ELN European LeukemiaNet

















INFORMATION LETTER N°2 JUNE 2006

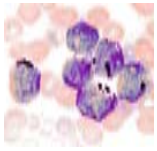
Dear colleagues,

Within the second year after the start of the network the main structures concerning management, communication and information of the European LeukemiaNet have been enhanced and consolidated. Web-based information is available on the central website (www.leukemianet.org) which was relaunched early in 2006 after implementation of a Content Management System. Communication is accomplished via the information center (ELIC) and by the network management center (NMC) through annual symposia, regular network and WP-meetings, website and the biannual newsletters.
Nearly 60 workpackage-meetings were held, several studies are ongoing on a European level and more than 300 publications were published or completed. In 2005 several consensus recommendations and guidelines on diagnostics and therapy were published or submitted, e.g. guidelines on CML, management of relapsed APL, vaccination for stem cell transplant recipients, defining post-SCT management and standardizing indications for SCT. Further guidelines are under preparation e.g. for anti-infection prophylaxis and treatment of bacterial and fungal infections and for therapy in MDS.
Regular meetings of all network members have supported communication and cooperation of all workpackages. Beside the cooperation of the WPs within the network itself collaboration with other European structures like the EBMT or ESH was enhanced. An example is a consensus conference on supportive care with participants from ELN, EBMT, ICHS, and EORTC with 56 representatives from 24 countries in October 2005.
Furthermore eight new participants were integrated so that the European LeukemiaNet now brings together 125 participating institutions and approximately 900 researchers from 22 countries.

Prof. Dr. Rüdiger Hehlmann
Network Coordinator

WP 6 - ALL

Acute Lymphoblastic Leukemia



N. Gökbuget, R. Bassan, H. Dombret, R. Foà, J.-M. Ribera, R. Willemze, D. Hoelzer

At the end of 2002 the European study groups for adult ALL met in Frankfurt to define topics and aims for future collaboration and decided to participate in the European Leukemia Network (ELN). Nearly all European study groups for adult ALL made an active contribution to the joint application (table 1). They involve more than 300 centers and more than 8000 adult ALL patients in their last studies. All major research fields in adult ALL, as illustrated by Figure 1, are represented in their activities. Beside large patient numbers with biological and clinical data on more than 10.000 patients with ALL, they provided high quality scientific publications and major contributions to basic research and clinical implementation of innovative diagnostic and therapeutic procedures.
In the first two years of funding the members of WP6 first established central management structures, founded a steering committee and a formal group named European Working Group for Adult ALL (EWALL). Additional European Study Groups were integrated from UK (MRC), Poland, Czech Republic and Turkey.

Standards in diagnosis
In order to provide the prerequisites for future collaborative studies, meta-analyses, registries etc. the group aimed to define standardized laboratory protocols and quality control procedures. These activities are important to get an overview on definitions, diagnostic procedures, prognostic factors etc. used in different study groups. Based on these overviews consensus definitions can be made. Information on relevant diagnostic procedures were collected as basis for the definition of standards, diagnostic methods, definitions of diagnostic subgroups and preserved patient materials in the different study groups. As next step a proposal for basic standards applicable also in countries with less elaborated laboratory facilities and a proposal for elaborated standards for European trials was prepared and consented.

Study registry
A further very important goal was the creation of an overview on ongoing European studies in ALL. A registry with ongoing European studies on adult ALL was created. So far the registry includes studies on de novo ALL, Ph/BCR-ABL positive ALL and new drugs. Structured information on 17 studies is available on the website including e.g. inclusion/exclusion criteria, contact address, treatment overview and short protocols. This study registry will be extended and updated continuously and furthermore will be adapted to the WHO guidelines for registered studies.

Table 1
European Study Groups Participating in the EWALL

Group	Country	Lead Participants	Further representatives
Founding Members			
EORTC	European	R. Willemze	B. Labar
GIMEMA	Italy	R. Foà	F. Mandelli, G. Martinelli, G. Meloni, P. P. Piccaluga
GMALL	Germany	D. Hoelzer, N. Gökbuget	O. G. Ottmann
GRAALL	France, Switzerland	H. Dombret	A. Delannoy, N. Ifrah, J.-M. Miclea, P. Rousselot, J.-P. Vernant
HOVON	Netherlands		A. Dekker
NILG	Italy	R. Bassan	
PETHEMA	Spain	J. M. Ribera	
PLRG	Poland		J. Walewski, B. Ostrowska
Swedish ALL	Sweden		H. Hallbook
Additional Members			
Czech	Czech Republic		M. Doubek, J. Mayer
MRC	Great Britain		A. Fielding, A. H. Goldstone, A. Lister, S. Proctor
PALG	Poland		S. Giebel, J. Holowiecki
Romanian	Romania		A. D. Moicean
TALS	Turkey		O. Ayyildiz, M. Cetiner, Z. Gülbas

Collaborative trials

One major aim of EWALL is the initiation of collaborative clinical trials. Intergroup studies are useful for rare subgroups of ALL in order to achieve relevant patient numbers and results in shorter time. Joint studies would be also of interest for the exploration of innovative approaches in SCT and for phase I/II studies with the pharmaceutical industry for the investigation of new cytostatic drugs, including monoclonal antibodies and targeted drugs. So far the following joint protocols have been initiated:

- Treatment of mature B-ALL and Burkitt's NHL with Chemotherapy and Rituximab (GMALL B-ALL/NHL 2002)
- Treatment of CNS relapse in ALL with liposomal Cytarabine (GMALL Depocyte)

Furthermore there are European trials of pharmaceutical companies involving the EWALL group with Forodesine-Hydrochloride, Dasatinib and AMN107. Important future steps are the initiation of European trials with Depocyte in de novo ALL and joint studies for Ph/BCR-ABL positive ALL.

