Prediction of treatment toxicity

#MASCC18 Workshop – Prognostication in Patients with Advanced Cancer

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Albury, Australia
Treatment toxicity – What treatments?

• Surgery
• Radiotherapy
• Systemic therapy
  • Chemotherapy
  • Molecularly Targeted Agents eg oral tyrosine kinase inhibitors
  • Immunotherapy
  • Hormonal therapy - androgen deprivation, progestogens, antioestrogen
  • Radiolabelled molecules eg Radium-223, Lutate therapy.

• Supportive care measures eg bisphosphonates
Predicting treatment toxicity – What toxicities?
• Early vs late
• “Grade 3-4”?
• Lower grade toxicities that threaten QOL and independence
• Common and reversible
• Uncommon and catastrophic/lethal
• Reversible vs permanent (eg neuropathy)
• Asymptomatic and irrelevant eg hypertension
• Toxicity as a predictor of response?
• Clinician assessment vs patient reported
• Unplanned hospitalisation
Predicting treatment toxicity – Methods?

• Fitness
• Frailty
• Predictive models of toxicity depending on treatment modality.
• “Host factors” – comorbidities
• Genomic markers of metabolism
Cancer is a disease of older adults – NIH data

SEER 18 2007-2011, All Races, Both Sexes

Figure 7.2: Cancer burden (DALY), by age and cancer type, 2011

Source: AIHW Burden of Disease Database.

What is GERIATRIC ASSESSMENT?

DOOMAINS TO ASSESS

- mental health
- cognition
- nutrition
- social support
- fatigue
- functional status
- polypharmacy
- co-morbidity

01 Identifies deficits not otherwise detected.
02 Optimizes non-oncologic domains.
03 Increases the precision of prognostication.
04 Influences chemotherapy intensity.
05 Improves chemotherapy tolerance.
(Comprehensive) Geriatric Assessment

- Mental health
- Cognition
- Nutrition
- Social support

- Fatigue
- Functional status
- Polypharmacy
- Co-morbidity

**IMPACT IN ONCOLOGY**

1. **Identifies** deficits not otherwise detected.
2. **Optimizes** non-oncologic domains.
3. **Increases** the precision of prognostication.
4. **Influences** chemotherapy intensity.
5. **Improves** chemotherapy tolerance.

*Slide courtesy of Camilla Wong*
Utility of Comprehensive Geriatric Assessment in Older Adults with Cancer

Risk Prediction
- Chemotherapy Toxicity
- Survival

Cancer Treatment Modification
- Modification of treatment/chemotherapy
- Modification of supportive care

Intervention
- General Geriatrics vs. Cancer-focused
- Goals

Slide courtesy of Tanya Wildes
FRAILTY

A STATE WITH HIGH VULNERABILITY TO ADVERSE HEALTH CARE OUTCOMES
FRAILTY
A STATE WITH HIGH VULNERABILITY TO ADVERSE HEALTH CARE OUTCOMES
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log (Hazard ratio)</th>
<th>Frailty or pre-frailty</th>
<th>Fit</th>
<th>Hazard ratio</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>Total</td>
<td>Total</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1.1.1 30 day post-operative mortality (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kristjansson 2012</td>
<td>0.98207847</td>
<td>0.46351139</td>
<td>75</td>
<td>21</td>
<td>2.67 (1.03, 6.62)</td>
</tr>
<tr>
<td>Kristjansson 2012</td>
<td>0.84586827</td>
<td>0.33835321</td>
<td>80</td>
<td>21</td>
<td>2.33 (1.20, 4.52)</td>
</tr>
<tr>
<td>1.1.3 6 month mortality (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pils 2011</td>
<td>1.5060716</td>
<td>1.1306676</td>
<td>47</td>
<td>38</td>
<td>4.51 (0.49, 41.38)</td>
</tr>
<tr>
<td>1.1.5 5 year mortality (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clough-Gorr 2012</td>
<td>0.62953843</td>
<td>0.16253235</td>
<td>146</td>
<td>514</td>
<td>1.87 (1.36, 2.57)</td>
</tr>
<tr>
<td>1.1.8 10 year mortality (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clough-Gorr 2012</td>
<td>0.58388511</td>
<td>0.11513048</td>
<td>146</td>
<td>514</td>
<td>1.74 (1.39, 2.18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log (Odds ratio)</th>
<th>Frailty or pre-frailty</th>
<th>Fit</th>
<th>Odds ratio</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>Total</td>
<td>Total</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1.2.1 Severe post-operative complications (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kristjansson 2012</td>
<td>1.16032092</td>
<td>0.32930695</td>
<td>75</td>
<td>21</td>
<td>3.19 (1.68, 6.04)</td>
</tr>
<tr>
<td>1.2.2 Poor treatment tolerance (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clough-Gorr 2012</td>
<td>1.58105841</td>
<td>0.40654259</td>
<td>106</td>
<td>230</td>
<td>4.86 (2.10, 10.78)</td>
</tr>
<tr>
<td>1.2.3 Grade 3-5 chemotherapy toxicity (frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pils 2011</td>
<td>0.27750174</td>
<td>0.66269948</td>
<td>47</td>
<td>38</td>
<td>1.32 (0.36, 4.84)</td>
</tr>
<tr>
<td>1.2.4 Grade 3-5 chemotherapy toxicity (Pre-frailty)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pils 2011</td>
<td>0.3074647</td>
<td>0.67923159</td>
<td>27</td>
<td>38</td>
<td>1.38 (0.36, 5.15)</td>
</tr>
</tbody>
</table>


