Interim Report 2000 on the

Medical Research Network
Pediatric Oncology and Hematology

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Medical Research Network Pediatric Hematology and Oncology Page

Introduction

In Germany, about 95% of children with malignant diseases are treated uniformly according to protocols of the Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH). The structure of the GPOH includes the Kinderkrebsregister (Children's Cancer Registry), Mainz, the Kindertumorregister (Children's Tumor Registry), Kiel, the Cooperatives pädiatrisches Stammzelltransplantationsregister (Cooperative Pediatric Stem Cell Transplant Registry), reference laboratories for immunophenotyping, cytogenetics and molecular genetics, the central business office of the GPOH, as well as more than twenty trial offices where children with different malignant diseases are registered and data related to diagnosis and treatment are collected and analysed.

Treatment protocols are designed and planned according to current scientific knowledge by pediatric oncologists (study committees) and are distributed to the approximately one hundred participating childrens' hospitals. About two thirds of patients are treated in 25 pediatric oncology centers (at least 25 new patients per year), mostly university hospitals. These conditions form the basis for high standard diagnostics and treatment.

These various institutions have cooperated over the past 30 years in order to develop the above mentioned structures, to coordinate clinical and also basic research, and thereby to improve the outcome of the affected children.

Cure rates for children with malignancies are currently approaching 75%. Whereas in the past years, the treatment protocols were based on relatively non-selective chemotherapy, modern protocols require much more complex structures and procedures in order to make precise diagnoses, e.g. molecular genetics, and to tailor treatment to individual needs, eg. pharmacodynamics and pharmacokinetics.

In addition, it has become mandatory to collect data on delivered doses and side-effects of chemotherapy and radiotherapy. For certain malignancies like Hodgkin's disease, central planning of radiation therapy has led to superior treatment results by achieving better local disease control. Hence, over the past years, a structured patient care organized in multicentric trials has been established, and these trials are now instruments of both high level nation-wide quality control as well as of reknown clinical research internationally.

As a consequence of these developments, cure rates in Germany are among the highest in the industrialized countries. According to figures of the Children's Cancer Registry, there are about 22,000 survivors of childhood cancer living in Germany. This is about 1 in 1,000 young adults.

For many former patients, information on general and individual late sequelae together with general and individualized guidelines are necessary throughout their life. For example, obstetricians should be aware that cesarean section is recommended in case of anthracycline-induced heart disease. Thus, the existing structures have to be refined in order to reach the broad medical community and also the patients.

These aspects led to the conclusion that an improved, intensified, and structured networking of all these institutions would be necessary. Therefore, the Medical Research Network Pediatric Oncology and Hematology has been established in late 1999 aiming at tightening and consolidating the cooperation and addressing specific scientific questions and problems in ten multicentric projects.

Results

Only few network projects were started already in 1999. The majority of the projects could only be started by mid 2000. Thus, the active time period has been quite limited. During the first one to two years of funding, multiple cooperations and interactions have been established and the interim results will be given in the following sections.

The projects can be subdivided into four projects addressing more general collaboration aspects (A to C), four projects addressing basic scientific research (D to G), and three projects addressing clinical research (H to K). The reports are structured into aims sections with corresponding results sections.

Coordination and Management

The major purpose of the Coordination and Management group is to build up networking structures between single cooperating institutions, to improve the transfer of information –also to private practitioners and affected families („vertical networking")–, and thereby the cooperation and interaction of the partners in patient care and research.

Aims – Results

To coordinate and manage the structures and instruments of the Medical Research Network Pediatric Oncology and Hematology

The ten different projects of this medical research network were established as an integrated system. By-laws were formulated and agreed upon, and cooperation contracts were made between participating institutions. Contacts to other networks and to the Telematics Platform were initiated. Collaboration between participants of this network was fostered by organizing three nation-wide meetings. Meetings with speakers and working groups of other networks were attended.

