3rd Asia Pacific Oncology Pharmacy Congress

Significant Papers in Geriatric Oncology

Yeoh Ting Ting, Pharmacist

National Cancer Centre, Singapore

An Introduction to Geriatric Oncology

Overview

• **Aging** is the most significant risk factor for the development of cancer
• Elderly cancer patients are often under-represented in oncology trials
•Dr R Yancik organized a symposium in 1983 and published the monograph ' Perspectives on Prevention and Treatment of Cancer in the Elderly'

Lichtman SM, Curr Treatm Option Oncol. 2009; 10: 141-3

Overview

In US:
• From 2010 to 2030, the total projected cancer incidence will increase by approx. 45% (from 1.6mil to 2.3 mil)
• A 67% increase in cancer incidence is anticipated for older adults (vs 11% in younger adults)
• From 2010 to 2030, the percentage of all cancers diagnosed in older adults will increase from 61% to 70%

Smith BD JCO 2009; 27(17): 2758-65

Overview

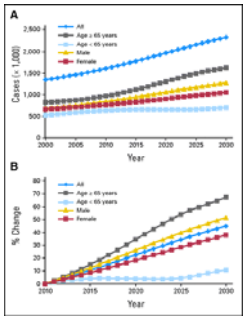


Figure: Projected cases of all invasive cancers in the United States by age and sex.

Smith BD JCO 2009; 27(17): 2758-65

Overview

In Singapore:
• The number of residents aged ≥ 65 will multiply threefold from current 300,000 to 900,000 in 2030
• By then, one out of every five residents will be a senior
• Cancer is currently the number one killer in Singapore
• At the National Cancer Centre Singapore (NCCS), patients aged 70 years or older account for about 40% of the 130,000 clinic attendances/year.

1. http://www.mcys.gov.sg/successful_ageing/Report.html
2. http://www.moh.gov.sg/mohcorp/statistics.aspx?id=5526
3. Poon, D Asia- Pacific Oncol & Hematol. 2008: 67-8

How does old age influence oncologists cancer management?

- Survey in 200 medical oncologist
- Intensive therapy was significantly less likely to be offered to an older than for a younger, otherwise identical patient
- Advanced age can deter oncologists from choosing intensive cancer therapy, even if patients are highly functional and lack comorbidities
- Education on tailoring cancer treatment and greater use of CGA may reduce cancer under- treatment in the geriatric population

Foster JA et al. The Oncologist 2010; 15:584-92

Current Challenges

- Geriatric assessments:
  - which tool?
  - practicality of selected tools
- Prediction and prevention of chemotherapy ADRs among elderly patients
- Interactions between various comorbidities and cancer treatment
- Under- treatment of elderly patients

Development and Validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal and prostate cancer. Hosmer et al. Support Care Cancer Feb 2010 [Online]

Study Objective

- To create a clinical prediction model for the risk of febrile neutropenia in the first cycle of chemotherapy in elderly patients receiving chemotherapy

Methodology

- **Data source:** SEER- Medicare database
- **Study population:**
  - subjects with breast, lung, prostate, and colorectal CA (1994-2005)
- **Exclusion:**
  - carcinoma in- situ/ unknown cancer stage
  - disabled/ ESRD
  - chemotherapy could not be identified
  - die within 28days of initiation of chemotherapy (unless they are hospitalised for FN prior to death)
  - received GCSF within 7 days of chemo administration

Methodology

- **Defining Febrile Neutropenia:**
  - limited to the 1st cycle of chemotherapy (within 28 days of the 1st chemotherapy administration)

Methodology

Statistical Analysis:

- sample was randomly divided into **'training set'** (2/3) and **'validation set'** (1/3)
- **Logistic regression** was used to estimate the association of the predictor variables with FN
- A prediction model was created using the beta-coefficients from the logistic regression
- The regression coefficients were multiplied by 10 and rounded to the nearest integer
- The points assigned to each predictor ranged from **-13 to 6**

