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Impressum

Dear colleagues,

after four years the European LeukemiaNet (ELN) has set up an efficiently operating network.

Current outcome and immediate perspectives include:

1. Establishment of information, communication and management structures. Communication is mostly accomplished via the information center and by the network management center through annual symposia, regular network- and WP-meetings, an ELN website, and biannual newsletters. A European Leukemia Trial Registry was developed in accordance with the guidelines of the International Committee of Medical Journal Editors and the World Health Organization providing information about current clinical trials and assuring transparency on recruitment, therapies and study outcomes across Europe.

2. European registries have been started for CML, ALL, ET and MDS. Clinical laboratory and data collection is done for developing and validating prognostic scores, standardization of diagnostic and therapeutic procedures, evidence-based guidelines and meta-analyses.

3. Clinical trials on an European level are ongoing or planned including studies of tyrosine kinase inhibitors in CML, HES, myelofibrosis, MDS and PV, trials of chemotherapy protocols in CLL, mature B-ALL, Burkitts Lymphoma, APL, ALL and AML in the elderly.

4. Quality control rounds and consensus recommendations on an European level were developed for molecular monitoring in CML (Hughes et al., Blood 2007), cytogenetic analysis in CLL and morphological diagnosis of leukemias (Jovanovic et al., Blood 2007).

5. Guidelines and management recommendations were completed and in part published for CML (Baccarani et al., Blood 2006; Hehlmann et al., Lancet 2007), for detecting BCR-ABL transcripts and kinase domain mutations (Branford et al., Leukemia 2007), for microarray analyses (Staal et al., Leukemia 2006), for definition of transplant-associated microangiopathy (Ruutu et al., Haematologica 2007), for standardizing indications for SCT (de Witte et al., Haematologica 2006; Dreger et al., Leukemia 2007) and for prophylaxis and empirical antifungal therapy in neutropenic leukemia patients (Ljungman et al., BMT 2005).

6. A close cooperation between ELN and industry (CML-Alliance) was started in 2007 including standardized molecular monitoring, spread of excellence on leukemia and registry activities for gaining a real-world pan-European picture of incidence, management and outcome of CML. Eight new participants were integrated in 2007 bringing the number of institutions participating in the European LeukemiaNet to now 133 with approximately 1000 researchers in 24 countries.

I wish you an exciting reading of this fourth issue of our newsletter where further developments within the ELN are described in detail.

Prof. Dr. Rüdiger Hehlmann
Network Coordinator
The CML Group within the European Leukemia Network agreed on a long term Collaboration with Novartis to improve Understanding and Treatment of chronic myeloid Leukemia

S. Saußele, R. Hehlmann

On 28. June 2007 the European LeukemiaNet (ELN) and Novartis launched a collaboration committed to improving understanding and treatment of chronic myeloid leukemia (CML-alliance). The collaboration was initiated by the signature of a Scientific Collaboration Agreement between the CML-ELN group represented by the University of Heidelberg, Germany, and Novartis, Switzerland (see Fig. 1).

The objectives of the CML alliance with Novartis are to:

- Increase understanding of the epidemiology of CML, its treatment and real life outcomes by collecting baseline-, treatment- and outcome data of representative samples of CML patients of major European countries
- Develop and validate a comprehensive prognostic model which allows to optimize individual treatment choices
- Evaluate the implementation of the ELN recommendations for CML management (Baccarani et al., Blood 2006;108:1809-20.) as reference; encourage uptake of ELN recommendations for the management of CML and measure clinical benefit of their implementation
- Promote quality controlled molecular monitoring using standardized RQ-PCR technologies and an international definition of major molecular response
- Assess impact of drug monitoring, pharmacokinetics and patients’ compliance on the course of CML
- Foster continued medical education and spread of excellence
- Provide a platform for the expedited evaluation of new treatments

To reach these goals four subprojects are created (see Fig. 2).

Subproject Registry
A key activity of the collaboration is to expand the already existing CML Registry in collaboration with work-package 17. The major idea is to collect baseline-, treatment- and outcome data of representative samples of CML patients in European countries by implementing and enlarging the current ELN-CML Registry and its related sub-registries. Its activities will be enhanced through the collaboration agreement with Novartis. Due to the limited funding by the European Commission (EC) the registry, at the moment, enrolls only study patients. With the additional financial support more countries and population based data can be included. This will lead to a real-world pan-European picture of the incidence, distribution and control of CML and will provide a clear picture of the current management of CML.

Subproject Molecular Monitoring
This subproject strengthens the registry by providing quality controlled outcome data and improves the availability of molecular monitoring for CML patients by reshaping existing European infrastructure. The distribution of internationally standardized RQ-PCR analyses for BCR-ABL quantification and for detection of BCR-ABL mutations will facilitate the investigation of response and acquired resistance to existing treatments, helping to inform on therapeutic choices for these patients.

Subproject Pharmacological Monitoring
This initiative will expand the availability of imatinib monitoring to a European level in order to optimise therapy for a greater number of patients. This will be achieved by providing a Europe-wide monitoring service free of charge (sample transportation and dosing) for a period of 3 years. During this period, a database will be constructed to i) verify the pertinence of the therapeutic threshold by following patients with imatinib levels < 1000 ng/ml and ii) to define a toxic concentration. Potential dosing laboratories will be selected across Europe (one or two for each participating country) and a dosing service established in the respective countries by collaboration with the Bordeaux center which will also manage a centralised quality control system.
The objective of this subproject is to raise awareness of the CML alliance with the definite goal to foster ELN-activities, promote implementation of ELN management recommendations, improve understanding and treatment of CML and enhance outcome of CML across Europe and globally. The SoE project will support all activities that promote realization of a European CML registry and of the other subprojects of the CML-alliance. The activities for the spread of excellence can be broken down to various scientific, organizational, educational and PR activities.

