Targeted therapy of B cell malignancies – Rituximab and all of its friends!

Which CD20 antibody? (if any?!)

How much?

‘By the end of this study day participants will have a greater understanding of dose banding, the science behind it and rationale for introducing harmonisation across England.’

Martin J.S. Dyer
Ernest and Helen Scott Haematological Research Institute.
Financial disclosures

Honoraria received from:
  Abbvie
  Gilead
  Roche
  Sandoz

Research funding from:
  Gilead
  ONO Pharmaceuticals
Some CD20 Mabs for B cell malignancies in 2017

- Rituximab both iv and subcut
  (how do they do this? AMAZING technology)
- Biosimilars
- Obinutuzumab
- Ofatumumab
- Ublituxumab
- Radiolabelled CD20 Mabs/CD20 ADCs

Which patients?
Which antibody?
How many different lines of treatment?
(what constitutes Rituximab refractoriness)
What dose? Does one size fit all?
Dose banding
When should Rituximab be given?
How long for?
Do all patients with follicular lymphoma merit maintenance?
What dose of rituximab should we use?

- There is a paucity of data on rituximab PK in lymphoma
- BMI, age and gender may influence PK
- But what dose should we be using?
- No evidence that dose banding will adversely affect outcomes if done “sensibly”!!
- No evidence that giving more rituximab improves outcomes
  Poor PK may be due to inherent tumour resistance – low level CD20 expression, rapid internalisation, lack of immune effectors etc – see the GOYA study
- More is always more but more is not always better!
Antibody Therapy for Diphtheria 1900’s.

The Nobel Prize in Physiology or Medicine 1901 "for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths"
116 years of antibody therapy for malignancy.

• 1890 antibodies discovered......
• 1895 Hericourt and Richet – first use of antisera to treat malignancy!!! (Richet Nobel prize for work on anaphylactic reaction! And ZOMOTHERAPY!!!!)
• 1953 – radiolabeled antisera localize within tumours.
• 1972 – review of effects of polyclonal antisera
  
• 1982 – review of effects of first MAbs in haematological malignancies
  
Preliminary Communication

REMISSION INDUCTION IN NON-HODGKIN LYMPHOMA WITH RESHAPED HUMAN MONOCLONAL ANTIBODY CAMPATH-1H

G. HALE  M. J. S. DYER
M. R. CLARK  J. M. PHILLIPS
R. MARCUS  L. RIECHMANN
G. WINTER  H. WALDMANN

Departments of Pathology and Haematology, University of Cambridge, and Laboratory of Molecular Biology, Cambridge

Summary  A genetically reshaped human IgG1 monoclonal antibody (CAMPATH-1H) was used to treat two patients with non-Hodgkin lymphoma. Doses of 1–20 mg daily were given intravenously for up to 43 days. In both patients lymphoma cells were cleared from the blood and bone marrow and splenomegaly resolved. One patient had lymphadenopathy which also resolved. These effects were achieved without myelosuppression, and normal haemopoiesis was restored during the course of treatment, partially in one patient and completely in the other. No antiglobulin response was detected in either patient. CAMPATH-1H is a potent lympholytic antibody which might have an important use in the treatment of lymphoproliferative disorders and additionally as an immunosuppressive agent.
CD20 – a good therapeutic target for B-cell malignancies?

Function?

- Not mutated or deregulated as a consequence of malignancy
- Low level expression in some diseases (CD20negative CLL)
- Modulates/internalises/exosomes
- Little efficacy of rituximab or obinutuzumab as single agent

Would CD20 be developed as a therapeutic in 2017?
Rituximab improved outcomes in B-cell malignancies

Can we improve on rituximab?  
Can we dispense with chemotherapy?
Addition of rituximab to chemotherapy does NOT overcome chemotherapy resistance mediated by TP53 mutation.

Precise tumour type probably of primary importance.
How do we identify prospectively those patients destined to relapse early?
How can we treat them more effectively?

Usually highly aggressive malignancies with short doubling times.
Genetically very heterogeneous.
ANY role of chemotherapy for some of these malignancies??

Single agent unlikely to have marked efficacy in most patients.
Cf marked efficacy of Brentuximab in classical Hodgkin lymphoma.
Maintenance rituximab in FL - how much for how long? In all patients?

- Median follow up 73 months post-randomisation 6y
  PFS: 59.2% (MxR) vs 42.7%
- No overall survival difference emerging

PETREA study – using PET to guide maintenance treatment during 1st remission
Recent studies linking cancer genomics and immunity have reinforced the concepts that some mutations trigger T cell effector responses and that the likelihood of an immunogenic mutation increases with increasing mutation load. Importantly, these data highlight the potential utility of such markers in identifying patient subsets likely to respond to cancer immunotherapies. This study investigated the clinical impact of mutation load and its association with T cell gene expression in newly diagnosed patients with follicular lymphoma (FL).

