

2012...2015.

T-Cell Lymphomas: We are illuminating the darkest of tunnels



NK/T-cell lymphoma: the role of asparaginase Japanese experience



Motoko Yamaguchi
Mie University Graduate School of Medicine
Tsu, Japan



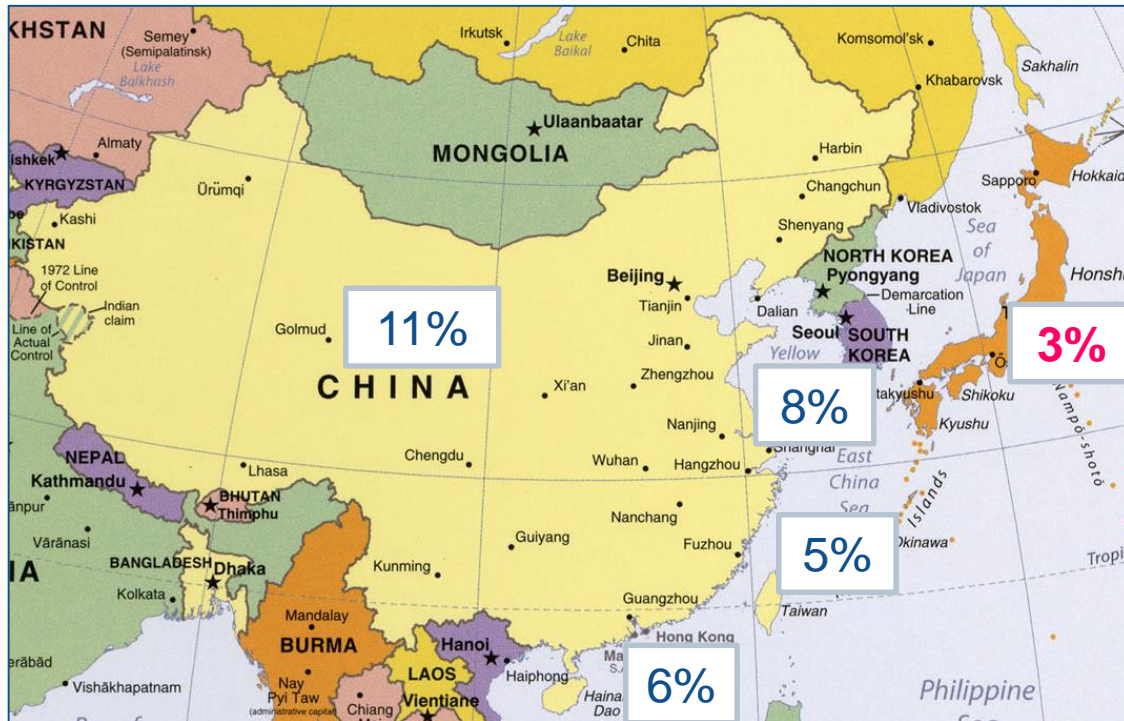
*April 28, 2015
Royal Hotel Carlton, Bologna, Italy*

NK/T-cell lymphoma: the role of asparaginase Japanese experience

- **Final results of clinical trials for NK/T-cell lymphoma in Japan**
- **The role of L-asparaginase for NK/T-cell lymphoma in Japan**
- **Summary**

Extranodal NK/T-cell lymphoma (NKTCL), nasal type (ENKL)

- Incidence in East Asia (cf. <1% in Western countries)