During a start symposium in Heidelberg in September 2007 milestones and activities of all four subprojects were discussed and planned. At a booth of the ELN at the ASH congress in December 2007, this registry project will be further introduced and educational material will be also available. A first progress report is planned for the annual ELN-Symposium end of January 2008.

Figure 1: Signature of the Collaboration Agreement between CML-ELN and Novartis on 28. June 2007 in Heidelberg: ahead rightwards: R. Hehlmann (ELN Coordinator), P. Hommelhoff (Rector University of Heidelberg), G. Guidi (Head of Oncology Region Europe, Novartis); back rightwards: A. Jacobs, U. Haus (Novartis), N. Huber, S. Saußele (University of Heidelberg), L. Montrucchio (Novartis), A. Hochhaus (University of Heidelberg), P. Schuld (Novartis)

Figure 2: Organizational structure of the CML-Alliance: The executive committee directs the Alliance scientifically. The management board is responsible for the management and controlling of the whole project. The Registry project is led by a Steering Committee with two central units (Scientific Registry Headquarter in Bologna and Central Data Center in Munich). The other three subprojects are led by chairs as indicated.
The AML Intergroup: A Model of Cross-Trial Networking


The AML Intergroup is a cooperation of independent groups conducting clinical trials on AML in Germany. After two of the initial five groups have fused, the Intergroup is now comprised of four different trial groups.

AML Intergroup Cross-Trial Networking

In order to combine the efforts of all pre-existing trial groups the participants of the Intergroup designed a structure of cross-trial networking (Figure 1). The main instruments combining the single trials to a network are a common standard treatment arm and a general upfront randomization (1). The common standard arm has been derived from a strategy by the CALGB (2) where standard dose araC/daunorubicin (7+3) for induction is followed by three courses of postremission therapy with high-dose araC 3g/m² x 6 in a monthly sequence. By the general upfront randomization 10% of patients in each trial are assigned to the common standard arm. This design provides a comparison of the therapeutic outcome from each trial with the outcome in the standard arm and indirectly with the outcomes in the other single trials. The number of recruited patients now amounts to 2909 with 288 in the common standard arm. The first official update in 2004 is shown in Figure 2. Figure 3 shows the official 2006 update of the survival probabilities estimated by the Kaplan-Meier method. In addition to the overall survival, also the relapse-free survival, event-free survival, and relapse-risk show similar results between the common arm and the study groups with no significant differences among the compared endpoints. New important conclusions may be drawn after this preliminary data will be confirmed by a forthcoming update.

AML Intergroup Cross-Trial Networking in Older Patients

While present networking is limited to patients younger than 60 years a new similar network has been activated for patients 60 years of age and older with no age limit. For his age group chemotherapy has been adapted in that patients receive postremission therapy by two instead of three monthly courses of high-dose araC and 1 instead of 3g/m² q 12 hr x 6.

Meta-analyses of the AML Intergroup

In addition to the networking projects the AML Intergroup is used for meta-analyses of patient populations characterized by particular cytogenetic abnormalities. Thus, new insights could be obtained by an Intergroup-wide investigation on CBF-leukemias in the largest number of patients published so far (3). A recent similar meta-analysis has focused on patients exhibiting trisomy 8 (4).

Prognosis of AML Patients ≤ 60 years with +8


Individual patient data-based meta-analysis was performed on 131 patients (median age 50 (18-60) years) with +8 as a sole aberration or +8 with one additional aberration treated between 1993 and 2002 in eight prospective German AML treatment trials. All patients received state-of-the-art treatment including high-dose cytarabine with the option for autologous or allogeneic hematopoietic stem cell transplantation (HSCT). In total, the 131 patients had a 3-year overall survival (OS) of 29% and a 3-year relapse-free survival (RFS) of 32%. Independent prognostic factors contributing to shorter OS were age ≥ 45 years, extramedullary disease, and a percentage of +8 positive metaphases ≥ 80%. Combining these three prognostic variables established a hierarchical model for OS. The 3-year OS was 13% for the high-risk group, 36% for the intermediate-risk group, and 55% for the low-risk group (p<0.0001). Age <45 years and allogeneic HSCT (as treated) were independent prognostic factors for longer RFS. Additional cytogenetic aberrations other than t(8;21), inv(16), t(16;16), t(15;17) or 11q23 had no influence on treatment outcome. We provide a new prognostic model for risk stratification of AML patients with +8. The data indicate that allogeneic HSCT may prolong RFS compared to that achieved with other strategies of postremission therapy (Figure 4).

The European AML Network: Progress and Outlook

Following the previous status report in the first ELN Information Letter in August 2005 the European AML Network performed further steps of achievement.

The AML Intergroup as a European pilot project has almost now been entering 3000 patients of < 60 years. While the update of 2004 due to restricted observation time did not allow to draw any...
conclusions, the 2006 update strongly suggests comparable outcomes among the different strategies and the standard arm. In the meantime, an AML Intergroup network for patients of ≥ 60 years has been activated and recruited 350 patients so far.

