Assessing Older Adults with Cancer: Understanding Functional vs. Chronological Age

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Cancer is a Disease Associated with Aging

60% of cancer occurs in people ≥ age 65

CDC, Morbidity and Mortality Weekly Report 2013
GU Cancer and Aging

Bladder
Kidney & Renal Pelvis
Prostate

< 65
> 65

SEER 18 2007-2011
US Population Age ≥ 65 (millions)

Largest growth in 2010:

Shift in 2030:
Largest growth in the 80+ age groups
Projected Rise in Cancer Incidence from 2010 to 2030

- 67% in patients 65+
- 11% in patients <65

Smith et al, J Clin Oncol, 2009
The Population is Aging

The Number of Older Adults With Cancer is on the Rise

Are we prepared?
Few Patients Older Adults on NCI Trials
No Change Over Time
The Older Patient: Key Questions Not Addressed

- Do we need to treat the cancer?
  - Who will die of disease vs. with disease?
- If we treat, who is vulnerable to toxicity?
- How to modify therapy based on:
  - their organ function
  - their functional status
  - their cognitive status
  - their social situation
Aging

- Heterogeneous process
- Characteristic universal changes in physiology
- Affects each individual at a unique pace
- Depletion of physiologic reserve
Hallmark of Aging: Decreased Physiologic Reserve

Physiologic Reserve = Fuel Available
Determining Eligibility for Cisplatin

Methods:

- Survey of 120 oncologists specializing in urothelial cancer
- Review of published literature on ineligibility for cisplatin

Consensus definition of unfit patients for cisplatin-based therapy:

- WHO/ECOG PS of 2
- CrCl < 60 mL/min
- Grade ≥ 2 hearing loss (~25 db)
- Grade ≥ 2 peripheral neuropathy
- NYHA class III heart failure

Age alone should not be used to classify unfit patients in clinical trials

Galsky, Lancet Oncol, 2011
Key Organ Function Considerations in Urothelial Cancer

- Renal Function
- Cardiovascular Changes
- Neuropathy
- Ototoxicity
- Bone Marrow Toxicity
### Decline in Organ Function Not Obvious

Renal Function Decreases with Aging

<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine (mg/dL)</th>
<th>CrCl* (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1.4</td>
<td>79</td>
</tr>
<tr>
<td>50</td>
<td>1.4</td>
<td>71</td>
</tr>
<tr>
<td>60</td>
<td>1.4</td>
<td>63</td>
</tr>
<tr>
<td>70</td>
<td>1.4</td>
<td>55</td>
</tr>
<tr>
<td>80</td>
<td>1.4</td>
<td>47</td>
</tr>
<tr>
<td>90</td>
<td>1.4</td>
<td>39</td>
</tr>
<tr>
<td>100</td>
<td>1.4</td>
<td>32</td>
</tr>
</tbody>
</table>

Creatinine: Not an adequate measure of renal function
## Calculating Creatinine Clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cockroft &amp; Gault Jeliffe</strong></td>
</tr>
<tr>
<td>Commonly used</td>
</tr>
<tr>
<td>Not validated in older adults</td>
</tr>
<tr>
<td><strong>MDRD</strong></td>
</tr>
<tr>
<td>More accurate in pts with chronic renal disease</td>
</tr>
<tr>
<td>Ethnicity, BUN, &amp; albumin are taken into account</td>
</tr>
<tr>
<td><strong>Wright</strong></td>
</tr>
<tr>
<td>Accurate in patients with GFR &gt; 50</td>
</tr>
</tbody>
</table>

None are perfect
All are better than creatinine alone

*Hurria & Lichtman, BJC 2008*
Cardiovascular Disease and Aging

- Hypertension
  - Most common comorbid condition in older adults
  - 50-70% prevalence in age 65+

- Heart failure
  - Most common cause of hospitalization in age 65+
  - Evaluate ejection fraction
  - Avoid fluid overload
  - Careful monitoring of I’s/O’s
Decline in Organ Function Becomes Apparent with a Stressor

Older Heart: Poorer Response to Stress
Decreased Maximum Heart Rate with Aging

Maximum HR = 208 – (0.7 x age)

Tanaka, JACC 2001
Neurological Considerations with Platinum

- Neuropathy
  - Risk is associated with cumulative dose
  - Worsens in 30% after treatment is discontinued