The University of Texas Libraries

Lymphoma Study Group of Japanese Pathologists. Pathol Int 2000

Ko YH, et al. Cancer 1998

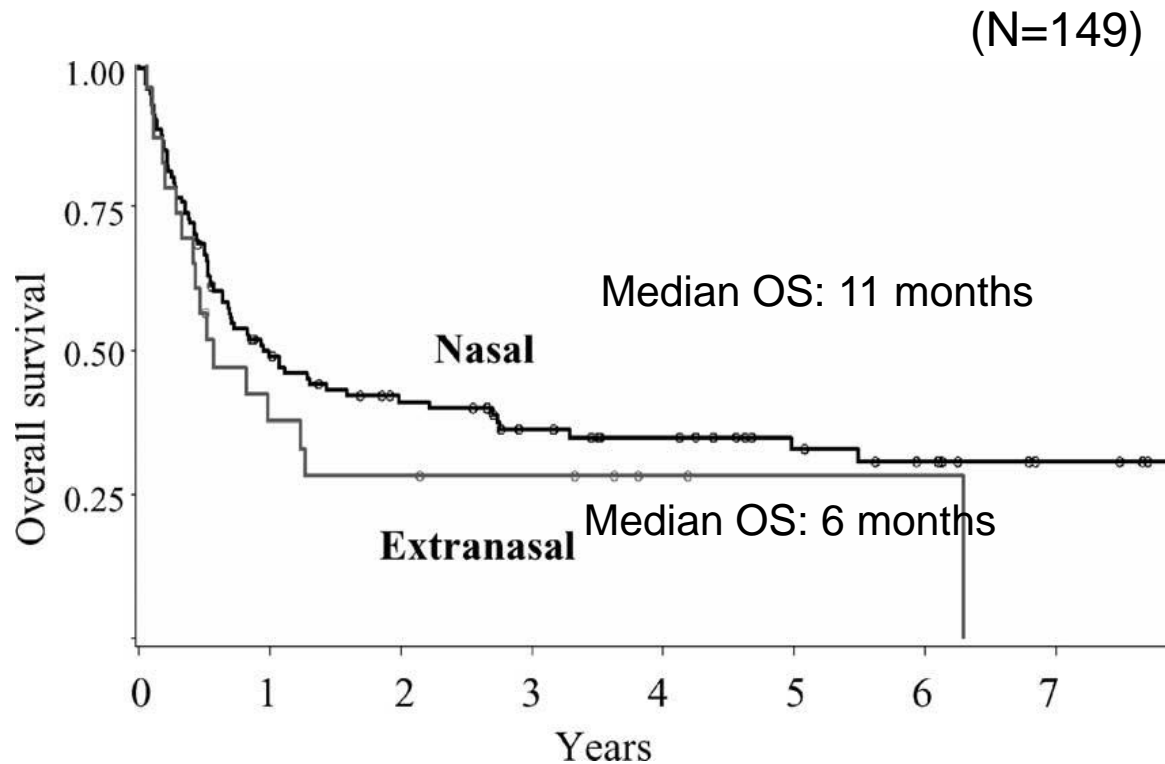
Chen CY, et al. Ann Oncol 2004

Au WY, et al. Ann Oncol 2005

Sun J, et al. Am J Clin Pathol 2012

- Localized nasal NKTCL: >65%
- P-gp/*MDR1*(*ABCB1*) - positive

Prognosis of NKTCL in Japan (1994-1998)



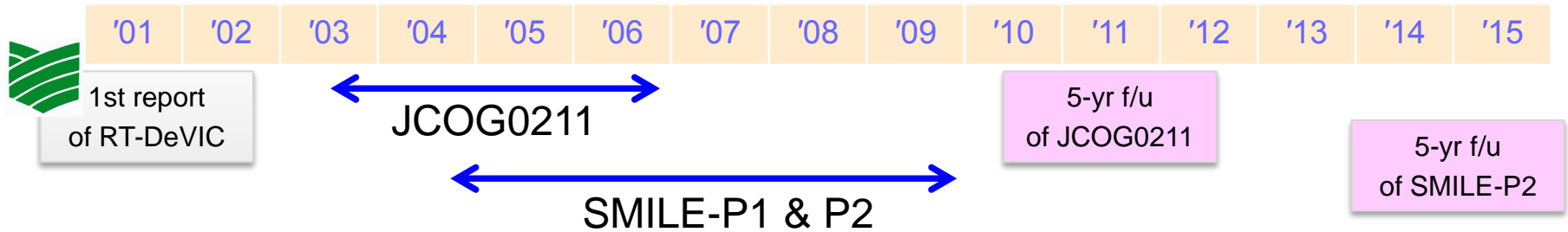
Oshimi K, et al. Hematology 2005

NKOTSG
NK-cell Tumor Study Group

Since 1998

→ Innovative therapeutic approaches were needed

Development of the treatment for NKTCL in Japan



- Newly-diagnosed, localized, nasal NKTCL

- JCOG-LSG
- JCOG0211 (PI/II)
- Concurrent chemoradiotherapy (RT-2/3DeVIC)

