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EDITORIAL

The German competence network 'Acute and chronic leukemias'

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Specialization in medicine as in most other fields of modern science has increased dramatically in the last decades. In contrast to 50 years ago, no single representative of any specialty or even subspecialty is capable any more of overseeing the continuously growing information in this field. The timely answer to this development is the creation of cooperation units of specialists and their interdisciplinary cooperation partners in any given area that have become known under the terms 'competence centers' when they are locally confined or 'competence networks' or 'networks of excellence' when they are spread over many centers. In Germany, competence networks in medicine have been formally initiated by the Federal Ministry for Education and Research (BMBF) since 1997, mostly on a national basis.[1] One of currently 14 German networks in medicine is the competence network 'Acute and chronic leukemias', which started its work in September 1999. More recently, similar structures have been promoted by the European Union as European Networks of Excellence[2] and are planned by a 'road map' of the US National Institutes of Health.[3]

Acute and chronic leukemias are still characterized by high morbidity and mortality rates. The disease frequency of the patients spread over all age groups and their mortality make the leukemias a health problem of high societal visibility. Advances in the management of this patient group as a consequence of improved health-care structures and faster information flow are rewarded by a high degree of attention by patients, doctors and the population at large. Since leukemias can be triggered by environmental factors (radiation, chemicals, pesticides, insecticides, viruses and others), they are indicators par excellence for our basic living conditions and environment.

The leukemias serve as a model for a number of diseases (neoplastic, genetic, infections). With regard to our understanding of pathogenesis, development of innovative treatment approaches, new diagnostic procedures and new insights in oncology, pioneering results were achieved by research on leukemias.

In Germany, research and patient care in acute and chronic leukemias are accomplished, to a large extent, within investigator-driven multicenter treatment optimization trials. The current support of these trials stems from various sources (government, foundations, pharmaceutical industry and others) and is limited to coordination and management costs not covered by reimbursement of insurances.

The competence network 'Acute and chronic leukemias' is an answer to the following *current deficits* in research and patient care:

- *Incomplete recognition of leukemia patients and thereby of the magnitude of the problem*: This applies especially to CML, AML and the leukemia-related syndromes. A more complete recognition would lead to the inclusion of larger proportions of patients in modern treatment approaches, which is particularly relevant for elderly patients and might facilitate the recognition of etiological factors.
- Incomplete and delayed information and knowledge transfer for the leukemias at large.
- *Parallel activities and fragmentation of leukemia trial groups*: There is a need for coordination and harmonization of treatment optimization trials and for across-trial comparability.
- *Insufficient diagnostic standardization*: This includes inter-observer variability in morphology, nondefined antibody panels for immunophenotyping, deficits in standardization of methodology in cytogenetics, and highly variable procedures and lack of control rounds in molecular diagnostics.
- *Lack of uniform definitions*: There is a lack of uniform data sets, standardized therapeutic criteria and definitions of prognostic factors and end points.
- *Fragmentation of treatment research*: Many groups pursue high quality experimental research on pathogenesis, recognition of prognostic parameters, detection of new targets and development of new drugs, but due to the fragmentation of trial groups suboptimal use is made of the patients' data and material available from controlled trials.
- *Deficits in clinical translation*: The transfer of new developments is frequently too slow and incomplete due to insufficient information, communication, and organization structures. An example is the incomplete recruitment of patients with leukemia into controlled clinical trials with an estimated proportion of only 30% for CML and less than 50% for AML.
- *Deficits in cost effectiveness*: The lack of standardized diagnostics and uniform standardized treatment strategies influences cost effectiveness. This is particularly evident for supportive care in neutropenic patients and for stem cell transplantation (SCT) procedures.

The German competence network was initiated to address these deficits in an attempt to find concepts to their improvements, in particular, for current research and patient care in

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leukemia, and to use synergies for an added value of all partners.

