Competence Network
Malignant Lymphoma

First Annual Report

Funding Period
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## Abbreviations

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<td>BM</td>
<td>Bone marrow</td>
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<tr>
<td>BMBF</td>
<td>Ministry of Education and Research (Bundesministerium für Bildung und Forschung)</td>
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<td>BMT</td>
<td>Bone marrow transplantation</td>
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<td>B-NHL</td>
<td>B-cell lymphoma</td>
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<tr>
<td>cDNA</td>
<td>Complementary desoxyribonucleic acid</td>
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<td>CHMG</td>
<td>Cochrane Haematological Malignancies Group</td>
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<tr>
<td>CHOEP</td>
<td>A five substances containing chemotherapy schedule</td>
</tr>
<tr>
<td>CHOP</td>
<td>A four substances containing chemotherapy schedule</td>
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<tr>
<td>CLL</td>
<td>Chronic lymphoblastic leukaemia</td>
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<td>CMS</td>
<td>Content management system</td>
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<td>CTA</td>
<td>Cancer-testis antigen</td>
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<td>DFG</td>
<td>Deutsche Forschungsgemeinschaft</td>
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<td>DGHO</td>
<td>German Society of Oncology and Haematology (Deutsche Gesellschaft für Hämatologie und Onkologie)</td>
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<td>DGiIM</td>
<td>German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin)</td>
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<td>DLH</td>
<td>German leukemia and lymphoma patients' representation (Deutsche Leukämie- und Lymphom Hilfe)</td>
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<td>DRST</td>
<td>German Registry for Haematopoietic Stem Cell Transplantation (Deutsches Register für Stammzelltransplantationen)</td>
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<tr>
<td>EbM</td>
<td>Evidence-based medicine</td>
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<td>EBM</td>
<td>European Group for Blood and Marrow Transplantation</td>
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<tr>
<td>GCLLSG</td>
<td>German CLL Study Group</td>
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<td>GHNHLMSG</td>
<td>German High-Grade Non-Hodgkin’s Lymphoma Study Group</td>
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<td>GHSG</td>
<td>German Hodgkin Lymphoma Study Group</td>
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<tr>
<td>GIT-NHL</td>
<td>Study Group for Gastrointestinal Lymphoma</td>
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<td>GLSG</td>
<td>German Low-Grade Lymphoma Study Group</td>
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<tr>
<td>HDT</td>
<td>High-dose therapy</td>
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<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>IBMTR</td>
<td>International Bone Marrow Transplant Registry</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>ID</td>
<td>Identity</td>
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<tr>
<td>IHECE</td>
<td>Institute of Health Economics and Clinical Epidemiology, University of Cologne</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>IMISE</td>
<td>Institute of Medical Informatics, Statistics and Epidemiology, University of Leipzig</td>
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<td>ISDN</td>
<td>Integrated services digital network</td>
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<tr>
<td>ISST</td>
<td>Institute for Software and System Technology (Fraunhofer Institut für Software und Systemtechnik)</td>
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<td>IT</td>
<td>Information technology</td>
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<td>KML</td>
<td>Competence Network Malignant Lymphoma (Kompetenznetz Maligne Lymphome)</td>
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<tr>
<td>LDAP</td>
<td>Lightweight Directory Access Protocol</td>
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<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<td>MCL</td>
<td>Mantle cell lymphoma</td>
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<td>MERG</td>
<td>Medical Economics Research Group, University of Cologne</td>
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<td>NHL</td>
<td>Non-Hodgkin’s Lymphoma</td>
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<td>NLL</td>
<td>North German Leukaemia and Lymphoma Study Group (Norddeutsche Leukämie- und Lymphomstudie)</td>
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<td>OSHO</td>
<td>Eastern German Study Group for Haematology and Oncology (Ostdeutsche Studiengruppe für Hämatologie und Onkologie)</td>
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<tr>
<td>ÖGHO</td>
<td>Austrian Society of Haematology and Oncology (Österreichische Gesellschaft für Hämatologie und Onkologie)</td>
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<tr>
<td>PBPC</td>
<td>Peripheral blood progenitor cells</td>
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<td>ProMiSe</td>
<td>Project Manager Internet Server</td>
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<td>RCT</td>
<td>Randomised clinical trials</td>
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<td>RDE</td>
<td>Remote Data Entry</td>
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<td>RT-PCR</td>
<td>Real-time polymerase chain reaction</td>
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<td>SOP</td>
<td>Standard operating procedures</td>
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<td>SR</td>
<td>Systematic review</td>
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<tr>
<td>TCO</td>
<td>Total cost of operation</td>
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<td>TMF</td>
<td>Central telematic platform of the BMBF</td>
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<td>T-NHL</td>
<td>T-cell lymphoma</td>
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<td>VPN</td>
<td>Virtual private networks</td>
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<td>WG-QM</td>
<td>Working group on quality management</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WWW</td>
<td>World Wide Web</td>
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1 Introduction

1.1 Grant application period

In a BMBF hearing with Prof. Diehl in 1997, the German Hodgkin Lymphoma Study Group (GHSG) was chosen as an excellent example of a promoter of clinical trials for treatment optimisation. The experience of the GHSG helped to structure the tendering procedure for the medical competence networks. The GHSG decided not to restrict the proposal for a competence network of Hodgkin’s disease but to extend it to all lymphomas. Together with the two further major lymphoma study groups, the German High-Grade Non-Hodgkin’s Lymphoma Study (GHNHLSG) and the German Low-Grade Lymphoma Study Group (GLSG), the GHSG wrote the proposal. All these groups are well organised and have several years’ experience with large multicentre treatment optimisation trials.

1.2 The network’s subprojects

The “Competence Network Malignant Lymphoma” (KML) was approved in early 1999. In the period from September 1999 to January 2000, 9 out of 12 subprojects could start their work. Since the clinical study groups and the corresponding trials were already well established, the applicants chose projects for the KML which aim to develop an elaborate IT-based communication infrastructure and implement a high-level quality management for the treatment of lymphoma.

As outlined in the following chapters, subprojects 1-4 are designed to install IT-based structures for communication between different groups inside and outside the KML. Data exchange via internet is to be established to optimise data handling and to gather all relevant data for special investigations. Furthermore, workstations for telemedical conferences and electronic picture transfer will be set up. By this means, physicians should be enabled to exchange patient data and to obtain expert advice on problems in the therapy of individual patients. Telematic devices shall also be used to spread information on new therapies and clinical trials to patients and the public. The central part of this information service is the homepage of the KML “www.kompetenznetz-lymphome.de”. At the same time, the homepage serves as an information exchange platform for the members of the network.

Health care and economic research are the topics of subprojects 5–7. Epidemiological approaches are used to investigate the spread of effective therapies as well as the cost effectiveness of these therapies. Primary health care centres specialized in the treatment of lymphoma have formed a network within the KML in order to analyse the current status of treatment in their field.
The growing impact of evidence-based medicine (EbM) on diagnosis and treatment has been taken into account by integrating two subprojects in this field (subprojects 8A and 8B). As a first result, the Cochrane Haematological Malignancies Group has been founded.

The last group of subprojects (9-11) is closely related to the work of the lymphoma study groups. High-dose chemotherapy and secondary haematological neoplasias are in the focus of two subprojects which aim to standardize therapeutic proceedings and documentation and to develop novel treatment strategies. Subject 11 aims to develop strategies for immune and gene vaccine therapies of malignant lymphoma and represents an excellent example of a combined basic and clinical research approach.

1.3 Association of new study groups

The KML wants to be an open platform for all groups working in research and treatment of lymphoma. In consequence, the KML invited interested groups to submit an application for association. To date, three further clinical study groups have been associated: the German CLL Study Group (GCLLSG), the Study Group for Gastrointestinal Lymphoma (GIT-NHL) and the Eastern German Study Group for Haematology and Oncology (OSHO). The representatives of these groups are members of the extended board of the KML and have full access to all information tools offered by the network.

Recently, an epidemiological working group joint the network. Together with the project leader of subproject 10, members from the Bremer Institut für Präventionsforschung und Sozialmedizin (BIPS) and from the Deutsches Krebsforschungszentrum (DKFZ) in Heidelberg submitted three projects which formed the basis of the group’s ongoing work.

In the following chapters, we give an overview of the network’s organisation and management and the overall activities, followed by the reports of the subprojects. In the beginning of these reports, the reader will find the addresses of the project leaders who are responsible for the corresponding chapter and who may be contacted for further information. Finally, the last chapter summarizes the objectives for the forthcoming funding period until September 2002.
2 Organisation and Management of the Network

2.1 The legal structure
For the future, the KML plans to constitute itself in form of a registered society or a foundation. The general intention to implement a legal form is caused by the current necessity to set up an official frame in order to manage the network activities and to offer interested partners outside the funded subprojects the possibility to join the network. After the 5-years’ funding period by the BMBF, such a legal form may also help consolidating the network in order to maintain and further develop the structures that will be established during the next years.

The current version of rules (Satzung) which may be downloaded from the homepage of the network defines

- the categories of membership
- the election and constitution of the board
- the obligations of each individual member
- the utilization of research results and patents

To date, full members of the KML are the members of the board of directors and the extended board, the project leaders and a second project partner. Associated members are the cooperating partners of the project leaders (as laid down in the grant proposal to BMBF from 1999). In addition, an associated membership may be obtained by clinical study or other research groups after submission of a project proposal.

2.2 The committees
The rules of the KML include a board of directors (Engerer Vorstand) and an advisory extended board (Erweiterter Vorstand). As defined by the rules, the heads of the three major lymphoma study groups GHLS, GHNHLSG and GLSG are members of the board of directors. In addition, the members of the KML decided in their first general meeting that four further professionals from pathology, radiotherapy, epidemiology/informatics and from primary health care centres (Schwerpunktpraxen) should join the board. A list of all board members is given in Chapter 6.

To date, the extended board consists of eight members. Also defined by the rules, up to three representatives of associated clinical study groups, i.e. GCLLSG, GIT-NHL and OSHO, are members of this committee. Besides those, five further representatives from patient organisations, the health care system, federal ministries and the pharmaceutical industry could be gained for this committee. A survey of the current activities of these committees is given in Chapter 3.1.
### 2.3 Coordination

To assure the quality and efficiency of the collaboration within the network, the members of the network attend several kinds of meetings, which are organized by the central office:

**General meeting**

The general meeting takes place once a year and is open to all members of the network. The meeting aims to inform the members about the network’s activities and to offer a discussion platform for administrative and scientific issues. To date, the meeting took place twice. In the beginning of the funding period (January 2000), this meeting was used to pass the rules of the network and to elect or make proposals for the members of the different committees. One major topic of the second meeting in March 2001 was the presentation of the associated study groups and further groups which had submitted an application for membership and were positively evaluated by the review committee.

**Meeting of project leaders**

Two times per year, the project leaders and their close collaborators meet for an informal presentation of current results. Besides that, this meeting serves to discuss network projects in which several different subprojects are involved. This applies especially to approaches of the central co-ordinating office (subproject 1) and subproject 2 which provides the IT infrastructure of the network. For example, the homepage of the KML, the installation and the technical equipment were major issues of the first meetings. Usually, the meetings are organized in two parts: a plenum session and working groups in which actual strategies and problems are discussed in detail.

In addition to these official meetings, members of the network participate in the working group for quality management (see Chapter 3.3.4), the network assistants meet regularly (see progress report of subproject 1), and the IT-specialists join the workshops either organized by subproject 2 or by the official telematics platform of the BMBF (TMF, see Chapter 3.3.5).

In order to evaluate the current status of the project, each project leader submits an annual report of to the speaker of the network. This obligation is also defined by the rules of the KML.

Controlling instruments which are implemented in the work of the board of the KML are described in Chapter 3.1.

### 2.4 IT infrastructure

The KML has to be supported by a networked computer infrastructure. This requires the conception and construction of a suitable overall and specific IT infrastructure.

The IT infrastructure’s construction has to satisfy the main goals:
1. Installing a service for information exchange between different groups inside and outside the network
2. Installing a communication service for data exchange between the partners (subprojects) within the network.

In order to achieve these goals, in subproject 2 the following working steps are to be taken:

1. Purchase of the technical equipment and putting the new infrastructure into operation
2. Conception, organisation and coordination of a communication network
3. Conception and realisation of an integrated information service
4. Conception and realisation of the communication and data exchange between the partners

**Technical equipment and infrastructure**
The server, the network, and the communication technology have already been obtained, configured, and put into service after a test phase (see also subproject 2).

An IT security concept is being developed. Following this concept, the network’s central server and network components were located in an air-conditioned server room and are connected to a UPS (uninterruptible power supply) and emergency electricity supply, to guarantee high server availability for everyday operation. Furthermore, the network’s server data is backed up regularly, according to the data backup concept that is integrated into the IT security concept.

The IT security furthermore comprises the firewall concept, which provides a division of the network into a public and an internal area, in order to protect sensitive data from unauthorised access. This concept’s implementation started already.

**Communication Network**
The network’s partners communicate using encryption facilities via the Internet as well as via an ISDN router. This is based on the use of Virtual Private Networks (VPN), which facilitate distributed, highly secure communication over the Internet. This technology will be implemented and evaluated for the first time within the communication network when connecting the reference centres for lymph node pathology.

**Information Service**
Due to the high requirements and resultant complexity in the management and maintenance of the information service, it is necessary to use suitable tools. Therefore, the content management system (CMS) VIP by Gauss Interprise was chosen after careful evaluation of a number of different CMSs. To satisfy the CMS’s technical requirements, an information and editorial server was installed, which is the basis for the network’s homepage.
Communication and Data Exchange
Communication facilities between the network’s partners are being established, based on the IT infrastructure, to enable data and information exchange. Observing data privacy requirements, only disguised patients data is exchanged (applying ‘Pseudonymisierung’). The pseudonyms are created using a minimal data set. This data set was defined to identify patients ID while the data exchange between the pathology’s reference centres has been established.
3 Network Activities

3.1 Activities of the board

The board of directors held its first meeting in March 2000. The major task of this first meeting was to assign the responsibilities for the different scientific and non-scientific activities of the KML, e.g. association of new project groups, industrial support, public relations. The board decided to meet twice a year, in addition a meeting together with the members of the extended board was scheduled once per year.