Methodology

Statistical Analysis (cont'd):

- Performance of the risk- stratification system in the training and validation set was quantified and compared using the receiver operating characteristic analysis.
- The predictive accuracy of the model to identify patients at high risk of developing FN was estimated using the C- statistic:
- 0.5= model performs no better than chance alone
- 1.0= perfect prediction

Results

- 86,693 subjects included
- **lung CA** is more commonly ass'd with comorbid conditions
- subjects with lung CA had the most episodes of FN in the first cycle
- In multivariate analysis, independent predictors of FN:
  (1) Cancer Type
  (2) Cancer Stage (stage II and above)
  (3) Increasing no. of comorbid conditions
  (4) Myelosuppressive chemotherapy
  (5) < 1 mth from time of diagnosis to initiation of chemo

Results

Predictor (reference)	Odds ratio	*P* value	95% CI	Prediction model points
Cancer type (Breast)				
Lung	2.01	<0.001	1.65-2.44	7
Colon	1.26	0.001	1.09-1.45	2
Prostate	0.27	<0.001	0.22-0.33	-13
Stage at Dx (stage I)				
2	1.29	0.003	1.09-1.53	3
3	1.38	<0.001	1.19-1.60	3
4	1.57	<0.001	1.35-1.32	4
Time from dx. to 1st chemo (< 1 mth)				
1-3 mths	0.70	<0.001	0.62-0.80	-4
>3 mths	0.63	<0.001	0.55-0.73	-5
1 or more myelosuppressive chemo regimen (chemo with low myelosuppressive potential)	1.11	0.19	0.94-1.32	1
Comorbid conditions at diagnosis				
1	1.13	0.02	1.02-1.28	1
2	1.39	<0.001	1.22-1.57	3
3	1.81	<0.001	1.61-2.04	6

Table: Multiple logistic regression predicting febrile neutropenia in the first cycle of chemotherapy

Results

- the C- statistics was 0.75 for both the training and validation set
- correlation between the predicted probability from the multivariate model and the prediction model score was 0.93
- For each patient, individual risk score values were summed to create a total risk score
- maximum possible score = 19

Results

- those with higher risk scores had a higher predicted and observed risk of FN in the first 28 days
- a cutoff of 10 points (score ≥ 10) on the FN risk score was associated with a predicted FN of greater than 10%
- sensitivity= 24%
- specificity= 93%
- positive predictive value= 12%
- negative predictive value= 97%

Results

	Training dataset			Validation dataset		
Score	N	Obs FN %	Predicted FN %	N	Obs FN %	Predicted FN %
0 or lower	37,003	1.6	1.6	18,254	1.6	1.6
1-3	7,055	5.2	5.0	3,543	5.4	5.0
4-6	4,365	7.7	6.6	2,285	6.5	6.6
7-9	5,354	8.6	8.6	2,675	8.3	8.6
10-12	2,443	11.9	11.2	1,241	10.0	11.2
13 or higher	1,833	12.8	15.0	912	15.5	15.0
Overall	58,053	3.9	3.9	28,910	3.9	3.9

Table: Observed and predicted proportion of patients with FN in the first cycle by prediction score in the derivation and validation database

Discussion

Age

- Other studies have found that persons age ≥65 have higher risk of FN than those who are younger
- This study did not find any association between age and FN among persons older than 65
- Reflect the use of lower doses or less aggressive chemotherapy in older patients
- Or, it could mean that the risk of FN may not vary substantially among those older than 65 ye*ars*

Discussion

Chemotherapy regimens:

• Neutropenic complications were found to be associated with anthracycline regimens in other studies

• This study found a number of other agents that are associated with FN

• suggesting that the elderly may have a different risk of FN compared to younger population

• may also be due to the large database which allow identification of other agents normally not captured in smaller studies

Discussion

Rationale for limiting episodes of FN in the first 28 days:

• In order to approximate the first cycle of chemotherapy

• Clinicians often make changes to the chemo doses based upon patients' experience in the first cycle

