Lymphomas
One of the most frequent tumors in TYA

15-19 years

2000-2008 France, E. Desandes
Incidence of lymphomas according to age

Hodgkin

Median age : 30 y

3.6% of the patients < 30 y

Roman, Histopathology 2011
Lymphoma: therapeutic challenges

- 5-y survival rates over 90% in HL and 75% in NHL in Europe (Trama 2016)

- Therapeutic challenges:
  - to early identify the small group of patients at high risk of failure requiring new therapeutic approaches
  - to reduce the burden of treatment in low and intermediate risk patients in order to limit short and long-term morbidity related to treatment.
Lymphomas in TYA

Heterogeneity of treatment according to age and site of care in patients in transition between childhood and adulthood

15-19 y

15-25 y

15-39 y
Specific centers requirement

- a multi-professional approach
- opportunity to propose inclusion in trials available for this age group,
- fertility counselling,
- adapted psycho-social support
- a long-term follow-up in order to detect late morbidity of treatment
staging
Lymphomas
TEP in initial staging

**Pediatric protocols**
- optional for NHL
- mandatory for HL

**Adult protocols**
- Included in initial staging for HL and NHL
Ann Arbor classification

I  A single nodal or extra-nodal tumour

II : ≥2 nodal areas or extranodal tumours on the same side of the diaphragm

III : > 2 nodal areas on both sides of the diaphragm

IV : non contiguous extra-lymphatic involvement
St Jude’s staging system for childhood NHL

I : A single nodal or extra-nodal tumour except mediastinum and abdomen
II : ≥2 nodal areas or extranodal tumours on the same side of the diaphragm
III : > 2 nodal or extra-nodal areas on opposite site of the diaphragm
Extensive thoracic or abdominal disease
IV : Bone marrow or CNS involvement
## Hodgkin lymphomas

### Group of risks

<table>
<thead>
<tr>
<th>Low/early favorable</th>
<th>Pediatric</th>
<th>Adult (LYSA/EORTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and IIA</td>
<td>I and IIA without risk factors</td>
<td></td>
</tr>
</tbody>
</table>
| Intermediate/Early-stage unfavorable | IIB, IIIA  
No E extension | I and II with $\geq 1$ risk factor |
| High/Advanced stage | IIB with E extension  
IIIB IV | III and IV |

### Risk factors
- **Pediatric:** Bulky mass $> 200$ ml, ESR $> 30$
- **Adult:** Large mediastinal mass, age $> 50$, elevated ESR, $> 4$ nodal areas
Agressive NHL
International prognostic Index

Table 2. — Variables in the International Prognostic Index (IPI) and the Age-Adjusted IPI

<table>
<thead>
<tr>
<th>IPI</th>
<th>Age-Adjusted IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Advanced stage of disease (III, IV)</td>
</tr>
<tr>
<td>Advanced stage of disease (III, IV)</td>
<td>Elevated lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1 site</td>
<td>Poor ECOG performance status ≥ 2</td>
</tr>
<tr>
<td>Elevated lactate dehydrogenase (LDH)</td>
<td></td>
</tr>
<tr>
<td>Poor ECOG performance status ≥ 2</td>
<td></td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group.
Use age-adjusted IPI (aa IPI) for younger patients

<table>
<thead>
<tr>
<th>Groups risks</th>
<th>Standard IPI</th>
<th>aa IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>Low intermediate risk</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>High intermediate risk</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>High risk</td>
<td>4-5</td>
<td>3</td>
</tr>
</tbody>
</table>

Ziepert M, JCO 2010
Survie en fonction du score IPI

6696 patients inclus dans les études randomisées du GELA

Overall survival

Progression-free survival
Hodgkin Lymphoma
Hodgkin: a TYA tumor

Median age: 30 y

Roman, Histopathology 2011
European trial for HL < 18
Inclusion: 2007-2013
Aims:
- Avoid radiotherapy for pts with TEP negative after 2 courses
- Replace procarbazine by Dacarbazine (COPP vs COPDAC) during maintenance

