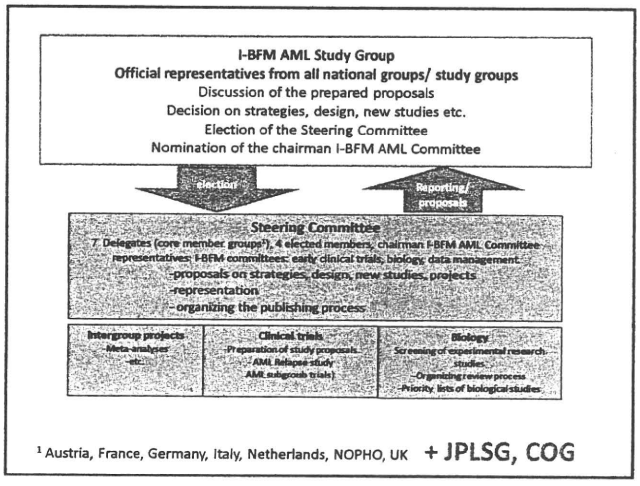

I-BFM AML Study Group
Official representatives from all national groups/ study groups
Discussion of the prepared proposals
Decision on strategies, design, new studies etc.
Election of the Steering Committee
Nomination of the chairman I-BFM AML Committee
election
Reporting/ proposals
Steering Committee
7 Delegates (core member groups?), 4 elected members, chairman I-BFM AML Committee
representatives I-BFM committees: early clinical trials, biology, data management
-proposals on strategies, design, new studies, projects
-representation
-organizing the publishing process
Intergroup projects
-Meta-analyses
-etc.
Clinical trials
-Preparation of study proposals
-AML Relapse study
-AML subgroup trials)
Biology
-Screening of experimental research studies
-Organizing review process
-Priority lists of biological studies
[1] Austria, France, Germany, Italy, Netherlands, NOPHO, UK + JPLSG, COG

2010.11.14 JPLSG総会

I-BFM-SG報告
CML

慶應義塾大学医学部小児科
嶋田博之

Room A2

SCT & CML Committee
Chairs: D Webb, F Millot and P Bader

Acute myeloid leukemia & Stem Cell Transplantation
CML
14:30: Interim results of protocol CML-paed II, M Suttorp
14:45: Identification of the genomic BCR-ABL breakpoint in DNA extracted from blood specimen archived on filter paper in pediatric patien
Krumbholz
14:55: CML SCT Protocol, S Matthes /J Stein

Room A5

CML Committee
Chairs: F Millot

Main Session

8:30: Introduction, A Biondi
8:35: Update of Glivec Phase IV study, F Millot
8:50: Imatinib in Italy, A Biondi

9:05: Effects of imatinib on bone metabolism, M Suttorp

9:30: Imatinib discontinuation in children with CML in complete molecular response, E De Bont 9:45: Dasatinib phase II study, P Kearns

10:00: Nilotinib phase I study, P Kearns
10:10: CML Registry, F Millot

3. Imatinib discontinuation
E De Bont

Focus on imatinib stop studies

- Previous French adult studies showed that 50% of CML patients relapsed within 6 months after the stop of imatinib.
  n=12 *Rousselot Blood 2007*
- Responses seen also without IFN pretreatment
- Reinstalling of IM after relapse successful
  Update n=50 *Mahon ASH 2008*

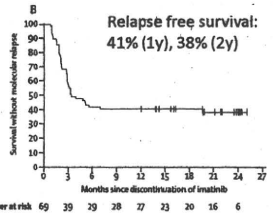
⬇

- International pediatric study

Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial

François-Xavier Mahon, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Franck Nicolini, Laurence Legros, Aude Charbonnier, Agnès Guerci, Bruno Varet, Gabriel Etienne, Josy Reiffers, Philippe Rousselot, on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC)

Lancet Oncology 2010.



Relapse free survival:
41% (1y), 38% (2y)

For those who relapsed,
- 400mg IM daily
- 16/42: decrease in BCR-ABL/ABL
- 26/42: CMR, median 3 months (1 – 5 months)
- No progression to AP
- No acquired mutation

N=69 (follow up >12mo, 13 – 30mo)

Relapseの詳細

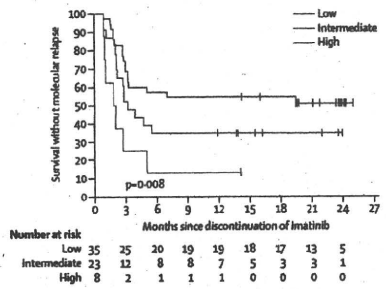
- Molecular relapse in 42/100 patients
- 1 months: 7
- 2 months: 15
- 3 months: 13
- 4 months: 1
- 5 months: 3
- 6 months: 1
- 7 months: 1

ほとんどが6か月以内の再発
Leukemic blastは1 log/month の割合で増加

- 19 months: 1

Mahon et al. Lancet Oncology 2010.

Factors related to higher relapse rate



Mahon et al. Lancet Oncology 2010.

Pediatric study

- Possible design: international randomized
- Inclusion criteria
  - Age 1 to 18
  - CML diagnosed >=3 yrs
  - Sustained imatinib response (CMR 4.5 log below diagnosis for at least 2 years)
    - Undetectable bcr-abl mRNA by qRT-PCR in 2 consecutive blood samples, sensitivity $>10^4$
- Endpoint
  - Sustained CMR or Molecular relapse
- Expected patient number 60

International randomized study protocol CML-WG, I-BFM

Title	An international collaborative study to discontinue imatinib (IM) therapy in pediatric CML patients with complete molecular response
Indication	Philadelphia chromosome positive patients treated with imatinib and with complete cytogenetic and complete molecular response
Objectives	To determine the percentage of RT-PCR negative pediatric CML patients in which treatment discontinuation result in sustained complete molecular remission To determine the relapse-free survival of patients in case of molecular relapse and in a molecular remission again
Endpoints	Duration of complete molecular remission in ongoing treatment-free of (molecular) relapse Death efficacy of restarting imatinib in a group of 6 months after relapse
Number of patients	60 patients
Outline and timing	5 yrs international protocol of the BFM-CML study group
Inclusion criteria	Pediatric CML patients treated with imatinib and for at least 2 years in complete molecular remission
Exclusion criteria	Non-CML patients, or CML patients with confirmed cytogenetic relapse but with a moderate molecular response
Study plan	Investigate duration of complete molecular response after discontinuation of imatinib, rate of relapses, death and efficacy of restarting imatinib after molecular relapse
Study medication	none

Additional study

Imatinib intermittent study for those without CMR but with CCyR for expecting catch-up growth.

Comments

- One month on and one month off of IM may control CML but it is uncertain whether the off-duration of IM is enough for restoring bone metabolism.
- From the adult study, higher Sokal score is related to higher relapse rate. So we should take care and deal with this information.
- We should take care in maintaining the same level of molecular analysis among international samples.

ELTEC

ELTEC: Early and Late Toxicity Educational Committee

- Early toxicity: Collaboration, if possible, with treatment Committees
- Late toxicity: Incorporate into PanCare and propose leukemia-oriented studies
- Educational: Expand and provide open access to the Booklet for Hemato-Oncologists
  - and interact with PanCare

I-BFM ELTEC

Committee Report

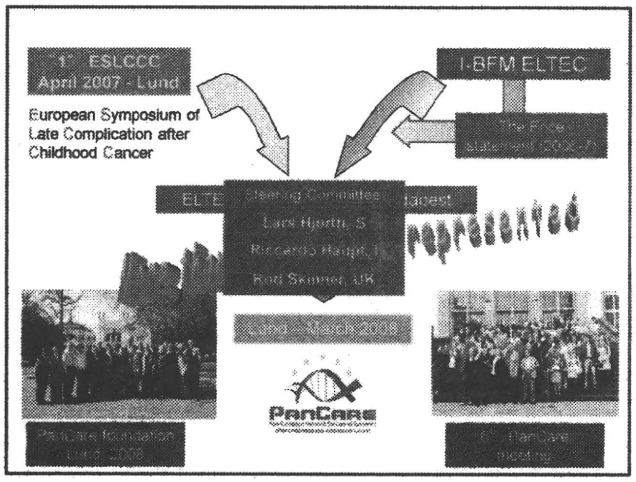
34 partecipants!
from 12 Countries!
(our record!!)

