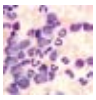
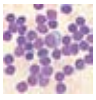
ELN European LeukemiaNet

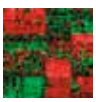
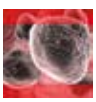


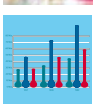






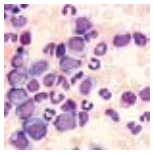

INFORMATION LETTER N°3 JANUARY 2007

Dear colleagues,

three years after the start of the network the main structures concerning management, communication and information of the European LeukemiaNet have been optimized and consolidated. Web-based information is available on the central website (www.leukemianet.eu). The website was equipped with a content-management-system (CMS). A new study registry was developed according to the guidelines of the International Committee of Medical Journal Editors (www.icmje.org) and the World-Health-Organization (WHO). This European Leukemia Trial Registry (ELTR) meets all required criteria and will be connected to the WHO Meta-Registry, as soon as the WHO has defined definitive interfaces for data-transfer. Communication is accomplished via the information center (ELIC) and the network management center (NMC) through annual symposia, regular network and WP-meetings, website, and biannual newsletters.
About 50 WP-meetings were held, several studies are ongoing on a European level and more than 300 manuscripts were published or completed in the past year. In 2006 several consensus recommendations and guidelines on diagnostics and therapy were published or submitted, e.g. management recommendations for CML, recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results, guidelines for microarray analyses, guidelines on definition of transplant-associated microangiopathy (TAM), recommendations for standardizing indications for SCT, guidelines on primary antifungal prophylaxis and empirical antifungal therapy in neutropenic leukemia and cancer patients. More guidelines are under preparation e.g. AML guidelines and guidelines for virus infections in neutropenic patients such as herpes virus infections and virus hepatitis.
Regular meetings of all network members have supported communication and cooperation of all WPs. Beside the cooperation of the WPs within the network itself collaboration with other European structures like the EBMT or ESH was enhanced.
Eight new participants were integrated bringing the number of institutions participating in the European LeukemiaNet to now 125 with approximately 950 researchers in 22 countries. Eight new institutions will be included in 2007 after approval by the General Assembly.
I wish the network and you continued success to make leukemia a curable disease everywhere and for everybody.

Prof. Dr. Rüdiger Hehlmann
Network Coordinator

Recommendations for the Treatment of CML



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When Workpackage 4 was established, the treatment of chronic myeloid leukemia (CML) was undergoing a revolution due to the rapid introduction of a protein tyrosine kinase inhibitor (TKI) (STI 571, Imatinib mesylate) and to the equally rapid development of other agents of the same family, like Dasatinib and Nilotinib. Imatinib replaced almost completely Interferon-alfa and Hydroxyurea and shifted allogeneic stem cell transplantation to second line, even before information on the long-term effect of treatment was available. These changes were so rapid and had so many important implications that the steering committee of WP4 felt that it was necessary to appoint a panel of experts with the purpose of providing the medical community with an updated and critical review of the treatment of CML and with a whole of shared recommendations for the proper use of TKI. ELN WP4 members from France, Germany, Italy, Spain, Sweden, Switzerland and the United Kingdom were convened and associated with experts from Australia and the United States of America. The panel met several times and submitted the results of its work to Blood, where the report was published in September 2006 (Baccarani M et al, Blood 2006;108:1809-1820).

For almost one decade – in the nineties – the medical treatment of Philadelphia positive (Ph pos) chronic myeloid leukemia (CML) was based on Interferon-alfa (IFNα), either alone or in combination with Hydroxyurea (HU) or low dose Arabinosyl Cytosine (LDAC). It was recognized that some patients, especially low risk patients, had a substantial benefit from this treatment, with a median survival exceeding 10 years, but because of the relatively small proportion of responders and of the persistence of minimal residual disease during remission, allogeneic stem cell transplantation (alloSCT) remained the treatment of choice for all the patients who were eligible for that procedure, with the promise of a cure at a price of a substantial mortality and morbidity.
The introduction of the first tyrosine kinase inhibitor (TKI), namely Imatinib mesylate (formerly STI 571), was revolutionary, and spread as rapidly as a revolutionary idea. The strength of Imatinib was based on its specific biologic properties – targeting bcr-abl proteins and inhibiting their kinase activity – coupled with a high therapeutic efficacy, a good compliance and a very low toxicity.

In less than 2 years it became clear that almost 50% of the patients who were treated with Imatinib in late chronic phase (LCP), after IFNα failure, achieved a complete cytogenetic response (CCgR) and that more than 50% of patients who were treated with Imatinib in accelerated phase (AP) or in blast crisis (BC) achieved an hematologic response (HR), with a significant survival benefit. Therefore, it took less than 6 months to enroll more than 1000 patients with previously untreated Ph pos CML in early chronic phase (ECP) in a pivotal phase 3 prospective study of Imatinib vs IFNα and LDAC. This was the IRIS study, that was reported in 2003 (1) and updated in 2006, with information on the durability of the response (2).

Other independent studies, both monocentric and multicentric, have confirmed and extended the results of the IRIS study and have provided supplementary information and insights on response, response duration, compliance, side effects, dosing and resistance. Since the long term results of treatment cannot yet determined, because only 6 years have lapsed from the treatment of the first ECP patients, it has become abundantly clear that treatment optimization must rely on the evaluation of the response, and the identification of surrogate markers of survival.