- 269 patients from PRIMA trial
- We estimated mutation load per megabase (Mb) as a proxy for neoantigen formation using FoundationOne Heme (Foundation Medicine, Inc).

The mutation load estimate among newly diagnosed patients with FL was highly variable (range, 0-33 mutations/Mb). Patients with > 15 mutations/Mb (n = 19) were considered to have a high probability of neoantigen formation, and the remaining patients were stratified into mutation-low (< 6.6 mutations/Mb; n = 112) or mutation-mid (≥ 6.6 mutations/Mb and ≤ 15 mutations/Mb; n = 85) groups.

- The 3-year PFS in patients with high mutation load was 83% compared with 66% for mid-mutation load and 68% for low-mutation load groups, but mutation load was not independently prognostic in either the rituximab (P = .13) or observation (P = .66) arms.

- Mutation load was also associated with benefit from rituximab maintenance: FL patients with low mutation load experienced a significant benefit from rituximab maintenance (HR, 0.29 [95% CI, 0.15-0.54]; P < .001), whereas no statistically significant benefit was seen among FL patients with medium (HR, 0.81 [95% CI, 0.43-1.5]; P = .51) or high mutation load (HR, 0.29 [95% CI, 0.026-3.3]; P = .32).
Possible mechanisms of action of CD20 Mabs in B-cell malignancies.

- ADCC – but which are the crucial effector populations? Can these be enhanced/activated?
- NOT CDC – although complement activation is necessary.
- Direct induction of cell death? Lysosomal cell death/apoptosis (does this occur in vivo?)
- Down-regulation of key anti-apoptotic molecules (eg BCL2) resulting in chemosensitization?
- Non-specific immune stimulatory response as with IVIG?
- Induction of a specific anti-tumor immune response?
- Other considerations
  - Does CD20 modulate/internalize in some cases of DLBCL?
  - Role of FcRγ polymorphisms
  - Role of CD20 containing exosomes

REAL-TIME PK MONITORING OF SERUM LEVELS MANDATORY FOR THE RATIONAL USE OF THERAPEUTIC ANTIBODIES??
Pharmacokinetics of 8 doses of rituximab (375 mg/m²) given in combination with 2-week cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone/prednisolone (CHOP-14) was determined by ELISA in 20 elderly patients with diffuse large B-cell lymphoma (DLBCL) 10 minutes before and after each infusion and 1 week and 1, 2, 3, 6, and 9 months after the last infusion. Population pharmacokinetic modeling was performed with nonlinear mixed-effect modeling software (NONMEM VI). Concentration-time data were fitted into an open 2-compartment model and total clearance, central compartment volume, intercompartment clearance, and volume of distribution at steady-state (V_{ds}) were investigated. Total clearance was 9.43 ml/h and V_{ds} was 9.61 l. Rituximab clearance was reduced (8.21 ml/h vs 12.68 ml/h; \( P = .003 \)) and elimination half-life was prolonged in women compared with men (12.28 ± 30.7 vs 24.7 days; \( P = .003 \)). Body weight also affected V_{ds} (0.1 increase of V_{ds} per kilogram above median of 75 kg). A sex-dependent effect and the higher weight of males contribute to their faster rituximab clearance, which might explain why elderly males benefit less from the addition of rituximab to CHOP than females. This trial was registered on www.clinicaltrials.gov as numbers NCT00062936, EU-20243 (RICOVER-60 Trial), EU-20534, and NCT00726700 (Pegfilgrastim Trial). (Blood. 2012;119(14):3276-3284)
Optimization of rituximab for the treatment of DLBCL (I): dose-dense rituximab in the DENSE-R-CHOP-14 trial of the DSHNHL

N. Murawski¹, M. Pfreundschuh¹*, S. Zeynalova², V. Poeschel¹, M. Hänel³, G. Held¹, N. Schmitz⁴, A. Viardot⁵, C. Schmidt⁶, M. Hallek⁷, M. Witzens-Harig⁸, L. Trümper⁹, T. Rixecker¹ & C. Zwick¹

Background: To improve outcome of elderly patients with diffuse large B-cell lymphoma, dose-dense rituximab was evaluated in the prospective DENSE-R-CHOP-14 trial.

Patients and methods: Rituximab (375 mg/m²) was given on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99 together with six CHOP-14 cycles. Results were to be compared with patients who had received the same chemotherapy in combination with eight 2-week applications of rituximab in RICOVER-60.

Results: One hundred twenty-four patients are assessable. Dose-dense rituximab resulted in considerably higher serum levels during the first 50 days of treatment, but rituximab exposure time was not prolonged. Grade 3 and 4 infections were exceptionally high in the first 20 patients without anti-infective prophylaxis, but decreased after introduction of prophylaxis with aciclovir and cotrimoxazole in the remaining 104 patients (from 13% to 6% per cycle and from 35% to 18% per patient; \( P = 0.007 \) and \( P = 0.125 \), respectively). Patients with international prognostic index \( \leq 3 \rightarrow 5 \) had higher complete response/complete response unconfirmed rates (82% versus 68%; \( P = 0.033 \)) than in the respective RICOVER-60 population, but this did not translate into better long-term outcome, even though male hazard was decreased (event-free survival: from 1.5 to 1.1; progression-free survival: from 1.7 to 1.1; overall survival: from 1.4 to 1.0).