In February 2006 and 2007 the AML Intergroup conducted two international symposia, addressing “AML in the Elderly” and “Randomization Strategies”, reported in the minutes. The two ELN workpackages 5 (AML) and 8 (MDS) have been increasingly coordinating their work by sharing a part of their group sessions at the occasions of the annual ELN symposia in Heidelberg and the EHA annual meetings, thus combining the efforts of both groups in classification, molecular genetics and treatment.

In order to elaborate European guidelines in AML and APL, a conference of international experts was held at Frankfurt Airport on November 27, 2006. At this meeting outlines were discussed and panels were appointed. In the meantime, drafts are in progress.

The panel members for the APL guidelines in alphabetic order are:

- Thomas Büchner, Alan Burnett, Elihu H. Estey, Pierre Fenaux, David Grimwade, Eva Lengfelder, Francesco LoCoco, Bob Löwenberg, Tomoki Naoe, Miguel Sanz, Martin Tallman

Members of the AML panel are:


The next steps of the European AML Network will

- assess more detailed differences in outcome in the AML Intergroup trial
- assess novel biomarkers on the basis of a large scale prospective multicenter AML trial
- conduct a new international symposium in February 2008 focusing on allogeneic transplantation
- combine efforts in AML and MDS at molecular and therapeutic levels
- establish and publish European AML and APL guidelines

References:


Figure 2: AML Intergroup cross-trial networking update 2004. Survival probabilities according to Kaplan-Meier for the four single trials and the common standard arm. The allocation of curves to special trials remains blinded to the Intergroup.

Figure 3: AML Intergroup cross-trial networking update 2006. For details see Figure 2.

Figure 4: Prognostic model for overall survival of AML patients with +8. Low risk (dashed line): age <45 years, no extramedullary disease and ≤ 80% +8 positive metaphases at diagnosis; high risk (solid line): age ≥ 45 years and extramedullary disease and/or ≥ 80% positive metaphases at diagnosis; intermediate risk (dotted line): all other patients.
The European Working Group for Adult ALL was founded in 2002 as part of the European Leukemia Net. Acute lymphoblastic leukemia (ALL) in adults is a rare disease with a variety of subtypes showing highly significant differences in terms of clinical manifestation, disease biology and outcome. Therefore most ongoing trials for de novo ALL are subtype adjusted and risk stratified. Fortunately a number of new drugs is currently under evaluation for ALL. Some of these drugs are subtype specific such as monoclonal antibodies or even targeted to pathogenetic mechanisms such as tyrosine kinase (TK) inhibitors in Ph-/BCR-ABL positive ALL.

In this general context the design of prospective trials in adult ALL is challenging since trials in small, well defined subgroups of ALL and window studies with new drugs are of increasing importance. These trials will only be possible in larger, international study groups which are able to recruit sufficient patient numbers. Therefore from the beginning the initiation of European collaborative trials was one of the central aims of EWALL.

Mature B-ALL is a rare subtype of ALL with an incidence of 4% and is treated with specific short intensive chemotherapy cycles combined with Rituximab. The EWALL started therefore with the extension of the German Multicenter Trial for Adult ALL (GMALL) study for mature B-ALL and Burkitt’s lymphoma to several other countries including Italy, Spain and Poland where they were conducted under the auspices of the respective national study group leader. The next EWALL trial explored liposomal cytarabine for intrathecal application in ALL with CNS relapse. This is a very rare indication since the incidence of CNS relapses could be reduced to less than 5% in most ongoing trials due to intensive prophylaxis with intrathecal therapy, systemic high-dose therapy and partly CNS irradiation. Beside Germany several other countries joined the trial in order to recruit more patients. During the activation procedure of this investigator initiated trial much experience was collected regarding the regulatory difficulties of conducting international trials under the EU Clinical Trials Directive.

This trial which recruited patients from Germany, France, Austria, Spain and Italy was closed in June 2007. Now several EWALL members plan trials with prophylactic application of liposomal cytarabine in de novo ALL.

The most recent and largest initiative started in 2006 when the EWALL decided to focus on the treatment of elderly patients with ALL which is an unmet medical need. Several study groups had not activated national study protocols for elderly ALL patients – either Ph-positive or Ph-negative. Therefore the chance came up to agree on a joint protocol. Based on French and German prospective trials for elderly ALL the group decided on a chemotherapy backbone protocol with intensive induction for Ph-negative ALL and less intensive induction for Ph-positive ALL. The aim was to add different new drugs to this backbone and to explore them preferably in a randomised design (Figure 1). The first study based on this design was activated under the leadership of the French GRAALL group (P. Rousselot) in July 2007. It evaluates the TK-inhibitor Dasatinib in combination with the backbone chemotherapy in Ph-positive ALL. A second study with the same design but with Nilotinib as TK-inhibitor will follow (O. G. Ottmann). Further trials e.g. with Forodesine, a new drug for B- and T-cell-ALL (N. Gökbuget, D. Hoelzer) are in the planning phase.

The preparation of joint protocols also underlined the need for standardisation of diagnostic methods – particularly for analysis of minimal residual disease (MRD) which is both an entry criterium and end-point of these trial. The standardisation will be attempted in close collaboration with existing European expert groups for MRD evaluation.