To support the conduct of clinical trials as instruments of both quality control and clinical research by establishing and improving the systematic exchange of data and material (tissue, blood, bone marrow) between treating institutions, trial offices and the German Childhood Cancer Registry (GCCR), to be achieved by employing additional personnel, Forschungs- und Studienassistenten (Research and Trial Assistants, FSA) in the pediatric oncology centers

Research and Trial Assistant (FSA) is a term for a new medical profession. Applicants were nurses, technical or documentation assistants. Over a period of one year, thirty individuals were recruited and started to work in 27 pediatric oncology centers across Germany.

To establish training and certification of the FSA

A training concept has been developed and put into practice. Four educational meetings for all FSA have been held. The training concept initially focussed on practical aspects of clinical trials. Thereafter, general topics were also addressed, e.g. principles of medical documentation, legal and ethical issues, study design and analysis, and computer usage including DOSPO (cf. next section). Speakers and teachers were pediatric oncologists and invited clinical research assistants. Considerations about harmonizing the training course with similar courses organized by other (adult) cancer organizations and a common procedure for certification are in progress.

To support the clinical trials in respect to data management, data base design, resolving common data problems, harmonization of information techniques, reduction of data queries, simplification of documentation

An investigation of the equipment with data bases, of practical shortcomings and of existing tumor banks was conducted in trial offices and reference laboratories. Accordingly, a general-purpose data base was designed, which is now used in laboratories in Hannover and Freiburg. Annual meetings of data managers were organized. Difficulties in documentation and proposals for improving existing structures and documentation tools were discussed.

In addition, exchange of information on problems and solutions in study management and documentation was promoted, partly by means of a special email distribution list. Baseline data quality was assessed in three trial offices for comparison with future changes brought about e.g. by the FSA.

To employ new media for interaction and information transfer

Since April 19, 2000, an Internet webserver dedicated to the Coordination and Management is online. An innovative content management system was employed, enabling data sharing and remote collaboration. Page templates were provided to other participants of the network. Daily, about one hundred page hits with about 2 MB data transfer are registered.

From the start on, topics such as relevant time schedules, organisational documents and the presentation of the project aims were covered. In the mean time, contents that cover quality standards, guidelines, and relevant literature in the field of pediatric oncology and hematology were published on this webserver or on the linked knowledge server (cf. section B2/b). These contents also serve aspects of the vertical networking.

A newsletter called ”Die Mitteilungen” was established to communicate news from the medical research network as well as from the GPOH. The third issue was released in May, 2001 in 300 copies and for downloading.

To support the reference laboratories of the leukemia and non-Hodgkin's lymphoma studies with respect to cell banking and to establish a data base for merging biological data

The planned data base has been established. Data collection is in progress. Data quality has been assessed.

To implement a system for documentation of pediatric stem cell transplantations in coordination with the trial offices and the international stem cell transplantation registries

The planned data base has been established. Figures and in part also detailed data on specific disease entities are now available. Kaplan Meier plots to assess the prognosis of children having received stem cell transplants in Germany and Austria can be constructed.

To evaluate the network by an independent, external consultant agency

At the beginning of the project, a baseline evaluation has been performed by WIAD and Prognos, two independent consultant agencies. This evaluation disclosed the specific needs and problems as perceived by 53 pediatric oncology units. To continue and extend the evaluation of the network's progress, a further cooperation with these agencies is planned and requires additional funding. A respective grant application has been submitted.

Websites

http://www.knm-poh.charite.de/ – Coordination and Management Group

http://www.kompetenznetz-paed-onkologie.de/ – Knowledge Server

The websites of the network's projects are linked with each other.

Computer-based Application Systems

General Aims

The aim of this project is to provide computer-based application systems for the Medical Research Network Pediatric Oncology and Hematology that support clinicians, trial offices and other research institutions in respect to their daily tasks. In detail, the following application systems are currently under development.