- Ototoxicity
  - Systematic hearing loss 20%
  - Audiometric hearing loss 75%
Hearing Loss with Aging

- Presbycusis: “older hearing”

![Bar chart showing percentage of hearing loss with aging.](Nash, Arch Otolaryngol Head Neck Surg 2011)
Bone Marrow and Aging

- Bone marrow reserve decreases with age
- Majority of death and serious infection occur in the 1st cycle
- NCCN guidelines:
  - Empiric growth factor for chemo of CHOP like intensity
- ASCO guidelines:
  - Empiric growth factor if febrile neutropenia rate > 20%
  - Older patients: population at risk

Gomez et al. JCO, 1998
Ozer et al. JCO, 2000
NCCN Guidelines® Myeloid Growth Factors, v2.2014
Smith et al. JCO, 2006
Chronological Age ≠ Functional Age

- Aging is heterogenous
- The aging trajectory is modifiable
- A hallmark of aging: decline in organ reserve
  - May not be obvious at rest
  - Becomes apparent with a stressor

Chemotherapy is a physiologic stressor that can unmask the decline physiologic reserve
Advanced Urothelial Cancer

“Unfit”:  
- Impaired renal function (GFR 30-60 mL/min)  
- Performance status of 2

Randomize

N=119  
GC  
(Gemcitabine/Carboplatin)  
Median Age: 70 (36-87)

N=119  
M-CAVI  
(Methotrexate/Carboplatin/Vinblastine)  
Median Age: 72 (34-86)

De Santis, J Clin Oncol, 2009
**EORTC Study 30986**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Complete/Partial Response</th>
<th>Overall Survival</th>
<th>Severe Acute Toxicity</th>
<th>Toxic Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>41.2%</td>
<td>9.3 mo.</td>
<td>9.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>M-CAVI</td>
<td>30.3%</td>
<td>8.1 mo.</td>
<td>21.2%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

**Conclusion:**
- No difference in response or survival
- Decreased side effects with GC
- PS of 2 + GFR < 60 ml/min:
  - 20% only received 1 cycle of tx
  - 26% experienced severe toxicity

More clinical trials are needed

*De Santis, J Clin Oncol, 2009*
Age 80 with High Risk GU Cancer:
What treatment will you recommend?
The Ultimately Efficient Clinic

- Vitals Taken
- Patient in Gown
- Sitting on Exam Table
What is old?

65
Integrating Geriatrics into Oncology

Factors other than chronological age that predict morbidity & mortality in older adults

- Functional status
- Comorbid medical conditions
- Nutritional status
- Cognition
- Psychological state
- Social support
- Medications (polypharmacy)

Geriatric Assessment
Developing a Geriatric Assessment for Oncologists

- **Functional Status:**
  - Activities of Daily Living (subscale of MOS Physical Health)
  - Instrumental Activities of Daily Living (subscale of the OARS)
  - Karnofsky Performance Rating Scale
  - Timed Up & Go
  - Number of Falls in Last 6 Months

- **Comorbidity:** Physical Health Section (subscale of the OARS)

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

- **Validity**
- **Reliability**
  - Length
  - Time to complete
  - Ability to self-administer
  - Multidisciplinary input
  - Alliance Cancer in Elderly Committee
Can Geriatric Assessment Predict Chemo Toxicity? (CARG)

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

- Timepoint 1:
  - Pre-chemo Geriatric Assessment

- Timepoint 2:
  - Post-chemo Geriatric Assessment
  - Chemotherapy: toxicity grading at each visit

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

Hurria et al, JCO 2011
Predictors of Toxicity

- Age ≥ 72 years
- GI/GU Cancer
- Standard Dose
- Polychemotherapy
- 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)