Today it is yet undetermined how many patients can be cured with Imatinib, and the goal of treatment is to reduce the leukemic cell mass to a level that would be hardly detectable, a so called major molecular remission or response (MMolR), and to maintain that level indefinitely. Imatinib can prolong significantly survival and can improve substantially the quality of life also if a MMolR is not achieved, but in such cases alternative treatment should or could be applied, including an increase of standard Imatinib dose from 400 up to 800 mg, allogeneic stem cell transplantation, second-generation TKI, and also other investigational agents alone or in combination with Imatinib.
With the purpose of providing a putative guideline for the management of the patients who are put in Imatinib front-line, in ECP, a panel of experts was appointed by ELN. The panel has provided shared definitions of hematologic response (HR), cytogenetic response (CgR) and molecular response (MolR) and has recommended that CgR should be assessed at least every 6 months until a complete CgR (CCgR) is obtained and confirmed, hence at least every 12 months; that MolR should be assessed every 3 months by real time quantitative PCR measurement of BCR-ABL transcripts in peripheral blood cells; and that a mutational analysis of

the BCR-ABL kinase domain should be performed in case of failure or suboptimal response. The panel has proposed working definitions of treatment results in two cathegories, failure and suboptimal response. In the clinical setting of ECP CML failure of Imatinib means that the patient is highly unlikely to achieve the goal of a MMolR. Such a patient could do well with Imatinib for a long time, but alternative treatments should be activated, if they are available and if he/she is eligible. Suboptimal response means that continuing on the standard Imatinib dose (400 mg daily) the patient can still have a substantial and as yet undefined benefit, but that standard dose Imatinib may not be the best choice, so that the patient can become eligible for alternative treatment.

With these premises, the shared definitions of failure are:

a) no hematologic response (HR) after 3 months
b) non complete HR (CHR after 6 months
c) no cytogenetic response (Ph pos > 95%) after 6 months
d) less than partial cytogenetic response (Ph pos > 35%) after 12 months
e) less than complete cytogenetic response (Ph pos α 1%) after 18 months
f) loss of CHR
g) loss of CCgR
h) appearance of BCR-ABL kinase domain mutations highly insensitive to Imatinib

and the shared definitions of suboptimal response are:

a) non CHR after 3 months
b) less than partial cytogenetic response (Ph pos > 35%) after 6 months
c) less than complete cytogenetic response (Ph pos α 1%) after 12 months
d) less than major molecular response after 18 months
e) other chromosomal abnormalities in the Ph pos clone
f) appearance of BCR-ABL kinase domain mutations with a low level of insensitivity to Imatinib.

Moreover, the panel identified a set of "warning" criteria which should alert the clinician to monitor the patients very carefully. The warning criteria include the relative risk at baseline (3) or (4), the presence of other chromosomal abnormalities at baseline, the detection of Ph neg clones with other chromosomal abnormalities, and an increase of the level of the BCR-ABL transcripts.

The concepts and the recommendations that have been put forward on behalf of ELN are not frozen. The concepts are evolving, treatment results are continuously updated, new data are expected, and new therapeutic agents are becoming available, in particular the new TKI Nilotinib and Dasatinib. It is a challenge for the scientific and medical community to adapt recommendations in real time. For that purpose it is necessary to register, treat and monitor as many patients as possible, in controlled, prospective, investigational or observational studies of the treatment of CML, so as to ensure the quality and the timing of the information. WP4 helps fulfilling this mission through a number of national and international studies, which are running in Spain, France, Italy, Germany, Scandinavian and other European countries and the establishment of an European Registry of CML.

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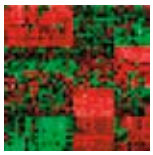
WP 10 - Diagnostics
WP 13 - Gene profiling



European LeukemiaNet (ELN) WP10 + WP13 Joint Meeting at MLL - Munich, November 17-19, 2006

M. C. Béné, Université Henri Poincare Nancy, France
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A joint meeting of ELN workpackages 10 and 13, involved in the diagnosis of leukemia, gathered 23 persons last November in Munich. The idea was to compare achievements and discuss common projects for the coming months within ELN.

A short update was presented by Marie Christine Béné (Nancy) of WP10 achievements (mandatory diagnostic panels for acute leukemias and lymphoproliferative disorders, preanalytical recommendations) and ongoing work (antibody mixtures and MRD recommendations). The importance of defining the immunophenotypic patterns that have to be expected from normal bone marrow in order to detect abnormal cells, at diagnosis, for MDS, but mostly for accurate assessment of MRD was stressed. This concept was illustrated by a presentation of the results of the GTLLF (Groupe de Travail sur les Leucémies et Lymphomes en Francophonie, issued from the French Group for Immunophenotyping of Leukemia, GEIL) who have studied 36 normal bone marrow samples with a 12 tubes panel in 4 colours. These combinations have proven useful to define normal reproducible maturation patterns. GTLLF has already presented these results in various meetings and is in the process of preparing an illustrated atlas of normal bone marrow patterns and a related publication. Some of this material will be posted on the ELN website.

A summary of partly already published results on MRD detection in AML in three colours flow cytometry was then presented by Wolfgang Kern (Munich). With three colours, a 2.11 log reduction provides significant prognostic information on day 16, but MRD detection is indeed significant at all check points. As technology progresses from 3 to 4 then 5 colours, the sensitivity and significance of the method also improves, now reaching 3.66 log difference. Comparison of flow cytometry and molecular detection of MRD yields at least 75% of similar results, in some entities PCR reaches more sensitivity than flow cytometry but in other cases flow was more sensitive to detect persisting leukemia cells and to better predict outcome. Yet more comparative studies are needed, as well as bone marrow/peripheral blood comparisons. The discussion also stressed preanalytical and trial-related issues, and allowed Anna Porwit MacDonald (Stockholm) to show examples of MRD+ patients receiving allo-HSCT doing better than MRD- not transplanted and similarly as MRD- transplanted, in AML. The issue of immunophenotype changes (different disease or markers loss at diagnosis or relapse) was also addressed.

Peter Valent (Vienna) reported the conclusions and consensus of a symposium he organized in July 2006 in Vienna on myelodysplasia diagnosis and management. This group stressed the need for minimal definition criteria, in the multiple clinical conditions observed associating cytopenia, karyotypic anomalies, + dysplasia. This conference proposed a strategy and staging of bone marrow histology examination for MDS, minimal immunophenotyping and in situ hybridization panels. A first consensus paper will be published soon in Leukemia Research. The marker tryptase was also presented, assayed in plasma, as an interesting predictor of relapse in AML.