Most recently the EWALL identified the treatment of adolescents as an important issue and all groups exchanged their plans to transfer paediatric treatment elements to studies for adult ALL.

Overall the EWALL cooperation was stabilised and strengthened by regular meetings and open friendly discussion based on the awareness of all participants that several important questions in adult ALL can only be answered through collaborative international trials. It became also evident that the group can take a stronger position towards pharmaceutical companies by approaching them as a large European consortium. The future will show whether the ambitious study programme can be realised in the environment of the EU Clinical Trials Directive and whether it can thereby contribute to improved outcome of adult ALL and a strengthened position of European clinical research in adult ALL.

Figure 1: Design of Prospective EWALL Trials with Chemotherapy Backbone and Addition of New Drugs
Patients with chronic lymphocytic leukemia (CLL) follow heterogeneous clinical courses. Although the Rai and Binet staging systems have provided valuable information regarding survival, they have been unable to accurately predict at diagnosis who among early stage or intermediate risk patients will actually progress during the course of the disease. Therefore, novel identifiers of the clinical subsets with favorable versus poor prognosis would be very helpful for patient management.

Recently, there has been major progress in the identification of molecular and cellular markers that may predict the tendency for disease progression in CLL patients. A major breakthrough came in 1999, when the Hamblin, Stevenson and Chiorazzi groups independently demonstrated that somatic mutations can be present in rearranged immunoglobulin heavy chain variable (IGHV) genes in CLL and define two disease subtypes associated with a different clinical course (1-2). In particular, patients carrying mutated IGHV genes generally follow a more indolent course than those with unmaturated IGHV genes, who tend to show evidence of advanced, progressive disease, adverse cytogenetic features, clonal evolution, and resistance to therapy. An important exception to this rule is the IGHV3-21 gene, which is associated with an inferior outcome regardless mutational status (3).

Since 1999, several studies have confirmed that IGHV gene mutational status has prognostic value independent of the clinical stage (4). Furthermore, an important advantage of this variable over several other genetic, cellular or serum markers is that it remains constant during the disease course (including clonal evolution). Given the importance of the determination of IGHV mutational status for clinical decision making, recommendations on how to perform and interpret IGHV mutational analysis in CLL were until recently strongly warranted in order to set standards and avoid discrepancies between studies.

Several members of the European LeukemiaNet WP7 (ERIC - European Research Initiative on CLL, www.ericll.org) from different European countries, including France, Germany, Great Britain, Greece, Italy, Spain and Sweden, gathered to critically discuss the current and most updated literature as well as their own laboratory experience on this issue. This resulted in a critical analysis of the pros and cons of several technical aspects allowing the authors to reach a consensus on the minimum requirements for a reliable and reproducible analysis of the rearranged IGHV sequences in CLL. These ERC-WP7 recommendations on IGHV gene mutational status analysis in chronic lymphocytic leukemia were published earlier this year as an Editorial in LEUKEMIA (5).

Although this report provided a frame for methodological standardization, it was felt that there was also a clear need for a practical approach for training investigators involved in IGHV analysis for clinical purpose. Therefore, under the auspices of the ELN, several ERC-WP7 members including some authors of the Guidelines organized the Educational Workshop on Immunoglobulin Gene Analysis in Chronic Lymphocytic Leukemia which was held on June 14-15, 2007 in Uppsala, Sweden. This Workshop comprised a mixture of lectures and applied sessions held by experts in the field on immunoglobulin gene interpretation in CLL and was attended by 60 scientists from Europe, the US and Australia. All lectures and educational material are freely downloadable at http://www.igcll.com/download.htm, http://imgt.cines.fr/textes/IMGTMedical/ cancer/ and http://imgt.cines.fr/textes/IMGTeducations/. A second Workshop is planned for 2008.

The use of consensus procedures will allow direct comparison of IGHV sequence data between laboratories, which will be especially important for new multicenter treatment studies in which IGHV mutational status analysis will be used to stratify patients. Nevertheless, cases exist that are difficult to analyze or categorize (e.g. single non-productive rearrangement, double in-frame rearrangements with discordant mutational status). To this purpose, as part of an ERC-WP7 project, an online discussion forum was launched at www.ericll.org/projects/index.php for: (i) support and troubleshooting for interpretation of IGHV sequences by a review board of experts which is available to discuss general queries on IGHV gene interpretation or analyze actual IGHV sequences that can be difficult to interpret in everyone’s daily activity; (ii) collection of problematic cases, which, though probably known to anyone working in IGHV analysis in CLL, are limited in frequency, hampering a meaningful analysis at a single-institution level. This forum has been active since January 2007 and has so far received several queries from different institutions in Europe and the US.

The experience gained over the last decade has established the important prognostic role of IGHV gene mutational analysis in CLL. A technically demanding test is now performed widely (if not on a routine basis), even in nonspecialized, diagnostic laboratories. The question then arises: should we do it or not? Our answer is: Let’s do it, but in style!

