Chemotherapy in lymphoma: Questions and currently available evidence

Prof. Dr. Peter Borchmann
1st Department of Internal Medicine
University of Cologne
Evidence? Cochrane!


Σ: Insufficient data and studies
Is there a controlled randomized trial comparing chemo with no-chemo?

Follicular lymphoma, first diagnosis

Ardeshna et al., Lancet, 2003
If there is no evidence, why are we then using chemotherapy in lymphoma?

Because we do see an obvious benefit!
A tribut to our pioneers:
Louis S. Goodman and Alfred Gilman

Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders

Goodman, J Am Med Assoc, 1946
Skipper and Schabel (1964):

- Doubling time of proliferating cancer cells is constant

- Cell kill by chemotherapy follows first-order kinetics (% of cells killed at a given dose is constant, regardless of tumor size):

  \[ \text{Ctx A (90\%) + Ctx B (90\%) = 99\% cell kill (2\log)} \]
Development of polychemotherapy: MOPP, CHOP, and ABVD in the 60ies and 70ies


How to use chemotherapy? 2/2

Goldie and Coldman (1976):

- assumptions: Tumors have an inherently higher mutation rate vs. normal cells and with progression, there appears to be an increase in mutation rate

- Probability of resistance cells depends on tumor size – Based on size of detectable tumors ($10^9$) and mutation frequency ($10^{-5}$) ~ $10^4$ resistant cells at time of diagnosis

Use multiple agents in short intervals to avoid resistance: „Alternating schedules“ of the 80ies
Chemotherapy of Advanced Hodgkin's Disease with MOPP, ABVD, or MOPP Alternating with ABVD

No improvement!

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>No. (%) of Treatment Failures</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP</td>
<td>123</td>
<td>44 (36)</td>
<td>None</td>
</tr>
<tr>
<td>ABVD</td>
<td>115</td>
<td>32 (28)</td>
<td>None</td>
</tr>
<tr>
<td>MOPP–ABVD</td>
<td>123</td>
<td>31 (25)</td>
<td>None</td>
</tr>
<tr>
<td>All</td>
<td>361</td>
<td>107 (30)</td>
<td>None</td>
</tr>
</tbody>
</table>
Applied theory in aggressive B-NHL: Improving CHOP by adding drugs


Survival (%)

- CHOP
- MACOP-B
- ProMACE-CytaBOM
- m-BACOD

<table>
<thead>
<tr>
<th></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>

Years after registration

„the more the better“ is too simple

G-CSF and Dose Intensification, the 90ies

Conventional therapy
i.e. 8 x ABVD

BEACOPP escalated

0 3 6 9 12 15 18 21 weeks

0 3 6 9 12 15 18 21 weeks

1 4 8 12 16 20 24 28 weeks
COPP/ABVD versus BEACOPP: Proof of principle in advanced HL

The GHSG HD9 trial

COPP/ABVD
BEACOPPbase  A (75%)
BEACOPPesc  B (80%)

p <0.001

Limits of intensification in lymphoma therapy: The HDR2 trial

- 2x DHAP + G-CSF
  PR or CR: continue

- Single agent HD Ctx
  - Cyclophosphamide
  - Mtx, Vcr
  - Etoposide

- BEAM + APBSCT
HDR2: Increase of toxicity overcomes efficacy

However, even 60% of relapsed patients will be cured

Josting et al., 2010 Dec 1;28(34):5074-80
Where to go from here?
First of all: Understanding Malignancy

From Hanahan and Weinberg, *Cell, Vol. 100, 57–70, January 7, 2000*
Hallmarks of Malignancy

From Hanahan and Weinberg, *Cell*, 2011
HL and the Hodgkin Reed Sternberg (HRS) cell

A B-cell without B-cell receptor: why can it survive?

Surrounded by cells of the immune system: why is it not being attacked?
Antibody therapy: the revolution

From Paul Ehrlich, 1900 to therapeutics, 100 years later

From Schulman et al., 2001
How do antibodies work in contrast to chemotherapy?

- **CDC (complement dependent cytotoxicity)**
- **ADCC (antibody dependent cellular cytotoxicity)**
- **Signal transduction (induction of apoptosis)**
- **Indirect**: inhibition of pro-proliferative factors or angiogenesis
Rituximab: the billion dollar antibody

Do we have evidence?

- No clear phase I result: optimal dose and schedule are unknown
- No proven concept of its complex mechanism of action, however, CD20 positive B-cells are depleted
- Single agent activity in B-NHL is modest ("50% drug"), even in indolent lymphoma
- therefore, it is not being used frequently in its first approved indication

Is this a case for Dr. Cochrane?
Meta-analysis of overall survival among patients who received **rituximab** with chemotherapy (R-chemo) or chemotherapy alone.