Aims – Results

Development, introduction and maintenance of the documentation and therapy planning system for pediatric oncology (DOSPO)

The DOSPO functions for the acquisition of study protocol integration and the calculation of individual chemotherapy have been considerably extended as well as the procedures for individual update, installation (e.g. conservation of already documented data, even if the database has changed), and for data exchange (e.g. possibility of exchanging trial specific data and hierarchically structured data).

We have also begun to develop a tool for comprehensive documentation of diagnosis and procedures for administrative purposes and a scheduling tool. The trial-specific module for the medulloblastoma-study is currently being redesigned.

In 2000, DOSPO was introduced into routine use at the medical centers of Homburg/Saar and Berlin Charité. We supported several requests for the installation of DOSPO in further hospitals. Interested users and FSA have been trained in using DOSPO in tight cooperation with the Coordination and Management Group.

Development of a computer-based data dictionary for pediatric oncology

There is a working prototype for the data dictionary, where standardized items for the clinical trials in pediatric oncology can be entered and maintained. The data structure for the storage of the items is concept-oriented and very flexible.

Development of a generic tool for trial databases, electronic and conventional case report forms and interfaces for the trial centers

In the framework of this project, the basic data set of pediatric oncology has been refined and its items have been entered into the data dictionary. For this task, a dedicated working group has consulted several experts. As a result, all items that were not relevant for all trials have been eliminated, the structure of items has been adjusted to international standards, and items have been adapted according to new research results. A concept for the procedure of standardising the items beyond the basic data set has been worked out.

In the course of the requirements analysis, an object-oriented business process analysis was carried out in two trial offices. After the results had been modelled as UML (Unified Modeling Language) Use Cases, they were compared systematically. The identified business processes were the basis for the development of a System Use Case for the automatic generation of a database that is derived from the data dictionary (cf. second aim). For this System Use Case an object-oriented software

component was designed. A working prototype for this software component was implemented, which can automatically generate database schemes basing on an arbitrary selection of items of the data dictionary.

Further Information

The project has been awarded with an international prize for the most successful telematics application in August 2000 by the German Minister of Health (A. Fischer).

Project Status

Because of active exchange with clinicians and trial centers, the priorities for the further development of DOSPO have changed since the formulation of the proposal. To be able to flexibly and systematically react to changing requirements, a new working group has been established that discusses and constitutes the priorities (DOSPO Task Force).

Instead of trial specific data items, items of the basic data set have been entered into the data dictionary. This has been proved necessary for the further standardisation process due to fundamental refinement of the basic data set. The data dictionary is used for the automatic generation of the trial specific (module) databases.

The focus in the third part of the project has been laid on the specified milestones, namely the implementation of the access to the database of the data dictionary and the implementation by a concept for the automatic generation of electronic case report forms, which should comprise the possibility of an interactive and comfortable adaptation of the layout.

Website

http://dospo.uni-hd.de/

Data Protection and IT Security, Knowledge Server

Aims – Results

Establishment of a secure communication for data protection

This project consists of two parts. Part one is „Data Protection and IT Security" (B 2/a), part two „Knowledge Server" (B 2/b). Due to a delayed start the project is 4 1/2 months behind schedule. The delay affects only part one.

A secure communication by PGP was established and concepts for data protection and IT security were worked out, in particular with regard to access control on servers, confidentiality of communication and integrity of information. A market analysis for a smart card based public key infrastructure was carried out.

The results on IT security as well as the algorithms for pseudonymisation will be useful for other medical networks as well.

Establishment of a working web-server

A working web server was established that already offers a considerable body of information. Furthermore start pages for the other projects and some mailing lists were prepared. Daily access statistics are generated.

Project Status

The test installation for a smart card is postponed until a consensus is reached in the Telematic Platform for the Medical Research Networks of the BMBF (TMF).

