Immunotherapy in haematological malignancies

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Bellinzona
Conflicts of interest

Roche
Celgene
Mundipharma
Janssen
Gilead
Bayer
Millenium
What do we mean by ‘immunotherapy’ when speaking about lymphoma?

- **MONOCLONAL ANTIBODIES**
  - ‘Naked’
  - Radio-immunotherapy
  - Immuno-toxins

- **ENGAGING T-CELLS**
  - Interferon
  - Vaccination
  - Immune checkpoint inhibition
  - CAR T cells
  - Bispecific antibodies
Rituximab: mechanisms of action
Patients usually respond to upfront R

**RR of prolonged rituximab in first-line FL**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Count (n)</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombat 2001</td>
<td>50</td>
<td>73%</td>
</tr>
<tr>
<td>Hainsworth 2002</td>
<td>60</td>
<td>73%</td>
</tr>
<tr>
<td>Witzig 2005</td>
<td>37</td>
<td>72%</td>
</tr>
<tr>
<td>Ghielmini 2005</td>
<td>202</td>
<td>75%</td>
</tr>
<tr>
<td>Kimby 2008</td>
<td>123</td>
<td>78%</td>
</tr>
<tr>
<td>Ardeshna 2010</td>
<td>192</td>
<td>85%</td>
</tr>
</tbody>
</table>
R vs R2 in FL patients in need of treatment

Week 10
p<0.0001

Week 23
p=0.002

Proportion of patients (%)

Rituximab (N=77)

Kimby E, et al. ASH 2014; Abstract 799
FL: the response to upfront rituximab (RR 70%) can be long lasting if maintained

2. Taverna C, et al. ASH 2013; Abstract 508

- Median EFS = 4.4 years
- Median PFS = 7.4 years
- Median EFS = 2.5 years
- Median PFS = 3.5 years

\[ p = 0.045 \]
\[ P=0.04 \]
Two Types of anti-CD20 mAbs

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20 clustering in B-cell membrane</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Induction of CDC</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Induction of ADCC</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

– = no activity; + = some activity; ++ = significant activity

Cragg MS, et al. Curr Dir Autoimmun 2005  
Chl vs R-Chl vs G-Chl in CLL

Elderly non-fit patients, 1. line

PFS

Tendency of a superior OS with obinotuzumab

Obinutuzumab vs rituximab in relapsed iNHL preliminary analysis of the GAUSS study

Figure 1. Progression-free survival assessed by investigator in follicular lymphoma patients

In FL:
ORR
GA101: 44.6%
R: 26.7%

\[ p = 0.01 \]

Targeted irradiation: radio-immuno-therapy

<table>
<thead>
<tr>
<th>Properties</th>
<th>$^{90}$Yttrium (Zevalin)</th>
<th>$^{131}$Iodine (Bexxar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>64 hours</td>
<td>192 hours</td>
</tr>
<tr>
<td>Energy emitter</td>
<td>Beta (2.3 MeV)</td>
<td>Gamma (0.36 MeV) Beta (0.6 MeV)</td>
</tr>
<tr>
<td>Path length</td>
<td>$\chi_{90}$ 5 mm</td>
<td>$\chi_{90}$ 0.8 mm</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>Minimal 7% in 7 days</td>
<td>Extensive/variable 46 - 90% in 2 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>Based on weight and platelet count</td>
<td>Clearance based dosing using whole body dosimetry</td>
</tr>
<tr>
<td>Administration</td>
<td>Outpatient</td>
<td>Inpatient or restrictions to protect family/public</td>
</tr>
</tbody>
</table>
Radio-immunotherapy as initial therapy for indolent NHL

I-131 Tositumomab
n=76 patients, 95% OR, 75% CR

90-Y Ibritumomab
n=50 patients, 94% OR, 86% CR

GELF, Groupe d’Etude des Lymphomes Folliculaires
Brentuximab vedotin (SGN35)
Anti-CD30 conjugated to an antitubulin agent