10月3日午後
ELTEC委員会開催
12カ国から出席者34名
ヨーロッパ以外も多い

Agenda:

- Interaction with PanCare
- Involvement in European projects
  - ENCCA
  - PanCareSurFup
  - HOLLY
- Development of the Educational Booklet for young hemato-oncologists

Riccardo Haupt, Antalya October 3, 2010



PanCare

Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer

PanCare is a multi-disciplinary pan-European network of professionals, survivors and their families established to to ensure that every European survivor of childhood and adolescent cancer receives optimal long-term care

- Promote and support optimal long-term care
- Develop ways to achieve equality of access to care
- Collaborate on research into late effects of cancer and its treatment
- Develop, disseminate and implement evidence-based guidelines for care of survivors
- Raise awareness and knowledge on survivorship within Europe

ELTEC institutions in PanCare

- Austria
  - Vienna
  - Graz
- Belgium
  - Ghent
- Chech Republic
  - Brno
- Germany
  - Erlangen
  - Mainz
- Hungary
  - Budapest
- The Nederlands
  - Nijmegen
  - Amsterdam
- UK
  - London

PanCare was funded by ELTEC members

ELTEC is (in) PanCare

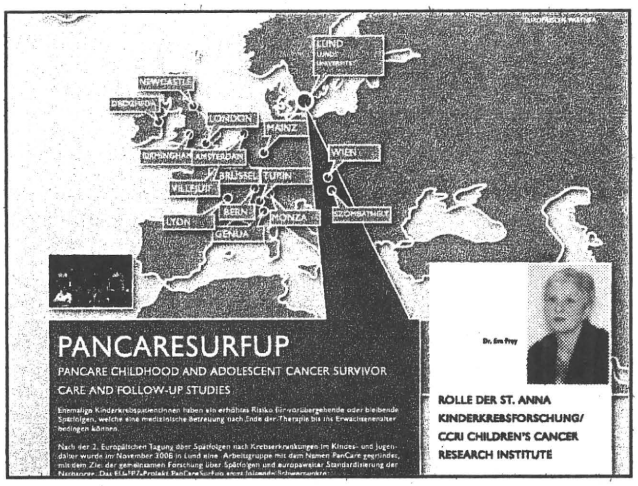
基本的にEUのFund.昨年×, 今年からobseverならいいよと。

I-BFM ELTEC

Interaction with: PanCare

And involvement in European projects:
ENCCA
PanCareSurFup
HOLLY

Riccardo Haupt, Antalya October 3, 2010



PanCare in EU projects

- ENCCA
  - Quality of survivorship (WP 13 – Haupt - I)
  - Survivorship passport (WP 13.2)
  - Education and training (WP 15)
- Pan
  - D. Grabow – D)
  - – F)
  - nested case control study (L. Kremer – NL)
  - hort and nested case control study (M.
  - Late m (S. Garwicz – S)
  - Guidelin or follow-up (R. Skinner – UK)
  - Dissemination and training (M. Jankovic – I)
- HOLLY (Health Outcomes Lymphoblastic-Leukemia-infancY)
  - To estimate the total burden of morbidity, in terms of comprehensive health status and HRQL scores of survivors of ALL in infancy

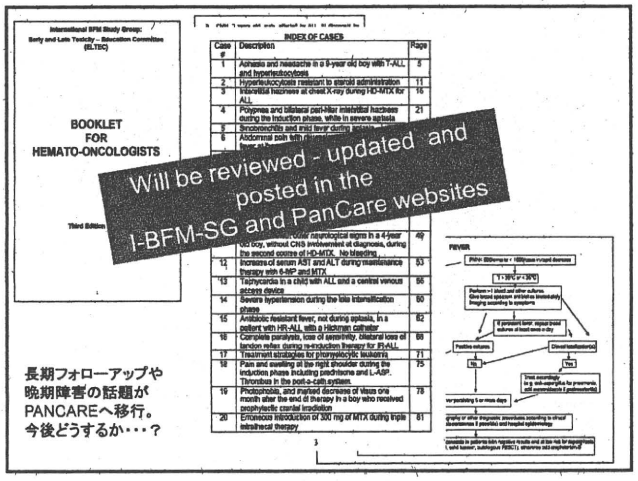
International Guideline-Harmonization Initiative
COG/CCSS
New Zealand
Japan

ELTEC:

ELTEC: Early and Late Toxicity Educational Committee

- Early toxicity: Collaboration, if possible, with treatment Committees
- Late toxicity: Incorporate into PanCare and propose leukemia-oriented studies
- Educational: Expand and provide open access to the Booklet for Hemato-Oncologists
  - and interact with PanCare

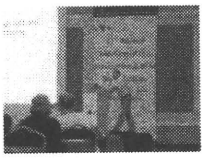
今回の会議では、小グループに分かれBookletの修正作業を行った



長期フォローアップや晩期障害の話題がPANCAREへ移行。今後どうするか・・・？

21st Annual Meeting of the International BFM Study Group SCT committee

Oct 2-4, 2010
Antalya Turkey



Contents

- SCT Committee (P. Bader)
  1. Effect of ATG preparations on NK cell function
     J.H. Dalle (Canada)
  2. Half-life of ATG and its clinical implications
     A. Lankester (Leiden)
  3. Thymoglobin in haploidentical SCT
     J.Palma (Chile)
  4. Update of the BMT trials North America (COG, PBMTC)
     K. Schulz (Canada)
  5. Results from BFM ALL SCT study
     C. Peters
- Closed meeting
  Mesenchymal stromal cells for treatment of GVHD

1. Effect of ATG preparations on NK cell function

- Genzyme-ATG はNK細胞の増殖・アポトーシス・細胞障害活性に影響しないが、NK細胞によるIFN-γの分泌を促進させる.

2. Half-life of ATG and its clinical implications

- 104人の移植症例に対しATGまたはCampath-1H (C1H)を使用し、血中濃度をモニタリング.
- ATGに比しC1Hは半減期が長く，免疫系の回復も遅い.
- 急激にATGの血中濃度が低下した例では抗ATG抗体の中でも，特にIgG型が出現.
- 抗体産生によるATGの急激な血中濃度の低下は移植成績の悪化につながる傾向がみられた.
- IgG型抗ATG抗体の移植後早期モニタリングの有用性が示唆された.

