Therapeutic choices and medical decision-making: Geriatric Oncology Perspective

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I have no financial disclosures
I will not discuss off label use and/or investigational use in my presentation
Session Objectives

1. Recognize the cardiac toxicities of cancer therapies specific to the geriatric population
2. Identify cancer treatment-specific considerations in the geriatric population
3. Recognize the need for a multidisciplinary approach to older cancer patients both during treatment and in surveillance
Estimated and Projected Number of Cancer Survivors in the U.S. From 1975 to 2040

- 1975, 3.6 M
- 2016, 15.5 M
- 2040, 26.1 M

Signifies the year at which the first baby boomers (those born 1946-1964) turned 65 years old.
Assessing the geriatric oncology patient

- Oncologists face uncertainty when making management decision for older adults
- Gap in literature:
  - Clinical trials primarily enroll healthy individuals with few comorbidities
  - Frail older adults are typically treated in community oncology practices
Framework around the care of older patients with cancer

- ASCO, NCCN, ISGO, American Geriatrics Society
- Framework:
  1. Determining age related vulnerabilities
  2. Consider the benefits and harms of cancer treatments in light of this vulnerability
  3. Consider patient values, preferences and trade-offs
     - (prolonging survival while minimizing treatment burden and toxicity)
Chronological age vs. functional age

What does being elderly mean?

- Elderly is a subjective cultural concept that varies from culture to culture, depending on a mixture of health-related, social and economic factors.
- In industrialised societies, 70 years old is a standard cut-off point used to define elderly; however, in other, poorer or more traditional societies, a lower age may be more appropriate (such as 65, 60 or even 55).
- Chronological age and functional age can differ greatly from person to person.

In geriatric oncology, it is functional age that determines management – and therefore a great deal of effort is dedicated to accurately evaluating and maintaining functionality during treatment.
Aging is a heterogeneous process

Not all “young persons” are healthy and functional

Not all “elderly persons” are sick and dependent

Age cut-off exists to promote awareness, not to determine management!

The aging process – Impact on organs and systems

Heart: Decreased heart rate, decreased responsiveness to adrenergic stimuli, increased afterload

Brain: Neuronal loss, changes in synaptic function, hyperactivation of microglial cells

Immune system: Reduced immune response to aggressors

Lungs: Decreasing lung volumes and maximal rates of airflow; decreasing forced vital capacity; decreased diffusing capacity

Kidney: Increasing renal cortical loss; progressive decrease in glomerular filtration rate and renal blood flow

The end result = Increased risk of acute illness and of complications during cancer treatment
The aging process – Frailty

Frailty is a state of increased vulnerability to stress, which increases the risk of adverse outcomes during cancer treatment.

It is very important to note that risk factors for frailty include psychological and social issues, such as being in a minority ethnic group, being unmarried or being depressed.

Reprinted from The Lancet, Vol. 381, Issue 9866, Clegg A. et al., Frailty in elderly people, 752-762, Copyright 2013, with permission from Elsevier.
Comprehensive Geriatric Assessment – Principles

Comprehensive Geriatric Assessment (CGA) should be the standard form of evaluation and follow-up for elderly patients before and during cancer treatment.

CGA can be defined as “multidimensional interdisciplinary diagnostic process focused on determining a frail older person’s medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up.”

It identifies problems that are not identified by routine patient history and physical examination.
## Comprehensive Geriatric Assessment

<table>
<thead>
<tr>
<th>Domains</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional status</td>
<td>Eastern Cooperative Oncology Group performance status, Kalz basic Activities of Daily Living Scale, Simplified Lawton's Instrumental Activities of Daily Living Scale</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Charlson comorbidity index</td>
</tr>
<tr>
<td>Medications</td>
<td>Number, type, indication</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Folstein Mini-Mental State Examination, Schultz-Larsen Mini-Mental State Examination</td>
</tr>
<tr>
<td>Geriatric syndrome</td>
<td>Repeated falls, fecal and/or urinary incontinence</td>
</tr>
<tr>
<td>Depression/mood</td>
<td>Geriatric Depression Scale 5, Emotional questionnaire</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Body mass index</td>
</tr>
<tr>
<td>Mobility</td>
<td>Timed Up and Go test</td>
</tr>
<tr>
<td>Situational assessment</td>
<td>Accessibility of services, mobility, social environment, accessibility of home rooms</td>
</tr>
</tbody>
</table>
### Comparison of 4 tools for evaluation of frailty