OEPPA

Prednisone: 60 mg/m² J1-15
Vincristine: 1,5 mg/m² J1, J8, J15
Adriamycine: 40 mg/m² J1, J15
VP-16: 125 mg/m² J1-5
2111 patients (median age 14)
50% of patients treated with RT
EFS at the latest interim analysis (median FU 48m)
- TG1 (716 pts) : 88% (OS : 98%)
  • TG2 (490 pts) : 91%
  • TG3 (805 pts) (86.6%)
- No difference with and without RT
- No difference COPP vs COPDAC
Treatment in adults

Early stage favorable
- 2-3 courses of ABVD + IFRT 20-30 Gy

Early stage unfavorable
- 4 courses of ABVD + IFR 30 Gy

Advanced stages
- 6-8 BEACOPP or ABVD
Multiple head-to-head, randomized comparisons of these 2 regimens:

- **Overall results**
  - similar 10 y-OS 75% to 85%
  - improved 10 y PFS with BEACOPP (75%-80%) vs ABVD (65%-70%) in ABVD

- esc BEACOPP: increased rates of
  - acute toxicity (neutropenia, infection)
  - long term toxicity (infertility, secondary malignancies)
Early PET response adapted strategy in adults
Early-stage HD patients

2006-2011 1950 pts included

H10F
- 2 ABVD
  PET
- 2 ABVD
  - 1 ABVD + INRT
  + 2 BEACOPPesc + INRT

H10U
- 2 ABVD
  PET
- 4 ABVD
  + 2 BEACOPPesc + INRT

Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Marc PE. André, Théodore Girinsky, Massimo Federico, Oumédały Reman, Catherine Fortpied, Manuel Gottí, Olivier Casasnovas, Pauline Briée, Richard van der Maazen, Alessandro Re, Véronique Edeline, Christophe Ferré, Gustauvan Imhoff, Francesco Merli, Réda Bouabdallah, Catherine Sebben, Lena Specht, Aspasia Stamatsoullas, Richard Delarue, Valeria Fiaccadori, Monica Belli, Tiana Raveloarivahy, Annibale Versari, Martin Hutchings, Michel Meignan, and John Raemaekers
Stage I and II A PET after 3 ABVD

- PET positive: 4th cycle ABVD + IFRT
- PET negative: randomization
  - No further treatment
  - IFRT
- 2003-2010: 602 pts included
# Cumulative dose of drugs

<table>
<thead>
<tr>
<th>mg/m²</th>
<th>OEPAx2 + COPDACx2</th>
<th>ABVDx6</th>
<th>BEACOPPesc x6</th>
</tr>
</thead>
<tbody>
<tr>
<td>bleomycin</td>
<td>0</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>doxorubicine</td>
<td>160</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>etoposide</td>
<td>1250</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0</td>
<td>2000</td>
<td>0</td>
</tr>
<tr>
<td>Vincristine /vinblastine</td>
<td>9</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>dacarbazine</td>
<td>0</td>
<td>1500</td>
<td>4500</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3000</td>
<td>0</td>
<td>3360</td>
</tr>
</tbody>
</table>
Previously untreated stage III and IV HL
1334 pts > 18 y randomized between 2012 and 2016
Brentuximab + AVD (A–AVD) vs ABVD

Peripheral neuropathy
67% A+AVD
43% ABVD
Treatment of relapses

- Second line of CT and a consolidation with BEAM and autologous HSCT
- Several second line regimens
  - ICE (ifosfamide, carboplatin, etoposide),
  - DHAP (dexamethasone, cytarabine and cisplatinum),
  - BeGEV (bendamustine, gemcitabine, prednisolone, vinorelbine)
- Role of new drugs: Brentuximab vedotin, PD1 inhibitors ++++
Long term morbidity

- second malignancies
- cardiotoxicity including coronary heart disease and congestive heart failure
- fertility impairment
- pulmonary fibrosis
- hypothyroïdy
Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: a systematic review and meta-analysis of randomized clinical trials