On behalf of WP13, Martin Dugas (Münster) presented the ELN gene analysis platform, a web-based tool now available for ELN users, providing a file manager allowing to upload the files to be analyzed, as .cel and .txt files. Data analysis is achieved with the new "Gene Analysis Platform" (GAP), after describing the request to Dugas group in Münster. This can now be used as a service for members in the ELN, especially for WP13 and is an important deliverable of WP13 for 2006. Within a few hours to a few days, analyses can provide categorical results, quantitative information, survival-associated responses, and heat maps. In all approaches, an unsupervised analysis is performed first, with hierarchical clustering and principal component analysis. Then supervised analysis of differentially expressed genes and p-value adjustments are carried out. Classifications can be made with estimation of accuracy/statistical significance/confidence, as well as lists comparisons, and even pathway analyses can be provided. Foreseen evolutions include miRNA, ChIP- and SNP-arrays.

Enrico Tagliafico (Modena) then reported on a molecular signature predictive of sensitivity to differentiation induction in AML. A first study performed on cell lines was validated on fresh blast cells from patients and different platforms. This allowed to determine that 11 genes could be used to derive prediction profiles related to chemotherapy-induced differentiation.

Gene expression profiling (GEP) in CBF leukemias was the next issue, tackled by Lars Bullinger (Ulm). Unsupervised clustering identifies distinct CBF groups, notably two large groups with different outcome and not strictly superimposed on karyotypic anomalies. A similarly worse outcome of „group I" was seen in both inv 16 and t(8;21). The existence of these CBF subgroups suggests different oncogenic pathways. Among involved genes, upregulation of BCRA1, RAD51, FOS and JUN was seen in group 1, and upregulation of RICTOR, MLL5, FOXO1A and AKT1 in group 2.

MAGE signatures associated with early relapse in 15 pediatric BCP ALL were reported by Truus te Kronnie (Padua). The analysis identified 97 upregulated genes characterizing relapse, while no gene was shown to be downregulated at relapse. The genes involved included clusters associated with immune response, cell proliferation and cell death. Three CD antigens also were upregulated at relapse: CD16, CD88 (C5aR) and CD89 (FcalphaRI).

The results of the 2015 cases so far analyzed in the retrospective phase 1 of the MILE study were described by Torsten Haferlach (Munich) who also emphasized on the MDS data obtained and analyzed for WP13 by Ken Mills (Cardiff). Nearly on schedule, the 519 genes leukemia chip is ready (produced by ROCHE/ Affymetrix) and the first specimen was there for display. It will now be tested in phase 2 of the MILE study prospectively in another 2000 cases.

An update on the development of this „AmpliChip Leukemia Test" was given in detail by Alexander Kohlmann, from ROCHE. The laboratory work flow has been revised and optimized and data should be available by 12:00 pm on day 2 for a sample received before 2:00 pm on day 0. The kit will be designed to allow performing 3x8 assays.

Other events of this well-filled day and a half were a round table of WP10 on its ongoing consensus documents and two general discussions about the comments and suggestions from the reviewers of the ELN report and further cooperation between the four WP (10-13) all involved in diagnosis.

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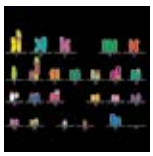

Development of real-time quantitative PCR assays to monitor response to molecularly targeted therapy with imatinib mesylate in FIP1L1-PDGFRA associated hypereosinophilic syndrome

D. Grimwade, King's College, London, UK

Idiopathic hypereosinophilic syndrome (HES) is a potentially life-threatening condition associated with end-organ damage due to release of granular contents from infiltrating eosinophils (Figure 1A). A significant breakthrough in the understanding of this group of disorders came with the discovery by Jan Cools and colleagues (New Engl J Med. 2003) of the fusion between genes encoding Fip 1-like 1 (FIP1L1) and Platelet Derived Growth Factor Receptor Alpha (PDGFRA) due to a cytogenetically cryptic interstitial deletion involving chromosome 4q12 (Figure 1C/D). Importantly, presence of the FIP1L1-PDGFRA fusion gene was shown to predict a dramatic response to imatinib mesylate, with rapid normalisation of peripheral eosinophil counts; indeed, such responses have been achieved with relatively low doses (i.e. 50mg-200mg/d) as compared to those routinely employed for treatment of BCR-ABL+ disease (400mg/d). The relative frequency of the FIP1L1-PDGFRA fusion has varied markedly in reported series, ranging between 3 and 56%. This may reflect differing levels of stringency in the diagnosis of idiopathic HES and other eosinophilia-associated haematological malignancies, but may also be compounded by difficulties in establishing a molecular diagnosis. The latter relates to the considerable heterogeneity in breakpoints within the FIP1L1 locus, variable mechanisms leading to formation of an in-frame fusion product involving use of cryptic splice sites, in addition to the marked alternative splicing between FIP1L1 exons. FIP1L1-PDGFRA transcripts can be difficult to detect by single-step reverse transcriptase polymerase chain reaction (RT-PCR) and in some instances nested PCR is required for reliable identification of the fusion (Figure 1B). This implies that the level of fusion gene expression may be relatively low in this disease and indeed fluorescent in situ hybridisation using a probe for the CHIC2 locus (Figure 1C/D), which is deleted as a result of the FIP1L1/PDGFRA rearrangement, has shown that the proportion of cells harbouring the fusion varies considerably between cases.

To investigate the frequency of this condition, molecular screening was undertaken in Prof. Nick Cross' laboratory (University of Southampton, UK) of 376 cases with persistent unexplained hypereosinophilia, revealing 40 (11%) cases with the FIP1L1-PDGFRA fusion. Given the relative rarity of this entity, the establishment of European LeukemiaNet WP12 afforded the opportunity to recruit a large number of cases from across the network. To date, breakpoint junction sequences of over 100 cases have been defined in Prof. Andreas Reiter's laboratory (University of Heidelberg, Mannheim, Germany). In order to provide a tool to enhance our understanding of the biology of this disease and its response to molecularly targeted therapy, real-time quantitative PCR (RQ-PCR) assays were developed by Jelena Jovanovic (King's College London, UK) and applied to patients treated with imatinib.

