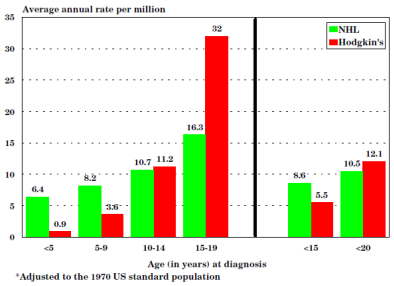
Treatment challenges in childhood and adolescents lymphoma : role of FDG PET/CT

Laurence Brugières
Institut Gustave Roussy,
Villejuif, France

Lymphoma in children and adolescents

- 10-15% of all childhood cancer



SEER data 1990-95

Hodgkin's lymphoma

Hodgkin's lymphoma in children

- Very similar to adults LH
- Subtypes distribution:
  - Lymphocyte-predominant HL 5%
  - Classic LH 95%
    - Nodular-sclerosing 70%
    - Mixed cellularity 20%
    - lymphocyte-rich 2-5%
    - Lymphocyte-depleted < 1%

EuroNet PHL-C1

EUDRACT-2006- 000995-33

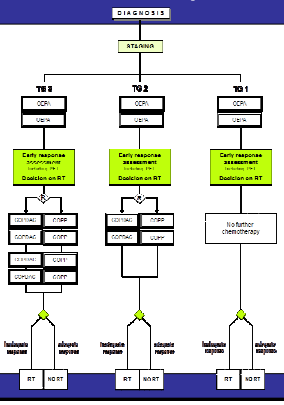
- Aim : to limit the long term side effects :
  - Secondary malignancies (25% at 30 years)
  - Male infertility
- Objectives:
  - To evaluate whether radiotherapy can be safely omitted in patients with adequate PET response after 2 courses of OEPPA
  - To evaluate whether procarbazine can be safely replaced by dacarbazine in therapy groups TG2 and TG3

Hodgkin lymphoma

Staging in on-going pediatric trials

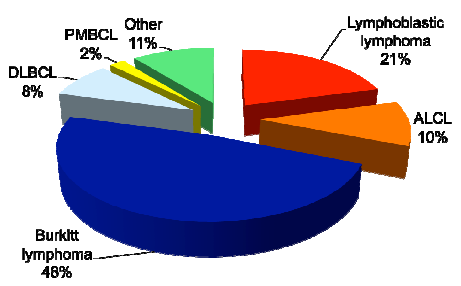
- FGD PET and conventional imaging mandatory
- 3 groups in the European protocol **Euronet PHL C1 :**
  - TG1 : I, IIA
  - TG2 : IIB, IIIA
  - TG3 :IIB_E, $IIIA_E$, IIIB, IV,

Euronet PHLC1 protocol



Non Hodgkin's lymphoma

Distribution of childhood NHL

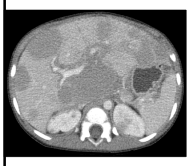


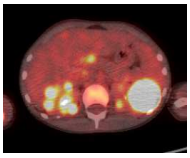
Childhood NHL

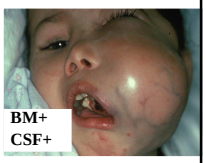
- Diffuse high grade lymphomas
- Mostly extra-nodal localisations
  - Abdomen : 37 %
  - ENT 17%
  - Mediastinal 28%
  - Lymph nodes 9%
  - Other 9%
- Specific staging system (St Jude classification)
- Rapid growth and risk of dissemination in bone marrow and CSF requiring **URGENT TREATMENT**

B-CELL LYMPHOMAS

High proliferation rate, large tumor (abdomen),
Rapid dissemination especially to the CNS





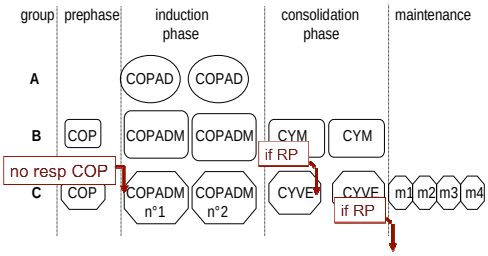


TREATMENT STRATEGY in B-NHL

EFS reaches 90% in Burkitt and DLBCL with a treatment of

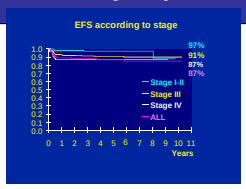
- **short duration** (2 to 8 months)
- made of **intensive pulse courses**
- adapted **to**
  - **prognostic factors** (stage, resection in localized disease, LDH level in advanced stage, CNS involvement)
  - **early tumors response**