Dennis A. Eichauer,1 Ingrid Becker,2 Ina Monsef,3 Nicholas Chadwick,4 Vitaliana de Sanctis,5 Massimo Federico,6 Catherine Fortpied,7 Alessandro M. Gianni,8 Michel Henry-Amar,9 Peter Heskin,10 Peter Johnson,11 Stefano Luminari,6 Monica Bello,6 Alessandro Pulsoni,12 Matthew R. Sydes,13 Pinuccia Vaigussa,8 Simonetta Viviani,8 Andreas Engert,1 and Jeremy Franklin2

Figure 3.
Additional radiotherapy, cumulative incidence of SMN (Peto meta-analysis). Vertical bars depict approximate 95% confidence intervals (CI) for cumulative incidence rates. CT chemotherapy; RT: radiotherapy.

Figure 5.
Intensified chemotherapy, cumulative incidence of SMN (Peto meta-analysis). Vertical bars depict approximate 95% confidence intervals (CI) for cumulative incidence rates. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine.
Non Hodgkin’s Lymphomas
Repartition of histologic subtypes according to age
Mature B cell lymphomas
Mature B cell lymphomas

- > 50% of NHL in TYA
- 3 main subtypes
  - Burkitt’s lymphoma
  - Diffuse large B cell lymphoma
  - Primary mediastinal B cell lymphoma
  - Grey Zone lymphomas
  - Follicular lymphomas
  - Marginal zone lymphomas
  - Primary CNS lymphomas
Burkitt lymphomas

- **Clinical characteristics**
  - Rapidly progressive *abdominal mass* + ascites or ENT sites
  - Advanced stages with high rates of bone marrow and CNS involvement
  - Early relapses (< 1 y)

- **Urgent medical intervention**
  required for diagnosis, staging and treatment

- **Tumor lysis syndrome** +++
Burkitt lymphomas
Biology

- Proliferation of lymphoblasts with specific cytology and histologic characteristics

  - Immunophenotype:
    - B phenotype - CD20+
    - CD10+ (germinal center)
    - bcl6+ / bcl2 -
    - Ki67 > 90%

- Translocation MYC/IGH (80%) or MYC/IGL (10%) - t(8;14) or variant t(8;22) ou t(2;8)

- Recurrent additional abnormalities: gains 1q et 13q, et del17p
Overlap between Burkitt and DLBCL

- **GEP studies identify**:
  - Histologically defined Burkitt lymphomas (BL)
  - Molecularly defined Burkitt lymphomas (mBL) : 30% of histologically defined children and adolescent DLBCL

- **Characteristics of DLBCL in TYA**
  - High proliferation rate
  - Germinal center subtype in most cases
  - High incidence of \textit{MYC} translocation (>30%) de \textit{MYC} (in mBL) vs 10-15% in adult DLBCL
  - Low expression of \textit{bcl2}
  - High incidence of translocations \textit{IG/IFR4} as compared to adults

Swerdlow 2016, Ott 2017, Klapper 2008
No clear cut-off between children, TYA and older adults

The incidence of biologic features associated with a poor prognosis (ABC subtype, double hit translocations or genetic complexity) increases with age

Very few data on patients aged 18-30 since young adults are defined in NHL as < 60 y
Treatment of mature B cell lymphoma in children and adolescent

- Same regimens for Burkitt and DLBCL
- Treatment stratified on:
  - Initial resection
  - LDH level
  - Bone marrow and CNS involvement
  - Early response to prephase
- Principles of treatment:
  - Short and intensive chemotherapy (2-4 months)
  - Fractionated cyclophosphamide
  - CNS prophylaxy by HDMTX et IT
  - Rituximab only for high risk patients (stage III high LDH and IV)
LMB89 : EFS according to histology

- Burkitt's
- Large cell
- Not classified

Years: 0 1 2 3 4 5 6 7 8 9 10 11

Survival rates:
- 92%
- 89%
Advanced Stage, Increased Lactate Dehydrogenase, and Primary Site, but Not Adolescent Age (≥ 15 Years), Are Associated With an Increased Risk of Treatment Failure in Children and Adolescents With Mature B-Cell Non-Hodgkin’s Lymphoma: Results of the FAB LMB 96 Study