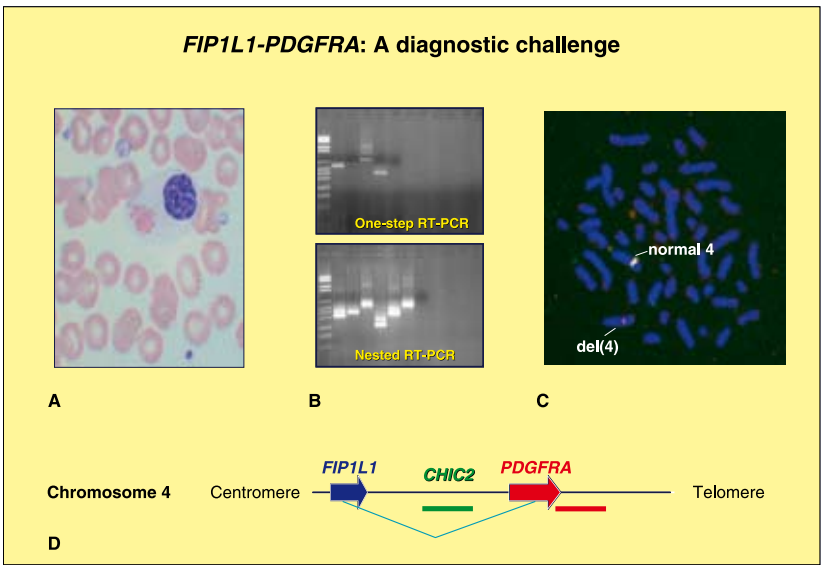

Figure 1

The FIP1L1-PDGFRA fusion presents a particularly challenging target for RQ-PCR assay design in view of the marked breakpoint heterogeneity. In the first instance an assay was designed to detect the fusion transcript in the EOL-1 cell line, which could be detected at a sensitivity of 1 in 105 in serial dilution studies. Consideration of breakpoints observed in primary patient samples, revealed that the Taqman probe and reverse primer designed for the EOL-1 breakpoint pattern, was suitable for 75% of cases. The common probe and reverse primer were used in conjunction with one of a range of forward primers according breakpoint location (see Figure 2). The level of FIP1L1-PDGFRA expression was observed to vary markedly (by up to 3-logs) between cases, which may provide an explanation for the difficulty in detecting the fusion by single-step RT-PCR in some cases (Figure 1B). The variability in level of FIP1L1-PDGFRA expression was not correlated with the percentage or absolute numbers of eosinophils and could not be accounted for by treatment with steroids or other agents at the time of sampling.

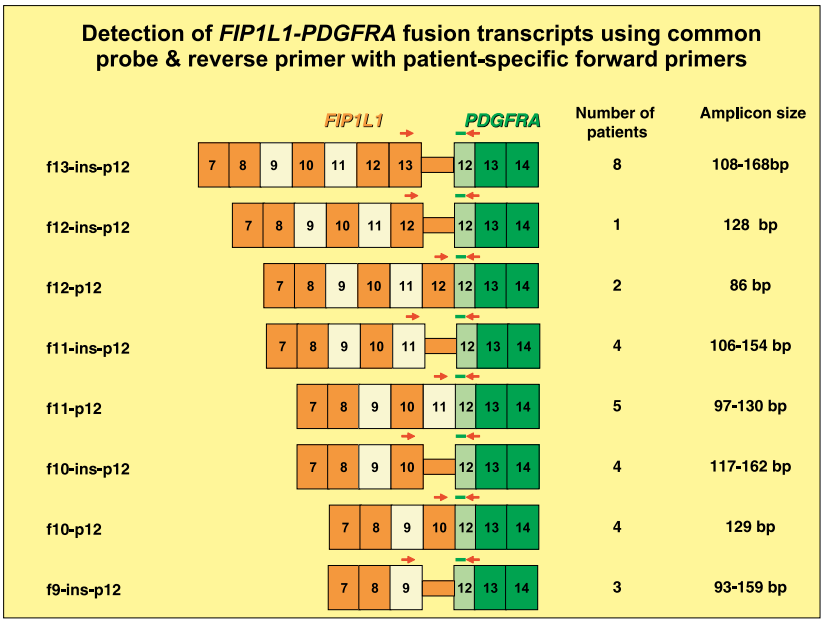

Figure 2

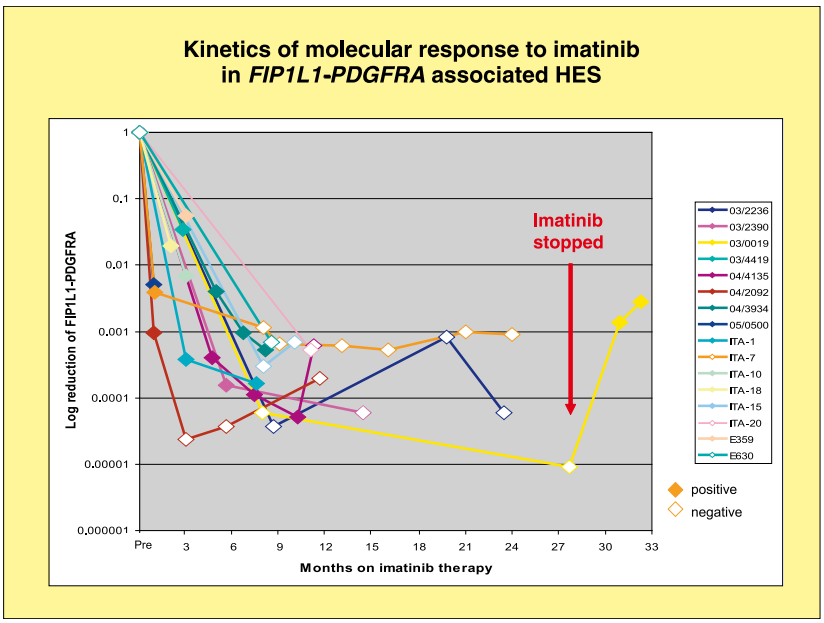

Figure 3

Serial monitoring by RQ-PCR was undertaken in patients where FIP1L1-PDGFRA expression in the pre-imatinib sample was high enough to afford assay sensitivities of at least 1 in 1000 (typically ~1 in 104). In 11 of 11 evaluable patients FIP1L1-PDGFRA fusion transcripts were observed to fall by at least 3-logs relative to the pre-treatment level within 12 months, with achievement of molecular remission in 9 of 11 cases (assay sensitivities 1 in 103-5). Molecular remissions were documented in patients receiving low dose imatinib (100-200mg/d). In two patients, withdrawal of imatinib was followed by a rapid rise in FIP1L1-PDGFRA transcript levels. In one of these patients a further molecular remission was achieved following reinstatement of imatinib, while the other ultimately died of cardiac disease that predated imatinib treatment.