Prognostic factors

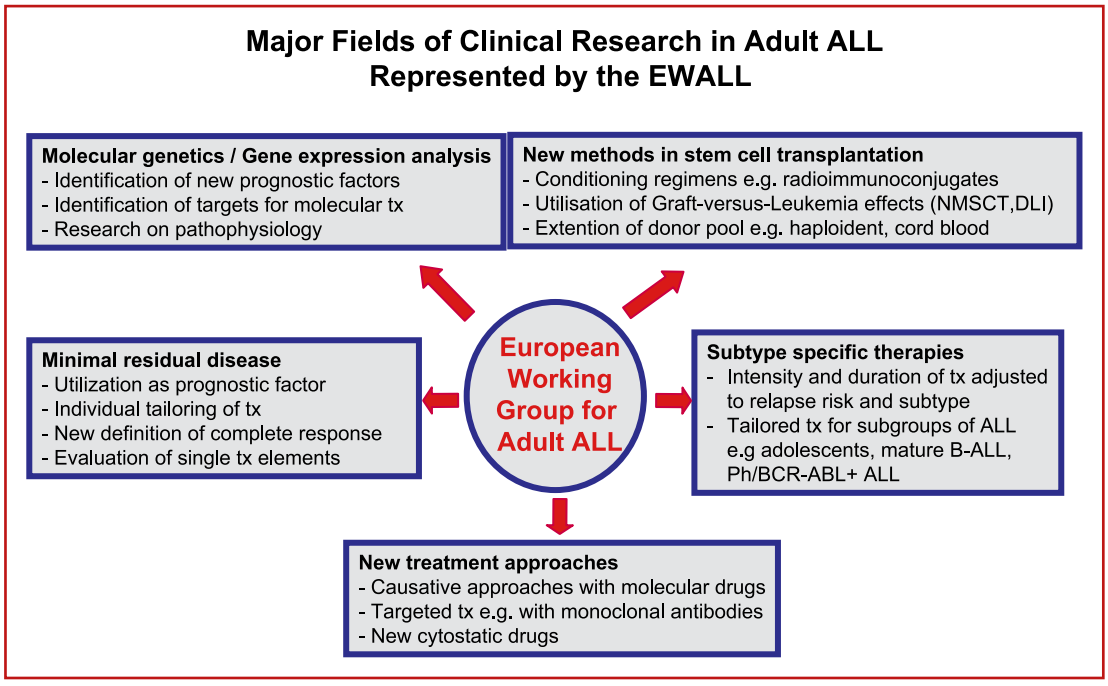
Most study groups on adult ALL conduct trials with treatment adapted to prognostic factors. Therefore an overview on prognostic subgroups and definitions used in the different European study groups was created including the prognostic scores from 5 study groups (GIMEMA, GMALL, GRAALL, NILG, PETHEMA, EORTC-HOVON). With the more and more complicated risk stratification in trials for adult ALL it is of utmost importance to have this overview readily available.

Future activities

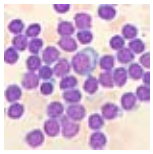
In the near future further activities will be started including a European registry of defined rare subtypes of ALL. Biphenotypic ALL was selected as a topic of interest since neither prognosis nor adequate treatment are defined so far. Furthermore several topics for a joint analysis within the EWALL group were discussed.

The group will furthermore extend Internet-based information exchange. Presentation of the network at national and international meetings will be continued and the group is open for additional network participants from European countries.

Figure 1



European Research Initiative on CLL (ERIC)



C. Schweighofer, M. Hallek
Medical Clinic I, University Hospital of Cologne, Germany

The ERIC is a young European organization devoted to improve treatment and outcome of patients with chronic lymphocytic leukemia (CLL) and related diseases. There are many more open questions and new drugs available in the treatment of CLL than trial or research initiatives or active protocols. To achieve faster progress, open communication between study groups, physicians and scientists is a key element. Founded 2001 in Francfort (Germany) by Guillaume Dighiero, Daniel Catovsky, Emili Montserrat, Jacques-Louis Binet and Michael Hallek the ERIC aimes at improving intergroup communication about project ideas, trial information and exchange of biologic samples.

The ERIC is currently funded by the European LeukemiaNet (ELN) and acts within the European Hematology Association (EHA). It is open to every physician or scientist working/interested in the field of chronic lymphocytic leukemia or related disorders. Over the last 5 years ERIC has been growing constantly and counts now more than 100 members. A central homepage for ERIC has been established and offers detailed information on current topics within the organization (www.ericll.org). The structure of ERIC is shown in fig. 1.
Two separate subcommittees take care for the development and promotion of clinical, translational and basic research acitivities within the organization. There are annually scientific symposia and semiannual business meetings initiated by ERIC.

The upcoming "4th Scientific Workshop: What is new in CLL?" will be held during the EHA congress in Amsterdam on June 15th 2006 (for further information please visit www.ericll.org). ERIC will become a legitimated and registered asscociation (ERIC e.V.) by German law in 2006.
The standardization of relevant diagnostic procedures in CLL is currently one major focus of ERIC. The aim is to develop standardized methods for monitoring of the most important disease parameters, which are currently used to assess risk profiles, response to therapy and efficacy of therapeutic regimens in CLL patients.
One of these parameters is the analysis of minimal residual disease (MRD). Most recent therapeutic strategies in CLL are valuated by their ability to clear MRD from blood and/or bone marrow in patients achieving a clinical complete remission. The eradication of residual disease is associated with improved remission durability and has great potential in offering the possibility of cure. The European wide harmonization of MRD diagnostics in CLL is coordinated by P. Hillmen/Dr. A. Rawstron (Leeds, UK), M. Kneba/Dr. M. Ritgen (Kiel, Germany) and E. Montserrat/Dr. N. Villamor (Barcelona, Spain) and has achieved great success (CLL MRD group). So far a standardized flow cytometry assay (out of 58 individual 4-colour combinations) could be developed which works sufficiently rapid and sensitive to guide therapy to an MRD negative status in real time. Currently the CLL MRD group is investigating its comparability with a standardized PCR technique.
Second important prognostic parameters in CLL are delivered by the cytogenetic/FISH analysis of CLL cells. The definition of genetic subgroups with distinct clinical features (i.e. 11q-deletion associated with rapid disease progression, 17p- correlates with higher risk of treatment failure) has been a significant step in the understanding of disease and setup of treatment approaches in CLL. There is a need for a standardized and comparable technique in the assessment of cytogenetic aberrations/ FISH analysis. The European wide harmonization of cytogenetic/FISH analysis is coordinated by Hartmut Doehner and Stephan Stilgenbauer (Ulm, Germany). Currently there is an exchange of sample specimen between participating centers throughout Europe.
Other biological markers with adverse prognostic impact in CLL are the intracellular or surface expression of ZAP70 and CD38. As one of the ERIC projects standardization and harmonization of cytometric analysis of ZAP70 and CD38 is guided by Florence Cymbalista (Paris/ France). Currently different cytometric approaches are under investigation and sample specimen circulated between different European centers.
On the clinical side a first common trial initiative between the German and French CLL study group could be launched in October 2005: the CLL7 trial comparing early treatment with FCR versus deferred treatment in previously untreated CLL patients Binet A (randomized phase III trial, www.dcllsg.de). Up to now almost 100 patients have been recruited. Further harmonization of trial initiatives throughout Europe even with regard to European regularities are planned, especially on the Phase I/II level.
Further projects of ERIC will include the collection and evaluation of disease course and treatment aspects in p53 deleted CLL patients (European survey), a general European survey on current treatment modalities in CLL patients within or without clinical trials (responsible V. Levy, Paris/France), the collection of atypical and familial cases of CLL (responsible: D. Catovsky, London/UK, http://www.icr.ac.uk/haemcyto/fcll/) and the definition of major/new diagnostic and therapeutic targets in CLL.

