Rituximab in Non-Hodgkins Lymphoma

Fatima Bassa,
Dept. of Haematology
October 2008
World Health Organization lymphoma classification (2001)

- **Peripheral B-cell neoplasms:**
  - B-chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma
  - Mantle cell lymphoma
  - Follicular lymphoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Nodal marginal zone B-cell lymphoma
  - Splenic marginal zone B-cell lymphoma
  - Hairy cell leukemia
  - Diffuse large B-cell lymphoma (DLBCL)
  - Burkitt’s lymphoma (including Burkitt-like lymphoma)
  - Plasmacytoma/plasma cell myeloma
**DLBCL**

- DLBCL if untreated, can be fatal in 4-12 months
  - Most patients present with advanced stage disease
  - Best chance for cure – at presentation
  - Relapsed / Refractory DLBCL’s have a Poor Prognosis

- 2nd – line chemotherapy regimens include:
  - ESHAP
  - ICE
  - DHAP
  - +/-Consolidation with Autologous transplantation

- 2nd line regimens can achieve responses of 50 - 60% with only 20 – 30% achieving complete remission.

*Kewalramani T et al, Blood, May 2004, Vol 103, No 10*
*Haematologica 2004:89 (7)*
Follicular lymphoma

- Indolent Lymphoma
- Grade 1-111-histology
- Lymphadenopathy/BM involvement 50%
- Clinical course variable
- Low risk patients-watch/wait
- Advanced/aggressive disease :Rx
- FLIPI index/GELF criteria
Follicular Lymphoma

- Standard chemotherapy is not curative
- Course of follicular lymphoma is marked by periods of relapses and remissions
- Response rates decrease with each relapse
Follicular lymphoma

- Treatment options *
  - DXT
  - Chemoimmunotherapy
    - R-CHOP
    - R-CVP
    - R-Fludarabine
  - Chemotherapy alone
  - Rituximab monotherapy
  - High dose chemotherapy/transplantation

* Blood:109,11 1 June 2007:4617-25
Rituximab

- **Pharmacology**
  - Chimeric mouse / human antibody
  - Binds to CD20- pre-B / B lymphocytes
  - B cell NHL

- **MOA**
  - Immunologic reactions → cell lysis
  - Sensitises cells to cytotoxic effects of chemotherapy.
Rituximab

- **Side effects**
  - Generally well tolerated
  - Severe adverse events develop in only small number of patients
  - Most common AE’s are infusion-related
    - Most frequently occur during / shortly after 1st infusion
    - 95% of which are mild – moderate and resolve after temporary interruption of the infusion
Rituximab
Registered Indications

- Non Hodgkins Lymphoma
  - Diffuse large B cell Lymphoma (DLBCL) + CHOP
  - Follicular lymphoma
    - Untreated stage I-IV + CVP
    - Relapsed/resistant disease
    - Maintenance Rx

- Rheumatoid Arthritis
Rituximab
Efficacy-DLBCL

Landmark studies:

- GELA
  - Rituximab in older patients

- MInT trial
  - Young patients
Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma

J Clin Oncol ;23 June 2005 :1-9
GELA

- HIV negative pts 60-80yrs
- Untreated DLBCL stage 11-1V
- CHOP vs R-CHOP - 8cycles

First results -2002
- Increased CR
- Decreased relapses
- Improved OS

Updated results -5yr follow up
- CR : 47.5% vs 28%
- 5 yr PFS : 54% vs 30%
- 5 yr OS : 58% vs 45%
GELA-LNH 98-5 EFS and Overall Survival: median follow-up 7 years

Event-free survival

Overall survival

Probability

$\text{R-CHOP}$

$\text{CHOP}$

$p < 0.0001$

$p = 0.0004$

Time (years)

Coiffier *J Clin Oncol* 2007;25:A8009
DLBCL – young patients

- CHOP-like Chemotherapy plus Rituximab versus CHOP-like Chemotherapy alone in Young Patients with good-prognosis DLBCL: a randomised controlled trial by the MInT Group