Mitchell S. Cairo, Richard Sposto, Mary Gerrard, Anne Auperin, Stanton C. Goldman, Lauren Harrison, Ross Pinkerton, Martine Raphael, Keith McCarthy, Sherrie L. Perkins, and Catherine Patte
Protocol LMB: standard risk group

**Group A:** Stage I and II completely resected

- COPAD
- COPAD

**Group B:** Stage II non-resected and III LDH < 2N;

**Induction**

- COP
- COPADM
- COPADM

**Consolidation**

- CYM
- CYM

- HDMTX 3 g/m² i.v. 3h

---

**EFS - LMB**

- Stage I: 98.2% at 2 years
- Stage II: 98.2%

---

**EFS - Stage III without PMLBCL**

- BFM Stage III LDH<500: 89.9% at 2 years
- BFM Stage III LDH>500: 88.9% at 2 years
- LMB Stage III LDH<2N: 96.7% at 2 years
- LMB Stage III LDH>2N: 88.4% at 2 years

---

At risk
# LMB protocol high risk group:

- LMB chemotherapy
- Randomisation +/- rituximab 375 mg/m² (↑) - 6 doses

### Group B: Stage III LDH > 2N; Stage IV SNC neg

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP</td>
<td>(R)COPADM</td>
</tr>
<tr>
<td>(R)COPADM</td>
<td>(R)CYM</td>
</tr>
<tr>
<td>(R)CYM</td>
<td>(R)CYM</td>
</tr>
</tbody>
</table>

**HDMTX 3 g/m² i.v. 3h**

### Group C: B-AL or SNC pos

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP</td>
<td>RCOPADM1</td>
<td>RCYVE</td>
</tr>
<tr>
<td>RCOPADM2</td>
<td>RCYVE</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M2</td>
</tr>
</tbody>
</table>

**HDMTX 8 g/m² i.v. 4h (C1) ou 24h (C3)**
INTER-B Ritux trial: positive impact of rituximab on high risk mature B cell lymphoma

At risk  Months since randomization

With Rituximab  155  101  71  36  21  7  1
Without Rituximab  155  89  56  33  18  6

1-year EFS (95%CI)
- With Rituximab  94.2% (88.5%-97.2%)
- Without Rituximab  81.5% (73.0%-87.8%)
Rituximab and dose-dense chemotherapy for adults with Burkitt’s lymphoma: a randomised, controlled, open-label, phase 3 trial

Vincent Ribrag, Serge Koscielny, Jacques Bosq, Thibaut Leguay, Olivier Casasnovas, Luc-Mathieu Fornecker, Christian Recher, Hervé Ghersiques, Franck Morschhauser, Stéphane Girault, Steven Le Gaouil, Mario Ojeda-Urba, Clara Mariette, Jerome Cornillon, Guillaume Cartron, Veronique Verge, Catherine Chassagne-Clement, Hervé Dombret, Bertrand Coiffier, Thierry Lamy, Hervé Tilly, Gilles Salles

No rituximab

<table>
<thead>
<tr>
<th>Group</th>
<th>Prephase</th>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B</td>
<td>COP</td>
<td>COPADM1</td>
<td>COPADM2</td>
<td>CYM1</td>
</tr>
<tr>
<td>Group C</td>
<td>COP</td>
<td>COPADM1</td>
<td>COPADM2</td>
<td>CYE1</td>
</tr>
</tbody>
</table>

Rituximab

<table>
<thead>
<tr>
<th>Group</th>
<th>Prephase</th>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B</td>
<td>COP</td>
<td>COPADM1</td>
<td>COPADM2</td>
<td>CYM1</td>
</tr>
<tr>
<td>Group C</td>
<td>COP</td>
<td>COPADM1</td>
<td>COPADM2</td>
<td>CYE1</td>
</tr>
</tbody>
</table>

Cranial radiotherapy (18 Gy) if CNS involvement

**A**

Event-free survival (%)