#### All tools predict 1-year mortality

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. (%) of Patients</th>
<th>No. (%) of Events</th>
<th>( \beta^* )</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlucci</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>97 (12.9)</td>
<td>11 (11.3)</td>
<td>(&lt; .001, &lt; .001)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Vulnerable</td>
<td>113 (14.9)</td>
<td>31 (27.4)</td>
<td></td>
<td>1.91 (0.96 to 3.86)</td>
</tr>
<tr>
<td>Frail</td>
<td>544 (72.2)</td>
<td>278 (61.1)</td>
<td></td>
<td>2.94 (1.69 to 5.24)</td>
</tr>
<tr>
<td>SIOG1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>147 (19.5)</td>
<td>19 (12.9)</td>
<td>(&lt; .001, &lt; .001)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Vulnerable</td>
<td>234 (31.1)</td>
<td>66 (28.2)</td>
<td></td>
<td>1.75 (1.03 to 2.97)</td>
</tr>
<tr>
<td>Frail</td>
<td>286 (37.9)</td>
<td>167 (58.4)</td>
<td></td>
<td>3.31 (2.00 to 5.50)</td>
</tr>
<tr>
<td>Too sick</td>
<td>87 (11.5)</td>
<td>68 (78.2)</td>
<td></td>
<td>6.12 (3.45 to 10.85)</td>
</tr>
<tr>
<td>SIOG2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>134 (17.8)</td>
<td>11 (8.2)</td>
<td>(&lt; .001, &lt; .001)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Vulnerable</td>
<td>112 (14.8)</td>
<td>29 (25.0)</td>
<td></td>
<td>2.03 (1.02 to 4.22)</td>
</tr>
<tr>
<td>Frail</td>
<td>508 (67.4)</td>
<td>261 (65.3)</td>
<td></td>
<td>3.69 (1.97 to 6.86)</td>
</tr>
<tr>
<td>LC tylosity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatively healthy</td>
<td>227 (30.1)</td>
<td>27 (11.9)</td>
<td>(&lt; .001, &lt; .001)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Malnourished</td>
<td>252 (33.4)</td>
<td>110 (43.6)</td>
<td></td>
<td>2.15 (1.34 to 3.47)</td>
</tr>
<tr>
<td>Cognitively and/or mood impaired</td>
<td>103 (13.7)</td>
<td>44 (42.7)</td>
<td></td>
<td>2.66 (1.54 to 4.61)</td>
</tr>
<tr>
<td>Globally impaired</td>
<td>172 (22.8)</td>
<td>139 (60.8)</td>
<td></td>
<td>4.84 (2.82 to 8.31)</td>
</tr>
</tbody>
</table>

Consideration for the Geriatric Oncology patient

Box 2: Summary of a Minimum Data Set for Practical Assessment of Vulnerabilities in Older Patients With Cancer

See Table 1 for more details and rationale.

1. Predict chemotherapy toxicity (if clinically applicable): Cancer and Aging Research Group or Chemotherapy Risk Assessment Scale for High-Age Patients tool
2. Estimate (noncancer) life expectancy (if clinically applicable): ePrognosis
3. Functional assessment: instrumental activities of daily living
4. Comorbidity assessment: medical record review or validated tool
5. Screening for falls, one question: how many falls or falls with an injury have you had in the previous 6 months (or since your last visit)?
6. Screening for depression: Geriatric Depression Scale or other validated tool
7. Screening for cognitive impairment: Mini-Cog or Blessed Orientation-Memory-Concentration test
8. Screening for malnutrition: weight loss/body mass index
Consider benefits of cancer treatment

1. Evaluate whether the patient’s cancer will cause symptoms in their remaining lifetime
   - Aggressiveness of the cancer vs noncancer life expectancy
2. If cancer is likely to affect a patient during their remaining lifetime, what evidence is there regarding beneficial treatments?
Consider harms of cancer treatment in older adults