The procedure how to associate clinical study and other research groups was an essential topic of the following meetings. In collaboration with the CEO, the board developed a category list which defines the requirements for a study or research group to be associated. This list has become an appendix of the rules of the KML. The board decided to make the applications undergo a review process, including an external expert as reviewer. To date, one epidemiological research group and three clinical study groups have been associated, a further one is close to be accepted.

Another important activity is to develop guidelines for the interaction of the KML study groups and their cooperating partners. In this context, an agreement has been reached which rules the cooperation of the three major lymphoma study groups with the lymph node pathology reference centres.

The consolidation of the network after the five years funding period is one of the major tasks of the network within the next years. The board decided to invite the pharmaceutical companies for founding a committee to discuss potential projects for common funding. Such a structure may help to maintain the KML in the long run. A first result is a joint project financed both by KML and industry to improve the study documentation in non-universitarian hospitals. The project is scheduled to start in autumn 2001 and has been designed for a period of two years.

Actual problems in the health care system are a further topic of the board meetings. In a common attempt with the other competence networks in medicine, the board called attention to the dissatisfying federal legislation for the necessity of multiple ethic votes in multi-centre clinical trials.

Especially for such kind of political issues, the extended board forms a perfect discussion panel. The members of the extended board join the meetings once to twice a year. The task of this board is to advise and support the board of directors in managing the affairs of the KML. The participation of two members of patients’ organizations has already contributed to the fact that a close interaction of the KML was established with the major lymphoma patients’ representation “Deutsche Leukämie- und Lymphom-Hilfe” (DLH).
3.2 Public relations

3.2.1 Media Work

The public shall particularly be informed about the network’s activities and its scientific results by media, i.e. print, radio, television. In the period under review, several activities have been realized in order to reach public and/or specialized media.

Two press conferences have been held: one on the occasion of the start up-symposium in January 2000 and one during the network’s 1st annual symposium in March 2001. In addition, several press statements have been released. The network’s central office has published an article about the KML in “Kölner Universitäts-Journal” in December 2000. A further article for the same journal has been written and will be published soon.

A special area for journalists has been established on the network’s homepage, and the network has been registered in “Informationsdienst Wissenschaft” (idw) which has developed to be the leading scientific news agency in German language within the last few years. Furthermore, a press kit has been fashioned. It is used for the presentation of the network’s press material since the 1st annual symposium.

The public relations manager takes part in the public relations work group of all medical competence networks which has been initiated by the funding organisation in March 2001. This work group projects several activities as a collective web site, a press kit with information about competence networks in general and each of the networks in particular, a collective brochure and a press conference as well as events for the public in large.

Some articles on the KML have appeared mostly in local and medical press in January 2000 and in spring 2001. By now, it can be noticed that journalists get an increasing knowledge about the network and the competence networks in general. Therefore, increasing media response is to be expected in the future.

3.2.2 Newsletter

The network’s newsletter is published by the central office in cooperation with the heads of the study groups and subprojects, with special regard to the haematologists in primary health care centres. The newsletter appears twice per year and provides information on the network activities as current projects or presentation of new study protocols. Its target audience are the members of the KML, lymphoma specialists, health care physicians, patients’ groups and the specialized medical press. Above all, it is an instrument for vertical communication between research and clinical practice.

It contains the following categories:

- Kompetenznetz (reports from the network’s projects)
- Forum der niedergelassenen Hämat-o-Onkologen (information for haematologists working in primary health care centres)
• Studiengruppen (presentation of the study groups, new study protocols, study results)
• Kongressbericht (actual reports from international congresses)
• Kongresse/Aktuelle Termine (announcement of symposia, patients’ seminars etc. organized by the network or external)

The first issue (July 2000) aimed to present the network in general: the idea and the initiative, the projects in a survey and the German lymphoma study groups, which build the network’s basis. The focus of the second issue (January 2001) lay on the network’s subprojects. Besides, the GHSG presented their new study protocol.

The next issue will appear in September 2001. This time, there will be a focus on the study groups (CLL, High-grade NHL).

3.2.3 Homepage

On 13th December 2000, the homepage of the KML was released to the public. The general aim was to develop a comprehensive information portal for scientists and patients on malignant lymphomas. The following diagram illustrates the anticipated growth in topic of the portal.
At present, the existing homepage contains the most recent clinical findings in malignant lymphomas as well as information about the KML. All major German clinical trial groups on malignant lymphomas are represented with latest data on their trials.

A part of the homepage has been specifically designed for patients. In cooperation with different self-help groups and patients’ associations, an easier to comprehend guide on current information and data on malignant lymphomas has been installed. Access to the scientific part of the homepage is also available to all patients.

A quality management unit for the portal has been established in the network’s central office. This unit will ensure that a high standard of information is maintained in each Web Page. Using a content management system (CMS) with an increasing number of online editors for the different topics will provide a highly dynamic information stream. Furthermore, the CMS provides an interface to editors and allows different specialists (authors, designers, computer scientists) to edit and manage their content independent to each other on every computer with Internet access. The CMS is available through subproject 2 and part of the IT infrastructure in Leipzig.

The next step in developing the portal will focus on the creation of a user identification and registration system. Depending on user privileges, special services of the portal will be available (i.e. confidential information on each project). Registered patients may be invited to participate in discussion circles with doctors and other patients.

### 3.2.4 Symposia

The competence network started its work in January 2000 by organizing a so-called „start-up symposium“ held at the University of Cologne, where the central office is based. The project leaders outlined in oral presentations subject and aims of their projects. Additionally, several study groups intending to join the KML presented their on-going clinical trials. The symposium was open to a medical and scientific audience as well as to patients and representatives of the health care system. Because of the high interest, the KML decided to continue this kind of presentation once a year. The 1st annual symposium was held in March 2001. This time, selected projects presented their first results by oral and poster presentations. During a round-table discussion experts talked about the role of the Competence Networks in Medicine within the health system. This discussion was of high interest for the audience which participated with numerous active contributions.

Furthermore, the KML organizes symposia for the annual conferences of the DGIM (German Society for Internal Medicine) and the DGHO (German Society for Haematology and Oncology). The purpose of these symposia is dual: First, the audience should be informed about the current activities and services of the KML, e.g. presentation of clinical trials via the homepage of the network. The second focus is laid on the presentation of actual results and new strategies in
research and treatment of lymphoma. Since the topics of these symposia are closely related to those of the Competence Network Leukaemia, both networks organize regular joint symposia.

The Symposia of the KML:

2000, January 14  Start-up Symposium, Cologne
2000, May 3      DGIM Congress, Wiesbaden
2000, October 25  DGHO/ÖGHO Congress, Graz (Austria)
                 Joint symposium with the Competence Network Leukaemia
2001, March 16    First Annual Symposium, Cologne
2001, April 24    DGIM Congress, Wiesbaden
                 Joint symposium with the Competence Network Leukaemia
2001, October 1   DGHO/ÖGHO Congress, Mannheim

3.3 Added value through networking

3.3.1 Activities of the clinical study groups

The German Hodgkin’s Study Group (GHSG) involves more than 430 clinical centres including university hospitals, community hospitals and specialists in haematology/oncology. In recent years this study has become a pan-European multicentre study including many centres from most European countries. The ongoing studies are HD10 (early stages), HD11 (intermediate stages), and HD12 (advanced stages) for patients with first diagnosis. In addition, a collaborative study together with the EORTC and the EBMT has been initiated in early 2001 for patients with relapsed disease. All together, more than 8,000 patients are included in the database of the GHSG.

Since its establishment in 1993, the German High-Grade Non-Hodgkin’s Lymphoma Study Group (GHNHLSG) recruited more than 2500 patients from 210 centres in clinical phase I/II and phase III trials. The on-going, second study generation comprises three protocols for previously untreated high grade NHL according to the interim’s results of the previous NHL-B trial: Patients > 60 years are treated with conventional chemotherapy and a monoclonal antibody (RICOVER-60); patients < 60 years with a more aggressive schedule (High/CHOEP). In an international cooperation with the EBMT and IBMTR, results of a dose-intensified chemotherapy followed by autologous PBPCT are compared for high-risk patients (Mega-CHOEP).

As for the German Low Grade Lymphoma Study Group (GLSG), more than 350 clinical institutions including academic centres, community hospitals and practitioners from all over Germany are involved in clinical studies. Currently, three prospectively randomised multicentre studies are being performed recruiting almost 1500 patients so far. In indolent lymphomas, the impact of anti-CD20 antibody in addition to combined chemotherapy will be evaluated. Additionally, intensive consolidation with high dose radiochemotherapy and autologous stem
cell transplantation is being compared to continuous interferon alpha maintenance in patients < 60 years. In elderly patients, two different schedules of interferon alpha have been compared. In mantle cell lymphoma, an aggressive disease with a median survival of 3 years and virtually no long term survivors, the first randomised study has been initiated to confirm the superiority of high dose therapy treatment. Finally, for relapsed indolent lymphoma, the potential benefit of a fludarabine-containing chemotherapy with or without a monoclonal antibody is being investigated.

All these activities demand a continuous and intensive exchange of information between peripheral clinical institutions, study coordinators and data centres. During the last two years, a growing information network has been influenced or initiated by the KML, which guides the interaction of patient's support groups, other lymphoma study groups as well as representatives of the public health system and health insurances. Examples are:

- Use of the internet presentation (homepage of KML) as a common information platform for patients and medical professionals with special regard to a clinical trials registry.
- Installation of a new computer platform, which enables the intensified data exchange between the different study groups.
- Introduction of new quality measures into the study group trials harmonizing standard operation procedures and data exchange between the different study groups.
- Activation of the so-called "Reisensburg Consensus" which standardizes the asservation of clinical samples for molecular analyses.
- Establishment of an epidemiological working group and a cytogenetic network with 6 centres.
- Activities to guide centres enrolling patients into the trials in terms of informed consent forms and ethic committee votes.
- Political activities to help general practitioners or specialists in oncology/oncology to enroll patients in clinical trials of the study groups involved in the KML, and consorted action of the study groups to promote the benefits of treatment optimisation studies for the general health system.

Within its concept of internal and external communication, the KML represents an essential platform to inform patients as well as medical doctors on the current state of the art of lymphoma treatment, treatment optimisation studies and biological research programs which will strongly influence future clinical concepts. In addition, the collaboration of an extending number of lymphoma study groups has been intensified and has led to a number of intergroup activities on the European level.
3.3.2 Activities of the haematologists working in primary care

In March 2000, the project group „Kompetenznetz der hämato-onkologischen Schwerpunktpraxen“ including 72 German primary health care centres for oncology and haematology (Schwerpunktpraxen) was established as a working community within the platform of the competence network. In August 2000 the office of the project group could start its work with the employment of a research assistant. The office coordinates together with individual teams all tasks regarding subproject 5 as well as the cooperation with other projects.

The office offers the opportunity for further development of guidelines to safeguard quality, the use of electronic data collection as well as the establishment and analysis of a community network.

In May 2001 an EbM course especially designed for haematologists working in primary health care took place for the first time in Cologne. At present, there are more than thirty applicants, mainly haematologists, who are members of the net.

There is also a cooperation with other projects of the KML. One third of all patients taking part in the study of subprojects 6 (Health Care Epidemiology) and 7 (Health Care Economy) are patients in primary health care centres of the project group. According to the analysis of the actual state it is expected that the number of surgeries as well as the number of patients will increase.

A further important goal of subproject 5 is to develop standard operating procedures (SOP) for therapy studies and clinical trials that are usable for primary health care centres. This work has already been started in cooperation with subproject 2 and the quality management working group.

The 72 primary health care centres are informed about the tasks of the net via information letters from the office of subproject 5 and the newsletter from the KML. With the beginning of the project an information exchange between basic health care and research has begun. Practitioners are writing for the newsletter, others submit their ideas about quality management and health care. These ideas can help to build quality management structures for basic health care in haematology/oncology.

3.3.3 EbM and the establishment of the Cochrane Haematological Malignancies Group

By definition, EbM is the conscious, explicit and judicious use of current best evidence in making decisions about the care of individual patients\(^1\). Evidence-based medicine/healthcare is a new paradigm, replacing the traditional medical paradigm which is based on authority. It depends on the use of randomised controlled trials (RCT), as well as systematic reviews (of a series of trials) and meta-analysis, although it is not restricted to these. There is also an

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emphasis on the dissemination of information, as well as its collection, so that the evidence can reach clinical practice. The establishment of the Cochrane Haematological Malignancies Group (CHMG, subproject 8b) bridges the gap in the rapidly increasing knowledge transfer between scientists, clinicians and patients involved in the management of malignant haematological disorders.

The scope of the CHMG has a clear focus on the treatment of haematological malignancies, and restricts its review activities largely to following disease entities: Acute and Chronic Lymphoblastic Leukaemia, Acute and Chronic Myeloid Leukaemia, Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma, Multiple Myeloma, Myelodysplastic Syndromes and Aplastic Anaemia. In this context, there is a commonality between the concept underpinning the KML, i.e. the improvement of oncology services for lymphoma patients both horizontally and vertically, and to link it with the idea of research-based practice. Subproject 8B is also closely linked with the Cochrane Collaboration, a worldwide network of health and academic centres, whose aim is to promote and foster this approach.