FRAILTY IS ASSOCIATED WITH MORTALITY AND POOR TREATMENT TOLERANCE
PREDICTING TOXICITY

Cancer and Aging Research Group (CARG) Chemo-Toxicity Calculator
Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 72</td>
<td>2</td>
</tr>
<tr>
<td>GI or GU cancer</td>
<td>2</td>
</tr>
<tr>
<td>Chemotherapy dosing, standard dose</td>
<td>2</td>
</tr>
<tr>
<td>Polychemotherapy</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin &lt; 11 g/dL</td>
<td>3</td>
</tr>
<tr>
<td>CrCl (&lt; 34 ml/min)</td>
<td>3</td>
</tr>
<tr>
<td>Hearing, fair or worse</td>
<td>2</td>
</tr>
<tr>
<td>≥ 1 fall in last 6 months</td>
<td>3</td>
</tr>
<tr>
<td>IADL: needs help with meds</td>
<td>1</td>
</tr>
<tr>
<td>Somewhat limited walking 1 block</td>
<td>2</td>
</tr>
<tr>
<td>Decreased social activity because of health</td>
<td>1</td>
</tr>
</tbody>
</table>

**CARG Chemo-Toxicity Calculator**

*Geriatric variables increase the predictive precision*

Slide courtesy of Camilla Wong
CARG Chemo-Toxicity Calculator

Geriatric variables increase the predictive precision

Slide courtesy of Camilla Wong
CARG Chemo-Toxicity Calculator
Geriatric variables increase the predictive precision

Slide courtesy of Camilla Wong

Mr PL

- 81yo
- Metastatic NSCLC
- Pleural effusion – failed VATS pleurodesis.
- TTF1+, EGFR WT, ALK -
- Lives at home with supportive wife
- Mobile but but needs to walk with frame.
- Recent falls
Mr PL

- Standard of care is combination platinum-based chemotherapy eg carboplatin gemcitabine or carboplatin and paclitaxel
- Single agent chemotherapy (eg gemcitabine or vinorelbine is an option)
- However, further testing reveals

PD-L1 = 100%

**DIAGNOSIS:**

Pleural biopsy: Poorly differentiated adenocarcinoma. in keeping with a lung primary.

**SUPPLEMENTARY REPORT: (24/10/17)**

The PD-1 immuno stain (Ventana, clone SP263) shows positive membranous staining in 100% of the tumour cells.
# CARG Chemo-Toxicity Calculator

Geriatric variables increase the predictive precision

## Prediction Tool

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Patient's Age</td>
<td>81</td>
</tr>
<tr>
<td>Patient's Height</td>
<td>Centimeters</td>
</tr>
<tr>
<td>Patient's Weight</td>
<td>Kilograms</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Other</td>
</tr>
<tr>
<td>Dosage</td>
<td>Standard</td>
</tr>
<tr>
<td>Number of chemotherapy agents</td>
<td>Poly-chemo therapy</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥11 g/dL</td>
</tr>
<tr>
<td>Hearing (with hearing aid)</td>
<td>Fair</td>
</tr>
<tr>
<td>Number of falls in the last 6 months</td>
<td>1 or more</td>
</tr>
<tr>
<td>Can you take your own medicines?</td>
<td>With some help</td>
</tr>
<tr>
<td>Does your health limit you in walking one block?</td>
<td>Limited a lot</td>
</tr>
<tr>
<td>During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?</td>
<td>Most of the time</td>
</tr>
<tr>
<td>Select Serum Creatinine</td>
<td>0.7</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>70</td>
</tr>
</tbody>
</table>

