THE FUTURE OF CANCER CARE IN THE ELDERLY PATIENT: Personalized Therapy and Targeted Agents Hold Promise

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Learning Objectives:
- Review cancer statistics in the elderly population
- Describe current treatment of common cancers in the elderly population and new targeted agents
- Explain reasons for toxicity of cancer treatments and strategies to improve outcomes

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DISCLOSURE
Research Grants
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Honoraria
Pharmacytics, Cerulean

Off Label Usage
Will discuss investigational agents in clinical trials

Presentation Objectives
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• Describe current treatment of common cancers in the elderly population and new targeted agents
Cancer Statistics In the Elderly

- An aging population
  - 1970: 9.8% > 65 yrs
  - 2010: 13.0% > 65 yrs
  - 2030: 20.0% > 65 yrs (70 million)
- Diagnosis of common cancers is median of 68-74 yrs and median age at death is 70 – 79 yrs.
- Death rates are disproportionally higher in the elderly
- The cost of cancer care in elderly patients is significant, especially with the advent of new targeted agents.
  - Medicare cancer payments about 150 billion in 2010
  - Increasing costs passed to the patient


Why Cancer Develops as We Get Older?

- Longer duration of carcinogenic exposure and susceptibility of aging cells
- Decreased ability to repair DNA
- Oncogene activation and/or decrease in tumor suppressor gene activity
- Telomere shortening and genetic instability
- Microenvironment alterations: increase in IL-6 “the geriatric cytokine”.
- Decreased immune surveillance

How to Assess Suitability/Tolerance for Cancer Therapy?

- Comprehensive Geriatric Assessment
  - Scale developed by Hurria et al. Mostly self reported items, takes about 22 min and 87% can complete without assistance

- Phenotype model
  - Unintentional weight loss, self reported exhaustion, Low energy expenditure, slow gait speed and weak grip strength.
  - Frail: 3/5 factors (7 yr sur 12%)
  - Pre Frail: 1-2 factors (7 yr sur 23%)
  - Not frail: (7 yr survival 43%)


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**Oncologists Assessment of Activity**

<table>
<thead>
<tr>
<th>Karnofsky Status</th>
<th>Karnofsky Grade</th>
<th>ECOG Grade</th>
<th>ECOG Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no complaints</td>
<td>100</td>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>Able to carry on normal activities</td>
<td>80</td>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>60</td>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>Care for self. Unable to carry on normal activity or to do active work</td>
<td>70</td>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about 50% of waking hours</td>
</tr>
<tr>
<td>Require occasional assistance, but able to care for most of his needs</td>
<td>60</td>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about 50% of waking hours</td>
</tr>
<tr>
<td>Require considerable assistance and frequent medical care</td>
<td>50</td>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>Disabled. Requires special care and assistance</td>
<td>40</td>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 53% of waking hours</td>
</tr>
<tr>
<td>Severely disabled. Hospitalization indicated through death non-imminent</td>
<td>30</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>Very sick. Hospitalization necessary</td>
<td>20</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>Moribund</td>
<td>10</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

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**Catgorize patients with CGA**

- Group 1: Functionally independent, no serious comorbidity, standard cancer treatment
- Group 2: Partially dependent, <3 comorbid conditions, limited usual treatment
- Group 3: Dependent, ≥4 comorbid conditions, any geriatric syndrome, palliative treatment
Systemic Chemotherapy and Targeted Agents—How to Dose Patients?

- Inadequate data from clinical trials, thus extrapolate from a younger population.
- Barriers to enrollment:
  - Stringent eligibility criteria (trials now have an average of 49 criteria, travel, expense, caregiver etc).
- Review of 28,000 patients in 55 trials from 1995-2002:
  - Only 36% of trial participants ≥ 65 yrs, (compared with 60% of the population).
  - 9% of trial participants were ≥ 75 yrs, (compared with 31% population).


Age Related Physiologic Changes

- Surgery, radiation and drug therapy affected by decreased functional reserve in every organ.
- Sarcopenia—Loss of strength and muscle
- Changes in skin
- Decreased GI absorption and motility
- Decreased kidney function
- Decreased CNS activity and neuronal loss
- Changes in immune system
- Bone marrow compromise


Dose Adjustment by Age for Cancer Patients

- Current guidelines recommend standard doses during first cycle of chemotherapy for “fit patients” based on chronologic age.
- Patients in practice not the same as in clinical trials.
- Polypharmacy increases the risk of side effects and interactions with the p450 system
  - 234 patients, median age 80 yrs
  - # medications 9.2 (prescription 6.1)
  - 43% took > 10 meds
  - 75% had potential interactions in cycle 1

Nightingale G et al. JCO, 2015:1453-1459
**Decision Making**

- Adjuvant setting (therapy increases "cure rate" by 10-20%)
  - Patient has had a potentially curative surgery and has recovered.
  - What is chronological age and life expectancy?
  - Perform a CGA and therapy if life expectancy > 7-10 years.
- Metastatic Setting
  - Goal is to increase life expectancy (usually months not years) with QOL.

