The European LeukemiaNet: achievements and perspectives

Rüdiger Hehlmann,[1] David Grimwade,[2] Bengt Simonsson,[3] Jane Apperley,[4] Michele Baccarani,[5] Tiziano Barbui,[6] Giovanni Barosi,[7] Renato Bassan,[6] Marie C. Béné,[8] Ute Berger,[1] Thomas Büchner,[9] Alan Burnett,[10] Nicolas C.P. Cross,[11] Theo J.M. de Witte,[12] Hartmut Döhner,[13] Hervé Dombret,[14] Hermann Einsele,[15] Georg Engelich,[1] Robin Foà,[16] Christa Fonatsch,[17] Nicola Gökbuget,[18] Elaine Gluckman,[14] Alois Gratwohl,[19] Francois Guilhot,[20] Claudia Haferlach,[21] Thorsten Haferlach,[21] Michael Hallek,[22] Jörg Hasford,[23] Andreas Hochhaus,[24] Dieter Hoelzer,[18] Jean-Jaques Kiladjian,[14] Boris Labar,[25] Per Ljungman,[26] Ulrich Mansmann,[23] Dietger Niederwieser,[27] Gert Ossenkoppele,[28] José M. Ribera,[29] Harald Rieder,[30] Hubert Serve,[18] Petra Schrotz-King,[1] Miguel A. Sanz,[31] and Susanne Saußele[1] for the European LeukemiaNet

[1]III. Medizinische Klinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany; [2]Department of Medical & Molecular Genetics, King's College London, School of Medicine, Guy's Hospital, London, United Kingdom; [3]Dept. Hematology, University Hospital, Uppsala, Sweden; [4]Department of Haematology, Imperial College, London, United Kingdom; [5]Department of Hematology/Oncology "L. and A. Seràgnoli" S.Orsola Malpighi Hospital, University of Bologna, Bologna, Italy; [6]Dipartimento di Ematologia, Ospedali Riuniti di Bergamo, Bergamo, Italy; [7]Epidemiologia Clinica, Fondazione IRCCS Policlinico San Matteo, Pavia; Italy [8]Immunologie, CHU & Nancy Université, Vandoeuvre-lès-Nancy, France; [9]Department of Internal Medicine A, University of Münster; Germany [10]Department of Haematology, School of Medicine, Cardiff University, Cardiff; United Kingdom [11]Wessex Regional Genetics Laboratory, Salisbury, and Human Genetics Division, University of Southampton School of Medicine, Southampton, United Kingdom; [12]Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands; [13]Department of Internal Medicine III, University of Ulm, Germany; [14]Hôpital Saint-Louis, AP-HP, University Paris 7, Paris, France; [15]Universitätsklinik Würzburg, Würzburg, Germany, [16]Division of Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University of Rome; Italy [17]Department of Medical Genetics, Medical University of Vienna, Vienna, Austria; [18]University Frankfurt am Main, Department of Hematology and Oncology, Frankfurt/Main, Germany; [19]Hematology, Department of Medicine, University Hospital, University of Basel, Switzerland; [20]CIC 802 INSERM, CHU de Poitiers, Poitiers, France; [21]MLL Munich Leukemia Laboratory, Munich, Germany; [22]Department of Hematology and Oncology, University of Cologne, Germany; [23]Department of Medical Informatics, Biometrics, and Epidemiology; University of Munich, Germany; [24]Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany; [25]Department of Internal Medicine, Clinical Hospital "Rebro", Zagreb, Croatia; [26]Karolinska Institute University Hospital, Stockholm, Sweden; [27]Hematology & Oncology, University Hospital Leipzig, Germany; [28]Vrije Universiteit Medical Centre, Amsterdam, Netherlands; [29]Servei d'Hematologia Clínica, Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [30]Heinrich-Heine-Universität, Institut für Humangenetik und Anthropologie, Düsseldorf, Germany; [31]Hospital Universitario La Fe, Valencia, Spain

ABSTRACT

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.[1] 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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Correspondence: Rüdiger Hehlmann, Medizinische Fakultät Mannheim der Universität Heidelberg, Pettenkoferstr. 22, 68169 Mannheim, Germany. Phone: +49.621.3836931.Fax: +49.621.3836932. E-mail: r.hehlmann@urz.uni-heidelberg.de

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[2-3] and updated in 2009[4] (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, CETLAM, 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;[36] 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.