3. Thymoglobin in haploidentical SCT
   ChileでのHaploidentical RIST (ATG + TNI 7Gy)の成績
   2y-OS 78.6%, 2y-EFS 57%を提示

4. Update of the BMT trials North America
   北米における PBMTC (Pediatric bone marrow transplantation consortium) とCOGのnetwork, ongoing projectsの紹介

5. Results from BFM ALL SCT study
   ALL SZT-BFM 2003
   MD or MSD?
   MSD/MD vs. MMD (mmUD, haplo, mmCB)?
   近日publish予定

Closed meeting: Mesenchymal stromal cells
Results of recent studies

1. Leiden (Netherlands) and Pavia (Italy)
   Steroid-refractory grade III-IV aGVHD
   n = 37 (2005 – 2009)
   CR rate: 2005 – 2008: 13/23, 2009 – : 9/14
2. Monza (Italy)
   Multiple immunosuppressant-refractory aGVHD or cGVHD
   n = 11 (2008 – 2009)
   response rate: 71% (CR in 24%)
3. Prospective non randomized phase I-II study (Monza, Italy)
   Steroid-refractory grade II-IV aGVHD and cGVHD
   n = 13 (7 adults and 6 children)
   5 PR, 4 CR, 4 non-responder (6 months follow-up)

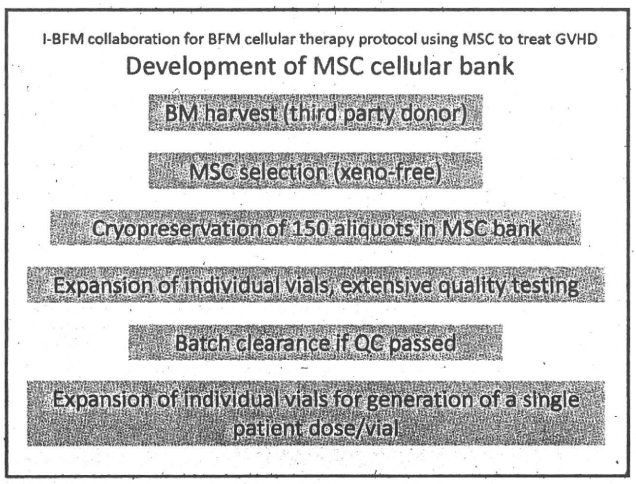
Closed meeting: Mesenchymal stromal cells
Summary

治療効果

- cGVHDよりもaGVHD治療で有効
- GVHD発症後早期治療例で有効性が高い
- MSC治療により免疫抑制剤の使用が減少し，感染症予防につながる

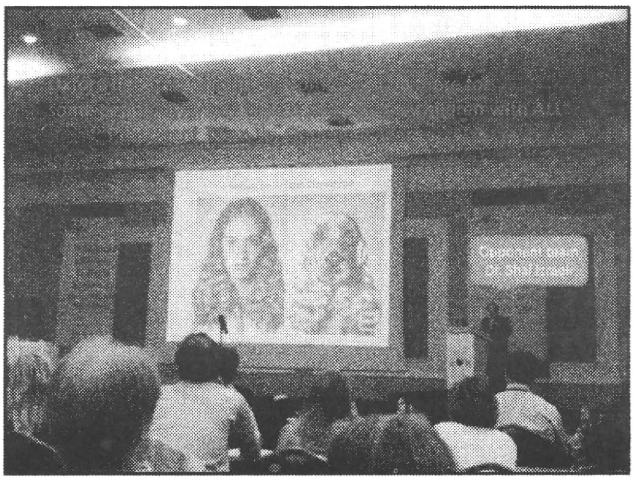
問題点

- HLAについて不明な点が多い
  - Haploidentical donor or third party donor?
- Frozen sampleとfresh sampleの効果の違い
- Expansionによる付加的遺伝子異常の懸念


I-BFM collaboration for BFM cellular therapy protocol using MSC to treat GVHD
Development of MSC cellular bank
BM harvest (third party donor)
MSC selection (xeno-free)
Cryopreservation of 150 aliquots in MSC bank
Expansion of individual vials, extensive quality testing
Batch clearance if QC passed
Expansion of individual vials for generation of a single patient dose/vial

I-BFM 2010
Biology & Diagnosis 報告
Oct 2-4, 2010

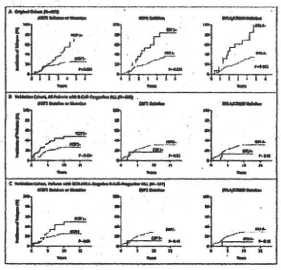
名古屋大学小児科 嶋田 明



ResDis & B&D Committee
Etiology of relapse and high risk markers BCR-ABL like, IKAROS, JAK, CRLF2 and others

Deletion of *IKZF1* and Prognosis in Acute Lymphoblastic Leukemia (Mullighan CG, NEJM 2009)

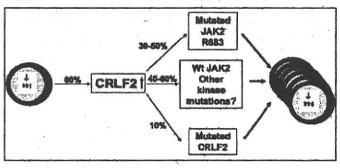
221 high-risk ALL patients except for very-high-risk ALL subtypes (BCR-ABL1-positive, hypodiploid, infants)
Copy number alteration:
- CDKN2A/B 45.7%,
- PAX5 31.7%,
- IKZF1 28.6%
- ETV6 12.7%
- RB1 11.3%
- BTG1 10.4%



cytokine receptor-like factor 2 (CRLF2) overexpression in DS-ALL

Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of *CRLF2* is associated with mutated *JAK2:* a report from the International BFM Study Group (Blood. 2010;115:1006-1017)

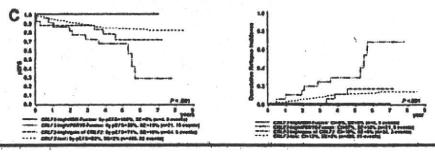
62% (33/53) of the DS-ALL samples showed high expression of CRLF2
IgH@CRLF2 or *P2RY8-CRLF2*
In these 33CRLF2 highly expressed patients, 3 (9.1%) had F233C mutation in CRLF2, and 10 (30.3%) had JAK2 R683 mutation.



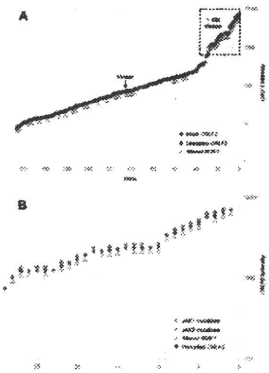
P2RY8-CRLF2 rearrangement in BCP-ALL

Presence of the *P2RY8-CRLF2* rearrangement is associated with a poor prognosis in non-high-risk precursor B-cell acute lymphoblastic leukemia in children treated according to the ALL-BFM 2000protocol (Blood 2010, 115; 5393-5397)

555 unselected BCP-ALL according to the ALL-BFM 2000(BCR-ABL 9, MLL-AF4 5, TEL-AML1 146) CRLF2 high expression group (49/555, 8.8%) showed 6-year relapse incidence 31+/-8% compared with 11+/-1% in the CRLF2 low expression group.
P2RY8-CRLF2 patients showed extremely high relapse rate (71+/-19%) [IgH@CRLF2 (4/49, 8.2%), *P2RY8-CRLF2* (21/49, 42.8%) and CRLF2>2 copies (7/49, 14.3%)], *P2RY8-CRLF2* (21/555, 3.8%) was found in unselected BCP-ALL. JAK I682F or R683S was found in 5 *P2RY8-CRLF2* and 1 *IGH@CRLF2* 2 CRLF2 mutation was found in *P2RY8-CRLF2*



Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphpblastic leukemia (Blood 2010, 115; 5312-5321)



http://target.cancer.gov/

Is JAK inhibitor effective for subgroup of ALL (JAK2 mutated)?
Incyte: INCB018424, Pfizer: CP-690550

CRLF2 Lesions: Associated Factors

	CRLF2 lesion	CRLF2 intact	P value
IKZF1 alteration	21/26 (81%)	35/161 (21.8%)	<0.0001
JAK mutation	18/26 (69.2%)	2/161 (1.2%)	<0.0001
BCR-ABL like GEP	18/29 (62.1%)	20/178 (11.2%)	<0.0001
Hispanic Race	18/29 (62.1%)	22/176 (12.5%)	<0.0001
4-Yr RFS	35.3% (SE 9.5)	71.3% (SE 3.6)	0.0001

Is JAK inhibitor effective for subgroup of ALL (JAK mutated)?
Incyte: INCB018424, Pfizer: CP-690550

AML&B&D Committee

1) BFM/DCOG typeI mutation
NPM1 mutation was found in 21% NK-AML with favorable outcome
WT1 mutation is independent poor prognostic factor
IDH mutation 3.5%

2) COG Type I mutation
TET2 5% (OS、RFSは悪い), FLT3 12%, CEBPA 4.5%, NPM 6%, KIT 19%,
WT1 8.3% (予後には関係なし), IDH1 ?
次世代シークエンサーで100症例検討中 (TARGET project)

AML&B&D Committee

St.Jude, COG AAML1031, BFM2010 use Sorafenib for AML with FLT3-ITD I

BFM2010
HAM+Sorafenib for FLT3-ITD
HAM+AMD3100 for CXCR4 high expressed AML
C-Kit mutated/Ph1 HAM+Dasatinib

COG
ADE+/-sorafenib or AC220 for FLT3-ITD
ADE+/-Bortezomib
Dasatinib for KIT mutated-AML
Upcoming.....
SAHA(HDAC inhibitor), Decitabine (Dacogen, anti-metylation drug), AMD3100 (CXCR4 antagonist, Plerixafor), INCB018479(Ruxolitinib, JAK inhibitor) for AML

VPA for ML-DS 50mg/kgをprephaseで併用

AML-MRD (flow or PCR?)