- Variation in harms of cancer therapies
  - i.e. local surgery, large abdominal surgery, intensity of chemotherapy, stereotactic radiation

- Other considerations:
  - Time in infusion center away from home and family
  - Financial implications

- From this information, oncologists decide 1. adjust treatment decisions? 2. prescribe appropriate interventions for GA deficits
Toxicities of chemotherapy

The Cancer and Aging Research Group (CARG) Chemotoxicity Risk Score

<table>
<thead>
<tr>
<th>Risk Factors for Grade 3-5 Toxicity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI/genitourinary cancer</td>
<td>3</td>
</tr>
<tr>
<td>Standard dose chemotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Low hemoglobin level:</td>
<td></td>
</tr>
<tr>
<td>&lt;11 g/dL for men and &lt;10 g/dL for women</td>
<td>3</td>
</tr>
<tr>
<td>Low creatinine clearance (based on Jelliffe equation): &lt;34 mL/min per 1.73 m²</td>
<td>3</td>
</tr>
<tr>
<td>1 or more falls in last 6 months</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt;/=73 years</td>
<td>2</td>
</tr>
<tr>
<td>Polychemotherapy</td>
<td>2</td>
</tr>
<tr>
<td>Fair or worse hearing</td>
<td>2</td>
</tr>
<tr>
<td>Limited ability to walk one block</td>
<td>2</td>
</tr>
<tr>
<td>Assistance needed with medications</td>
<td>1</td>
</tr>
<tr>
<td>Decrease in social activity</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: Possible score range: 0-25. Risk: 0-5 = low risk, 6-11 = intermediate risk, 12+ = high risk.

Considering values, preferences and trade-offs

Each clinician is focused on treating his individual conditions.

Is this what Mr. K wants?
Minimizing undertreatment vs overtreatment

- What are your treatment options from an oncology perspective?
SAFE HEaRt trial

- Stage 1-4 her2 positive breast cancer
- Her2 based therapy
- LVEF 40-49%, no symptoms of HF
- All patients underwent:
  - Cardiology visit
  - Serial echo
  - Received BB, ACEI
- Primary endpoint: completion of her2 directed therapy without cardiac event (HF, MI, arrhythmia, or cardiac death or symptomatic worsening LVEF)

Lynce F, Barac A. Breast Cancer Res Treat 2019
Other considerations

• Caregivers and culture
  ◦ Real life decision making is embedded in social context
  ◦ Shared decision making studies rarely have included underrepresented minorities
  ◦ Decision making: predominant leader, single individual, single group
Psychology, cognitive biases and informed consent

### TABLE 2. Selected Biases to Avoid in Decision Making Involving Older Adults With Cancer

<table>
<thead>
<tr>
<th>Bias Name</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affect heuristic</td>
<td>A decision overly influenced by emotion and not logic can occur in scenarios with time-sensitive decisions</td>
<td>An older patient anxious over new diagnosis of AML immediately opts for intensive treatment, fearing the effects of the cancer without carefully evaluating treatment benefits and harms</td>
</tr>
<tr>
<td>Ageism</td>
<td>Attitudes or stereotypes on the basis of a person’s age</td>
<td>Not recommending a beneficial treatment for an older patient on the basis of age alone (a form of undertreatment)</td>
</tr>
<tr>
<td>Anchoring</td>
<td>Adhering to an initial choice despite new evidence supporting an alternative</td>
<td>Continuing to recommend intensive chemotherapy in a frail older adult despite minimal response and evidence of toxicity</td>
</tr>
<tr>
<td>Availability</td>
<td>Estimating the probability of an event on the basis of a readily available case that may not be representative</td>
<td>Recommending radical prostatectomy in all older adults with prostate cancer because of one case of early metastasis in a patient who chose active surveillance</td>
</tr>
<tr>
<td>Framing</td>
<td>Decision is influenced by the way facts are presented, not by the facts themselves</td>
<td>Selectively emphasizing the harms of a treatment and minimizing its benefits</td>
</tr>
</tbody>
</table>

Abbreviation: AML, acute myeloid leukemia.