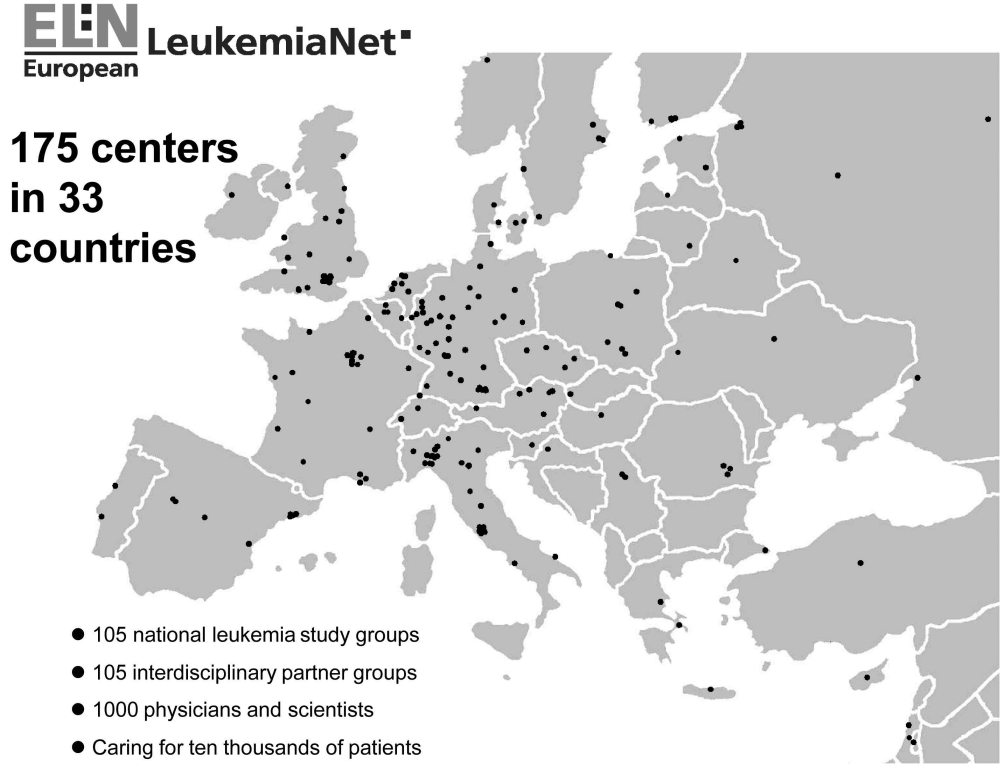

Figure 1. Participants of the European LeukemiaNet according to their location. According to the rules of the European Commission, only institutions can be participants. One participating institution may comprise more than one leukemia trial or interdisciplinary partner group. Participating institutions are listed in the *Online Supplementary Appendix*.

Management recommendations have been completed for AML[8] and APL[9] (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 (GMALL, 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-

