NK/T-cell lymphoma: the role of asparaginase

The French experience

Arnaud Jaccard
Hematology Unit
Universitary Hospital
Limoges
France

NK/T-cell lymphoma is a very rare disease in Europe

VOLUME 26 · NUMBER 25 · SEPTEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	% North America	% Europe	% Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	6.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

NHL in Europe: 85 % B-cell origin

Percentage of all T/NK-cell lymphoma

NK/T-cell lymphoma = 4,3% of 15% = **0,6% of all lymphomas**

In France : 40 to 60 cases each year

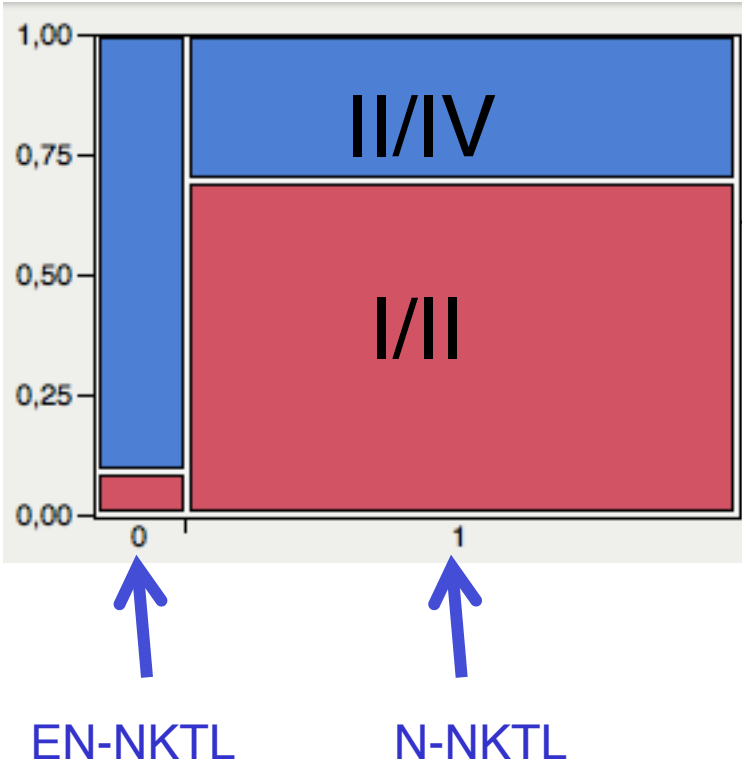
Clinical presentation in France

89 patients from 35 centers in France

- Median age : 52 years (16-83)
- European origin: 75%
  - From Asia: 2 patients
  - From North-Africa: 9 patients

- 87% nasal NKTL / 13% extra nasal NKTL

- Stage I/II : 64%,
- Stage IV: 36 %

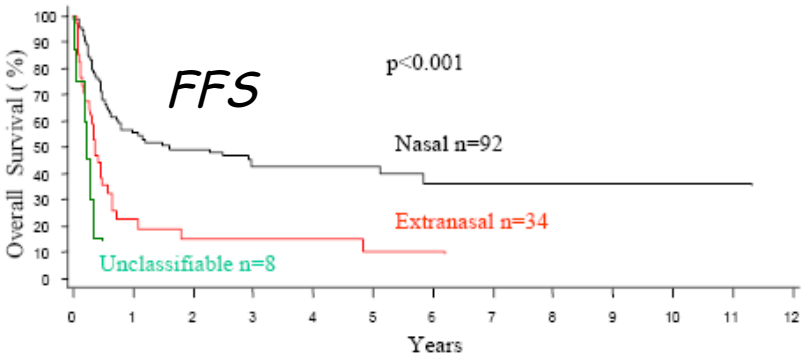


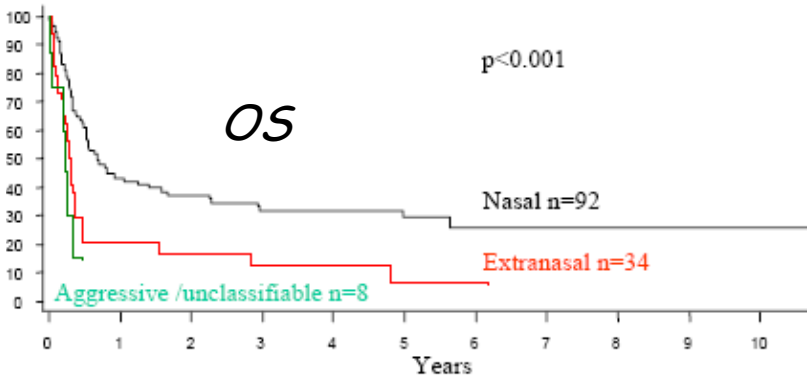
Before the asparaginase era: poor prognosis

136 pts from 21 clinical centers in 13 countries in North America, Europe and the Far East

- median OS 7.8 months
- median FFS 5.8 months

"The FFS and OS curves were similar at one year since most relapses were not salvageable."





The International Peripheral T-cell Lymphoma Project.
Blood *2009 Apr 23;113(17):3931-7.*

First papers on L-asparaginase and NK/T-cell lymphoma

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Display Settings: Summary, Sorted by Recently Added

Send to:

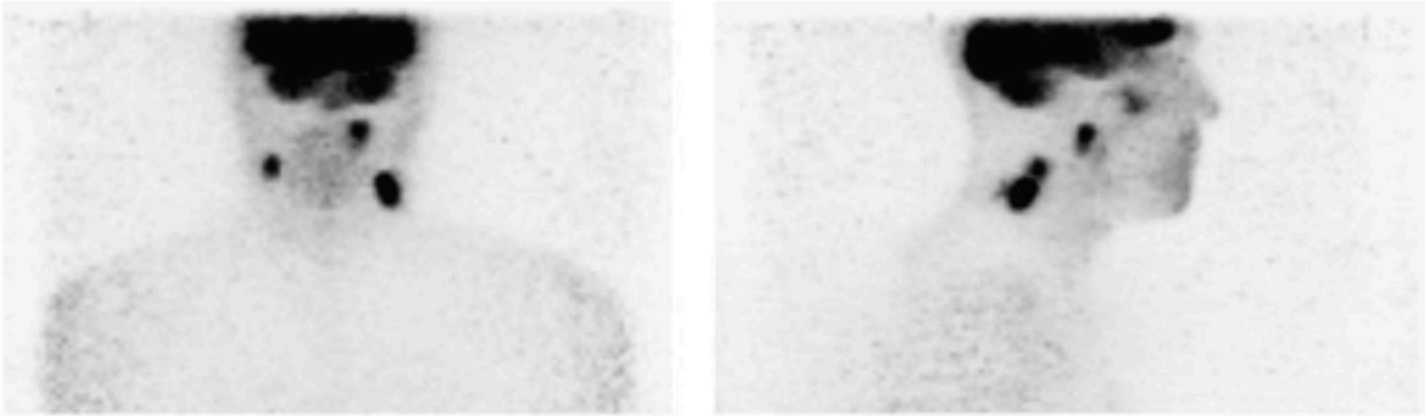
Results: 2

1. [Clinical characteristics and treatment of midline **nasal** and **nasal** type NK/T cell **lymphoma**].
Yong W, Zheng W, Zhang Y.
Zhonghua Yi Xue Za Zhi. 2001 Jul 10;81(13):773-5. Chinese.
PMID: 11798962 [PubMed - indexed for MEDLINE]
Related citations

2. **L-asparaginase** induced durable remission of relapsed **nasal** NK/T-cell **lymphoma** after autologous peripheral blood stem cell transplantation.
Nagafuji K, Fujisaki T, Arima F, Ohshima K.
Int J Hematol. 2001 Dec;74(4):447-50.
PMID: 11794702 [PubMed - indexed for MEDLINE]
Related citations