Through its primary activity, that is to produce and maintain systematic reviews, subproject 8B adds another important dimension to other quality assurance measures within the KML structure. Between January 2000 and July 2001, the CHMG has published one systematic review and five review protocols on CD-ROM (Cochrane Library) for all members of the KML, the international medical and scientific community and the public.

### 3.3.4 Quality management

The improvement of quality in all aspects of lymphoma clinical trials is an aim spanning all subprojects of the network. Forum and working teams have been built up, and projects initiated, which bring together those who work in the subprojects, collaborators of the study groups and quality experts from inside and outside of the network.

One important aspect of improving quality in lymphoma clinical trials is to improve and simplify interaction and communication between all professionals involved. Therefore, the aim is to apply computer science and telematic concepts as well as to develop quality management tools and to make them available for other partners of the KML. An example is the conception and establishment of an environment for developing an integrated information and communication service. Network partners such as the pathology (subproject 3) and radiotherapy reference centres (subproject 4) will have access to all quality instruments developed within subproject 2.

Furthermore, harmonising and defining standard operating procedures for the clinical trials within the network will also improve quality. Most clinical trials running in the network are treatment optimisation trials rather than new drug approvals. Therefore, it is the aim to interpret the guidelines for good clinical practice (GCP in the International Conference on Harmonization (ICH) Guidelines) and to put it in concrete terms for these kind of trials.
A working group on quality management (WG-QM) was established. The regular meetings of the WG-QM are attended by members of subproject 2, the three quality managers of the KML, network assistants, representatives of other subprojects (e.g. subproject 3 and 5), and external quality management groups (like the “Fachgruppe QM des Verbunds der Koodinierungscentren für Klinische Studien” and the “SOP Working Group” from Cologne). In these meetings, all projects of the WG-QM are discussed (see report, subproject 2) until an agreement between the study groups is reached. Furthermore, appropriate methods for the evaluation of future quality assurance steps are developed.

For example, a common system of SOPs for study centres, its review process in the study groups and the authorisation of SOP via the board of directors of the network have been defined by the WG-QM. The creation, administration and user specific distribution of SOP will be supported by a management tool for SOPs which is conceived and developed by the WG-QM.

As a second example, the competence network aims toward harmonisation of study documents and clinical definitions. This matter involves cooperation with the network assistants (see report of subproject 1). The network assistants are an important pillar of the quality management in the KML. They cooperate and initiate projects concerning the quality assurance of clinical trials documentation (see report about network assistants), and compare the methods of documentation and definitions of terms between the three study groups. The results obtained are the basis for harmonisation discussions between representatives of participating clinical institutions, biometricians, data managers and quality managers. Moreover, the results of this inquiry are an important input for the conception and build-up of an electronic data dictionary. Conception of and care for this integrative, biometric, knowledge-based data dictionary for all patient-related characteristics within treatment protocols is done by the WG-QM.

On the basis of first monitoring results in the main lymphoma studies and the above mentioned comparison of study documentation, the network assistants started to develop a specific teaching program for data nurses in lymphoma studies. In cooperation with the pharmaceutical industry, a project for improvement of study documentation is in the start-up phase (see report of subproject 1).

Besides, members of subproject 2 participate in the TMF working group “IT Quality Management”. In cooperation with the Fraunhofer ISST and other medical networks a guideline for basic documentation of IT projects and a evaluation concept for this guideline is worked out (see report TMF).

### 3.3.5 Telematics

The BMBF installed a central telematic platform (TMF) in April 1999 with a management office at the Fraunhofer Institut für Software and Systemtechnik (ISST) in Berlin. The aim was to
establish an IT infrastructure for medical research in Germany. Comprehensive solutions to general telematic problems should be found and shared by the different medical research networks (i.e. competence networks, coordination centres for clinical trial).

The members of each medical research network were encouraged to join the TMF’s different working groups:

- data security and confidentiality,
- IT quality management,
- system components for medical research and clinical trials, and
- legal aspects.

A short summary of each topic is included below, and has been written by the participating members of subprojects 1, 2 and 6.

**Data security and confidentiality**

The competence network participates in this working group since the end of 2000. It is especially interested in the following three topics:

1. Development of prototype scenarios for research designs meeting data protection requirements
2. Pseudonymisation of data and its implementation in subproject 6 acting as a model for other research projects
3. Development of data security concepts for medical research collaborators

To date, the competence network has written three research proposals concerning these topics as part of a research programme of the TMF. In addition, the network has appointed a coordinator for data security and confidentiality who will support the projects in finding solutions for current problems and gather information on emerging problems concerning data security and confidentiality in general.

A partial proposal for the TMF project for the period 2001 to 2003 has been outlined. This part of the proposal focuses on the development of generic security concepts for medical research associations. After evaluating these security concepts within the KML, the results will be made available to other research associations through the TMF.

**IT Quality Management**

Founded in May 2000, the group’s primary objective is to ensure and continually improve the quality of research associations’ IT infrastructure and IT services. The group worked on the following projects:

**Project 1:** Web-based working and communication infrastructure for the working groups

**Project 2:** Guideline for basic documentation of IT projects

The participating KML-members contributed to project 2, which is aimed to design a guideline, in order to ensure the quality of management processes in executing information technology projects. The group collaborated with the Fraunhofer ISST and members of other competence
networks in the preparation of a guideline for basic documentation of IT projects, including template documents, and of an evaluation concept.

Furthermore, a checklist was assembled in cooperation with the ISST reflecting the need for guidance in IT project planning for future medical research networks.

Besides that, a contribution to the TMF project proposal for the period 2001-2003 was supplied.

**System Components for Medical Research and Clinical Trials**

The working group was founded in Berlin in May 2000. This working group aims to support research associations by installing and running knowledge and information servers, as well as by introducing tools for executing clinical trials and documentation (e.g. remote data entry).

Three projects were selected for 2000:

- **Project 1**: TMF information and knowledge server
- **Project 2**: Installation and operation of information and knowledge server
- **Project 3**: Recommendation for the internet-based data editing (RDE)

The group works together with the ISST on project 2. The subject of this project is the evaluation of a Content Management System (CMS) for the development of information services, as well as the generation of recommendations for the procedure of establishing information services. A catalogue of requirements for CMSs was created. Based on this catalogue, various CMS were evaluated. The evaluation involved a number of product demonstrations (e.g. VIP Suite by Gauss Interprise, and PiroBase by PiroNet) and test installations (e.g. VIP Suite by Gauss Interprise, Network Productivity System by InfoPark AG, Zope (Opensource)).

In addition, a proposal for the TMF project concerning the period 2001 to 2003 was supplied. This proposal focuses on the design of prototype solutions for the implementation of an information service within the research associations, as well as its transfer to up to five research networks serving as reference points.
4 Progress Reports

4.1 Progress report of subproject 1

Topic
Central office of the Competence Network Malignant Lymphoma

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Summary
Management and coordination of the Competence Network’s projects and activities is the main task of the central office. This comprises administration of the network’s subprojects as well as coordination of network-wide cooperation between them. To achieve this aim, the central office organizes network conferences, i.e. general meetings of the members, project leader conferences, or meetings of the board.

The second major task of the central office is to provide information on the network’s activities and the lymphoma study groups. The homepage of KML is the central part of this information service. It has been developed in close collaboration with subproject 2. In order to complete this service, print media are published which are distributed inside and outside the network. In addition, symposia of the network at major congresses for internal medicine and haematology/oncology are organized by the central office.

Media work is closely related to the network’s information service and is also part of the central office’s activities. Two press conferences have been held on the occasion of the network’s annual symposia. Moreover, press releases and smaller articles are published regularly.
Status of work and results

The progression of the project is in line with the objectives of the grant proposal and the time schedule outlined. The central office started its work in November 1999. At that time, the vacant positions for the chief executive officer, the clinical coordinator, the computer scientist and the public relations manager could be filled. The major tasks of the central office can be divided into four categories:

- Administration and coordination of the networking activities
- Public relations
- Installing an information service for lymphoma research and treatment
- Quality management

Administration and coordination

The clinical departments and research institutions affiliated with the KML are distributed over Germany. To intensify the exchange between the subprojects and the implemented study groups, the central office organized several meetings for the members of the network: General meetings of the members (January 2000, March 2001), meetings of the project leaders (November 1999, May 2000, November 2000), meeting of the board of directors and the extended board (March 2000, September 2000, October 2000, November 2000, March 2001).

As one of the first tasks, the office wrote a proposal for the rules of the KML which define the different categories of membership and the obligations of each member. The rules which were confirmed by the general meeting in January 2000 serves as an essential instrument for the internal quality control of the network. Other instruments are the annual reports of each subproject which have to be submitted to the speaker of network and the project leader conferences where the members have to report the current status of their project (see also Chapter 2.3)

The central office also coordinates the submission of the annual reports which have to be prepared for the funding organization. In close collaboration with the latter and the board of directors, the scientific advisory board was installed.

Public relations / organization of symposia

The visibility of the activities of the competence networks has been defined as an essential goal by the funding organization. The central office tries to meet this obligation by various approaches:

In January 2000 the central office organized the so-called start up symposium which was open both to the medical/scientific audience and to patients and the general public. A second symposium followed in March 2001 when the KML presented the results of funding period’s first year. Furthermore, the central office regularly organizes symposia for the annual congresses of the societies of internal medicine and haematology/oncology (DGIM/DGHO). In chapter 3.2.4, the reader will find a list of symposia of the KML in 2000 and 2001.
The media work of the KML which is organized and performed by the central office has been described in detail in chapter 3.2.1. Major milestones were the two press conferences which have been held on the occasion of the start-up and the 1st annual symposium. In addition, a special column for journalists has been established on the network’s homepage, and the network has been registered in “Informationsdienst Wissenschaft” (idw).

On the occasion of the start-up symposium, the central office published a brochure which has been designed for the “general public”: Kompetenznetz Maligne Lymphome - Medizin 2000. In short review articles the subprojects of the network are described. In addition, the reader finds a list of all contact persons of the KML. In July 2000, the KML published its first newsletter. The newsletter reports about the projects of the KML, the clinical trials of the study groups and the work of the specialists in haematology/oncology working in primary health care centres (Schwerpunktpraxen). Further reports, e.g. on medical conferences complete these basic columns (see also Chapter 3.2.2). The newsletter is released twice per year, the central office manages the editorial work.

Information service
The homepage of the KML serves as the central part of the information service of the KML: www.kompetenznetz-lymphome.de. The homepage was developed in close collaboration with subproject 2. While subproject 2 is responsible for the technical concept and consecutive realisation, the central office creates the concepts for the contents, the graphical design and is responsible for the further performance. The homepage was activated in December 2000, about 4000 accesses per month were counted in March 2001. In chapter 3.2.3, the different columns of the homepage are described in detail. The contents are usually generated in collaboration with subprojects of the KML and the lymphoma study centres. An intensive collaboration with patients’ self-help groups has been developed when creating the special column for this group.

Quality management
The central office coordinates the activities of the network assistants who work in the clinical study centres in Homburg, Kiel and Cologne. In a first pilot phase, the assistants studied the clinical trial protocols and adopted special tasks for the study centres. In addition, some persons attended a training course organized by the KKS (Coordinating Centre for Clinical Studies) in Leipzig. The first major project has recently been started in close collaboration with the quality managers. The goal of this project is the harmonisation of study documents and clinical definitions. In a first step, they compared the methods of documentation and definitions of terms between the three study groups. On the basis of this results, the network assistants are to develop a special teaching program for data manager in lymphoma studies.

For the near future, a project which aims to improve the study documentation in clinical non-universitarians institutions is planned. The network assistants will support the data manager in
the documentation process or potentially adopt the documentation. Additional funding by the pharmaceutical industry will allow the engagement of two further data manager.

**Cooperation with other subprojects**

According to its tasks, central office collaborates with all the network’s subprojects. Especially, the development and maintenance of the homepage and the regular publication of the newsletter requires a close interaction with the subprojects and clinical study centres. The closest collaboration has been established to subproject 2 for the information service. At the university of Cologne, the project leaders and co-workers of subprojects 6 and 8B attend the weekly meetings of the office and support the office’ activities.

**Publications (non-scientific)**

Kompetenznetz Maligne Lymphome - Medizin 2000 (Brochure)
Newsletter Kompetenznetz Maligne Lymphome (2 issues per year)

**Objectives for the forthcoming funding period**

The central office aims to make substantial progress in the following areas:

**Public relations:**
- regular release of press statements
- intensification/establishment of contact to journalists and editorial offices of public media

**Symposia**
- organisation of special symposia for patients

**Information service:**
- publication of a brochure for patients about the treatment of low-grade NHL
- creation of a patient consulting module for the homepage
- development of a user identification and registration system for the homepage
- establishment of an editorial committee with workstations in the subprojects and the clinical study centres

**Quality management:**
- starting a project in cooperations with the pharmaceutical industry for the improvement of the study documentation in clinical non-universitarian institutions
4.2 Progress report of subproject 2

Topic
Telematics and computer-based quality management in a communication network for malignant lymphomas

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Summary
Subproject 2 drafts and installs information technology concepts and tools for the network in order to support data and information flow between research and applied health care.

Within the report’s timeframe, telematics focused on a central communication service’s conception and establishment, as well as on the conception and organisation of a communication network. The establishment of the communication network requires the partners’ integration. This process was initialised by integrating the reference centres for pathology (subproject 3).

Computer-based tools for quality assurance in clinical trial management are being developed as the project’s other main aspect is quality assurance. To coordinate the clinical trial groups’ cooperative efforts, a combined working group has been formed. It focuses primarily on the conception of a SOP system as well as on the computer-based support of SOPs.

Status of work and results
The project leader executed conceptual and content planning; progress was made according to the timeframe set.

