Approche thérapeutique en oncologie:

Le point de vue de l'oncologue

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Background

Background

- Systemic therapy choices are informed by clinical research
- Stringent inclusion criteria in clinical trials restricts entry to those with adequate organ function
- So how do we make good therapeutic decisions with our patients with serious cardiac, renal or hepatic dysfunction

Most patients are trial ineligible

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- 528 consecutive stage 4 NSCLC pts at our institution
- Standard but limited trial eligibility criteria applied:
  - ECOG PS 0/1
  - No CNS disease
  - No second malignancy
  - Renal function <1.5x ULN
- **Only 27% met these criteria**

Al-Baimani et al. WCLC 2015. Abstract 1398

Presented By Al-Baimani et al. WCLC 2015 Abstr

Practice changing trials: Eligibility in organ failure

Practice changing trials: Eligibility in organ failure

Trial	Author	Journal	Year	Renal failure	Liver failure	Heart failure
1st line chemo	Schiller	NEJM	2002	Excluded	Excluded	Unstated
2nd line chemo	Hanna	JCO	2004	Excluded	Excluded	Unstated
Chemo + Bev	Sandler	NEJM	2006	Excluded	Excluded	Excluded
Maintenance	Ciuleanu	Lancet	2009	Excluded	Excluded	Excluded
EGFR+ (gefitinib)	Mok	NEJM	2009	Unstated	Excluded	Unstated
ALK+ (crizotinib)	Shaw	NEJM	2013	Excluded	Excluded	Excluded
Nivolumab	Brahmer	NEJM	2015	Excluded	Excluded	Unstated
Pembrolizumab	Herbst	Lancet	2016	Excluded	Excluded	Unstated

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What is a reasonable approach?

What is a reasonable approach?

- Multi-disciplinary team
- Understand the organ failure
- Understand the impact of organ failure on potential benefits and toxicities of systemic therapy
- Identify reversible issues
- Honest discussion of uncertainty

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Mortality in advanced non-cancer illnesses

Mortality in advanced non-cancer illnesses

- Treatment decisions in advanced illness are difficult:
  - Prognostic uncertainty
  - Lack of evidence of efficacy
- Can we identify factors associated with a high chance of mortality?

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Non-cancer illnesses with prognosis < 6 months

Non-cancer illnesses with prognosis < 6 months

- Heart failure with hospital admission
- Renal failure on dialysis
- COPD with hospital admission
- Decompensated hepatic cirrhosis
- Advanced dementia
- Geriatric failure to thrive

- These presentations, with other poor prognostic features, can predict short median survival
- Malnutrition, advanced age, comorbid illness, poor PS, hospitalization

Salpeter et al. Am J Med 2012

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Cancer and dialysis

The CANDY study (CANcer and DialYsis)

- Multi centre retrospective study
- 178 dialysis patients who developed cancer (13% lung)
- Only 28% received systemic therapy
- Of these, 44% developed '*iatrogenic toxicity*'
- Cancer was the most common cause of death, but still less than half (48%)

Janus et al. Annals of Oncology 2013

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So you decide to go ahead with therapy

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Which drug to pick?

Which drug to pick?

- Close liaison with oncology pharmacist
- Literature review to determine prior experiences
  - Largely limited to case reports
- Heart failure considerations
- Are the drugs metabolized through kidney or liver, or neither?
- Are there cardiac / renal or hepatic toxicities, either direct or indirect?

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Drug	Elimination	Liver	Renal	Dialysis
Cisplatin	Renal	Not applicable	↓ depending on CrCl	50% post HD or non-HD days
Carboplatin	Renal	Not applicable	Calvert Formula	Calvert's formula give on non-HD day
Docetaxel	Liver	Adjust	Not applicable	before or after HD not removed by HD
Pemetrexed	Renal	Caution in severe dysfunction	avoid if CrCl ≤ 45	Avoid
Paclitaxel	Liver	Adjust	Not applicable	not removed by HD
Gemcitabine	Urine (inactive metabolites)	Consider adjustment if Bilirubin > 27	Caution (D/C if HUS)	Give 6-12 hours before HD
Vinorelbine	Liver	Adjust depending on Bilirubin	Not applicable	Limited data Consider 20mg/m2 on non-HD day
Etoposide	Liver/Renal	Adjust depending on Bilirubin	Adjust	50% before or after HD

Janus et al. Ann Onc 2007
Brandes et al. Cancer Invest 2006
Product monographs

Drug	Elimination	Liver	Renal	Dialysis
Gefitinib	Liver	Caution	Caution if CrCl <20	No information
Erlotinib	Liver	Caution	Not applicable	No information
Afatinib	Liver	Caution	Caution if CrCl <30	No information
Crizotinib	Liver	Adjust	Caution if CrCl <30	No information
Ceritinib	Liver	Adjust	Caution if CrCl <30	No information
Bevacizumab	Reticulo-endothelial system	Not involved	Not involved	No information
Nivolumab	Biochemical degradation. No liver or kidney involvement	No effect in mild impairment (not studied in severe)	no effect if CrCl>/= 15mL/min (not studied if less)	No information

Janus et al. Ann Onc 2007
Brandes et al. Cancer Invest 2006
Product monographs

Is there a right to try ?