Pfreundschuh M, Trumper L, Osterberg A, Pettengell R et al

Lancet Oncology ; 7 May 2006 :379-91
CD20+ DLBCL
18–60 years
IPI 0,1
Stages II–IV, I with bulk

Randomisation

CHOP-like
+ 30–40 Gy (Bulk, E)

CHOP-like
+ rituximab
+ 30–40 Gy (Bulk, E)

MabThera International Trial (MInT): trial design

MInT study

Event-free survival

Overall survival

R-chemo

chemo

R-chemo

chemo

$p < 0.0001$

$p = 0.0001$
MInT study

- Results
  - Relapses: 41% vs 21%
  - Reduction in need for salvage chemotherapy

- Conclusions:
  - Improved outcome
  - Without increased toxic effects
  - New standard of care in young patients
Consistent efficacy of R-CHOP HGBCL

GELA 98-5\textsuperscript{1}

\begin{itemize}
\item Overall survival
\item \textit{R-chemo}
\item \textit{chemo}
\item \textit{p} = 0.0073
\end{itemize}

ECOG\textsuperscript{3}

\begin{itemize}
\item Failure-free survival
\item \textit{R-chemo}
\item \textit{chemo}
\item \textit{p} = 0.003
\end{itemize}

MInT\textsuperscript{2}

\begin{itemize}
\item Overall survival
\item \textit{R-chemo}
\item \textit{chemo}
\item \textit{p} = 0.0001
\end{itemize}

\begin{itemize}
\item Failure-free survival
\item \textit{R-chemo}
\item \textit{chemo}
\item \textit{p} = 0.000025
\end{itemize}

RiCOVER-60\textsuperscript{4}

\begin{itemize}
\item \textit{R-chemo}
\item \textit{chemo}
\item \textit{p} = 0.000025
\end{itemize}

\textsuperscript{1}Coiffier J Clin Oncol 2007;25:A8009; \textsuperscript{2}Pfreundschuh Lancet Oncol 2006;7:379–91
\textsuperscript{3}Habermann J Clin Oncol 2006;24:3121–7; \textsuperscript{4}Pfreundschuh Lancet Oncol 2008;9:105–16
Rituximab
Follicular lymphoma

- **Rituxumab Monotherapy**
  - Weekly for 4 weeks
  - Initial good responses ± 50% CR
  - Median time to Dx progression 18-24 mths

- **Rituxumab with chemotherapy**
CVP ± Rituximab in previously untreated follicular lymphoma (FL): study design

- Follicular NHL
- Stage III–IV

SD = stable disease; PD = progressive disease

CVP ± Rituximab in previously untreated follicular lymphoma (FL)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CVP</th>
<th>R -CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR(%)</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>CR (%)</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>Median TTF(mths)</td>
<td>7</td>
<td>27</td>
</tr>
</tbody>
</table>

CVP ± Rituximab in previously untreated FL: Time to Treatment Failure

Median follow-up: 53 months

Event-free probability

Study month

CVP: median 7 months
R-CVP: median 27 months

Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>CVP</th>
<th>R-CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>159</td>
<td>162</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>123</td>
</tr>
<tr>
<td>12</td>
<td>51</td>
<td>113</td>
</tr>
<tr>
<td>18</td>
<td>34</td>
<td>98</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>30</td>
<td>21</td>
<td>76</td>
</tr>
<tr>
<td>36</td>
<td>17</td>
<td>69</td>
</tr>
<tr>
<td>42</td>
<td>14</td>
<td>63</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>54</td>
<td>6</td>
<td>37</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>66</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CVP ± Rituximab in previously untreated FL: Conclusions

- Addition of Rituximab to CVP significantly improved:
  - Overall Response Rates and Complete Response rates
  - Disease Free Survival
  - Overall Survival

- Addition of Rituximab to CVP did not substantially increase regimen toxicity

- Eight cycles of R-CVP should be considered as a standard treatment for previously untreated FL

Chemotherapy+Rituximab vs chemotherapy

Cochrane Collaboration

- 7 RCT – indolent lymphoma
  - 1480 patients with Follicular lymphoma
  - 5 trials untreated FL
  - 2 trials relapsed FL