### B.

<table>
<thead>
<tr>
<th>Sub-category, study</th>
<th>R-chemo N/n</th>
<th>Chemotherapy N/n</th>
<th>HR 95% CI</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follicular lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forstpointner 2004*</td>
<td>4/35</td>
<td>8/30</td>
<td>3.24</td>
<td>0.38 (0.12 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Hiddemann 2005</td>
<td>14/105</td>
<td>24/96</td>
<td>10.31</td>
<td>0.45 (0.24 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>Marcus 2005</td>
<td>6/223</td>
<td>17/205</td>
<td>23.89</td>
<td>0.60 (0.40 to 0.92)</td>
<td></td>
</tr>
<tr>
<td>van Oers 2006</td>
<td>21/162</td>
<td>28/159</td>
<td>13.33</td>
<td>0.70 (0.40 to 1.23)</td>
<td></td>
</tr>
<tr>
<td>Total no. patients:</td>
<td>759</td>
<td>721</td>
<td>31.82</td>
<td>0.74 (0.52 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Total no. events:</td>
<td>97</td>
<td>142</td>
<td>82.59</td>
<td>0.63 (0.51 to 0.79)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 2.83, df = 4 (P = .59), I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.97 (P&lt;.001)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Mantlecell lymphoma** |             |                  |           |            |             |
| Forstpointner 2004*    | 8/24        | 18/24            | 3.26      | 0.19 (0.06 to 0.59) |
| Hiddemann 2005        | 14/44       | 17/46            | 8.43      | 0.68 (0.34 to 1.37) |
| Lenz 2005             | 10/62       | 11/60            | 5.71      | 0.96 (0.41 to 2.26) |
| Total no. patients:   | 130         | 130              | 17.41     | 0.60 (0.37 to 0.9) |
| Total no. events:     | 32          | 46               |           |            |             |
| Test for heterogeneity: $\chi^2 = 5.21, df = 2 (P = .07), I^2 = 61.6\%$ |
| Test for overall effect: $Z = 2.04 (P = .04)$ |

Spreading of Rituximab in lymphoma since 1998

- **Approved as single agent** in patients
  - In relapsed or resistant *follicular lymphoma* patients

- **In combination with chemotherapy** in patients with
  - untreated follicular NHL, stage III-IV
  - CD20 positive untreated *diffuse large B-cell lymphoma* (CHOP)
  - Untreated or relapsed or refractory *chronic lymphocytic leukemia*

- **As maintenance** therapy after
  - response to first line therapy
  - response to second line therapy
Beyond naked antibodies: Magic bullets!?

Antibody drug conjugate Brentuximab vedotin
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody

ADC binds to CD30
MMAE disrupts Microtubule network
ADC-CD30 complex traffics to lysosome
MMAE is released
Apoptosis
G2/M cell cycle arrest
Brentuximab Vedotin (SGN-35): dramatic response rate in relapsed HL (phase II)

94% (96 of 102) of patients achieved tumour reduction

**Complete remission by PET**

**PLUS: Excellent tolerability!**

Chen et al ASCO 2011
Hallmarks of Malignancy

- Emerging Hallmarks
  - Deregulating cellular energetics
  - Avoiding immune destruction
  - Genome instability and mutation
  - Tumor-promoting Inflammation

From Hanahan and Weinberg, *Cell*, 2011
Understanding malignancy becomes more and more sophisticated

From Hanahan and Weinberg, *Cell*, 2011
Targeted therapy in lymphoma 2011

<table>
<thead>
<tr>
<th>Research Name</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Drug Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bcl-2-targeted drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT-101</td>
<td>Gossypol (levo gossypol)</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>GX15-070</td>
<td>Obatoclax</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>ABT-263</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>RAD-001</td>
<td>Everolimus</td>
<td>Certican®</td>
<td>Small molecule</td>
</tr>
<tr>
<td>--</td>
<td>Rapamycin (also called sirolimus)</td>
<td>Rapamune®</td>
<td>Small molecule</td>
</tr>
<tr>
<td>CCI-779</td>
<td>Temsirolimus</td>
<td>Torisel®</td>
<td>Small molecule</td>
</tr>
<tr>
<td>AP23573</td>
<td>Deforolimus</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>OSI-027</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>KRX-0401</td>
<td>Perifosine</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>--</td>
<td>Triciribine</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td><strong>m-TOR inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK690693</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>BGT226</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>CAL-101</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td><strong>Akt inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAHA (suberoyl anilide hydroxamic acid)</td>
<td>Vorinostat</td>
<td>Zolinza®</td>
<td>Small molecule</td>
</tr>
<tr>
<td>PXD101</td>
<td>Belinostat</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>SNDX-275</td>
<td>Entinostat</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>MS-275</td>
<td>Panobinostat</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>LBH589</td>
<td>Romidepsin (also called depsipeptide)</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td><strong>PI3-K inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITF2357</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>PCI-24781</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>--</td>
<td>--</td>
<td>Small molecule</td>
</tr>
</tbody>
</table>
Perspectives of systemic therapy in malignant lymphoma

Likelihood of cure?
Currently available evidence of chemotherapy in lymphoma?

The golden era of chemotherapy has passed by, however, cytotoxic chemotherapy obviously cures lymphoma patients and will remain the comparator and the backbone for any new development.
Questions concerning systemic therapy in lymphoma?

To do´s for lymphomaniacs in 2011 (first 5/1 Mio):

1. To restrict the burden of chemotherapy to those being in need of it
2. To refine our understanding of the immune system and the microenvironment of tumors
3. To keep academic independence
4. To implement molecular diagnostics into the selection process for therapeutic developments and interventions
5. To perform high quality studies allowing the CHMG to easily perform high quality meta-analyses
The ABC rule for an obvious benefit

- A benefit that clearly outweighs all possible 
  *adverse* effects (whether frequent and mild, or rare and severe);

- However, is there anything worse than 
  dying from lymphoma?

- An intervention that is obviously beneficial in 
  all *contexts* in which it will be applied