Is there a right to try?

- Clinical research based on a tenet of patient safety
- Can informed consent with unknown risk override safety concerns?

The Boston Globe

A Case for Taking Risks on Drugs for the Dying, by Ed Silverman – October 2015

Should the regulatory authorities be willing to alter the odds based on the severity of the disease and availability of treatments?

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Discussion and conclusions

Discussion and Conclusion

- This topic is almost an evidence free zone
- As a community we should perform trials in these patients
- Should pharmaceutical companies be mandated to perform studies in these populations?
- Multi-disciplinary approach required
- Understand the prognosis of the non-cancer organ failure
- If you decide to treat, work with your pharmacists
- Open and honest discussion with your patients

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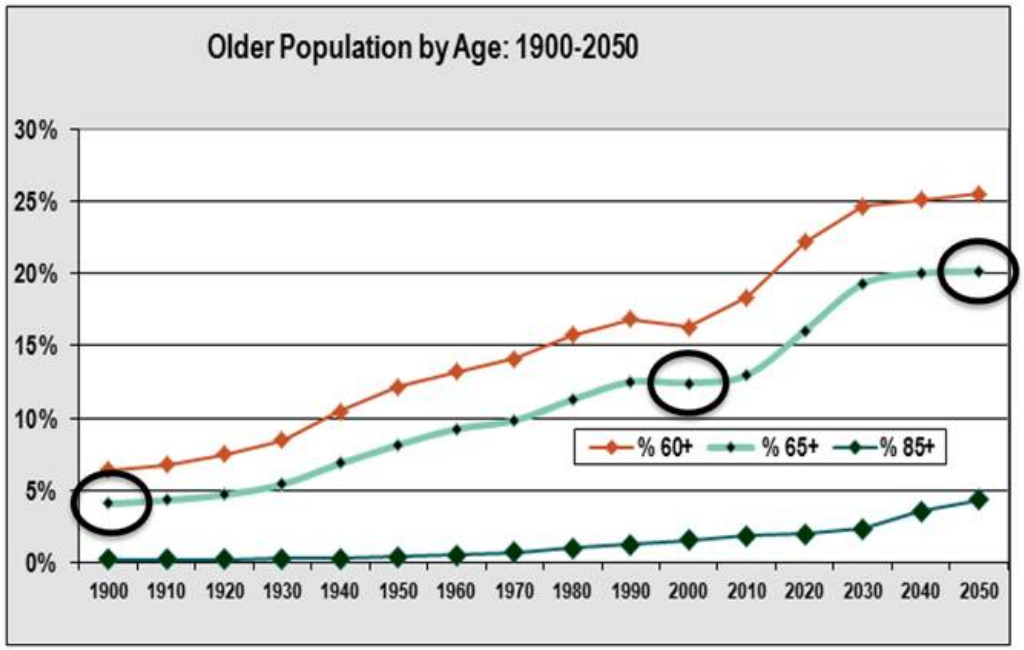
Aging Tsunami

Why we need to rethink the way we deliver hospital care for elders

Presented By William Tse at 2015 ASCO Annual Meeting

Older Adult Population on the Rise

Older Adult Population on the Rise



http://www.aoa.acl.gov/Aging_Statistics/future_growth/future_growth.aspx#age

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Lindsay Peterson at 2015 ASCO Annual Meeting

Dr. Peterson's Cancer Aging and Research Group Addressed Contemporary Realities and Challenges with the U.S. Cancer Burden

American Cancer Society
Estimated New Cancer Cases by Sex and Age (Years), 2014

	All ages	Younger than 45	45 and Older	Younger than 65	65 and Older
All sites, men	855,220	53,990	801,230	370,890	484,340
All sites, women	810,320	87,920	722,400	390,910	419,410
Colon & rectum, men	71,830	3,680	68,150	30,160	41,670
Colon & rectum, women	65,000	3,260	61,740	22,820	42,180
Lung & bronchus, men	116,000	1,690	114,310	38,190	77,810
Lung & bronchus, women	108,210	2,020	106,190	34,410	73,800
Breast, women	232,670	25,500	207,170	133,310	99,360
Prostate	233,000	1,430	231,570	98,010	134,990

Projected cases are based on 1995-2010 incidence rates from 49 states and DC as reported by the North American Association of Central Cancer Registries (NAACCR).
Note: Estimates should not be compared with those from previous years because of ongoing changes in the method for estimating new cancer cases.