**Breast Cancer in the Elderly**

- 50% develop in women > 65 yrs and 13% >80 yrs.
- More favorable status (ER/PR and Her2/neu +) but women > 75 yrs have a worse outcome.
- Hormonal therapy more likely to be used than systemic chemotherapy
- Targeted agents everolimus, trazatuzumab and pertuzumab better tolerated.


**Colorectal Cancer**

- Median Age is 71 yrs, more likely to present on the right side with anemia.
- Consider palliative colectomy early to prevent obstruction
- Adjuvant therapy is of benefit but elderly less likely to be offered, 30% discontinue prematurely
  - 5 FU remains standard, addition of oxaliplatin (FOLFOX) questionable benefit.
- Targeted agents can be considered (VEGFR and EFGFR agents)

**Lung Cancer**

- Median Age is 70 yrs
- Radiation therapy (SBRT) is a viable option for patients who are medically unfit for surgery
- Chemotherapy has the same benefit in elderly fit patients as younger patients
- Check for EGFR mutations (seen in 25-30% of non smokers, women, Asian) and ALK/ROS translocations
  - EGFR oral agents (erlotinib, afatanib) have impressive single agent activity.


**Acute Myeloid leukemia**

- Median age is 68 yrs and more aggressive in the elderly
- Elderly have more underlying myelodysplastic syndrome
- Standard induction therapy (7+3 regimen) has 10-14% (30 day) mortality in fit patients aged 55-80 yrs
- Bone marrow transplant contradicted.
- Targeted agents increasingly used in the elderly
  - CD33 antibody (Gemtuzumab)
  - Hypomethylating agents (azacitidine)


**Multiple Myeloma**

- Median Age is 70 with 37% > 75 yrs.
- Standard therapy of melphalan/predisione and thalidomide is toxic
- Newer agents such as lenalidomide and pomalidomide are better tolerated.
- Second generation proteosome inhibitor carfilzomib better tolerated in the elderly.

Why we Need Precision Therapy: One Size Does Not Fit All

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effective in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants (SSRIs)</td>
<td>60-65%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>60-65%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>40-50%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer's Drugs</td>
<td>30-35%</td>
</tr>
<tr>
<td>Cancer</td>
<td>20-25%</td>
</tr>
</tbody>
</table>


Personalized Therapies in Cancer

- Steroid receptors: ER+ breast cancer,
- HER2: Breast and gastric cancer
- KRAS: Colon cancer
- EGFR & ALK/ROS for NSCLC
- CD20: Lymphoma
- BCR/Abl: CML
- c-Kit: GIST
- Hedgehog: Basal cell & medulloblastoma
- RET: Medullary thyroid cancer
- B-RAF: Melanoma

The Gold Standard for Targeted Therapy

- Imatinib: Took 3 years. FDA approval in 2001 for treatment of CML
- CML: Incurable disease prior to 2001 Rx with IFN and bone marrow transplant highly toxic
- In phase III trial: OS 88% at 6 years and 95% when CML-related deaths were considered. 66% still receiving drug.
- Annual sales $5 billion/year

Visualization Of Complete Genome By Circos Map

Circos map legend:
- Coverage
- All De Novo changes
- Copy tics
- Somatic synonymous
- Orange tics
- Somatic non synonymous
- Red tics
- Somatic copy number
- Deletion

Actionable Signalling Pathways in Common Solid Tumors

Vascular Endothelial Growth Factor (VEGF) family.