Yamaguchi M, Tobinai K, Oguchi M, et al. J Clin Oncol 2009, 2012 (correspondence)



- Newly-diagnosed stage IV, relapsed/refractory NKTCL

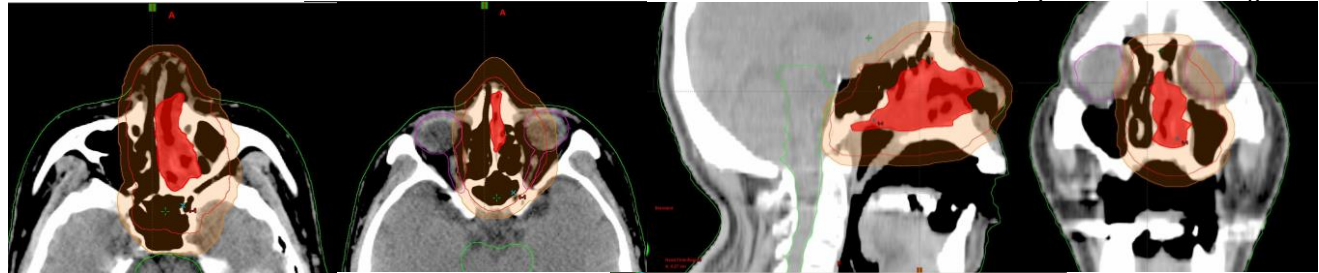
- NKTSG (Multinational trials in East Asia)
- SMILE-P1 & P2
- SMILE chemotherapy

Yamaguchi M, Kwong YL, Kim WS, et al. J Clin Oncol 2011



RT-2/3DeVIC

Courtesy of Dr. Masahiko Oguchi

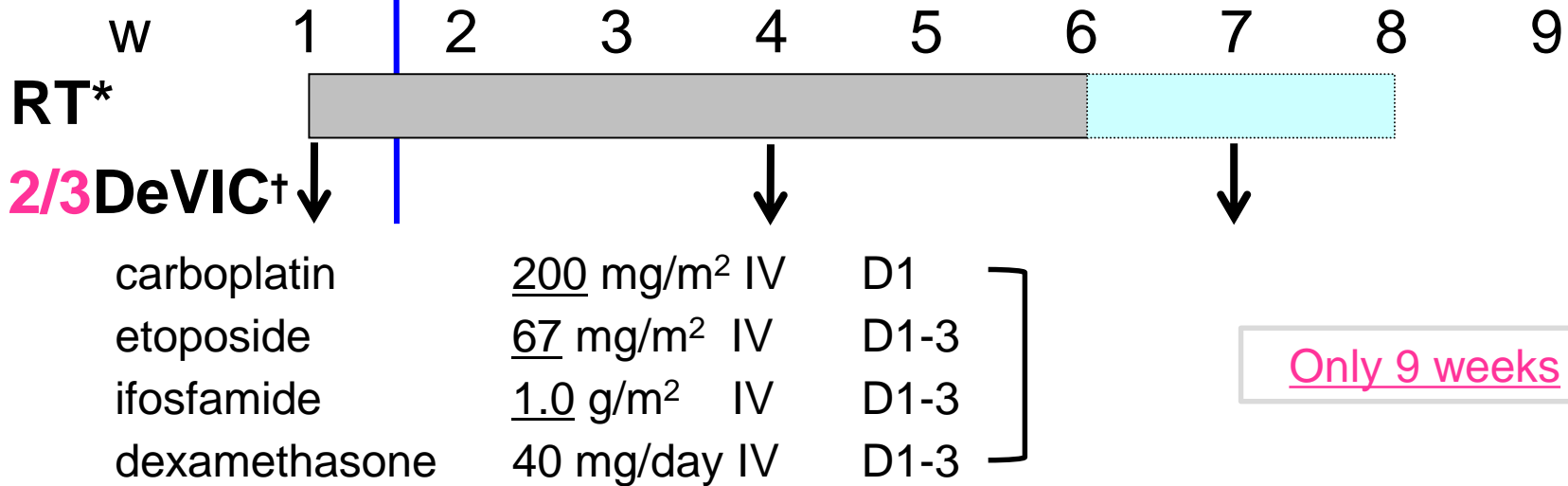


REGISTRATION

7 days

* 50-50.4 Gy (1.8-2.0 Gy/ fx)

