The only way to cure leukemia is by cooperative research. To optimize research, the European LeukemiaNet integrates 105 national leukemia trial groups and networks, 105 interdisciplinary partner groups and about 1,000 leukemia specialists from 175 institutions. They care for tens of thousands of leukemia patients in 33 countries across Europe. Their ultimate goal is to cure leukemia. Since its inception in 2002, the European LeukemiaNet has steadily expanded and has unified leukemia research across Europe. The European LeukemiaNet grew from two major roots: 1) the German Competence Network on Acute and Chronic Leukemias; and 2) the collaboration of European Investigators on Chronic Myeloid Leukemia. The European LeukemiaNet has improved leukemia research and management across Europe. Its concept has led to funding by the European Commission as a network of excellence. Other sources (European Science Foundation; European LeukemiaNet-Foundation) will take over when the support of the European Commission ends.

Key words: Cooperative leukemia research, European LeukemiaNet, transnational and interdisciplinary cooperation on leukemia, cure of leukemia, leukemia management guidelines.


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Introduction

Before the creation of the European LeukemiaNet (ELN), there were a number of pre-existing networks in Europe that were each individually developing diagnostic methodology, running clinical trials and producing management guidelines. The main goal of the ELN was to create an environment in which these organizations could work more closely together, to harmonize their efforts and bring their advances to a wider community in a more timely fashion.

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The first step was to bring together national leukemia trial groups in an attempt to provide common definitions and standards, to share information on ongoing and planned trials, to work together to avoid duplicating activities, and to share the benefits of infrastructure. In a second step, the interdisciplinary cooperation partners common to all leukemia trial groups were included (Figure 1). The structure of the ELN is shown in Figure 2.

**Achievements**

The ELN is a model of transnational cooperation. Working together successfully has created a spirit of cooperation and mutual trust.

The most visible results are: 1) those due to the cooperative research projects and trials (Table 1) as reflected by a large number of high impact publications; 2) the guidelines and management recommendations for virtually every leukemia and interdisciplinary speciality (Table 2) which have lain the groundwork for uniform definitions and standards required for common clinical trials and projects; and 3) the website of ELN’s leukemia information center for physicians, patients, their carers and the general public (www.leukemia-net.org, www.leukemianet.eu).

- The CML working-group (Work-Package WP 4) originated from the European Investigators on Chronic Myeloid Leukemia (EI-CML) which itself met for the first time in 1992. EI-CML has an impressive heritage of accomplishments including meta-analyses, long-term observation of cytogenetic responders, and the development of a new prognostic CML-score (Euro-score). WP4 coordinates clinical trials between participating countries and facilitates pan-European trials whenever feasible, e.g. discontinuation of imatinib in stable complete molecular responders. International management recommendations were first published in 2006 and updated in 2009 (Table 2). WP4 was the first group to initiate a public-private partnership with industry (Novartis) known as the European Treatment and Outcome Study [EUTOS] for CML: to build a European CML registry together with the Registry working-group (WP17) (currently close to 5,000 patients registered and followed for outcome annually), to standardize molecular and pharmacological monitoring across Europe (58 laboratories in 29 countries standardized for BCR-ABL monitoring) and to spread the information to non-participating colleagues and countries by annual educational symposia (five events since 2006), training events for young hematologists, and lectures.

- The AML working-group (WP5) evolved from 16 European AML study-groups: MRC, GOELAMS, ALFA, Polish AML-group, Russian AML-group, GIMEMA, EORTC, HOVON, SAKK, Swedish AML-group, CET-LAM, PETHEMA and four German AML study groups cooperating in the German AML Intergroup to study cross trial comparability with upfront randomization into a common standard arm. The AML working-group currently uses three approaches to improve the prognosis of AML: 1) harmonization of criteria for the alignment of protocols with stratification according to molecular and cytogenetic risk markers, thus creating a platform for meta-analyses; 2) establishment of a European network on AML-management including geriatric assessment of elderly AML which represents a poor risk population and the largest proportion of AML patients; 3) consensus approach for risk adapted integration of transplantation in AML balancing risk of disease versus risk of transplantation, including a newly defined frailty index. A European network on management of de novo and relapsed acute promyelocytic leukemia (APL) has been established.
Management recommendations have been completed for AML\textsuperscript{a} and APL\textsuperscript{a} (Table 2).