Network structure

The network consists of a coordination unit, providing central information, communication and management structures, a network information center, providing structured information services, a central informatics unit with server and biometric trial support, and 26 clinical trial and interdisciplinary research projects (see the appendix on web). The network is supervised by the executive board (Netzwerkvorstand), consisting of the trial coordinators and the head of the informatics unit. It is supported by the network coordinator (Koordinator) and the network manager (Geschäftsführerin). Each project reports on progress with its objectives every 2 months (one page standardized report, bullet point style), which is sent to the executive board. The board monitors and discusses progress, problems and future strategies.

The coordination unit is responsible for management, communication and all matters needed for smoothly functioning networking.

The spread of information is accomplished by the information center through printed media (eg biannual newsletters or press statements) and, most importantly, the internet. The information center collects all information relevant to leukemia, prepares the information according to user needs, for example, health personnel, patients and their relatives and the interested public at large, publishes all available network trial protocols and categorizes protocols according to disease entities, prognostic and age groups and stages of the disease. It also runs and updates the network homepage (www.kompetenznetz-leukaemie.de).

The central informatics unit provides the technical and methodological infrastructure needed for networking.

The 26 trial and research projects are grouped according to forms of leukemia (CML, AML, ALL, MDS, CMPD), diagnostics (morphology, immunophenotyping, cytogenetics, molecular genetics), treatment research and development (supportive care, immunotherapy and SCT, gene and targeted therapies) and application-oriented basic research (signal transduction, genomics and proteomics). One project deals with the economic aspects of leukemia treatment. Regular trial and research group meetings, an annual network symposium, biannual newsletters, telemicroscopy conferences, educational and teaching workshops, and the exchange of material, data and researchers complement the network structure.

An organigram of the network structure is provided in the appendix on web.

The network is advised and evaluated by an external advisory board consisting of eight internationally known specialists in leukemia, science and informatics, and is strengthened by an extended executive board that includes important persons of German and international public life (see the appendix on web). The German network is proud to have Mr. José Carreras and Mr. Rudi Völler, manager of the national football team, among the members of its board.

At its start in September 1999, the network comprised 320 centers, among them 50 university hospitals, 20 research institutes, 200 large community hospitals, 50 specialty practices, and about 1000 participants. It comprised the major study groups in CML, ALL, AML, MDS and CMPD in Germany. Meanwhile, about 400 centers and 1400 participants work together (Figure 1) and some additional, smaller study groups have joined. The information center provides protocols and information on about 80 trials and structured information for the most important user categories. By now, six newsletters have been edited and four network symposia organized (attendance: about 250). The 2-day symposia are structured in parallel meetings of 16 working groups and in plenary sessions for communication of the results to all network participants.

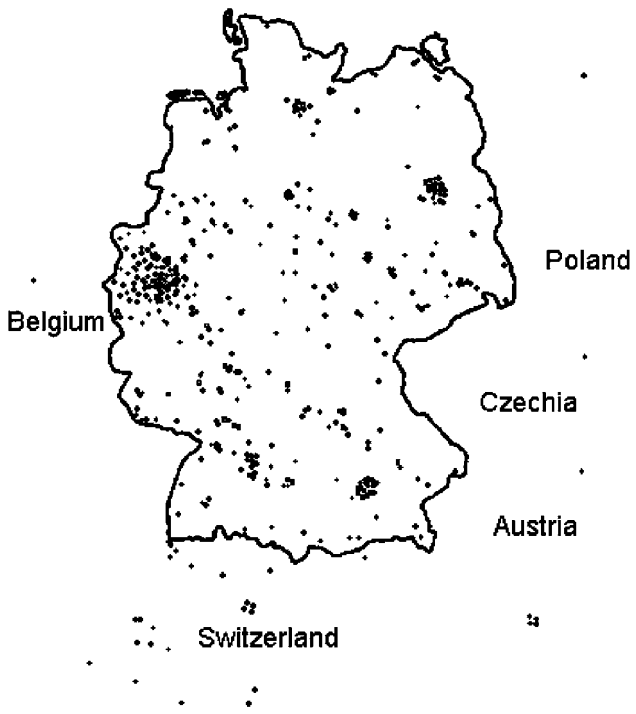

Figure 1 Network participants and project (=expert) groups.