Integrated approach to MRD in childhood AML

1.Immunophenotyping (8-Color-Flow-Cytometry)
2.qPCR Fusion genes (AML1-ETO, CBF-MYH11, MLL)
3.qPCR Type I/II Mutations (FLT3-ITD/TKD; NPM1; CEBPα; ras, c-kit, WT1)
4.qPCR WT-1-expression
5.Gene expression CCL23, GAGED2, MSLN, SPAG6, ST18, WT1, PRAME
6. New approaches (Next generation sequencing)

Modul	Methode	Material	respons Dr.
Coordination			M.Dworzak
Immunophenotyping	Flowcytometry	cells	
Gene-expression 7-Gene-set WT1	qPCR	RNA	
Fusion genes	qPCR	RNA/DNA	
Type I/II Mutation	qPCR	DNA	
New approaches	Next generation sequencing	DNA	
Clinical data			

WT1mRNAの国際標準化 EUのABL補正vs.日本のGAPDH補正
(Miyawaki S, et al. Leuk&Lymp 2010)

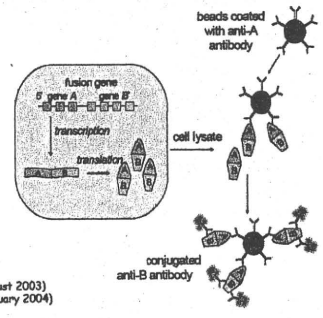
B&D Comittee

1) Molecular genetic analysis of childhood leukemia in Turkey
人口約7,000万人、国立イスタンブール大学で一括検査？
PAX5 deletion、WTX gene mutationなどしっかりデータを作っていた。

2) Advanced flow cytometry
moAb NG2(7.1): NG2 detects many, but not all 11q23 aberrations, however, it does not react with healthy BM cells

To detect BCR-ABL chimera by flowcytometer : BCR-ABL RUO immunobeads assay, BD (Weerkamp F., et al. Leukemia 2009)

Bead-based flow cytometric assay for fusion proteins



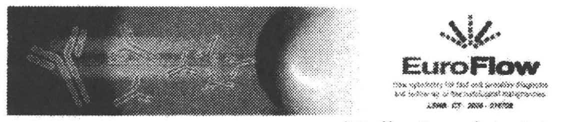
US 6,610,498 B1 (26 August 2003)
US 6,686,165 B2 (3 February 2004)

Molecular techniques vs Flow cytometry

in hematological malignancies

	Molecular techniques	Flow cytometry
Speed	2-3 days (up to weeks)	fast: 4.5 hours !!
Target	DNA or RNA (RNA is an instable target)	protein/cells ("end-product")
Applicability	depends on disease (chromosome aberrations)	broad
Multiplexing	technically demanding	relatively easy (even 25 to 100 tests per tube)
Accuracy	semi-quantitative	quantitative
Focus	all cells in sample (or: prior purification)	any subpopulation
Facilities	special laboratories needed	only standard lab needed

Testing of the BCR-ABL RUO kit on clinical samples by EuroFlow*



Introduction (http://euroflow.org/index.php)

EuroFlow consortium consists of two SME's and 8 diagnostic research groups, which are regarded as experts in the fields of flow cytometric and molecular diagnostics. Together the 10 participants have sufficient complementarily and congruence to cover all aspects of development, standardization, and validation of highly sensitive tests for diagnosis and follow-up.

The main objective of the EuroFlow Consortium is the development and standardization of fast, accurate, and highly sensitive flow cytometric tests for diagnosis and prognostic (sub) classification of hematological malignancies as well as for evaluation of treatment effectiveness during follow-up. This includes the introduction of novel flow cytometric methods for replacing several types of molecular techniques (particularly PCR-based detection of fusion genes and oncogenes).

Participant 1 (Coordinator): Erasmus MC, Rotterdam
Participant 2: USAL, Salamanca
Participant 3: CIPB, Lisbon
Participant 4: UNIKIEL, Kiel
Participant 5: AP-HP, Paris
Participant 6: HMDS, Leeds
Participant 7: DPH/O, Prague
DYNOMICS, Amsterdam
CYTOGNOS, Spain

The EuroFlow acute leukemia orientation tube (ALOT) was designed and approved for assessment of the nature of immature blast cell populations in acute leukemia samples (B, T versus non-lymphoid or mixed phenotype) and consequent orientation towards the most appropriate complementary antibody panel(s):
BCP-ALL, T-ALL, and/or AML/MDS. The precise composition of the ALOT is provided in Table 1. The markers CD45, CD34 and CD19 serve as backbone markers when the information of the ALOT is combined with the BCP-ALL panel (using the INFINICYT software), whereas the markers cyCD3, CD45,and smCD3 serve as backbone markers when the information of the ALOT is combined with the T-ALL panel (using the INFINICYT software). CD45 and CD34 are also used as part of the backbone marker set in the AML/MDS protocol (see Section 7).

TABLE 1. Single tube EuroFlow screening combinations for acute leukemias (ALOT)*

Pacific Blue	Pacific Orange	FITC	PE	PerCP-Cy5.5	PE-Cy7	APC	APC-H7
cyCD3	CD45	cyMPO	cyCD79a	CD34	CD19	CD7	smCD3

* Further information about the markers and the availability of hybridoma clones is summarized in Appendix A. Backbone markers are indicated in bold; cy= cytoplasmic; sm= surface membrane.

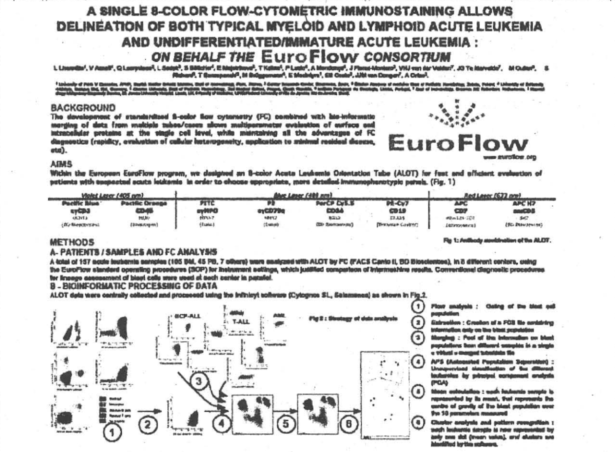
Background

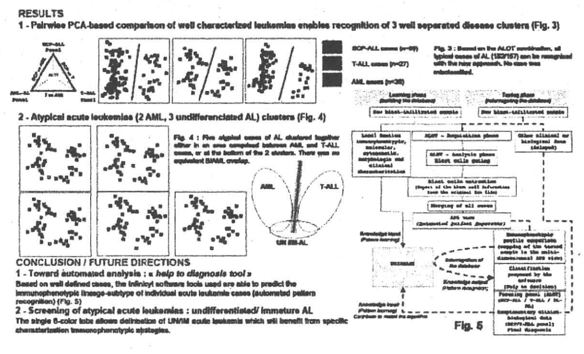
The EuroFlow BCP-ALL panel aims at the recognition and classification of all classically defined BCP-ALL (pro-B-ALL, common-ALL, pre-B-ALL) or alternative BCP-ALL classifications, including immunophenotypic classifications associated with well-defined molecular aberrations, such as specific fusion genes. The information obtained with the BCP-ALL tube set needs to be combined with the ALOT (Table 1), based on the backbone markers CD45, CD34 and CD19 and using the INFINICYT software (Table 5).

