Progress in Indolent Lymphoma: Is Chemotherapy Dead?

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Head of Hematology
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Treatment Modalities in Oncology
History of Chemotherapy: Alkylating Agents

WWI/WWII – chemical warfare
- Skin ulcerations
- Blindness
- Lung Damage
- Nausea, vomiting
- Mutagenic
- Carcinogenic
History of Alkylating Agents in Cancer Chemotherapy

• WWI/WWII – Mustard gas as chemical warfare (inhalation)
  – Accidental exposure led to low WBCs
  – May have similar effect on cancer cells
• 1940’s – first i.v. tx of lymphoma with mustard – impressive, brief responses
• Success led to development of others
### Alkylating Agents in Lymphoma/CLL

<table>
<thead>
<tr>
<th>NHL</th>
<th>Hodgkin’s</th>
<th>CLL</th>
<th>Various</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>MOPP</td>
<td>FCR</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>R-CVP</td>
<td>ABVD</td>
<td>BR</td>
<td>Busulphan</td>
</tr>
<tr>
<td>B-R</td>
<td>BEACOPP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEAM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
S8516
OS by Treatment

CHOP
MACOP-B
ProMACE-CytaBOM
m-BACOD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Death</th>
<th>5-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>225</td>
<td>150</td>
<td>46%</td>
</tr>
<tr>
<td>MACOP-B</td>
<td>218</td>
<td>149</td>
<td>45%</td>
</tr>
<tr>
<td>ProMACE-CytaBOM</td>
<td>233</td>
<td>150</td>
<td>46%</td>
</tr>
<tr>
<td>m-BACOD</td>
<td>223</td>
<td>146</td>
<td>46%</td>
</tr>
</tbody>
</table>

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Rationale For Eliminating Chemotherapy

• Non-specific effects
• Toxicity (acute and long-term)
• Many patients cannot tolerate it
• Most patients don’t want it
• New targeted agents
• Biological combinations have activity comparable to chemoimmunotherapy
Paul Ehrlich 1854-1915

“You see we must take aim - aim by chemical variation! The marvellous effect of an antibody in the serum is due to the fact that in no case it has affinity for the body substances but flies straight onward without deviation, upon the parasites.

The antibodies are therefore MAGIC BULLETS which find the targets themselves... we must therefore concentrate all our powers and abilities on making the aim as accurate as we can contrive, so as to strike the parasites as hard and the body cells as lightly as possible.”

circa 1904
Antibodies/Antigens
7-Year Results of GELA Study of CHOP ± Rituximab in Older Patients With DLBCL: OS

Survival probability

Years

7-y OS (%)

R-CHOP 53
CHOP 36

P=0.0004

The Important Questions

• Where are we going?

• How are we going to get there?
The Important Questions

• Where are we going?
  – Chemo-free therapies
  – Personalized treatments

• How are we going to get there?
  – Understanding tumor biology
  – Recognizing patient/tumor diversity
  – Good clinical trials
EFS for previously untreated patients responding to induction treatment

Martinelli G et al. JCO 2010;28:4480-4484
### CALGB-50402: Galiximab+Rituximab in Previously Untreated FL

<table>
<thead>
<tr>
<th>FLIPI Score</th>
<th>ORR (p=0.059)</th>
<th>CR (p=0.03)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>11 (92%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>2</td>
<td>20 (80%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>3-5</td>
<td>12 (55%)</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>

- ORR not associated with stage, gender, bulky disease, marrow involvement, or age > 60

Overall Survival

N = 59
Events = 5
**Brentuximab Vedotin Mechanism of Action**

- **Brentuximab vedotin (SGN-35) ADC**
  - monomethyl auristatin E (MMAE), potent antitubulin agent
  - protease-cleavable linker
  - anti-CD30 monoclonal antibody

1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis
# Relapsed/Refractory ALCL