This study shows that the kinetics of molecular response in FIP1L1-PDGFRA associated leukemia to even low doses of imatinib are markedly different to those observed in CML, where only around 40% of patients achieve a major molecular response (3-log reduction in BCR-ABL transcript level relative to a pre-defined baseline) by 12 months. Moreover, imatinib only rarely induces molecular remission in CML due to persistence of a quiescent leukemic stem cell pool that is relatively resistant to this agent; whereas, in the present study all FIP1L1-PDGFRA+ patients maintained on imatinib achieved molecular remission. These data are consistent with the exquisite sensitivity of the FIP1L1-PDGFRα fusion to imatinib, as compared to BCR-ABL. However, in common with CML, HES has been reported to progress in some patients due to outgrowth of subclones harbouring mutations in the fusion protein that confer imatinib resistance, but which may still be sensitive to other inhibitors. Overall, this WP12 study indicates that prolonged imatinib therapy is required to maintain molecular response in FIP1L1-PDGFRA associated HES and lends further support for RQ-PCR monitoring to guide patient management using molecularly targeted therapies.

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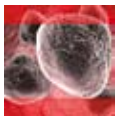
The unmet need for infrastructure in hematopoietic stem cell transplantation (HSCT)



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Data from the EBMT activity surveys indicate that transplant rates for HSCT increase in all European countries in a near linear pattern but distinct by gross national income (GNI) per capita. Such a pattern without sign of saturation is indicative for a lack of infrastructure. It is one of the goals of the WP14 to find answers and solutions for this problem.

Differences in transplant rates (numbers of transplants per 10 millions inhabitants) between European countries have long been recognised and were shown to be based primarily on lower GNI per capita in some countries. The sudden decrease of transplants for certain indications, e.g. autologous transplants for breast cancer or allogeneic transplants for chronic myeloid leukemia, in recent years have given the impression that infrastructure for hematopoietic stem cells transplants (HSCT) in Europe is abundant with the exception of the few countries with limited resources. This is not the case.

Data from the Annual Activity Surveys from 1990-2005 give additional, more precise information as illustrated in the figures. Transplant rates were analysed for each country from 1990-2005 and countries were grouped according to their GNI per capita by World Bank definitions into high, middle and low income categories. Weighted means, according to their populations, were calculated for the transplant rates in Europe. Transplant rates were summarized for all autologous indications except breast cancer and for all allogeneic indications except chronic myeloid leukemia.

As shown in the figures, transplant rates did increase with a near linear pattern distinct but similar in all World Bank categories and with a very narrow margin of variation and R2 between 0.95-0.99. There is no hint for saturation what so ever. These data are novel and surprising. They warrant an explantation. They could indicate that transplants are limited only by resources of the participating institutions. Teams apparently strive to be able to do a few more transplants every year but no saturation is insight. More patients would be transplanted, if resources could permit.

These data illustrate the value of an instrument such as the EBMT activity survey within the Leukemia NET. The data will be analysed in more details for further insight into the mechanisms behind these patterns. Such information should provide tools for a better organisation of transplant infrastructure in Europe and to serve the needs of the patients affected with hematological malignancies requiring an HSCT.

Legend to the figures

Weighted means (weighted by population size of participating countries) of transplant rates for allogeneic HSCT (without CML) (left) and for autologous HSCT (without breast cancer) (right) in European countries according to World Bank category and Gross National income (high (blue), middle (green), low (red)) from 1990 to 2005.

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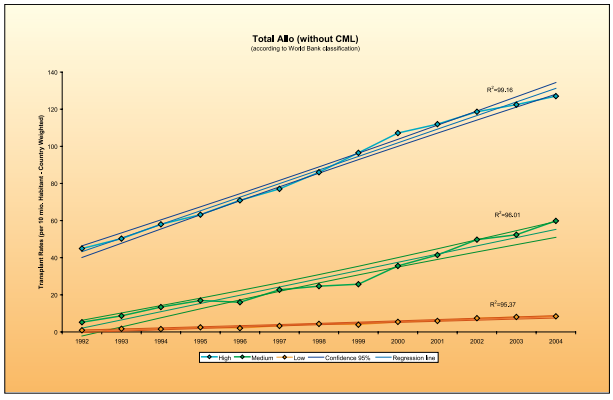
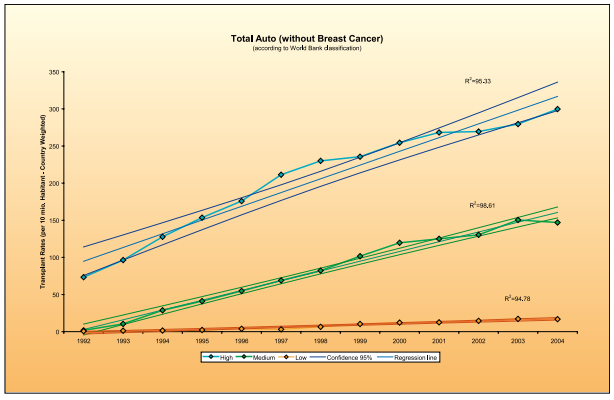
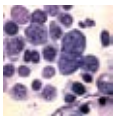
Leukemia (in press) 2006.