- The ALL working-group (WP6) brings together pediatric and adult hematologists and has successfully used the advent of advanced technologies for monitoring residual disease to optimize the outcome of ALL. The rarity of ALL has accelerated the formation of a European Working Party for ALL (EWALL) and the performance of common trials in several European countries. New drugs are under study (nelarabine, clofarabine, herceptin, anti-CD22, dasatinib, depocyte and forodesine), and a chemotherapy backbone for elderly ALL was activated by three groups (GMAIL, GRAALL and PETHEMA). The latter have activated the first joint European trial with dasatinib for older patients with Ph+ ALL. Supportive care and infection prophylaxis were optimized on a European basis. EWALL has recently been recognized as a scientific working-group within the European Hematology Association (EHA), thereby achieving synergy between the ELN and the EHA.

- The CLL working-group (WP7) has formally cooperat-
ed since the foundation of the European Research Initiative for CLL (ERIC) in 2001. ERIC is an incorporated legal entity (ERIC e.V.) in Germany, and in 2009 ERIC was recognized as a scientific working-group within EHA. The development of new potentially curative treatment modalities for CLL is one of the long-term goals of WP7/ERIC. Several protocol exchanges addressing immunochemotherapy have been made between European CLL-groups (German and French groups). Rare subentities are addressed by combined European CLL-groups (German and French groups). Rare immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab for T-prolymphocytic leukemia (T-PLL) (lead group Austria), with fludarabine, cyclophosphamide and rituximab for B-PLL (lead group in Erfurt, Germany) and recommendations for stem cell transplantation in T-PLL (lead group in Heidelberg and Cologne, Germany). The harmonization of clinical protocols between national CLL study-groups is ongoing. Several guidelines on diagnostic procedures and therapy in CLL have been published11-13 (Table 2).

- The MDS working-group (WP8) is the second WP to start a European registry (EUMDS) with a private partner (Novartis). About 650 low and intermediate risk-1 patients have so far been registered. Extensive data on transfusions and associated iron load are being collected. An extension to high-risk patients is in progress. WP8 conducts European trials on all MDS-subtypes with various agents (lenalidomide, bortezomib, demethylating agents [azacytidine, decitabine], cytarabine and growth factors: erythropoietin, GCSF, AMG 531) and explores the impact of iron chelation (deferasirox) on the prognosis of MDS. Recommendations for diagnosis and treatment of MDS

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<thead>
<tr>
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<th>Reference</th>
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<tbody>
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are published on the ELN-website (Table 2). Also the MDS working-group was recently recognized as a scientific working-group within the EHA.

- The CMPD working-group (WP9) in cooperation with groups in North America has explored the impact of JAK2 mutations on the diagnosis and therapy of myeloproliferative neoplasms (MPN). Harmonization of assay methods for JAK2-V617F has been undertaken in close collaboration with WP12. Several consensus protocols were published on response criteria in essential thrombocythemia (ET) and polycythemia vera (PV),\(^{19,20}\) and on the use of hydroxyurea in PV and myelofibrosis\(^{17}\) (Table 2). A new risk factor (leukocytoysis) relevant for the management of thrombosis in MPN has been identified. Management recommendations for PV, ET and myelofibrosis have been completed.\(^{15}\) European trials are being developed to test proteasome- and JAK2-inhibitors and other drugs (e.g. pomalidomide) in myelofibrosis.

- A good example of the potential of networking is provided by the diagnostic working-groups (WP10-13) with the Microarray Innovations in Leukemia (MILE) study. The MILE-study, which was coordinated by WP13, involved 11 laboratories (7 from ELN, 3 from the US, one from Singapore) and integrated data from morphology, cytogenetics, molecular genetics, immunophenotyping and gene expression profiling from 3,334 patients to reveal new patient subgroups with specific prognosis and survival.\(^{17,37}\) The MILE-study analyzes patients with all types of leukemia in cooperation with WP4-9. Recommendations for gene expression profiling and microarray analyses have been published (Table 2).