- No rituximab
- Rituximab

**B**

Overall survival (%)

- No rituximab
- Rituximab

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rituximab</td>
<td>129</td>
</tr>
<tr>
<td>Rituximab</td>
<td>129</td>
</tr>
</tbody>
</table>

**Table**

<table>
<thead>
<tr>
<th>Number of events/number at risk</th>
<th>EFS</th>
<th>Log-rank p value</th>
<th>Number of deaths/number at risk</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>80/257</td>
<td>0.68 (0.62–0.74)</td>
<td>61/257</td>
<td>0.76 (0.71–0.81)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>55/182</td>
<td>0.70 (0.62–0.76)</td>
</tr>
<tr>
<td>Male</td>
<td>25/75</td>
<td>0.66 (0.54–0.76)</td>
<td>39/182</td>
<td>0.78 (0.72–0.84)</td>
</tr>
<tr>
<td>Female</td>
<td>22/75</td>
<td>0.71 (0.60–0.81)</td>
<td>22/75</td>
<td>0.71 (0.60–0.81)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>25/75</td>
<td>0.66 (0.54–0.76)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>22/101</td>
<td>0.78 (0.68–0.85)</td>
<td>14/101</td>
<td>0.86 (0.77–0.91)</td>
</tr>
<tr>
<td>40–60</td>
<td>30/98</td>
<td>0.69 (0.59–0.77)</td>
<td>22/98</td>
<td>0.77 (0.67–0.84)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>28/58</td>
<td>0.52 (0.39–0.65)</td>
<td>25/58</td>
<td>0.60 (0.47–0.71)</td>
</tr>
<tr>
<td>Albumin concentration</td>
<td></td>
<td></td>
<td>25/58</td>
<td>0.60 (0.47–0.71)</td>
</tr>
</tbody>
</table>

Ribrag 2016
Standard treatment for DLBCL in young patients

R-CHOP
## Phase 3 trials in DLBCL

Table 1. Phase 3 trials evaluating alternative regimens to R-CHOP or evaluating high-dose therapy approaches

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimens</th>
<th>Outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recher et al(^{59})</td>
<td>380</td>
<td>R-ACVBP vs R-CHOP</td>
<td>3-year PFS 87% vs 73%</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 92% vs 84%</td>
<td>.007</td>
</tr>
<tr>
<td>Cunningham et al(^{71})</td>
<td>1080</td>
<td>R-CHOP-14 vs R-CHOP</td>
<td>2-year PFS 75% vs 75%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-year OS 83% vs 81%</td>
<td>NS</td>
</tr>
<tr>
<td>Delarue et al(^{72})</td>
<td>602</td>
<td>R-CHOP-14 vs R-CHOP</td>
<td>3-year EFS 56% vs 60%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 69% vs 72%</td>
<td>NS</td>
</tr>
<tr>
<td>Le Gouill et al(^{78})</td>
<td>340</td>
<td>R-HDT + ASCT vs R-CHOP-14</td>
<td>3-year PFS 76%*</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 83%</td>
<td>NS</td>
</tr>
<tr>
<td>Schmitz et al(^{79})</td>
<td>275</td>
<td>R-Mega-CHOEP vs R-CHOP-14</td>
<td>3-year EFS 61% vs 70%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 77% vs 85%</td>
<td>.08</td>
</tr>
<tr>
<td>Vitolo et al(^{80})</td>
<td>399</td>
<td>R-HDT + ASCT vs R-dose dense CT</td>
<td>3-year PFS 70% vs 59%</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 81% vs 78%</td>
<td>NS</td>
</tr>
<tr>
<td>Stiff et al(^{81})</td>
<td>253</td>
<td>(R)-CHOP × 6 + ASCT vs (R)-CHOP × 8†</td>
<td>2-year PFS 69% vs 55%</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-year OS 74% vs 71%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant; R-HDT, rituximab with a high-dose therapy regimen; R-dose dense CT, rituximab with a dose dense chemotherapy regimen.