**Submit**

Toxicity Score: 15
Risk of Chemotherapy Toxicity: 92%

**What does this mean?**

* Dose delivered with first dose for chemotherapy
** Jelliffe formula
Grade 3-5 Toxicity

Patient Total Risk Score: 15
Patient Toxicity Risk: 92%
Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer


Table 1. Prediction Model and Scoring Algorithm for Chemotherapy Toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value/Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>≥ 72 years</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt; 72 years</td>
<td>0</td>
</tr>
<tr>
<td>Cancer type</td>
<td>GI or GU cancer</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Other cancer types</td>
<td>0</td>
</tr>
<tr>
<td>Planned chemotherapy dose</td>
<td>Standard dose</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dose reduced upfront</td>
<td>0</td>
</tr>
<tr>
<td>Planned No. of chemotherapy drugs</td>
<td>Polychemotherapy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Monotherapy</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; 11 g/dL (male), &lt; 10 g/dL (female)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥ 11 g/dL (male), ≥ 10 g/dL (female)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine clearance (Jelliffe, ideal weight)</td>
<td>&lt; 34 mL/min</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥ 34 mL/min</td>
<td>0</td>
</tr>
<tr>
<td>How is your hearing (with a hearing aid, if needed)?</td>
<td>Fair, poor, or totally deaf</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Excellent or good</td>
<td>0</td>
</tr>
<tr>
<td>No. of falls in the past 6 months</td>
<td>≥ 1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Can you take your own medicine?</td>
<td>With some help/unable</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Without help</td>
<td>0</td>
</tr>
<tr>
<td>Does your health limit you in walking one block?</td>
<td>Somewhat limited/limited a lot</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Not limited at all</td>
<td>0</td>
</tr>
<tr>
<td>During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?</td>
<td>Limited some of the time, most of the time, or all of the time</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Limited none of the time or a little of the time</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: See Huerta et al.2
Abbreviation: GI, gastrointestinal; GU, genitourinary.
Retrospective review  
\(n = 120\)  
Recruited over 12 months 2011-12.  
Age \(> 65\) years  
Scheduled to received chemotherapy

Risk score predicts grade 3-5 toxicity better than KPS in this retrospective review

- But how do we use it in practice?
- What is the cut-off for combination therapy?
CRASH Score

Geriatric variables increase the predictive precision

Cancer 2012;118:3377-86.

https://www.moffitt.org/efoms/crashscoreform
Predicting the Risk of Chemotherapy Toxicity in Older Patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score

Martine Extermann, MD1; Ivette Boler, ARNP1; Richard R. Reich, PhD1; Gary H. Lyman, MD2; Richard H. Brown, MD3; Joseph DeFelice, MD4; Richard M. Levine, MD5; Eric T. Lubliner, MD5; Pablo Reyes, MD6; Frederic J. Schreiber III, MD5; and Lodovico Balducci, MD1

- n=518
- Patients ≥ 70 years (Mean age 75.5)
- Severe toxicity in 64% pts
- Grade 4 haem tox in 32%
- Grade 3-4 non haem tox in 56%

Patient on chemotherapy. We demonstrated that patient differences contribute 2 to 3 times more than chemotherapy differences to the risk of toxicity. Our study con-...
CRASH Score
Geriatric variables increase the predictive precision

Cancer 2012;118:3377-86.
Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

Doris L. van Abbema a,b,1, Marjan van den Akker c,d, Maryska L. Janssen-Heijnen e,f, Franchette van den Berkmortel g, Ann Hoeben a, Judith de Vos-Geelen a, Frank Buntinx c,d, Jos Kleijnen c, Vivianne C.G. Tjan-Heijnen a,*

Review of 30 articles from 27 studies in patients aged >65 years

Chemotherapy Intolerance
• Grade 3-5 toxicity
• Unplanned hospitalisation
• Chemotherapy discontinuation
• Chemotherapy dose reduction
• Functional Decline
• “Chemotherapy mortality"
Patient-related factors
- > 1 fall in last 6 months
- Mobility problems
- Poor Performance Status
- Presence of severe comorbidities

Tumour-related factors
- Certain chemotherapy regimens eg platinum, irinotecan
- “polychemotherapy vs monochemotherapy”