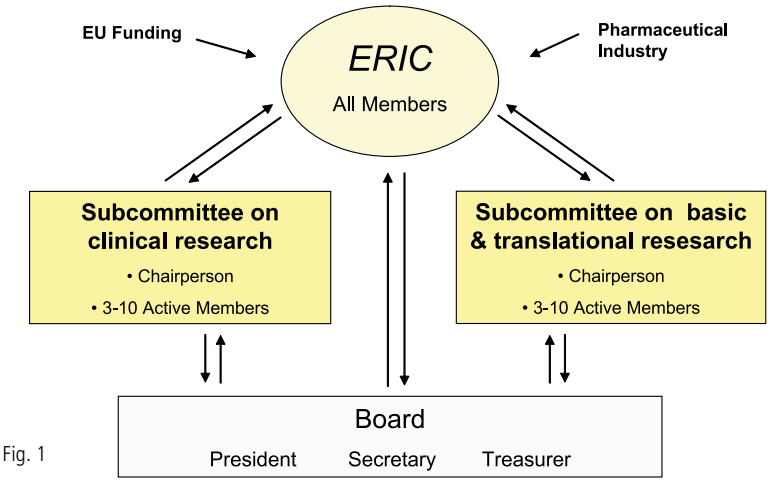
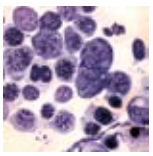


Fig. 1

Actual state of WP 8 (MDS)



O. Huber, University Medical Centre St Radboud, Nijmegen, The Netherlands

In general, we speculate that WP8 has been an active and productive work package within LeukemiaNet. Many deliverables have already been fulfilled and new deliverables are initiated continuously. MDS WP8 has interacted with AML WP5 in shared meetings and cooperates as well with Gene Profiling WP13, Cytogenetics WP11 and „New targets, new drugs" WP16.
A considerable number of documents have been prepared and are presented on the LeukemiaNet website: Standardized diagnostic and prognostic procedures in MDS (coordinator E. Hellström-Lindberg), links to MDS study groups and to pharmaceutical companies active in MDS, datasets for a European MDS registry (coordinator D. Bowen), a list of all trials by MDS study groups in Europe, and a standard protocol to be used as a template for development of studies on MDS.
In the context of LeukemiaNet a study has started on the efficacy and safety of Lenalidomide in red blood cell (RBC) transfusion dependent subjects with low- or intermediate-1-risk MDS associated with a deletion 5q[31] cytogenetic abnormality. A proposal for a protocol for treatment of high-risk del 5q myeloid disease with Lenalidomide has been presented by E. Hellström-Lindberg (see http://www.leukemia-net.org section MDS WP8/Study proposals).

Furthermore, a number of studies were initiated or defined as a deliverable in cooperation with the AML WP. A study on treatment decision-making for older patients with AML or MDS was presented in Heidelberg (Jan. 2006) and will be published this year (coordinator M. Lübbert). We aim at development of a common prognostic score for MDS and AML treated with intensive therapy. Results of an observational study on AML and MDS patients treated with low-dose Decitabine indicate that geriatric assessment appears to be a valuable tool to support the decision-making proccess. Validation in larger numbers of patients is necessary to reveal possible prognostic relevance. This study will be included in the frailty index to be developed as a method for treatment decision-making for elderly AML and MDS patients (coordinator A. Burnett).

Two other planned studies concern the outcome for patients with RAEB-t in AML and MDS trials according to morphology and cytogenetics (coordinator M. Lübbert) and a retrospective study of the role of RIC for allografting in AML and MDS (coordinators R. Martino and T. de Witte).
The need for updated and widely recognized therapeutic recommendations is perceived and is expected to result in optimizing the management of patients with MDS (coordinators M. Cazzola, L. Malcovati, M. Della Porta).

The development of the guidelines is a multistep process:

1. An Expert Panel has been selected;
2. A systematic review of the literature has been performed and the level of evidence and the grades of recommendations were rated;
3. A list of key clinical questions has been formulated based on the major issues emerged from the first panel meeting held in Madrid on October 26-27, 2005. The Expert Panel will formulate in an independent manner proper evidence-based statements for each question;
4. Scenario analysis will be used to reach a consensus, besides the rontiers of evidence. For each clinical scenario the members of the Expert Panel will be asked to rate the appropriateness of providing a certain treatment;
5. Based on evidence from the literature, question-specific statements and scenario analysis final recommendations will be formulated and a conference will be hold to reach a definite consensus.

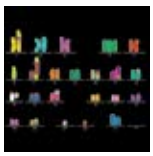
In addition, a web-based training program will be developed using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians.

