Lymphoma update: turning biology into cures

Peter Johnson
Selected highlights of recent research

1. Using FDG-PET to modify treatment and avoid long term toxicity in Hodgkin lymphoma
2. Understanding how monoclonal antibodies treat non-Hodgkin lymphoma and how to make them work better
3. Finding ways to target the key signalling pathways in non-Hodgkin lymphoma
Hodgkin lymphoma

- Mainly affects young adults
- Curable in a high proportion of cases (97% of early stage, 85% of advanced stage)
- Conventional treatment comprises combination chemotherapy +/- radiation
- Many survivors experience long-term toxicity

Late effects to avoid as cures increase

- Secondary MDS/AML from alkylating agents
- Solid tumours from extended field radiation
- Pulmonary fibrosis from bleomycin
- Ischaemic heart disease from mediastinal irradiation and doxorubicin
- Infertility from alkylating agents
Even quite modest doses of radiation cause accelerated coronary disease

Frederika A. van Nimwegen et al. JCO 2016;34:235-243
Fluorodeoxyglucose-positron emission tomography (FDG-PET)

- Hodgkin lymphoma is inflammatory and highly metabolic
- FDG uptake is a highly sensitive marker of active disease
- Resolution of FDG uptake during treatment is a good prognostic indicator
This is good...

Baseline

Interim PET
This is not...
2 cycles ABVD
Full dose, on schedule

PET 1(Staging)

PET 2

PET 2 +ve

4 cycles BEACOPP-14
or 3 eBEACOPP

PET 3

PET 3 +ve
RT or salvage regimen

PET 3 -ve

2 cycles BEACOPP-14 or 1 eBEACOPP
No RT

PET 2 -ve
Randomise

4 cycles ABVD
4 cycles AVD

Follow-up (no RT)
Primary Endpoint: PFS for PET-negative randomized patients
(Median follow up 41 months)

HR: 1.14 (0.82 – 1.58), p = 0.44
3 Year PFS, ABVD: 85.6% (95% CI: 82.0 – 88.6)
3 Year PFS, AVD: 84.2% (95% CI: 80.4 - 87.1)
RATHL: Overall PFS and survival

3 year PFS
82.4% (80.2 – 84.8)

3 year OS
95.8% (93.8 – 96.6)
Response-adapted treatment for Hodgkin lymphoma

• By using selective intensification / de-escalation of therapy we have produced results as good as or better than previously

• We have reduced the proportion of patients irradiated from 40% to 6.5%

• We have shown that we can reduce exposure to bleomycin in those responding well

• We have shown that intensifying treatment early improves the results for those doing badly
Anti-B cell antibodies for non-Hodgkin lymphoma

- Rituximab has been in use since the late 1990s
- It has boosted survival in aggressive NHL

Potential Effects of anti-CD20 on Lymphoma cells

Complement Fixation

ADCC

CD20 on malignant cell surface

Active signalling

CR3

FcγR
In vitro effects of different anti-CD20 antibody types

YFP-CD20 in Bcl₁-3B3 cells

Homotypic adhesion: Ramos

Cragg et al., Blood. 2003;101:1045-1052
Modulation of surface CD20 mAb by 488 quenching.

Ritux (type I)

Tosit (Type II)

Lim S. et al., Blood 2011; 118:2530-2540
FcγRIIb (CD32b) expression correlates to antibody internalisation and clinical outcome

Lim S. et al., Blood 2011; 118:2530-2540
Can inhibiting CD32 binding improve the response to rituximab?