Predictors of Toxicity

Review article
Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

# Patient- and tumor-related predictors of chemotherapy intolerance in older patients with cancer: A systematic review

**Objective**
To develop and validate a predictive score for older cancer patients receiving chemotherapy

**Setting**
6 hospitals of the Moffitt Affiliate Research Network (USA)

**Population**
- n = 518 (derivation cohort, N = 331; validation cohort, N = 187)
- Patients aged ≥70 years

**Exclusion**
Planned concomitant radiation therapy, dementia, and aplasia-inducing chemotherapy

**Design**
Prospective cohort study

**Measurement times**
Patients were followed throughout the chemotherapy to a maximum of 1 month after the last cycle. If chemotherapy was continued beyond 6 months, follow-up was ended at 6 months.

**Predictors used**
- Demographics; nutrition; diastolic blood pressure; comorbid conditions; polypharmacy; quality of life; performance status; functional status; mood; tumor stage; bone marrow invasion; prior chemotherapy; tumor response; chemotherapy toxicity risk score; laboratory values

**Outcome measurement**
Non-hematologic chemotherapy toxicity grades 3–4 and hematologic chemotherapy toxicity grade 4

**Items in the instrument**
- Model for hematologic toxicity: diastolic blood pressure ≥72 mm Hg; impaired IADL; lactate dehydrogenase ≥0.74 times the upper limit of normal; MAX2 score
- Model for non-hematologic toxicity: poor performance status; impaired cognition; malnutrition or at risk for malnutrition; MAX2 score

**Area under the ROC curve**
- ROC non-hematologic toxicity = 0.76; ROC hematologic toxicity = 0.66; ROC for hematologic toxicity and non-hematologic toxicity = 0.65

**Cancer and Aging Research Group (CARG)**
To identify risk factors for chemotherapy toxicity in older cancer patients and develop a risk stratification score for chemotherapy toxicity

7 outpatient oncology practices (USA)

N = 500

Patients aged ≥65 years, scheduled to receive a new chemotherapy cycle

No fluent English

Prospective cohort study

- Age, cancer type, chemotherapy dose, number of chemotherapy agents, Karnofsky performance status, functional status, falls in the last 6 months, nutrition, chronic liver or kidney disease, hearing problems, housework, number of medications, decreased social activity because of health or emotional problems, limited social activity, laboratory values (white blood cell, red blood cell, hemoglobin, albumin)

Chemotherapy toxicity grades 3–5

- Age ≥72 years; gastrointestinal or genitourinary cancer; standard chemotherapy dosing; polychemotherapy; hemoglobin <11 g/dL in male and <10 g/dL in female; creatinine clearance of 34 mL/min; hearing impairment; ≥1 falls in last 6 months; walking limited to 1 block; decreased social activity because of physical or emotional health; requiring some help in taking medications

ROC = 0.72

---

Geriatric assessment and chemotherapy toxicity

- 13/411 publications met criteria
- 49-64% of older patients experience ≥ grade 3 toxicity
- No consistency found amongst GA criteria for chemotherapy toxicity.

Toxicity due to
- Polychemotherapy
- Nutritional status
- Poor function
- Comorbidities

GA revealed new (unknown) geriatric issue in >50% patients
- Dose modification in 21-53% patients.
Geriatric Assessment and chemotherapy toxicity

• 49-64% of older patients experience ≥ grade 3 toxicity

• But clinical value of these numbers is unclear as:
  1. Grade 3-4 haematological toxicity often not relevant
  2. Lower grade non-haematological toxicity is of clinical importance eg fatigue and neuropathy.

No consistency was found amongst geriatric assessment criteria for chemotherapy toxicity.
Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study

- 71 patients age >70yrs
- Multidimensional geriatric assessment
- Vulnerable population
  - 74% scoring impaired on the objective physical performance
  - 30% screening positive for cognitive impairment
  - 36% having > 3 comorbidities.
Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study

Allison Magnuson¹ · Tatyana Lemelman² · Chintan Pandya¹ · Molly Goodman¹ · Marcus Noel¹ · Mohammed Tejani¹ · David Doughtery¹ · William Dale³ · Arti Hurria⁴ · Michelle Janelins¹ · Feng Yankee Lin¹ · Charles Heckler¹ · Supriya Mohile¹

- 71 patients age >70yrs
- Multidimensional geriatric assessment
- Including the CARG score for prediction of grade 3-5 toxicity
- Predicted toxicity of 58-60%
- Observed toxicity 57-61%