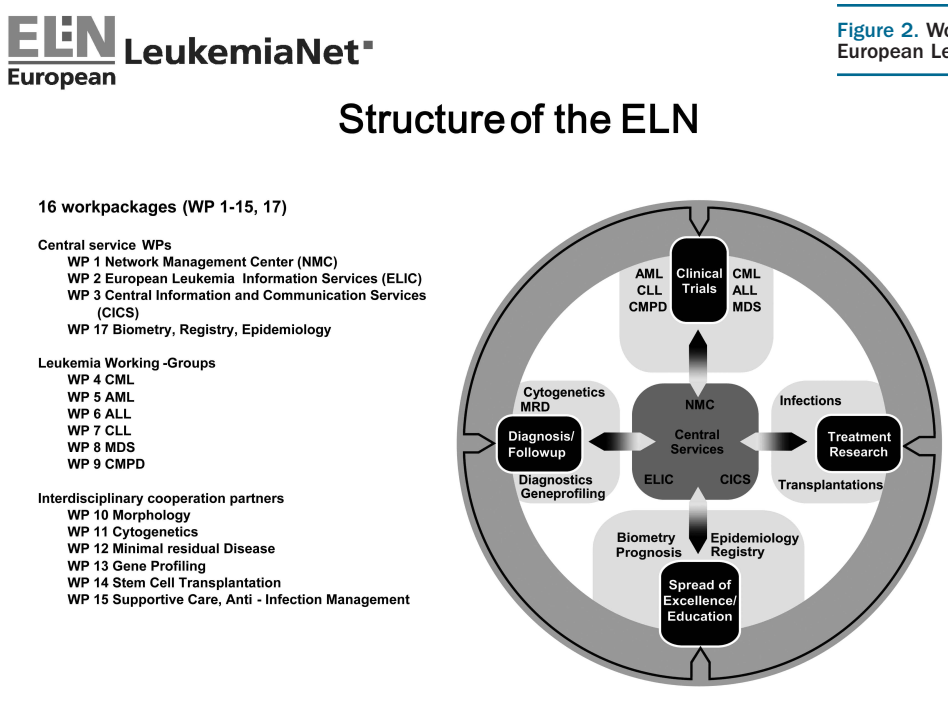

Figure 2. Working-groups and organigram of the European LeukemiaNet.

Table 1. Key results.

• The network: Uniform definitions for diagnosis and treatment outcome; Common clinical trials and projects; Management recommendations for each leukemia entity; Website to spread information on leukemia (www.leukemianet.eu); ELN-Foundation
• CML (WP4): Pan-European trials; European CML-registry; Standardization of BCR-ABL monitoring
• AML (WP5): Protocol alignments across Europe; Assessment of geriatric AML; Risk-adapted transplantation
• ALL (WP6): Pan-European trials ; MRD-guided management; MRD-monitoring by advanced technologies; Optimization of supportive care
• CLL (WP7): Protocol alignments; Chemoimmunotherapy; Study of rare subentities
• MDS (WP8): European MDS-registry; European trials on all MDS-subtypes
• CMPD (WP9): Harmonization of assay methods for JAK2-V617F; European trials e.g. on JAK2-inhibitors; Recognition of leukocytosis as a risk factor for thrombosis
• Morphology (WP10): Development of flow-cytometry for diagnosis and monitoring of MRD; Atlas of flow-cytometry
• Cytogenetics (WP11): Harmonization of techniques; Proposal for standardization; Identification of cryptic and complex aberrations and of minimal chromosomal imbalances by aCGH and SNP-arrays
• MRD (WP12): Novel RQ-PCR assays for FIP1L1-PDGFRA and WT1; Standardization of assays for BCR-ABL and mutated JAK2; Computer-software for reporting MRD-data in a standardized fashion; Sequential monitoring for BCR-ABL, FIP1L1 PDGFRA and PML-RARA transcripts for guidance of treatment
• Gene profiling (WP13): Recognition of new patients subgroups by gene expression profiling; Standardization of techniques
• Stem cell transplantation (WP14): Assessment of key prognostic factors; Adaptation to elderly patients
• Infectious complications and supportive care (WP15): Care of neutropenic patients after stem cell transplantation and intensive chemotherapy; Management of bacterial, viral and fungal infections in neutropenia; Monitoring of transfusion policy in Europe

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 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 published[11-13] (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, AMG531) and explores the impact of iron chelation (deferasirox) on the prognosis of MDS. Recommendations for diagnosis and treatment of MDS