References:
1. Hamblin TJ et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94:1848-1854

Finding Solutions for IGHV gene mutational Analysis in CLL

P. Ghia, C. Belessi, F. Davi, A. Langerak, K. Potter, R. Rosenquist, K. Stamatopoulos
Acute myeloid leukemia or myelodysplastic syndrome (AML/MDS) patients carrying 11q amplifications involving the mixed lineage leukaemia (MLL) gene belong to a group of patients with complex aberrant karyotype (CAK), characterised by a later onset, fast progression of the disease and extremely poor prognosis (reviewed in (1) and (2)). It has been shown that AML patients with CAK exhibit a characteristic expression profile (1). However, data on the genes contributing to the disease severity observed specifically in 11q amplified cases is currently missing. As generally assumed and according to recent real-time RT-PCR based expression studies of Poppe et al. (3) and our group (4), the MLL gene is overexpressed in MLL amplified cases and is believed to be the prominent target of 11q23 amplification. However, in most of the cases the amplified region was found not to be restricted to the MLL locus. Previously we defined a minimal MLL-including amplicon of 700kb and we identified two additional 11q regions, namely 11q13.5 and 11q23-24, which are frequently co-amplified in AML/MDS patients (2). Recently, we further narrowed down the minimal amplicon in 11q13.5 and showed a significant transcriptional upregulation of a scaffold adaptor protein GAB2 (GRB2-associated binding protein 2) in the patients who have GAB2 coamplified with MLL (4). Thus, GAB2 that has already been shown to enhance oncogenic signalling in other neoplasias appears to be one of the targets of 11q amplification in AML/MDS (see also ELN Information Letter N°2, page 6).

Mainly through the ELN-WP11, we have so far collected 56 adult AML/MDS patients carrying amplification of MLL gene. The aberration was frequently associated with deletions of 5/5q (73%), and/or 17p- (30%), and 7/7q- (19.6%). Fifteen AML (two secondary, following MDS and PV; three therapy related) and four MDS cases (two therapy related) for which suitable amount of DNA and/or RNA was available were investigated in the present study (manuscript in preparation). We characterized the patterns of chromosomal gains and losses in 12 AML/MDS cases with 11q/MLL amplification using a whole genome submegabase resolution array CGH. Figure 1 summarizes results of the analysis in all patients in a genomic view. The DNA copy number status of the sequences within chromosome 11 in eight of the studied cases was correlated to the expression levels of genes from this regions as measured by Affymetrix U133plus 2.0 array analysis performed in 15 cases. Altogether 100 significantly upregulated and 62 downregulated genes were identified within chromosome 11 in 11q/MLL amplified cases when compared to a control group of healthy volunteers (n=15). Array CGH results show that three independent 11q regions were amplified in all 12 patients: 11q23.3/11q1: (495kb); 11q24.2- q24.3/11qI (2.9 Mb); and 11q24.3-q25/11q11 (1.3 Mb). Also several novel recurrent regions were identified co-amplified in smaller proportion of the patients. We found that, in addition to MLL, several other genes from the 11q-amplicons were overexpressed, including UBE4A, STS-1, TBRG1, FLI1, NFRKB, ST14, and SNX19.

All of the recurrent amplicons map between chromosomal bands 11q13.5 and 11q25. While 47 (47%) of the upregulated genes map directly to the minimal amplicons, indicating that also neighbouring genes that are not directly included in amplicons are differentially regulated. Interestingly, a number of genes from chromosome region 11q12-q13.5 (centromeric to the amplicon in 11q13.5 containing GAB2 gene) show significant downregulation, whereas deletion within this region was evident in only two of the cases included in our expression analysis. Taken together, our results indicate that in the majority of identified 11q amplifications several genes might be contributing to leukemogenesis. No single gene was identified to be highly upregulated in all samples. It is, thus, conceivable that simultaneous deregulation of many genes contributes to the severity of the disease observed in cases with 11q amplification.

Detailed tiling array CGH analysis and expression study enabled also delineation of the minimal deleted regions within 5q and 17p and the identification of significantly downregulated genes that might be targets of these deletions frequently observed in AML/MDS.

Furthermore, whole genome expression profiles of fifteen cases with 11q/MLL amplification were compared to healthy controls and to the groups of AML/MDS patients with CAK but without MLL involvement, with 11q23/MLL translocation alone, and to AML with normal karyotype (for each group n=15). Similar to AML/MDS cases with normal karyotype and/or those with 11q23/MLL translocations, our patients show an overexpression of HOXAS5, 7, 9, 10, and HOX85, 6 genes as well as of HOX-cofactors MEIS1 and PBX3. Differentially expressed probe sets from all pairwise analyses were analysed using DAVID functional annotation tools (http://david.abcc.ncifcrf.gov). For any given gene list the DAVID tools are able to identify enriched biological themes, discover enriched functional-related gene groups and visualize genes on BioCarta & KEGG pathway maps. Our results indicate a significant enrichment of genes involved in ‘Notch signalling pathway’ among the probe sets upregulated in group with 11q/MLL amplification. Moreover, clustering analysis using the top 100 differentially expressed probe sets from comparisons of each AML subgroup with healthy controls was sufficient to discriminate the MLL amplified cases from all others, thus indicating specific pathogenesis present in this group.
References:

Supported by:
This study was supported by Austrian Science Fund FWF P18555, and German Nationales Genomforschungsnetzwerk, grant 01GR0203.