- The morphology working-group (WP10) has developed recommendations for immunophenotyping, an atlas of flow-cytometry of normal bone marrow and a consensus morphology collection of hematopoietic cells posted on the ELN-website (Table 2). WP10 has closely collaborated with the clinical groups regarding the development of flow-cytometry for the diagnosis and monitoring of minimal residual disease,\(^{16}\) particularly in MDS.\(^{14}\)

- A major challenge for the cytogenetics working-group (WP 11) has been the harmonization of techniques and the identification of cryptic and complex chromosome aberrations. Consensus protocols for the diagnostic workup of all types of leukemia and related syndromes, and a proposal for standardization of cytogenetic analyses have been developed\(^{20}\) (Table 2). In order to identify minimal chromosomal imbalances not detectable by classical chromosome banding or FISH analysis, comparative genomic hybridization using arrays (aCGH) has been performed, and loss of heterozygosity, a phenomenon often found in leukemias, is studied by single nucleotide polymorphism (SNP) arrays.

- The monitoring of minimal residual disease (MRD) by WP12 has gained great importance by the advent of well defined molecular markers with prognostic relevance in virtually all leukemias. WP12 has developed novel assays to increase the proportion of patients with myeloid/myeloproliferative disorders who might benefit from MRD monitoring such as RQ-PCR assays for \textit{FIP1L1-PDGFR\textalpha}\(^{21,22}\) in chronic eosinophilic leukemia and assays to detect overexpression of the Wilms’ Tumor gene (\textit{WT1}) in AML.\(^{23}\) (Table 2). This has been complemented by standardization of established assays (e.g. RQ-PCR for \textit{BCR-ABL}\(^{16}\) and JAK2-V617F, in collaboration with WP4 and WP9, respectively) and the development of an individual computer software-package to standardize the interpretation of MRD-data. Using the optimized ELN-WT1 assay, WP12 has shown that the kinetics of disease response provide an independent prognostic factor in AML, and WP12 has highlighted, through studies involving RQ-PCR detection of \textit{BCR-ABL}, \textit{FIP1L1-PDGFR\textalpha}\(^{21,22}\) and \textit{PML-RARA} transcripts,\(^{5,6,9,10,21,22}\) how sequential MRD monitoring can be used to track response to molecularly targeted therapies in a more individualized approach.

- The stem cell transplantation working-group (WP14) makes use of their productive collaboration with the European Group for Blood and Marrow Transplantation (EBMT). The main activities include regular surveys on transplantation activity in Europe, recommendations for the use of stem cell transplantation (Table 2), assessment of key factors responsible for outcome\(^{46}\) and, as a current focus, the adaptation of transplantation conditions to the needs of elderly patients, mainly with AML and ALL. In CML, an improvement in transplantation outcome has been achieved with low transplantation mortality (<10%) and 3-year survival rates of approximately 90% in chronic phase and more than 50% in advanced phase patients.\(^{46}\) These favorable developments are mediated by improvements in patient and donor selection, transplantation procedures and supportive care.

- The Working-group on management of infectious complications, infection prophylaxis and supportive care (WP15) has addressed the management of neutropenic patients after stem cell transplantation or intensive chemotherapy. Recommendations on the diagnosis and management of bacterial, viral and fungal infections have been published (Table 2). Guidelines for the management of hepatic, respiratory and adenovirus infections are in preparation as well as protocols to assess the genetic risks for fungal infections and to monitor transfusion policy in Europe.

**Perspectives**

It is not easy to measure the individual contribution of the ELN towards the general advancement of research and improvement of prognosis in the field of leukemia. However, we can point to the number of common clinical trials, projects and publications, and the steadily increasing numbers of ELN participants to demonstrate its success. Various ELN-studies have been completed\(^{41,42}\) and ELN-criteria are widely used.\(^ {46,45}\) A number of activities point to sustainability and further development of the ELN.

- Common observational and interventional studies on a European level continue in realization of the need for cooperation on rare diseases such as the leukemias.

- Leukemia-registries will expand, answer questions, and promote progress of leukemia research. Multiple public-private partnerships are envisaged.

- New projects and trials will be defined by working-groups and delivered with support by the ELN-Foundation, the European Science Foundation and other sources.

- In view of current legislation which threatens treatment optimization studies, the ELN-Foundation might serve as ‘Sponsor’. The ELN supports every effort to achieve a modification of the European drug legislation for treatment optimization studies.

- Due to its structured and long-term cooperation, the
ELN is likely to have a durable impact on leukemia research in Europe. Infrastructure and the productive collaboration provided by the ELN have provided a valuable contribution to progress in the field of leukemia.

- By promoting cooperation over the competition that is necessary for good research, the ELN provides a competitive advantage for all participants to the benefit of every patient with leukemia worldwide.

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