Communication services
This project aims to establish a computer-based communication infrastructure to interweave the project partner’s working on malignant lymphoma. The communication centre’s construction started with an analysis of requirements regarding hardware and software communication technology, as well as telematic and quality management in clinical trial execution. The whole technical infrastructure for the competence network, i.e. all server systems and workstations ordered for subproject 2 in 1999, was installed: Setup, testing, and launch into operation. A
backup solution for all servers and workstations was implemented. The conception and realisation of a multi-level security and access concept was started.

**Information service**
The development of informational concepts and tools for the standardised preparation and presentation of information on the WWW is this project’s objective. The partners specified the requirements in cooperation. The requirements’ analysis called for a commercial content management system (CMS). Based on the evaluation of a number of CMSs, the product VIP Suite by Gauss Interprise was chosen. The CMS was installed, experience in its use obtained, and the initial design implemented using functional extension, developed in-house. A navigation database was designed and implemented. The information service is in everyday operation since the end of 2000.

**Quality management**
This project cares for the quality management procedures for the competence network’s clinical trials. So far, content definition and computer-based support for SOPs were stressed.

Structure, design requirements, and a procedure for the creation of a SOP system, supporting a number of clinical trials, were defined. To advance the computer-based support of SOPs, a first concept providing multiple views (functional/procedural view, content view) and granularity aspects (clinical trial phases, excellences, user groups, etc) was developed; procedures for their realisation were agreed upon. In cooperation with network assistants, work has started to harmonise clinical trial documents and to evaluate quality assurance.

**Biometrical, knowledge-based data dictionary**
An initial conceptual proposal for the declarative description of conceptual structures in the clinical trial context was created as contribution to a future biometrical knowledge-based data dictionary.

**Cooperation with other subprojects**
The cooperation with other subprojects is highly important within the central telematic project, especially regarding the partners’ integration. Therefore, subproject 2 runs telematic workshops twice a year. The staff of the projects involved presented to one another the progress of work and discussed the future communication and integration concepts.

The project “Conception and Realisation of a Central Information Service” involves close cooperation with the network’s central office (subproject 1). The central office collects the content and prepares it for presentation. Subproject 2 conceives and implements informational concepts and tools for the information service’s construction based on the partners’ agreed requirements.
Moreover, a close cooperation with the reference centres for lymph node pathology (subproject 3) has been established as these partners are to be integrated first.

**Publications**


**Objectives for the forthcoming funding period**

The IT infrastructure’s extension stresses the data security concept’s completion as well as the implementation of further components. The firewall concept is of primary importance to achieve that goal. The reference centres for lymph node pathology’s network will be used to evaluate the use of virtual private networks.

A central directory service’s (Lightweight Directory Access Protocol – LDAP) conceptualisation and implementation shall contribute to the information service’s advance. The definition of an access control concept, based on the central directory service LDAP, will be integrated into these efforts. The information and communication portal’s basic functionalities are to be further enhanced; groupware features need to be implemented.

As for the quality management, several SOPs should be drafted, and the competence network’s management board should release a SOP. For the computer-based support, the conceived SOP management tool should complete the first development cycle. Work on clinical trial documents’ harmonisation and the evaluation of implemented quality assurance measures are to be continued. To advance the data dictionary, terms will be collected using an appropriate tool.
4.3 Progress report of subproject 3

Topic
Network of the reference panel for lymph node pathology

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Summary
The aim of this project is to establish a computer network that enables a fast and reliable exchange of patient information (e.g. histo-pathological diagnosis) for cases which are enrolled in clinical trials between the six pathology reference centres and the clinical trial coordination centres. To achieve this, each reference centre needs to be equipped with a local database containing all its relevant patient information. Each local database should then be connected via internet or ISDN with a central pathology server located in Leipzig (subproject 2). Finally, the central pathology server should be linked to the clinical trial coordination centres to enable exchange of information in both directions.

Status of work and results
Fast communication between the lymph node pathology reference centres and clinical trial coordination centres is a decisive factor for the correct treatment of patients enrolled in various clinical trials. This project was initiated in order to enhance the velocity and reliability of this communication.

The following tasks were scheduled for the first year of the project's existence:

1. Purchase of the hardware and software required for the central pathology server and the local data bases in the six reference centres.
2. Definition of the database’s structure.
3. Programming of the database in ORACLE.

In addition to the tasks above, the initiation of the following activities was planned:

4. Set-up of the prerequisites for communication (Internet or ISDN).
5. Definition of the common diagnostic criteria for clinical trials (WHO classification).
6. Definition of translation tables in order to transfer the information held by the reference centres to the requirements of the corresponding clinical trials.
7. Preparation of each of the established local computer systems to extract the relevant data for storage on the new local databases.

**Purchase of the hardware and software required for the central pathology server**

All hardware for central and local databases was ordered at the end of 2000, unfortunately due to the late availability of financial resources, the order could not have been made any earlier. To avoid an interference of the function of the database hardware with other computer requirements, a second computer was ordered for each project co-worker in each reference centre.

**Definition of the structure of the data base**

One major task during the first year for all parties involved in subproject 3, was the definition of the data base structure.

In order to identify patients enrolled in clinical trials, four basic parameters were chosen: Family name, forename, date of birth and sex. These parameters will be used to match the patients enrolled in the trials with the lymphoma patients diagnosed at the lymph node pathology reference centres. Matched patient data will then be supplemented with the information concerning the identification number (ID) of the corresponding clinical trial, the branch of the trial, and the date the patient was randomised. After the completion of reference diagnosis, the data set for each patient will be completed with the final diagnosis, the date of diagnosis, the ID of the reference centre, and any further data necessary for the corresponding clinical trial (e.g. immunophenotype etc.). The complete set of information will then be transferred from the local data bases to the central pathology server and on to the coordination centres of the clinical trials.

**Programming of the data base in ORACLE**

The transmission of the data base structure into ORACLE will be realized by Ronald Speer, the project collaborator of subproject 3 who is located at the IMISE in Leipzig (subproject 2). This task includes the central pathology server as well as the local data bases. The programming of the local data bases will be particularly time-consuming, reflecting the heterogeneous prerequisites of the various reference centres. In addition, a communication protocol has to be implemented.
Set-up of the prerequisites for communication (Internet or ISDN)
The communication between the reference centres and the central pathology server in Leipzig is important for the entire network. The various possibilities and variations, based on the different situations at each location, require further discussion. At the project's inception, ISDN was the preferred means of communication, however the exchange of information via INTERNET has now become the preferred method for the majority of reference centres. This change became possible because of the introduction of pseudonyms which will be generated at each location prior to the transport of the patients’ data via INTERNET. The programming of these modules, however, requires a significant amount of additional work, which will constitute an additional task for 2001. Furthermore, it will be necessary to establish the technical requisites for communication through existing firewalls used for protection in most medical centres.

Definition of the common diagnostic criteria for clinical trial (WHO classification)
The WHO classification's definition of lymphoproliferative disorders is, fortunately, due to be released during 2001. This will enable the establishment of a common platform for all reference centres for any clinical trials. It will, however, take a certain amount of time to implement this at all levels, and in order to transfer available information, it will be necessary to establish translation tables for an interim period.

Definition of translation tables to transfer the information of the reference centres to the requirements of the corresponding clinical trials
The generation of translation tables is required for several purposes, as already mentioned above, the transformation of diagnosis into a common “language” will, at least, be necessary for a transitional (interim) period. The preparation of this task will be initiated by all reference centres by generating a database field which will represent a diagnosis code. This field will be used to transfer this information into the local data base automatically. This diagnosis code can then also be used as a basis for the translation - into a diagnostic term - that is understood and used by the corresponding clinical trial. In addition to this translation table, several other tables will be necessary. These comprise of the translation of the ID of the clinical trials into the name, the ID of the trial branch into the treatment modalities, and, in the other direction, the name of the reference centre for lymph node pathology into the reference centre ID.

Preparation of the established local computer systems to extract the relevant data for storage on the new local data bases.
The extraction of the relevant data from the existing local computer systems is a major task for this sub-project. As a first step, we have analysed the structure of each existing system and have developed strategies for the extraction of data necessary for communication within the competence network. Unfortunately, three completely different systems are currently used by
the six reference centres. This implies that three different concepts will have to be developed to achieve automatic transfer of the relevant patient data into the respective local data bases.

**Cooperation with Other Subprojects**
This project is very closely linked to subproject 2 which has been responsible for the establishment of the central pathology server which is located in Leipzig at the IMISE. Subproject 2 is also responsible for the establishment of communications between the lymph node pathology reference centres, the central pathology server, and the clinical trial coordination centres.

**Publications**
None

**Objectives for the forthcoming funding period**
In 2001, the local data bases and the central pathology server will be programmed in ORACLE. This part of the project will be performed by project associate Ronald Speer in Leipzig. The establishment of communication between the reference centres and the central pathology server will be the second task in 2001. This includes the installation of the hardware in each reference centre, installation and individual configuration of the software as well as the exchange of patient information in a test phase prior to production. The installation and testing of the individual tools for the extraction of lymphoma patient data from the existing systems in each reference centre is also a central task in 2001.
4.4 Progress report of subproject 4

Topic
German lymphoma studies as an example for quality assurance in radiotherapy

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Summary
The aim is a nationwide quality assurance with blanket coverage in radiotherapy with the help of telemedical conference possibilities and electronic picture transfer.

The pilot stretch for imaging data communication was established between two radiotherapy reference centres. Actually, further centres with high numbers of patients are being connected. Other cooperation partners may also deliver imaging data on mobile data carriers or via an ISDN connection. The possibility of central online documentation was achieved in two locations with the cooperation of other subprojects’ working groups.

The aims for the period of assistance in 2001 are to optimise central installations, to expand the integrated communication systems and task tackling going beyond the scope of the project.

Status of work and results

Schedule of the application
Apart from prospective radiotherapy prescriptions, new communication structures should assure a short-term check of the therapy between the radiotherapy centres and the participants of the study combined with a possible exchange of further patient characteristics and a short-term adjustment of the documentation. Besides continuous quality control and quality assurance processes, already practiced during the last study generations, the following is envisaged for radiotherapy as a pilot within the framework of the integrated system’s project KML:
• building up of electronic imaging transfer between the radiotherapy reference centres
• establishment of the possibility for telemedical and teleradiological conferences between the participating study centre and the radiotherapy reference centre and as well as between the radiotherapy reference centres within a panel of experts
• creation of a possibility to store imaging data at a central location with radiotherapeutic supervision

Long-term aim is networking in a cooperative integrated system of participating hospitals, institutions, and private facilities which are able to:
• communicate continuously via transfer of imaging data
• complete and immediate delivery of imaging and patient data to plan individual therapy based on standardized prescriptions
• check during therapy the implementation into practice
• carry out final quality assessments and possible relapse analyses with the help of the imaging data archive

All participating centres have to be equipped with hardware and software to guarantee a quick and high quality transfer of imaging data as well as immediate interactive consultations (conferences). The logistics for keeping track of patients and the documentation of planning and therapy assessments are to be integrated into the general data flow of the study-related competence network telematics project subproject 2. Each patient’s state of study should be updated quickly.

**State of affairs**

Besides the continuation of the documentation on paper, the assessment of imaging exchanged by mail, the elaboration of prospective standards and retrospective assessment of radiotherapy, the planning and expansion of the DP-assisted processing could be started in early 2000. The up-take, analysis and formulation of the characteristics and demands of the work related to the study secretary as well as radiotherapy reference centre is completed. The biometrics of the GHSG installed online-documentation programs for study data in Cologne. Similar possibilities exist in Homburg/Saar.

The planning and conception of the telemedical-teleradiological service unit of the Klinik für Strahlentherapie in Köln (Cologne Clinic for Radiotherapy) started in May 2000. Based on the demand for a low-cost commercial solution, easy to be administered, a combined model workstation was installed with taking standards largely into account and also fulfilling certain quality requirements. The structure is: standard PCs with Windows NT as operating system and the commercial picture management software HIPAX®. Since 1996 this software has been developed as an independent product and part of other established information systems in the medical field. It is already used in other networks for the processing, administration and
communication of imaging data. Its modular structure allows easy adaptation to the tasks and needs.

Complementary aspects:

- The existing technical infrastructure differs from location to location. A concept for the integration and connection to the telecommunication network will be elaborated for each location with the aim of mostly comparable installations. The workflow of the different studies will be taken into account.
- Because of reduced staff in the involved IT departments, there are delays in the integration into the clinical networks, in the installation and in the operation of central components for the connection to public networks.
- Communication via Internet is built up at the same time as the planned integrated ISDN system, because the larger clinics increasingly install their own central telemedicine ports. Furthermore, the cooperation partners are asked to send in a growing number of images in electronic form, and participants from outside the centres should be able to perform electronic imaging data communication.

Results

The building up and the operating of teleradiological bridge heads in scientific centres with help of commercial standard technology is possible and useful.