41 years old patient relapsing 1 year after initial treatment in 2003

After DHAP Chemotherapy



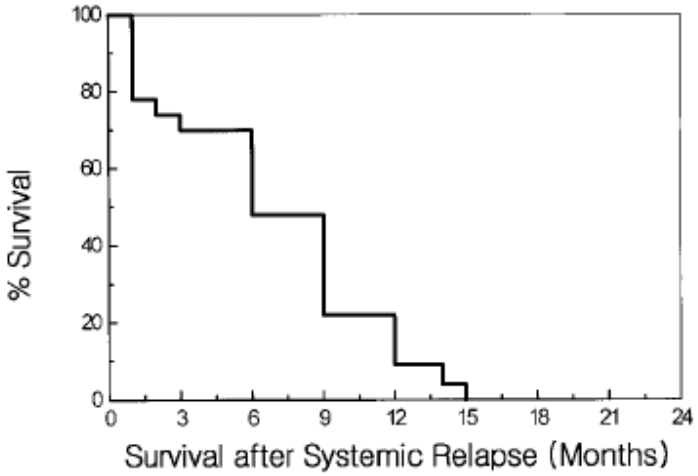
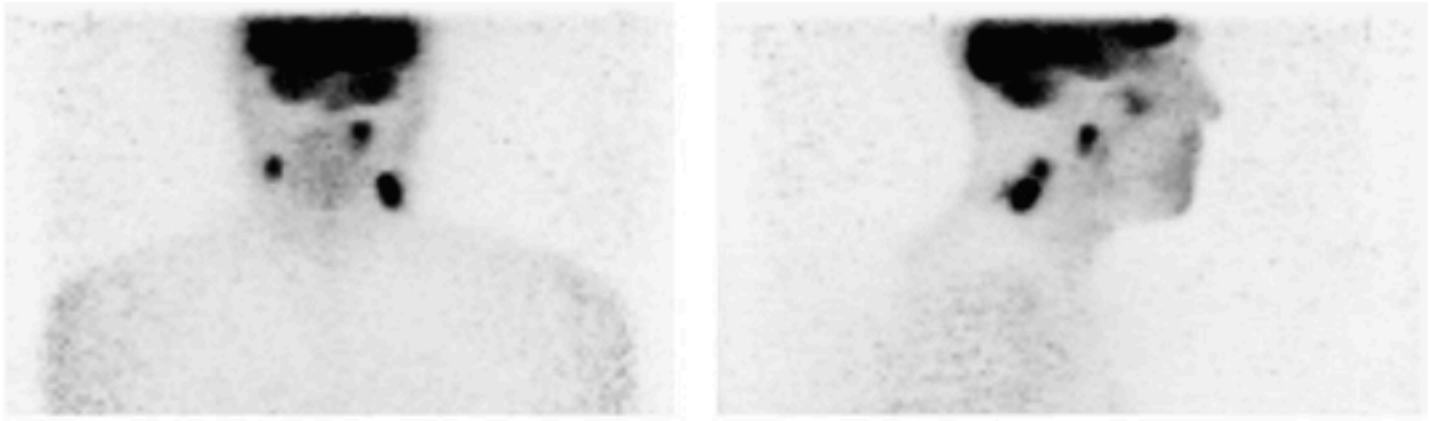


Fig 5. Overall survival rate for 23 patients with systemic failure.

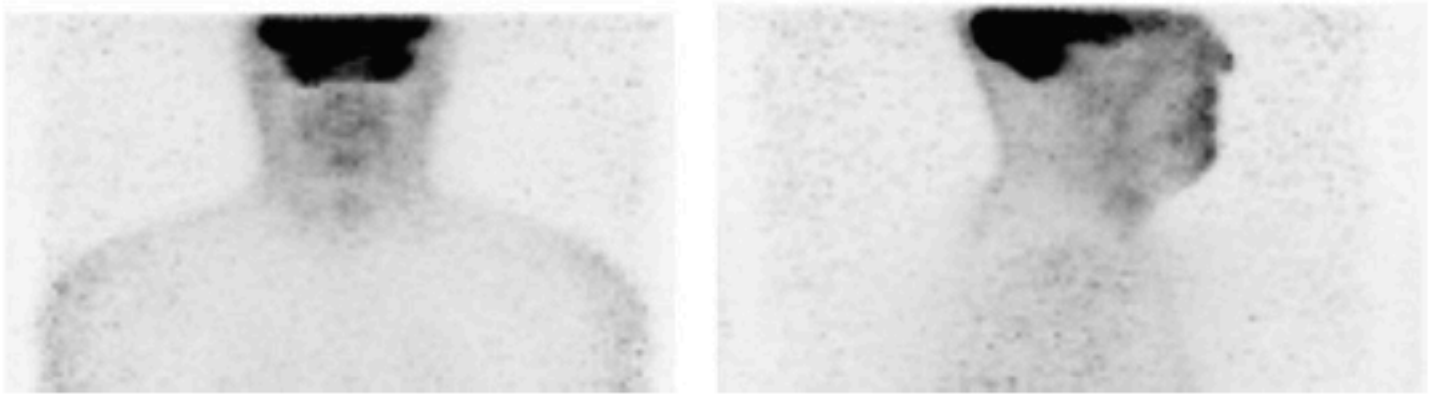
Kim GE et al,
JCO 2000, 18; 54-63

41 years old patient relapsing 1 year after initial treatment in 2003

After DHAP Chemotherapy



After 1 cycle
af L-asparaginase
+ dexamethasone



Retrospective study

Annals of Oncology 20: 110–116, 2009
doi:10.1093/annonc/mdn542
Published online 13 August 2008

L-Asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature

A. Jaccard[1*], B. Petit[2], S. Girault[1], F. Suarez[3], R. Gressin[4], J.-M. Zini[5], V. Coiteux[6], C. Larroche[7], A. Devidas[8], C. Thiéblemont[9], P. Gaulard[10], B. Marin[11], N. Gachard[12], D. Bordessoule[1] & O. Hermine[3]

13 relapse/refractory patients
(2 aggressive NK-cell leukemia)

CR : 46%

2 de novo stage IV patients

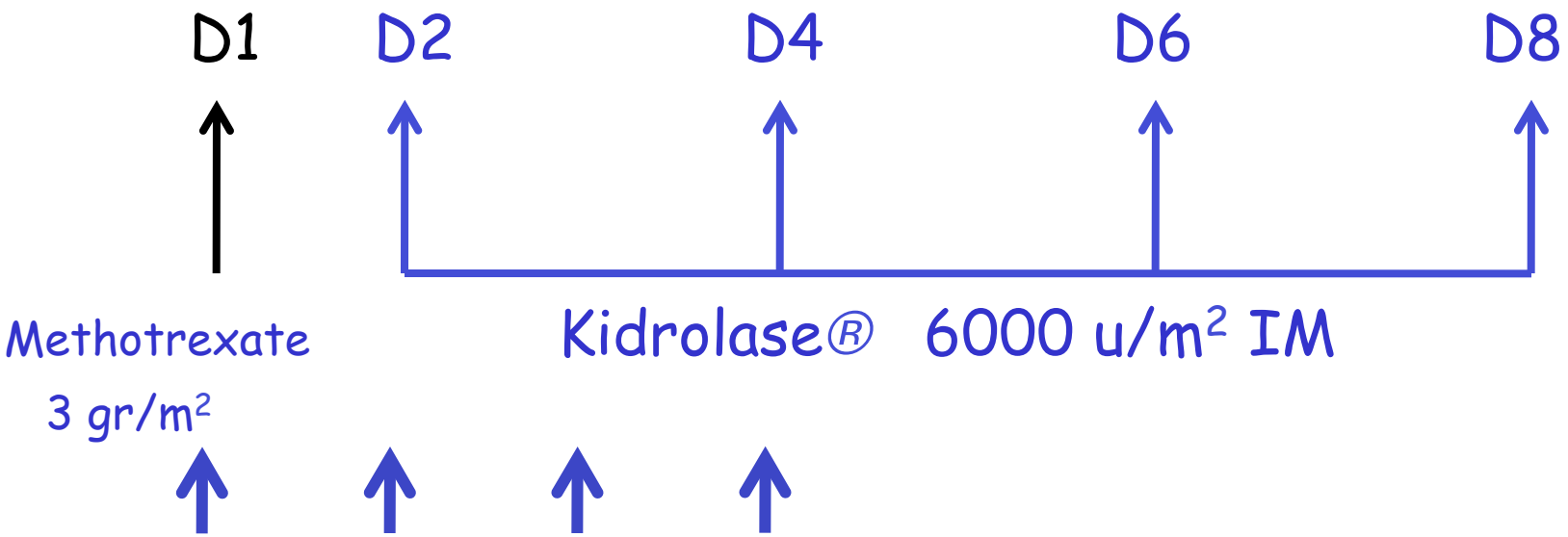
ORR: 86%

Various regimens
Most of the time
L-aspa + Methotrexate + dexamethasone

5 patients in continuous complete remission
(median follow-up : 3.5 years)

Aspa-Met-Dex regimen

3 cycles with a 21 days interval



if > 70 years :
Methotrexate : 2 gr/m²
Dexamethasone : 20 mg

19 relapse/refractory patients: responses after 3 cycles

- Median age : 60 years (45-77)
- Stage I/II: 12 pts, stage IV: 7 pts

- Progression : 3 pts
- Stable disease : 1 pt (progression after 1 year)