TABLE 5. Multi-tube EuroFlow classification panel for BCP-ALL*

Tube	Pacific Blue	Pacific Orange	FITC	PE	PerCP-Cy5.5	PE-Cy7	APC	APC-H7	Aim**
1	CD20	CD45	CD58	CD66c	CD34	CD19	CD10	CD38	Diagnosis and classification of BCP-ALL; Detection of LAP markers; Detection of phenotypes associated with molecular aberrations
2	smIgκ	CD45	cyIgμ	CD33	CD34	CD19	smIgμ and CD117	smIgλ	Diagnosis and classification of BCP-ALL
3	CD9	CD45	nuTdT	CD13	CD34	CD19	CD22	CD24	Diagnosis and classification of BCP-ALL; Detection of phenotypes associated with molecular aberrations; Detection of LAP markers
4	CD21	CD45	CD15 and CDw65	NG2	CD34	CD19	CD123	CD81	Subclassification of BCP-ALL; Detection of LAP markers; Detection of phenotypes associated with molecular aberrations

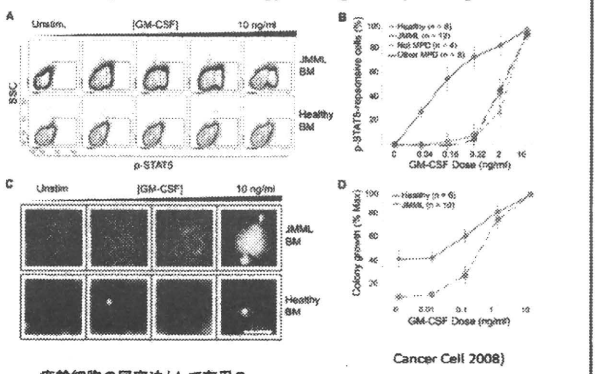
* Further information about the markers and the availability of hybridoma clones is summarized in Appendix A. Backbone markers are indicated in bold; cy= cytoplasmic; sm= surface membrane; nu= nuclear; LAP= leukemia associated phenotype.
** The described marker combinations can also be applied for disease staging and monitoring of treatment effectiveness (MRD diagnostics)





http://euroflow.org/imagenes/publications/lhermitte,_alot_poster,__eha_2009,_berlin.pdf

Phopho-flow technology for single cell profiling

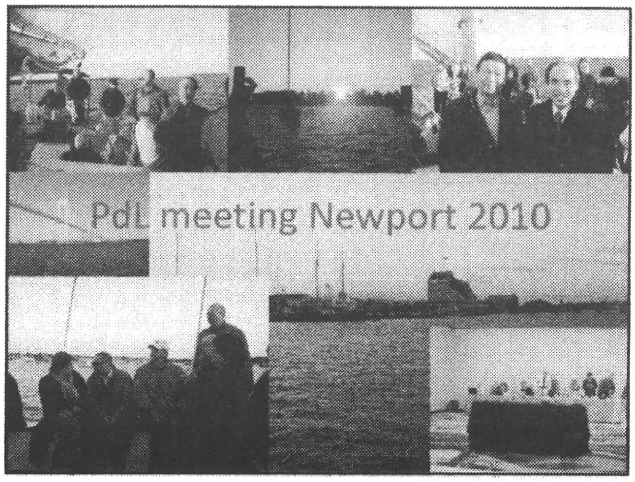


Cancer Cell 2008)

癌幹細胞の同定法として有用？

私的な感想

1) 日本からのデータの継続的創出とそのための組織作り
（日本版TARGET?)
人種差もあるので、COG、I-BFMのデータとは別
ここで先行しておかないと近い将来アジア人のデータでもなくなる?
2) BCP-ALLはIKZF1, JAK2, CRLF2については日本でもすぐ検討が必要
3) DS-ALLのentityの確立とCRLF2データの検証は必要？
DS-AMKLとの比較の上からも今後は一つのカテゴリーに
4) AMLはデータをとりこぼさないことが重要
本邦は1年100例の新患としても10年で1,000例を超える
AML99のロスタイム（2003-2005年)のデータ収集に御協力をお願いします。
5) 欧米のB&Dとそれを分子標的とする新規治療薬は表裏一体で、どんどん進んでいる。日本の置かれている状況は徐々に良くなりつつある？
6) どこまでが研究でどこからが検査か？そのための資金作り



Ponte di Legno Pediatric ALL Working Group Meeting Agenda

Oct. 18	Welcome Reception
Oct. 19	8:30-16:30 (Sessions: 90 x4, Breaks: 30, 60, 30)
	ALL induction failure
	Update t(1;19) and t(17;19)
	Update SMN
	Genome-wide association studies (GWAS)
	PdL in coming decade
	iAML21
	CD10-negative/11q23 ALL
	Incidence of TEL-AML1, hyperdiploidy by race/geographic area
	ETV6/ABL1 (TEL/ABL)-positive ALL
	16:45-
	Harbor Cruise & Dinner (Clambake at Chez Sallan)
Oct. 20	8:30-12:30 (Sessions: 90, 120, Break: 30)
	New International Ph+ ALL trial
	Other HR subsets: EPT-ALL, ABD-T-ALL, CRLF2/JAK/IKZT
	Prophylactic CNS Radiation
	Prioritization of projects
	Future plans

Ponte di Legno Pediatric ALL Working Group Future plans

ALL induction failure	writing paper
t(1;19) and t(17;19)	collect data (1995-2007) for t(1;19), and (1990-2010) for t(17;19)
SMN	under cleaning data
Genome-wide association studies (GWAS)	next project
iAML21	under collecting data till 2010
CD10-negative/11q23 ALL	collect data (1995-2007)
Incidence of TEL-AML1, hyperdiploidy by race	ask to CLIC
ETV6/ABL1 (TEL/ABL)-positive ALL	
Ph+ ALL trial	
Other HR subsets: EPT-ALL, ABD-T-ALL, CRLF2/JAK/IKZT	clarify the definition, next discussion
Prophylactic CNS Radiation	discuss protocols without CRT
	protocol for mixed lineage leukemia

Next meeting

Dec. 2011 before ASH in La Jolla, San Diego
May 2013 before I-BFM-SG in Kiel, Germany

Treatment Outcome after Remission Induction Failure in Childhood Acute Lymphoblastic Leukemia

Martin Schrappe, Ching-Hon Pui, Owen B. Eden, Paul Gaynon, Stephen Hunger, Giuseppe Masera, André Baruchel, Jacques Otten, Keizo Horibe, Kjeld Schmiegelow, Gritta Janka, Masahiro Tsuchida, Stephen E. Sallan, Rob Pieters, James Nachman, Helmut Gadner, Jochen Harbott, Hansjörg Riehm, Martin Zimmermann

Background

Remission induction failure in pediatric acute lymphoblastic leukemia is rare and associated with a dismal prognosis.
The clinical heterogeneity and the optimal treatment for this subset of patients are not known.