We are about to test this in a clinical trial of rituximab + anti-CD32

Roghanian A et al., Cancer Cell 2015; 27:473-488
Outcomes of treatment of diffuse large B-cell lymphoma: HMRN data

- R-CHOP 14/21 trial
- R-CHOP population
- Not fit for R-CHOP
Practical use of molecular phenotyping

• Understand which are the bad groups in need of better therapy

• Understand their biology in order to target that therapy
Protein expression
Good when its clear

More subtle models of biological heterogeneity seem likely to hold the key……

Class gene analysis

ABC meta-profile

GCB meta-profile
B-cell receptor signalling

Adapted from Mackay et al. *Immunol Rev.* 2010 Sep;237(1):205-25
Ibrutinib is more active against activated B-cell type lymphoma.
REMoDL-B Trial outline

Adaptive design:

Safety analysis:
After 55 GCB followed 1 yr: Stop if PFS < 70%

Futility analysis:
After 73 GCB followed 1 yr: Stop if PFS < 85%

Plan total 452 - 800 pts with GEP to detect 10% increase in PFS

Completed accrual of 1132 pts in May 2015….
**Progression-free survival by molecular profile**

**Characteristic**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th><strong>FAIL (n=159)</strong></th>
<th><strong>ABC (n=248)</strong></th>
<th><strong>GCB (n=477)</strong></th>
<th><strong>Unc. (n=201)</strong></th>
<th><strong>Total (n=1085)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS at 12 months – % (95% CI)</td>
<td>79.3 (71.2, 85.4)</td>
<td>79.0 (73.0, 83.9)</td>
<td>79.5 (75.3, 83.1)</td>
<td>77.6 (70.2, 83.4)</td>
<td>79.0 (76.2, 81.5)</td>
</tr>
<tr>
<td>PFS at 24 months – % (95% CI)</td>
<td>70.5 (61.0, 78.1)</td>
<td>68.9 (61.5, 75.1)</td>
<td>75.0 (70.2, 79.1)</td>
<td>67.8 (58.1, 75.8)</td>
<td>71.7 (68.4, 74.8)</td>
</tr>
<tr>
<td>No. of events observed</td>
<td>36</td>
<td>65</td>
<td>98</td>
<td>46</td>
<td>245</td>
</tr>
<tr>
<td>Proportion of patients with an event</td>
<td>23.1%</td>
<td>26.6%</td>
<td>20.6%</td>
<td>23.2%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Median follow up, in months (95% CI)</td>
<td>16.9 (14.3, 24.7)</td>
<td>17.2 (15.8, 21.6)</td>
<td>16.5 (15.7, 17.7)</td>
<td>14.3 (12.9, 15.8)</td>
<td>16.3 (15.7, 17.0)</td>
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Genomic changes and expression profiling give complementary information

<table>
<thead>
<tr>
<th></th>
<th>NF-kB &amp; TLR</th>
<th>B cell differentiation</th>
<th>Apoptosis regulation</th>
<th>Immune modulation</th>
<th>Epigenetic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABC</strong></td>
<td>47.5%</td>
<td>19.7%</td>
<td>6.6%</td>
<td>13.1%</td>
<td>18.0%</td>
</tr>
<tr>
<td><strong>GCB</strong></td>
<td>23.5%</td>
<td>3.9%</td>
<td>14.7%</td>
<td>18.6%</td>
<td>49.0%</td>
</tr>
<tr>
<td><strong>Unclassified</strong></td>
<td>39.3%</td>
<td>0.0%</td>
<td>25.0%</td>
<td>25.0%</td>
<td>32.1%</td>
</tr>
</tbody>
</table>
We are edging towards cell-of-origin as a partial guide to therapy

Non-GC type
- NF-κB activated
- BCR signalling
- TLR/IRAK signalling
- Bortezomib
- Ibrutinib
- Fostamatinib
- Lenalidomide

GC type
- Epigenetic regulators mutant/lost
- EZH2, CREBBP
- EPOCH, DHAP
- GSK 126
- EPZ 6438
Applying the biology...

- We are unravelling the biology using genomics and transcriptomics
- We are doing the prospective randomised studies to test our hypotheses
- We envisage more complex study design in the future, targeting multiple molecular sub-types
Acknowledgements

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...and of course, many, many patients