Conclusions: Dose-dense rituximab achieved higher rituximab serum levels, but was not more effective than eight 2-week applications in the historical control population, even though minor improvements in poor-prognosis and male patients cannot be excluded. The increased, though manageable toxicity, precludes its use in routine practice. Our results strongly support anti-infective prophylaxis with aciclovir and cotrimoxazole for all patients receiving R-CHOP.
\[^{111}\text{Indium-Zevalin imaging demonstrates tumour penetration but only after 48h}\]

It’s all got to go SOMEWHERE

WHEN TO GIVE RITUXIMAB?
IF SEEKING SYNERGY WITH CHEMOTHERAPY SHOULD BE AT LEAST 48 HOURS BEFORE (THEORETICALLY)
Rituximab biosimilars

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

Different levels of glycosylation in different Mabthera batches with different levels of ADCC!!!!

Schiestel M et al. Nature Biotechnol April 2011

We have characterized commercial batches of Rituxan/Mabthera with expiry dates from September 2007 to October 2011 using glycan mapping, cation exchange chromatography (CEX) and antibody-dependent cellular cytotoxicity (ADCC) in vitro bioactivity (Fig. 2). In 2008, an abrupt change in the quality profile became apparent for batches with expiry dates in 2010 or later. The most obvious difference was found in the amount of the C-terminal lysine and N-terminal glutamine variants when analyzed by cation exchange chromatography (Fig. 2a,b and
Gazyvaro® (Obinutuzumab, GA-101): A glycoengineered Type II anti-CD20 antibody engineered for increased ADCC and direct cell death

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial Name</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>Key secondary endpoint</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>GOYA</td>
<td>Naive DLBCL: Rituiximab + CHOP vs Obinutuzumab + CHOP</td>
<td>PFS (3 years): 67% 70% (p=0.38)</td>
<td>OS: R-CHOP vs G-CHOP. HR 1.00 (0.78, 1.28) (p=0.99)</td>
<td>Vieg U, et al. Blood 2016;128:470</td>
</tr>
</tbody>
</table>

**A**

![Diagram of antibody interaction with CD3](image)

**B**

![Diagram of antibody complex](image)

**C**

![Diagram of antibody complex](image)
Chemotherapy-free, combination targeted therapy of CLL and MCL

Slow rate of progression of most cases allows sequential targeted therapy based on different anatomical compartments.

a) BTK inhibitors – rapid reduction in lymph nodes. Concurrent lymphocytosis.

b) Type II CD20 antibodies – clear peripheral blood +/- bone marrow

c) BCL2 inhibitors – “mop up” residual disease!!!
Gedankenversuch

- 538 kinases in the human genome (and at least 995 kinase inhibitors available known to affect more than 250 specific intracellular signaling pathways for the treatment of more than 142 different tumor types.)
- 211 phosphatases
- A lot of ubiquitin-activating enzymes, ubiquitin-conjugating enzymes, and ubiquitin ligases!
- 102 deubiquinating enzymes
- Acetylases/deacetylases
- Methyl transferases/demethylases etc etc etc etc

- **NOW INHIBITING PROTEIN-PROTEIN INTERACTIONS**

- Molecules which inactivate
- Molecules which activate
- Genome sequence in 20 minutes for $50?

- Genetic heterogeneity of malignancy
- Cancer stem cells
- Role of the tumor environment
- Reprogramming
Developing immunotherapy combinations that make sense

Steven H. Bernstein, MD
Bristol Myers Squib
Empirical vs mechanism-based medicine

- **Chemotherapy** based on empirical use of combinations of very non-specific drugs applied in all cases (one size fits all)

- **Precision medicine** based on rational use of combinations of targeted molecules – mandates careful matching of malignancy with specific combinations of precision medicines (companion diagnostics)

- **Can we cure B cell malignancies using combinations of monoclonal antibodies?**
  - ADCC
  - ADCP
  - Complement activation
  - T-cell activation and recruitment

- **“Hybrid” monster** – precision medicines being added empirically to existing chemotherapy regimens
  - R-CHOP, FCR *etc etc etc*
  - Not only expensive, but wasteful and potentially dangerous
Combinations of idelalisib with rituximab and/or bendamustine in patients with recurrent indolent non-Hodgkin lymphoma
How can we use antibodies rationally for tumour-specific therapy?

Mabs with improved **effector** functions (direct/indirect via tumour microenvironment)

**Bispecific Abs / Antibody conjugates / Monovalent Abs / Ab fragments etc etc**

MRD negative remissions induced by Alemtuzumab

MRD negative remissions induced by Obinutuzumab