French Experience with Lymphoblastic Lymphoma

LMT & EORTC Protocols

C Patte, Gustave Roussy, France

Cesme, May 6th 2016
TPOG meeting

pT-LL
mainly MEDIASTINAL

pB-LL
mainly (sub)cutaneous or bone

The CCSG randomized trial

Lymphoblastic lymphoma

Anderson J, NEJM, 1983:308, 559
AFTER 1980: for lymphoblastic lymphoma

Necessity of a specific treatment SIMILAR to those of HIGH RISK LEUKEMIAS
- Intensive, semi-continuous
- numerous drugs
- ~ 2 years duration
- CNS prophylaxis

- LSA2L2 derived protocols
- non-B BFM protocol → EFS ≥ 75%
LMT 81 protocol (Gustave Roussy)

= LSA2L2 protocol with HD-MTX
84 patients (1981-1989)

Similar results by stage
EFS = 75%
Only 1 CNS relapse
SFOP LMT 89 protocol

Derived from the LMT81 protocol,
But with « intensified » induction phase (2 COPAMD)

No improvement of EFS

EFS = 69% ± 9 ; OS = 79% ± 9 (5-y median FU)
SFOP LMT 96 protocol

« Derived » from the BFM non-B protocols
with elements of the previous LMT protocols

From BFM: general BFM scheme with non modified re intensification

With "LMT arrangements":
- BFM induction modified by earlier introduction of cyclo and HDMTX
- HD MTX = 3g/m², 10 courses
- Re inductions during maintenance
- Maintenance reduced to 18 m for st I-III
SFOP LMT 96 protocol

<table>
<thead>
<tr>
<th>Protocole I A / IB</th>
<th>Protocole M</th>
<th>Protocole II</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>MACAO</td>
<td>MACAO</td>
<td>Inter $\phi$</td>
</tr>
</tbody>
</table>

- Days: 7, 36, 64
- Weeks: 1, 9, 20, 28, 52, 104
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRED</td>
<td>p.o.</td>
<td>60 mg/m²/d</td>
</tr>
<tr>
<td>VCR</td>
<td>i.v.</td>
<td>1.5 mg/m²</td>
</tr>
<tr>
<td>DNR</td>
<td>i.v.</td>
<td>(24h) 40 mg/m²</td>
</tr>
<tr>
<td>L-ASP</td>
<td>i.v.</td>
<td>10,000 U/m²</td>
</tr>
<tr>
<td>CPM</td>
<td>i.v.</td>
<td>1000 mg/m²</td>
</tr>
<tr>
<td>HD MTX</td>
<td>i.v.</td>
<td>3000 mg/m²</td>
</tr>
<tr>
<td>ARA-C</td>
<td>i.v.</td>
<td>75 mg/m²/d</td>
</tr>
<tr>
<td>MTX</td>
<td>i.th.</td>
<td></td>
</tr>
</tbody>
</table>
MACAO 2

VCR i.v. 1.5 mg/m²
L-ASP i.v. 10,000 U/m²
CPM i.v. 1,000 mg/m²
HD MTX. 3,000 mg/m²
ARA-C i.v. 75 mg/m²/d
MTX i.th.  

Day 1  8   15  22  29
Interphase

6-MP p.o. 50 mg/m²/d

MTX 3 g/m² 3h infusion

MTX i.t.

Day 1 8 15 22 29
### Maintenance therapy + 6 pulse re-inductions

**Maintenance therapy:**
- 6 mercaptopurine 50 mg/m²/D
- Methotrexate PO 25 mg/m²/week

<table>
<thead>
<tr>
<th>Pulse A (month 1, 3, 5)</th>
<th>Pulse B (month 2, 4, 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine 1,5 mg/m² D1</td>
<td>Prednisone PO 60 mg/m² D1 to 5</td>
</tr>
<tr>
<td>Methotrexate 3 g/m² D1</td>
<td>Aracytine SC 50 mg/m² D1 to 4</td>
</tr>
<tr>
<td>Methotrexate (IT) D2</td>
<td>E. Coli asparaginase 25 000 U/m² D2</td>
</tr>
</tbody>
</table>

**Total duration:** 18 months for st I - III
- 24 months for st IV

**E. Coli asparaginase 25 000 U/m² D2**
median age: 10 y (1.9–17)
89%: mediastinal involvement

3 st I/II (3%),
47 st III (59%).
22 st IV (29%)
(BM=17, CSF=3, and both=2)
7 non staged (corticosteroids)

5y OS = 89% (11 deaths: 1 early progr, 8 relapse, 2 2nd K)