- ORR : 15 pts (78 %)
- CR : 12 pts (61%)
- PR : 3 pts

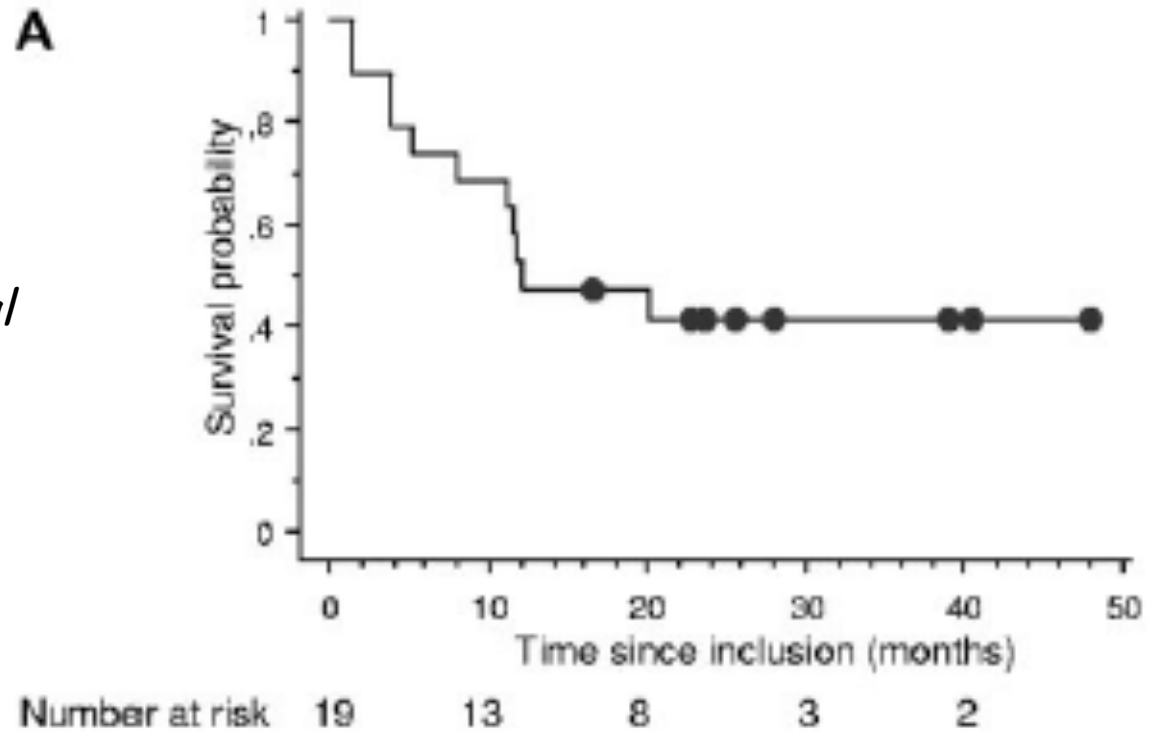
blood

2011 117: 1834-1839
Prepublished online December 1, 2010;
doi:10.1182/blood-2010-09-307454

Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study

Arnaud Jaccard, Nathalie Gachard, Benoit Marin, Sylvie Rogez, Marie Audrain, Felipe Suarez, Hervé Tilly, Franck Morschhauser, Catherine Thieblemont, Loic Ysebaert, Alain Devidas, Barbara Petit, Laurence de Leval, Philippe Gaulard, Jean Feuillard, Dominique Bordessoule, Olivier Hermine and for the GELA and GOELAMS Intergroup

Overall survival



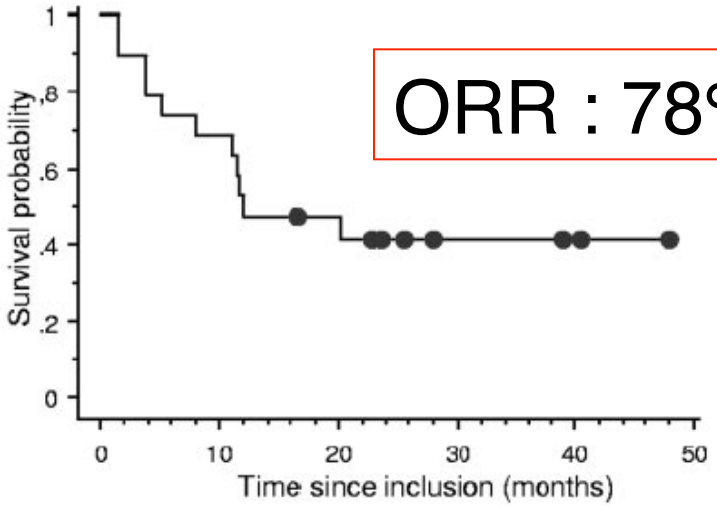
In Asia : SMILE

Table 2. SMILE protocol for advanced stage and relapse natural killer cell malignancies

Drugs	Dosage	Administration	Days
Methotrexate with leucovorin	2 g/m^2	Intravenous	1
Ifosfamide with mesna	1.5 g/m^2	Intravenous	2, 3, 4
Dexamethasone	40 mg	Intravenous or oral	2, 3, 4
Etoposide	100 mg/m^2	Intravenous	2, 3, 4
L-asparaginase	6, 000 U/ m^2	Intravenous	8, 10, 12, 14, 16, 18, 20

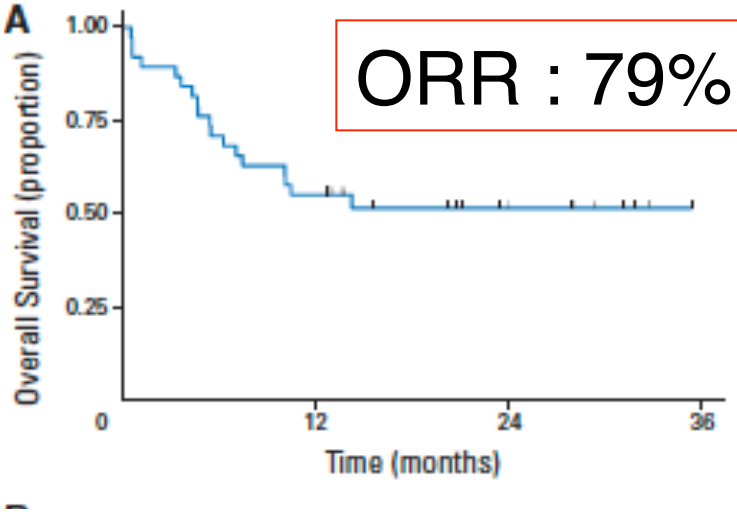
Granulocyte colony stimulating factor started on day 6. Cycles to be repeated every 28 days.

Aspa-Met-Dex Blood Jan 2011

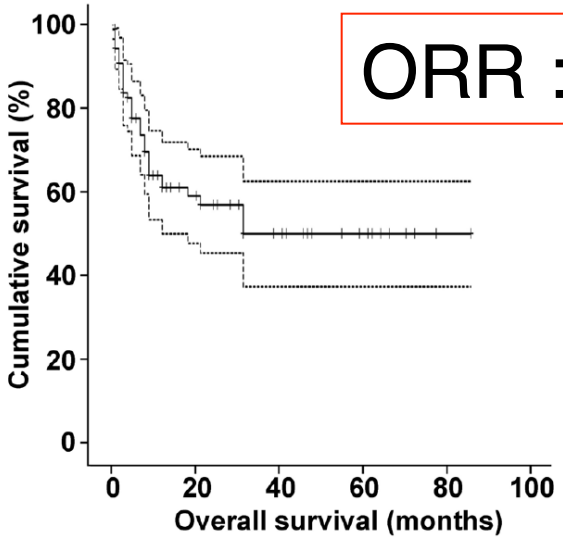


ORR : 78%

SMILE : JCO Nov 2011



ORR : 79%



ORR : 81%

SMILE : Blood Aug 2012

SMILE /Aspa-Met-Dex

- Major component: asparaginase
- 80% of patients respond to asparaginase

20 % of patients are primary refractory to asparaginase

Responses to asparaginase are rapid

Patient with extra-nasal disease muscles and nodes involvement

PET scan :