Methods

Induction failure was defined by the persistence of leukemic blasts in blood, bone marrow, or extramedullary sites after 4 to 6 weeks of remission induction treatment.
Induction failures were identified in 1041 patients (2.3%) among 44,554 newly diagnosed ALL patients up to 18 years of age enrolled in clinical trials of 14 cooperative study groups from Europe, North America, and Asiabetween January 1985 and December 2000.
Data of 1041 patients with induction failures were reviewed.
The median follow-up time was 8.3 years (range, 1.5 to 22.1 years).

Table S1. Patients Enrolled and Number of Induction Failures per Study Group

Study group	Patients treated	Induction failures N (%)
AIEOP	2938	88 (3.0)
BFM	5828	137 (2.3)
CCG	5122	120 (2.3)
COALL	1686	49 (2.9)
DCOG	1729	30 (1.7)
DFCI	1457	31 (2.1)
EORTC	2316	69 (3.0)
FRALLE	3455	81 (2.3)
JACLS	1263	62 (4.9)
MRC	5637	139 (2.5)
NOPHO	1546	53 (3.4)
POG	8511	119 (1.4)
SJCRH	929	14 (1.5)
TCCSG	2137	49 (2.3)
Total	44554	1041 (2.3)

Table S2. Definition of Induction Failure per Study Group: Non-Response to the First Phase of Induction Treatment

Study Group	Day of response evaluation	Definition
AIEOP	33	M2/M3
BFM	33	M2/M3 (or extramedullary disease)
CCG	29	M3 d 29, or M2, followed by M2/3 at the end of extended induction (d43)
COALL	36	M2/M3 d 29 (+ 7 days for prophase/windqw)
DCOG	33	M2/M3 (or extramedullary disease)
DFCI	28	M2/M3 (or extramedullary disease)
EORTC	33	M2/M3 (or extramedullary disease) after phase Ia
FRALLE *	35	M2/M3 d 35-42
JACLS	33	M2/M3 (or extramedullary disease)
MRC	28	M3
NOPHO	29	M3 d 15 or M2/3 d 29
POG	29	M3 d 29, or M2, followed by M2/3 at the end of extended induction (d43)
St. Jude	42	M2/M3 after 6 weeks of treatment
TCCSG#	35	M2/M3 d 43-50

* FRALLE: day 35-42 (some flexibility for end of induction)
#TCCSG: date of response evaluation changed to 43 in 1999

Table S3. Treatment Strategies for Patients Resistant to Induction Therapy

Study Group	Strategy
AIEOP	continue on study, different treatment arm
BFM	continue on study, different treatment arm
COALL	continue on study, same therapy as CR pts (BFM-HR therapy for some pts)
CCG*	off study, different trial
DCOG*	continue on study, different treatment arm (or off study, different trial (phase I/II))
DFCI*	off study, individual therapy
EORTC	continue on study, different treatment arm
FRALLE	off study, individual therapy or entering different trial
JACLS	continue on study, different treatment arm
MRC*	off study, different trial
NOPHO*	off study, individual therapy
POG*	off study, different trial
St. Jude	combined standardized and individual therapy
TCCSG	continue on study, different treatment arm

*strategy has changed over the last 20 years

Table 1. Patient Characteristics, Response Parameters and Recruitment period: Impact on Probability of Survival (1)

Presenting Feature	No. of Patients (%)	10-years Survival (%±SE)	p (log-rank)
All patients	1041	32±1	
Gender			
Male	651 (63)	29±2	0.032
Female	390 (37)	36±3	
Age at diagnosis *			
< 1 year	53 (5)	28±6	<0.0001
1-5 years	337 (32)	47±3	
6-9 years	236 (23)	30±3	
10-13 years	256 (25)	23±3	
14-18 years	159 (15)	16±3	
WBC at diagnosis (x 10^9/L) #			
<20	389 (38)	40±3	<0.0001
20 -< 50	161 (16)	40±4	
50 - <100	148 (14)	31±4	
100 - <200	128 (12)	22±4	
≥200	207 (20)	17±3	
Cell Lineage			
B	600 (65)	35±2	<0.0001
T	326 (35)	27±3	
NCI-criteria §			
B-lineage standard risk	220 (25)	54±4	<0.0001
B-lineage high risk	335 (38)	23±2	
T-lineage standard risk	66 (8)	36±6	
T-lineage high risk	256 (29)	25±3	

Table 1. Patient Characteristics, Response Parameters and Recruitment period: Impact on Probability of Survival (2)

Presenting Feature	No. of Patients (%)	10-years Survival (%±SE)	p (log-rank)
All patients	1041	32±1	
CNS leukemia (CNS 3)			
Yes	68 (7)	20±6	0.012
No	929 (93)	33±2	
Karyotype&			
normal	159 (25)	36±4	<0.0001
t(9;22) / BCR/ABL1	110 (18)	12±3	
11q23 / MLL	50 (8)	16±5	
High-hyperdiploidy	55 (9)	71±6	
Other	250 (40)	30±3	
BM End Induction °			
M1	30 (3)	60±9	<0.0001
M2	373 (43)	40±3	
M3	475 (54)	22±2	
Complete remission according to protocol **			
Yes	581 (75)	43±2	<0.0001
No	190 (25)	10±2	
Year of diagnosis			
1985-1988	112 (11)	26±4	0.02
1989-1992	272 (26)	27±3	
1993-1996	334(32)	34±3	
1997-2000	323 (31)	37±3	

** The information whether a patient reached a late complete remission or not was available in 771 patients.

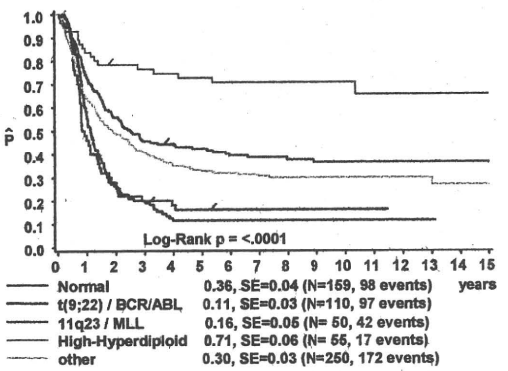


Figure 1. Kaplan-Meier Analyses o Survival in Patients with Induction Failure According to Genetic Abnormalities

Table S4. Early Treatment Response and Outcome

Response Parameter	No. of Patients (%)	10-year pSurvival (%±SE)	P (log-rank)
Day 8 PB ('Prednisone response')			
Good	187 (45)	29±4	0.51
Poor	229 (55)	30±3	
Day 8-9 BM M1	10 (5)	42±17	0.81
M2	26 (12)	36±10	
M3	174 (83)	34±4	
<50% blasts in BM	69 (33)	43±6	0.37
50-<75%	43 (20)	32±7	
≥75%	98 (47)	31±5	
Day 12-16 BM M1	45 (11)	24±6	0.20
M2	72 (18)	38±6	
M3	286 (71)	30±8	
<50% blasts in BM	202 (50)	32±4	0.64
50-<75%	103 (26)	25±5	
≥75%	98 (24)	33±5	
BM End Induction M1	30 (3)	50 ±9	<0.0001
M2	373 (43)	40±3	
M3	475 (54)	22±2	
Without POG (M3 only) M1	30 (4)	50±9	
M2	373 (49)	40±3	
M3	356 (47)	22±2	

Table S5. 10-Year Survival Estimates According to Gender, Age and WBC by Lineage and *BCR/ABL* Status