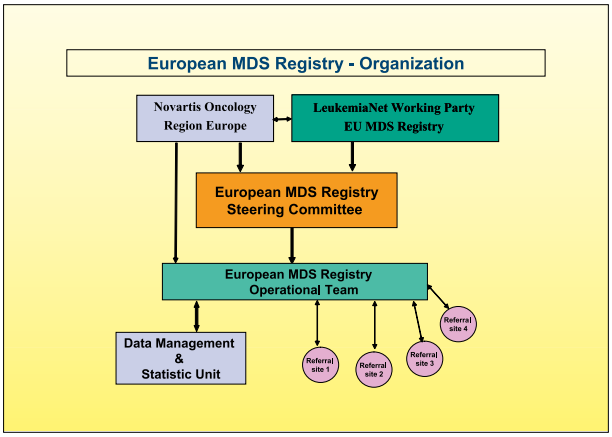


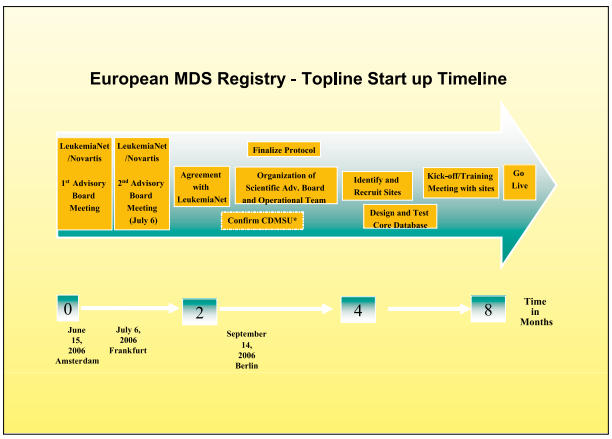
MDS-Registry



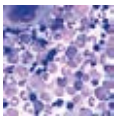
O. Huber, University Medical Centre
St Radboud, Nijmegen, The Netherlands

The current MDS-register is designed to collect information about a large cohort of newly diagnosed MDS patients with low-risk disease defined as IPSS low or intermediate-1 categories. In a number of countries, MDS Registration projects are ongoing. These registries aim at improving the knowledge of the local incidence and management of these patients. In this project, data will be collected using registries in several European countries as the platform for registration. This will create an international registry to study the demographics, clinical characteristics, disease-management and relevant outcomes of patients with MDS. After a lead time of about 8 months, the project is almost ready to start. To this moment, ten hematology centres in ten different countries (Austria, Czech Republic, France, Germany, Italy, Netherlands, Rumania, Spain, Sweden and United Kingdom) will participate in this Registry. The recruitment target is a minimum of 1000 and a maximum of 2000 cases during an enrollment time of 18 to 24 months. Data on patients with low or intermediate-1 risk MDS will be collected prospectively at diagnosis and at 6-months intervals after diagnosis and patients will be followed for 5 years. Data analyses will be conducted by one central statistical unit after every 400 patients included in the European Registry and at the end of the follow-up period.





Consensus definition of resistance to Hydroxyurea in Essential Thrombocythemia



Guido Finazzi, on behalf of the "ad hoc" Working Group (1)
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The European Agency for the Evaluation of Medicinal Products (EMEA) has recently approved Anagrelide as a second-line drug for the treatment of "at risk ET patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy" (2). "Current therapy" in most of patients with ET and a high-risk of thrombosis is Hydroxyurea (HU), according to evidence-based guidelines (3) and recommendations from experts in the field (4),(5). However, there is neither widely accepted definition of resistance nor of intolerance to HU, making clinicians uncertain regarding the correct indication to start a second-line therapy, such as Anagrelide.

To tackle this problem, the Chronic Myeloproliferative Disorders Working Party (WP9) of the ELN established an "ad hoc" international working group (WG), chaired by drs. Tiziano Barbui and Giovanni Barosi, with the intention to produce, by a consensus process, a proposal for a definition of resistance/intolerance to HU in high-risk ET patients. The consensus was reached through a multistep decision-making technique. The steps consisted of selecting the candidate criteria for defining resistance/intolerance; identifying the motivations that could influence the preference of the WG for any individual criterion; comparing the candidate criteria in a pairwise manner, grading them according to their ability to fulfill the motivations. Every step in the model was derived by questionnaires or group discussion. At the end of the process, the WG was able to propose a unified definition of clinical resistance/intolerance to HU in ET that is reported in the table.

The results of this work are important to decide when to switch ET patients from therapy with HU to that with other molecules. This consensus definition will guide clinicians in the use of drugs such as anagrelide that are licensed by the EMEA only after resistance or intolerance to first-line therapy has been documented. Moreover, these results may be adopted in protocols of clinical trials in ET as stopping rule of the first-line therapy with HU or inclusion criteria of second-line therapy after HU.

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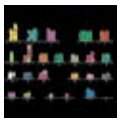
Definition of resistance/intolerance to Hydroxyurea in patients with high-risk Essential Thrombocythemia according to an International Consensus.[1]

1) Platelet count higher than 600,000/µl after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight > 80 kg), or
2) Platelet count higher than 400,000/µl and WBC less than 2,500/ul at any dose of HU, or
3) Platelet count higher than 400,000/µl and Hb less than 10 g/dL at any dose of HU, or
4) presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU, or
5) HU-related fever.

t(16;21) (AML1-MTG16) with karyotype evolution identified in a de novo AML M1 patient



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The rare chromosomal translocation t(16;21)(q24;q22) has been observed mainly in therapy-related myeloid malignancies (1). It has been shown recently that a resulting transcriptional co-repressor AML1-MTG16 plays a role in myeloid maturation, and is capable of specifically recruiting histone deacetylases (HDACs), thus repressing the expression of the AML1 target genes (2), (3).

We reported recently a 76 years old patient with de novo acute myeloid leukemia (FAB subtype M1) with eosinophilia who already at first diagnosis in July 2005 showed the translocation t(16;21)(q24;q22) (karyotype was as follows: 46XY,t(16;21)(q24;q22),46XY (3)) (4). Four months after the last consolidation therapy cycle, the patient had an early relapse with 82% blast cells in the bone marrow aspirate. Cytogenetic investigation at relapse revealed a karyotype evolution with an isochromosome of the long arm of chromosome 8: 46XY,i(8)(q10),t(16;21)(q24;q22) (3).