1)Initial PET SUV = 28

Responses to asparaginase are rapid

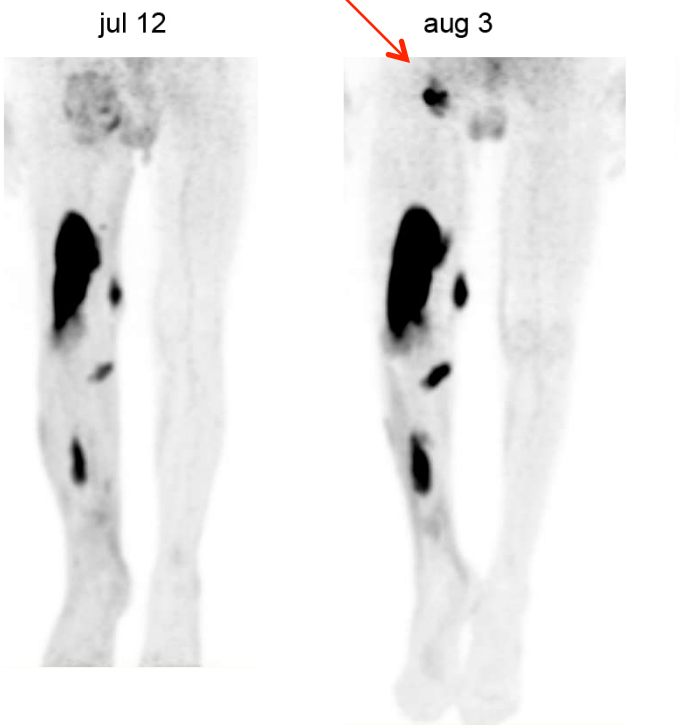
Patient with extra-nasal disease muscles and nodes involvement

PET scan :

1)Initial PET SUV = 28

2)After CHOP chemotherapy,

progression on inguinal node SUV = 30



Responses to asparaginase are rapid

Patient with extra-nasal disease muscles and nodes involvement

PET scan :

1) Initial PET, SUV = 28
2) After CHOP chemotherapy,
   progression on inguinal node SUV = 30
3) After 1 cycle of Aspa-Met-Dex SUV= 2

jul 12 aug 3 sept 13

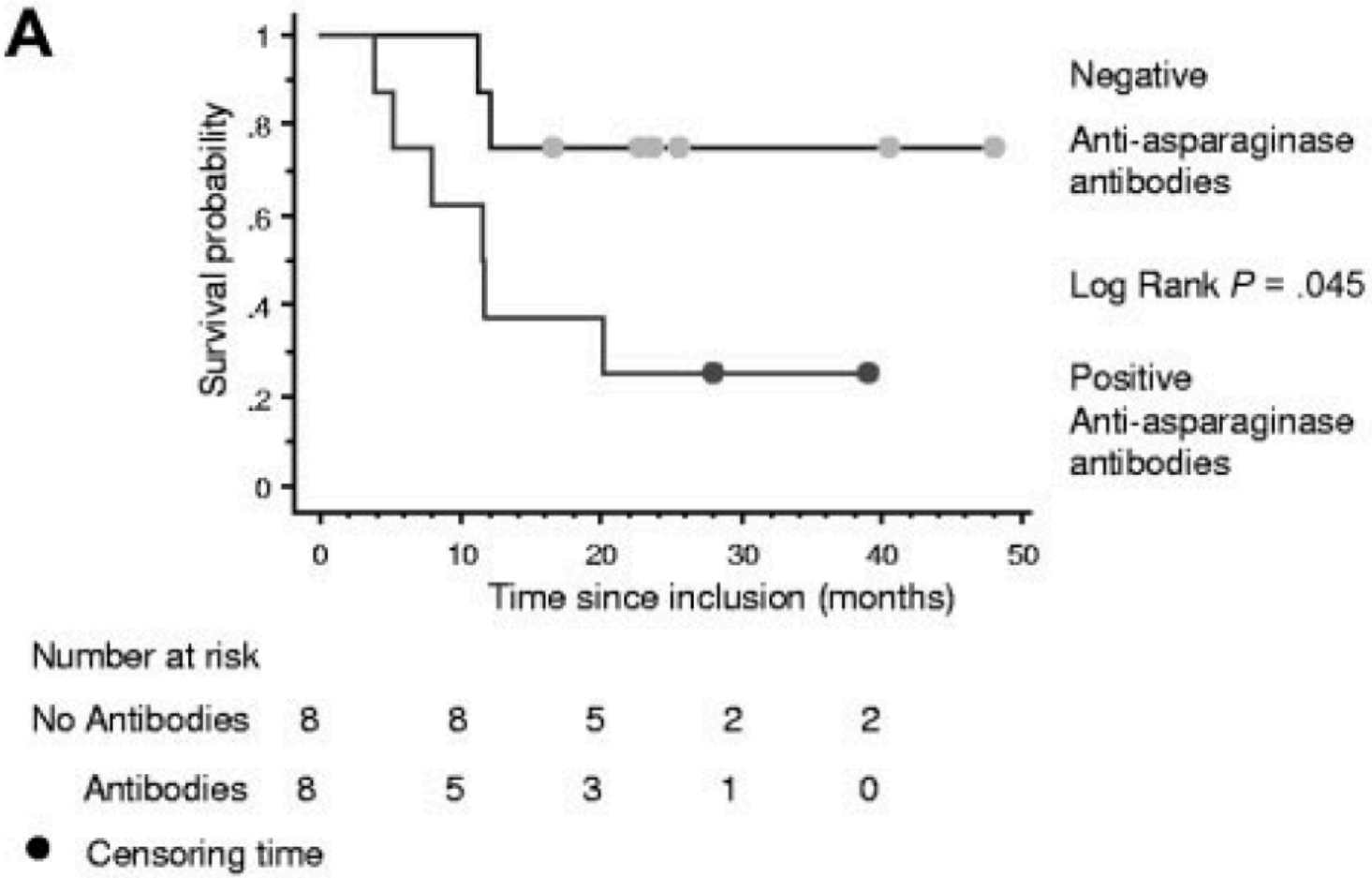
Probably useless to continue if no evidence of response after the first course

Anti-aspa antibodies

blood 2011 117: 1834-1839
Prepublished online December 1, 2010;
doi:10.1182/blood-2010-09-307454

Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study

Arnaud Jaccard, Nathalie Gachard, Benoit Marin, Sylvie Rogez, Marie Audrain, Felipe Suarez, Hervé Tilly, Franck Morschhauser, Catherine Thieblemont, Loic Ysebaert, Alain Devidas, Barbara Petit, Laurence de Leval, Philippe Gaulard, Jean Feuillard, Dominique Bordessoule, Olivier Hermine and for the GELA and GOELAMS intergroup



19 naive patients: responses after 3 cycles

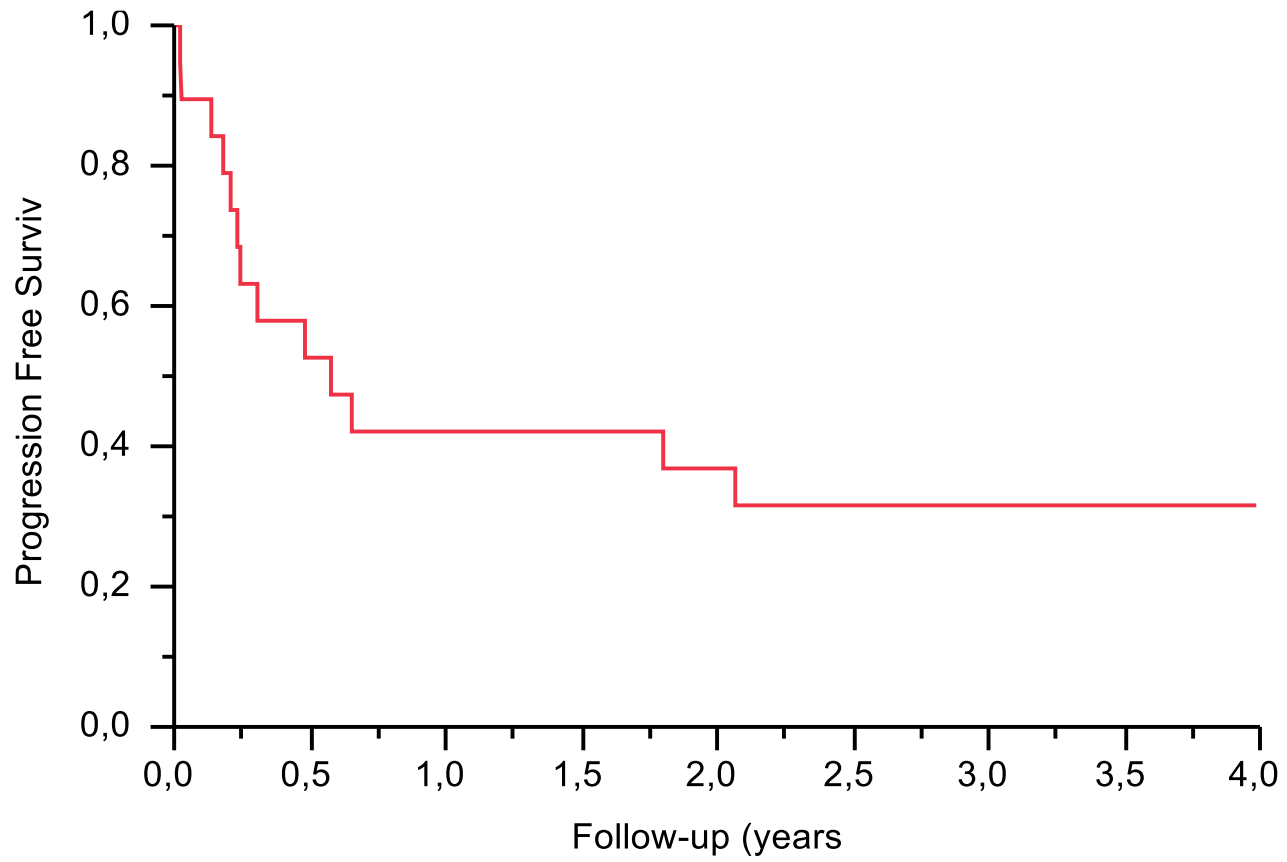
- Median age: 49 years (33-78)
- Stage I/II: 11 pts, stage IV: 8 pts
- 4 early deaths before 3 cycles: evaluation in 15 pts
  - 10 pts : CR
  - 1 pt : PR
  - 3 pts : progression