American Cancer Society, Surveillance Research, 2014

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Renal Function Declines with Age

Renal Function Declines with Age

Endogenous Creatinine Clearance (Ccr) * by Decade of Life in "Normal" Subjects (n=254) (Adapted from Reference (11))

Age Group (Years)	Mean ± SEM Ccr (ml/min)	Slope of Ccr (ml/min/year)
30–39.9	156 ± 5	+0.67 ± 0,4
40–49.9	145 ± 3	−0.32 ± 0.2
50–59,9	136 ± 2	−0.57 ± 0.2
60–69.9	119 ± 3	−1.24 ± 0.3
70–79.9	107 ± 3	−1.49 ± 0.3
80–89.9	94 ± 6	−3.25 ± 0.7
All ages	130 ± 2	−0.75 ± 0.1

Glasscock R, et al. Ageing and the Glomerular Filtration Rate: Truths and Consequences. Trans Am Clin Climatol Assoc. 2009; 120: 419–428.

Presented By Lindsay Peterson at 2015 ASCO Annual Meeting

Muss et al., Journal of the American Medical Association 2005

Cassidy et al., Journal of Cancer Research and Clinical Oncology 2010

Rocha Lima et al., Cancer 2002 Argiris et al., Journal of Clinical Oncology 2004

Hurria et al., Journal of Clinical Oncology 2011

Hudes et al., New England Journal of Medicine 2007 Quoix et al., Lancet 2011

Older adults are at risk for cancer therapy toxicity

Muss et al., Journal of Clinical Oncology 2007

Zauderer et al., Journal of Geriatric Oncology 2013

Schild et al., Journal of Clinical Oncology 2003 Goldstone et al., Blood 2001

Machtay et al., Journal of Clinical Oncology 2008

Zhu et al., Journal of the American Medical Association 2012

Pinder et al., Journal of Clinical Oncology 2007

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There is little evidence to guide management decisions

There is little evidence to guide management decisions

- Older adults are under-represented on cancer clinical trials

  Example: only 30% of patients on registration trials ≥65 yrs

- Older adults on clinical trials are often not representative of those seen in practice

Clinical trial patients

A patient seen in practice

1.Hurria et al. J Clin Oncol. 2012 June 10; 30 (17): 2036-2037
2. Lewis et al. J Clin Oncol. 2003 April 1; 21 (7): 1383-1389.

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Most older adults are taking multiple medications

Most older adults are taking multiple medications

Data from a pharmacist-led medication assessment among ambulatory seniors[1]

(N=234, mean age 80 years)

Medication variable	Mean (SD) or %
Total number medications	9.23 (4.79)
Prescription medications	6.1 (3.58)
Non-prescription medications	2.76 (2.11)
Excessive polypharmacy (≥10 meds)	43%
Potentially inappropriate medication use (Beers)	40%

1. Nightingale G. et al. *J Clin Oncol* Vol 33, no 13, May 1, 2015

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Polypharmacy increases the risk of drug interactions

Polypharmacy increases the risk of drug interactions

- Prospective pilot[1]
- N=112 (mean age 74)
- Newly diagnosed cancer
- **44%** moderate to severe potential drug problems at baseline

- Retrospective study[2]
- N=244 (median age 75)
- Received chemotherapy
- **75%** potential drug interactions cycle 1
- Level 1 PDI associated with non-hematologic toxicity

1. Puts et al. *Drugs Aging* 2009; 26 (6): 519-36; 2. Popa et al. *J Geriatr Oncol* 2014;5: 307-314.

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Association between renal function and chemotherapy toxicity in older adults with cancer

L. Peterson, A. Hurria, T. Feng, S. Mohile, C. Owusu, H. Klepin, C. Gross, S. Lichtman, A. Gajra, I. Glezerman, V. Katheria, L. Zavala, D. Smith, W. Tew

On Behalf of the Cancer and Aging Research Group

Paul B. Beeson Cancer Development Award in Aging (K23 AG026749-01) - Hurria
American Society of Clinical Oncology Career Development Award - Hurria

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Study Design - Outcomes

Study Design- Outcomes

- Standard outcomes:
  - Progression free survival (primary)
  - Global quality of life (primary)
- Novel outcome: Overall treatment utility (OTU) (composite measure)
  - Good OTU= no evidence of progression, no major treatment affects in terms of toxicity OR patient acceptability
  - Intermediate OTU = either progression or negative treatment effect
  - Poor OTU = progression and major negative treatment effect

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Serum Creatinine and Chemotherapy Toxicity

Serum Creatinine and Chemotherapy Toxicity

	Odds Ratio	P-Value	95% CI
Serum Cr and Toxicity	0.67	0.15	0.37-1.14

Serum creatinine was not associated with odds of toxicity

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Renal Function and Chemotherapy Toxicity (Cockcroft-Gault, Actual Body Weight)

Renal Function and Chemotherapy Toxicity (Cockcroft-Gault, Actual Body Weight)

	Odds Ratio	P-Value	95% CI
Creatinine Clearance and Toxicity	1.12	<0.01	1.04-1.20

For every 10 mL/min decrease in CrCl, the odds of toxicity increased 12%

Presented By Lindsay Peterson at 2015 ASCO Annual Meeting

Merci pour votre attention!

Klik om het opmaakprofiel van de modelondertitel te bewerken