- The introduction of new forms of communication requires changes and rethinking of the users.
- Sufficient user acceptance will only be achieved with a comprehensively integrative approach respecting the existing local structure.
- The availability of digital imaging data cannot be assured through the digitalisation work of the centres alone. Considerable amounts of resources are needed. The transfer of digital imaging without a break has to be supported peripherally within the integrated system in the future. (Principle: "Digitally generated documents must subsequently be processed digitally.") Peripheral cooperation partners should be integrated as early as possible.
- With the expectation of increasing amounts of sent in material and the need for additional interactive case discussions as well as increasing documentation, further training courses are to be established and probably an expansion of the basic units of work as well as numbers of staff is required.
- Actually, there are no standards for a secure, system-independent communication with patients’ data. Incompatible standards of the different teleradiology system suppliers reduces cross-network cooperation.
Cooperation with other subprojects

- extension of online-documentation possibilities and research for the reference centres based on study data (subproject 1 and subproject 2)
- securing and expanding electronic communication via public networks: encoding, authentication, online-research, etc. (following the standards of subproject 2, TMF)

Publications

Müller RP, Staar S Schneeweiß A, Eich HT, Hansemann K, and Roehl M. Qualitätssicherung in der Strahlentherapie am Beispiel der Deutschen Lymphomstudien [German Lymphoma studies as an example for quality assurance in radiotherapy], poster presentation on the occasion of the annual symposium of the competence network 2001

Müller RP, Staar S Schneeweiß A. Qualitätssicherung in der Strahlentherapie am Beispiel der Deutschen Lymphomstudien [German lymphoma studies as an example for quality assurance in radiotherapy]. Telemedizin-Atlas NRW (Telemedicine atlas North Rhine-Westfalia) 2000

Müller RP, Staar S Schneeweiß A. Qualitätssicherung in der Strahlentherapie am Beispiel der Deutschen Lymphomstudien durch Aufbau eines Teleradiologie-Netzwerks [German lymphoma studies as an example for quality assurance in radiotherapy by establishing a teleradiology network]. Poster presentation on the occasion of the annual meeting of the Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie [German Society for Medical Informatics, Biometrics and Epidemiology] 2001

Objectives for the forthcoming funding period

Expansion within the core installations

- when operating is taken up: check and adaptation of the installations (workflow, hardware and software, the need for memory, the interface problem), expansion of the work locations (concerning panels, further training; interactive teleconferences)

Expansion of the integrated communication system

- integration of further centres
- building up of communication via internet at the same time as the planned ISDN-integrated system
- long-term aim: networking of all those hospitals, institutions and private facilities taking part in the lymphoma studies to achieve an integrated cooperation system

Aims going beyond the scope of the subprojects

- expansion of online-documentation and establishment of electronic communication of case documentation: cooperation with the telematics subproject and the department of biometrics (continuous comparison of data and later integration into the integrated telematics system)
- use of cross-competence network synergies as regards imaging data communication (e.g. the work of the TMF working groups which can be expected)
4.5  Progress report of subproject 5

Topic
Quality management of the basic health care in haematology/oncology primary health care centres.

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Summary
Preliminary work has been done between January and August 2000. This work consisted especially in founding a consortium „Kompetenzznet der hämatoonkologischen Schwerpunktpraxen” in March 2000 with 72 German primary health care centres for oncology and haematology (Schwerpunktpraxen) and searching for the staff of the project. In August 2000 the project group, responsible for the coordination, could start its work with the employment of a research assistant and the confirmation of funding from the BMBF.

The place of the medical documentary could be occupied from September at least part-time. The complete infrastructure, renting of office-areas, purchase of office furniture, purchase and administration of the hard- and software, furnishing of communication possibilities, was completed in middle of September 2000.

At the same time, the project office started to coordinate all tasks of the project in cooperation with the contact persons of each individual team. The work includes further layout of guidelines in detail, implementation of electronic data collection as well as analysis of a communication network.

A first software type has been developed to analyse the current situation of health care. The software obtains essential data from the refund electronic data system of the information system in the primary health care centres. Additionally, a questionnaire was designed in order to collect data not included in the electronic database. Beside quality indicators of care, the number of patients included in the studies will be recorded.

In cooperation with the working group “clinical economy” at the university of Ulm, the project group developed a curriculum for an EbM course, which will take place for the first time in
Cologne in May 2001. The two-day course consists of three modules: diagnostic, therapy and guidelines.

**Status of work and results**

The entire project is subdivided into three spheres of action:

- Prospective recording of the actual situation in the routine care lymphoma-patients
- Evidence-based medicine and guidelines for therapy
- Increase of the participation in therapy-optimisation-studies

**Prospective recording of the actual situation in the routine care lymphoma patients**

The collection of data will be done in two steps: Main purpose is the use of the existing information which is stored in the health information systems of the primary health care centres and to format them in such a way, that they are accessible to automatic data-processing and evaluation.

With the proposed collection method not all of the desired data can be obtained, so that a health care professional needs to check the collected data in order to guarantee its quality. For this second check of the data a validated questionnaire was designed.

A working group of haematology practitioners defined the items of the questionnaire in cooperation with the research assistant. Beside a basic data set, the questionnaire consists of 31 items that ask for the important quality-indicators in diagnostics, therapy and care. All information regarding the lymphoma entities are obtained. The entities will be classified according to the ICD 10 key.

The programme for automatic data extraction from the billing data system of the health care information system had been completed in the programming language QBasic. With several Access-SQL-operations, the information is brought from ASCII-coded billing data into the form of a Jet-4.0-database. In cooperation with Dr. Jacobs, an oncologist working in a primary health care, the project developed a complete software solution in form of a prototype. This prototype was completed in April 2001. It is able to extract the data from the health care-information system in an MS-Access working environment. This first solution for the data collection still had too many problematic elements for the use in the primary health care centres, but it demonstrated the feasibility of the project clearly. In order to notice further problems as early as possible, the prototype is used for tests already in some surgeries.

In cooperation with a company for professional software development, the project team works now on a windows-based, user-friendly solution that will be evaluated in August 2001. While the data collection was originally planned only in the first and in the last year in order to get an impression of the improvement of the study group, now it appears more meaningfully to raise data quarterly.
Evidence-based medicine (EbM) and guidelines for therapy

On the second German EbM symposium in Berlin in October 2000 there was an experience exchange of organizers from EbM courses. The project team established contact to the task force of the medical main office for quality-protection (ÄZQ) that produces an EbM curriculum for the Federal State Medical Board of Registration (Bundesärztekammer). Under consideration of the experience gathered on the symposium, the team specifically elaborated an individual curriculum for an EbM course especially for oncologists in cooperation with Prof. Porzsolt. The first course takes place in May 2001.

Increase of the participation-degree at therapy-optimisation-studies

With the prospective acquisition of the actual state, the aspect of the participation-degree in therapy-optimisation-studies will be detected, too. The questionnaire determines the number of patients, that are already included in therapy optimisation trials. Also the part of the patients, that would be suitable for a study, but are not included yet, is determined. In a pilot study in primary health care centres of the study group the more exact causes for not-participation at studies at the moment will be examined. The results are in-taken into the further planning of the project.

Cooperation with other subprojects

In designing the contents of the newsletter on the homepage, subproject 5 works in cooperation with the central office of the competence network (subproject 1).

Additionally, work was done in cooperation with subproject 2 in order to develop standard operating procedures (SOP) for therapy studies and clinical trials.

Moreover, one third of all patients taking part in the study of subprojects 6 (Epidemiology of Health Care) and 7 (Health Economy) are patients of the surgeries of the haematology competence net. According to the analysis of the actual state, it is to be expected that the number of surgeries taking part in the project as well as the number of patients will increase.

Publications


Objectives for the forthcoming funding period

- Analysis of the actual state: After a test-phase in the second quarter 2001, the first data-collection takes place in September 2001 with ADT-Extraction-Software and the questionnaire. The data of the first and the second quarter can be gathered retrospectively, because the information of this quarter is held in the old ADT-Files.
intended, the first valid data of actual state analysis should be introduced after two years of project-run time.

- Realization and mediation of EbM common study group that occupies itself with the possibilities in therapy and diagnostics and their effectiveness and efficiency shall be developed from participants of the EbM course. The members of the network will receive recommendations from this group.

- For a better information exchange between research and basic health care, a handbook will be produced providing information on different lymphoma-entities, on current studies and their treatment-regime as well as on standard-therapy outside clinical trials.
4.6 Progress report of subproject 6

Topic
A population based survey of management and outcome of patients with malignant lymphoma.

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Summary
The aim of this prospective observational study is to survey the medical care and treatment results of lymphoma patients (Hodgkin’s disease and NHL) with first diagnosis in 2000 - 2003, and to compare those participating in a clinical trial with non-participants.

In order to reach generally valid conclusions, a population based survey of all lymphoma patients in a defined geographical area is necessary. The parameters to be investigated include patient characteristics, type of institution, diagnostic measures, type and quantity of treatment and treatment results. Data are collected prospectively, mainly by means of patient notebooks. Analysis of data collected by the public health insurance organisation is planned and was prepared in order to assess the completeness of the notebook data and to answer further questions concerning medical interventions.

Survey, feasibility and coverage are tested in a pilot phase (May 2000 – May 2001) in two regions (city of Cologne and Saarland) with a total of 2 million inhabitants. The inclusion of at least 30% of all patients with a first lymphoma diagnosis has to be attained in order to justify extending recruitment beyond the pilot phase, and this goal has been achieved.

Status of work and results
The project status is in accordance with the application plan. Patients who are reported until end of May 2001 will be available for the pilot phase. The interim analysis will take place in October 2001.

The staff for the project, i.e. a physician, statistician and data-manager in Cologne and a physician in Saarland, were recruited in the end of 1999 and the beginning of 2000 respectively. The patient notebook and the forms for quality of life and health economic data collection as well as a structured interview were conceived and designed in cooperation with physicians.
treating lymphoma patients, quality of life experts and health economic experts. Problems with protection of privacy were discussed with the responsible person of the university of Cologne, and a solution was found.

It was decided that the distribution of the patient notebook should be mainly achieved by the pathologists diagnosing the lymphoma. Therefore, all pathologists of the two regions (10 in Cologne and 12 in Saarland and neighbourhood) had to be informed and their cooperation enlisted. The physicians ask the patient to participate in the project and to perform the documentation. All the physicians in Cologne and Saarland treating lymphoma patients were informed and asked for cooperation, mostly by a visit of the project staff or by letter and handouts. 42 out of 48 treating institutions in Cologne (9 practices, 15 surgical departments, 18 haematological departments) and 40 treating institutions in Saarland (2 practices, 26 surgical departments, 12 haematological departments) confirmed their cooperation. Local newsletters and television published articles and features at the start of the pilot phase in May 2000. Information sheets for physicians and patients were conceived and widely distributed. As a result of the information campaign, the project is accepted by pathologists, physicians and patients. Patients of all age groups, all types of lymphoma and from all the different treatment institutions have been recruited.

Since the start of the pilot phase the pathologists report their lymphoma cases to the project centre and send a patient notebook with the diagnosis to the treating physician. The reported numbers 447 are in accordance with the estimated ones and are comparable with those of the Saarland cancer registry.

The numbers of recruited patients are compared with the incidence rate of the Norddeutsche Leukämie- und Lymphomstudie (NLL), a German incidence study. In total, 167 patients were recruited until end of May 2001, i.e. 37.4% (expected in Cologne 259 patients, in Saarland 273 patients) of the estimated incidence (16 Hodgkin’s disease, 92 NHL, 29 CLL, 12 plasmocytom). From the experience of the last year we expect that this percentage will increase considerably during the next 3 months, as more patients who are reported before end of May 2001 are included in the project. Only 6% of the patients refuse to participate in the project. The limiting factor for recruiting patients is the extra workload for the physicians. In future, the project staff will offer increased support for informing patients and for documentation. There are differences in treatment institution and recruiting rates of patients with different lymphomas between the city of Cologne and the mostly rural Saarland. For example in Cologne outpatient treatment is more frequent.

In May 2001 a opinion survey was undertaken by the project centre to determine the acceptance of the project and to reveal the critical points. 239 out of 770 physicians in Cologne who were addressed answered. Their remarks will help to improve the recruiting rate and the documentation.
Concurrent to data collection via patient notebooks, a population based survey of inhabitants insured with the Local Health Care Fund (AOK, N=1.9 Mio. persons) in the region of Hesse has been prepared. Relevant data will be collected in two institutions: in the AOK (e.g. prescription data, hospital-data) and in the Association of Statutory Health Insurance Physicians in Hesse (KV Hessen) in order to collect claims cards with diagnoses. Data confidentiality problems have been solved in cooperation with the data protection officer of Hesse. In order to meet legal requirements, a “trust centre” responsible for pseudonymisation of personal and institutional identifiers will be implemented. This task will be fulfilled by the cancer registry of Rhineland-Palatinate. Furthermore, the data collection in two different institutions necessitated the development of special computer programs for the identification of lymphoma patients. These programs have been developed and tested.

Cooperation with other subprojects
The planning of the project, especially the conception of the patient notebook and the data forms, was performed in collaboration with subprojects 5 and 7. Data are collected together with subproject 7. The combined projects are named “Kölner Lymphomprojekt” in Cologne and “Saarländisches Lymphomprojekt” in Saarland. The public relations for the “Lymphomprojekt” was supported by the central office (subproject 1). Preliminary incidence data are reported from the associated epidemiological project “Norddeutsche Leukämie- und Lymphomstudie”.

Publications


Objectives for the forthcoming funding period
The pilot phase has to be evaluated: The reported patients who are not yet included must give their permission for participation in the project, the missing documentation in the patient notebook and the data forms for quality of life and economic data of all the recruited patients have to be completed. Then the interim evaluation will take place in October resulting in:

- the number of recruited patients in Cologne and Saarland as a percentage of the incidence rate according to age, diagnosis and treatment institution
- the status of documentation and difficulties concerning documentation
- a description of diagnostic procedures, therapies, and results
- a description of the patient’s contact with care givers from suspicion of lymphoma diagnosis to the end of therapy
The results of the pilot phase analysis will enter the planning of the main phase and the application for the next phase of support by the BMBF. The aim is to continue the project with increasing number of recruited patients and to complete documentation in the city of Cologne and the rural Saarland as planned until 2004.