• The decision to use G-CSF should ideally occur at the start of the first cycle

Discussion

Rationale for choosing FN risk of 10% as cutoff for clinical prediction rule:

• Approximately 50% of FN episodes occur after initial chemo cycle

• Based on the assumption that those with risk of >10% after initial cycle are similar to the population with cumulative risk greater than 20% across all cycles of chemotherapy

Discussion

	Hosmer et al.	Klastersky et al. (MASCC Risk Index)	Moreau et al.
Study Design	Retrospective analysis of SEER database	Prospective multinational study	Prospective study
Sample size	86,693	756	266
Cancer type	Lung, breast, colorectal, prostate	Any cancer type	Haematological malignancies
Predictive value	Positive PV= 12% Negative PV= 97%	Positive PV = 91%	Positive PV= 42.7% Negative PV= 89.1%
Predictive factors of FN	Cancer Type; Cancer stage, no. of comorbid conditions; myelosuppressive chemotherapy; time from diagnosis and initiation of chemo	Burden of illness; Hypotension; COPD; Non-solid tumour; Previous fungal infection; Dehydration; Hospitalization; Age	Aggressive chemotherapy; Underlying disease; Bone marrow involvement; BSA≤2m^2; Baseline monocyte count <150/mcL; Interaction between the first cycle in the same treatment line and a baseline Hb dosage

Klastersky J et al JCO 2000; 18(16): 3038-51
Moreau et al . Ann Oncol 2009; 20:513-9

Discussion

Strengths:
- potentially useful tool for clinicians treating elderly patients with chemotherapy
- easily used with available data prior to initiation of chemotherapy

Discussion

Limitations:
- retrospective data
- use is limited to 4 types of cancers
- chemotherapy were identified from Medicare claims, which does not accurately capture dose, ANC and PS

Discussion

Potential studies:
- prospective cohorts
- incorporating detailed clinical data:
  - laboratory data (ALP etc), PS, chemotherapy dosing
- testing of current prediction model in other cohorts

Impact of Diabetes Mellitus on Complications and Outcome of adjuvant chemotherapy in older patients with Breast Cancer.

Srokowski TP et al. JCO May 2009; 27(13): 2170-6

Objective

- To evaluate whether diabetes affects patterns of adjuvant chemotherapy use, toxic effects of chemotherapy, and breast cancer outcomes in elderly cancer patients

Methodology

- **Data source:**
  - SEER- Medicare database
- **Inclusion:**
  - 66 years or older
  - stage I to III breast cancer (AJCC)
  - treated with definitive surgical therapy
- **Exclusion:**
  - previous cancers
  - incomplete Medicare claims
  - unknown date of cancer diagnosis

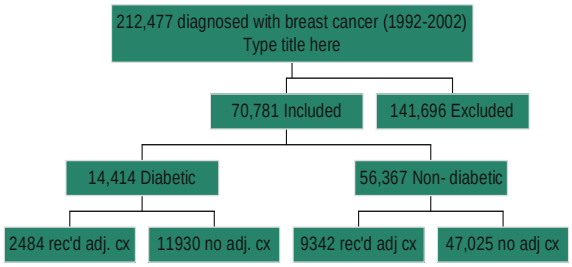
Methodology

Statistical analyses:

Variables	Statistical Methods
Differences in distribution of pts demographic and tumour characteristics	X^2 - test
Patterns of adjuvant chemotherapy use	Multivariate logistic regression models
Hospitalisation (outcome variables)	Logistic regression
Probabilities of all- cause mortality and BCS mortality	Kaplan- Meier method

Results

Patients



Results

- Diabetes was associated with significantly reduced odds of receiving chemotherapy
- Of the 11,826 patients who receive adj chemo, 2484 (21%) were diabetics
- Diabetes was independently ass'd with reduced odds of receiving **anthracyclines** (OR=0.78; 95% CI 0.71-0.87) or **taxanes** (OR= 0.86; 95% CI 0.75-0.99)