Early achievements

Although it may be too early to report on the impact of the network, some early achievements should be highlighted:

- A functioning network with supportive and monitoring structures has been established, and instruments have been created for networking that bring network members together and induce a spirit of cooperation and corporate identity. The instruments include information and communication structures, bimonthly strategic meetings of the executive board and an information center for the analysis of the requirements for and the development of homepage structure and contents. The structured information on trial protocols is available on internet (www.kompetenznetz-leukaemie.de). The success of the information center is reflected by a user acceptance of, on average, 150 000 hits per month. Structured information is provided for all user groups. A comprehensive policy to safeguard member privacy has been implemented, and in consultation with state officials procedures for data protection have been worked out that comply with German law and local ethics committees.
- Another highlight is progress with standardization of diagnostic procedures and its reinforcement by control rounds. Morphological diagnostics are monitored by weekly telemicroscopy conferences for up to 20 participants and by trials

of interobserver concordance. Power-point presentations of various types of hematologic and lymphatic neoplasias have been prepared for continuing medical education.

- Corresponding to recent international consensus recommending five-parameter immunophenotyping as the minimal standard for hematologic malignancies, a restricted and cost-effective three-color diagnostic 'core panel' for immunophenotyping of acute leukemias has been defined.[4] Two nation-wide quality rounds with approximately 85 participants have been performed that mainly aimed at external quality assessment of data analysis and interpretation of immunophenotyping.
- A leukemia cytogenetics network was initiated providing central review and a large cytogenetic database.[5–7]
- In molecular genetics and detection of minimal residual disease, a quality controlled program using the BCR/ABL fusion gene as a model for qualitative and quantitative molecular analysis was started. Qualitative and first quantitative control rounds have been successfully completed. BCR/ABL transcript levels have been successfully correlated with response to therapy.[8,9]
- A new treatment optimization trial for CML in the imatinib era was activated. A protocol for a four arm randomized controlled trial to study imatinib monotherapy *vs* imatinib in combination with interferon alpha or low-dose araC *vs* imatinib after interferon failure has been developed and approved by study group and control agencies. The trial scheme is shown in Figure 2a. The trial has recruited 330 newly diagnosed CML patients during the first 12 months. A phase I/II study of the combination of imatinib with pegylated IFN (Pegasys) has been completed.
- An AML intergroup has been established combining five hitherto separately working AML study groups by a uniform upfront randomization and a common standard arm that allows to compare complete treatment strategies across different trials. By this strategy, high numbers of patients can be used to answer therapeutic questions, which will further accelerate therapeutic progress in AML. The patients randomized into the common control arm are quality controlled according to diagnostics, treatment procedures and biometry at regular intervals to guarantee uniform quality across studies. By the last reporting, 900 patients had been randomized, 85 to the control arm. The randomization strategy of the AML intergroup is depicted in Figure 2b.
- A similar approach has been started with the myelodysplastic syndromes. Two hitherto separate mylodysplastic syndromes study groups were combined to form the German MDS Study Group.
- Two platforms have been established for central diagnostics and for basic research groups that deal with genomics and proteomics to detect new molecular targets and develop new targeted treatment strategies. A third platform comprising the biometrical projects of the network provides the methods support for treatment optimization trials, elaboration of prognostic scores, epidemiological evaluations and the preparation of meta-analyses and treatment guidelines.
- Guidelines have been prepared and published for the management of infectious complications in neutropenic patients, substitution with blood products, treatment with hematopoietic growth factors, management of graft-versus-host disease and antiemetic treatment. Guidelines for the management of leukemias and related syndromes have been prepared and published for the German Society of Hematology and Oncology (DGHO).
- An achievement was also the rapid recruitment of Philadelphia (BCR-ABL) positive CML and ALL patients to the international imatinib studies. It is the result of networking that the German contingent became the second largest worldwide.
- A number of contributions to trial infrastructure have been achieved. A common uniform data set has been finalized in close cooperation with the group of European Investigators in CML (EI-CML) to make international CML studies and their outcomes better comparable. A similar data set is being worked out for AML and needs finalization by international partners. Further, indications for SCT in CML in the imatinib era have been worked out and approved by CML study participants and transplantors. In addition, a protocol has been finalized to compare reduced intensity conditioning for SCT in CML in patients older than 45 years with an age-adjusted standard in order to improve cost-effectiveness. It is assumed that this approach will improve treatment and also will be highly cost effective. It will be part of the new randomized imatinib trial, which compares imatinib monotherapy with imatinib in combination (Figure 2a) and closely cooperates with international groups conducting randomized trials of similar design.
- Finally, research funded by other sources was fostered by cooperations within the network resulting in close to 200 reports published in international journals[10] within a 2-year period. Examples of successful experimental research are the recognition of myeloblastin and its characterization in CML[11] and the characterization of FLT3 mutations of