*Results not reported separately per arm.
†Only 47% of patients received rituximab.
<table>
<thead>
<tr>
<th>Score aalPI</th>
<th>Induction / conso</th>
<th>intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>aalPI = 0</td>
<td>R-CHOP21 (x6)</td>
<td>no</td>
</tr>
<tr>
<td>aalPI = 1</td>
<td>R-ACVBP + conso ou 6 R-CHOP21 + RTX</td>
<td>no</td>
</tr>
<tr>
<td>aalPI ≥ 2</td>
<td>R-ACVBP + conso ou 6 à 8 R-CHOP+RTX</td>
<td>Auto HSCT according to PET at C2 and C4</td>
</tr>
</tbody>
</table>

Tilly 2015
Total doses of anthracyclins

**Pediatric protocols**
- Dose: 120-180 mg/m²
- Duration of infusion: 1 hour to 10 mg/m²/h

**Adult protocols**
- Dose: 300-450 mg/m²
- Cardiac complications:
  - 2837 pts included in GELA trials 1984-1998
  - 54 cardiac events including 14 deaths
- Long term risk not well known in adults

Tukenova 2010
Andre 2004
Lymphoblastic lymphomas
Lymphoblastic lymphoma

- Proliferation of small blue round cells expressing TDT
- > 80% of T phenotype
  - T phenotype (CD3+, CD7+)
  - Mutations of NOTCH/FBXW, PTEN
  - Rearrangement of TCR
  - Similar to T ALL
- Precursor B phenotype rarer (20%)
Lymphoblastic lymphomas

- Median age: 8.7 y in children, 22 y in adults

Clinical presentation

- T lymphoblastic lymphomas:
  - Mediastinal mass + pleural effusion
  - High incidence of renal and bone marrow (20%) inv<sup>t</sup>
  - CNS involvement rare (4%)
  - **Urgent medical intervention required**

- Pre B lymphoblastic lymphomas
  - Peripheral lymph nodes
  - Bone (30%), skin (12%) Soft tissue lesions
  - Bone marrow inv<sup>t</sup> 20%
Treatment of lymphoblastic lymphomas in children

Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma

319 patients analysed
5-y EFS 81%
5-y OS 86%

Prephase | Induction | Consolidation | Reintensification | Maintenance
---|---|---|---|---
Steroids | Steroids | Purinethol | Steroids | Purinethol
MTX it | Dauno | MTX | VCR | MTX
MTX It | Aspa | MTX | Doxo | MTX
Aspa | VCR | Endoxan | Asparaginase
Endoxan | Cytarabine | Cytarabine | MTX it
Cytarabine | | | Purinethol |
# Lymphoblastic lymphomas in adults