We would like to thank ELN-WP11 members for support and in particular Drs. Martine Jotterand (Service de génétique médicale, Unité de cytogénétique du cancer, Maternité – CHUV, Lausanne, Switzerland), Clelia T. Storlazzi and Cecilia Surace (Department of Pathological Anatomy and Genetics, Section of Genetics, University of Bari, Italy), Mette K. Andersen (Department of Clinical Genetics, Section of Hematology/Oncoogy, Rigshospitalet Copenhagen, Denmark), Bertil Johansson (Department of Clinical Genetics, University Hospital, Lund, Sweden), Christine Mannhalter (KIMCL, MUW, AKH, Vienna, Austria), and Frank Speleman (Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium) for the patient’s material and all clinical and karyotypes data contribution.
The German Leukemia and Lymphoma Patients’ Association and the European Cancer Patient Coalition

U. Holtkamp (Deutsche Leukämie- & Lymphom-Hilfe)

The German Leukemia and Lymphoma Patients’ Association (DLH e.V.) is the federal German association of patient support groups helping adults with leukemia and lymphoma. It was founded in 1995 with its headquarters in Bonn. The DLH is generously funded by the German Cancer Association (Deutsche Krebshilfe e.V.). At the moment, 84 local and specialized support groups across Germany, Switzerland, Austria and Belgium belong to the DLH.

Endorsement of patient support groups
A main goal of the DLH is the endorsement of local and regional patient support groups. Emerging groups are offered assistance in founding, developing and becoming acquainted. Furthermore, the group leaders are trained by the DLH in special seminars. Newsletters with up-to-date information are regularly sent out. The DLH answers particular questions and helps solving problems which can occur when caring for patients and their relatives. Of course, organizational issues can be addressed as well.

Information: helpline, booklets and patient information days
At the headquarters a patients’ advocate team runs a helpline. Every year, several thousands of requests are dealt with. Patients and relatives want to learn more about their disease, therapies, and possible side effects. They ask for specialists, support groups and study groups. Of course, lots of other linked topics like social welfare benefits or complementary medicine are addressed. There is a wide scale of booklets and other educative material available in understandable language in the headquarters. But not only patients and relatives are seeking advice. There are also requests from journalists, health care providers or people who want to become a bone marrow donor, for example.

The DLH publishes own booklets and fact sheets and works together with other publishers. The DLH magazine „DLH-INFO“ is released three times a year. All editions since 1999 are available on the DLH website. Extensive information is offered there as the internet is becoming more and more important. In 2006, about one third of the requests reached the headquarters via email.

Several local patient information days and one national congress for leukemia and lymphoma patients are organized every year.

Advocating
In 1995, apart from individual help for patients and their relatives, there had been a growing demand for the public representation of patients’ interests towards politics, health insurances, medical organizations and further institutions. Giving leukemia and lymphoma patients a voice was one of the main springs for founding the DLH.

The DLH points out deficiencies in health care and wants to contribute to their reduction. This affects for example capacity problems, the scaling down of medical supply as well as deficiencies in aftercare, interpersonal treatment and research on causes of hematologic malignancies. The DLH sends out appealing letters, addresses petitions, publishes statements, passes resolutions, and carries out panel discussions on diverse up-to-date topics. The DLH also advocates towards improving the conditions for carrying out clinical trials as they may provide faster access to new, promising drugs. Successful advocacy work needs cooperation. The DLH therefore cooperates with a vast scale of national and international organisations and is member of numerous committees.

Leukemia patient organisations across Europe
The DLH has been networking during the past years with many European leukemia, lymphoma, and myeloma patient advocacy groups. Links about 30 patient organisations across Europe are implemented into the ELN-website (Figure 1).

European Cancer Patient Coalition (ECPC)
The European Cancer Patient Coalition was established in 2003 by 15 European Cancer Patient Initiatives. With its motto „Nothing about us without us!“ ECPC represents nowadays over 250 patient organisations from across the 27 EU member states, among them the DLH. Two lists of ECPC full and associate mem-

Figure 1: Overview on patient organisations across Europe on the ELN-website
Development of a frailty Index for elderly Patients with MDS and AML by applying a multimodal geriatric Assessment including Quality of life Evaluation

B. Deschler, J. Hummel, C. Perinchery, B. Rüter, M. Lübbert

It is well established that conditions like cancer predict mortality. The addition of simple measures of functional limitation, such as a questionnaire on „Activities of Daily Living“ (ADL), significantly refine prediction of morbidity and mortality (1).

Risk stratification is crucial in selecting appropriate treatment options and improving treatment outcomes in the patient population mainly affected by cancer, the elderly.

Studies have demonstrated an independent effect on treatment selection and outcomes from age, disease burden and functional assessment in older cancer patients. They also suggested that deterioration of functional status reflects coexisting illnesses rather than cancer itself, as only 14% of cancer individuals with a functional limitation subjectively attribute their limitation to cancer. There is a significant heterogeneity in alterations of function, disease burden, and risk of death from competing illnesses, yet, all dramatically increase with age (2-4). Comprehensive geriatric assessment (GA) provides an overarching method of assessment of elderly patients and can be applied before, during and after treatment. Growing evidence demonstrates that the variables examined in a GA predict morbidity and mortality and uncover problems relevant to cancer care that would otherwise go unrecognized. While still no standardized GA has been developed, it’s increased application can stimulate the development of novel end points for clinical trials that address quality of survival and functional independence in addition to traditional end points, which evaluate disease-free and overall-survival (5).