One of our translational projects concerns the exploration of the expression pattern of apoptosis and cell cycle-related genes in MDS using Microfluidic Card-Quantitative PCR (table 1) (coordinator J. Jansen). This method has been validated as shown by the detection of increased expression of erythroid differentiation markers in sorted CD71+ cells compared to sorted CD34+ cells and the comparable expression levels of these markers in MDS and normal sorted CD71+ BM-cells. The results show over expression and misexpression of WT-1 in MDS bone marrow subfractions which further validates this method. Preliminary results indicate that several genes show an MDS-specific gene expression pattern: some are CD34 specific, others CD71, some both. These results need to be confirmed in a larger panel of samples. 384 genes (Table 1) will be tested for normal, MDS and sAML patients, using CD34+, the CD71+ and in the CD33+/CD13+ fractions. In addition, response to therapy (such as Revlimid-Bortezomib) will be measured in patient samples. Finally, software is created for joint analysis of micro-array- and PCR CARD-expression data. The aim is to use this software to analyze patient samples in the European 5q-Revlimid (Lenalinomide) study mentioned before. If you are interested to contribute samples to these translational projects, please contact j.jansen@chl.umcn.nl

Table 1
Microfluidic Card-Quantitative PCR: genes to be tested for normal, MDS and sAML patients

- TNF Receptor Family
- BCL2 Family
- Caspase Family
- IAP Family
- TRAF Family (TNFR associated factor)
- CARD Family
- Death Domain Family
- Death Effector Domain Family
- CIDE Domain Family
- P53/ATM Pathway
- Phosphatidylinositol kinase-related
- kinase (PIKK) Family
- NFKB
- Growth Factor (receptor)
- BTG1 Family
- Programmed cell death protein
- DNA Mismatch repair proteins
- Histone deacetylases
- Inhibitor of Growth Family
- Cyclins
- Cyclin-dependent kinases
- CDK-inhibitors
- E2F transcription factors
- Mitogen activated protein kinases
- DNA polymerases
- DNA replication
- Transcription factors
- Minichrom maintenance deficient
- Onco/tumor suppressor genes
- PCTAIRE protein kinases
- P21 activated kinases
- Cell division control proteins
- Other cell cycle proteins
- Erythroid function/ structure
- Stem cell genes
- Other Household

Analysis of AML/MDS Patient with 11q/MLL Gene Amplification



A. Zatkova[1], M. Wendehack[2], C. Schoch[3], M. Jotterand[4], C. T. Storlazzi[5], C. Surace[5], M. K. Andersen[6], B. Johansson[7], C. Mannhalter[8], F. Speleman[9], C. Fonatsch[1], K. Wimmer[1], R. Ullmann[2]

1 Abteilung für Humangenetik, KIMCL, MUW, Wien, Austria

2 Max Planck Institute for Molecular Genetics, Department Ropers, Berlin, Germany

3 MLL - Münchner Leukämie Labor, München, Germany

4 Service de génétique médicale, Unité de cytogénétique du cancer, Maternite – CHUV, Lausanne, Switzerland

5 Department of Pathological Anatomy and Genetics, Section of Genetics, University of Bari, Italy

6 Department of Clinical Genetics, Section of Hematology/Oncology, Rigshospitalet Copenhagen, Denmark

7 Department of Clinical Genetics, University Hospital, Lund, Sweden

8 KIMCL, MUW, AKH, Wien, Austria

9 Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Gain/amplification of 11q regions including the MLL gene is a rare but recurrent aberration reported so far in about 100 patients with de novo or secondary AML/MDS (compiled in 1). The aberration is prevalently observed in elderly patients with highly complex aberrant karyotypes and is associated with loss of 5q and a very poor prognosis.

The identification of true target genes of amplification and deregulation is important for understanding the pathogenesis of cancer, and also for clinical application including selection of optimal targets for cancer therapy in individual cases. A recent study of Poppe et al. (2) identified the MLL gene as a prominent target of 11q23 amplification. However, several AML/MDS patients have been reported to carry 11q amplicons not including the MLL gene (reviewed in 1,3,4), suggesting that other genes with possible oncogenic potential might be triggering 11q amplification. In a recent study employing 1 Mb-array-CGH we demonstrated that the core sequence around the MLL gene consists of maximally 700 kb and that at least two further 11q regions, namely 11q23-24 and 11q13.5, are co-amplified in 10/11 (90%) and 8/13 (60%) AML/MDS patients, respectively (1).

We have further narrowed down the minimal amplicon in 11q13.5 to 1.17 Mb region that contains 7 genes including the GRB2-associated binding protein 2 (GAB2). Using real-time RT-PCR we show a significant transcriptional up regulation of GAB2 in the patients who have GAB2 co-amplified with MLL. Thus, the adaptor molecule GAB2, that has already been shown to enhance oncogenic signaling in other neoplasias, appears as a novel target of 11q amplification in AML/MDS (5).

In cooperation with the ELN we have collected by now 55 patients carrying 11q amplification. Since the majority of patients show complexly aberrant karyotypes, still, some recurrent changes, within 11q or also in other chromosomes, might remain hidden behind the complexity of the rearrangement that cannot be fully resolved by lower resolution methods. In order to uncover such possible new regions we used in 12 of the patients a whole genome, submegabase resolution tiling set array CGH consisting of more than 36,000 BAC clones. Analysis was performed in the laboratory of Dr. Reinhard Ullmann, Max Planck Institute for Molecular Genetics, in Berlin. Our results revealed an astonishing complexity of rearrangements, including the delineation of several novel regions frequently co-amplified with the MLL gene. Loss of genomic sequences within chromosome arms 5q, 17p, 7q, and 20q, were observed in 11/12, 9/12, 5/12, and 4/12 cases, respectively. The precise definition of shortest regions of overlap in these recurrently deleted regions of 5q, 7q and 17p will lay the ground for uncovering genes possibly involved in this and other leukemias. In some of the patients we also identified several small aberrations that need further analysis. The study is very recent and our data are still being explored. To our knowledge this is one of the first efforts to fully characterize gains/losses on a whole genome basis with submegabase resolution in a distinct group of leukemia patients. It proves the potential of array CGH to detect non-random copy-number aberrations responsible for neoplastic transformation that have been masked under complex karyotypes.