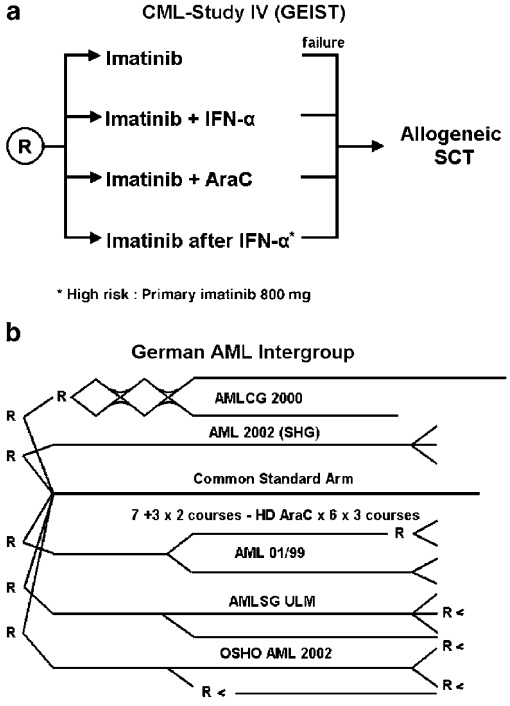

Figure 2 (a) Trial scheme of CML-Study IV. *G*erman *e*valuation of *i*nterferon α, *S*TI571 and *t*ransplantation (GEIST, German for Spirit). (b) Networking design in the German AML intergroup comprising five individual AML trials. By a general upfront randomization, 10% of patients from each trial are assigned to a common standard treatment arm containing two courses of standard dose AraC with daunorubicin for induction and three courses of high-dose AraC for postremission treatment. Treatment assignments in the individual trials are carried out by randomization (R) or according to risk groups (no R). This design provides a validation and comparison of complete strategies across the trials.

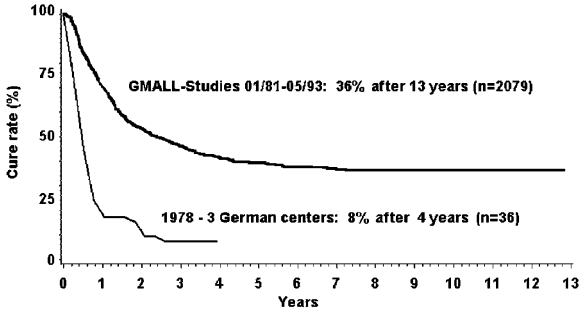

Figure 3 Prolongation of survival in ALL as achieved by the German ALL-Study group since the beginning of prospective multicenter trials in 1980.

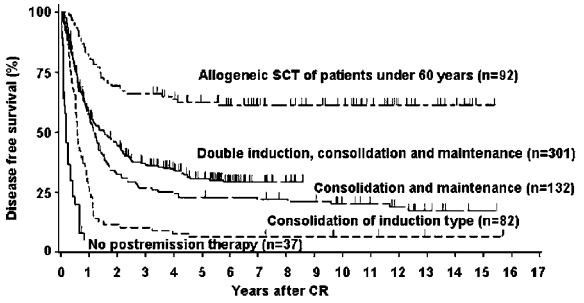

Figure 4 Prolongation of progress-free survival in AML as achieved by AML-CG over the last 25 years. The upper curve shows the results after allogeneic SCT in younger patients. In this curve, the positive selection of patients (young age, stable condition, no relapse) has to be considered.