DuMontier et al, JCO 2021
FIG 1. Framework for decision-making in older adults with cancer. *Current toxicity calculators exist for chemotherapy only. For surgical risks, consider the ACS NSQIP Surgical Risk Calculator, which was recently updated to include outcomes for older adults.** ASC, American College of Surgeons; CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High Age Patients; NSQIP, National Surgical Quality Improvement Program.

- Use of personalized calculators encouraged
  - Include geriatric assessment variables recommended by ASCO guidelines
  - In the United States, use the Law-Schomberg Index for 4-, 5-, 10-, and 14-year mortality

- Estimate noncancer-specific life expectancy
- Estimate likelihood of treatment effectiveness
- Estimate likelihood of treatment toxicity

(a) Was my patient represented in studies looking at treatment effectiveness?
(b) Do treatment benefits vary by age-related factors?
(c) Is the studied outcome relevant for my patient?

Disease-specific calculators and nomograms

Geriatric assessment-based chemotherapy toxicity calculators

CRASH, Chemotherapy Risk Assessment Scale for High Age Patients

Other outcomes may be more important than survival

- Quality of life
- Cognition
- High treatment burden and toxicity

Quality of life

- Functional status
- Quality of life
- Cognition
- High treatment burden and toxicity

Perform a geriatric assessment on the basis of recommendations from the ASCO Guideline for Geriatric Oncology

- Function: Instrumental activities of daily living
- Falls: Number of falls in last 6 months
- Comorbidity: Three or more chronic conditions
- Depression: Geriatric depression scales
- Nutrition: Unintentional weight loss > 10%
- Cognition: Cognitive screening tools
Case examples

- 72 y/o female with T4N1 colon cancer treated with hemicolecotomy
- Age related vulnerabilities:
  - BMI 24, independent ADLs and IADLs, cognitively intact, walks independently with an aid, comorbidities (htn, dm, former smoker)
- Estimated noncancer survival: 70-74% at 5 years, 40-47% 10 years
- Adjuvant chemotherapy options:
  - CAPOX 3 months 5yr DFS 65.4%, FOLFOX 6 months 63.4%, 5FU alone, Capecitabine alone 57.8%, no treatment: 45.8%
- CARG toxicities: neuropathy grade 3-5 44-59%
- Pt is concerned about intensity of treatment impacting QOL but has a fear of recurrence and is willing to accept some toxicity for a goal of complete remission
Second example
Controlling risk factors

Odds of congestive heart failure with cardiovascular risk factor cluster, anthracycline exposure, or both

Relative excess risk due to interaction between anthracyclines and HTN = 44.5


Anthracyclines, Trastuzumab

Age >60
Diabetes
Hypertension
Atrial Fibrillation
Coronary Artery Disease
Summary and Future Directions

- Oncologists face uncertainty when making management decisions for older adults.
- Incorporating geriatric assessments into clinical practice can improve overall care of the older oncology patient.
- There is a need to build the underlying evidence base around the care of the older oncology patient:
  - Clinical trials primarily enroll healthy individuals with few comorbidities.
  - Frail older adults are typically treated in community oncology practices.
  - More diverse individuals are needed in cancer clinical trials.
Minnesota's Cancer Center

Masonic Cancer Center

University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute

Minnesota’s Cancer Center
Risk factors for cardiotoxicity
Anthracyclines, Trastuzumab

- Anthracyclines
- Anthracyclines + Trastuzumab
- Trastuzumab
- Non-anthracycline, non-trastuzumab

Age >60
Diabetes
Hypertension
Atrial Fibrillation
Coronary Artery Disease

Thavendiranathan et al, JCO May 2018
Figure 1. Unadjusted Kaplan-Meier failure curves and adjusted hazard ratios (HR) for overall mortality (first panel) and cumulative incidence function, cause-specific HR (csHR) and subdistribution HR (sHR) for CVD-related mortality (second panel) among a population-based sample of breast cancer survivors and age-matched women without breast cancer. The Long Island Breast Cancer Study, 1996-2009.