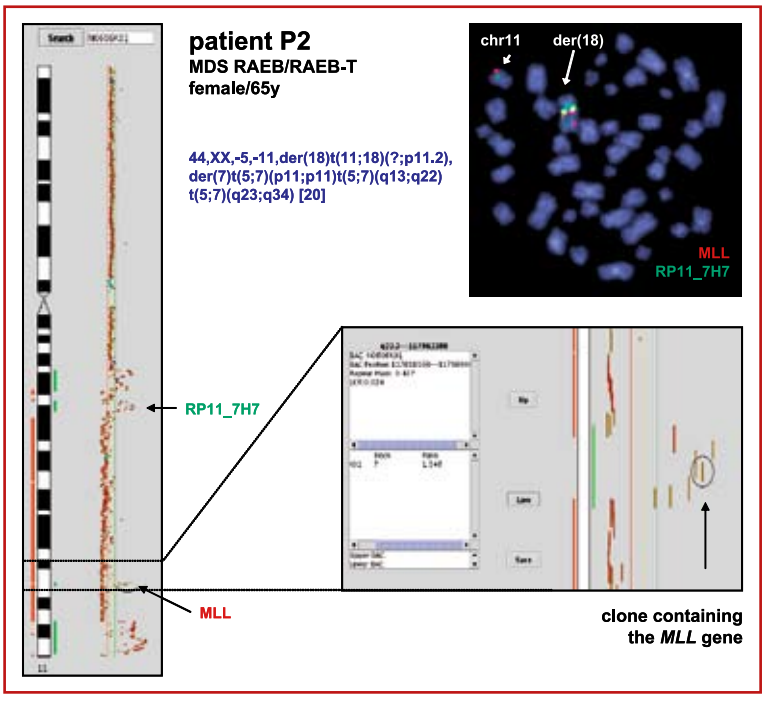


Figure 1: A tiling array CGH profile of chromosome 11 in patient P2 illustrates complex rearrangements within this chromosome involving both amplifications and deletions of various regions (indicated as green and red bars on the right and left hand side of the chromosome 11, respectively). Zoom in picture presents small MLL amplicon with an encircled BAC clone containing the MLL gene. FISH figure shows that 11q13.5 amplicon represented by clone RP11-7H7 is co-amplified within the same der(18) as MLL gene itself.

References

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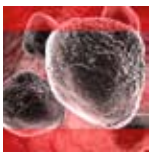
Stem Cell Transplantation Activity in Europe 2004



A. Gratwohl, H. Baldomero, Hematology, Department of Internal Medicine, University Hospital Basel, Switzerland
J. Apperley, Department of Haematology, Hammersmith Hospital, London, UK
D. Niederwieser, Division of Haematology & Oncology, University of Leipzig, Germany

Within the work package stem cell transplantation, the annual survey on transplantation activity in Europe covers an important part. All participating institutions list their transplants by disease indication, donor type and stem cell source for the preceeding year. In 2004, there were 22,216 first hematopoietic stem cell transplants (HSCT), 7,407 allogeneic (33%), 14,809 autologous (67%) and 4,378 additional re- or multiple transplants reported from 592 centres in 42 European countries. Main indications were leukemias (7,045 (32%; 78% allogeneic)); lymphomas (12,310 (55%; 94% autologous)); solid tumours (1,759 (8%; 93% autologous)) and non-malignant disorders (1,015 (5%; 92% allogeneic)). Stem cell source was peripheral blood in more than 95% of autologous, in 70% of allogeneic HSCT. A steady increase of 5-10% per year was observed over the last years for leukemias in allogeneic, for lymphoproliferative diseases in autologous HSCT. Data of this survey are essential for patient counselling and decision making for health care professionals.

Transplantation of hematopoetic stem cells is considered standard therapy for many patients with severe malignant or non malignant, acquired or congenital disorders of the hematopoetic system or with chemo- radiosensitive tumors. HSCT has seen rapid expansion over the last decade and the increasing demand for this high cost procedure can present a challenge for health care systems in any country. Precise information on current use and trends is essential for patients, physicians and health care providers alike. In order to gather this information and to disseminate it rapidly, the work package stem cells has integrated the annual activity survey of the European Group for Blood and Marrow Transplantation (EBMT). It was designed in 1990 to provide this information in a most efficient way. All EBMT members and affiliated teams, known to perform transplants were requested to report their numbers of patients by indication, stem cell source and donor type on an annual basis. The initial survey sheet was slightly changed over the years, to respond to changes in indication and to collect additional generic information on the numbers of re- or multiple transplants, on the percentage of cord blood HSCT and on the percentage of transplants with reduced intensity conditioning (RIC HSCT).

665 teams in 43 European countries were contacted for the 2004 report, of which 612 submitted their numbers. 53 reported being inactive. This corresponds to a 97% return rate of active teams and includes 481 of the 494 active EBMT member teams. We received information that in 2004 no blood or marrow transplants were performed in the following European countries: Albania, Andorra, Armenia, Georgia, Liechtenstein, Malta, Moldavia, Monaco, San Marino and The Vatican. By EBMT tradition, information is also obtained from some non European countries, Algeria, Iran, Israel, Saudi Arabia, Tunisia. The survey lists patients and transplants separately. For the determination of transplant rates, only first transplants were considered.

In 2004 a total 22,216 first transplants, 7,407 (33%) allogeneic and 14,809 (67%) autologous were carried out (Table). This represents an increase of 1,188 transplants or an increase of 5% compared to 2003, when there were 21,028 first transplants (7,091 allogeneic, 13,937 autologous). Numbers of allogeneic HSCT increased by 4% from 7,091 in 2003 to 7,407 in 2004; numbers of autologous HSCT by 6% from 13,937 in 2003 to 14,809 in 2004. The development in numbers of transplant teams and transplants since 1973 when EBMT was founded is illustrated in figure 1. In 1990, at the introduction of the survey, 143 teams did 4,234 HSCT (2,137 allogeneic (50%) and 2,097 autologous (50%).

Main indications were lymphoproliferative disorders with 12,310 patients (55%), 768 patients with allogeneic HSCT (6%), 11,542 with autologous HSCT (94%); leukemias with 7,045 patients (32%), 5,524 patients with allogeneic (78%), 1,521

Evolution of transplant numbers for the main disease categories in Europe 2004, Figures 3a and 3b.