CTV: GTV + 2 cm, nasal cavity & nasopharynx



Only 9 weeks

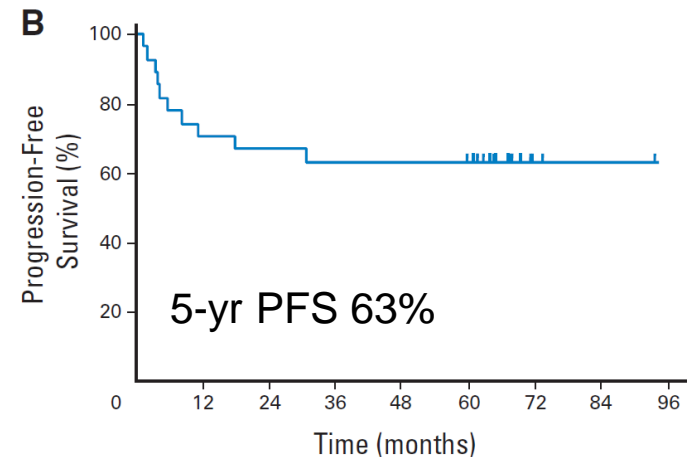
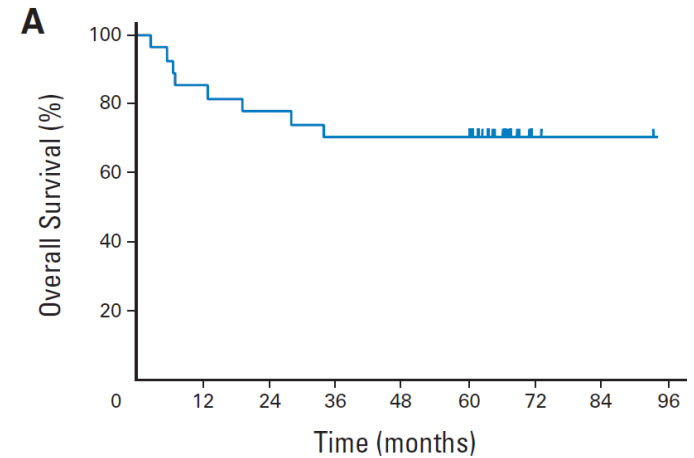
[†], Recommended dose determined in the phase I portion

Final results of JCOG0211

- Baseline characteristics
 - Median age **56 yrs**, B symptoms **37%**, stage IIE **33%**
- RT-2/3DeVIC (n=27)
 - 5-yr OS 70%** (90% CI, 53-82%: H0=40%)
 - %CR 77%, ORR 81%
- Acute toxicity
 - G3 mucositis due to RT (30%)
- Late toxicity
 - Mild and manageable

RT-2/3DeVIC is one of the most recommendable options as a first-line treatment for localized NKTCL.

Median follow-up: 67 months (61-94)



SMILE chemotherapy

Agent	Dose (/day)	Route	Day
Methotrexate	2 g/m ² *	IV (6hrs)	1
Leucovorin	15 mg x 4	IV or PO	2, 3, 4
Ifosfamide	1,500 mg/m ²	IV	2, 3, 4
Mesna	300 mg/m ² x3	IV	2, 3, 4
Dexamethasone	40 mg/day	IV or PO	2, 3, 4
Etoposide	100 mg/m ² *	IV	2, 3, 4
<u>L-asparaginase</u>	6,000 U/m ²	IV	8, 10, 12, 14, 16, 18, 20
G-CSF		SC or IV	Day 6 - WBC > 5,000/mm ³