Toxicity based upon CARG chemotherapy score

The baseline CARG chemotherapy toxicity score was used to evaluate the likelihood of chemotherapy toxicity for each patient and averaged for each arm [9, 11]. The average CARG chemotherapy toxicity score for the usual care arm was 8.06, with a mean likelihood of toxicity of 58%. Compared to the anticipated toxicity of 58%, observed toxicity in the usual care arm was 61% ($p = 0.56$). The average CARG chemotherapy toxicity score for the intervention group was 8.78, with a mean likelihood of toxicity of 60%. Compared to the anticipated toxicity of 60%, observed toxicity in the intervention group was 57% ($p = 0.55$).
Study underpowered to detect a difference between the 2 arms.

Uptake of guided interventions was 35.4%
Patients over the age of 70yrs with solid tumours

N = 301

Undergoing chemotherapy

Geriatric assessment prior
53.8% of patients experienced grade ≥ 3 toxicity.

Risk factors:
- Serum protein <6.7g/dL
- Initial full dose chemotherapy
- Psychological stress or acute disease in last 3 months
- Water consumption <3 cups/day
- Unable to obey simple command
- Self perception of poor health
Chemotherapy Toxicity Risk Score (CTRS)

- n= 51 patients aged ≥65yrs
- Patients given chemotherapy (standard or reduced dose)
- Clinician blinded to result

Figure 1. Ability of the chemotherapy toxicity risk score (CTRS) to predict chemotherapy toxicity. (A): Three CTRS categories, low (0 to 5 points), medium (6 to 9 points), or high risk (10 to 19 points), versus toxicity risk. (B): Two CTRS categories, low and medium risk combined (0 to 9 points) or high risk (10 to 19 points), versus toxicity risk.
CTRS ≥ 10 = high risk
CTRS < 10 = non-high risk

Table 5. Comparison of toxicity outcomes between concordant and discordant treatment decisions

<table>
<thead>
<tr>
<th>Chemotherapy choice</th>
<th>Risk score</th>
<th>Gr 3–4 AEs, %</th>
<th>p value</th>
<th>Hospitalization, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard therapy</td>
<td>≥10 (n = 16)</td>
<td>88</td>
<td>.006</td>
<td>50%</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>&lt;10 (n = 20)</td>
<td>40</td>
<td></td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Reduced therapy</td>
<td>≥10 (n = 11)</td>
<td>55</td>
<td>1.00</td>
<td>27%</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>&lt;10 (n = 8)</td>
<td>50</td>
<td></td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

The bold-italic values show statistically significant differences (p < .05).
Abbreviations: AEs, adverse events; Gr, grade.
## Life Expectancy

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>18.3</td>
<td>21.5</td>
</tr>
<tr>
<td>70</td>
<td>14.5</td>
<td>17.3</td>
</tr>
<tr>
<td>75</td>
<td>11.1</td>
<td>13.4</td>
</tr>
<tr>
<td>80</td>
<td>8.2</td>
<td>9.9</td>
</tr>
<tr>
<td>85</td>
<td>5.9</td>
<td>7.1</td>
</tr>
</tbody>
</table>
Geriatric oncology 2

Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer

Enrique Soto-Perez-de-Celis*, Daneng Li*, Yuan Yuan, Yat Ming Lau, Arti Hurria

Figure 4: Selected life expectancy calculation tools for community-dwelling older people\textsuperscript{60,69}
www.eprognosis.org
Combined Lee Schonberg Index

- Population: Community dwelling adults aged 50 and older
- Outcome: All cause 4, 5, 10 and 14 year mortality

Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).

Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67.57% female, 81% white, 12% 4-year mortality)
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
Schonberg Scale: 11 items