A pseudonymisation service turned out to be of fundamental importance for the network. As an additional working package for project B 2/a, the installation of such a service was adopted and could almost be completed.

The progress in the development of the Knowledge Server is in time.

Website

http://www.kompetenznetz-paed-onkologie.de/ – Knowledge Server

Telemedicine

Aims – Results

To promote research and to further increase the standards of care in pediatric oncology and hematology

The telemedicine project has started in 07/2000. As a first step, a questionnaire was sent to pediatric oncology and hematology units in Germany, asking about experience, motivation, existing infrastructure, and anticipated benefits and obstacles regarding the implementation of telemedicine. Of the 54 largest German pediatric oncology institutions asked, 46 completed the questionnaire.

The majority of institutions expected practical advantages from telemedicine communication, especially in teleradiology expert consultation and in telemicroscopy. It was anticipated that telemedicine will increase quality and reduce costs in medical care. Data security and standardisation, transmission speed and quality were regarded most important. There were only 6 (14%) institutions with established telemedicine equipment, 37 of 46 institutions (80%) were prepared to invest into telemedicine. Lack of medical informatics competence and manpower was regarded the largest obstacle. The need for further information on and for help in realisation of telemedicine communication was expressed by all participants.

A summary of mandatory and of potentially useful features of telemedicine applications for use in pediatric oncology and hematology was established; a market survey of available telemedicine systems was performed and compared to this list.

Next, a test phase with suitable candidate applications is planned from June to September, 2001. For this test phase, a detailed evaluation plan and evaluation forms have been prepared. Both technical features including data transmission quality, speed, reliability etc., and clinical usability, including image quality for medical purposes, handling, time- (i.e. cost-) efficiency and others, will be evaluated.

In parallel, a second questionnaire will be circulated in June 2001 among radiology institutions evaluating their attitude towards, and their technical infrastructure for a potential national teleradiology network in pediatric oncology and hematology. This questionnaire and the evaluation forms of the teleradiology systems tests will additionally be made available on the internet and may be completed online.

To enhance communication standards and to enable ambitious network activities in research and patient care by implementation of telemedicine

The successive project phase will use the results of the questionnaires and of the tests performed to exactly define prerequisites for the use of telemedicine applications in pediatric oncology and hematology, and to give recommendations for further extended tests, including suggestions for preferable applications, requirements of staff and equipment, etc. These tests will be open to participants from all GPOH institutions, and include further telemedicine applications apart from teleradiology, e.g. telemicroscopy, where a preliminary market survey and tests were completed in a preceding project.

These efforts will be paralleled by continuous discussion of methodology used and results achieved within the Telematic Platform in order to achieve a coordinated approach in implementation of telemedicine in several BMBF Medical Research Networks, the ultimate aim being systematic standardised telemedicine infrastructures and approaches nationwide.

Project Status

There have been some problems to find qualified coworkers for this project. The technical details for the teleradiology systems including requirements of staff and equipment are not yet solved.

Website

http://medweb.uni-muenster.de/telemed/

Molecular Parameters of Drug Resistance

General Aims

Identification of molecular parameters for prediction of the individual risk for treatment failure by analysis of function and expression of apoptosis molecules. Individual risk adapted therapy and identification of molecular target structures for future development of leukemia therapy.

Aims – Results

Development of an acquisition system for collection of patient material for cellular-, protein-, RNA- and DNA-analysis

Frozen patient material from the participating laboratories in Berlin and Hamburg were sent to Ulm and tested in functional drug response assays (cellular), protein-, RNA- and DNA- isolation. The cellular assays and RNA isolation were identified as the most critical procedures regarding sample quality. Different methods for freezing, shipment and RNA isolation are currently being tested for optimization of sample collection.