Alvarez RH et al. JCO 2010;28:3366-3379

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**VEGF Inhibitors in Practice**

- No Biomarker used in practice
- VEGF Antibodies (Given IV).
- Arterial TE events increased > 65 yrs
  - Ramucirumab: Gastric and colon
  - Aflibercept: colon


**VEGF Inhibitors in Practice**

- No Biomarker used in practice
- VEGF small molecules (oral agents). Multi-targeted agents. Metabolized by P450 system
- Side effects: GI, rash, HTN, fatigue
  - Sorafenib: HCC, kidney cancer
  - Sunitinib and everolimus: kidney cancer and pancreatic neuroendocrine tumors
  - Axitinib and Pazopanib for kidney cancer


**Epidermal Growth Factor Receptor (EGFR) family.**

Ricardo H. Alvarez et al. JCO 2010;28:3366-3379
**EGFR (EGFR1) Inhibitors**

- **EGFR Antibodies:** Generally safe in the elderly
- **Side effects:** Allergic reactions (cetuximab) and skin toxicity, hypomagnesaemia
- **Not effective in lung or other cancers.**
  - Cetuximab: Colon (Ras wild type only) and advanced H & N cancer
  - Panitumumab: Colon cancer (Ras wild type only)


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**EGFR (EGFR1) Inhibitors**

- **EGFR small Molecules:** metabolized by P450 system
- **Side effects:** rash and pneumonitis
- **Not effective in colon cancer
- **EGFR mutations:** about 2-3% of all lung cancers, higher in non smokers, women and Asians (upto 30-35%)
  - Afatinib: Lung cancer with EGFR mutations
  - Erlotinib: lung cancer with EGFR mutations, pancreas and refractory lung cancer

Wood SL et al. Cancer Treat Rev. 2015 41:361-75

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**Epidermal Growth Factor Receptor (EGFR) family.**

Ricardo H. Alvarez et al. JCO 2010;28:3366-3379
EGFR2 or HER2/neu Inhibitors

- Use only in Her2/neu amplified (IHC or FISH) tumors. About 25% of breast and gastric cancers
- HER2 neu, small molecule
- Lapatinib: breast cancer
- Her2/neu Antibodies (IV agents)
  - Side effects: CHF risk increased in the elderly
    - Trastuzumab: Adjuvant and metastatic breast cancer. Gastric cancer
    - TDM1 and pertuzumab: Breast cancer
    - Trastuzumab and pertuzumab: Neoadjuvant and metastatic breast cancer


The Programmed Cell Death Protein 1 (PD-1) Immunologic Checkpoint.

Postow MA et al. JCO 2015;33:1974-1982

Immune Modulators-PD 1 inhibitors

- "Changing the landscape of Cancer"
- Side effects: "Generally safe in the elderly". Rash, diarrhea, pruritus, fatigue and rare cases of pneumonitis
  - LFTs, endocrine function and respiratory status should be closely monitored.
- Remarkable durable responses in multiple tumor types in refractory patients
  - Pembrolizumab (9/2014): Advanced melanoma
  - Nivolumab: Melanoma and lung cancer

http://mycancergenome.org/content/drug-class/pd-1-inhibition-and-inhibitor
Nature Biotechnology 32, 847–848 (2014)
A Lot More Work to be done

- What are the druggable genes? Most are passenger mutations.
- The most common mutation in cancer is p53. In 40 years of research unable to target P53.
- Targeted therapy often leads to short-lived responses, impact on survival?
- Redundant Pathways: Targeting one pathway is not enough.
- Accuracy: 70% are true positive & true negative.
- Reimbursement, Ethics, & drug approval process.
- Costs associated with gene sequencing: The $1000 genome? But storage and interpretation >$ 30,000.

Molecular Screening and Targeted Therapy

- The goal is to rapidly bring new effective agents to market that significantly improve outcome for patients
- Resistance seen to 1st generation agents, design superior drugs based on mechanisms of resistance
- Efforts ongoing mainly in Academia, but > 80% of patients seen in community
- A broad based screening program possible-SAFIR program in France

Lancet Oncol. 15: 267: 2014

Now We Have Financial Toxicity!!

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1956 - 2015

- [Graph showing the increase in cost of cancer drugs over time]

Source: Peter S. Bach, MD, Memorial Sloan-Kettering Cancer Center
About 100-150 New Agents in Clinical Development- >700 Active Phase I Trials

Garraway L A JCO. 31:1806-1814: 2013

Precision Medicine

How do we get the right drug to the right patient?

Mayo-TGen Platform for Genomic Medicine

Key Points

• Elderly patients have a high cancer burden
• Do not withhold standard therapy to the elderly, but first do comprehensive assessment (CGA etc)
• Chemotherapy for advanced metastatic cancer, especially 3rd line and beyond has little benefit
• Poly pharmacy a hazard, limit drugs
• We are moving away from cytotoxic therapy
• Ask about clinical trials for your patients
Q & A

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