Meanwhile, the recruitment of patients will continue and data will be gathered for the main phase of the project.
4.7 Progress report of subproject 7

Topic
Prospective health economic evaluation of medical care for patients with malignant lymphomas

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Summary
Together with subproject 6, this project is part of the „Kölner Lymphomprojekt“ in the Cologne region and the „Saarländisches Lymphomprojekt“ in Saarland. The aim of the project is to assess clinical benefits and costs of the treatments of patients with newly diagnosed malignant lymphomas, focusing on three main influencing factors: (1) Whether treatment is mainly carried out in the ambulant or hospital sector, (2) whether patients are treated in a clinical trial or not, and (3) whether patients are regularly treated by a haematologist/oncologist or not. The study questions are analysed using cost-effectiveness analyses which take the perspectives of the German sickness funds, i.e. the payers in the statutory health insurance system in which more than 90% of the population is covered, of a hospital, and of society. Typical patterns of care will be evaluated clinically and financially. On the basis of these analyses, clinical pathways and guidelines will be drawn up in cooperation with clinical trial groups and sickness funds.

The project is carried through by a physician on a full-time basis. He is supported by non-academic staff and receives scientific support from the Institute of Health Economics and Clinical Epidemiology (IHECE) of the University of Cologne and the Medical Economics Research Group (MERG) of the First Medical Department of the University of Cologne.
The data used in both sub-projects are gathered simultaneously by means of patient books. The recruitment of patients has been successfully started. Details of recruitment are reported in sub-project 6.

Main current areas of activity in this subproject are: (1) the completion of the health economic evaluation plan for cost-effectiveness analyses with respect to the above named influencing factors, (2) tracking down data missing in the patients books which are relevant from a health economic point of view, and (3) the recruitment of new patients.

The health economic evaluation plan will be used in the first interim analysis which is due in October 2001. In this plan, resource use is related to cost. Taking the perspective of sickness funds, per diem charges and case fees will be used for inpatients. Treatment carried out in the ambulant sector will be valued financially by means of the „Einheitlicher Bewertungsmaßstab“ and the „Gebührenordnung für Ärzte“, the two official lists of remuneration of medical services. Average real cost data of treatment in the in- and outpatient departments of the haematology and oncology unit of the University Hospital Cologne (UHC) have been calculated and reflect the perspective of a hospital. Cost-driving factors such as chemotherapy drugs, blood products, and growth factors are extracted from the UHC average costs and are added individually on the basis of patient book data. Taking the perspective of society, indirect costs are calculated by means of the human capital approach and patient book data on time of inability to work or invalidity. Future costs and benefits are discounted at a rate of 5 %, from the start of the study. Key cost factors are varied using sensitivity analyses.

Data missing in the patient books are tracked down by contacting health care providers, i.e. hospitals and practices, by phone and site visits, and by structured interviews of patients. So far, cooperation of physicians and patients has been satisfactory.

Recruitment of new patients requires continued maintenance of human relations with pathologists who report new diagnoses of malignant lymphomas to the project centres, physicians who obtain consent to take part in the study from patients, and patients who consider to take part.

**Status of work and results**

The time schedule laid down in the proposal for the Competence Network of March 2000 has been observed. Patient recruitment has been according to plan in both the Cologne region and Saarland. Nearly all pathologists, haematologists/oncologists and hospitals in the two regions have confirmed their cooperation in writing. Details of the project have been announced in the local press. Cooperation with the Physicians´ Association (Kassenärztliche Vereinigung) Hessen and the General Local Sickness Fund (Allgemeine Ortskrankenkasse) Hessen has been ensured in order to compare resource use documented in patient books with statutory health insurance data from another region.
Health economically relevant resource use items have been identified and incorporated into the patient book in a user-friendly manner. Costing tools specifically designed for the treatment of patients with malignant lymphomas have been developed for the perspectives of payers, hospitals, and society. A methodology for the development of clinical pathways and guidelines has been developed and reported (see above). The role of the Competence Network and, in particular, of this subproject for quality management in the German health care sector has been evaluated and reported (see above).

Cooperation with other subprojects
The patient book was designed in cooperation with subprojects 5 and 6. Cooperation is particularly close with subproject 6 as both projects rest on the same data base and collect data together. Regular project meetings are held by the project managers, project physicians, representatives from the IHECE and MERG and non-academic staff. For the costing of treatment in the ambulant sector, we cooperate with subproject 5 (oncological practices), using extensive data on resource use for patients with malignant lymphomas.

Publications


Objectives for the forthcoming funding period
In addition to the above specified main current activities, the first interim analysis of the „Kölner und Saarländisches Lymphomprojekt“ which is scheduled for October 2001 will be a focal point of our activities. We expect to arrive at a first short-term overview of costs and clinical benefits of treatment with respect to three main influencing factors (ambulant and hospital sectors; clinical trials; regular treatment by a haematologist/oncologist). Depending on the interim results, first steps towards the development of clinically and health economically based clinical pathways for the first year of treatment may be taken.
4.8 Progress report of subproject 8A

**Topic**

Model based meta-analysis of chemotherapy comparing randomised trials.

**Project leader**

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**Summary**

Objective: (1) To develop a method to meta-analyse chemotherapy comparing randomised clinical trials (RCT) in order to estimate the steepness of the effective dose/outcome relationship and to provide information on the relative potency of cytotoxic drugs. (2) Apply method to all chemotherapy comparing RCTs in lymphoma.

Conventional meta-analysis techniques are not adequate to jointly analyse all chemotherapy trials in a given disease. There is a large heterogeneity of the chemotherapy 'cocktails' compared in RCTs. Thus a simple unifying question cannot be formulated.

The main idea developed in the project is: (1) Define a summary measure of chemotherapy treatment strength containing unknown relative weights for the cytostatic drugs used. (2) From published RCTs one can try to extract a) the log hazard ratio of the progression free survival curves as a measure of treatment difference (and its standard error) and b) the drug doses and the duration of the planned treatment for both treatment arms. (3) It can be shown that with a good choice of the summary measure the log hazard ratio should be proportional to the difference in treatment strength of the planned treatment. (4) Non-linear regression analysis can then a) be used to estimate the proportionality factor describing the steepness of the treatment strength outcome relationship and b) estimates for the relative potency of the drugs used.

**Status of work and results**

(1) The summary measure ‘effective dose’ is derived from the generalised Skipper model of chemotherapy. This is an extension of the well known Skipper chemotherapy textbook model adding heterogeneity in form of two latent distributions: a) Heterogeneity in chemosensitivity and tumour burden and b) heterogeneity in latency time, i.e. in regrowth dynamics. Information on these latent distributions may be derived from the form of the time to progression curves.
Building upon Hasenclever 1995 (dissertation), the theory of the generalised Skipper model was reformulated in 2000 and its qualitative properties explored. It was shown that a suitable measure of treatment strength for use in meta-regression is the log effective dose defined as total dose (weighted sum of drug doses) divided by (1+ treatment duration/average latency time specific for the disease). Note that this formula is intuitive: duration/latency time is a proxy for the fraction of the tumour that re-grows during treatment intervals. For cure, the treatment has thus not only to eradicate one tumour, but (1+treatment duration/average latency time) tumour. The effective dose is both conceptually and empirically better to predict cure rates than the well-known concept of dose intensity by Hryniuk.

(2) An extensive search was performed to identify RCTs in lymphoma. More than 500 papers and abstracts reporting RCTs were found. Data extraction of chemotherapy trials is ongoing. Data is entered into specifically developed ACCESS databases. Methodological difficulties in extracting the relevant data in some publications were investigated.

(3) Preliminary meta-analyses in Hodgkin’s disease and aggressive Non Hodgkin’s lymphoma were performed to check the feasibility of the approach and to identify problem areas. In Hodgkin’s disease which is rather homogeneous, a clear effective dose/outcome relationship was found based on 68 pair-wise comparisons. Relative weights for frequently used cytostatic drugs could be derived that agree with clinical judgement. The existence of a relevant dose response relationship was confirmed by the HD9 dose escalation trial of the German Hodgkin’s lymphoma study group in the design of which first versions of the model played a role (see Hasenclever 1996 for a quantitative prediction). Thus the method lead to relevant and interpretable insights at least under favourable circumstances.

In aggressive NHL, there is a much higher heterogeneity of patients and between trials. The generalised Skipper model implies that the steepness of the dose response relationship decreases with increasing heterogeneity. Results in NHL are compatible with a less steep but still relevant effective dose outcome relationship, but less clear than in Hodgkin’s disease. The major insight was that the typical latency time in NHL was estimated to be 132 days in contrast to 490 days in Hodgkin’s disease. It is thus in the order of a typical treatment duration. This would predict that just shortening of treatment intervals may relevantly improve the outcome particularly in patients with aggressive growing lymphoma. The NHL-B trials of the German aggressive NHL study group recently showed that indeed shorting CHOP therapy from 3 to 2 week intervals using growth factor support improves the outcome. Subgroup analysis suggests that this effect is mainly seen in patients with high LDH, i.e. more aggressive lymphoma growth.

From this experience we now try to develop methods to incorporate information on the study population composition in the model to reduce heterogeneity and to obtain more stable results. To further support the hypothesis that patients with high risk aggressive lymphoma profit from
time intensified treatment, we are in contact with study groups to perform a respective meta-
subgroup analysis.

**Cooperation with other subprojects**

We cooperate with the German Hodgkin’s lymphoma study group and German aggressive NHL study group concerning trial design, and we support subproject 8B (Cochrane review group Haematological Malignancies) with methodological consulting.

**Publications**


**Objectives for the forthcoming funding period**

- Ongoing search and data extraction
- Further theoretical work on the generalised Skipper model with focus on better handling of heterogeneity in preparation of a publication between studies.
- Publication draft Meta-regression Hodgkin’s disease
- Project: meta subgroup analysis of time intensification studies with data provided from study groups
4.9 Progress report of subproject 8B

Topic
Establishment of the Cochrane Haematological Malignancies Group (CHMG)

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Summary
To bridge a gap in the rapidly increasing knowledge transfer between scientists, clinicians and patients involved in the management of malignant haematological disorders, subproject 8B was approved by the BMBF in 1999. Project specific activities commenced on 1st July 1999, following the recruitment of a coordinator (Mr. Thilo Kober, Australia). From the beginning, there was close consultation with relevant other network’s subprojects, i.e. 1, 6, and 8A, and the International Cochrane Collaboration (Dr. Iain Chalmers, UK Cochrane Centre; Dr. Chris Williams, Coordinator, Cochrane Cancer Network) and the German Cochrane Centre (Dr. Gerd Antes, Director). A broad-based information campaign was started from July to December 1999 at national and international level to promote wide multidisciplinary and international participation.

After a comprehensive application process for registration with the Cochrane Collaboration, the proposed CHMG was granted Cochrane status on 3 October 2000. As of 1 June 2001, the CHMG has published one systematic review (SR) and five protocols (preliminary systematic reviews). Nine more haematology/oncology review titles are registered with the international Cochrane Collaboration and are in various states of the CHMG editorial process. The CHMG has currently about 38 active contributors worldwide.

Status of work and results
The Cologne-based Cochrane Haematological Malignancies Group (CHMG) is the only Cochrane collaborative review group worldwide which undertakes and maintains systematic reviews in the area of defined malignant haematological disorders. The following activities are considered the most important achievements to date:
• **Establishment of the editorial base.** This process commenced in July 1999 and was completed by December 1999. It included the setting up of internal infrastructures, i.e. procurement of equipment and furniture and the recruitment of staff. Other activities included an intensive public relation and information campaign and the planning for an exploratory meeting.

• **Staging of Exploratory Meeting.** In February 2000, fifty-two people from eight countries attended a meeting in Cologne to discuss the founding of a proposed Cochrane Haematological Malignancies Group as soon as possible.

• **Establishment of the international editorial team.** A team of eight editors from Canada, Denmark, Germany, USA, and UK was nominated and has taken up work since February 2000.

• **Submission for Cochrane registration.** A comprehensive 50-page application for registration was submitted in May 2000 to the Cochrane Monitoring and Registration Subgroup. The CHMG received Cochrane entity status on 3 October 2000.

• **Development of CHMG editorial policies.** Between October 2000 and March 2001, a variety of editorial draft policies were developed and disseminated to all CHMG contributors for comment. During the inaugural editors meeting in March 2001, these policies were finalised, endorsed and published in the Cochrane Library and on the Internet.

• **Commencement of manual journal search (handsearching).** Since August 2000, two haematology/oncology journals (American Journal of Hematology; Annals of Haematology) are being hand searched for relevant randomised studies. The handsearching is being conducted by the Germany Cochrane Centre (but ceased in May 2001 due lack of funding) and Dr. Donald Stanley, a semi-retired pathologist from Maine, USA.

• **Publication of one systematic review (SR) and five protocols (review outlines) in the Cochrane Library.** For details see the publication list. In addition, nine review titles have been registered with the CHMG editorial base and are in various stages of the editorial process (i.e. draft protocol or draft SR).

• **Grant application.** To date four grant applications have been submitted to different funding agencies. Funding is being sought for three staff positions (Trials Search Coordinator, Consumer Coordinator, Research Assistant) and two systematic reviews. All applications are still under consideration for approval.

• **Scientific and promotional presentations.** The project was represented at major national and international cancer conferences and symposia (some are listed under publication, full details upon request)

• **Establishment of a consumer network.** The CHMG is developing a consumer health network to integrate lay persons and patients in the review process. There is close cooperation with key patient interest groups (DLH and others).

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**Cooperation with other subprojects**

This project liaises particularly with subprojects 1, 6 and 8A. This cooperation is best demonstrated in the internet presentation of the CHMG as part of the network’s homepage and information exchange relating to clinical trials and methodological issues. Due to its international focus,
subproject 8B also liaises with researchers in Australia, Canada, Denmark, Germany, Spain, USA and the UK and the Competence Network Leukaemia.