The special aspects of caring for oncogeriatric patients gain increasing attention and are of pronounced relevance for physicians caring for patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). These two entities have been described as a biological continuum and are as such a heterogeneous group of hematological malignancies affecting mainly patients above 65 years, an age group considered „elderly“ in hematological literature. While results of treatment have improved steadily in younger adults, there have been limited changes in survival among individuals >60 years. Treatment options range from best supportive care, to low-dose chemotheraphy or novel agents (e.g. demethylating agents) and intensive chemotherapy. Maximum curative treatment is not always feasible.

As the basis for treatment decision-making is not well defined, GA is expected to offer rationale support in this process. The need for validated instruments for age-specific functional and quality of life (QOL)-assessment is obvious.

To investigate whether a multidimensional GA, consisting of a battery of QOL and 7 geriatric instruments evaluating activities of daily living, depression, mental functioning, mobility, morbidities and performance status, can be successfully performed in this patient group prior to initiation and in the course of treatment, newly diagnosed patients with MDS and AML >60 years of age were assessed from 11/03 to 05/07 at the University Hospital Freiburg, Medical Center (Table 1). Treatment decision-making has thus far not been based on results of the assessment.

We have been able to show that GA is readily feasible and results in a high degree of patient satisfaction. Interim statistical analyses indicated a prognostic impact of instruments on overall survival in patients receiving either best supportive care, best supportive care plus low-dose decitabine (DACOGEN 6) or intensive induction chemotherapy (6). The Freiburg Version of GA has so far been applied to 130 of the anticipated 160 patients. In addition to above mentioned data, laboratory values (reflecting disease activity, nutritional status and organ function) have been documented. The median age was 71 years (range: 61-87 yrs). The primary treatment allocation was as follows: best supportive care: n=28 (median age: 74 yrs); decitabine: n=63 (73 yrs); intensive chemotherapy: n=39 (65 yrs). Major subjective impairment at treatment initiation was due to fatigue, dyspnoea and functional deficits.
3 general treatment choices for older AML patients

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Fit</th>
<th>Vulnerable</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle (Balducci)</td>
<td>A: do not under-treat &quot;go go&quot;</td>
<td>B: treat carefully &quot;slow go&quot;</td>
<td>C: do not over-treat &quot;no go&quot;</td>
</tr>
<tr>
<td>Possible Treatment</td>
<td>Induction</td>
<td>novel, nonintensive single-agent approaches: • mylotarg • low-dose azanucleosides • clofarabine • HDAC Inhibitors (Zolinza/SAHA, Dapsipeptide etc. • Lenalidomide (with 5q-)</td>
<td>Best Supportive Care</td>
</tr>
</tbody>
</table>

Deschler, Lübbert 2007

Figure 1: Possible rationales for treatment allocation

The Freiburg Geriatric Assessment: Assessment Measures

<table>
<thead>
<tr>
<th>(Geriatric) Domain</th>
<th>Measure</th>
<th>No. of Items</th>
<th>Administration</th>
<th>Time required (min)</th>
<th>Score Range</th>
<th>Cutoff Point for Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
<td>EORTC QLQ C30</td>
<td>30</td>
<td>Self-administered</td>
<td>5-10</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>- Activities of Daily Living (ADL), - Hamburger Manual / Barthel</td>
<td>6</td>
<td>Self- or interviewer assessed</td>
<td>5-10</td>
<td>0-100</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>- Instrumental Activities of Daily Living</td>
<td>7</td>
<td>‘*’</td>
<td>5-10</td>
<td>0-14</td>
<td>&lt;12</td>
</tr>
<tr>
<td></td>
<td>Performance Status</td>
<td>1</td>
<td>Assessment Team</td>
<td>1</td>
<td>0-100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Objective physical performance</td>
<td>Timed Up and Go</td>
<td>1</td>
<td>Assessment Team</td>
<td>5</td>
<td>Time (seconds)</td>
<td>&gt;8.5 sec</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Charlson Score</td>
<td>18</td>
<td>Assessment Team</td>
<td>10</td>
<td>0-54</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Cognition</td>
<td>Folstein Mini Mental State Examination</td>
<td>7</td>
<td>Assessment Team</td>
<td>5-10</td>
<td>0-30</td>
<td>&lt;24</td>
</tr>
<tr>
<td>Depression</td>
<td>Geriatric Depression Scale</td>
<td>15</td>
<td>Self-administered</td>
<td>&lt;5</td>
<td>0-15</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>

Table 1: Freiburg Version of the Geriatric Assessment

With multivariate statistical analyses, we will evaluate the possible association of the initial GA with treatment allocation, age, hematological and laboratory parameters, treatment outcome and global quality of life. At defined time points follow-up assessments are performed to ask whether treatment influences GA and QOL values.

This study is about to finish recruiting patients and is in preparation for analysis to demonstrate the most relevant geriatric parameters for overall survival and quality of life under three different treatment allocations. According to these results, expansion to more centers will test multicenter feasibility as well as the definition and possibly validation of a „Frailty Index for Elderly Patients with MDS or AML“.

Further information on the website (MDS/Research): http://www.leukemia-net.org

This work is supported by the Deutsche José Carreras Leukämie-Stiftung; Grant: DJCLS F 06/04

References:
Patient Information for ALL in Eight European Languages

J. Ribera

As one of the lead participants of the EWALL (European Working Group for Adult acute Lymphoblastic Leukemia) J. Ribera has developed an information leaflet for ALL patients and their relatives. After agreement in the EWALL group different members have translated the leaflet in 8 European languages. It provides basic information for better understanding of the disease and treatment of ALL. Furthermore, it describes coping strategies and offers links for further information. The leaflet is available for free download at the ELN Website.