No prognostic factor was found
Protocoles EORTC 58881 & 58961

- **Common protocols with ALL**
  - BFM scheme with total duration of 24 months without local, nor cranial irradiation
- **EORTC 58881**: 3 randomizations:
  - Asparaginase E. Coli vs Erwinia
  - Adjunction of HD Arac (interval therapy)
  - 6-mercaptopurine IV during maintenance
- **EORTC 58961**: 3 randomizations
  - pred vs Dexa
  - Long vs short aspa
  - pulses VCR
Protocole EORTC 58881
119 pts

median age: 10 y (1.9–17)
81%: mediastinal involvement

14 st I/II (16%),
79 st III (66%).
26 st IV (22%), CNS=3

6y OS = 86% (SE = 3%)
Non significant differences between the 3 arms of randomization

EFS = 77.5% (SE = 4%)
Protocoles EORTC 58881 & 58951

- EORTC 58881
  - N=119
  - 6 y EFS : 77.5%
  - OS 6 yrs: 86%

- EORTC 58951
  - N=74
  - EFS 8 yrs: 85.1%
  - OS 8 yrs: 86.5%
58951: EFS and OS according to response to prephase

EFS

OS

Wald test for linear trend: P=0.003

Wald test for linear trend: P=0.004

Slides from Y Bertrand
58951: randomization: Pred vs dexa

**EFS**

- 89.2% (SE= 5.1%)
- 81.1% (SE= 6.4%)

**OS**

- 91.9% (SE= 4.49%)
- 81.2% (SE= 6.44%)

*Slides from Y Bertrand*
58951: randomization: short vs long aspa (71 NHL)

58951: DFS from random. (step 2)

NHL

93.3%

82.9%

Overall Logrank test: p=0.195

EFS status (4 cat)

<table>
<thead>
<tr>
<th></th>
<th>ShortAspa (N=41)</th>
<th>LongAspa (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoCR</td>
<td>1 (2.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CCR</td>
<td>34 (82.9)</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td>relapse</td>
<td>3 (7.3)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>TRM</td>
<td>3 (7.3)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

HR: 0.37, 99% (0.05, 2.91)

58951: OS from random. (step 2)

NHL

96.7%

82.9%

Overall Logrank test: p=0.076

HR: 0.19, 99% (0.01, 2.91)
From 1989 to 2008
53 patients

Stage I 10
Stage II 9
Stage III 9
Stage IV 25

BM: 23
CNS: 3
Sites: cutaneous = 12
bone = 12

B Lymphoblastic lymphoma:
LMT 96 + EORTC 58881 & 58951 studies

5y EFS = 82% (95%CI: 69-90%)
5y OS = 85% (95%CI: 72-93%)

Events:
2 progressions
6 relapses
2 2nd K

5y EFS
stage I-III = 93%
Stage IV = 71%

Ducassou, BJH, 2010
Very poor outcome of Relapses

BFM experience
(Burkhardt JCO 2009, 27, 3363)

LMT 96 + EORTC 59881: 23 patients
(18 T-LBL and 5 pB-LBL).
8 y OS = 8.7% (21 deaths).
no prognosis factor found in lymphoblastic NHL (BFM)

<table>
<thead>
<tr>
<th>Factor</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>ns</td>
</tr>
<tr>
<td>Age &gt;10 years</td>
<td>ns</td>
</tr>
<tr>
<td>Stage</td>
<td>ns</td>
</tr>
<tr>
<td>LDH&gt; 2N</td>
<td>ns</td>
</tr>
<tr>
<td>T immunophenotype</td>
<td>ns</td>
</tr>
<tr>
<td>Response at D33</td>
<td>ns</td>
</tr>
<tr>
<td>Response after induction</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ Challenge to find clinical and biological prognosis factors
BFM trials 95, 90, and 86.

5 y EFS for all lymphoblastic lymphoma patients

<table>
<thead>
<tr>
<th>study</th>
<th>Induction Phase I/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL-BFM</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Dauno</td>
</tr>
<tr>
<td>(days)</td>
<td>mg/m²</td>
</tr>
<tr>
<td>NHL 86</td>
<td>42</td>
</tr>
<tr>
<td>86</td>
<td>4 x 40</td>
</tr>
<tr>
<td></td>
<td>8 x 10,000</td>
</tr>
<tr>
<td>E.coli</td>
<td></td>
</tr>
<tr>
<td>NHL 90</td>
<td>35</td>
</tr>
<tr>
<td>90</td>
<td>4 x 30</td>
</tr>
<tr>
<td></td>
<td>8 x 10,000</td>
</tr>
<tr>
<td>E.coli/Erwinia</td>
<td></td>
</tr>
<tr>
<td>NHL 95</td>
<td>35</td>
</tr>
<tr>
<td>95</td>
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<td></td>
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<td>E.coli</td>
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From Burkardt, JCO, 2006, 24:491-499
EURO-LB-02: European study for lymphoblastic lymphoma
Based on BFM90 protocol without cranial RTH

1. To define pc factors and ameliorate knowledge on biology in a large series of patients
2. To see if BFM results can be reproduced in a large inter-group study
2. does Dexamethasone vs Prednisone in induction improve outcome of T-LBL patients? (R)
3. can the duration of maintenance be reduced by 6 months for T-LBL-patients? (R)
4. to evaluate the prognostic impact of clinical (early response) and biological parameters

