

16th Meeting of the EUROPEAN RESEARCH INITIATIVE ON CLL (ERIC/WP7) Heidelberg, Tuesday Jan 29 2008

(in context of the ELN Annual Symposium)
11.30 a.m. to 01.30 p.m.

DKFZ Convention Center, Heidelberg, Germany

Chair: Michael Hallek (Cologne), Eva Kimby (Stockholm)
Participants: 22 members (according to signature of attendance list): A. Hinke, S. Stilgenbauer, S. Raynaud, S. Böttcher, P. Ghia, A. Langerak, H. Bumbea, V. Teleanu, A. Moicean, A. Dumitrescu, J. Gabert, P. Dreger, M. Zucknick, M. Gregor, A. Gazzda, J. Gora-Tybor, M. Trbusek, M. Doubek, F. Bosch, M. Kneba

TOP 1: E. Kimby, M. Hallek

Michael Hallek and Eva Kimby welcomed all participants. It was noted, that the major goal of the meeting should be to assess what ERIC has achieved so far and what future goals for a long lasting initiative could be. All discussed projects are collected under the following TOP2.

TOP 2: Running projects – where are we? Future goals of ERIC - where do we go?

Prior the meeting project leaders of ERIC had been asked by the ERIC office via email to prepare summary slides of the current status of their project work. The following “1-slide-summaries” with respect to the status of running ERIC projects were presented:

S. Stilgenbauer: 17p Deletion and p53 in CLL

The slide features a central diagram on the left and a list of achievements on the right. The diagram consists of a central light blue circle labeled 'ERIC' surrounded by nine white circles, each containing a city name: Amsterdam, Sutton, Bournemouth, Paris, Nice, Liverpool, Czech, Ulm, and another circle at the bottom. The list of achievements is as follows:

- Comparison of FISH techniques, evaluation and results (French-British-German)
- Multinational exchange of samples (e.g. CLL7, CLL20, clonal evolution, FISH 17p-)
- P53 mutation detection techniques and database
- Functional p53 testing (e.g. MLPA, FACS, mutational analysis, gene expression)
- Identification of 17p- / p53 independent agents
- Output: Trials (CLL7, CLL20), publications (ASH)

Stephan Stilgenbauer noted that the results of comparing and harmonizing FISH results between labs in Germany, France and Britain could be summarized as a manuscript soon. Currently feedback of the British coworkers is required and awaited to complete this work. Experiments in the participating labs for p53 mutational analysis are currently ongoing in the cooperating labs displayed in the figure slide.

Harmonization of ZAP70 analysis

Since the ZAP70-project leaders Florence Cymbalista and Remi Letestu could not be present at the meeting and had not sent new results Carmen Schweighofer showed a summary of the talk Remi Letestu had presented at last year's EHA meeting in Vienna. Paolo Ghia, who is also attached to the project, helped to explain the current status of the project.



Harmonization of ZAP70 analysis

Current Status:

- E-trial: The exchange of raw data was a success (exchange of blood specimen in the first part was not successful)
- E-trial allowed testing of gating strategy, different modes of expression of the results for ZAP-70, intercenter variability
- E-trial allowed identification of unmet needs:
 - Difficulty in discriminating between normal residual B cells and CLL cells
 - There is still a need for a reference population or a reference value that helps expressing the results
 - Personal reports will allow auto evaluation in each center
- Optimization of techniques:
 - Gating strategy
 - Different antibody combinations tested for differentiation normal – pathologic B-cells: CD2/5/19 or CD2/5/20,
 - Optimization of antibody concentration, optimal incubation time with antibody

Next Steps:

- Confirmation of current results in a second e-trial
 - Summary of validated "reference technique" for publication soon
 - Validation of new upcoming ZAP70 antibodies (so far only 1 antibody tested)?
 - Comparison with PCR results?
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Michael Hallek mentioned that during preparation of the new IWCLL WG guidelines it had been discussed that ZAP70 may never be standardized due to the difficult analysis technique and interpretation of results. Paolo Ghia noted, that there are many factors influencing the ZAP70 test result, i.e. antibody, the cytometer, incubation time etc. He suggested that either the second French e-trial of the ZAP70 group will help to establish a harmonized recommendation for ZAP70 analysis or a "lab conclave" has to be performed (with a certain number of scientists performing their ZAP70 analysis under standardized conditions with subsequent evaluation of the results). Another problem discussed is that the limited shipment duration of specimens is a disadvantage of ZAP70 flow analysis compared to other prognostic factors like VH mutational status. Although ZAP 70 seems to be discriminative with regard to progression free survival of CLL patients, it has to become easily assessable by routine flow testing, otherwise it may lose importance for routine diagnostics in CLL. Even immunohistochemistry (Eva Kimby) may be rather of qualitative than quantitative relevance and too long as routine procedure. It was suggested by the Board members that at the next ERIC meeting at EHA a first draft for recommended ZAP70 testing should be presented by the project leaders (Florence Cymb./Remi Letestu) and be discussed for further steps.

P. Ghia: IgVH Mutational Analysis

Paolo Ghia presented the following slide clearly summarizing what has been achieved by the IGVH group and is planned to do in 2008. Importantly a next ***IgVH workshop*** is planned to be held in ***Paris in October 9-10 2008***. Paolo emphasized that one major goal of ERIC besides standardization of CLL relevant clinical or scientific procedures should be the spread of knowledge on CLL by teaching/educational activities.

IG GENE ANALYSIS AND INTERPRETATION

Achievements in 2007

- Online support and troubleshooting for interpretation of IG sequences (start: February 2007)
- IG workshop, Uppsala (June 2007)
- Web site for the IG workshop (www.igcll.com)
- Harmonization of IG databases (IgBlast → IMGT) (August 2007)
- CLL-oriented organization of IMGT web site for Ig analysis (September, 2007)

Projects for 2008

- IG workshop, Paris (October 2008)
- Book on IG analysis and interpretation (ongoing)
- Organization of online IG Database (ongoing)
- Online support and troubleshooting for interpretation of IG sequences (continuing)

Harmonization of MRD analysis

Andy Rawstron and colleagues could not be present but had sent the following summary of their ongoing project:



ERIC CLL MRD flow cytometry

- Transfer 4-CLR approach to 6-CLR: quicker acquisition – possibly more sensitive/specific?
 - Determine optimal combination using electronically manipulated data in 4/5/6-CLR formats
 - Several dilution studies acquired: representative data files sent to Milano, Kiel & Barcelona
- “Rapid screening approach”
 - Tested in over 500 cases: identifies MRD status in over 50%
 - Highly effective during treatment but response assessment usually requires full MRD panel.
- MRD QC data analysis scheme
 - First trial results in from 16 centres (of 31 registered)
 - “Easy” sample containing 0.12% CLL
 - Reported result: median 0.11%, range 0.06-0.26%
 - For CD20/CD38/CD19/CD5: median 0.11%, range 0.08-0.14%
 - Most variation in CD19/CD5/CD43/CD79b tubes
 - More difficult cases to follow...

WP7 of the FP6

Andy Rawstron, Leeds, UK

Currently they are working on the 6-colour approach for MRD flow. The data analysis for MRD quality control is still ongoing, first results available as noted above. Paolo Ghia mentioned, that there is a lot of interest by companies like BD Biosciences or Coulter in the MRD project, which may offer possibilities for antibody reagents, funding etc. Furthermore it was discussed that the international acceptance of the published MRD flow by Rawstron is still low and may be improvable.

European Survey on CLL Treatment

Vincent Levy was not present at the meeting. Carmen Schweighofer presented the current status of the project as currently know to ERIC. It was emphasized by several members that the contact to hematologic associations in different European countries should be initiated by representative ERIC members.