- Age
- Sex
- Smoking
- BMI
- Prior cancer
- Diabetes

- COPD
- Hospitalizations in the past 12 mths
- Self-rated health
- Dependent in 1+ IADL
- Difficulty walking a few blocks (1/4 mile)
<table>
<thead>
<tr>
<th>Points</th>
<th>Risk of FIVE YEAR mortality</th>
<th>Risk of TEN YEAR mortality</th>
<th>Risk of FOURTEEN YEAR mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>&lt;3%</td>
<td>5 - 11%</td>
<td>19 - 21%</td>
</tr>
<tr>
<td>2 - 3</td>
<td>3 - 6%</td>
<td>9 - 12%</td>
<td>19 - 24%</td>
</tr>
<tr>
<td>4 - 5</td>
<td>7 - 8%</td>
<td>15 - 21%</td>
<td>27 - 36%</td>
</tr>
<tr>
<td>6 - 7</td>
<td>10 - 12%</td>
<td>26 - 37%</td>
<td>42 - 52%</td>
</tr>
<tr>
<td>8 - 9</td>
<td>17 - 27%</td>
<td>37 - 44%</td>
<td>42 - 52%</td>
</tr>
<tr>
<td>10 - 11</td>
<td>26 - 29%</td>
<td>53 - 60</td>
<td>74 - 78%</td>
</tr>
<tr>
<td>12 - 13</td>
<td>37 - 41%</td>
<td>60 - 68</td>
<td>81 - 83%</td>
</tr>
<tr>
<td>14 - 15</td>
<td>47 - 52%</td>
<td>74 - 76</td>
<td>87 - 88%</td>
</tr>
<tr>
<td>16 - 17</td>
<td>60 - 61%</td>
<td>86 - 87</td>
<td>100%</td>
</tr>
<tr>
<td>≥17</td>
<td>70%</td>
<td>92%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Non-chemotherapy?
Q: What are the risks of serious adverse events in patients on treatment that is not chemotherapy?

– MTA’s – Molecularly Targeted Agents

(NB This is 2008 so pre-immunotherapy)
MTA’s

EGFR inhibitors
VEGFR inhibitors
Proteosome inhibitors
Cyclin dependent kinases
RAF, multikinases
mTOR
Nomograms to Predict Serious Adverse Events in Phase II Clinical Trials of Molecularly Targeted Agents

**Predictors**
- ECOG
- Age
- Comorbidities
- LDH
- Albumin
- Disease burden
- Creatinine (not CrCl?)
- BSA = dose?

**Table 3. Predictors via Multivariate Analysis of Cycle 1 Dose-Limiting Toxicities**

<table>
<thead>
<tr>
<th>Predictors of all SAEs</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status</td>
<td>1.91</td>
<td>1.36 to 2.69</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age/10-year increase</td>
<td>0.90</td>
<td>0.78 to 1.05</td>
<td>.181</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.18</td>
<td>0.94 to 1.49</td>
<td>.158</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>0.79</td>
<td>0.56 to 1.11</td>
<td>.176</td>
</tr>
<tr>
<td>No. of target lesions</td>
<td>1.06</td>
<td>0.98 to 1.14</td>
<td>.161</td>
</tr>
<tr>
<td>log (LDH ULN)</td>
<td>1.39</td>
<td>1.03 to 1.88</td>
<td>.030</td>
</tr>
<tr>
<td>Albumin ULN</td>
<td>0.13</td>
<td>0.02 to 0.93</td>
<td>.043</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictors of attributable SAEs</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status</td>
<td>1.37</td>
<td>1.01 to 1.88</td>
<td>.046</td>
</tr>
<tr>
<td>Body-surface area</td>
<td>0.27</td>
<td>0.10 to 0.70</td>
<td>.007</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.20</td>
<td>0.98 to 1.48</td>
<td>.079</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>0.72</td>
<td>0.46 to 1.14</td>
<td>.164</td>
</tr>
<tr>
<td>log (LDH ULN)</td>
<td>1.23</td>
<td>0.93 to 1.63</td>
<td>.152</td>
</tr>
<tr>
<td>Creatinine ULN</td>
<td>2.91</td>
<td>1.14 to 7.44</td>
<td>.026</td>
</tr>
<tr>
<td>No. of prior systemic chemotherapy regimens</td>
<td>1.21</td>
<td>0.91 to 1.60</td>
<td>.184</td>
</tr>
</tbody>
</table>

*J Clin Oncol 26:1324-1330.*
Nomograms to Predict Serious Adverse Events in Phase II Clinical Trials of Molecularly Targeted Agents

Fig 1. (A) Nomogram for predicting any serious adverse event during cycle 1. (B) Nomogram for predicting any attributable serious adverse event during cycle. Abbreviations: ULN, upper limit of normal; LDH, lactate dehydrogenase; RT, radiation therapy; BSA, body-surface area.
Lower CrCl associated with increased grade 3/4 toxicities of MTA’s in phase 1 trials
Immunotherapy?