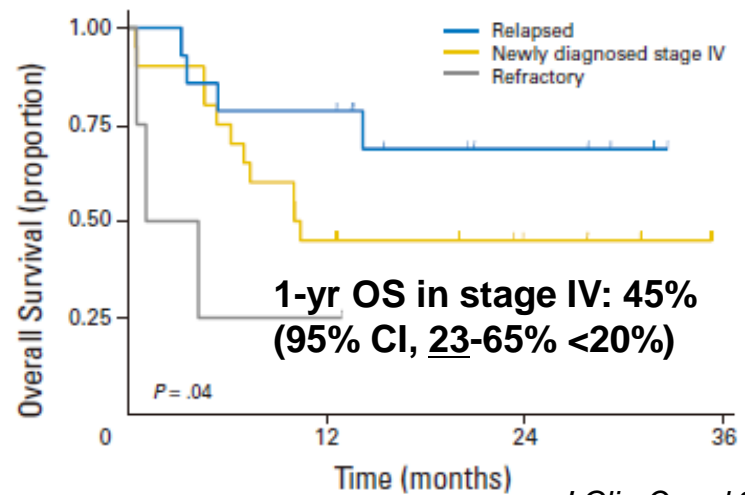
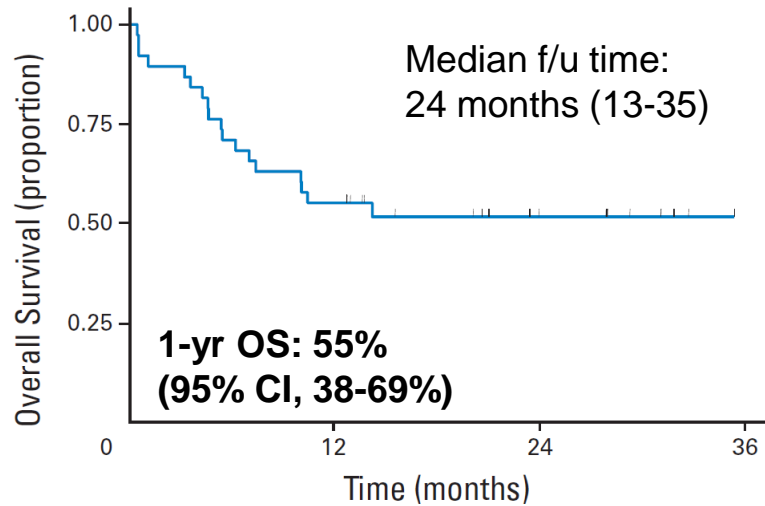
Every 28 days.

*, recommended dose determined in the preceding phase I study. (Yamaguchi M, et al. Cancer Sci 2008)

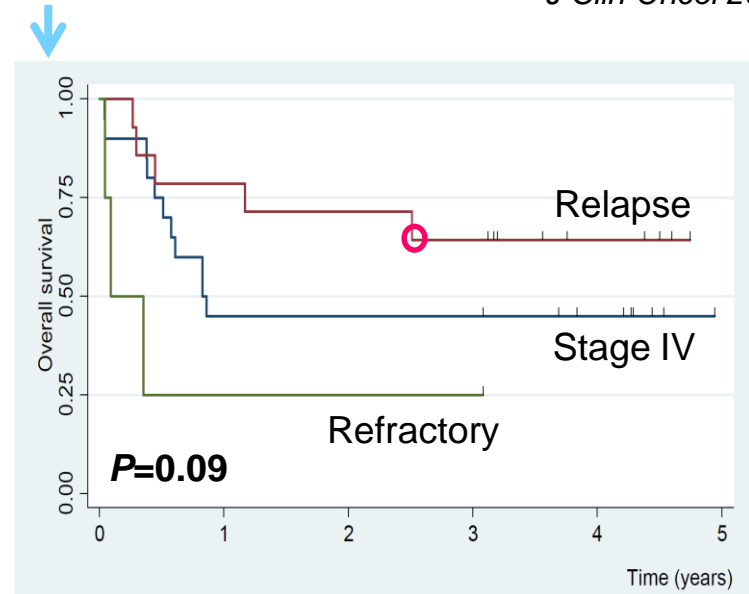
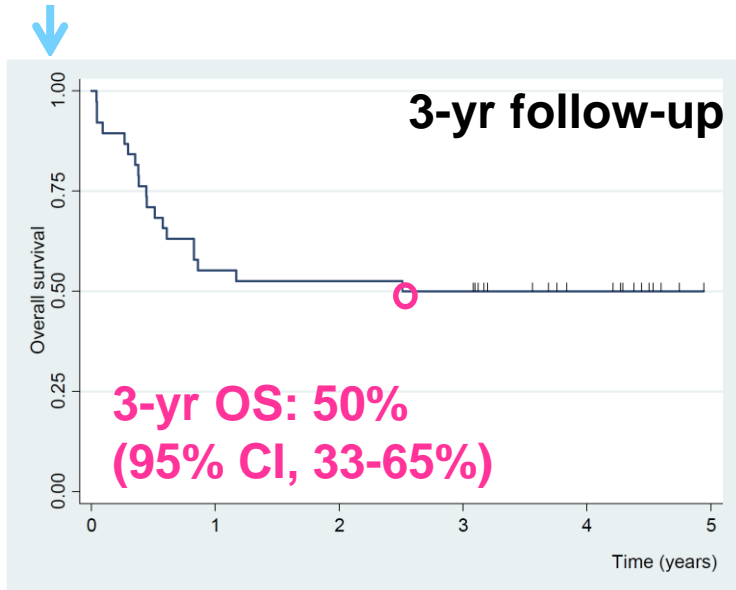
SMILE-P2 for newly-diagnosed stage IV, rel/ref NKTCL