Presenting Feature	Precursor B-cell *BCR/ABL* negative			*BCR/ABL* positive			T-ALL		
	N (%)	*10-year Survival (%±SE)*	*P*	*N (%)*	*10-year Survival (%±SE)*	*P*	*N (%)*	*10-year Survival (%±SE)*	*P*
All patients *	358	44±3		110	12±3		307	27±3	
Gender									
male	206 (58)	43±4	1.0	77 (70)	13±4	.56	206 (67)	23±3	0.01
female	152 (42)	44±4		33 (30)	9±5		101 (33)	37±5	
Age at diagnosis									
< 1 year	15 (4)	65±13	<.0001	-	23±9	.16	4 (1)	25±22	0.14
1-5 years	148 (41)	63±4		22 (20)	13±6		78 (25)	31±5	
6-9 years	67 (19)	35±6		37 (34)	6±4		82 (27)	32±5	
10-13 years	76 (21)	25±5		33 (30)	6±5		92 (30)	28±5	
14-18 years	52 (15)	21±7		18 (16)			51 (17)	15±5 **	
WBC (x 10^9/L)									
<100	296 (83)	48±3	.0001	49 (45)	7±4	.96	178 (58)	30±3.5	0.27
≥100	62 (17)	21±6		60 (55)	15±5		129 (42)	24±4	
BM End Induction									
M1	9 (3)	56±17	.03	-	-	.10	18 (7)	49±12	.001
M2	152 (48)	48±4		25 (27)	20±8		111 (40)	35±5	
M3	157 (49)	34±4		68 (73)	8±3		146 (53)	19±3	

Estimates of Survival According to Bone Marrow Status a the End of Induction

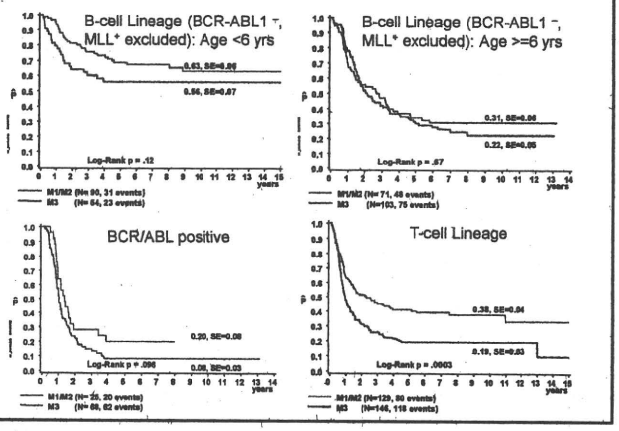


Table 2. Cox Regression Analysis of Survival by Lineage and BCR/ABL-Status (2)

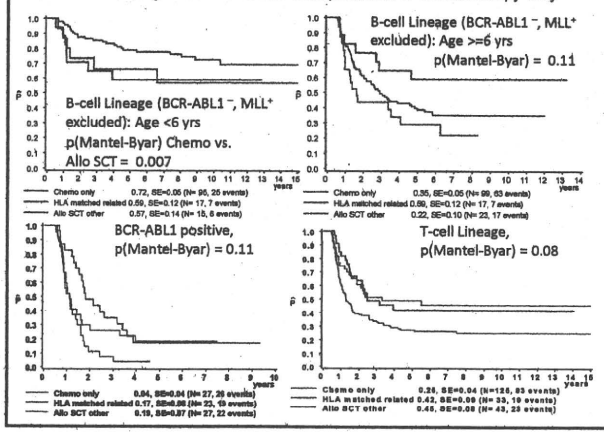
	N	*Hazard ratio*	*95% CI**	*p-value*
All patients with cytogenetic data (N=525, 10-year-survival 32±2%)*				
BM end induction M3	207	1.5	1.2-2.0	0.0005
BCR-ABL1 or MLL	121	1.9	1.4-2.6	<0.0001
T-ALL	172	1.6	1.2-2.1	0.0004
Age ≥ 10 years	183	1.4	1.1-1.8	0.007
High-Hyperdiploid	51	0.7	0.4-1.2	0.23
Matched rel. donor SCT	82	0.8	0.6-1.1	0.27
Other allogeneic SCT	56	1.2	0.8-1.7	0.35

In a separate Cox regression analysis on the 525 patients with data on transplantation and leukemic cell genetics, age ≥ 10 years, M3 marrow at the end of induction, T-cell disease, and the presence of t(9;22)/*BCR/ABL1* or 11q23 aberrations were independent adverse prognostic factors.

Table S6. 10-Year Survival Estimates for Patients with Stem Cell Transplantation and with Chemotherapy Only *

	N	*10-year pSurvival % (±SE)*
All patients *		
Chemotherapy		
Chemotherapy only total	606	31 (2)
Min. survival 6 months	509	36 (2)
SCT	304	39 (3)
Min. survival 6 months	294	40 (3)
autologous	35	45.5 (8)
allogeneic nfs #	42	20 (6)
allogeneic matched related	118	47 (5)
allogeneic mismatched related	26	35 (9)
allogeneic matched unrelated	53	40 (8)
allogeneic mismatched unrelated	18	28 (11)

According to Treatment with Transplantation or Chemotherapy Only



Conclusion

1. Pediatric acute lymphoblastic leukemia and induction failure is a highly heterogeneous disease.
2. Allogeneic transplantation is the preferred treatment for patients with Philadelphia chromosome-positive or T-cell leukemia and chemotherapy only for those with precursor B-leukemia without other adverse features.

2010 Ponte di Legno meeting　報告 (2)

埼玉県立小児医療センター 血液腫瘍科
康勝好

2010.11.14 JPLSG総会

t(1;19) & t(17;19)
A. Baruchel

（1） t(1;19):4~6%

- 晩期再発少ない？
  FRALLE 2000では治療開始後3y以降の再発例は2例のみ（1例は2nd leukemia?）
- 予後良好？
  FRALLE 2000では5y-EFS 81%, OS 88%
- 再発例の予後は不良？
  FRALLE 2000では5y-OS 28%
- 均衡型と不均衡型転座による予後の差は？

t(1;19) & t(17;19)
A. Baruchel

（2） t(17;19):< 1%

- DIC、高Ca血症の合併が多い
- 予後不良:早期再発
- phenotypeはBCPで、ほとんど10歳以上
- 発現解析で拾えるかも？
- Biologyの解明のため、Biobankが必要

t(1;19) & t(17;19)
A. Baruchel

Ponte di Legno projectの提案

- t(1;19)は1995-2007、
  t(17;19)は1990-2010の症例の
  retrospectiveな解析
- t(17;19)のbiobankはpending

SMN　K Schmiegelow

Ponte di Legno project: preliminary data

- 15グループから計615例
- 1st eventのみで、再発後は除外
- St.Judeのみは1960年代からの症例があるが、
  他のグループの症例はほとんど1980年以降
- Leukemia 2010の各グループからの報告数と
  結構違う
- 1st draftを2011年4月、full paperは6月に完成予定

SMN　K Schmiegelow

Ponte di Legno project: preliminary data

615例の内訳

- AML/MDS 216
- CNS 133
- Carcinoma 81
- NHL 45
- Sarcoma 36
- HD 23
- Other 81

SMN　K Schmiegelow

Ponte di Legno project: preliminary data

発症時期

- AML/MDS、HDは比較的早い。80%は5-6年以内
- Carcinomaは遅い。80%発症は20年以内
- CNSとSarcomaは中間で、80%発症は12-13年以内

SMN　K Schmiegelow

Ponte di Legno project: preliminary data

Survival（592例のデータ）

- AML/MDS: 約20%
- HD: 85%
- Carcinoma: 約70%。メラノーマ、皮膚がん、甲状腺がんは全例生存
- CNS: 12%。Low grade astrocytomaのみ25%生存しているが、それ以外はほとんど死亡。
- Sarcoma: 58%
- NHL: 67%だが、組織型によりheterogenous