**Brentuximab Vedotin: Key Response Results**

<table>
<thead>
<tr>
<th></th>
<th>IRF</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>86% (75, 94)</td>
<td>81% (69, 90)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>53%</td>
<td>59%</td>
</tr>
<tr>
<td>Partial remission</td>
<td>33%</td>
<td>22%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Histologically ineligible</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Median duration of OR (95% CI)</td>
<td>Not reached (36, –)</td>
<td>36 weeks (31, –)</td>
</tr>
<tr>
<td>Median duration of CR (95% CI)</td>
<td>Not reached (36, –)</td>
<td>Not reached (35, –)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>Not reached</td>
<td>41 weeks (23, –)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>
## Brentuximab Vedotin in HL: Response Results

<table>
<thead>
<tr>
<th></th>
<th>N=102</th>
<th>IRF</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate (95% CI)</strong></td>
<td></td>
<td>75% (65, 83)</td>
<td>72% (62, 80)</td>
</tr>
<tr>
<td>Complete remission</td>
<td></td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Partial remission</td>
<td></td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td></td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td></td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Younes A et al. JCO 2012;30:2183-2189
B-cell Receptor

Cell Proliferation, Migration, Growth, Survival

Efficacy in FL Patients
(Evaluable population with ≥ 1 response assessment, n=15)

<table>
<thead>
<tr>
<th>Strength</th>
<th>1.25 mg/kg/day (n=4)</th>
<th>≥2.5 mg/kg/day (n=11)</th>
<th>≥5.0 mg/kg/day (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25%</td>
<td>27.3%</td>
<td>33.3%</td>
</tr>
<tr>
<td>PR</td>
<td>25%</td>
<td>27.3%</td>
<td>22.2%</td>
</tr>
</tbody>
</table>

Median DOR: NE
Median PFS: NE 10.3 months 13.4 months 12.3 months 19.6 months
NF-κB Upregulated in WM via a MYD88 L265P mutation involved in TLR signalling pathway

- MYD88 is a TLR “adaptor protein” involved in the IRAK4 signaling leading to NFκB activation
- Ibrutinib occupies the BTK active site and prevents downstream phosphorylation caused by MYD88\textsubscript{L265P} in WM cells
- Selective BTK inhibition with ibrutinib blocks MYD88 signaling downstream of BTK and leads to apoptosis of WM cells

Presentation at the ASCO Annual Meeting 2012.
Bcl-2
Mcl-1
Bcl-xL

Idelalisib

Cell Proliferation, Migration, Growth, Survival

In iNHL, Single-Agent GS-1101 (CAL-101) at Doses $\geq 100$ mg BID Delivered a High Response Rate and Durable Tumor Control

**ITT Response Rate**

- **All** <100 mg BID \( \geq \)100 mg BID
- 0
- 20
- 40
- 60
- 80
- 100
- 38%
- 59%
- 12%

**a Cheson 2007 criteria**

**CAL-101 Dose**

- N=60
- N=26
- N=34

**Progression-Free Survival**

- All (N=60): Median = 8 cycles
- <100 mg BID (N=26): Median = 4 cycles
- $\geq 100$ mg BID (N=34): Median = 16 cycles

% Progression-Free
Lenalidomide in CLL and B-NHL

<table>
<thead>
<tr>
<th>Histology</th>
<th>ORR (%)</th>
<th>CR/CRu (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>32-45</td>
<td>7-9</td>
</tr>
<tr>
<td>Follicular/Indolent</td>
<td>23-51</td>
<td>7-13</td>
</tr>
<tr>
<td>DLBCL</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>MCL</td>
<td>28-53</td>
<td>8-20</td>
</tr>
</tbody>
</table>
### Response and event-free survival