Results

Reasons for Hospitalisation	No. Overall	Without DM (n=9342) (%)	With DM (n=2484) (%)	*P*
Any cause	3201	25.6	32.6	<0.0001
Chemo. Toxicity	1850	14.4	20.3	<0.0001
Infection/ fever	783	6.01	8.9	<0.0001
Neutropenia	833	6.8	8.01	0.0340
Anemia	858	6.7	9.4	<0.0001

Table: Distribution of patients who were hospitalised or who developed chemotherapy toxicities by diabetic status

Results

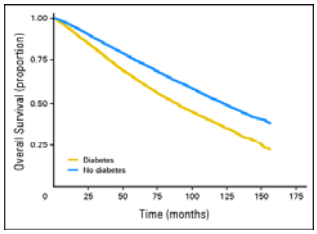


Figure: Unadjusted all-cause mortality curve of patients with and without diabetes and breast cancer. Five- and 10-year all-cause survival probabilities: 0.64 (95% CI, 0.63 to 0.65) and 0.37 (95% CI, 0.36 to 0.39), respectively, for patients with diabetes, and 0.75 (95% CI, 0.75 to 0.75) and 0.51 (95% CI, 0.50 to 0.52), respectively, for patients without diabetes (*P* < .0001 for each).

Results

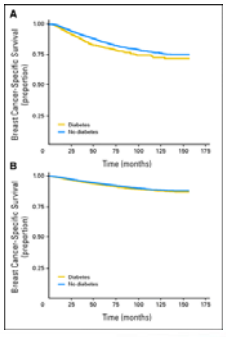
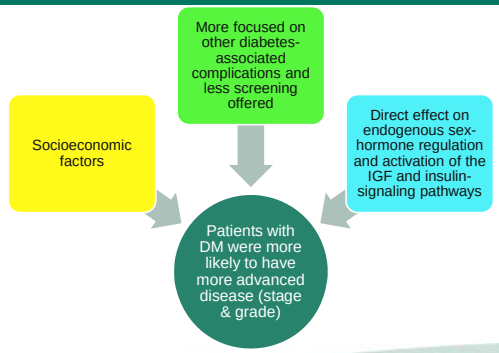
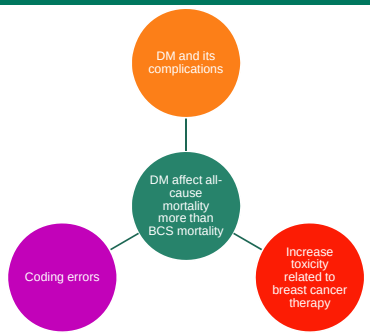


Figure: Unadjusted breast cancer–specific (BCS) mortality curve of patients with and without diabetes and breast cancer who (A) received chemotherapy and who (B) did not receive chemotherapy.

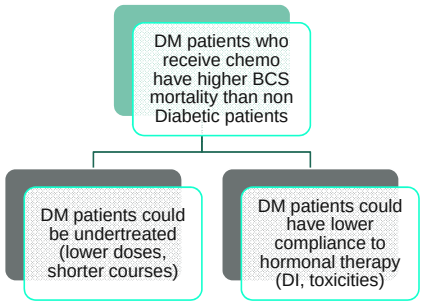
Discussion



Discussion



Discussion



Discussion

Strengths:

- large, population- based cohort
- may include patients who are excluded in randomized trials

Discussion

Limitations:

- Retrospective data
- Patients were not stratified according to severity of diabetes, end- organ damage and blood glucose control
- Relied solely on hospitalisation records to assess toxicities
- Selection bias: patients with severe DM may not be offered chemotherapy

Discussion

Questions to be answered:

(1)In view of the increased toxicity experienced by diabetic patients, can we still give standard chemotherapy to this group of patients?
(2)Will tighter blood glucose control improve tolerance to standard chemotherapy regimens?
(3)How do cancer and its treatment affect diabetes control?

Thank you

My email add:
yeoh.ting.ting@nccs.com.sg