Down synd. ALL　S. Izraeli

Ponte di Legno project

- 16グループから計658例: 1995/1/1～2005/1/1 curativeに治療した例のみ
- 染色体: 488例中、+21のみ223例、aberrant 265例
- 男 345, 女313、 age,WBCはmedian 5.1y, 13300
- follow-upは5.7y(median)で、死亡は156例（24%）
  このうち、白血病死73例（再発69例）、非白血病死83例
  非白血病死のうち、感染49、chemoの毒性13、その他21
- 治療開始後6週以内の死亡: 29例（死亡全体の4.4%）
  感染13、chemoの毒性8、その他8

Down synd. ALL　S. Izraeli

Ponte di Legno project

- 5y-EFS 63%, 5y-OS 70%, relapse 27%
  → TRMのimpactは10%
- WBC 5万以上と未満、age 10y以上と未満で差がありそう
- 3剤導入 vs 4剤導入:
  10y-EFS: 65% vs 61%
  10y-OS: 74% vs 68%
  再発には差がないが、InductionのTRMは 1/210 vs 11/408

Down synd. ALL　S. Izraeli

Ponte di Legno project

染色体

- 11q23　0.4%
- Ph1　0.6%
- E2A-PBX1　1.8%
- TEL-AML1　7.5%
- high HD　8.2%
- low HD　17.4%
- t(8;14)　1.4%
- normal　45.7%

21%はdataなし
+X,+Yがしばしば合併し、CRLF-2と関係あり？
今回はCRLF-2のdata一部のみ

GWASの提案　M. Relling

- ALLの症例とコントロールを比較するGenome-wide association studyをやりたい
- ALLのsubtypeの解析や治療反応性、毒性、PKを見るためにはlarge sample sizeが必要
  case 1000, control 1000例！
- 700K(?)のアレイチップを使って（100Kではだめ）、300,000のSNPsを解析する。臨床dataも集めて解析する。

→ 検体の集め方や、dataのpoolの方法などが議論になり、次回以降へ持ち越しとなった。

1才以上の11q23 ALL　A. Moericke

BFM95/2000の80例を解析した

- 男38、女42例
- WBC < 10万 53、 >10万 27例
- Non-T 71例, T 8例
- CNS：－が65、＋が7、TLPが8例
- PGR 63、PPR 17例
- MRD(2000のみ)：SR 15, MR 18, HR 8
- t(4;11) 36, (9;11) 10, (11;19) 12, other 12, FISH(+)のみ10

1才以上の11q23 ALL　A. Moericke

成績

- 5y-EFSはBFM95(22例)で73%、2000(58例)で68%
- MLLの相手、age(<2y, 2-5y, >5y)でEFSに差は無い
- CR1でのSCT(6例) EFS 100%、chemo(74例) 67%
- 2000MRD：SR 90%, MR 62%, HR 63%
- 他グループ：FRALLE(22例)のEFS 60-70%
  COGもDFCIもほぼ同じ

→ Ponte di Legno projectとしてのretroの共同研究が合意された

New International Ph+ALL: Implications for other HR subsets　S. Hunger

COG AALL0031

- JCOのpaperよりfollow-upを長くして、全例が治療開始後4yを超えたが、良好な成績はconfirmされた。
  Cohort 5の3y-EFSはchemo群84%, RBMT 77%, UBMT 83%
- しかしchemoの内容は、intensive phaseが71wと長い、HD-MTXが9回、itが多い、CPMが11g/m2と多い、IFMやVP-16も多い(3500mg/m2)など,CNS毒性やfertilityの問題が大きい
- 現在COGは0031のbackboneにdasatinibを使ったtrialをしている(intermittent phaseが終了し、continuous phaseに入った)。
- Chemoのbackboneを0031に固執する必要があるか疑問。chemoの内容よりもTKIをいかにうまく使うかの方が重要ではないか

New International Ph+ALL: Implications for other HR subsets　S. Hunger

International Study: COG + EshALL

- ChemoのbackboneはEshALL(BFM)にする
- SCT適応は、TP2のIg/TCR PCRによるMRDで決定する
- 当初はdasatinib vs imatinibのRCTを計画したが、CMLの1st lineのRCTでdasaが勝ったことを考慮して、dasa 1armのphase II trialとする。
- COGとヨーロッパの始めての前向きの共同研究であり、この遂行過程で、
  COGの各centerはEshALL(BFM)のchemoに慣れる
  COGはIg/TCR PCRのインフラを整備する
- 今後は他のHR subset(IKAROS, CRLF-2, hypodiploid,etc)の共同研究がやりやすくなる

CRLF-2　M. Loh

- Cytokine receptorの1つ
- Overexpressionは予後不良？
- Alterationの種類として、CRLF2-P2RY8 fusion、CRLF2-IgH fusion、point mutationがある
- 評価方法は、flowcytometry、RQ-PCR、FISH、gene expression解析など
- Down synd.の50-60%、non-Downの10%の頻度
- IKAROSのalterationやJAK2のmutationと相関する？
- 新たな分子標的薬のtargetになる？

CRLF-2　M. Loh

UKのdata

- DSでは14/26、non-DSでは865例中、CRLF2-P2RY8 52例、CRLF2-IgH 9例だった
- IKAROSのdeletionは19/49, 39%、JAK2のmutationはDSで6/9、non-DSで4/11にあった
- TEL-AML1, Ph1, MLLには無く、HHDで6/52
- Clinivcal featureでは、age, WBC数などCRLF2の有無で差はなかった
- MRC 97/99で治療した群の予後は、5y-EFSでCRLF2+ vs -群58% vs 79%と、やや不良。多変量解析では予後因子とならず。

CRLF-2　　M. Loh

BFMのdata

- DSでは7/49、non-DSでは42/499
- age, WBC数には関係しない
- TP2 MRDはすべてlow
- 予後は、6y-EFSでCRLF2 high vs low群で
  61% vs 83%
  特にCRLF2-P2RY8のEFSは28%と不良だった。
  逆にCRLF2-IgHは100%と良好

CRLF-2　　M. Loh

サマリーと今後

- BCP-ALLの10%で、少なくともCRLF2-P2RY8は予後不良
- CRLF2の90%は現在の予後因子ではつかまらない
- 新規のsignal transduction inhibitorが効くかも
- IKAROS, JAK2との相関の解析が重要
- 解析方法はQT-PCRがもっともいい。

→ Ponte di Legno Projectとしての共同研究に合意された

平成22年度第3回堀部班班会議

日時: 平成22年12月3日(金)17:00～21:00
場所: 名古屋医療センター サービス棟4階 第4会議室
〒460-0001 愛知県名古屋市中区三の丸4-1-1

1. 挨拶　　名古屋医療センター臨床研究センター 堀部敬三

2. 小児造血器腫瘍の病理中央診断システム確立のための研究
独立行政法人国立成育医療研究センター研究所 中澤温子

3. 小児固形腫瘍の病理中央診断システムの確立と病理診断の標準化に関する研究
千葉県こども病院 堀江 弘

4. 小児造血器腫瘍微小残存病変の分子診断システム確立ための研究
愛知医科大学医学部 鶴澤正仁、堀壽成

5. 小児造血器腫瘍微小残存病変の免疫学的診断システム確立ための研究
三重大学医学部附属病院 出口隆生

6. 小児造血器腫瘍の分子・細胞遺伝学的中央診断システム確立のための研究
群馬県立小児医療センター 林 泰秀

7. 小児固形腫瘍の中央診断システムに基づく分子遺伝学的予後因子の探索と生物学的リスク分類に関する研究
千葉県がんセンター 上條岳彦、中川原 章

8. 小児固形腫瘍の分子・細胞遺伝学的中央診断システム確立のための研究
独立行政法人国立成育医療研究センター研究所 大喜多 肇

9. 小児造血器腫瘍臨床研究の質の向上に関する研究
国立病院機構名古屋医療センター臨床研究センター 齋藤明子

10. 小児がん臨床研究の質の向上に関する研究
大阪市立総合医療センター 原 純一

11. 総合討論

Ⅳ. 研究組織・関連資料