The presence of an AML1-MTG16 fusion gene was confirmed by FISH analysis (clones used: RP11_830f9 (MTG16 gene) and RP11_299d9 (AML1 gene)), as well as by RT PCR using primers AML1ex5f and MTG16r2 (1) that confirmed the presence of a 545bp long AML1-MTG16 fusion PCR product. Sequencing analysis of this fragment showed the in frame fusion of exon 5 of AML1 with exon 4 of MTG16 genes (4).

As summarized by La Starza et al. the t(16;21) translocation is specifically observed in therapy-related MDS or AML with a median latency of 3 years between drug exposure and appearance of the secondary disease (5). To our knowledge this is the first patient with a primary (de novo) AML showing a t(16;21). Our results show that the breakpoint between exons 3 and 4 of MTG16, believed to be characteristic of secondary leukemias (1), (5), (6), can be present also in primary leukemia cases in that no known mutagenic exposure could be identified.

Interestingly, in secondary leukemias with t(16;21) additional chromosome abnormalities, especially trisomy 8, have also been described (in 5 of 9 cases reported by La Starza et al) (5). In our case, the karyotype evolution led also to trisomy 8q, which indicates a similar disease process in both primary and secondary leukemias.

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Development of a European Leukemia Trial Register according to WHO guidelines

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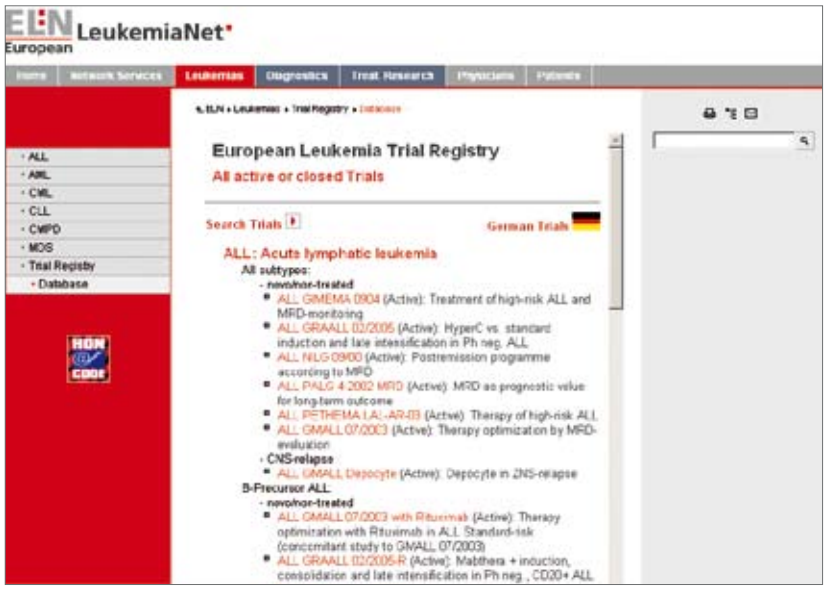
In September 2004 the Committee of Medical Journal Editors (ICMJE) in co-operation with the World Health Organization (WHO), postulated the registration of clinical studies in public Registers as precondition for publication of study results. So far, www.clinicaltrials.gov was mentioned as only appropriate Register. It was projected, to import a minimal-data-set of 20 study information-items, from existing national or disease specific registers into a meta-register of the WHO / International Clinical Trial Registry Platform (ICTRP).



Overview of ELTR

A German Leukemia Trial Register was created as a national register in 1999 by the German Leukemia Information Center, which is a central project of the German "Kompetenznetz Leukämie".

In 2005, the German register was completely overworked according to the WHO criteria and an additional European Leukemia Trial Register (ELTR) was established. The ELTR provides short-protocols of ongoing studies for free download and gives detailed information about European leukemia study groups, laboratories and participating hospitals.

The Register is publicly available, searchable and applied as "member-Register" by the WHO.

It is - to our knowledge - the first European leukemia register, which meets the WHO criteria.

For structure and maintenance, detailed procedures for quality assurance are defined. Since the Register is created and maintained by an acknowledged expert group, completeness and quality are assured. Furthermore the register provides direct advantages for physicians, patients and study groups.
Currently about 40 European leukemia studies are listed in the register as presented in the overview of ongoing clinical studies of the ELN in this Information Letter (see page 12).

All European study groups but also coordinators of individual trials are encouraged, to join the register and to provide their studies. The procedure is easy by just completing the form for short protocols which can be downloaded on the website and send by e-mail to the ELIC.
For further information, contact the European Leukemia Information Center ELIC:
elic@leukemia-net.org

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Links:

European Leukemia Trial Register
http://www.leukemia-net.org/content/e35/index_eng.html
>direct link from startpage

German Leukemia Trial Register
http://www.kompetenznetz-leukaemie.de/
> Ärzte > Therapiestudien

International Clinical Trial Register Platform of the WHO (ICTRP)
http://www.who.int/ictrp/en/

International Committee of Medical Journal Editors (ICMJE)
http://www.icmje.org/

Dates/Meetings

1st Dutch Hematology Congress
We 2007/01/31 - Fr 2007/02/02
Chair: P. Huijgens, E. Vellinga
Arnhem, The Netherlands
Link: www.hovon.nl

EHA Scientific Workshop on the role of Epigenetics in Hematological Malignancies
Fr 2007/02/09 - Su 2007/02/11
Chairs: M. Esteller, J. Issa, M. Lübbert
Mandelieu (Cannes), France
Link: http://www.ehaweb.org/eha-web/content/view/full/781/month/2/year/2007

4th ESH - EHA Annual Diagnostic Work-Up for Hematological Malignancies
Fr 2007/03/02 - Su 2007/03/04
Chairs: G. Zini, B. Bain, R. Foà
Rome, Italy
Link: http://www.ehaweb.org/eha-web/content/view/full/781/month/3/year/2007