<table>
<thead>
<tr>
<th></th>
<th>L (N=45)</th>
<th>L + R (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall (ORR)</strong></td>
<td>51.1%</td>
<td>72.7%</td>
</tr>
<tr>
<td></td>
<td>95% CI (35.8-66.3)</td>
<td>95% CI (52.2-85.0)</td>
</tr>
<tr>
<td><strong>Complete (CR)</strong></td>
<td>13.3%</td>
<td>36.4%</td>
</tr>
<tr>
<td><strong>Partial (PR)</strong></td>
<td>37.8%</td>
<td>36.4%</td>
</tr>
<tr>
<td><strong>Median EFS</strong></td>
<td>1.2 yrs</td>
<td>2.0 yrs</td>
</tr>
<tr>
<td><strong>2 year EFS</strong></td>
<td>27%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Median F/U 1.7 years (0.1 – 4.1)
Unadjusted EFS HR of L vs L+R is 2.1 (p=0.010)
Adjusted (for FLIPI) EFS HR of L vs L+R is 1.9 (p=0.061)
**CALGB 50803: Best response**

<table>
<thead>
<tr>
<th></th>
<th>Overall N =57</th>
<th>FLIPI 0-1 N = 17</th>
<th>FLIPI 2 N = 36</th>
<th>FLIPI 3 N = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>53 (93%)</td>
<td>16 (94%)</td>
<td>33 (92%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>CR</td>
<td>41 (72%)</td>
<td>13 (77%)</td>
<td>25 (70%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (21%)</td>
<td>3 (18%)</td>
<td>8 (22%)</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>2 (4%)</td>
<td>1 (6%)</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
</tbody>
</table>

There was no significant association between CR rate and FLIPI score, presence of bulky disease, or grade.

Martin et al, Proc ICML 2013
RELEVANCE Study Design
(Rituximab and Lenalidomide versus Any ChEmotherapy)

1st line FL
N=1000

• R+Chemo:
  • Investigator’s choice of R-CHOP, R-CVP, BR

• Lenalidomide 20mg for 6 cycles, then 10mg if CR

• LYSA (PI: Morschhauser) + North America (PI: Fowler)
**PD-L1 plays an important role in dampening the anti-tumor immune response**

The Nature of the Disease
Which Target?

- JAK-2
- BTK
- BCR
- Ras
- MEKK-1
- Raf
- Raf1
- MKK-7
- Ras
- ERK
- JNK
- mTOR
- PI3-K
- AKT
The Target Interactome

Where's the target?

Courtesy of I. Serebriiskii and E. Golemis, Fox Chase Cancer Center
Earliest Published Clinical Trials

• Daniel 1:11-20
  – Health of Hebrews fed a Kosher diet vs. Babylonians fed on a state diet

• Scurvy on the HMS Salisbury
  – cider vs. vinegar vs. lemons
# Phases of Clinical Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Endpoint</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Safety/Toxicity</td>
<td>3-6/level</td>
</tr>
<tr>
<td>II</td>
<td>Activity</td>
<td>14-~50</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Efficacy</td>
<td>More</td>
</tr>
<tr>
<td>IV</td>
<td>New indications</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Post-marketing issues</td>
<td></td>
</tr>
</tbody>
</table>
The Current Problem

- >7000 trials open to accrual in the U.S. (clinicaltrials.gov)
- 3% of patients go on studies
- Studies compete for same patients
- 63% of trials are ever completed
Problems in New Drug Development

- Slow rate of accrual to clinical trials
- Lack of good preclinical models
- Lack of surrogate endpoints
- False negatives – missing an active agent
- False positives – waste resources on ineffective agent
Who Conducts Clinical Trials

- Investigator initiated trials
- National Cancer Institute
- NCI-funded cooperative groups, cancer centers
- Pharmaceutical companies
Cost of Development of New Drugs (millions)

- 1970’s - $140
- mid-1980s - $320
- Late 1990s - $800
- Early 2000s - $1.2 billion
Help is on the Way – FDA to the Rescue!