Table 3. Results of ALL-based regimens in adult patients with LBL

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>N</th>
<th>Lineage</th>
<th>Mediastinal radiation therapy</th>
<th>Stem cell transplant</th>
<th>Complete remission</th>
<th>EFS/PFS</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoelzer et al. [29]</td>
<td>GMALL</td>
<td>45</td>
<td>T</td>
<td>24 Gy</td>
<td>—</td>
<td>93%</td>
<td>62% (7 y)</td>
<td>51% (7 y)</td>
</tr>
<tr>
<td>Thomas et al. [30]</td>
<td>Hyper-CVAD</td>
<td>33</td>
<td>T + B</td>
<td>30–39 Gy</td>
<td>No</td>
<td>91%</td>
<td>62% (3 y)</td>
<td>67% (3 y)</td>
</tr>
<tr>
<td>Ellin et al. [31]</td>
<td>Several ALL-type</td>
<td>30</td>
<td>T</td>
<td>21–36 Gy</td>
<td>Autologous/allogeneic if needed post-relapse</td>
<td>57%</td>
<td>49% (5 y)</td>
<td>48% (5 y)</td>
</tr>
<tr>
<td>Song et al. [32]</td>
<td>Standard NHL or NHL/ALL hybrid protocols</td>
<td>34</td>
<td>T</td>
<td>No</td>
<td>Autologous/allogeneic</td>
<td>—</td>
<td>68% (4 y)</td>
<td>72% (4 y)</td>
</tr>
<tr>
<td>Bersvendsen et al. [33]</td>
<td>ALL-type</td>
<td>25</td>
<td>T + B</td>
<td>24–32 Gy</td>
<td>Autologous</td>
<td>84%</td>
<td>76% (5 and 8 y)</td>
<td>84% (5 and 8 y)</td>
</tr>
<tr>
<td>Bouabdallah et al. [34]</td>
<td>FMALL or standard NHL</td>
<td>62</td>
<td>T + B</td>
<td>No</td>
<td>Autologous/allogeneic</td>
<td>89% (FMALL)</td>
<td>45% (5 y)</td>
<td>49% (5 y)</td>
</tr>
<tr>
<td>Cortelazzo et al. [35]</td>
<td>NILG-ALL 09/00</td>
<td>24</td>
<td>T</td>
<td>24 Gy</td>
<td>Autologous + allogeneic</td>
<td>92%</td>
<td>71% (5 y)</td>
<td>69% (5 y)</td>
</tr>
<tr>
<td>Lepretre et al. [36]</td>
<td>GRAALL-LYSA LL03</td>
<td>131</td>
<td>T</td>
<td>No</td>
<td>CNS+, late CR (autologous)</td>
<td>91%</td>
<td>63% (3 y)</td>
<td>69% (3 y)</td>
</tr>
<tr>
<td>Gökbüget et al. [37]</td>
<td>GMALL</td>
<td>149</td>
<td>T</td>
<td>36 Gy (cohort 1)</td>
<td>—</td>
<td>76%</td>
<td>—</td>
<td>65% (5 y)</td>
</tr>
</tbody>
</table>

Lepretre 2017
A 4-gene NOTCH1/FBXW7/RAS/PTEN is now used for front line stratification in adult T-ALL (+/- T-LBL) in France...

Leprêtre et al, JCO 2015

*N/F mut* or *N/F GL & RAS/PTEN GL & TRG biallelic, N= 57*

*N/F GL and RAS/PTEN* mut or TGR ABD, N= 17
Anaplastic large cell lymphoma
Proliferation of large lymphoid cells

- Abondant cytoplasm and horse shoe-shaped nuclei
- Expression of CD30 and EMA
- T phenotype
  - Cytoxic granule Ag : perforine, Granzyme B, TIA1
  - Loss of pan -T antigens such as CD3 in 75% cases
  - clonal TCR rearrangement

- ALK in > 90% cases in children and adolescents and 50-60% in adults
ALK + Anaplastic large cell lymphoma

\( t(2;5) \) (p23;q35)

NPM

Nucléophosmine

anaplastic lymphoma kinase

ALK

Constitutive activation of ALK and multiple pathways such as

- JAK/STAT3
- AKT/PI3K
- RAS/ERK
<table>
<thead>
<tr>
<th>Translocation (t)</th>
<th>Partner 1</th>
<th>Partner 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(2;5)</td>
<td>NPM</td>
<td>ALK</td>
</tr>
<tr>
<td>t(1;2)</td>
<td>TPM3</td>
<td>ALK</td>
</tr>
<tr>
<td>t(2;3)</td>
<td>TFG</td>
<td>ALK</td>
</tr>
<tr>
<td>inv(2)</td>
<td>ATIC</td>
<td>ALK</td>
</tr>
<tr>
<td>t(2;19)</td>
<td>TPM4</td>
<td>ALK</td>
</tr>
<tr>
<td>t(2;17)</td>
<td>ALO17</td>
<td>ALK</td>
</tr>
<tr>
<td>t(2;23)</td>
<td>MYH9</td>
<td>ALK</td>
</tr>
<tr>
<td>t(2;9)</td>
<td>TRAF1</td>
<td>ALK</td>
</tr>
</tbody>
</table>

**Images:**
- t(2;5): NPM-ALK
- t(2;17): CLTC-ALK
- t(2;X): MSN-ALK
ALCL ALK +  
Front-line treatment

Children and adolescents: ALCL 99: 6 courses
- 5 days courses (hospitalisation)
- Acute toxicity ++
- Low cumulative doses of anthracyclines and alkylating agents