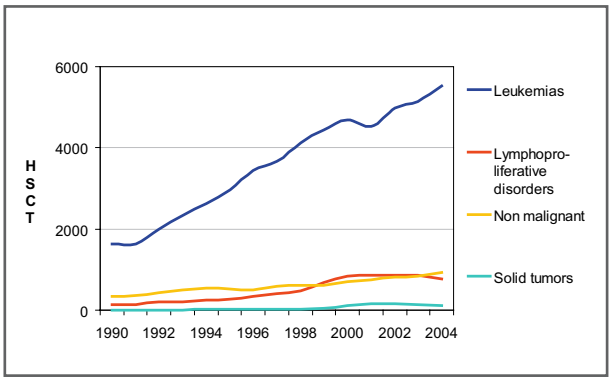


Figure 3a: Allogeneic HSCT

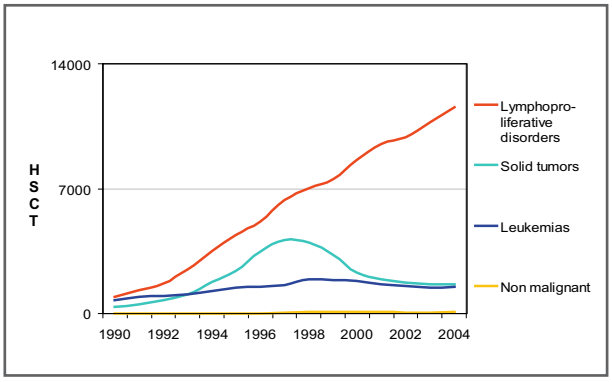
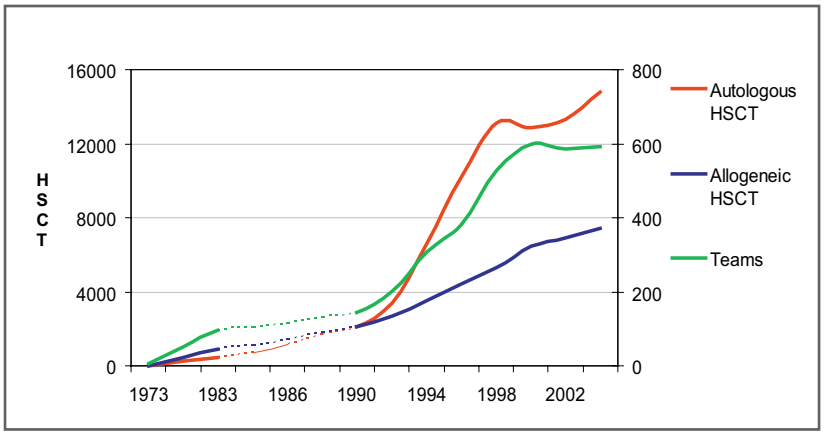


Figure 3b: Autologous HSCT

Figure 1: Numbers of transplants, autologous and allogeneic HSCT in Europe 1973 to 2004



Indications for hematopoietic stem cell transplants in Europe 2004*

Indication	Allogeneic HSCT	Autologous HSCT	Total
Leukemias	**5524**	**1521**	**7045**
Acute myeloid leukemia	2404	1029	3433
Acute lymphoblastic leukemia	1380	230	1610
Chronic myeloid leukemia	802	30	832
MDS/MPS**	748	37	785
Chronic lymphocytic leukemia	190	195	385
Lymphoproliferative disorders	**768**	**11542**	**12310**
Multiple Myeloma	164	5324	5488
Other plasma cell disorders	11	214	225
Hodgkin's lymphoma	104	1546	1650
Non Hodgkin's lymphoma	489	4458	4947
Solid tumours	**123**	**1636**	**1759**
Non malignant disorders	**938**	**77**	**1015**
Others	54	33	87
Total	**7407**	**14809**	**22216**

** Numbers reflect numbers of patients receiving their first HSCT for any of the diseases listed*
*** MDS/MPS = myelodysplastic/myeloproliferative syndroms*

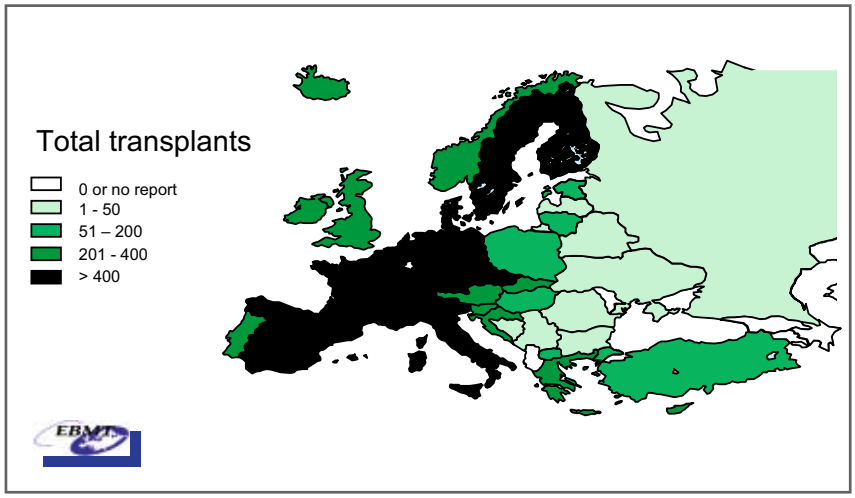


Figure 2: Number of transplants per 10 million inhabitants in European countries in 2004

with autologous (22%) HSCT; solid tumours with 1,759 patients (8%), 123 with allogeneic HSCT (7%), 1,636 with autologous HSCT (93%) and non-malignant disorders with 1,015 patients (5%), 938 with allogeneic HSCT (92%), 77 with autologous HSCT (8%). The latter, autologous HSCT for non-malignant disorders predominantly include patients with autoimmune disorders. An additional 87 patients, 54 with allogeneic HSCT and 33 with autologous HSCT were listed as „other indications". HLA-identical siblings were used as donors for 4,097 (55%), other family members for 432 (6%), a syngeneic twin for 40 (1%) and an unrelated volunteer donor for 2,838 (38%) of the 7'407 recipients of an allogeneic HSCT. 98% of the autologous and 69% of the allogeneic HSCT had peripheral blood as stem cell source, the reminder bone marrow. 3% of all allogeneic HSCT were cord blood transplants in 2004.