- SMILE x2, N=38, newly-diagnosed stage IV 53%
- **ORR: 79% (90% CI, 65-89%)** > H0 (35%), %CR 38%
- Major toxicity: G4 neutropenia 92%, G3/4 infection (45%/16%)

SMILE-P2: survival analysis (N=38)



J Clin Oncol 2011



Suzuki R, et al. 12-ICML, 2013

Final follow-up of SMILE-P2

- As of Nov. 2014 (5 years)
- No patients were lost to follow-up
- 5-yr OS, 5-yr PFS, subgroup analysis

16:50

075

5-YEAR FOLLOW-UP OF THE SMILE PHASE II STUDY FOR NEWLY-DIAGNOSED STAGE IV, RELAPSED OR REFRACTORY EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

R. Suzuki, Izumo (Japan)

June 18, 2015

Room A & Marquee

13-ICML

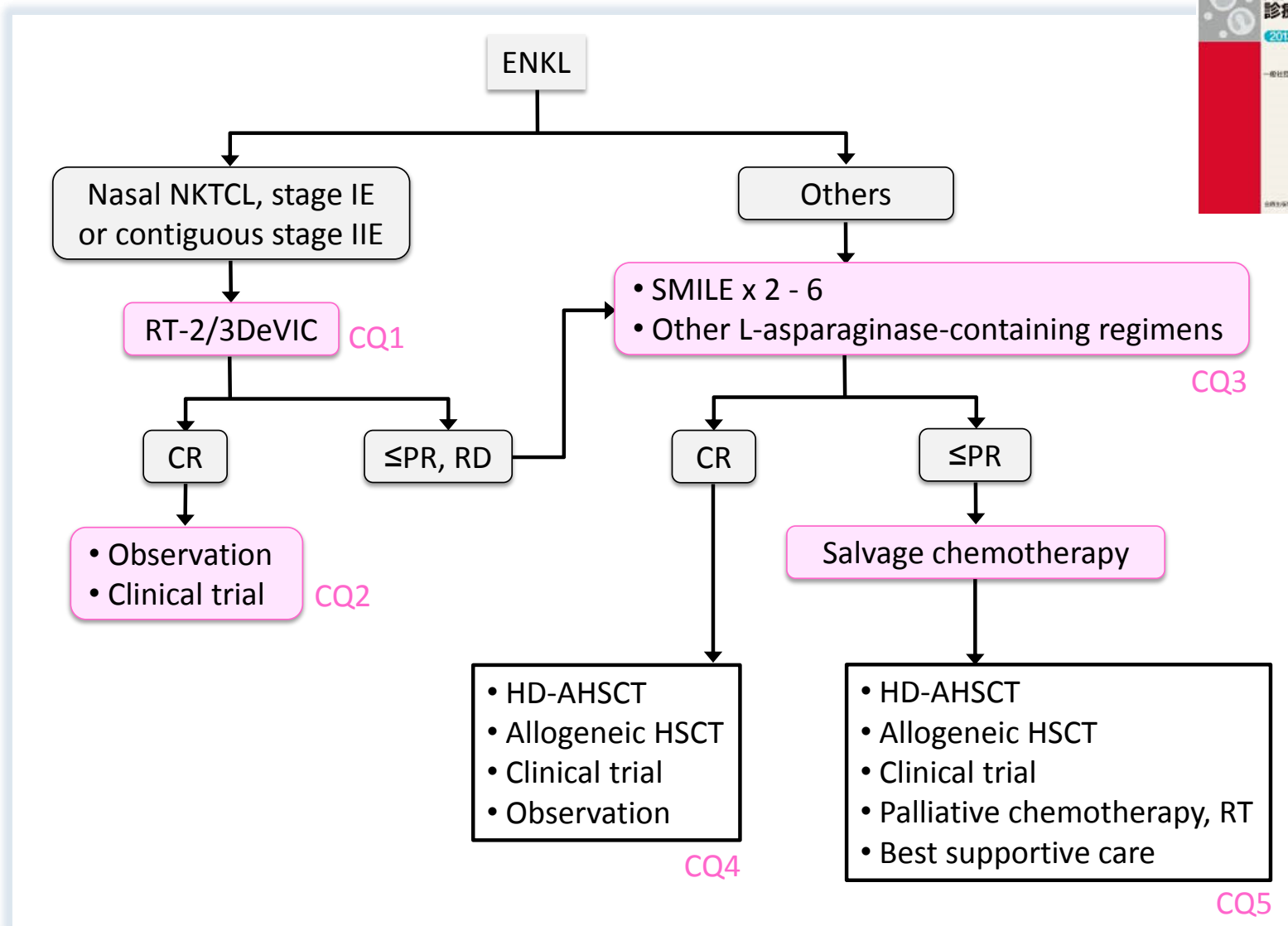


NK/T-cell lymphoma: the role of asparaginase


Japanese experience

- Final results of clinical trials for NK/T-cell lymphoma in Japan
- **The role of L-asparaginase for NK/T-cell lymphoma in Japan**
- Summary

Treatment algorithm for ENKL (JSH Guidelines 2013)



Ongoing project in Japan: NKEA - Part A -

- Observational study of NKTCL (2000-2013) to clarify the current status on the treatment of NKTCL in Japan
- Cooperate with a group of radiation oncologists (JROSG) 
- Information on toxicity and RT planning will also be collected
- 350 - 400 patients
- Planned analysis
 - Baseline clinical features
 - 1st-line treatment, transplantation
 - Response to the 1st-line therapy, survival
 - Acute and late toxicity

CRF
(Hematologist/
oncologist)


CRF
(Radiation
oncologist)

