To Cap or not to Cap: Chemotherapy Dosing for Obese Patients

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Obesity Pandemic

Estimated Mean Body Mass Index (kg/m²), Males, Aged 15+, 2010


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Obesity and overweight, WHO, Fact sheet, 2012
USA 36.5%
Mexico 32.4%
NZ 28.4%
Australia 28.3%
Canada 25.4%
New Zealand Health Survey 2011/2012. MoH
Table 10: Obesity, by ethnic group and sex

<table>
<thead>
<tr>
<th>Percent (%)</th>
<th>Total NZ</th>
<th>Men</th>
<th>Women</th>
<th>Estimated number(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total NZ</td>
<td>28</td>
<td>28</td>
<td>29</td>
<td>1,004,000</td>
</tr>
<tr>
<td>Māori</td>
<td>44</td>
<td>44</td>
<td>45</td>
<td>197,000</td>
</tr>
<tr>
<td>Pacific</td>
<td>62</td>
<td>59</td>
<td>64</td>
<td>127,000</td>
</tr>
<tr>
<td>Asian</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>59,000</td>
</tr>
<tr>
<td>European/Other</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>724,000</td>
</tr>
</tbody>
</table>

Adjusted rate ratios (comparing each ethnic group with people not in that ethnic group)\(^2\)

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Men</th>
<th>Women</th>
<th>Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>1.8*</td>
<td>1.8*</td>
<td>1.8*</td>
</tr>
<tr>
<td>Pacific</td>
<td>2.5*</td>
<td>2.4*</td>
<td>2.6*</td>
</tr>
<tr>
<td>Asian</td>
<td>0.5*</td>
<td>0.6*</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

Source: 2011/12 New Zealand Health Survey (15 years and over)
Obesity and Health

**Increased risk of:**
- Coronary artery disease
- High blood pressure
- Stroke
- Type 2 DM
- High LDL and reduced HDL
- Osteoarthritis
- Sleep apnoea and obesity hypoventilation syndrome
- Infertility
- Gallstones

*National Institutes of Health. USA. 2012*
Cancer and Obesity

- **Hormone related**
  - Excess amounts of estrogen and association with breast and endometrial cancers.
  - Increased level of insulin-like growth factor–1 (IGF–1), which may promote the development of certain tumours.
  - Increased leptin promotes cell proliferation
  - Reduced adiponectin, which may have antiproliferative effects.

- **Direct and indirect effects on other tumour growth regulators**
  - mTOR pathway

- **Chronic inflammation**

- **Adipose tissue and cancer cells share common metabolic pathway**
# Obesity and Malignancies

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (all)</td>
<td>NA</td>
<td>1.63 (1.44–1.85)</td>
</tr>
<tr>
<td>Breast (premenopausal)</td>
<td>0.76</td>
<td>(0.70–0.83)</td>
</tr>
<tr>
<td>Breast (postmenopausal)</td>
<td>1.12</td>
<td>(1.08–1.16)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>NA</td>
<td>1.33 (1.17–1.51)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.09</td>
<td>(1.05–1.13)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.02</td>
<td>(1.00–1.05)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.59</td>
<td>(1.50–1.68)</td>
</tr>
<tr>
<td>Oesophagus (all)</td>
<td>NA</td>
<td>1.39 (0.86–2.25)</td>
</tr>
<tr>
<td>Oesophagus (adenocarcinoma)</td>
<td>1.51</td>
<td>(1.31–1.74)</td>
</tr>
<tr>
<td>Oesophagus (squamous-cell carcinoma)</td>
<td>0.71</td>
<td>(0.60–0.85)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.59</td>
<td>(1.02–2.47)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1.17</td>
<td>(1.04–1.32)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.71</td>
<td>(0.60–0.85)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.11</td>
<td>(1.07–1.15)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.07</td>
<td>(1.00–1.14)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.12</td>
<td>(1.02–1.22)</td>
</tr>
<tr>
<td>Renal</td>
<td>1.34</td>
<td>(1.25–1.43)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.14</td>
<td>(1.06–1.23)</td>
</tr>
</tbody>
</table>

Chemotherapy Dosing in Cancer Patients

- Narrow therapeutic index
- Doses are determined by phase I studies, which tend to have a highly selected group of patients
- Obese patients are often excluded from trials due to co-morbidities
- High BMI is often associated with a high BSA
The Practice of Dose Adjustment

Nation wide survey in Australia, 188 responded (59.7%)

Inferior Survival with Under-Dosing

- Meta-analysis of 3 studies
- 4781 patients
- Patients with colorectal cancer receiving chemotherapy
- Full dosed led to better OS

*Figure 1.* Overall survival in obese (Body Mass Index 30+) patients (dose-reduced versus fully dosed patients).