Table 2. Recommendations and Guidelines

Topic	Reference
CML management recommendations	Baccarani *et al.*, Blood 2006 ;108 :1809-20[2] Hehlmann *et al.*, Lancet 2007;370:342-50[3] Baccarani *et al.*, J Clin Oncol 2009;27:6041-51[4]
CML molecular monitoring	Müller *et al.*, Leukemia 2009:1957-63[5] Hughes *et al.*, Blood 2006;108:28-37[6] Branford *et al.*, Leukemia 2006:1925-30[7]
AML management recommendations	Döhner *et al.*, Blood 2009, 10;115:453-474[8]
APL management recommendations	Sanz *et al.*, Blood 2009;113:1875-91[9]
APL molecular monitoring	Grimwade *et al.*; J Clin Oncol 2009;27:3650-3658[10]
CLL guidelines	Hallek *et al.*, Blood 2008;111:5446-56[11]
CLL molecular and flow-cytometric monitoring	Ghia *et al.*; Leukemia 2007; 21:1-3[12] Rawstron *et al.*, Leukemia 2007; 21 :956-64[13]
Evidence- and consensus-based European guidelines on MDS	ELN Homepage http://www.leukemia-net.org/ content/leukemias/mds/recommendations [14]
CMPD management recommendations (PV, ET, PMF)	Barbui *et al.*, J Clin Oncol ; in press[15]
Response criteria for ET and PV	Barosi *et al.*, Blood 2009;113:4829-33[16]
Definition of resistance and intolerance to hydroxyurea in PV and myelofibrosis	Barosi *et al.*, Br J Haematol 2010; 148:961-963[17]
Reference document for four- and five-color flow-cytometry	Arnoulet *et al.* Cytometry B Clin Cytom 2010, 78:4-10[18]
Flow-cytometry in MDS	van de Loosdrecht *et al.*; Haematologica 2009: 94:1124-34[19]
Consensual morphology collection	ELN homepage: www.leukemianet.eu[14]
Proposals for standardization of cytogenetic analyses	Haferlach *et al.*, Genes Chromosomes Cancer 2007;46:494-9[20]
FIP1L1-PDGFRA – recommendations for diagnosis & molecular monitoring	Jovanovic *et al.*, Blood 2007;109:4635-40[21] Score *et al.* Leukemia 2009; 23:332-339[22]
WT1 PCR standardization	Cilloni *et al.*, J Clin Oncol 2009;27:5195-201[23]
Gene expression profiling recommendations	Kohlmann *et al.*, Br J Haematol 2008;142:802-7[24]
Microarray analyses guidelines	Staal *et al.*, Leukemia 2006;20:1385-92[25]
Transplant-associated microangiopathy recommendations	Ruutu *et al.*, Haematologica 2007;92:95-100[26]
Stem cell transplantation recommendations	
- in CLL	Dreger *et al.*, Leukemia 2007;21:12-7[27]
- in MDS	De Witte *et al.*, Haematologica 2006;91:750-6[28]
Recommendations for management of infections	
- Quinolone prophylaxis for bacterial infections in afebrile neutropenia	Bucaneve *et al.*, EJC Supplements 2007 (Vol. 5, 5-12)[29]
- HSV, VZV and EBV	Styczynski *et al.*, Bone Marrow Transplant 2009;43:757-70[30]
- CMV, HHV-6, HHV-7 and HHV-8	Ljungman *et al.*, Bone Marrow Transplant 2005;35, 737-746[31]
- Empirical antifungal therapy in febrile neutropenic patients	Marchetti *et al.*, EJC Supplements 2007 (Vol. 5, 32-42)[32]
- Primary antifungal prophylaxis	Maertens *et al.*, EJC Supplements 2007 (Vol. 5, 43-48)[33]
- Candida and Aspergillus	Herbrecht *et al.*, EJC Supplements 2007 (Vol. 5, 49-59)[34]
- Vaccination in stem cell transplant recipients	Ljungman *et al.* Bone Marrow Transplant 2008;42:227-40[35]

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),[16] and on the use of hydroxyurea in PV and myelofibrosis[17] (Table 2). A new risk factor (leukocytosis) 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 consensual 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,[38] particularly in MDS.[19]

• 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 *FIP1L1-PDGFRA*[21,22] in chronic eosinophilic leukemia and assays to detect overexpression of the Wilms' Tumor gene (*WT1*) in AML[23] (Table 2). This has been complemented by standardization of established assays (e.g. RQ-PCR for BCR-ABL[5,6] and JAK2-V617F, in collaboration with WP4 and WP9, respectively) and the development of a tailor-made computer software-package to standardize reporting 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 *BCR-ABL*, *FIP1L1-PDGFRA* and *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[39] 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.[40] 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.[43-45] 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.