The Cochrane library 2008 issue 1
Cochrane meta-analysis: Characteristics of trials included

<table>
<thead>
<tr>
<th>Study author</th>
<th>Therapy</th>
<th>Previous therapy</th>
<th>Ann Arbor stage</th>
<th>Observation time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz, et al. 2005</td>
<td>R ± CHOP</td>
<td>No</td>
<td>III / IV</td>
<td>18</td>
</tr>
<tr>
<td>Rivas-Vera, et al. 2005</td>
<td>R ± CNOP</td>
<td>No</td>
<td>III / IV</td>
<td>24</td>
</tr>
<tr>
<td>Marcus, et al. 2005</td>
<td>R ± CVP</td>
<td>No</td>
<td>III / IV</td>
<td>18</td>
</tr>
<tr>
<td>Forstpointner, et al. 2004</td>
<td>R ± FCM</td>
<td>Yes</td>
<td>III / IV</td>
<td>18</td>
</tr>
<tr>
<td>Herold, et al. 2005</td>
<td>R ± MCP</td>
<td>No</td>
<td>III / IV</td>
<td>36</td>
</tr>
<tr>
<td>Hiddemann, et al. 2005</td>
<td>R ± CHOP</td>
<td>No</td>
<td>III / IV</td>
<td>36</td>
</tr>
<tr>
<td>van Oers, et al. 2006</td>
<td>R ± CHOP</td>
<td>Yes</td>
<td>III / IV</td>
<td>39</td>
</tr>
</tbody>
</table>

Cochrane meta-analysis: summary

- Addition of Rituximab to chemotherapy significantly improved
  - ORR
  - CR
  - Disease control
  - OS

- Addition of Rituximab to chemotherapy increased the risk of fever and leukocytopenia, but this was not associated with an increased risk of infections

- Conclusion
  - R/chemotherapy should be standard of care

ORR = Overall Response Rate
OS = Overall Survival
CR = Complete response

Follicular Lymphoma - Maintenance therapy

- Attempts to improve CR duration

- Studies in relapsed follicular lymphoma
  - Superiority of maintenance rituximab over observation post immunochemotherapy
  - Phase 111 – EORTIC trial
  - Randomised
    - RCHOP/CHOP
    - Maintenance rituximab/observation
    - Single infusion 3 mthly for 2 years
  - PFS: 51.5 mths vs 14.9 mths
  - OS: 85% vs 77% after 3 years

  *van Oers et al.; Blood 2006;108:3295-301*

- Several ongoing studies, maintenance ff 1st line Ror R/CT
Rituximab
Lymphoma Management Guidelines

- **HGBCL**
  - **BCSH**
    - *BJH 2003,121:44-48*
    - Firm recommendation
    - Cost effective
    - ‘Failure to support strongly conflict with professional opinion’

- **NCCN (v3 2008)**
  - R-CHOP-category 1 recommendation
  - + DXT if bulky Dx

- **ASH**
  - *Blood ;110,July 2007:29-36*
  - R-CHOP
Rituximab
Lymphoma Management Guidelines

Follicular Lymphoma
- NCCN
  - Elderly or infirm patients
    - Rituximab monotherapy
  - Stage 1-11
    - Involved field DXT
    - Immunochemotherapy
  - Stage 11-1V
    - R CHOP/COP - first line recommendation
  - Relapsed Dx
    - Immunochemotherapy with maintenance Rituximab
    - HDT with BMT
    - Radioimmunotherapy
Rituximab
Lymphoma Management Guidelines

- **Follicular Lymphoma**
  - ASH
    - *Salles G; American Society of Haematology ED book: Hematology-2007 p221*
    - “combinations with rituximab represent a new standard in the first line treatment of patients with follicular lymphoma”

- **How I Treat Indolent Lymphoma**
  - *Blood 109, June 2007 p4617-29*
    - Chemoimmunotherapy – First line Rx advanced Dx
    - Single agent chemotherapy/Rituximab-selected pts
    - Relapsed Dx
      - Watch wait
      - Immunochemotherapy ff by maintenance
      - ?HDCT/BMT
Rituximab
Off label use