Evaluation: about 120 pts per year in Europe
EURO-LB-02 PROTOCOL

Induction  | Consolidation  | Re-Induction  | Maintenance

I/1-PRED  |  |  | 24 mois

P  |  |  | 6-MP/MTX

Random 1  | I/2  | M  | Prot. II

6-MP/MTX

18 mois

Precursor-T-cell-LBL: Randomisation 1+2
Precursor-B-LBL: Bras de référence
EURO LB-02 TRIAL : Patients

351 patients included and 319 eligibles

<table>
<thead>
<tr>
<th>Study group</th>
<th>Total</th>
<th>Protocol patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>AIEOP</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>BFM+CoALL</td>
<td>192</td>
<td>171</td>
</tr>
<tr>
<td>DCOG</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>NOPHO</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>PPLLSG</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>SFCE</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>UKCCSG</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>351</strong></td>
<td><strong>319</strong></td>
</tr>
</tbody>
</table>
EURO LB-02 TRIAL : Patients

<table>
<thead>
<tr>
<th>Male gender</th>
<th>229 (72%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.7 y (0.3-18)</td>
</tr>
<tr>
<td>233 T et 66 p B</td>
<td>(other: biphenotypes)</td>
</tr>
<tr>
<td>Stage I</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>29 (9%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>176 (55%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>73 (23%)</td>
</tr>
</tbody>
</table>

BM positive: 67 (21%)
CNS pos: 11 (3%)
EURO LB-02 TRIAL : Results

(A. Reiter)

EVENTS

Toxic death 12 (3.8%)
No response 4 (1.3%)
Relapse 39 (12%)

Local +/- new 15
EURO LB-02 TRIAL: Results

(A. Reiter)
Euro-Lb 02: Randomizations

- **Randomization dexamethasone vs prednisone in induction**
  186 (78%) / 239 eligible patients were randomized:
  - 88 prednisone arm
  - 98 dexamethasone arm (2 received prednisone)

- **Randomization therapy duration: 18 vs 24 months**
  119 (74%) / 161 eligible T-LBL patients were randomized
  - 56 in 18 month arm
  - 63 in 24 months arm
Randomisation rate among the countries

<table>
<thead>
<tr>
<th>Study group</th>
<th>Total</th>
<th>Off protocol patients randomized (among those eligible)</th>
<th>Patients for the 2nd randomization eligible, randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIEOP</td>
<td>24</td>
<td>9 (50.0%)</td>
<td>6 (66.7%)</td>
</tr>
<tr>
<td>BFM+COALL</td>
<td>171</td>
<td>101 (82.8%)</td>
<td>70 (78.7%)</td>
</tr>
<tr>
<td>DCOG</td>
<td>16</td>
<td>6 (54.5%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>NOPHO</td>
<td>15</td>
<td>9 (75.0%)</td>
<td>6 (75.0%)</td>
</tr>
<tr>
<td>PPLLSG</td>
<td>33</td>
<td>19 (67.9%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>SFCE</td>
<td>52</td>
<td>37 (86.0%)</td>
<td>23 (85.2%)</td>
</tr>
<tr>
<td>UKCCSG</td>
<td>8</td>
<td>5 (100%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>319</strong></td>
<td><strong>186 (77.8%)</strong></td>
<td><strong>119 (73.9%)</strong></td>
</tr>
</tbody>
</table>
Euro-Lb 02: Randomizations: results

(A. Reiter)
• No CNS relapse in dexa arm while 7/38 progression/relapses were CNS relapses in the patients receiving prednisone in phase Ia
• BUT more toxicity in dexa arm with more grades 3 et 4 and more delay to start phase Ib

• Toxic death rate: more than expected
Stopping rules: twice. After a first suspension, the study had to close definitively in August 2008, because of the too high toxic death rate
No difference between pred (3.72%) and dexta (3.85%)
EURO-LB-02 TRIAL : conclusions

- Study difficult to manage, with a higher toxic death rate than expected, leading to the premature closure of the study, and in consequence the impossibility to answer to the randomized questions.

- However a large series of patients could be included with a good survival rate in a multicentric study and showing the possibility to run studies within Europe.

- National biological studies have started on the patients of the study.
How to progress in lymphoblastic lymphoma?

Better identification of the high risk patients?
- Early response: by imaging? PET?
- MDD/MRD?
- Biologic characteristics?
Conclusions on lymphoblastic lymphoma

• Survival > 75%, but treatment is difficult, prolonged and with toxicity

→ Necessity to find prognostic factors to try to adapt intensity of treatment, especially in "favorable forms"

• Place of PET to evaluate early response?
  - of new biological markers?

BUT, necessity to confirm on larger series

→ Importance of International clinico-biologic studies

• New therapeutic approaches? Notch inhibitors, nucleoside purine analogs …
Thank you for your attention