%
- Grade 4: 12%
- Grade 3: 26%
- Grade 5: 2%

Heme

- Grade 3-5: 40%
- Grade 4: 8%
- Grade 3: 18%
- Grade 5: 0%

Non-Heme

- Grade 3-5: 50%
- Grade 4: 5%
- Grade 3: 12%
- Grade 5: 0%
Most Common Gr 3-5 Toxicities

Heme

<table>
<thead>
<tr>
<th>Grade</th>
<th>ANC</th>
<th>WBC</th>
<th>Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-5</td>
<td>11%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Non-heme

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fatigue</th>
<th>Infection</th>
<th>Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-5</td>
<td>16%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Bivariate Analysis ($p<0.1$)

**Labs:**
1) Albumin ≤ 3.6
2) Hemoglobin <11

**Sociodemographic:**
1) Age ≥ 72

**Chemotherapy Toxicity**

**Tumor & Treatment:**
1) GI or GU tumor type

**Geriatric Assessment:**
1) Functional status
   - IADL (3 items)
   - MOS Physical (4 items)
   - MD-rated KPS
   - Timed Up & Go
   - Falls in Last 6 Months
2) Comorbidities
   - Liver/Kidney disease
   - Hearing Impairment
3) Cognition
   - B-OMC ≥ 6
4) Psychological
   - HADS (4 items)
5) Social Functioning
   - MOS Social Activity (2 items)
6) Nutrition
   - Unintentional weight loss
   - BMI ≤ 26.5
Predictors of Toxicity

- Age ≥ 72 years
- GI or GU Cancer
- Standard Dose
- Poly-chemotherapy
- Hemoglobin (male: <11, female: <10)
- Creatinine Clearance (Jelliffe-ideal wt <34)
- Fall(s) in last 6 months
- Hearing impairment (fair or worse)
- Limited in walking 1 block (MOS)
- Assistance required in medication intake (IADL)
- Decreased social activity (MOS)
## Predictive Model

<table>
<thead>
<tr>
<th>Risk factors for Gr. 3-5 Toxicity</th>
<th>OR (95% CI)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 72 yrs</td>
<td><strong>1.8 (1.2-2.7)</strong></td>
<td>2</td>
</tr>
<tr>
<td>GI/GU cancer</td>
<td><strong>2.2 (1.4-3.3)</strong></td>
<td>2</td>
</tr>
<tr>
<td>Standard dose</td>
<td><strong>2.1 (1.3-3.5)</strong></td>
<td>2</td>
</tr>
<tr>
<td>Poly-chemotherapy</td>
<td><strong>1.8 (1.1-2.7)</strong></td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin (male: &lt;11, female: &lt;10)</td>
<td><strong>2.2 (1.1-4.3)</strong></td>
<td>3</td>
</tr>
<tr>
<td>Creatinine Clearance (Jelliffe – ideal wt) &lt;34</td>
<td><strong>2.5 (1.2-5.6)</strong></td>
<td>3</td>
</tr>
<tr>
<td>1 or more falls in last 6 months</td>
<td><strong>2.3 (1.3-3.9)</strong></td>
<td>3</td>
</tr>
<tr>
<td>Hearing impairment (fair or worse)</td>
<td><strong>1.6 (1.0-2.6)</strong></td>
<td>2</td>
</tr>
<tr>
<td>Limited in walking 1 block (MOS)</td>
<td><strong>1.8 (1.1-3.1)</strong></td>
<td>2</td>
</tr>
<tr>
<td>Assistance required in medication intake</td>
<td><strong>1.4 (0.6-3.1)</strong></td>
<td>1</td>
</tr>
<tr>
<td>Decreased social activity (MOS)</td>
<td><strong>1.3 (0.9-2.0)</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Possible score range: **0-23**
Model Performance: Prevalence of Toxicity by Score

ROC: 0.72
Model Performance: Goodness of fit

Median score (Range): 8 (0-21)
MD-rated KPS vs. Predictive Model

Chi-square test $p=0.19$

Chi-square test $p<.0001$
Internal Validation:
The 10-fold Cross Validation

- Predictive Model (total risk score as predictor):
  - ROC (original) = 0.72
  - Average ROC (validation) = 0.72 (Range: 0.62-0.84)
Conclusions

Among older adults receiving chemotherapy:

- Grade 3-5 toxicity is common (53%)
- A predictive model was developed to stratify risk of toxicity
- Specific GA variables independently predicted risk of toxicity

Limitations

- Several tumor types
- Treatment per MD discretion
  - Heterogeneous treatment regimens
Ongoing Directions

- Externally validate model
  - 250 patient validation study
- Specific tumor types
  - Breast Cancer Adjuvant (R01)
  - Cooperative Group - Alliance (CALGB) Studies
    - Acute Leukemia (Klepin/Ritchie)
    - Colon Cancer (Jackson)
    - Breast Cancer (Hurria)
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