There were marked differences in transplant rates between European countries and countries affiliated with EBMT as presented in Figure 2. There was the previously reported difference between Eastern and Western European countries; these differences did relate to all transplants, to allogeneic HSCT and to autologous HSCT. Of interest to note is that countries with similar total transplant rates and higher transplant rates for allogeneic HSCT had lower transplant rates for autologous HSCT and vice versa.

There were marked changes in allogeneic (Fig. 3a) and autologous (Fig. 3b) HSCT for the main disease indications over time. HSCT did increase at a rate of about 5-10% per year for leukemias in allogeneic and for lymphoproliferative disorders in autologous HSCT and at about 1-3% for non-malignant diseases in allogeneic and for leukemias in autologous HSCT. Of interest to note, there was a marked increase in allogeneic HSCT for chronic myeloid leukemia up to the year 1999 (then the most frequent indication for an allogeneic HSCT) which was followed by a rapid decline up to the year 2003. Numbers of HSCT for chronic myeloid leukemia were similar in 2003 and 2004.
The present data document that HSCT is a well established procedure in Europe in 2004. Autologous and allogeneic stem cells from different sources were used for a broad variety of disorders. Peripheral blood was the main source of stem cells with the few exceptions of allogeneic HSCT for non malignant disorders. Autologous HSCT was the preferred choice for those disease categories, where primary focus lies on support for dose intensification of chemo-radiotherapy, e.g. in specified solid tumours and lymphomas. Allogeneic HSCT was the preferred choice where focus was on replacing a defective hemopoiesis as in congenital disorders or bone marrow failure syndromes or in diseases where a graft-versus-tumour effect is most desired, e.g. leukemias. As such, data reflect current status. They provide a basis for decision making for health care agencies as well as at the individual patient level.

The authors acknowledge the contribution of all participating teams, the support from the EBMT corporate members and from scientific grants.

WP 2 - ELIC

Clinical Trials Registry

www.leukemia

K. Ihrig, N. Gökbuget, A. Hellenbrecht (ELIC),
University Clinic of Frankfurt/Germany

ICMJE Guidelines

In 2004 (1) and again in 2005 (2) guidelines regarding study registration were issued by the International Committee of Medical Journal Editors (ICMJE), formerly known as the Vancouver Group, which is mainly comprised of journals or libraries outside of Europe only including some European journals as listed below. A large number of non-member journals also agree with the ICMJE's Guidelines. Main purpose of these adapted requirements are to provide a comprehensive, publicly available database of clinical trials (3).

International Clinical Trial Registry Platform (ICTRP)

At the same time the ICMJE Guidelines were issued, the World Health Organisation, in October 2004 with the "New York Statement " and again in May 2005, indorsed the importance of clinical trial registry to ensure transparency, to increase trust in the conduct of clinical research and to make results available to the public. Therefore, led by the WHO, an International Clinical Trial Registry Platform (ICTRP) was established in August 2005. With this approach, the WHO has no plans to administer its own register, but trialists should rather continue to register with existing registers (4).
The new Minimal-Data-Set of the ICTRP, which contains key information for every registered study, is now finalized and will remain unchanged until February 2008. The ICTRP network of registers is planned to be launched in the second quarter of 2006, after membership criteria has been established. To this time, only a draft version of primary register criteria is available and displays missing relevant subjects, e. g. the "Registry Platform's standard format" and the "standardized interchange format" (5). Further steps of the ICTRP are to assign UTRNs (Universal Trial Reference Numbers) and to launch the prototype of the Registry Platform Search Portal (all in the third quarter of 2006).

German study registry

Five Years before the regulatory requirements of the ICMJE and the endeavours of the WHO were under consideration, the German leukemia study register has been promoted (6). The goal was to facilitate transparency and enable review of ongoing studies. The register expanded continuously and provides currently study protocols of more than 80 ongoing German leukemia trials. User statistics from the past years are showing rising hits and up to 30.000 document downloads per year.
The existing registry is actually worked over to meet additional technical requirements to become a member register of the WHO. The Minimal-Data-Set will afterwards be uploaded from the national registry to the WHO-Metaregister. This procedure avoids double-registration in more than one register.
We are registered as an administrator and are receiving policies for the German leukemia study register as well for the ELN-study register to adapt on new developments. For this reason the German register is in the forefront to become a WHO-member registry as soon as the technical interface for data transfer of the WHO-Metaregister is finalized. In 2006, also European leukemia studies will be integrated into the register.
There are at least 50 registers of clinical trials around the world and some countries have plans to start their own register. The German government is actually funding a joint "national register of clinical studies" according to the ICTRP-Guidelines. Decisions about integration of registers of different medical fields as well as the German leukemia register to the national register are not finally concluded.

Members of the ICMJE

- Annals of Internal Medicine,
- Journal of the American Medical Association,
- New England Journal of Medicine,
- The Lancet,
- U. S. National Library of Medicine,
- Canadian Medical Association Journal,
- Croation Medical Journal,
- Nederlands Tijdschrift voor Geneeskunde,
- Tidsskrift for Den Norske Llegeforening,
- Ugeskrift for Laeger,
- New Zealand Medical Journal,
- The Medical Journal of Australia.

References

1. *De Angelis C, Drazen JM, Frizelle FA et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Lancet 2004; 364:911-912.*
2. *De Angelis CD, Drazen JM, Frizelle FA et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. Lancet 2005;365:1827-1829*
3. *www.icmje.org*
4. *www.who.int*
5. *www.who.int/ictrp/reg_criteria_B/en/int.html*
6. *www.kompetenznetz-leukaemie.de*

WP 2 - ELIC

Re-Launch of the ELN-Website

A. Hellenbrecht, N. Gökbuget (ELIC),
University Clinic of Frankfurt/Germany

The re-launched version of the new ELN-Website is now online www.leukemia-net.org.
Major reason for establishing a new Website was the limited functionality of the former version. The new Website provides enhanced technical features, e.g. central administration of Dates& Meetings, Literature and Links. Besides, it offers the opportunity for the Web-Editors, to get access to the system and to add content by themselves. Web-Editors need no special software or programming knowledge and training courses can be provided, if required.