Publications

1. Cochrane reviews and protocols


2. Other publications


3. Non scientific publications

Kober, T. and Engert, A. Evidence-Based Oncology: The Establishment of a Cochrane Haematological Malignancies Review Group in Germany. Poster on the 6th Conference of the European Hematology Association in Frankfurt 2001


Kober, T. and Engert, A. The establishment of the Cochrane Haematological Malignancies Group (TP8B). The first year in perspective. Poster beim 2. Kompetenznetz-Symposium, March 2001


Cochrane Haematological Malignancies Group. The establishment of a Cochrane Haematological Malignancies Group (CHMG) and the Editorial Base in Köln (Cologne), Germany. Flyer 2000, updated 2001


In addition to already published Cochrane reviews and protocols, following review titles are registered with the CHMG editorial base and are in various stages of the editorial process:

i. Chemotherapy and supportive measures for older patients with aggressive lymphoma (Meyer R et al, Canada)

ii. Chemotherapy versus radiotherapy versus combined modality for non-Hodgkin's lymphoma (Specht L et al, Denmark)

iii. Clinical use of haematopoietic growth factors in the treatment for myelodysplastic syndrome (Ganser A et al, Germany)

iv. Erythropoietin in the treatment for haematological malignancies (Langensiepen S et al, Germany)

v. Haematopoietic cell transplantation for acute myeloid leukaemia in adult patients in first remission (Bellido M et al, Spain)

vi. High-dose AraC for Acute Myeloid Leukaemia (Kern W et al, Germany)

vii. Interferon-alpha for follicular lymphoma (Dreyling M et al, Germany)

viii. Myeloablative high-dose therapy with autologous stem cell transplantation for follicular lymphoma (Nickening C et al, Germany)

ix. Role of maintenance and consolidation therapy in adult acute lymphoblastic leukaemia (Göckbuget N et al, Germany)

**Objectives for the forthcoming funding period**

The CHMG aims to:

- prepare and maintain systematic reviews for haematological malignancies, using predominantly randomised controlled trial evidence;
- establish a specialised trials register;
- facilitate and encourage health consumer involvement;
- establish a comprehensive network of clinicians, scientists and patient representatives which is international and multidisciplinary;
- establish a CHMG consumer network.

To achieve this, the group aims to increase the level of international and multi-disciplinary participation and numbers of contributors. A very high priority is the procurement of sufficient funding for the next five years in order to increase, or at least maintain, the current level of review activities.
4.10 Progress report of subproject 9

Topic
High-dose therapy and transplantation of haematopoietic stem cells in malignant lymphoma

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Summary
The project aims to improve on the documentation and to facilitate analyses of high-dose therapy (HDT) followed by transplantation of autologous or allogeneic haematopoietic stem cells in lymphoma patients. During the first 9 months of the project we focussed on the selection, testing and development of suitable tools to allow easy, standardised and high quality documentation. The Project Manager Internet Server (ProMISE) is the most suitable tool. As a demonstration project we currently use the Mega-CHOEP study of the German High-Grade NHL Study Group in order to allow data entry via Internet. Documentation tools for further studies will follow. To demonstrate the feasibility of international cooperation in the field of HDT and lymphoma we started a cooperation with EBMT and IBMTR to compare allogeneic BMT with PBPC in lymphoma. Goals for 2001 will be to complete the documentation of Mega-CHOEP and other protocols via ProMISE, to complete the analysis comparing allo PBPC and BMT and to start epidemiological projects elucidating the practice of lymphoma transplants in Germany and Europe.

Status of work and results
Subproject 9 started in October 2000. Main efforts so far have concentrated on
- Tools for documentation of high-dose therapy
- Comparison of allogeneic bone marrow transplantation with allogeneic transplantation of peripheral blood progenitor cells (PBPC) in lymphoma
- Other activities

Tools
High-dose therapy followed by transplantation of autologous or allogeneic haematopoietic stem cells is a complex treatment modality necessitating extensive documentation. Reporting is
usually done on paper forms which are sent to the respective study centre by regular mail. Forms are specifically designed for a particular study or study group and thus lack any standardisation, they are not very user-friendly and do not follow pre-determined guidelines to guarantee data safety and quality. Aim of this part of subproject 9 is to improve upon the current situation and to provide a tool which should facilitate, standardise and improve documentation of high-dose therapy in patients with lymphoma.

To this end, we have decided to cooperate with the German Registry for haematopoietic stem cell transplantation (Deutsches Register für Stammzelltransplantationen, DRST), the European Group for Blood and Marrow Transplantation (EBMT), and the International Bone Marrow Transplant Registry (IBMTR), and we use the project manager internet server ProMISe to achieve high quality data management and for exchange between the German Lymphoma Study groups, DRST, EBMT, and IBMTR. EBMT and more recently also DRST decided to use ProMISe because it shows the following key features and advantages:

- Data transfer with the ProMISe system is safe – access control and data transfer use strong cryptography, different levels of access can be granted for each user based on individual decision.
- ProMISe features a central database; access to the system is Internet/Java based. Therefore,
  - any modern PC with MS Internet Explorer and Internet access is a potential client
  - authorised persons can log in from any terminal
  - no local installation and updates are necessary, no interference with installed software occurs.
- The actual application is built with a flexible toolkit and allows encapsulated user extensions
  - documentation needs down to precise study details can be modelled
  - user extensions can be developed without interference with the core system.
- The core system is used for registration with DRST and EBMT
  - user know-how and client platforms will already be widely available
  - no need for multiple data collection and entry.
- Hardware, software and database management and maintenance is done in the central system only
  - lower TCO (Total Cost of Operation) for the clients
  - no need for local servers, maintenance periphery, and extra staff at the client’s location.
- The core system provides means for access control, data input, modification, retrieval, statistics and download and it is used in a number of projects.
- Extension of a stable system saves time when compared to a development from scratch.
- Base system functionally has a large user base which is of advantage to the system's evolution cycle.

During the first months after the start of subproject 9, the responsible physician and the information scientists have extensively evaluated ProMISe. Multiple contacts (via email and personal meetings) between Dr. R. Brand, a lecturer in biostatistics at the University of Leiden, The Netherlands, who developed ProMISe, and representatives of this subproject have occurred and continue on a regular basis. As a consequence of these contacts it became clear that ProMISe is an elegant tool fulfilling most of the criteria a successful documentation system in the area of high-dose therapy should guarantee. After EBMT and DRST had made up their minds to use ProMISe it would have been very unwise not to use ProMISe and embark on a different system with all the potential problems this would create. Currently, a further improved version of ProMISe is being developed and tested by the information scientists of the project.

At this time we also use the Mega-CHOEP protocol – a phase II study of the GHNHL SG - as a model how to present the study protocol itself and how to facilitate documentation of this study via ProMISe. As soon as this goal has been achieved further study protocols of other German Lymphoma Study groups will follow.

Allogeneic BMT versus PBPCT in lymphoma

As an example of European and International cooperation in the field of high-dose therapy in patients with lymphoma we are currently involved in an analysis to compare the results of allogeneic bone marrow transplantation and allogeneic peripheral blood progenitor cell transplantation (PBPCT) in lymphoma.

In 1999 already close to 50 % of all allogeneic transplants used peripheral blood progenitor cells (PBPC) instead of bone marrow (BM). Seven randomised studies have compared the outcome after allogeneic bone marrow transplantation (BMT) and PBPCT in patients with leukaemia. Nothing is known, however, about the risks and benefits of PBPCT compared to BMT in lymphoma. Therefore, we proposed a retrospective study to compare both sources of haematopoietic stem cells in patients with lymphoma. This is a cooperative study with EBMT and IBMTR. Until today, several meetings with representatives of IBMTR (Annual Meeting of the American Society of Hematology 2000, San Francisco) and EBMT (February 2001, London) took place in order to agree on the outline of the analysis and the respective questionnaires which will be sent to participants of the study world-wide. It was agreed that only patients grafted with unmanipulated BM or PBPC from HLA-identical sibling donors between 1994 and 1998 would be analysed. As a first step we then screened the EBMT lymphoma Registry in
London, identified centres which had done such transplants, and sent out a letter to all centres which had reported allo transplants in lymphoma patients in order to make sure that

1. centres were willing to participate in this analysis,
2. only patients who had been allografted following standard conditioning regimens were included.

These questionnaires have been received recently. Back-flow of questionnaires was excellent and we expect broad participation in the study.

Simultaneously, an extensive questionnaire was developed to fully address the comparison of allergenic BMT and PBPCRT. This questionnaire was sent out recently to centres which had indicated their interest to participate in the study.

Other activities
With regard to other goals described in our application the following aims have been met:

1. a complete list of transplant centres is available
2. a complete list of ongoing lymphoma trials in Germany is available
3. study protocols with other European lymphoma groups (GELTAMO, Italian groups) have been developed and are available
4. counselling for physicians planning high-dose therapy in lymphoma patients is available.

Cooperation with other subprojects
Subproject 10: Cooperation concerning the diagnosis of secondary neoplasms following high-dose therapy and transplantation of haematopoietic stem cells. Materials (blood and marrow biopsies) will be provided. Documentation will be implemented.

Subproject 2: The standardized documentation tool for high-dose therapy and transplantation is one additional aspect for improving the communication (e.g. discussion of results) between centres. Cooperation with the telematics subproject will be intensified at a later stage.

Publications
None

Objectives
- Complete the documentation of Mega-CHOEP and other protocols via ProMISe as a demonstration project
- Complete the analysis comparing allogeneic PBPCRT and BMT.
- Start epidemiological projects looking at lymphoma patients receiving high-dose therapy within or outside active study protocols.
- Start a project comparing trends in lymphoma transplants for different European countries.
4.11 Progress report of subproject 10

Topic
Long term effects of myeloablative radiochemotherapy with consecutive autologous peripheral blood stem cell transplantation in patients with malignant lymphomas - incidence and early diagnosis of secondary haematological neoplasias

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Summary
Within the last few years, high dose therapy with autologous stem cell rescue has been proven to result in a superior progression-free survival in different subentities of malignant lymphomas. However, this positive effect may be hampered by the cumulative occurrence of secondary malignancies in up to 20% of patients after 5 year follow-up.

This project focuses on the determination of incidence and early diagnosis of secondary haematological neoplasias in different lymphoma subtypes. In a first step, all patients with follicular and mantle cell lymphoma who received a high dose regime with autologous stem cell transplantation within the therapy studies of the GLSG will be followed for up to 5 years and bone marrow specimens will be systematically screened for morphological and molecular alterations. In the second phase of the project, these investigations will be extended to patients with multiple myeloma, chronic lymphocytic lymphoma and aggressive lymphomas to define the disease-related predisposition.

Currently, the central infrastructure for the reception and distribution of patient samples has been established. In addition, a formalistic sample collection and asservation concept for patient samples has been developed and coordinated with the second participating scientific centre in Göttingen.
Status of work and results

Background

High dose chemotherapy with autologous stem cell transplantation represents a well-established therapeutic option in different subtypes of malignant lymphomas. In relapsed aggressive lymphomas, higher rates of long term remissions can be achieved; therefore, an international consensus committee recommended the high dose approach as standard procedure in relapsed aggressive lymphoma. Similarly, a French randomised study proved the superiority of high dose therapy in multiple myeloma. In indolent lymphoma, the GLSG recently confirmed the beneficial effect of high dose therapy on the progression-free survival.

The frequency of long term effects of high dose therapy, particularly secondary haematological neoplasias which may occur several years after initial treatment, is not well defined. In previous smaller studies, secondary haematological neoplasias were detected in up to 20% of lymphoma patients within 5 years after high dose therapy. However, the exact incidence is not known. Similarly, it is well known that extensive conventional chemotherapy (especially the cumulative dose of alkylating drugs) per se and the addition of radiotherapy strongly influences the rate of secondary neoplasias. In addition, especially in Hodgkin's disease, it has been speculated that a disease-related T-cell defect may result in a higher predisposition for secondary neoplasias.

Previously, three subgroups of secondary myeloid neoplasias have been defined based on exposure to different chemotherapeutic drugs (alkylating drugs, anthracyclines or topoisomerase II-inhibitors), characteristic chromosomal alterations (monosomy 5 and 7, balanced translocations, 11q23 (i.e. MLL)-rearrangements), and clinical course. In addition, different pathogenetic pathways (including polymorphisms of detoxifying enzymes) have been correlated to secondary haematological neoplasias. Interestingly, some studies detected temporary clonal chromosomal aberrations which resolved spontaneously.

To systematically define the incidence and elucidate the molecular pathogenesis of secondary haematological neoplasias after high dose chemotherapy, a clinical screening program with a multimodal scientific working program has been developed:

- bone marrow morphology (T. Haferlach, F. Griesinger)
- chromosomal analysis (C. Schoch, D. Haase)
- fluorescence in situ hybridisation with probes of distinct genomic regions (C. Schoch, D. Haase)
- immunphenotyping in selected cases to evaluate the early detection of malignant cells (F. Griesinger, W. Kern)
- microsatellite instability (G. Herzog, W. Kern)
- retrospective MLL gene analyses in selected cases (S. Schnittger, F. Griesinger)
- functional DNA repair analysis (M. Dreyling)
• polymorphism of detoxifying enzymes: GSTM-1, GSTT-1 (T.G. Schultz)

Current status of project:
Due to the delayed funding (start: January 2001), the major focus of this project has been the establishment of the infrastructural prerequisites:

An official clinical coordinator (G. Herzog) has been named who is responsible for the coordination and direct interaction with the distinct study groups.

An internal network structure with the second scientific centre at the University of Göttingen has been initiated. The patient samples may be sent either to the study centre at the University of Munich or to the University of Göttingen, depending on geographic preferences. Data will be centrally collected and analysed at the data centre in Munich.