Authorship and Disclosures

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References

1. Hehlmann R, Berger U, Aul C, Büchner T, Döhner H, Ehninger G, et al. The German competence network 'Acute and chronic leukemias'. Leukemia. 2004;18(4):665-9.
2. Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia. Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006;108(6):1809-20.
3. Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. Lancet. 2007;370:342-50.
4. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-51.
5. Müller MC, Cross NC, Erben P, Schenk T, Hanfstein B, Ernst T, et al. Harmonization of molecular monitoring of CML therapy in Europe. Leukemia. 2009;23(11):1957-63.
6. Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood. 2006;108(1):28-37.
7. Branford S, Cross NC, Hochhaus A, Radich J, Saglio G, Kaeda J, et al. Rationale for the recommendations for harmonizing current methodology for detecting BCR-ABL transcripts in patients with chronic myeloid leukaemia. Leukemia. 2006:20(11)1925-30.
8. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-74.
9. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875-91.
10. Grimwade D, Jovanovic JV, Hills RK, Nugent EA, Patel Y, Flora R, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. J Clin Oncol. 2009;27(22):3650-8.
11. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111 (12):5446-56.
12. Ghia P, Stamatopoulos K, Belessi C, Moreno C, Stilgenbauer S, Stevenson F, et al. ERIC recommendations on IGHV gene mutational status analysis in chronic lymphocytic leukemia. Leukemia. 2007;21(1): 1-3.
13. Rawstron AC, Villamor N, Ritgen M, Bottcher S, Ghia P, Zehnder JL, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia. 2007;21(5):956-64.
14. ELN Homepage. http://www.leukemianet.eu
15. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, et al. Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations from European LeukemiaNet. J Clin Oncol 2010, in press.
16. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood. 2009;113(20):4829-33.
17. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch H, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. BrJ Haematol 2010;148(6):961-3.
18. Arnoulet C, Béné MC, Durrieu F, Feuillard J, Fossat C, Husson B, et al. Four- and five-color flow cytometry analysis of leukocyte differentiation pathways in normal bone marrow: a reference document based on a systematic approach by the GTLLF and GEIL. Cytometry B Clin Cytom. 2010;78:4-10.
19. van de Loosdrecht AA, Alhan C, Bene MC, Della Porta MG, Drager AM, Feuillard J, et al. Standardization of flow cytometry in myelodysplastic syndromes: report from the first European LeukemiaNet working conference on flow cytometry in myelodysplastic syndromes. Haematologica. 2009;94(8): 1124-34.
20. Haferlach C, Rieder H, Lillington DM, Dastugue N, Hagemeijer A, Harbott J, et al. Proposals for standardized protocols for cytogenetic analyses of acute leukemias, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myeloproliferative disorders, and myelodysplastic syndromes. Genes Chromosomes Cancer. 2007;46(5):494-9.
21. Jovanovic JV, Score J, Waghorn K, Cilloni D, Gottardi E, Metzgeroth G, et al. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. Blood. 2007;109(11): 4635-40.
22. Score J, Walz C, Jovanovic JV, Jones AV, Waghorn K, Hidalgo-Curtis C, et al. Detection and molecular monitoring of FIP1L1-PDGFRA-positive disease by analysis of patient-specific genomic DNA fusion junctions. Leukemia. 2009;23(2):332-9.
23. Cilloni D, Renneville A, Hermitte F, Hills RK, Daly S, Jovanovic JV, et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. J Clin Oncol. 2009;27(31):5195-201.
24. Kohlmann A, Kipps TJ, Rassenti LZ, Downing JR, Shurtleff SA, Mills KI, et al. An international standardization programme towards the application of gene expression profiling in routine leukaemia diagnostics: the Microarray Innovations in Leukemia study prephase. Br J Haematol. 2008;142(5):802-7.
25. Staal FJ, Cario G, Cazzaniga G, Haferlach T, Heuser M, Hofmann WK, et al. Consensus guidelines for microarray gene expression analyses in leukemia from three European leukemia networks. Leukemia. 2006;20(8):1385-92.
26. Ruutu T, Barosi G, Benjamin RJ, Clark RE, George JN, Gratwohl A, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica. 2007;92 (1):95-100.
27. Dreger P, Corradini P, Kimby E, Michallet M, Milligan D, Schetelig J, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia. 2007;21(1):12-7.
28. De Witte T, Brand R, van Biezen A, Delforge M, Biersack H, Or R, et al. The role of stem cell source in autologous hematopoietic stem cell transplantation for patients with myelodysplastic syndromes. Haematologica. 2006;91(6):750-6.
29. Bucaneve G, Castagnola E, Viscoli C, Leibovici L, Menichetti F. Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients. EJC Supplements. 2007;5:5-12.
30. Styczynski J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, et al. Management of HSV, VZV and EBV infec-