CR : 66%

ORR : 73%

Progression free survival

11 responses
5 relapses (at 6, 7, 8, 22 and 24 months)

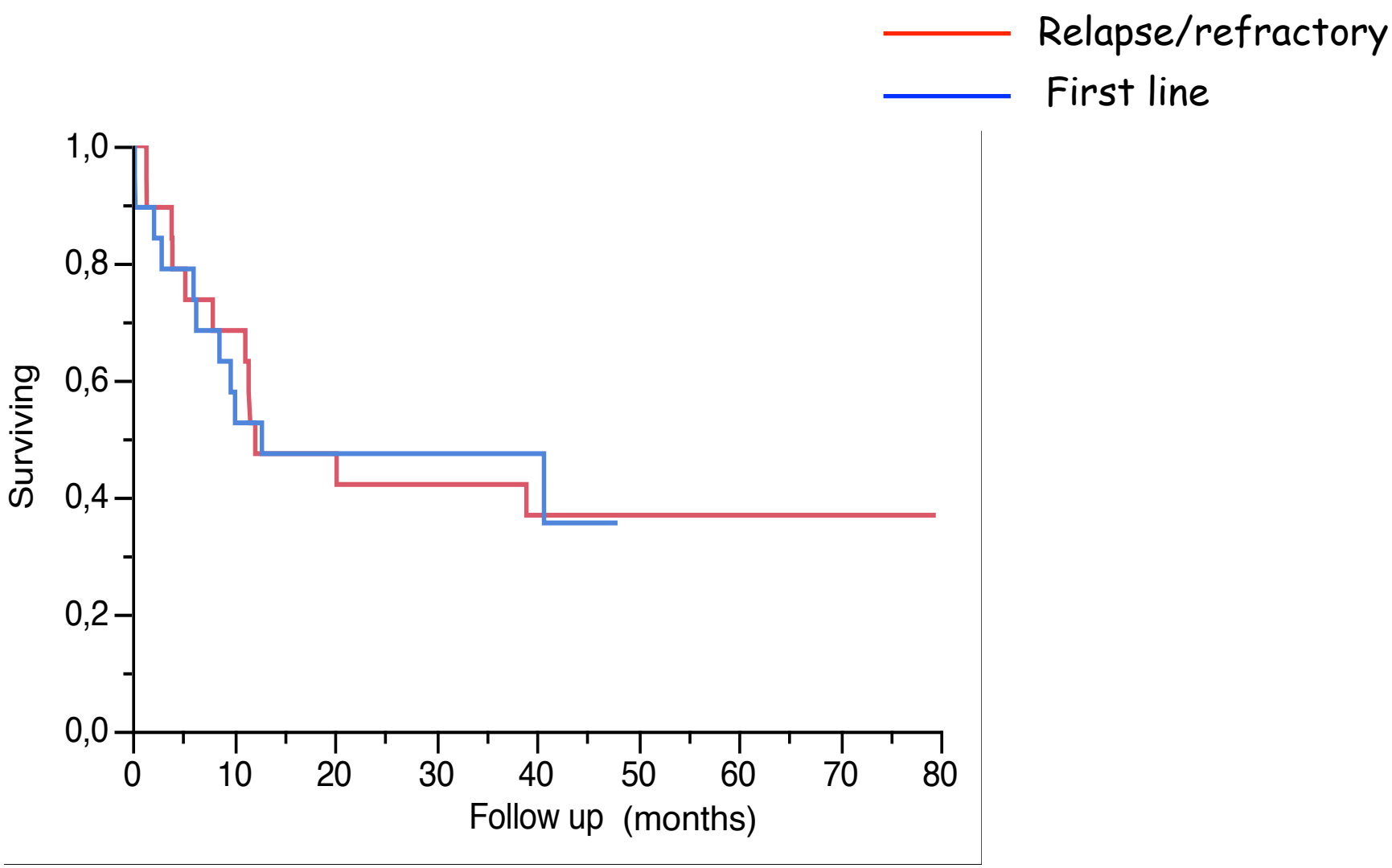


Anti-asparaginase antibodies ??

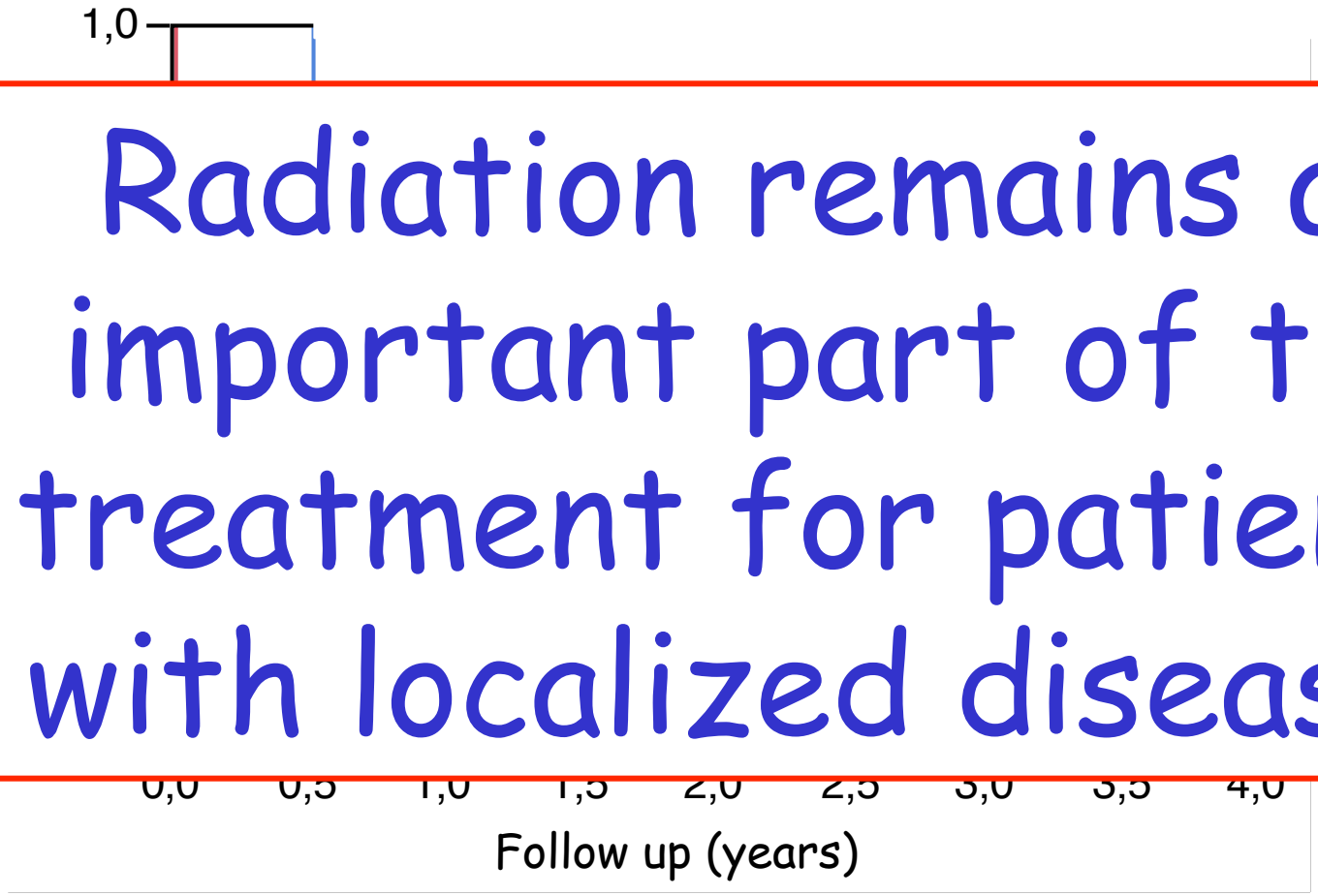
- All patients (except 2 patients who died early) have detectable antibodies at day 22 or day 44