New Guidelines for Preventing and Treating Infectious Diseases in Leukemic Patients

P. Ljungman

One of the main goals for WP 15 of the ELN was to produce and publish guidelines for prevention and treatment of infections in leukemia patients. To achieve this goal, a collaboration was initiated between the ELN WP15 and three international scientific organizations namely the Infectious Diseases Group of the European Organisation for Research and Treatment in Cancer (EORTC), the Infectious Diseases working Party of the European Group for Blood and Marrow Transplantation (EBMT), and the Immunocompromised Host Society (ICHS) European Guidelines on Antimicrobial Therapy in Patients with Acute Leukemia. This collaboration resulted in the First European Conference on Infections in Leukemia (ECLI-1) held in 2005 and chaired by Prof. Catherine Cordonnier, Creteil, France.

The ECLI-1 addressed six topics, three relating to bacterial infections and three relating to fungal infections:

- Fluoroquinolone prophylaxis in neutropenic patients, in the light of recently published large studies
- The place and indications of aminoglycosides in the antibacterial armamentarium for febrile neutropenic patients
- The place and indications of glycopeptides in the antibacterial armamentarium for febrile neutropenic patients
- The use of empirical antifungal therapy in neutropenic patients
- The main indications of antifungal prophylaxis in leukemia patients, including stem cell transplant recipients, and
- The management of both invasive candidiasis and aspergillosis

In developing the guidelines, six working groups reviewed data from the literature to answer specific questions on the prevention and treatment of bacterial and invasive fungal infections, which are major causes of morbidity and mortality in leukemic patients. The working groups mainly considered data from large prospective trials and meta-analyses and their conclusions were presented and debated at the ECLI-1 conference, by an expert panel of 59 infectious diseases specialists, microbiologists, clinical trial specialists or hematologists from 24 European countries, Israel and Australia. After consensus was reached, the guidelines were finalized, each proposal being scored according to the Centers for Disease Control and Prevention (CDC) grading for the level of evidence and level of recommendation before being published. Special attention was paid to developing evidence-based recommendations, identifying risk populations, and focusing on infection-related mortality, and risk-benefit ratio. The results have just been published in European Journal of Cancer (EJC supplement: European Guidelines on Antimicrobial Therapy in Patients with Acute Leukemia; 2007; 5; suppl. 2).

The success of this endeavour has resulted in a planned 2nd conference during which recommendations will also be produced regarding management of viral infections to be held in September 2007.
Workshops at the next network meeting in Heidelberg

Two workshops are currently planned in Heidelberg the day before the next network meeting. They will take place on Monday, January 28, 2008.

**Workshop on International European Trials**

N.Gökbüget, K.Ihrig

Several study groups plan or currently activate international, investigator-initiated trials (IITs) and face the same practical problems. The planned workshop aims to provide a platform to get an

- overview on regulations
- practical guidance on initiation and conduct of European IITs
- exchange of experience from ongoing European IITs

It is planned to invite external experts as well as speakers from the study groups of the ELN. All members of the network are encouraged to suggest topics and to express their interest in participation of this workshop (ihrig@med.uni-frankfurt.de).

**IT-Workshop**

U.Mansmann, M.Schmidberger

To continue the successful first ELN-IT-Workshop “IT for clinical trial support and registries” there is a second workshop planned for 2008. The aim of WP3 is to find IT-infrastructure for supporting clinical studies. To complete the “Workshop on International European Trials” the following topics are planned:

- Electronic Data Capture
- Data Security
- Microarray Analysis Pipeline

If you are interested in special topics don’t hesitate to contact us: schmidb@ibe.web.med.uni-muenchen.de

**ELN-Statistic-Workshop in Munich:**

“Advances in statistical models for risk and prognosis”

November 21 – 22, 2007

The workshop will present the state-of-the-art methodology for prognostic research. The following topics will be discussed:

- What is new, what is relevant? (Ulrich Mansmann, München)
- Relative Survival (Janez Stare, Lubljana)
- Competing risks and Multi State Models (Jan Beyersmann, Freiburg)
- What to do if the hazards are not proportional (Hans van Houwelingen, Leiden)
- Individual prognosis (Rob Henderson, Newcastle)
- Modelling continuous covariables (Willi Sauerbrei, Freiburg)

More information will be soon available at the ELN- and IBE-Website. (http://www.leukemia-net.org; http://ibe.web.med.uni-muenchen.de)
### Ongoing studies of the European LeukemiaNet (European Leukemia Trial Registry)

The European Leukemia Trial Registry (ELTR) includes active clinical trials administered by study groups of the ELN. Currently over 40 European leukemia studies are listed. Detailed study information and short-protocols are available for free download from the website (www.leukemia-net.org).

The ELTR is the first international leukemia register with expert service and an interface adapted to WHO criteria. Major goal for the next months is the integration of all clinical trials of the ELN. If you need more information, contact the European Leukemia Information Center ELIC (elic@em.uni-frankfurt.de).

**ALL: Acute lymphatic leukemia**

**AML: Acute myeloid leukemia**

**MDS: Myelodysplastic Syndrome**

**CMPD: Chronic myeloproliferative disease**

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