RT planning,
Image
studies

UMIN-CTR ID: UMIN000015491

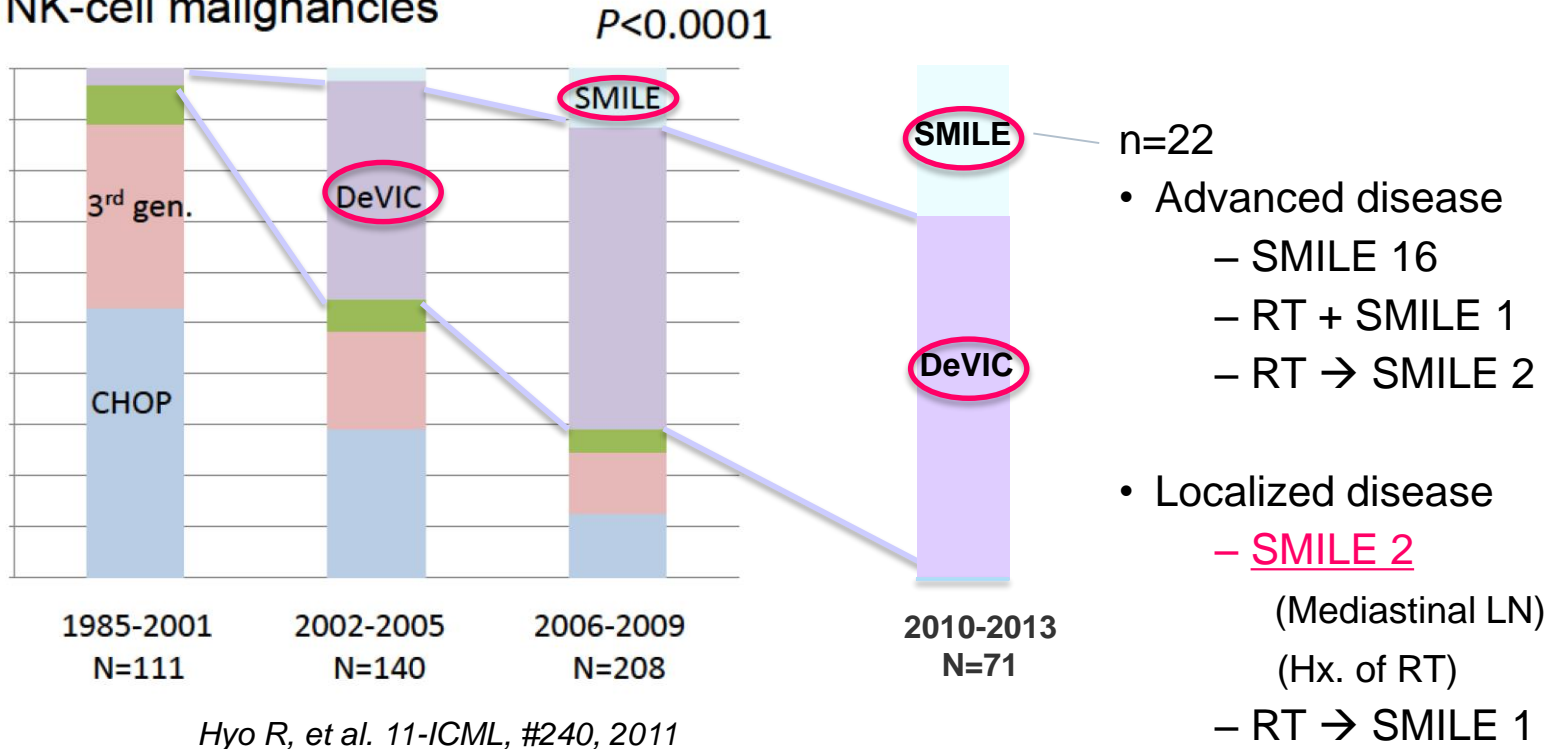
Grant support: MEXT in Japan (Yamaguchi M & Suzuki R)

Recent changes in the treatment of NKTCL in Japan

- NKTSG 2008 survey  NK-cell Tumor Study Group

- NKEA - Part A -
(Preliminary results)

NK-cell malignancies



JCOG0211
SMILE P1&P2



Current role of L-asparaginase for NKTCL in Japan

- A key agent in the treatment of advanced NKTCL
 - Newly-diagnosed stage IV or rel/ref NKTCL
- Usually used as a component of SMILE chemotherapy

- RT-2/3DeVIC: short treatment, excellent efficacy, acceptable AEs
- SMILE: excellent as a salvage chemotherapy
- Only *E. coli* asparaginase is available in Japan



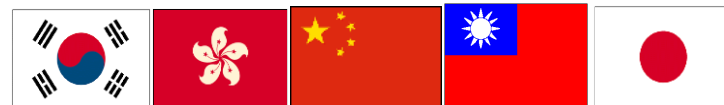
CCRT-/VIDL, AspaMetDex,
LVD, GELOX
...

RT-2/3DeVIC and SMILE in practice need to be evaluated

NK/T-cell lymphoma: the role of asparaginase Japanese experience - Summary -

- Management of NKTCL in Japan has changed
- JSH guidelines recommend RT-2/3DeVIC and SMILE for the first-line treatment of NKTCL
- L-asp is usually used in the treatment of advanced NKTCL in Japan
- A large retrospective study evaluating these new treatments in practice is ongoing in Japan

Acknowledgments



JCOG0211

Kensei Tobinai (National Cancer Center Hospital)

Masahiko Oguchi (Cancer Institute Hospital)

Kazuo Oshimi (Kushiro Hospital)



Feb 14, 2008 @NCCH

NKEA project

Ritsuro Suzuki (Shimane Univ.)

Masahiko Oguchi (Cancer Institute Hospital)

Won Seog Kim (Samsung Medical Center;
as a collaborator in Part C)



SMILE-P1 & P2

Ritsuro Suzuki (Shimane Univ.)

Yok-Lam Kwong (Univ. of Hong Kong)

Won Seog Kim (Samsung Medical Center)

Kazuo Oshimi (Kushiro Hospital)



June 24, 2006 in Osaka

Thank you for all patients, doctors, and staffs



Department of Hematology and Oncology
Mie University Hospital