Inhibition of asparaginase activity by antibodies is a major cause of treatment failure

Overall survival



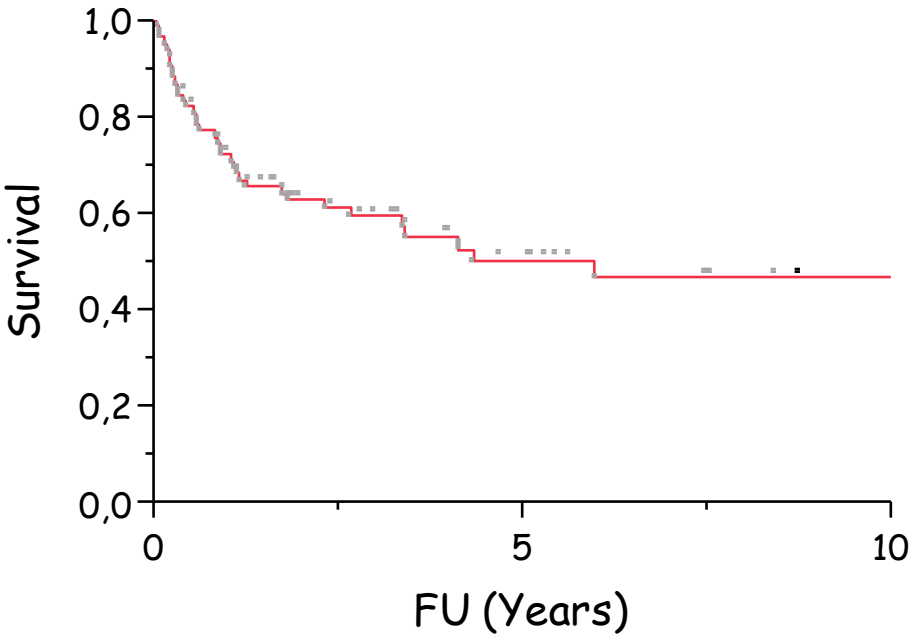
Overall survival with or without radiation



Radiation remains an important part of the treatment for patients with localized diseases

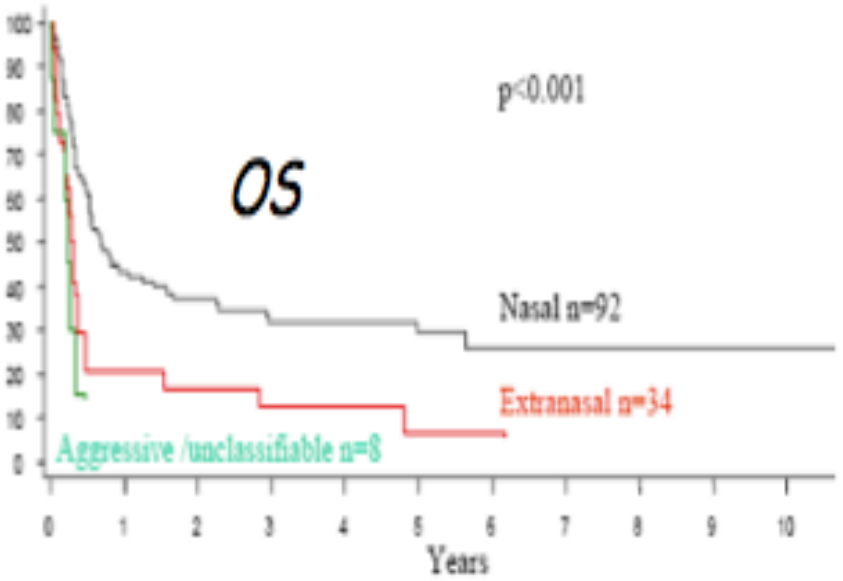
Progress since introduction of asparaginase

Median survival : 5.9 years



Asparaginase containing regimens:
86 patients
First line in 46 patients

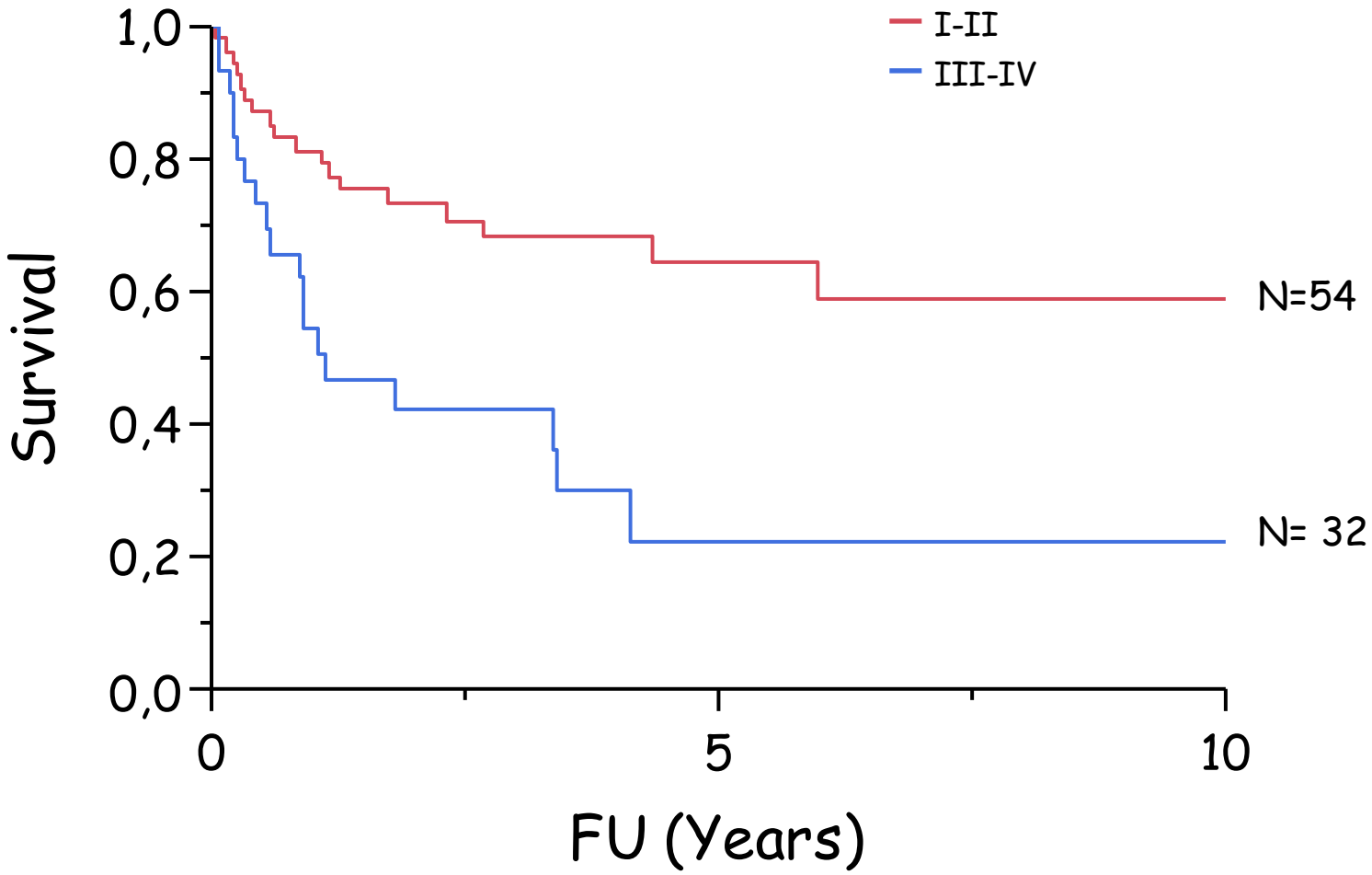
Median survival : 7.8 months



Anthracyclin based regimens:
136 patients

The International Peripheral T-cell Lymphoma Project.
Blood *2009 Apr 23;113(17):3931-7.*

Overall survival : localized / disseminated



How to improve these results

1) Avoid asparaginase inhibition by antibodies

3 types of asparaginase

Table 3. Preparations of asparaginase.

