Chemotherapy – a user’s guide

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Overview

- History of chemotherapy
- Cell cycle and principles of combination
- Specific agents
- Intrathecal chemotherapy
- Chemotherapy in the elderly
History of chemotherapy
Chemotherapy – a history 1

1943 – Bari air raid
100s of sailors and civilians exposed to mustard gas
Big cover up by Allied command

Goodman and Gilman
- Recruited by US dept of defense
- Post-mortem showed lymphoid and myeloid suppression
- Reasoned that might help lymphoma patients
- Mustine administered to patients (with Gustav Linskog)
- Saw dramatic reduction in NHL
- Short lived but responded to further injections
Sidney Farber (Harvard)
- ALL marrow similar to folate deficiency
- Gave folate to leukaemia children – BAD
- Got hold of aminopterin – caused regression
- Later amethopterin - methotrexate
Breakthroughs in treating TB were being made in the late 1950s – combination antituberculous therapy resulted in reduced resistance to treatment.

Holland, Freireich and Frei reasoned the same may apply for cancer.

POMP: 6-MP, vincristine, methotrexate and prednisolone used for ALL
Some cures seen in children

MOPP: developed by deVita and Canellos at NCI – mustine, vincristine, procarbazine and prednisolone; could cure HL and NHL
More is not always better

Seminal study
CHOP compared with 3 more intensive regimens

CHOP as good as other regimens

Other regimens significantly more toxic. Mortality:
• CHOP: 1%
• ProMACE-CytaBOM: 3%
• M-BACOD: 5%
• MACOP-B: 6%

This study has saved a lot of money and a lot of toxicity

Dose intensity is not necessarily a good thing

Fisher et al (1993) NEJM
Principles of combination
### Chemotherapy and cell cycle

#### Diagram:

- **G₁ 'gap 1' phase:** cell prepares for DNA synthesis
- **S 'synthesis' phase:** replication of DNA
- **G₂ 'gap 2' phase:** cell prepares for division
- **M 'mitosis':** division of the cell giving rise to two daughter cells

#### Table:

<table>
<thead>
<tr>
<th>Non-specific</th>
<th>G1</th>
<th>S</th>
<th>G2</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Steroids</td>
<td>Doxorubicin</td>
<td>Bleomycin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Melphalan</td>
<td></td>
<td>Cytarabine</td>
<td></td>
<td>Vinblastine</td>
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<tr>
<td>Cisplatin</td>
<td></td>
<td>Fludarabine</td>
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<td>Vinorelbine</td>
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<tr>
<td>Dacarbazine</td>
<td></td>
<td>Methotrexate</td>
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<tr>
<td></td>
<td></td>
<td>6-MP</td>
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Principles of combination chemo

1. Use drugs which are active as single agents
2. Drugs with different mechanisms of action
3. Drugs acting at different phases of cell cycle
4. Drugs with differing dose-limiting toxicities
5. Keep treatment-free interval to a minimum
6. Use drugs with differing resistance patterns

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Cell cycle</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Anti-CD20 mAb</td>
<td>Cycle non-specific</td>
<td>No DLT</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>Cycle non-specific</td>
<td>Myelo (also bladder)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Intercalates DNA</td>
<td>S-phase</td>
<td>Myelo (also heart)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Anti-metabolite</td>
<td>M-phase</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>glucocorticoid</td>
<td>G1 phase</td>
<td>Metabolic / neurol</td>
</tr>
</tbody>
</table>
Fractional kill

‘A certain type of chemotherapy at a certain dose for a certain exposure will kill a defined fraction of tumour cells each administration’

Therefore: 1 dose of drug will never lead to cure
Well proven for liquid cancers
Less applicable to solid tumours due to drug penetration issues

Will mean: start with $10^{11}$ cells. If chemo has a 99% fractional kill, need to apply 6 courses to result in < 1 cell remaining i.e. cure. NB tumours may regrow in between courses.

Usual explanation is cell-cycle specificity of drugs
The immune system and cure

- In mice models, cancers are only cured when they have an intact immune system
- So called ‘immunogenic cell death’ may play a role

Specific chemotherapy classes
Alkylating agents

- Add methyl group to guanosine base
- Cross-links DNA so cannot uncoil
- Cell-cycle non-specific
- Profound impact on fertility
- Immunosuppressive in smaller doses

**Cyclophosphamide**

- A pro-drug – needs good liver function to activate
- Acrolein is an important metabolite – irritant to bladder mucosa
- Haemorrhagic cystitis: prevent with hydration and mesna
- MUST give mesna at the same time as drug (and shortly after)
Anthracyclines

Doxorubicin most widely used

- Most effective anti-cancer treatment ever developed
- Used to treat more types of cancer than any other
- Intercalates DNA inhibiting replication
- Also inhibits topoisomerase II

Cardiotoxicity

- Acute: from start of Rx to few weeks after
  - ECG abnormalities, arrhythmias inc block, AF, VT
  - Subacute in elderly with decline in LV, ischaemia, pulm odema
- Chronic: 3 months – many years after, decline in LV function, can be fatal
- RFs: cumulative dose (avoid > 450mg/m²), mediastinal RT, other drugs e.g. herceptin, age, hypertension
- Reduce risk: avoid above, consider infusional (e.g. EPOCH), liposomal formulation, possible cardioprotectant
Vinca alkaloids

- Binds tubulin dimers which then disrupts microtubules
- Disrupts mitotic spindle formation
- Therefore strictly M-phase dependent
- Main SEs: neuropathy and constipation