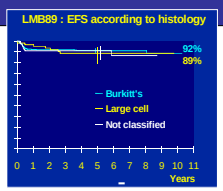
FAB LMB protocol



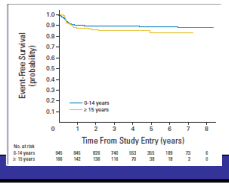
On going trial to evaluate the impact of adding rituximab in high risk patients : stage III and IV, high LDH

B cell lymphoma EFS

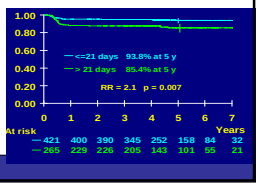




EFS according to age



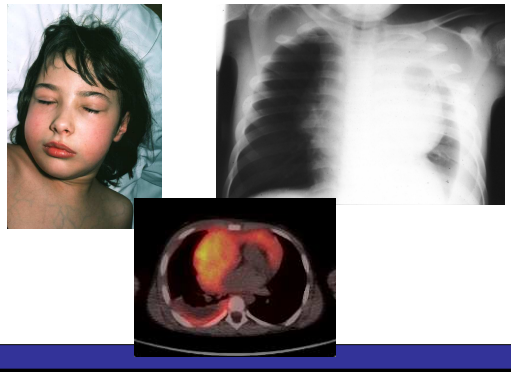
EFS according to dose intensity



PET in B cell lymphoma

- The impact of adding PET/CT in initial staging or for early response evaluation has not been assessed yet
- PET/CT may be usefull for assessment of remission but
  - Sensitivity and specificity not evaluated yet (high rate of false positive in small studies)
  - Short interval between courses requiring very precise organisation in order not to reduce dose intensity

Lymphoblastic lymphoma



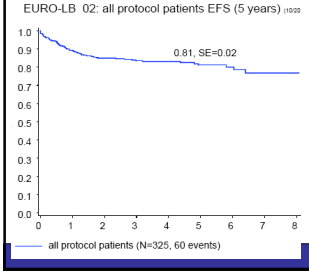
LYMPHOBLASTIC LYMPHOMA

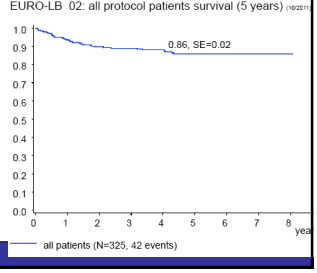
- Specific treatment SIMILAR to those of high risk ALL
  - Steroid prephase
  - Intensive, semi-continuous chemotherapy
  - Numerous drugs
  - 2 years duration
  - CNS prophylaxis

Final analysis of the European trial EuroLB02 presented at the 4th international conference on Childhood NHL *(A Reiter nov 2012)*

- 325 patients:
  - 74% T-LBL
  - 23% pB-LBL

Stages I/II	7%
III	61%
IV	23%





Lymphoblastic lymphomas : main prognostic factors

Outcome according to response to steroids

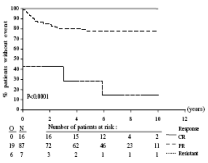
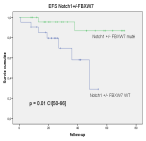
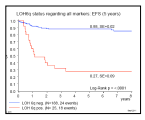


Fig. 2 – Event-free survival according to the response to prephase. O = observed number of events; N = number of patients. P-value was given by the logrank test.

Outcome according to biology



French studies (45pts)
NOTCH/FBXW7 mutations



BFM studies (230pts)
6qLOH

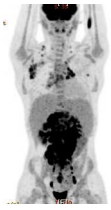
Uyttebroeck, Eur J Cancer 2008 *C Callens, JCO, 2012B* *Burkhardt Leukemia20*

Lymphoblastic lymphoma How to progress?

- **Better identification of the high risk patients**
  - **Early response: PET ?**
  - **MDD/MRD?**
  - **Biologic characteristics?**
- **And the following questions will be how to treat these patients**

Anaplastic large cell lymphoma

- Clinical characteristics:
  - lymph node involvement 80%
  - B symptoms 60%
  - visceral involvement 50%
  - Skin lesion 25%
- Biology : t(2;5) translocation



ALCL99 – Induction chemotherapy

P A B A B A B

Cyclophosphamide	200 mg/m²	D1-2
Dexamethasone	5-10 mg/m²	D1-5
Triple intra-thecal injection		D1