- Immune-checkpoint blockade
- Tumor-targeting monoclonal antibodies
- Adoptive cell transfer
- Immunostimulatory cytokines
- Anticancer vaccines
- Immunogenic cell death inducers
Physiological changes of ageing by organ system:
www.thelancet.com/oncology Vol 19 June 2018

CNS
- Cortical volume
- Synaptic density
- Processing speed
- Attention
- Memory

Respiratory system
- Elastic recoil
- Lung volume
- Ventilation-perfusion inequality

Liver
- Volume
- Blood flow
- First-pass metabolism
- Drug clearance

Cardiovascular system
- Cardiac output
- Arterial stiffness
- Heart rate modulation
- Myocardial hypertrophy
- Impaired endothelial function
- Conduction abnormalities

Kidneys
- Renal mass
- Glomerular filtration
- Drug clearance
- Hydration of renal vasculature

Digestive system
- Acid secretion
- Drug absorption

Bone
- Bone mineral density
- Fracture risk

Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer

Immune checkpoint blockade (ICB) toxicities

Endocrine
- Hyper or hypothyroidism
- Hyperparathyroidism
- Adrenal insufficiency
- Diabetes

Respiratory
- Pneumonitis
- Pulmonary sarcoïd-like granulomatosis

Cardiovascular
- Myocarditis
- Pericarditis
- Vasculitis

Gastrointestinal
- Colitis
- Inflammatory bowel disease
- Gastritis

Neurologic
- Neuropathy
- Guillain-Barré syndrome
- Malignant hypoamylase
- Encephalitis
- Myasthenia

Musculoskeletal
- Arthritis
- Dermatomyositis

Blood
- Hemolytic anemia
- Thrombocytopenia
- Neutropenia
- Hemophilia
Decreased ability to cope with toxicity
Not necessarily increased incidence of autoimmunity
Autoimmune disease and ipilimumab

Research

Original Investigation

Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Douglas B. Johnson, MD; Ryan J. Sullivan, MD; Patrick A. Ott, MD, PhD; Matteo S. Carlino, MBBS; Nikhil I. Khushalani, MD; Fei Ye, PhD; Alexander Guminski, MD, PhD; Igor Puzanov, MD; Donald P. Lawrence, MD; Elizabeth I. Buchbinder, MD; Tejaswi Mudigonda, BS; Kristen Spencer, DO; Carolin Bender, MD; Jenny Lee, MBBS; Howard L. Kaufman, MD; Alexander M. Menzies, MBBS; Jessica C. Hassel, MD; Janice M. Mehnert, MD; Jeffrey A. Sosman, MD; Georgina V. Long, MBBS; Joseph I. Clark, MD

IMPORTANCE
Ipilimumab and other immune therapies are effective treatment options for patients with advanced melanoma but cause frequent immune-related toxic effects. Autoimmune diseases are common, and the safety and efficacy of ipilimumab therapy in patients with preexisting autoimmune disorders is not known.

OBJECTIVE
To determine the safety and efficacy of ipilimumab therapy in patients with advanced melanoma with preexisting autoimmune disorders.

DESIGN, SETTING, AND PARTICIPANTS
Retrospective review of patients with advanced melanoma and preexisting autoimmune disorders who received ipilimumab at 9 academic tertiary referral centers from January 1, 2012, through August 1, 2015. The data analysis was performed on August 24, 2015.

EXPOSURE
Ipilimumab therapy.

MAIN OUTCOMES AND MEASURES
Safety, in terms of frequency of autoimmune flares and conventional immune-related adverse events (irAEs), and efficacy, in terms of response rates and overall survival, were evaluated descriptively.

RESULTS
Of the 30 patients who received ipilimumab (17 [57%] male; median [range] age, 59.5 [30-80] y), 6 had rheumatoid arthritis, 5 had psoriasis, 6 had inflammatory bowel disease, 2 had systemic lupus erythematosus, 2 had multiple sclerosis, 2 had autoimmune thyroiditis, and 7 had other conditions. Thirteen patients (43%) were receiving immunosuppressive therapy at the time of initiation of ipilimumab therapy, most commonly low-dose prednisone or hydroxychloroquine. With ipilimumab treatment, 8 patients (27%) experienced exacerbations of their autoimmune condition necessitating systemic treatment; all were managed with corticosteroids. Conventional grade 3 to 5 irAEs occurred in 10 patients (33%) and were reversible with corticosteroids or with infliximab therapy in 2 cases. One patient with baseline psoriasis died of presumed immune-related colitis after a 1-week delay prior to reporting symptoms. Fifteen patients (50%) had neither autoimmune disease flares nor irAEs. Six patients experienced an objective response (20%), including 1 with a durable complete response.