Can be considered for individual use in:

- Chronic refractory ITP
- Waldenstrom’s Macroglobulinaemia
- Acquired Haemophilia
- Multifocal motor neuropathy

Position statement NSW TAG 2007
Cost

- **Drug**
  - +- R15000/dose

- **Pharmaco-economic analysis**
  - cost effective
    - International models:
    - Local model

- R-Chemotherapy is endorsed by SAOC
  - HGBCL
  - Follicular lymphoma
Rituximab shown to be cost–effective

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Regimen</th>
<th>CE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Lewis <em>Blood</em> 2006;108:A345</td>
<td>R-CVP vs CVP</td>
<td>yes</td>
</tr>
<tr>
<td>France</td>
<td>Brice <em>J Clin Oncol</em> 2007;25(suppl):A8076</td>
<td>R maintenance vs observation</td>
<td>yes</td>
</tr>
<tr>
<td>Canada</td>
<td>Maturi <em>Blood</em> 2006;108:A343</td>
<td>R maintenance vs observation</td>
<td>yes</td>
</tr>
</tbody>
</table>
Cost

Consider:
- Cost of treatment failure
  - Hospitalisation
  - 2\textsuperscript{nd} line chemotherapy
  - ?BMT
  - Adjunctive Rx
    - Neupogen
    - Transfusions
    - Antibiotics
  - Investigations
  - Cost of palliation
- Additional load on already stretched health service
Conclusions

- Rituximab/chemotherapy
  - Rx of choice
  - HIV negative patients

  - High grade B cell lymphoma

  - Follicular lymphoma
    - Treatment
      - First line
      - Relapsed patients
      - Bulky stage 11
      - Stage 111/1V
    - Maintenance
      - Relapsed patients

- acceptable side effect profile
<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>Outcome (median)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP ± R(^1)</td>
<td>TTP 34 vs 15 mo</td>
<td>4 yr 83% vs 77%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.0001)</td>
<td>(p = 0.029)</td>
</tr>
<tr>
<td>CHOP ± R(^2)</td>
<td>TTF 60 vs 25 mo</td>
<td>4 yr 90% vs 81%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.0001)</td>
<td>(p = 0.039)</td>
</tr>
<tr>
<td>MCP ± R(^3)</td>
<td>PFS NR vs 29 mo</td>
<td>4 yr 87% vs 74%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.0001)</td>
<td>(p = 0.0096)</td>
</tr>
<tr>
<td>CHVP ± R + IFN-(\alpha)^(^4)</td>
<td>EFS NR vs 35 mo</td>
<td>5 yr 84% vs 79%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.0004)</td>
<td>(p = 0.15)</td>
</tr>
<tr>
<td>FLIPI ≥3</td>
<td>EFS 21 vs 51 mo</td>
<td>5 yr 77% vs 63%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.0002)</td>
<td>(p = 0.025)</td>
</tr>
</tbody>
</table>

TTP = Time to Progression
TTF = Time to Treatment Failure
PFS = Progression Free Survival
EFS = Event Free Survival

\(^1\)Marcus *Blood* 2006;108:A481; \(^2\)Buske *Blood* 2006;108:A482
Progression Free Survival at 7 years

PFS – Median follow-up 7 y

CVP ± Rituximab in previously untreated follicular lymphoma (FL)

ORR = Overall Response Rates
CR = Complete Response / Remission
CRu = Complete Response / Remission Unconfirmed
PR = Partial Response

Rituximab + chemotherapy
Eligibility Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Newly diagnosed DLBCL</td>
<td>• Significant organ function impairment</td>
</tr>
<tr>
<td>• Newly diagnosed or relapsed Follicular NHL’s</td>
<td>• HIV positive</td>
</tr>
<tr>
<td>• Stage II – IV disease</td>
<td></td>
</tr>
<tr>
<td>• Age &gt;18 years</td>
<td></td>
</tr>
<tr>
<td>• Survival of ≥6 months</td>
<td></td>
</tr>
</tbody>
</table>