Form of asparaginase	Notes	Half-life (days)[40] (intramuscular administration)
E. coli	Original form; Can induce hypersensitivity reactions	1.28 ± 0.35
Erwinia	Minimal cross-reactivity with *E. coli* preparation; shortest half-life	0.65 ± 0.13
Pegylated *E. coli* (pegasparagse)	Decreased immunogenicity; long half-life	5.73 ± 3.24

Douer D et al. Best Practice & Research Clinical Haematology. 2008;21(4):647–658.

Anti-aspa Antibodies (in ALL)

- Less frequent with pegylated form
  - 1% to 15 % (1)

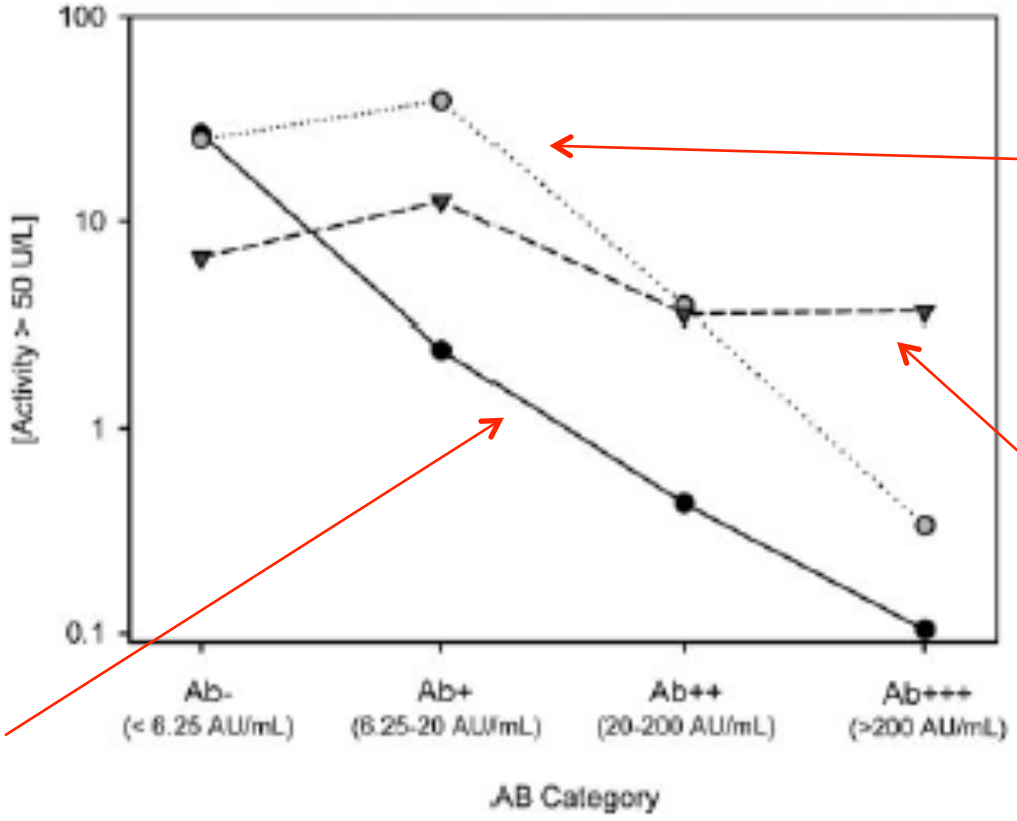
- Than with native form : 25-75 %
  - 58% in 410 children with ALL (2)
    - More frequent for less intense regimen (69% vs 47%)
    - Present in 39% of patients without clinical allergy

1) *Stock W et al. Leuk Lymphoma. 2011;52(12):2237–2253.*
2) *Douer D et al. Leukemia. 2012;26(11):2303–2309*

Asparaginase activity according to anti e-coli asparaginase levels and type of asparaginase in ALL

blood

2011 118: 5774-5782
Prepublished online September 22, 2011;
doi:10.1182/blood-2011-07-367904



PEG aspa

Erwinia aspa

E-Coli aspa

Figure 5. Odds of ASE activity > 50 U/L under different ASE preparations (native *E coli* ASE, black circle; pegylated *E coli* ASE, grey circle; *Erwinia* ASE, grey inverted triangle) at different Ab levels against *E coli* ASE. Results were generated by the application of a generalized linear model that was fitted by generalized estimating equations.

blood
2014 123: 2026-2033
doi:10.1182/blood-2013-10-534347 originally published online January 21, 2014

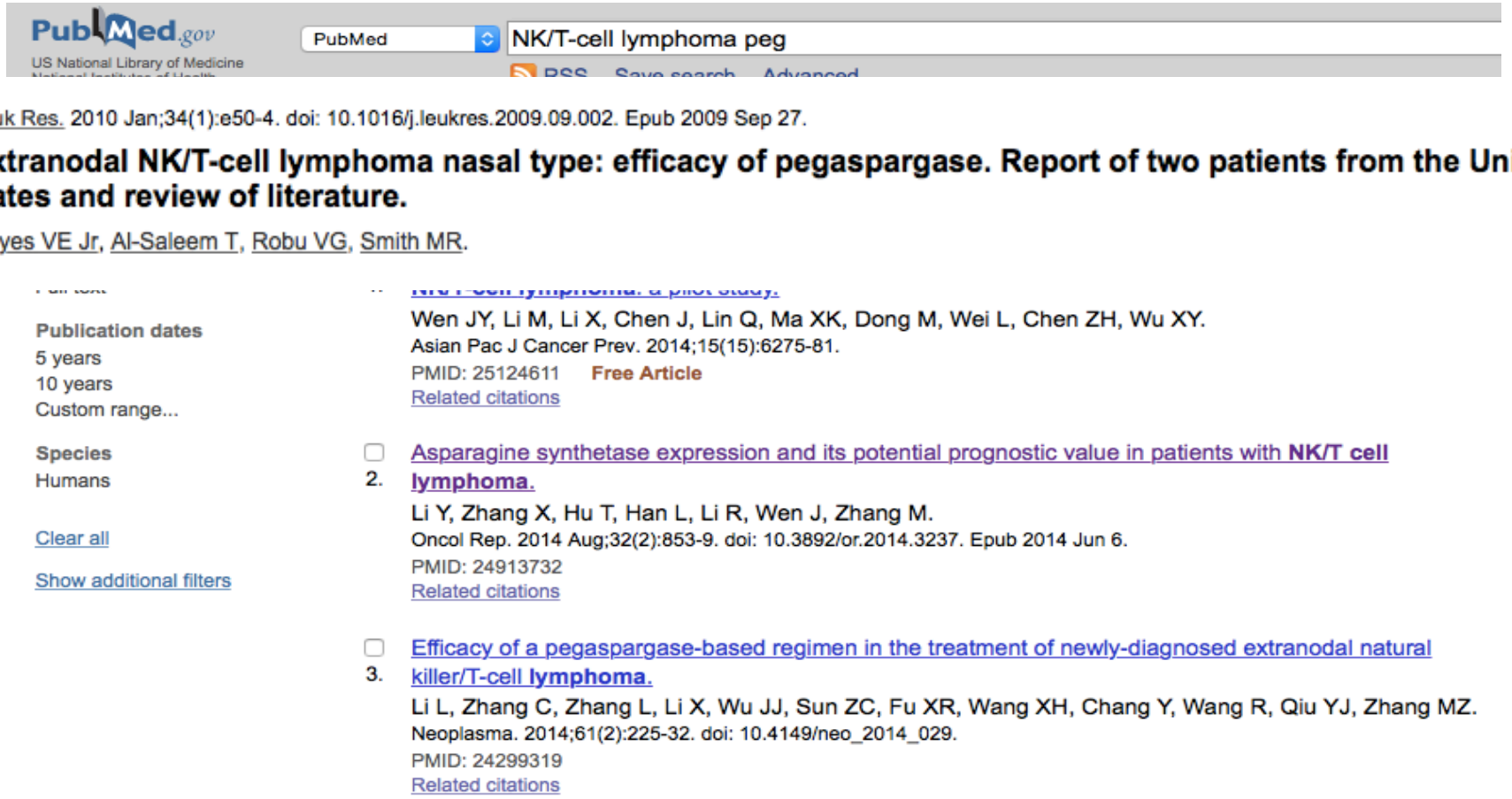
A prospective study on drug monitoring of PEGasparaginase and *Erwinia* asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia

Wing H. Tong, Rob Pieters, Gertjan J. L. Kaspers, D. Maroeska W. M. te Loo, Marc B. Bierings, Cor van den Bos, Wouter J. W. Kollen, Wim C. J. Hop, Claudia Lanvers-Kaminsky, Mary V. Relling, Wim J. E. Tissing and Inge M. van der Sluis

This study has therefore resulted in significant changes in the use of asparaginase in the DCOG ALL-11 protocol. PEGasparaginase is used instead of native *E coli* asparaginase upfront in the induction, and the starting dose of PEGasparaginase has been lowered to 1500 IU/m^2. Also, a therapeutic drug–monitoring program is now used to individualize the PEGasparaginase dose and to detect silent inactivation. In case of allergy or silent inactivation, patients are switched to *Erwinia* asparaginase

Strategies to avoid asparaginase inactivation

- Use first pegylated form of asparaginase



Strategies to avoid asparaginase inactivation

- Use first pegylated form of asparaginase
- Switch to Erwinia asparaginase if antibodies appear

Strategies to avoid asparaginase inactivation

- Asparagine activity is a simple way to check if antibodies are present
  - 48/72 hours after the last native asparaginase injection
  - 7/14 days after the pegylated asparaginase injection

If activity is low asparaginase molecule must be switched

How to improve these results

1) Avoid asparaginase inhibition by antibodies
2) Add effective drugs to asparaginase and radiation

Other drugs associated to asparaginase ?