- Accelerated approval
- Priority review
- Fast-track designation
- Breakthrough designation
From the Doctor’s Perspective
How do Doctors Benefit

• Attract patients
• Provide cutting edge therapy
• Potentially effective treatment options
• Leads to improved patient outcome
For Patients: Benefits

• Pleasing the health care team
• Earlier access to novel agents
• Free drugs
• Close monitoring
• Many layers of approval for care plan
• Help future patients
• Help make progress
• Hope
So ~ when should we consider clinical trials?

Until toxicities are minimal
Until everyone is cured
Drug Development: Present

New Agent

Phase I

Phase II

Active

Empiric Combinations

Limited Activity
Keys to Improving and Individualizing Therapy

- Recognize tumor diversity
- Understand tumor biology
The rule: Not all patients or diseases are created equal

The corollary: Therefore, not all therapies should be created equal
Antoni van Leeuwenhoek (1632-1723)

Invented the microscope around 1668
Contrast of Appearance vs. Gene Expression Profiling

Microscope

Low Risk

High Risk

Microarray

Treatment Advice

DLBCL

Germinal-center B-cell-like

Type 3

Activated B-cell-like
The Distinction Between the GCB and ABC Subtypes of DLBCL Retains Prognostic Significance with CHOP-Rituximab Therapy

A study of the Lymphoma Leukemia Molecular Profiling Project (LLMPP)
The better the treatment, the less relevant are the prognostic factors and the more relevant are the predictive factors

B. D. Cheson, 2013
Event-free survival by cytogenetic subgroups.
B Overall Survival

Probability of Overall Survival

- All patients
- No 17p or 11q deletions (n=29)
- 11q deletion (n=23)
- 17p deletion (n=28)

P=0.15 by log-rank test

Probability of Overall Survival

- Unmutated IGHV (n=69)
- Mutated IGHV (n=12)

P=0.86 by log-rank test

Byrd NEJM 2013
Prognostic Factors in WM

- Age more than 65 years
- Hemoglobin less than or equal to 11.5 g/dl
- Platelet count less than or equal to $100 \times 10^9/l$
- $\beta_2$-microglobulin more than 3 mg/l
- Serum monoclonal protein concentration more than 7.0 g/dl (estimated by densitometry)
Outcome By Prognostic Factor in WM
Issues For The Future

• How to select patients most likely to respond to a specific agent
• How to identify patients unlikely to respond
• How to treat patients who become resistant to treatment
• Do we approach iNHL as chronic diseases or go for cure?
• How to reduce the duration of treatment?
Conclusions

• Moving to a chemo-free world
• Novel new agents available that target
  – Cell surface (antibodies)
  – Intracellular pathways (kinases/proapoptotics)
  – Microenvironment (Imids, PD-1/PDL-1)
• Recognize the heterogeneity of lymphomas
• Develop rational combinations
• Leading to individualized therapy
• Important to accrue patients to clinical trials
• Increase the potential for cure
Towards a Chemo-free World in Indolent Non-Hodgkin Lymphoma

- MoAb
- MoAb#2 ADC
- PI3K
- BCR/Btk
- CD20
- CD-X
- Lenalidomide, PD-1/PDL-1

CURE

**Apoptosis**

**Proapoptotic**
Challenge to Trigger Paradigm Shift

CURE FOR CANCER

Paradigm Shift
Mind Shift

Patients & Advocates
Pharma. & Biotech Co.
Insurance & Guidelines $$$
Science & Medical
Government & Policy Makers
Breaking News

Long-Term Wine Drinking Linked to Low Lymphoma Death Rates

While scientists struggle to find common ground on alcohol consumption and its relationship to breast cancer, moderate wine drinkers may find comfort in a new study that links the beverage to lower death rates among female non-Hodgkin’s lymphoma sufferers.

According to an unpublished epidemiology study presented at the American Association for Cancer Research 100th Annual Meeting, held April 18–22 in Denver, those stricken with the ailment who drank wine regularly for 25 years before diagnosis enjoyed better survival rates five years after being diagnosed compared to nondrinkers. Wine drinkers were also more likely to be disease-free after five years.

Read more