*Chambers et al. Ann Oncol. 2012*
Evidence in Patients with NHL


Obese non-Hodgkin lymphoma patients tolerate full uncapped doses of chemotherapy with no increase in toxicity, and a similar survival to that seen in nonobese patients

Henry Chan, Sharon Jackson, Jessica McLay, Angela Knox, Jae Lee, Sarah Wang and Samar Issa

Department of Haematology, Middlemore Hospital, Auckland, New Zealand; Department of Statistics, University of Auckland, Auckland, New Zealand

ABSTRACT

The aim of this study is to compare the risk of treatment-related toxicities and long-term survival between obese and nonobese patients with non-Hodgkin lymphoma when treated with full uncapped doses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. A total of 133 patients and 733 cycles of chemotherapy were analyzed. Obese patients did not experience an increased risk of acute treatment-related toxicities (adjusted odds ratio 0.825, p = 0.197), or delayed toxicities (adjusted odds ratio 0.819, p = 0.779). In the subgroup of diffuse large B-cell lymphoma patients (n = 109), treatment response rate was similar between the two body mass index (BMI) groups, and obese patients tended to have superior overall and progression-free survivals, albeit not statistically significant. Full uncapped doses of R-CHOP chemotherapy administered to obese patients with non-Hodgkin lymphoma (NHL) are safe, well tolerated, and do not lead to inferior treatment response or long-term outcomes.

ARTICLE HISTORY

Received 1 November 2015
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KEYWORDS
Chemotherapy; non-Hodgkin lymphoma; obesity
Purpose of Study

- No physiological evidence to support the arbitrary capping at 2.00m²
- In Middlemore Hospital, chemotherapy treatment for all lymphoma patients is given according to actual BSA without dose capping or reduction.
- Review the toxicity outcomes and survival of DLBCL patients with high BSA (more than 2.00m²) compared to those with BSA less than 2.00m²
Study Design

- Retrospective analysis
- Consecutive newly diagnosed patients with NHL who were treated with R-CHOP chemotherapy at our lymphoma unit (2005–2015) were included in the study
- Exclude Burkitt’s Lymphoma, CLL, Waldenstrom Macroglobulinaemia, CNS involvement, HIV positive patients
- Review of electronic notes
  - Height and weight based on data from first cycle
Endpoints

- **Primary**
  - Acute treatment related toxicities
    - According to CTCAE
  - Delayed treatment related toxicities
    - Cardiac, marrow suppression, peripheral neuropathy, and malignancy

- **Secondary**
  - Overall survival
  - Progression free survival
133 patients
Median F/U 55.2 ms (range: 1.3–102.5 ms)
Median age for entire study cohort was 62.6 yrs
54.1% males
82% DLBCL
36 of 133 patients (27.1%) were obese, 23 BMI 30.0–34.9 kg/m2, 10 BMI 35– 35.9 kg/m2, 3 BMI of 40 kg/m2 or more
Median age in obese group younger than non-obese (57.1 vs. 64.4 yrs, p=0.007)
772 cycles of R–CHOP were given
Results

- Comparable treatment completion rate
- Equivocal treatment response rates
- No difference in delayed toxicities
R\textsuperscript{2} Linear = 0.002
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Adjusted relative risk</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>0.825</td>
<td>0.617 – 1.105</td>
<td>0.197</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.818</td>
<td>0.536 – 1.250</td>
<td>0.354</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.450</td>
<td>0.213 – 0.949</td>
<td>0.036</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2.135</td>
<td>0.876 – 5.206</td>
<td>0.095</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.643</td>
<td>0.185 – 2.232</td>
<td>0.487</td>
</tr>
<tr>
<td>Infection</td>
<td>1.625</td>
<td>0.535 – 4.934</td>
<td>0.391</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>0.516</td>
<td>0.112 – 2.379</td>
<td>0.396</td>
</tr>
</tbody>
</table>
**Overall survival**

Log-rank $P = 0.158$

<table>
<thead>
<tr>
<th></th>
<th>Non-obese (n = 74)</th>
<th>Obese (n = 28)</th>
<th>Non-obese (n = 69)</th>
<th>Obese (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>94.7 months</td>
<td>Not reached</td>
<td>94.7 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Estimated 3 year survival</td>
<td>75%</td>
<td>89%</td>
<td>69%</td>
<td>88%</td>
</tr>
<tr>
<td>Estimated 5 year survival</td>
<td>71%</td>
<td>84%</td>
<td>66%</td>
<td>78%</td>
</tr>
</tbody>
</table>

**Progression free survival**

Log-rank $P = 0.241$
Full dose chemotherapy is tolerable for obese patients with NHL
- Increased risk of infection could be due to increased rate of diabetes mellitus

There is no relationship between BSA and toxicities
- No evidence to support capping the dose at 2m²

Survival is similar between obese and non-obese
Thank You