Development of methods for measurement of apoptosis signaling in primary leukemia cells

A new method for combined measurement of caspase activity and mitochondrial membrane permeability transition was developed (patent pending). Evaluation of this method for application in primary cells revealed a limited applicability for primary leukemia cells (manuscript in preparation). Another method for flowcytometric detection of mitochondrial cytochrome-c release was developed which is currently being patented. Evaluation of this method showed applicability in ALL and AML samples (manuscript in preparation), the method will be applied in the project in the following year.

Analysis of leukemia cell apoptosis in drug response assays

A total of 10 primary leukemia samples from Ulm, Hamburg, and Berlin were analyzed in functional drug response assays (PI, Annexin, FSSC, MTT) with 6 different cytostatic drugs. In addition cytochrome-c release and caspase-3 activation under culture conditions inhibiting caspase activity were analyzed. Results confirmed applicability of the methods in frozen leukemia samples. Currently, culture conditions are optimized in order to reduce the high background apoptosis. Preliminary results indicate a heterogeneous involvement of caspase activation in different leukemia samples. The prognostic value of this property is currently analyzed.

Identification of apoptosis gene mutations inferring drug resistance

Within a broader project for analysis of apoptosis gene mutations in our group, methods for Bax gene mutations have been established on RT-PCR level. Methods were evaluated by analysis of Bax mutations in established cell lines.

Analysis of apoptosis gene expression profiles for prediction of drug resistance

As stated above., RNA isolation methods are currently optimized in order to obtain sufficient amount of high quality RNA for application of a c-DNA chip. An apoptosis gene chip is currently being developed in cooperation with a local company (Thermo-Interaktiva Ulm). The chip consists of 96 positions with 10 controls, and 86 apoptosis genes.

40 c-DNAs have already been synthesized. The chip has been successfully evaluated with cell lines using controls and major apoptosis regulators like caspase-3. Production of the remaining c-DNAs and evaluation of the chip with primary material is in progress.

Identification of apoptosis signaling in peripheral leukemia cells activated by in vivo *chemotherapy*

Apoptosis gene activation during in vivo chemotherapy has been analyzed in a pilot study in Ulm. We identified induction of apoptosis in an immature subpopulation of peripheral leukaemia cells, while no such induction was found in mature leukemia cells (manuscript in preparation). The finding of differential activation of apoptosis genes in different subpopulations of leukemia cells has major implications for pre-therapeutic drug testing in patient samples.

Project Status

Due to late supply with budgetary funds for the employment of a scientist in the coordinating center in Ulm, standardization of methods could not be fully completed in time. All other items are in time.

Characterization of Preleukemic Bone Marrow Disorders

Aims – Results

To investigate all hematological disorders known to predispose to hematopoietic neoplasm with respect to the acquisition of a number of potential oncogenic changes, development of clonality and apoptosis. The oncogenic changes to study include karyotypic aberrations, mutations of ras, the G-CSF receptor and the Fanconi anemia genes.

Karyotype studies

The two partners (Giessen, München) perform standard banding metaphase cytogenetics and interphase FISH studies for monosomy 7 and trisomy 8 on over 90% of patients samples. As a substantial number of patients is studied in both laboratories, exchange of data between the two partners was initiated.

ras mutations

Patients with primary MDS (Myelodysplastic Syndrome) have been evaluated by restriction enzyme length polymorphism and direct sequencing for the presence of activation point mutations in codons 12, 13 and 61 of N, H and K-ras.

G-CSF receptor mutations

All children with congenital neutropenia known to the investigators and more than 20 children with MDS or acquired aplastic anemia have been investigated for mutations in the cytoplasmic tail of the G-CSF receptor. G-CSF receptor mutations so far have only been noted in severe congenital neutropenia (Kostmann syndrome).

Mutations in Fanconi anemia genes

The investigation of the Fanconi A gene in non-Fanconi bone marrow disorders so far gave rise to the description of a number of polymorphisms and to the description of 2 cases Fanconi anemia mutations.

Analysis of clonality

The studies on clonality using the HUMARA assay have begun in summer 2000. Methodical problems could be resolved, results on a greater number of patients are expected shortly.