Hurria et al, JCO 2011
Risk of Toxicity by Score

- **Low (30%)**
  - 0-3: 25%
  - 4-5: 32%

- **Medium (52%)**
  - 6-7: 50%
  - 8-9: 54%

- **High (83%)**
  - 10-11: 77%
  - 12-19: 89%

*Hurria et al, JCO 2011*
MD-rated KPS vs. Predictive Model

Chi-square test $p=0.19$

Chi-square test $p<.0001$

Hurria et al, JCO 2011
Next Steps

- All Tumor Types: Validation Study
  - N=250; Completed Accrual

- Disease-Specific
  - Breast: Adjuvant Therapy (Dr. Hurria)
  - Ovarian: First Line Age ≥ 70 (Dr. VonGreunigan)
  - Breast: Endocrine Therapy +/- Bevacuzimab (Dr. Dickler)
  - Breast: Taxanes in Metastatic Breast Cancer (Dr. Rugo)
  - AML: First Line Age ≥ 60 (Dr. Klepin/Dr. Ritchie)
  - CLL: First Line Age ≥ 65 (Dr. Woyach)
  - GI: First Line Age ≥ 75 (Dr. McCleary)
The Past: Risk Factors for Chemotherapy Toxicity

- **Patient Factors**
  - Age
  - ECOG PS/KPS
  - Labs

- **Tumor and Treatment Factors**
  - Cancer Type
  - Chemotherapy
### The Present:
Geriatric Assessment Items Predictive of Chemotherapy Toxicity

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Aaldriks</th>
<th>Aparicio</th>
<th>Extermann</th>
<th>Freyer</th>
<th>Hurria</th>
<th>Kanesvaran</th>
<th>Soubeyran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Activities (ADL &amp; IADLs)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hearing (Fair or Deaf)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cognition</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychological Status</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Social Activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Aaldriks et al, Crit Rev Oncol Hematol 2011  
Aparicio et al, J Clin Oncol 2013  
Extermann et al, Cancer 2012  
Freyer et al, Annals of Oncology 2005  
Hurria et al, J Clin Oncol 2011  
Kanesvaran et al, J Clin Oncol 2011  
Soubeyran et al, J Clin Oncol 2012
- Predict toxicity to cancer treatment
- Predict survival of older patients with cancer
- Uncover problems not detected by routine H&P
- Leads to practical interventions

Is it feasible to incorporate these tools into oncology practice?
Geriatric Assessment is Feasible

CALGB 360401 (PI: Hurria)

Primarily self-administered (Paper/Pencil)

Eligibility Criteria
- Age 65 or older
- Diagnosis of cancer
- To start treatment on a cooperative group clinical trial

Pre-chemo Geriatric assessment Feasibility data

Treatment and follow-up per protocol

Geriatric Assessment is Feasible in Oncology Trials
(Time to Complete: Median 22 min.)

Hurria et al, JCO 2011
Geriatric Assessment Questions are Acceptable to Patients

92% Length is “Just Right"

95% Easy to comprehend
96% Not upsetting

87% Completed patient questionnaire w/o assistance

94% Completed healthcare provider portion

Hurria et al, JCO 2011
Facilitating Quality Cancer Care

Everyone Completes a Geriatric Assessment

Approximately 20 min. later
Facilitating Quality Cancer Care

Information Provided to the Healthcare Team

- Geriatric Assessment Results
- List of Potential Interventions
- Chemotherapy Toxicity Risk Score is Generated

<table>
<thead>
<tr>
<th>GA Results</th>
<th>Potential Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional Weight Loss</td>
<td>- Nutritional Consult</td>
</tr>
<tr>
<td>Fall Risk</td>
<td>- Rehabilitation</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>- Pharmacy Consult</td>
</tr>
<tr>
<td>Limited Social Support</td>
<td>- Social Work</td>
</tr>
<tr>
<td></td>
<td>- Life Line</td>
</tr>
</tbody>
</table>
Facilitating Quality Cancer Care

Facilitates Communication and Decision-Making Between the Oncologist and Patient
PREDICTION TOOL

Gender: 
Select

Patient's Age: 

Patient's Height
Select the Unit of Measure:
Select

Patient's Weight:
Select the Unit of Measure:
Select

Submit

Creatinine Clearance:
44 **
Toxicity Score:
10
Risk of Chemotherapy Toxicity:
72%

What does this mean?

* Dose delivered with first dose for chemotherapy
** Jeliffe formula

http://www.mycarg.org/mctc
Chronological Age 80

Functional Age 90

Functional Age 60
Conclusions

- The population is aging
- Cancer is a disease associated with aging
- Aging is a heterogeneous process
- Organ function declines with aging
- “Chronological age” $\neq$ “functional age”
- Clinical trials in older adults are needed
  - Requires a melding of geriatric and oncology principles
Thank you!