Invest New Drugs
DOI 10.1007/s10637-012-9889-4

SHORT REPORT

Gemcitabine alone and/or containing chemotherapy is efficient in refractory or relapsed NK/T-cell lymphoma

Hee Kyung Ahn · Seok Jin Kim · Deok Won Hwang · Young Hyeh Ko · Tiffany Tang · Soon Thye Lim · Won Seog Kim

Received: 3 September 2012 / Accepted: 8 October 2012

J Clin Oncol 27. © 2009

Phase I/II Study of Concurrent Chemoradiotherapy for Localized Nasal Natural Killer/T-Cell Lymphoma: Japan Clinical Oncology Group Study JCOG0211

Motoko Yamaguchi, Kensei Tobinai, Masahiko Oguchi, Naoki Ishizuka, Yukio Kobayashi, Yasushi Isobe, Kenichi Ishizawa, Nobuo Maseki, Kuniaki Itoh, Noriko Usui, Izumi Wasada, Tomohiro Kinoshita, Koichi Ohshima, Yoshihiro Matsuno, Takashi Terauchi, Shigeru Nawano, Satoshi Ishikura, Yoshikazu Kagami, Tomomitsu Hotta, and Kazuo Oshimi

Futur protocols: SWAN/NK

- Localized diseases:
  - Gemcitabine + Metho + Dex + PEG-aspa
  - Irradiation + cisplatine 30 mg/week
  - Gemcitabine + Metho+ Dex + Aspa ?

Depending on asparaginase activity at Day 8

if good : Peg-aspa

if not : Erwinia asparaginase

Futur protocols: SWAN/NK

- Disseminated diseases:
  - Gemcitabine + oxaliplatin + Metho + Dex + Peg-aspa
    then
  - Gemcitabine + oxaliplatin + Metho + Dex + aspa ?

  Depending on asparaginase activity at Day 8

  - 3 cycles then ASCT or 4th cycle

  - Allograft ? ? Probably for patients in PR

Waiting for prospective protocole with PEG-aspa

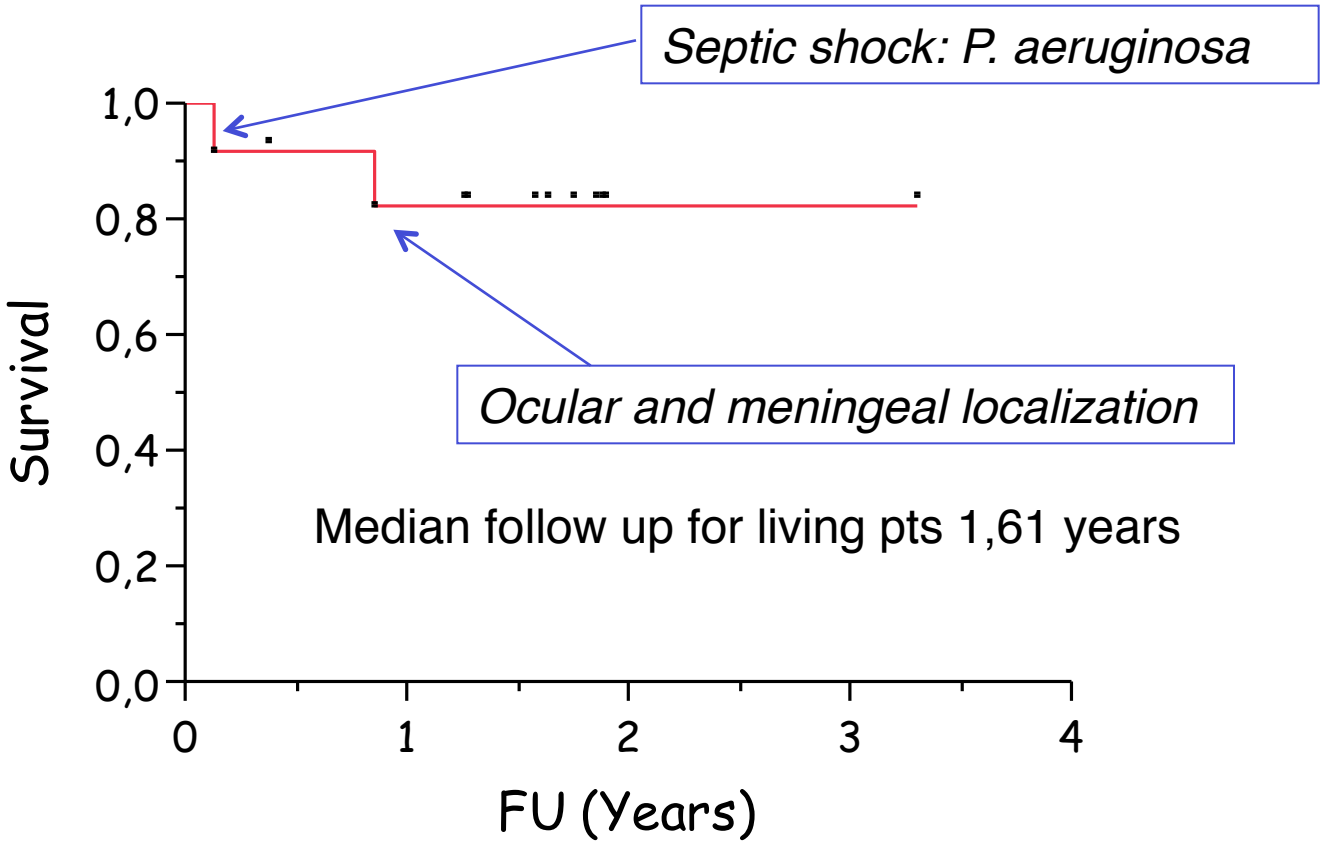
- Localized diseases: MGAD with systematic switch between aspa
  - Gemcitabine + Metho + Dex + e-coli aspa
  - Radiation + cisplatine 30 mg/week
  - Gemcitabine + Metho+ Dex + erwinia-aspa
- Disseminated diseases: MOGAD
  - Gemcitabine + Metho + Dex + e-coli aspa+ oxaliplatin

    then
  - Gemcitabine + Metho + Dex + erwinia-aspa + oxaliplatin

And then depending on asparaginase activity: PEG-aspa or Erwinia-aspa

14 patients MGAD/MOGAD with switch

- Median age: 49 (25-64)
- 9 patients stage I/II: MGAD + irradiation
- 5 patients stage IV: MOGAD



Conclusion

- Asparaginase containing regimens have transformed the prognosis of NK/T-cell lymphoma, particularly for disseminated or relapsing diseases

ACKNOWLEDGMENTS

- Nathalie Gachard and Jean Feuillard in Limoges, Philippe Gaulard and Olivier Hermine in Paris.
- GELA and GOELAMS : LYSA

- All participating centres :

  B. Corront (CH Annecy), O. Fitoussi (Polyclinique Bordeaux Nord), T. Legay (CHU Bordeaux), A. Devidas (Corbeil-essonnes), V. Coiteux, F. Morschhauser (CHU Lille), I. Cumin (CH Lorient), J-F Rossi (CHU Montpellier), P. Coppo (St Antoine Paris), P. Brice, L. Galicier, C. Thieblemont (St Louis Paris), P. Suarez (Necker Paris), P. Lenain, H. Tilly (Becquerel Rouen), G. Laurent , L. Ysebaert (CHU Toulouse).

- EUSA Pharma for providing Erwiniase®

Osaka, November 2014