**Vincristine polyneuropathy**

- Foot drop can be the first sign
- In patient with foot drop pre-Rx, consider CMT
- Key to Mx is early recognition, reduction / omission dose
- Large RCT showing that exercise helps to prevent PN
Nucleoside analogues

- Similar structure to DNA base
- Incorporated by growing DNA chain
- Causes chain termination and cell death
- Strictly S-phase dependent

Cytarabine:
- Cytosine base joined to arabinosyl sugar (cytosine arabinoside)
- Has distinct SE profile of:
  - Fever and arthralgias
  - Conjunctivitis (remember steroid eye drops) at high dose
  - Ataxia due to cerebellar damage
Bendamustine

- Bifunctional molecule
- Both alkylating agent and purine nucleoside analogue
- ‘designer’ drug made in old East Germany – only available elsewhere from 1990
- Theoretically may increase risk of TA-GvHD
- Useful in CLL, NHL, HL
- Causes significant CD4 T-lymphopenia

Hiddemann et al (2018) JCO
Intrathecal chemotherapy
Who is at risk of CNS involvement? No Clear Consensus!

However, large study published in JCO using > 2000 pts used to develop model. Then validated on 1,500 separate patients.
• Age > 60
• Performance status 2 or more
• Raised LDH
• > 1 extranodal site
• Stage III or IV
• Renal and / or adrenal involvement

0-1 RF: 0.6-0.8% developing CNS disease within 2 years
2-3 RF: 2.3-3.4%
4 or more: 10.2-12%

Schmitz et al 2016 JCO
Kidneys / adrenal seemed to confer particularly high risk
Other high risk site: testicular, breast, (epidural disease – not according to NICE)

Also note that:
1. Studies conflicting as to whether i.t. MTX reduces CNS relapse risk
2. Studies conflicting as to whether risk with R-CHOP is lower than with CHOP
3. Most CNS relapse in lymphoma is parenchymal, NOT leptomeningeal (this is not the case for ALL and Burkitt’s where i.t. makes more sense)
4. Some centres use just ITs; others use IV during RCHOP or at the end
At approximately 17.00hrs on Thursday 4th January 2001, Mr Wayne Jowett, a day case patient on Ward E17 at the Queen’s Medical Centre Nottingham (QMC), was prepared for an intrathecal (spinal) administration of chemotherapy as part of his medical maintenance programme following successful treatment of leukaemia. After carrying out a lumbar puncture and administering the correct cytotoxic therapy (Cytosine) under the supervision of the Specialist Registrar Dr Mulhem, Dr Morton, a Senior House Officer, was passed a second drug by Dr Mulhem to administer to Mr Jowett, which he subsequently did. However, the second drug, Vincristine, should never be administered by the intrathecal route because it is almost always fatal

Professor Brian Toft

Drugs licensed to administer intrathecally:

- Methotrexate
- Cytarabine
- Hydrocortisone
Chemotherapy in the elderly
CT and elderly – co-morbidities

- Co-morbidities clearly increase in the elderly
- Approx 70% of > 80 have significant co-morbidity

From: Maryska et al (2005)

<table>
<thead>
<tr>
<th>Condition</th>
<th>50-64</th>
<th>65-79</th>
<th>80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous cancer</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Heart and blood vessel disease</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>15</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

Janssen-Heijnen (2005) BJHaem

- Eindhoven cancer registry, 380 NHL patients
- Looked at impact of co-morbidities
- Found high-impact co-morbidities associated with worse outcomes
- Direct co-morbid death, reduction chemo, other
Renal function declines in the elderly
  - GFR reduces 1ml/min/yr over age of 40
  - Affects clearance of e.g. platins, methotrexate, etoposide
  - Measurement required if calculated levels borderline

Hepatic function reduces in elderly
  - Reduced liver mass
  - Reduced portal blood flow

Polypharmacy in elderly interacts with chemo
Haematological reserve in the elderly

- Anaemia far more common in the elderly
  - Partly related to comorbidities
  - Even if well, see increased pro-infl cytokines in elderly
  - Epo levels rise in healthy individuals as age (epo-resistance)
    - Epo rises LESS quickly in patients who are anaemic
- Marrow becomes less cellular with age (although precursors still abundant)
- Some evidence that precursors less efficient in elderly
Chemotherapy is more toxic in elderly

Various studies have shown increasing age as a risk factor for the following toxicities:

• Myelosuppression
• Mucositis
• Cardiac toxicity
• Central Neurotoxicity

But most did not control for age-associated changes rather than chronological age.
DLBCL in the very elderly (>80)

- SEER database search for DLBCL > 80yoa
- Showed poorer outcomes than younger patients
- R-CHOP outcomes better than other regimens (but retrospective study)

Using rituximab, may be possible to de-escalate chemo and maintain cure rates – R-miniCHOP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m2 d1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>400mg/m2 d1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25mg/m2 d1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Cap 1mg d1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40mg/m2 d1-5</td>
</tr>
</tbody>
</table>

2y PFS – 47%
2y OS – 59%

Payrade (2011) Lancet oncol
R-miniCHOP first choice in > 80s

- Retrospective study of 177 patients 70 or over treated with RCHOP
- Looked to see if INTENTION of clinician was full dose or mini-CHOP
- Recorded outcome

Eyre et al (2016) BJHaem

- In the over 70s, full dose RCHOP should be the aim
- In the over 80s, R-miniCHOP should be the aim (full dose MAY harm)
Summary

• Chemotherapy was born in the field of haematology and derived from chemical weapons
• Knowledge of mechanism has informed use
• Understanding of toxicity enables safer use
• Safety issues are paramount when delivering treatment safely e.g. intrathecal chemo
• Beware the elderly – a vulnerable group for chemo