The new website was realized in cooperation with the consultants of the Company Hoffmann+Liebenberg, Berlin. The used software was ZMS (= Zope-based content Management System for science, technology and medicine) which is a cost-free Content Management System. ZMS uses the open source application server ZOPE and is optimised for the building of structured contents. The system facilitates the editorial process by prescribing a homogeneous concept for the structure and the development of internet documents. Project costs and runtimes are reduced through standardized procedures. Even the long-term service costs can be minimized by use of standard models.

To promote and complete the new website, the support and contributions of all Workpackages is necessary.
The central website-structure was established, but it can still be adjusted for the individual needs of each WP. If not yet done, every WP should nominate a so called "Web-Editor" who will get access to the system to add documents and to make changes.

Besides:
All kinds of content/documents for the Website
are highly welcome.
Citations, can be integrated via XML-Upload
of RefMan or EndNote files.

Further Information:
European Leukemia Information Center ELIC
Dr. N. Gökbuget, A. Hellenbrecht
University Clinic of Frankfurt
Dept. of Hematology / Oncology
Theodor-Stern Kai 7
60590 Frankfurt am Main, Germany
Phone: +49 (0)69 6301 6365
Fax: +49 (0)69 6301 7463

2nd Workshop "Genetics of MDS", Göttingen, September 6th-7th 2006
Invitation and first Announcement

One year ago we organized the 1st Workshop „Genetics of MDS" at the University of Düsseldorf, Germany, under the auspices of the European Leukemia Net (ELN) and the "Kompetenznetz Akute und Chronische Leukämien". It was the 1st joint ELN workshop of two workpackages (8 - MDS and 11- Cytogenetics).
The positive feed-back we got from the participants and our own impressions encouraged us to plan a second meeting at the University of Göttingen, Germany, from 6th to 7th of September 2006. We cordially invite you to join this meeting, to present results of your recent research, to exchange ideas with colleagues and possibly to start cooperations on a European level.
Year by year our understanding of the genetic mechanisms in MDS and their consequences for the clinical management of this disease is increasing. At present, genetic data are integrated into prognostic scoring systems aiming for an individualization of therapeutic decisions. With the 5q-deletion the first (cyto)genetic subgroup in MDS with a preferential response to the new compound lenalidomide has been identified. With respect to pathogenesis there is a growing body of evidence that inborn or acquired deficiencies of protective systems like DNA-repair and detoxification might play a role in the etiology of de novo and secondary MDS.
The repertoire of methods ranges from classical cytogenetics over molecular cytogenetics and established molecular genetic procedures to very recent techniques like gene expression profiling, arrayCGH and proteomics. It is our firm belief that every method has its unique value and is indispensible. However, future progress may on the one hand essentially depend on correlating genetic data generated by different methods and on the other hand on international cooperation to overcome the limitations provided by the profound genetic heterogeneity of MDS.
We hope that the Second Workshop "Genetics of MDS" might be a platform to continue what has started one year ago: to combine our efforts in understanding and clinical management of MDS.
Hopefully, we will be able to carry travel and hotel expenses for a limited number of active (presentation) participants. There will be no registration fee.
If you want to give a presentation please send us an abstract of not more than 300 words (Times New Roman, 10 points) until the 1st of July. The abstracts will be published in Annals of Hematology.
For further information and registration form please contact haase.onkologie@med.uni-goettingen.de

D. Haase, C. Schoch, H. Rieder, U. Germing, R. Hehlmann, C. Fonatsch

Dates/Meetings

Immunogenetic, pharmacogenomics, proteomics and immunobiology (ESH)
June 6 - 7, 2006
Paris, France

11th Congress of the EHA
June 14 - 15, 2006
Amsterdam, The Netherlands

15th International CML-Workshop
June 30 to July 1, 2006
Mannheim, Germany

2nd Workshop "Genetics of MDS"
September 6 - 7, 2006
Göttingen, Germany

Myeloproliferative Disorders (ESH)
September 14 - 16, 2006
Madeira, Portugal

Training course, Infections in stem cell transplant recipiens
October 12 - 14, 2006
Dublin, Ireland

11th International Conference on Differentiation Therapy
November 4 - 8, 2006
Versailles, France

Iron Homeostasis, erythrocytes, erythropoiesis and related disorders (ESH)
November 10 - 12, 2006
Cascais, Portugal

ASH
December 9 - 12, 2006
Orlando, USA
Breakfast Session in preparation (10.12.2006)

4th Annual Symposium of the "European LeukemiaNet"
8th Annual Symposium of the Kompetenznetz "Akute und chronische Leukämien"
January 30 - February 1, 2007
Heidelberg, Germany

Workpackage Meeting of the 11th Congress of the EHA, June 14 - 15, 2006

Time Wednesday, June 14	Room Starlight I/II Okura Hotel 50 Persons Theatre Style	Room Breskens Okura Hotel 30 Persons Theatre Style	Room H RAI 88 Persons Theatre Style	Time Thursday June 15	Room C/D RAI 190 Persons Theatre Style
14.00 - 17.00	CML (WP4)		MRD (Grimwade) (WP12)	16.00 - 18.30	CLL (WP7)
17.00 - 17.15					
17.15 - 20.15	MDS/AML (WP8/WP5)	SCT (WP14)	MRD (Cross/BCR-ABL) (WP12)		

Amsterdam
RAI Convention Center
Europaplein 22
NL 1078 GZ Amsterdam
www.rai.nl

Hotel Okura Amsterdam
Ferdinand-Bol-Straat 333
NL 1072 LH Amsterdam
www.okura.nl
(10 minutes walking distance from Amsterdam RAI Convention Center)

3rd Annual Symposium of the European LeukemiaNet and
8th Annual Symposium of the Kompetenznetz „Akute und chronische Leukämien“
Heidelberg, Februar 1, 2006

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Network Management Center:
Dr. S. Saußele
III. Medizinische Universitätsklinik
Wiesbadener Straße 7-11
D-68305 Mannheim (Germany)
Phone: ++49 (0)621 383 4234
Fax: ++49 (0)621 383 4239
eMail: nmc@leukemia-net.org
Information Center:
Dr. N. Gökbuget
Medizinische Universitätsklinik II
Theodor-Stern-Kai 7
D-60590 Frankfurt (Germany)
Phone: ++49 (0)69 6301 6365
Fax: ++49 (0)69 6301 7463
eMail: elic@leukemia-net.org
Homepage:
www.leukemia-net.org
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