Prephase

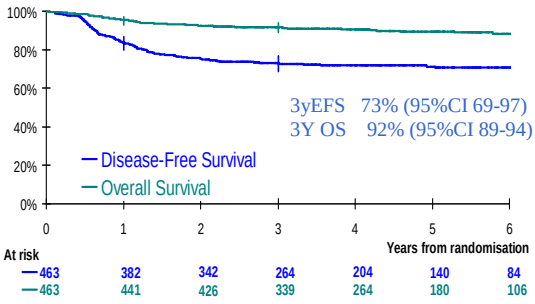
MTX according to randomization		D1
Ifosfamide	800 mg/m²	D1-5
Etoposide	100 mg/m²	D4-5
Ara-C	300 mg/m²	D4-5
Dexamethasone	10 mg/m²	D1-5

Course A

MTX according to randomization		D1
Cyclophosphamide	200 mg/m²	D1-5
Doxorubicin	25 mg/m²	D4-5
Dexamethasone	10 mg/m²	D1-5

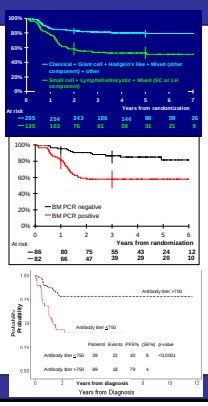
Course B

ALCL99 : survival



ALCL : prognostic factors

- Histologic subtype
- MDD : (t(2;5) in blood and/or BM
- Immunity against ALK : blood level of anti ALK antibody



ALCL : place of PET/CT?

- Low impact of initial staging in treatment decision
- Could the assessment of early response allow the identification of those patients at high risk of relapse?

PET/CT in childhood NHL

- At diagnosis:
  - very high uptake in most subtypes
  - not easy to organize in the context of very advanced disease requiring urgent treatment
  - impact on staging and treatment choice not assessed
- In the assessment of the remission :`
  - still to be evaluated (many false positive results requiring histologic confirmation of all residual masses)
- Prognostic value of early metabolic response to be evaluated

Table 1 Utility of FDG PET during staging of lymphomas in children

Study	Number of patients	Disease diagnosis	Staging changes	Conclusions
Depas et al. [13]	19	14HL/5NHL	10.5 % (1/19↑ and 1/19↓)	PET was useful for evaluation of children with lymphoma
Miller et al. [38]	31	24HL/7NHL	32.3 % (7/31↑ and 3/31 %↓)	PET/CT changed stage in 1/3 of lymphoma patients. After therapy, PET/CT negative study=disease-free period, and PET/CT positive study=residual malignant disease
Paulino et al. [43]	53	53HL/-NHL	9.4 % (3/53↑ and 2/53↓)	PET/CT changed the IFRT field design in 17 % of HL patients
Hermann et al. [24]	25	18HL/7NHL	24 % (4/25↑ and 2/25↓)	PET altered stage in 6/25 children with lymphomas
Cheng et al. [11]	51	30HL/21NHL	27.5 % (14/51↑)	FDG PET/CT is superior to contrast CT in the initial staging of children with lymphomas
Montravers et al. [40]	27	20HL/7NHL	50 % (6/12↑)	FDG PET was useful for staging and assessment of response to treatment in children with lymphomas

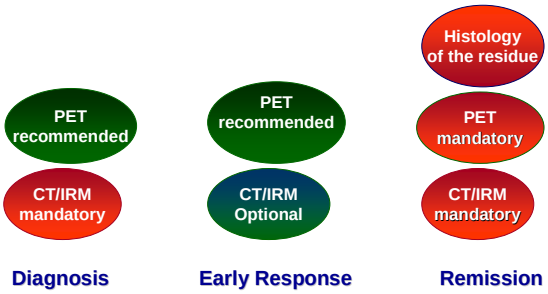
Sioka, Eur J Ped 2013

French PET lymphoma study

Eudract 2010-A01154-35

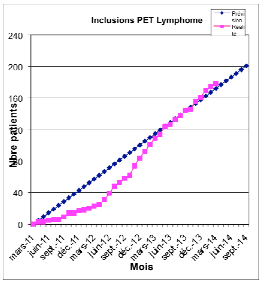
- Opened in 2011 for main NHL subtypes
- **Objectives :**
  - Estimate sensibility and specificity of PET/CT compared to other radiological exams completed by histology in the evaluation of remission
  - Evaluation of the feasibility and the concordance of PET/CT compared to classical radiological exams in initial staging
  - Evaluation of the prognostic value of early PET response on the risk of failure

Scheme of the French PET study



PET lymphoma study

- Accrual completed for main lymphoma subtypes
- Central review on-going
- Feasability:
  - PET at diagnosis : 72%
  - Early PET 72%



CONCLUSIONS: Challenges for the future

- Most lymphoma in children are curable with a first line therapy
- Challenges are :
  - To identify those children with very good prognosis for whom treatment intensity can be reduced
  - To identify very high risk patients for whom early intensification of therapy is required
- Whether PET/CT will play a role in the identification of these patients is
  - obvious in HL
  - still questionable in NHL