Aim of the project:

- Survey on treatment modalities and behaviour of clinicians in selecting treatment regimens for CLL patients

Current status and plans:

- 7 vignettes with representative CLL cases have been established
- Online webpage for remote access to vignettes will be finished in 1-2 weeks
- Nation wide start in France of the survey in about 1 month
- Contact with hematomol. society in France ongoing, email-list of hematologist will be provided, hematologist will be invited via email to complete the survey
- Contact with hematomol. societies in participating countries planned via ERIC
- Contact with CLL groups in Europe, Israel, South America, Australia, etc. ongoing
- Funding by French government
- No ethical agreement needed
- No linkage to the ERIC webpage planned to secure independency of the survey

WP7 of the 



Long-term Follow-up of CLL Patients in Trials

Barbara Eichhorst and Pete Hillmen could not be present at the meeting. They had presented the first draft of their project at the ASH meeting, summarized as follows:

Improvement in the long-term follow-up of CLL patients in European Trials

Peter Hillmen and Barbara Eichhorst

Current Plan:

- Development of a simple long-term follow up strategy for CLL pts in commercial or non-commercial trials

Next Steps:

- Finalization of a single follow-up CRF page & circulation to all ERIC members
- Contact between ERIC and study groups/commercial partners re: use of data by ERIC, funding
- Clarification of ethical issues (i.e. informed consent, contact with master ethical committees)
- Construction of a web-based system offering remote data entry (partner: Gabriele Strache, Munich o. a.)

The proposed CRF questionnaire for follow-up documentation will be attached at the end of the protocol. All members shall be invited to give their suggestions/ideas for improvement/simplification of the CRF sheet.

EBMT Proposal on Allogeneic SCT in T-PLL (Peter Dreger, Heidelberg)

See slides below presented by Peter Dreger (Heidelberg) and W. Wiktor-Jedrzejczak (Warsaw), Heidelberg, summarizing the current strategy for improved data collection via a registry trial on stem cell support in T-PLL. A first draft of an EBMT frame orientation for the diagnosis, transplant eligibility, remission requirements etc. in T-PLL patients prior potential stem cell support is currently circulated within the EBMT (in case of interest contact: Peter.Dreger@med.uni-heidelberg.de).

Retrospective T-PLL study

Final analysis submitted to EBMT2008 (WW)

- 33 informative patients with allo-SCT for T-PLL
- large heterogeneity in terms of patient and transplant characteristics
- 2-y NRM 25%
- biphasic survival curve with median EFS 7mo but still 32% EFS at 2 years since 10/11 relapses occurred <12mo post-transplant

→ allo-SCT might be beneficial in individual patients with T-PLL

Prospective observational T-PLL audit

1 **prospective** registration of each patient admitted for SCT for T-PLL (using a new one-page/three-question "MedB announcement form" to be submitted at admission for transplant to the registry),

mandatory submission of MedB for registered patients

2 transplant procedure standardized according to **EBMT frame of orientation** (diagnosis, transplant eligibility, pre-transplant remission induction strategies, remission requirements, timing of HSCT, donor compatibility, conditioning, GVHD prophylaxis, MRD monitoring)

CLL Registry (Michael Hallek, Cologne)

Michael Hallek presented a proposal for a new ERIC project regarding a CLL registry as summarized on the slide below.



European CLL registry

- Goal: assess therapeutic differences and **outcome** across Europe.
- Question: how do modern diagnostic and treatment options influence outcome in CLL?
- Approach:
 - Start with regional project, e.g. in Southern and Western Germany (Bavaria, Northrhine-Westfalia)
 - Expand to other European regions as soon as practicability test is OK
- Methods:
 - Contact the CML (or MDS) registry managers within the ELN (Hasford, de Witte) to set up project plan
 - Contact industry or European agencies for funding

WP7 of the 



According to Michael Hallek good experiences with registries have been made in the CML group (WP4 of the ELN) and by the Swedish colleagues (but it may be notable that in Sweden registration of cancer patients is mandatory by law). Regional in part high-valued cancer registries are available in Germany. These experiences could be taken as exemplar for a CLL registry. Several participants expressed their concerns, that motivation of centres/physicians to register patients in a central registry without any return may be very low. Nevertheless it was voted by the majority of participants by handsign, that a CLL registry would very valuable to gain more knowledge about CLL treatment especially outside of university centers and it would be worth to try such a project.

TOP 3: Next Meeting at EHA June 12-15 2008

The next ERIC meeting will be held in context of the EHA meeting in Copenhagen between June 12-15. The application of ERIC as a scientific working group of EHA is currently running. The exact date and time slot of the meeting will be determined as soon as possible.