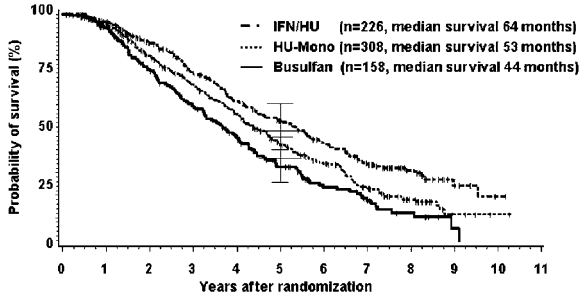

Figure 5 Prolongation of survival in CML as achieved by studies I and II of the German CML-Study Group during the past 20 years.

prognostic relevance for AML.[12–14] The prolongation of survival achieved over the years for the various leukemias by the study groups forming the network are depicted in Figure 3–5.[15–18]

The orientation of the network towards innovation and success makes the network attractive for new participants. The cooperation within the network and the thereby accomplished synergy yield an added value for all network partners.

Perspectives

Networking and clinical trials, notably treatment optimization trials, are increasingly limited by new regulations and legislations, in part in the context of European harmonizations. Ethic committees are expensive presenting a serious financial problem for multicenter studies for which multiple ethic votes are needed. The latest development is that not only protocols are evaluated but also investigators who request participation in the trials, further hampering inclusion of patients in trialsand thereby therapeutic progress. A problem would be the requirements of GCP standards for treatment optimization trials, which were required thus far for phase I/II trials only. It is foreseeable that study groups that traditionally have stringent quality controls among themselves would not be able to afford the expenses caused by the new regulations and development. The need for harmonization of clinical research regulatory requirements as well as promotion of a systematic infrastructure for clinical trials through networks and development of a standardized data system have also been recognized elsewhere.[3]

An important aspect is sustainability of the networks. As long as public funds are available to maintain network infrastructure, network goals can be achieved. It is still unclear which parties, in the future, will have sufficient interest and financial potential to maintain the networks in the long run. A leukemia foundation has been established with the help of the Deutsche Knochenmarkspenderdatei (DKMS), but it is anticipated that the donations will not suffice to keep the network functioning. A proposal for a European network of excellence against leukemia (European LeukemiaNet) is being negotiated within the 6th Framework Programme of the European Union, and it is hoped that this structure will extend networking in leukemia on a European scale.

There are some important perspectives that may prove to be supportive of the network in the future. The one most important is cost effectiveness. Patient's insurances should have an interest in quality controlled improvements of cost effectiveness in leukemia diagnostics and treatment. It is assumed that, in this respect, the added value of networking will by far exceed the costs. It also can be expected that pharmaceutical companies will have an interest in a partner for clinical translation of their products who is able to run phase I/II trials reliably of good quality. Finally, doctors and hospitals will have an interest in cost-effective, high-quality performance and might use the network as an instrument for providing cost-effective healthcare – and pay for it.

The principal aim of the network and its central projects is the continuation and further development of supporting excellence in research and patient care in the field of leukemia. The challenge for the years ahead is to incorporate insights from gene array research into clinical practice, e.g., to migrate rapidly to a molecular classification of leukemias. The network will disseminate state-of-the-art therapy into community practice, foster publications in scientific journals and organize conferences in order to promote progress and public visibility. Representative key stake holders, e.g. patient organizations, professional associations, politicians, artists are already or will be invited to participate. They are all expected to make important contributions for overcoming existing fragmentations and regulations. The network offers a competitive advantage for participating doctors and scientists from Germany and neighboring countries. The benefit will be for patients with leukemia and their prospects for prolongation of survival and cure. Lastly, because of the model character of the leukemias, advances made with the leukemias may be directly applicable to solid cancers.

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Supplementary Information

Supplementary Information accompanies the paper on the Leukemia website (http://www.nature.com/leu).

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