33rd Annual Meeting of the European Group for Blood and Marrow Transplantation
23rd EBMT Nurses Group meeting and the 6th EBMT Data Management Group meeting
Su 2007/03/25 - We 2007/03/28
Abstract Deadline: 2006/11/23
Cité Centre de Congrès Lyon, France
Link: http://www.akm.ch/ebmt2007/

12th Congress of the European Hematology Association
Th 2007/06/07 - Su 2007/06/10
Vienna, Austria
Abstract Deadline: 2007/03/01
Link: http://www.ehaweb.org/congress/

ESH International Conference on CML in association with the ELN
Fr 2007/09/28 - Su 2007/09/30
Chairs: John Goldman and Angelo Carella
Sofitel Royal Casino, Mandelieu (near Cannes), France
Link: www.esh.org

16th International CML Workshop, 20th anniversary of the German CML Study Group
Fr 2007/06/29 - Sa 2007/06/30
Mannheim, Germany

WP 2 - ELIC

Ongoing studies of the European LeukemiaNet (European Leukemia Trial Registry)

The European Leukemia Trial Register (ELTR) includes active clinical trials administered by study groups of the ELN. Currently about 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, please contact the European Leukemia Information Center, ELIC (Elic@em.uni-frankfurt.de).

ALL: Acute lymphatic leukemia

All subtypes:
De novo/non-treated
- ALL GIMEMA 0904: Treatment of high-risk ALL and MRD-monitoring
- ALL GRAALL 02/2005: HyperC vs. standard induction and late intensification in Ph neg. ALL
- ALL NILG 09/00: Postremission programme according to MRD
- ALL PALG 4-2002 MRD: MRD as prognostic value for long-term outcome
- ALL PETHEMA LAL-AR-03: Therapy of high-risk ALL
- ALL GMALL 07/2003: Therapy optimization by MRD-evaluation

CNS-relapse
- ALL GMALL Depocyte: Depocyte in ZNS-relapse

B-Precursor ALL:
novo/non-treated
- ALL GMALL 07/2003 with Rituximab: Therapy optimization with Rituximab in ALL Standard-risk (concomitant study to GMALL 07/2003)
- ALL GRAALL 02/2005-R: Mabthera + induction, consolidation and late intensification in Ph neg., CD20+ ALL

relapsed/refractory
- ALL GMALL Forodesin in B-Precursor ALL (on hold): Forodesine in B-cell ALL

PH+ALL/BCR-ABL:
De novo/non-treated
- ALL GIMEMA 0201: Imatinib in Ph+ and/or BCR/ABL ALL
- ALL GMALL-Imatinib/MRD-01/01: Imatinib + chemotherapy in de novo Ph+ALL or MRD after SCT
- ALL GRAAPH 02/2005: Imatinib-based vs. standard imatinib containing Hyper CVAD induction in de novo Ph+ ALL
- ALL NILG 09/00/Ph+: Intermittent Imatinib programme in Ph+ ALL and CML blast crisis

all stages / not specified
- ALL PALG Imatinib in Ph+ ALL: Imatinib as maintenance treatment after consolidation +/- auto SCT in Ph+ ALL

T-ALL / T-LBL:
relapsed/refractory
- ALL Forodesine in T-ALL: Forodesine in relapsed/refractory T-ALL

AML: Acute myeloic leukemia

AML all subtypes without FAB M3:
De novo/non-treated
- AML Sorafenib (Elderly): Efficacy of Sorafenib added to standard primary therapy in elderly patients with newly diagnosed acute myeloid Leukemia

all stages / not specified
- AML HOVON SAKK 42: Randomized induction + post induction in AML/RAEB/RAEB-T
- AML HOVON SAKK 43 (Elderly): Randomized induction + post induction in elderly patients with AML/RAEB/RAEB-T
- SZT Allo SCT with red. conditioning

CLL: Chronic lymphatic leukemia

To this moment no studies are included in the register.

CML: Chronic myeloic leukemia

Lymphatic blast crisis:
De novo/non-treated
- ALL NILG 09/00/Ph+ : Intermittent Imatinib programme in Ph+ ALL and CML blast crisis

CMPD: Chronic myeloproliferative disease

To this moment no studies are included in the register.

MDS: Myelodysplastic Syndrome

All subtypes:
relapsed/refractory
- MDS VION CLI-033: VNP4010M in AML or high-risk MDS

all stages / not specified
- AML HOVON SAKK 42A: Randomized induction (G-CSF) in patients with AML or RAEB, RAEB-t with IPSS score >=1.5
- AML HOVON SAKK 43 (Elderly): Randomized induction + post induction in elderly AML/RAEB/RAEB-T
- MDS 5-Azacitidine : Subcutaneous Azacitidine + best supportive care vs. conventional regimens + best supportive care
- MDS Aranesp®: Treatment of anemia with Aranesp in MDS
- MDS Darbepoetin-Filgrastim : Darbepoetin alpha and G-CSF vs. best supportive care
- MDS Deferasirox: Deferasirox (ICL670) in transfusion dependent iron overload
- MDS EORTC06011 (Elderly): Low-dose decitabine vs. best supportive care in elderly patients
- MDS GFM-EPO-ATRA-2004: Treatment of anemia in MDS by the association of Epoetin Beta and all trans retinoic acid
- MDS HOVON 60 SAKK 33/90: a randomized trial comparing antithymocyte globulin (ATG) and cyclosporine (CSA) with best supportive care
- MDS NMDSG02B: Maintenance treatment with Azacytidine in MDS patients in CR
- MDS NMDSG03A: Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS RICMAC/MDSsAML : Dose reduced vs. standard conditioning + SCT in MDS or sAML
- MDS Revlimid: Revlimid monotherapy in MDS 5q-

SCT: Stem cell transplantation

Stem cell transplantation:
all stages / not specified
- SZT Allo SCT with red. conditioning

Supportive: Supportive care

To this moment no studies are included in the register.

IMPRESSUM

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