Following formal milestones have been achieved:
• positive votum of the local ethics committee
• different measures to present the project to the scientific and general public:
  - contact and positive answer of the GCLLSG, the Study Group Multiple Myeloma and the GHNHLSG
  - project presentation on the internet web page of the Competence Network
  - oral presentation at the annual symposium of the Competence Network, March 16, 2001
  - overview article in the Newsletter 2/2001 of the Competence Network
• establishment of a central sample collection and asservation concept for patient samples
• preparation of a patient information and consent form
• preparation of a letter to the clinical institution referring to the scientific project
• preparation of a patient sample form

Cooperation with other subprojects
The central and complete asservation of patient samples which will be collected within the routine clinical follow-up is an important prerequisite of the molecular analyses. Consequently, the close embedding of this project into the central infrastructure of the Competence Network is essential, and an intensive interaction between the clinical study coordinator (G. Herzog) and the different study groups (GLSG, GCLLSG, the Study Group Multiple Myeloma and GHNHLSG) is mandatory. As only a regular update of the scientific projects will motivate the clinical institutions to participate, G. Herzog will present the study design and initial results on the annual study meetings of the distinct study groups. For the GLSG, clinical institutions will be directly contacted by the study centre to warrant an almost complete patient survey. This close collaboration will also allow to evaluate the prognostic meaning of various biological parameters.
Within the Competence Network, there is a close interaction with subproject 11 (coordination: N. Schmitz) which focuses on the clinical aspects of high doses therapy in malignant lymphomas.

Scientifically, this project is closely connected to the research program on secondary neoplasias in Hodgkin's disease (coordination: V. Diehl). In addition, there is an intensive scientific exchange with the recently established European MCL Research Network (coordination: M. Dreyling, W. Hiddemann) which investigates different aspects of molecular lymphomagenesis in close collaboration of basic researchers, pathologists and clinical investigators.

Publications
None

Objectives for the forthcoming funding period
In the first year of the project (2001), a pilot phase will focus on the patients with indolent lymphomas. Subsequently, in 2002 the systematical screening of secondary haematological neoplasias will be extended to patients with CLL, multiple myelomas and aggressive lymphomas (these entities were chosen because of study concepts with repetitive high dose therapies therefore potentiating the side effects of this treatment option and the frequent bone marrow aspirations within the clinical follow-up of the diseases).

According to the original working plan, first meaningful scientific results may be expected after a 3 year follow-up period (end of 2003), the final analysis will be performed after a 5 year follow-up (end of 2005).
4.12 Progress report of subproject 11

Topic
Development of strategies for immune and gene therapeutic vaccine therapies of malignant lymphomas.

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Summary
According to the working program of project 11 the emphasis of the scientific work during the first year of the grant period was on the analysis of the expression spectrum of tumor-specific antigens in malignant lymphomas. With the aim to develop an as widely as possible applicable vaccine therapy we analysed the expression of cancer-testis antigens (CTA). CTA are characterized by their peculiar expression pattern, i.e. they are expressed by a spectrum of tumors of different origin at varying frequencies, but not in normal tissues, except for testis. To date, nothing was known about the composite expression of these antigens in lymphomas. In cooperation with Prof. R. Parwaresch and Dr. M. Tiemann of the Institute for Pathology of the University of Kiel, the following CTA were included in the panel to be analysed: the serologically (by SEREX) defined antigens SSX-1, SSX-4, SSX-4, SCP-1, CT-7, HOM-TES-85, NY-ESO-1, as well as MAGE-3, which had been originally identified by its reactivity with cytotoxic T-cell lines (CTL). By RT-PCR with specific primers, a total of 78 B-cell NHL were analysed: 7 CLL, 9 mantlezone lymphomas, 9 MALT lymphomas, 15 centroblastic, 13 immunoblastic, 8 Burkitt, and 7 lymphoblastic B-NHL. The expression frequency of CTA by B-NHL was surprisingly low: the most frequent expression was observed for SCP-1, which was expressed in 15/78 cases, followed by SSX-1 (6/78) and CT-7 (4/78). SSX-4 and HOM-TES-85 were expressed in only one case each. T-NHL expressed even less CTA: in 15 of the analysed cases only SSX-4 and SCP-1 expression could be demonstrated; however, SCP-1 was expressed with high frequency, i.e. in 9/15 cases. We conclude that of the CTA known to date, only SCP-1, and to a lesser extent SSX-1 and CT-7 are expressed by a percentage of NHL high enough to warrant and justify their clinical use as targets for vaccine strategies.

Status of work and results
The stage of the project is in line with the projected work and time plan. The perspectives for achieving the objectives of the project are unchanged. Similarly, the objectives of the project for the second part of the grant period have not changed. This is due to the fact that no unforeseen
problems with the technical part of the project have emerged. Moreover, no results have been published by other groups which would affect the project.

The analysis of the expression of cancer testis genes by malignant lymphomas was the main goal of the first period of this project. Our results represent the first comprehensive analysis of the expression of these antigens in lymphomas. While the number of expressed cancer testis genes and their frequency is surprisingly low in most B-cell lymphomas, we could show that in the centroblastic and immunoblastic subtypes of diffuse large B-cell lymphomas and in peripheral T-cell lymphomas expression of HOM-TES-14/SCP-1 is frequent enough to warrant its use as a target structure for vaccine approaches in malignant lymphomas.

Cooperation with other subprojects
There is an intensive cooperation with the pathology project (subproject 3), especially with Prof. R. Parwaresch and Dr. M. Tiemann from Kiel. Most of the fresh-frozen lymphoma samples were provided by this group in a coded form. The coded samples were then analysed in our laboratory for the expression of cancer testis genes in a blinded fashion. The results were then sent to Kiel for unblinding and correlation of the results with the histological subtype. Moreover, the immunohistology of the samples expressing defined CTA is currently performed by this group using the respective monoclonal antibodies.

There is also a close cooperation with subproject 2 and the data centre in Leipzig and the secretariat of the GHNHLSG in Homburg. The secretariat organizes the procurement with blood and serum samples of patients to be tested for antibodies against lymphoma-specific or associated antigens. In cooperation with the data centre in Leipzig we try to correlate the results of our expression studies with clinical pre-treatment parameters of the patients and their response to therapy.

Publications


Objectives for the forthcoming funding period
As the expression of the hitherto known cancer-testis genes is surprisingly infrequent in the most common types of malignant lymphomas, it is our goal to identify new cancer testis antigens with a more frequent expression in lymphomas. Since the SEREX approach, by which

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1 The investigation on the expression of CTA by lymphomas at the mRNA level have to be complemented by the immunohistological demonstration of the expression of the respective CTA at the protein level using monoclonal antibodies and polyclonal antisera, respectively, against the respective cancer testis antigens. Once this has been accomplished, the results will be summarized in a manuscript and submitted for publication.
most of the known tumour-associated antigens have been defined to date, can not be applied to B-cell lymphomas, testis will be used as the source for the expression cDNA because due to genome-wide hypomethylation, testis expresses a maximally broad spectrum of the human genome. Sera from lymphoma patients which are supposed to contain antibodies against cancer testis antigens with preferred expression in lymphomas will be used to screen this cDNA library and the specificity of positive clones (i.e. antigens) will be determined as described for the classical SEREX approach.
5 Summary and Perspectives for the Year 2001/2002

5.1 General objectives

5.1.1 Quality management

The concept of the KML is to build up and support professional quality management of diagnostic procedures and treatment of patients with malignant lymphoma and to improve the quality in all aspects of lymphoma clinical trials. Forum and working teams bring together those who work in the subprojects, collaborators of the study groups and quality experts from inside and outside of the KML.

The quality management group of the KML has drafted several SOPs which are currently being discussed with the management board before release. For the computer-based support, the conceived SOP management tool should complete the first development cycle. Work on clinical trial documents harmonisation and the evaluation of implemented quality assurance measures are to be continued. To advance the data dictionary, terms will be collected using an appropriate tool.

Other new quality measures include the establishment of a new project involving mainly community hospitals. The project aims at improving the quality of documentation of patients enrolled into the GHSG, GLSG and GHNHLSG. This project is a cooperation between these three study groups and industrial partners and will also involve the GCLLSG.

5.1.2 Consolidation and extension of the KML

The founding member study groups of the KML were the GHSG, GLSG and GHNHLSG. After the official endorsement of the application, further study groups including the GCLLSG, the GIT-NHL and the OSHO were associated to the network. Additional groups that might become part of the network include the Plasmocytoma Groups, CNS Lymphoma Groups and transplant-associated Lymphoma groups. Together, these study groups represent nearly all officially registered lymphoma study groups in Germany. Furthermore, the association of the relevant epidemiological working groups in the field of lymphoma in Germany has been achieved. Thus, the network has become a major driving force in the treatment and research of malignant lymphoma in Germany.

Another important activity of the network is to actively discuss problems associated with the interaction between study groups and health care associations. One example is the agreement between the KML and the German lymphoma expert panel of pathologists. This agreement guides the interaction between the major lymphoma study groups and the lymphoma pathology experts including handling of primary material and publication of data resulting from the analysis of this material. Other activities were to help medical doctors working in primary health care
centres as specialists in haematology/oncology or in community hospitals with the achievement of ethic’s committee votes or insurance for the clinical trials of the KML groups in lymphoma.

A possible outlook for the KML in order to maintain its structure after the 5 year period is to create a special foundation in which research and clinical activities associated with the treatment of malignant lymphoma will be founded. This “German Lymphoma Foundation” could attract funding from private sponsors, companies and government-funded organisations alike.

5.2 Objectives of the different subprojects

5.2.1 Communication and information service (subprojects 1, 2, 3, 4)

One major achievement in the communication process between the KML and groups of potential users is the homepage “www.kompetenznetz-lymphome.de” which summarizes the most recent activities of the different groups and projects including ongoing clinical studies and latest developments in the field. Current and future activities focus on improving the basic functionalities of the homepage including the implementation of groupware features and the definition of an access control concept for different user groups (i.e. patients, medical doctors, members of the network). These activities are being coordinated by subprojects 1 and 2.

In addition, the network publishes a newsletter which bi-annually highlights the most interesting developments in the KML and the lymphoma study groups.

The establishment of communication between the reference centres and the central pathology server is the major task in 2001 in subproject 3. This includes the installation of hardware in each reference centre, the installation and individual configuration of the software as well as the exchange of patient information in a test phase prior to production. The installation and testing of the individual tools for the extraction of lymphoma patient data from the existing systems in each reference centre is also a central task. Similar activities are in progress to implement and further extent the photo-telegraphy communication system for specialized radiotherapists. This includes the communication via ISDN and internet of pictures and radiation plans to assure quality control for further centres (subproject 4).

The IT infrastructure’s extension stresses the data security concept’s completion. The reference centres for lymph node pathology’s network will be used to evaluate the use of virtual private networks.

5.2.2 EbM activities (subprojects 5, 8a, 8b)

Many different aspects of EbM are being investigated in several subprojects of the current network. In subproject 5, a group of medical doctors working in primary health care centres as specialists in haematology/oncology is working on implementing higher quality standards in their network of participants. Tools are the development of EbM-based guidelines which will be
summarized in a handbook to be developed. This handbook will include information on different lymphoma entities, current ongoing clinical studies, best evidence treatment, and standards outside clinical trials.

Subproject 8a is involved in developing a theoretical model which allows a better handling of heterogeneity between different studies and the development of better models to predict the impact of chemotherapy dose intensity on treatment outcome in lymphoma patients. Other activities in the next year include a meta-subgroup analysis on time intensification studies.

The major aim of project 8b was to establish a Cochrane review group for haematological malignancies. This goal has been fully achieved by the official endorsement of this group in October 2000. The group prepares and maintains systematic reviews for haematological malignancies including acute and chronic leukaemia, lymphomas, aplastic anaemias and plasmocytoma. The current work focuses on the preparation and publication of high-quality reviews as well as the establishment of a consumer input into this group. Other activities are the establishment of a specialized trials register and the active promotion of the Cochrane network in Germany.

5.2.3 **Health care and economic research (subprojects 6, 7, 9)**

The main task in 2001 of subproject 6 is the analysis of the pilot phase of the “Kölner und Saarländisches Lymphomprojekt” which will be followed by the initiation of the main phase. Analysis includes the characterization of patients recruited regarding incidence rate, age, diagnosis and treating institution. Other aspects are the evaluation of possible difficulties in the documentation procedure and a description of diagnostic procedures, therapy and outcome. The results of the interim analysis will influence the strategies in the main phase of the project.

In subproject 7, the interim analysis of the „Kölner und Saarländisches Lymphomprojekt“ will be a focal point of activities, too. This project expects to arrive at a first short-term overview of costs and clinical benefits of treatment with respect to three main influencing factors (ambulant and hospital sectors; clinical trials; regular treatment by a haematologist/oncologist). Depending on the interim results, first steps towards the development of clinically and health economically based clinical pathways for the first year of treatment may be taken.

5.2.4 **Clinical and basic research**

Projects evaluating lymphoma patients who receive high dose therapy within or outside clinical trials were initiated by subproject 9. In addition, this project has started a pan-European initiative comparing trends in lymphoma transplants for different countries.

Subproject 10 is focussing on secondary malignancies in patients with indolent lymphoma. It is planned to systematically screen patients for secondary neoplasias and then extend this work to patients with CLL, multiple myeloma and aggressive Non-Hodgkin’s lymphoma.
As the expression of the hitherto known cancer-testis genes is surprisingly infrequent in the most common types of malignant lymphomas, the goal of subproject 11 is to identify new cancer testis antigens with a more frequent expression in lymphomas. Since the SEREX approach cannot be applied to B-cell lymphomas, testis will be used as the source for the expression cDNA, because due to genome-wide hypomethylation, testis expresses a maximally broad spectrum of the human genome. Sera from lymphoma patients which are supposed to contain antibodies against cancer testis antigens with preferred expression in lymphomas will be used to screen this cDNA library and the specificity of positive clones (i.e. antigens) will be determined as described for the classical SEREX approach.
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