tions in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant. 2009;43(10):757-70.
31. Ljungman P, Engelhard D, de la Camara R, Einsele H, Locasciulli A, Martino R, et al. Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant. 2005;35(8):737-46.
32. Marchetti O, Cordonnier C, Calandra T. Empirical antifungal therapy in neutropienic cancer patients with persistent fever. EJC Supplements. 2007;5:32-42.
33. Maertens JA, Frére P, Lass-Flörl C, Heinz W, Cornely O. Primary antifungal prophylaxis in leukaemia patients. EJC Supplements. 2007;5:43-8.
34. Herbrechet R, Flückiger U, Gachot B, Ribaud P, Thiebaut A, Cordonnier C. Treatment of invasive Candida and invasive Aspergillus infections in adult haematological patients. EJC Supplements. 2007;5:49-59.
35. Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, et al. Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant. 2008;42(4):227-40.
36. Büchner T, Berdel WE, Haferlach C, Haferlach T, Schnittger S, Müller-Tidow C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. J Clin Oncol. 2009;27(1):61-9.
37. Haferlach T, Kohlmann A, Wieczorek L, Basso G, Kronnie GT, Bene MC, et al. Clinical utility of microarray-based gene expression profiling in the diagnosis and subclassification of leukemia: report from the International Microarray Innovations in Leukemia Study Group. J Clin Oncol. 2010;28(15):2529-37.
38. Bene MC, Kaeda JS. How and why minimal residual disease studies are necessary in leukemia: a review from WP10 and WP12 of the European LeukaemiaNet. Haematologica. 2009;94(8):1135-50.
39. Gratwohl A, Stern M, Brand R, Apperley J, Baldomero H, de Witte T, et al. Risk score for outcome after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Cancer. 2009;115(20):4715-26.
40. Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood. 2010;115(10):1880-5.
41. Baccarani M, Rosti G, Castagnetti F, Haznedaroglu I, Porkka K, Abruzzese E, et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet Study. Blood 2009;113(19):4497-504.
42. Rinaldi CR, Rinaldi P, Gemei M, Grimaldi F, Battipaglia G, Del Vecchio L, et al. JAK2V617F mutation persists in blasts and mature cells of transformed JAK2V617F-positive-myeloproliferative neoplasia: a European Leukemia Net ENL study. Am J Hematol. 2010;85(5):383-6.
43. Marin D, Milojkovic D, Olavarria E, Khorashad JS, de Lavallade H, Reid AG, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. Blood. 2008;112(12):4437-44.
44. Alvarado Y, Kantarjian H, O'Brien S, Faderl S, Borthakur G, Burger J, et al. Significance of suboptimal response to imatinib, as defined by the European LeukemiaNet, in the long-term outcome of patients with early chronic myeloid leukemia in chronic phase. Cancer. 2009;115(16):3709-18.
45. Carobbio A, Finazzi G, Antonioli E, Vannucchi AM, Barosi G, Ruggeri M, et al. Hydroxyurea in essential thrombocythemia: rate and clinical relevance of responses by European LeukemiaNet criteria. Blood. 2010;116(7):1051-5.