ADC binds to CD30
Internalised in lysosome
MMAE is released
MMAE disrupts microtubule network

MMAE – microtubule-disrupting agent
anti-CD30 monoclonal antibody
Brentuximab vedotin (SGN-35)
FDA approved for R/R HL and ALCL

102 post-auto transplant HL
- ORR 75%
- CR 34%
- 7 mos (20 mos in CRs)

58 relapsed or refractory ALCL
- ORR 86%
- CR 53%
- median duration of response 13 mos

Shustov et al., Abstr. 125, ICML-11
Younes et al., Abstr. 160, ICML-11
Brentuximab vedotin in PTCL-NOS and AITL

- n=29 (11 AITL and 18 PTCL-NOS) R/R
- 2 prior lines
- Primary refractory: 55%

ORR 36%, 50% in AITL (4/11 CR)

Responses also in low/undetectable CD30 by IHC

AITL, angioimmunoblastic T-cell lymphoma
PTCL-NOS, peripheral T-cell lymphoma not otherwise specified
Oki Y, et al. ICML-12 2013 Abstract 152
What do we mean by ‘immunotherapy’ when speaking about lymphoma?

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- **ENGAGING T-CELLS**
  1. Interferon
  2. Vaccination
  3. Immune checkpoint inhibition
  4. CAR T cells
  5. Bispecific antibodies
Can transplant cure?
Autologous: no            Allogeneic: yes

But at the cost of important risks and side effects

Today, with RIC, the curve is possibly here, but with 50% GVH and 30% extensive GVH

Hosing et al., Ann Onc 2003
Therapeutic strategies to overcome immune tolerance to cancer

1. Cytokines
2. Tumor vaccines
3. Immune checkpoint inhibitors

- Native T cell
- Engineered T cell
- Malignant B cell
- TCR
- CD3
- CD19
- CD20
- MHC I/II
- PD1
- PD-L1
- PD-L2

5. BiTE
4. CAR

Interferon prolongs survival in FL

META-ANALYSIS
10 randomised trials, 1922 patients

Survival benefit of 2 years (p=0.0008)
if IFN given
- With (NOT after) intensive chemotherapy
- At a dose of ≥ 5 million UI
- At a cumulative dose of ≥ 36 million UI / month

Vaccines are directed against idiotypes
Vaccinated patients developing anti-idiotype Ab have a longer response after chemotherapy.

Analysis of 136 patients with FL receiving idiotype (Id) vaccination.
Humoral represents patients with specific anti-Id Abs.

Negative vaccine trial

Mitumprotimut-T vs placebo

“Positive” vaccine trial

Analysis of patients with advanced stage previously untreated FL
Responses of HL to anti-PD1 in R/R HL

Nivolumab: RR 87%, CR 17%

Pembrolizumab: RR 66%, CR 21%

Armand P, et al. ASH 2014; Abstract 289

Moskowitz CH, et al. ASH 2014; Abstract 290
PD-1 blockade by pidilizumab plus rituximab in relapsed FL

Efficacy
n= 29 pts

ORR 66% (CR 52%)
Median PFS 19 months

Safety
No gr 3–4 AEs

9p24.1 amplification and PD-1L cell-surface expression in HL and MLBCL cell lines.

HRS Cells Express High Levels of PDL-1

Hodgkin and Reed Sternberg (HRS) Cells

EBV Infection

9p24.1 Gene amplification

JAK2

PDL1

CD30
PDL1 Expression in classical and NLP Hodgkin Lymphoma

PDL1 in cHL

Histiocytes
HRS cells

PDL1 in NLPHL

Hodgkin cells
Histiocytes

Courtesy of Chiu A, MSKCC
Two strategies to engage T-cells against B-cell lymphoma

A. Bispecific T Cell Engager (BiTE)

B. Chimeric Antigen Receptor (CAR)
CAR-T cells
(Chimeric Antigen Receptor)
CAR-T cells therapy

Kochenderfer and Rosenberg, Nat Rev Clin Oncol, 2013
CAR-T cells clinical results