CONCLUSIONS AND RELEVANCE
To our knowledge, this is the largest series of patients with preexisting autoimmune disease treated with immune checkpoint inhibitors. Ipilimumab was clinically active and was associated with exacerbations of autoimmune disease and conventional ipilimumab-induced irAEs that were readily manageable with standard therapies when started in a timely fashion. Ipilimumab therapy may be considered in this setting with vigilant clinical monitoring.

AID and ipilimumab

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)a (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>59.5 (30-80)</td>
</tr>
<tr>
<td>Autoimmune disorderb</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Crohn disease or ulcerative colitis</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Prior systemic therapies for autoimmune disorder</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>22 (73)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Disease-modifying antirheumatic</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Ongoing therapies</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Time since autoimmune diagnosis, median (range), y</td>
<td>13.5 (0.25-60)</td>
</tr>
</tbody>
</table>

- 27% AID flare
- 33% conventional irAEs
- Toxicities resolved quickly with standard Rx
- Several patients with IBD had low-grade flares, responded to steroids
- ORR 20%

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab


Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity

Ralf Gutzmer, Anika Koop, Friedegund Meier, Jessica C. Hassel, Patrick Terheyden, Lisa Zimmer, Lucie Heinzerling, Selma Uğurel, Claudia Pföhler, Anja Gesierich, Elisabeth Livingstone, Imke Satzger, Katharina C. Kähler, for the German Dermatooncology Group (DeCOG)
Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab

N = 52

<table>
<thead>
<tr>
<th>AI disordera</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic</td>
<td>27 (52%)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

Activity of AI disorder at PD1 start

- Not clinically active | 37 (71%)
- Clinically active | 15 (29%)

Treatment of AI disorder at PD1 start

- No immunosuppresion | 32 (62%)
- Corticosteroids | 9 (17%)
- Steroid-sparing agent | 5 (10%)
- Steroids and SSAs | 5 (10%)
- IVIG | 1 (2%)

RA 13, sarcoidosis 3, PMR 3, SLE 2, scleroderma 2, psoriatic arthritis 2, Sjogren’s 2, psoriasis 6, eczema, erythema nodosum CD 3, UC with colectomy 2, celiac disease 1 GBS 2, CIDP 1, MG 1, Bell’s palsy 1 Graves’ disease 4 Asthma 2 (1 severe on long-term oral steroids) ITP 2

11 rheumatologic (RA 5, psoriatic arthritis 2, Sjogrens 2, sarcoidosis 1, PMR 1), 3 psoriasis, 1 severe asthma

Mesalazine 2, leflunomide, hydroxychloroquine, apremilast Sulfasalazine, leflunomide, hydroxychloroquine, methotrexate, ibuprofen
Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity

Ralf Gutzmer a,*, Anika Koop a, Friedegund Meier b, Jessica C. Hassel c, Patrick Terheyden d, Lisa Zimmer e, Lucie Heinzerling f, Selma Ugurel e, Claudia Pföhler g, Anja Gesierich h, Elisabeth Livingstone e, Imke Satzger a, Katharina C. Kähler i, for the German Dermatooncology Group (DeCOG)

N=19
## AID and PD-1 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Menzies et al.</th>
<th>Gutzmer et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>Active</td>
<td>29%</td>
<td>n/a</td>
</tr>
<tr>
<td>On IS</td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td>Flare (discontinuation)</td>
<td>38% (4%)</td>
<td>42% (0)</td>
</tr>
<tr>
<td>Other irAEs (discontinuation)</td>
<td>29% (8%)</td>
<td>16% (0)</td>
</tr>
<tr>
<td>ORR</td>
<td>33%</td>
<td>32%</td>
</tr>
</tbody>
</table>

- Rheumatologic, skin conditions flare often (~50%). GI, neuro seldom.
- More likely to flare if AID active or on IS at PD1 start
- Lower ORR if on IS at PD1 start
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Timeline for toxicity from ipilimumab

- Rash, pruritus
- Liver toxicity
- Diarrhoea, colitis
- Hypophysitis

Toxicity grade

Time (weeks)
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Circles represent medians; bars signify ranges.

Combination ipilimumab + nivolumab:
Single agent nivolumab:
Supportive care in cancer. Which bridge would you rather cross?