Bradshaw et al, Epidemiology 2016
Risk Predication Models for Cardiotoxicity in Breast Cancer

- NSABP – B31 - Phase 3 adjuvant trial of 1830 breast cancer patients, node positive
- Adriamycin and Cytoxan followed by paclitaxel plus/minus trastuzumab
- At 7 year follow-up:
  - Paclitaxel: 1.3% CE
  - Paclitaxel plus trastuzumab: 4%
- Modeled the cardiac event rate up to five years after AC
- In the model, age and baseline LVEF were predictors

Romond EH et al, JCO 2012
#1 – NSABP B-31: Predicted Probability of Cardiac Event (CE) at Year 5 by CRS

age 65 years
LVEF = 55%
CRS = 86.1
Risk of CE = 13%
Trastuzumab prediction models

- Risk prediction model of cardiac toxicity using SEER/Medicare
- Using a split-sample design, they used a proportional hazards model to identify candidate predictors of HF/CM in a derivation cohort.
- Overall risk score 0-9 summed
- Grouped into low, middle and high risk strata:
  - Low < 20% incidence (<3 points)
  - Middle 20-39% (4-5 points)
  - High > 40% (>6 points)
### Cox Regression Coefficients and Point Assignment for Each Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>Regression Coefficient</th>
<th>P Value</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant therapy</td>
<td>1.93 (1.11 to 3.36)</td>
<td>0.66</td>
<td>0.020</td>
<td>2</td>
</tr>
<tr>
<td>Anthracycline chemotherapy</td>
<td>1.64 (0.99 to 2.73)</td>
<td>0.50</td>
<td>0.055</td>
<td>2</td>
</tr>
<tr>
<td>Non-anthracycline chemotherapy</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No identified chemotherapy</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age category, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67 to 74</td>
<td>Reference</td>
<td>Reference</td>
<td>0.125</td>
<td>1</td>
</tr>
<tr>
<td>75 to 79</td>
<td>1.36 (0.92 to 2.01)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 to 94</td>
<td>2.04 (1.29 to 3.24)</td>
<td>0.71</td>
<td>0.003</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular conditions and risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.16 (1.21 to 3.86)</td>
<td>0.77</td>
<td>0.009</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>1.69 (0.98 to 2.91)</td>
<td>0.53</td>
<td>0.058</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.50 (1.03 to 2.18)</td>
<td>0.41</td>
<td>0.034</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.44 (0.99 to 2.08)</td>
<td>0.36</td>
<td>0.054</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.99 (0.96 to 4.14)</td>
<td>0.69</td>
<td>0.065</td>
<td>2</td>
</tr>
</tbody>
</table>

*Source: Ezaz et al. Journal of the American Heart Association 2014*
#3 – Ontario Administrative CRS for Early-Stage Breast Cancer

- Women age 18-105 years old diagnosed with early-stage breast cancer (stages I-III) from 1/1/03-12/31/14 (n=90,104)
- Ontario, Canada resident, eligible for Ontario Health Insurance Plan (OHIP) coverage for at least 1 year before breast cancer diagnosis
- Outcome: MACE = composite of hospitalizations for acute MI, unstable angina, TIA, stroke, peripheral vascular disease, and HF, and deaths from circulatory disease

Abdel-Qadir et al. European Heart Journal 2019
## Risk Score

<table>
<thead>
<tr>
<th>Select age category</th>
<th>Select past medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>Heart failure</td>
</tr>
<tr>
<td>40–44 years</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>45–49 years</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>50–54 years</td>
<td>Hypertension</td>
</tr>
<tr>
<td>55–59 years</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>60–64 years</td>
<td>Diabetes</td>
</tr>
<tr>
<td>65–69 years</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>70–74 years</td>
<td>COPD</td>
</tr>
<tr>
<td>75–79 years</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>≥80 years</td>
<td>Total score</td>
</tr>
</tbody>
</table>
Ontario Administrative CRS: Proportion of patients at each value of the risk score, and predicted risk of MACE at 5 and 10 years

Score=25:
4.8% risk at 5 y, 10.0% at 10 y

C-index: 81.9% at 5 y
79.8% at 10 y
Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation 1

Which preventative strategies minimize risk before initiation of therapy?

Recommendation 2

What strategies minimize risk during potentially cardiotoxic therapy?

Recommendation 3

What are the preferred surveillance / monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4

What are the preferred surveillance / monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5