NCI, Bethesda
Responses in relapsed patients

4/5 FL
7/8 CLL
6/7 DLBCL (4 CR)

3/10 pat in relapse after allo-BMT (donor-derived CAR-T)

Side effects:
- Severe hypotensions
- Severe neurologic

Kochenderfer et al., Blood 2013 and JCO 2014.
Summary of available data for CAR T cells in R/R ALL

<table>
<thead>
<tr>
<th>Population</th>
<th>19-28z (MSKCC/Juno; n=39)</th>
<th>CTL019 (CHOP/UPenn; n=39)</th>
<th>CD19-CAR (NCI/Kite; n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults &gt;18 years</td>
<td></td>
<td>Children (age not specified)²</td>
<td>Children/young adults (1–30 yr)</td>
</tr>
</tbody>
</table>

**Status after conditioning chemotherapy, prior to CAR T-cell treatment**

| MRD+ CR (<5% BMB)                  | 46%                      | 23%²                      | 25%                      |

**Status after conditioning chemotherapy and CAR T-cell treatment**

| CR/CRi                              | 87%                      | 92%                      | 70%                      |
| MRD- (in evaluable patients)        | 81%                      | 82%                      | 60%                      |

**Clinically significant/ severe CRS**

| 23%                                  | 27**³                    | 29                       |

**Neurotoxicity (%)**

| 28 (Grade 3/4)                      | 43**³                    | 29                       |

Bi-specific antibodies

Design and mode of action of bispecific T-cell engager (BiTE®) antibody constructs

CR after Blinatumomab in ALL patients refractory or relapsed after allotransplant

<table>
<thead>
<tr>
<th>All responders</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All responders</td>
<td>189</td>
<td>43</td>
<td>36–50</td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Female</td>
<td>70</td>
<td>46</td>
<td>34–58</td>
</tr>
<tr>
<td>Male</td>
<td>119</td>
<td>41</td>
<td>32–51</td>
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<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>18 to &lt;35</td>
<td>90</td>
<td>43</td>
<td>33–54</td>
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<tr>
<td>35 to &lt;55</td>
<td>46</td>
<td>46</td>
<td>31–61</td>
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<tr>
<td>55 to &lt;65</td>
<td>28</td>
<td>36</td>
<td>19–56</td>
</tr>
<tr>
<td>≥65</td>
<td>25</td>
<td>44</td>
<td>24–65</td>
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<table>
<thead>
<tr>
<th>Prior Salvage</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>50</td>
<td>33–67</td>
</tr>
<tr>
<td>1</td>
<td>77</td>
<td>47</td>
<td>35–58</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>36</td>
<td>22–52</td>
</tr>
<tr>
<td>≥3</td>
<td>32</td>
<td>34</td>
<td>19–53</td>
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<table>
<thead>
<tr>
<th>Primary refractory</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Yes</td>
<td>16</td>
<td>38</td>
<td>15–65</td>
</tr>
<tr>
<td>No</td>
<td>173</td>
<td>43</td>
<td>36–51</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Prior SCT</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>64</td>
<td>45</td>
<td>33–58</td>
</tr>
<tr>
<td>No</td>
<td>125</td>
<td>42</td>
<td>33–51</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Bone marrow blasts</th>
<th>N</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>59</td>
<td>73</td>
<td>60–84</td>
</tr>
<tr>
<td>≥50%</td>
<td>130</td>
<td>29</td>
<td>22–38</td>
</tr>
</tbody>
</table>

Topp MS, et al. EHA 2014, Abstract S722 and oral presentation
Conclusions (for lymphomas)

- Chemotherapy is not likely to obtain more in B-cell malignancies
- Future progress most likely to be obtained by targeted drugs and immunotherapy
- One avenue of success may be the engagement of T cells against malignant B cells