PERSONALIZED TREATMENT OF LUNG CANCER

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OBJECTIVES

- Outline the burden of lung cancer in Canada
- Outline the potential preclinical and clinical targets in non-small cell lung cancer (NSCLC)
- Brief discussion of
  - The use of gefitinib in EGFR mutation positive NSCLC
  - The use of pemetrexed in adenocarcinoma of the lungs
  - Novel therapeutics in specific subgroups of NSCLC
- Implications of these novel molecular diagnostics and novel anti-cancer agents.
# BURDEN OF LUNG CANCER

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>12,800</td>
<td>10,700</td>
</tr>
<tr>
<td>Death</td>
<td>11,200</td>
<td>9,400</td>
</tr>
<tr>
<td>Incidence Rank</td>
<td>Second</td>
<td>Second</td>
</tr>
<tr>
<td>Death Rank</td>
<td>First</td>
<td>First</td>
</tr>
<tr>
<td>5-year Survival Rate</td>
<td>13%</td>
<td>17%</td>
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</table>
BURDEN OF LUNG CANCER

Figure 4.6
Age-Standardized Incidence Rates (ASIR) for Selected* Cancers, Males, Canada, 1980-2009

* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in incidence rate of at least 2% per year

Note: Rates are age-standardized to the 1991 Canadian population. Actual data were available to 2006 except for Quebec.

Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

Data source: Canadian Vital Statistics Death database at Statistics Canada

Canadian Cancer Statistics 2009
BURDEN OF LUNG CANCER

Figure 4.7
Age-Standardized Mortality Rates (ASMR) for Selected* Cancers, Males, Canada, 1980-2009

Note: Rates are age-standardized to the 1991 Canadian population.
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Canadian Cancer Statistics 2009
Figure 4.8
Age-Standardized Incidence Rates (ASIR) for Selected Cancers, Females, Canada, 1980-2009

Note: Rates are age-standardized to the 1991 Canadian population. Actual data were available to 2006 except for Quebec.
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Canadian Cancer Statistics 2009
Figure 4.9
Age-Standardized Mortality Rates (ASMR) for Selected Cancers, Females, Canada, 1980-2009

Note: Rates are age-standardized to the 1991 Canadian population.
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Canadian Cancer Statistics 2009
POTENTIAL THERAPEUTIC TARGETS IN NSCLC

Cell (2007) 131:1190-1203
EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION

EGFR has been shown to over-express and be activated in NSCLC and associated with poor survival.

Prior studies:

- Erlotinib improved survival in pretreated NSCLC patients as compared to placebo.¹
- Gefitinib was shown to be equally efficacious as docetaxel in pretreated NSCLC patients.²

EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION

- Most of the benefits were observed in:
  - Asian
  - Woman
  - No-smoker
  - Adenocarcinoma.

With response rate 54.8-81.6%.
EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION

- Mok et al.
  - Compared gefitinib with standard chemotherapy, carboplatin/paclitaxel in untreated Asian NSCLC patients who were non-smoker or light smokers and had adenocarcinoma.
  - Benefit was only observed in patients with EGFR mutation.
EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION

B  **EGFR-Mutation—Positive**

Hazard ratio, 0.48 (95% CI, 0.36–0.64)
P<0.001
Events: gefitinib, 97 (73.5%); carboplatin plus paclitaxel, 111 (86.0%)

C  **EGFR-Mutation—Negative**

Hazard ratio, 2.85 (95% CI, 2.05–3.98)
P<0.001
Events: gefitinib, 88 (96.7%); carboplatin plus paclitaxel, 70 (82.4%)

No. at Risk
Gefitinib 132 108 71 31 11 3 0
Carboplatin plus paclitaxel 129 103 37 7 2 1 0

No. at Risk
Gefitinib 91 21 4 2 1 0 0
Carboplatin plus paclitaxel 85 58 14 1 0 0 0

EFFECT OF HISTOLOGY ON THE USE OF PEMETREXED

Scagliotti and colleagues reported a phase III trial comparing cisplatin/gemcitabine with cisplatin/pemetrexed in untreated NSCLC patients.

The progression-free survival of cisplatin/pemetrexed was only observed in patients with adenocarcinoma or large cell carcinoma of the lungs.
Fig 2. Kaplan-Meier overall survival and progression-free survival (PFS) curves for the entire population, patients with nonsquamous histology (adenocarcinoma plus large cell), and patients with squamous histology.
EFFECT OF HISTOLOGY ON THE USE OF PEMETREXED

Based on this trial,

- EMEA and FDA implemented a label restricting the use of pemetrexed in only adenocarcinoma.
Soda et al. identified the presence of EML4-ALK inversion in chromosome 2p21-23, leading to overexpression and tyrosine kinase activity of ALK in NSCLC cell lines and patient derived patient samples.¹

At least 6 variants have been identified.¹,²,³

NOVEL THERAPEUTICS IN SUBGROUPS OF NSCLC

4% of all NSCLC harbours such translocation, and characteristics\textsuperscript{1}:

- Adenocarcinoma with predominantly acinar feature
- <50 years old
- Less differentiated
- Non-smokers or light smokers
- TTF1+.

NOVEL THERAPEUTICS IN SUBGROUPS OF NSCLC

- Shaw et al. presented the expansion cohort of ALK translocation positive NSCLC by FISH,
- 29 patients are evaluable for response.
- Response:
  - PR in 17/29 with duration of response 8-36+ weeks.
  - SD in 7/29 with duration of benefit ≥ 9 weeks
  - PD in 5.
  - Dramatic responses within the first 2-4 months.
This novel therapeutics in lung cancer illustrated that:

- Despite prior treatment with various agents, prolonged and dramatic responses and benefits were observed.
- Only in a very selected group of patients.
IMPLICATIONS

- The management of lung cancer is entering the era of personalized medicine.
- Many new gene aberrations are being identified through translational research.
- But these aberrations may only occur in a small proportion of patients.
IMPLICATIONS

Effect on drug development:
- Preclinical models of such aberration.
- Phase II or III studies only in patients with such aberrations:
  - Are they common?
  - Need central lab or reliable and reproducible tests to determine the presence or absence of such aberrations.
  - Are we missing out patients who may benefit from such therapy?
  - How big is the initial benefit observed?
  - Size and duration of the trial.
IMPLICATIONS

- Effect on translational research:
  - Need large number of cell lines
  - Confirmation with human tumour tissues
  - Preclinical models may be more predictive of the clinical benefits/effects
  - Need for easy and reproducible tests to identify such patients for clinical trials.
IMPLICATIONS

- Effects on clinical practice:
  - Collaboration with
    - Respirologists
    - Thoracic surgeons
    - Radiologists
    To obtain more tissues at the time of initial diagnosis.
  - The need of re-biopsy at the time of progression.
  - Collaboration with pathologists
    - The reporting of pathological subtypes.
  - The necessity of the molecular diagnostics for identification of the right patient for the right drug.
IMPLICATIONS

- Effects on society:
  - The clinical benefit of these novel therapies will be observed in a small number of patients:
    - Cost of drug
    - Cost to society
    - Loss of productivity
  - The costs of molecular diagnostic to identify the most appropriate patients for the treatment.
    - Who to pay?
  - The possibility of improving the 5-year overall survival of lung cancer from 17%.