Adults: 6 courses of CHO(E)P
- Given in day hospital
- Cumulative dose of doxo 300 mg/m² in all patients
- Risk of (very) long term acute cardiotoxicity

UK TYA CSS: Excess of cardiac deaths in survivors of NHL treated as AYA

Henson 2015
Survival after front-line treatment

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Nb of patients</th>
<th>Median age</th>
<th>3-5 y EFS</th>
<th>3-5 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugieres 2009</td>
<td>352</td>
<td>11</td>
<td>73 %</td>
<td>92 %</td>
</tr>
<tr>
<td>Alexander 2014</td>
<td>125</td>
<td>11</td>
<td>74 %</td>
<td>84 %</td>
</tr>
<tr>
<td>Schmitz 2010</td>
<td>78</td>
<td>37</td>
<td>76 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Sibon 2012</td>
<td>64</td>
<td>31</td>
<td>76 %</td>
<td>86 %</td>
</tr>
<tr>
<td>Cederleuf 2017</td>
<td>122</td>
<td>40</td>
<td>64 %</td>
<td>78 %</td>
</tr>
</tbody>
</table>
Prognostic factors in children and adolescents

Detection of the t(2;5) in blood at diagnosis

Histologic subtype

Level of AB anti ALK

MRD
Treatment of relapse

Children and adolescents

- Risk adapted treatment including
  - vinblastine in low risk
  - Autologous HSCT in intermediate risk
  - Allogeneic HSCT in high risk

Adults

- Reinduction chemotherapy followed by autologous or allogeneic STC
- Few publications
- Poor results: 3 y EFS < 20%

Chihara, Blood 2015, Sibon 2015
ALCL relapse  Results

### EFS

- **A** allogeneic SCT: 61 ± 7% (N=45, 17 events)
- **B** autologous SCT: 72 ± 7% (N=45, 12 events)
- **C** VBL monotherapy: 82 ± 9% (N=20, 3 events)

Log-Rank p = .0031

### OS

- **A 1+2a**, allogeneic SCT: 76 ± 8% (N=30, 7 events)
- **B 2b+3**, autologous SCT: 89 ± 7% (N=20, 2 events)
- **C 4**, VBL monotherapy: 82 ± 9% (N=20, 3 events)

Log-Rank p = .40
Multiple new drugs

- **Brentuximab vedotin**
  - Response rate:
  - Granted for relapsed ALCL in adults
  - Not available in children and adolescents

- **ALK inhibitors**
  - Response rate: ORR 60 to 90% according to trials
  - 2nd and 3rd line treatment: ceretinib, lorlatinib, alectinib, brigatinib, ……

- **Anti PD1**
  - Constitutive activation of PDL1
  - Trial ALCL nivo planned Q3 2018
Conclusions

▪ Most TYA with lymphomas are cured with intensive chemotherapy and the aim is now to reduce morbidity associated to treatment.

▪ For most lymphoma subtypes, therapeutic strategies are still different in children and adults and comparison between therapeutic results and burden of treatment should help to chose the best treatment for this population.

▪ DLBCL in teenagers are clearly different from DLBCL in adults:
  – What about young adults?
  – Are they closer from teenagers or older adults?
  – Is there a risk of long term cardiotoxicity as in children?
Conclusions

- International collaboration between adult and pediatric hemato-oncologists is mandatory
  - For rare lymphoma subtypes in this age group such as PMBCL, ALCL, LL
  - For more frequent NHL such as DLBCL to better define the best cut-off between children and adults DLBCL
  - For new drugs development in rare lymphoma subtypes
  - For research on long term morbidity of treatment and organization of long term follow-up
6th International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma

September 26-29, 2018
Rotterdam, The Netherlands
Venue: De Doelen International Congress Centre

Presenting the latest scientific and clinical advances in childhood, adolescent and young adult Non-Hodgkin Lymphoma

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Westchester Medical Center (WMC)
New York Medical College

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