Studies on apoptosis

Mechanisms of apoptosis have been studied in juvenile myelomonocytic leukemia. Other disorders are to follow.

Project Status

The grant approval was received on 01.07.2000. For partners who had already initiated their projects on 01.01.2000, reallocation of funds was possible. As noted above, some projects (mutations in the G-CSF receptor and Fanconi anemia genes) are ahead of schedule, others are in line (karyotype, morphology, ras mutations, clonality) or will have to catch up (apoptosis).

Minimal Residual Disease (MRD)

Introduction

During the last years, two large studies (Cave et al N Engl J Med 1998:339,591 and van Dongen et al Lancet 1998:352,1731) showed that the extent of MRD is an important independent prognostic factor and can be used for therapy stratification in childhood ALL. However, for other types of malignant diseases the clinical relevance of MRD is not yet clear. Therefore, a multicenter project was created within the Medical Research Network Pediatric Oncology and Hematology to analyze MRD in childhood ALL, relapsed ALL, AML, and lymphoma with different techniques.

Aims – Results

The aims of this project are the comparison of results gained by different methods to find the most suitable technique for each type of malignancy. Furthermore the best time points for therapy control should be evaluated. Finally, the most suitable marker for each type of disease should be evaluated. The following markers are tested cooperatively:

Fusion genes	*ALL Relapse*	*Seeger, Berlin*
Fusion genes	*AML*	*Harbott, Gießen*
Fusion genes	*NHL*	*Reiter, Gießen*
IgH/TCR genes	*ALL Relapse*	*Seeger, Berlin*
IgH/TCR genes	*ALL (BFM)*	*Bartram, Heidelberg* *Schrappe, Hannover*
IgH/TCR genes	*ALL (CoALL)*	*Kabisch, Hamburg*
Immmuno-phenotyping	*AML*	*Reinhardt, Münster* *Griesinger, Göttingen*

During the past 18 months the detection methods were established by the different groups and more than 12.000 blood and bone marrow samples were analyzed. After some difficulties with recruiting of follow up samples the compliance has increased in all subprojects. The cooperation between the subprojects works well and technical knowledge or missing samples are exchanged between the labs.

Some examples may elucidate the preliminary results: Analysis of IgH/TCR and fusion genes of relapsed ALL patients showed that the level of MRD at distinct time points might be important for this group as well.

Comparing MRD results of trial protocols ALL-BFM and CoALL based on the IgH/TCR marker, the influence of initial chemotherapy became obvious. Whereas only 9% of the BFM patients remained positive after induction ($\geq 10^{-2}$), 26 % of the children treated according to CoALL had still this high number of leukemic cells. This might be due to asparaginase, given late during consolidation.

Fusion transcripts of AML1/ETO persisted in all children after induction, but nearly half of them became negative after consolidation, whereas most of the adults remain positive during treatment. In contrast, the MLL/AF9 transcripts disappeared during the first month of treatment.

To compare all results with clinical data provided by the therapy studies ALL-BFM (Schrappe, Hannover), AML-BFM (Creutzig/Ritter, Münster), ALL-REZ (Henze, Berlin), CoALL (Janka-Schaub, Hamburg), and NHL-BFM (Reiter, Gießen).

The comparison of clinical data and laboratory results is regularly performed.

Project Status

The project is in time. First preliminary results were given in several oral and poster presentations at national and international conferences.

Clinical Relevance of Molecular Markers in Embryonal Tumors

Aims – Results

To give a basis for the central storage of tumors tissue by designing the standard tumor tissue set, and to distribute transport containers

Design of a standard tumor tissue set (10 sets per hospital) including frozen material, non-frozen touch preparation and reference tissue (blood, connective tissue). In addition, 62 participating centers received 1-3 legally approved transport containers.

The purchased Italian "Biocases" were unable to keep the material frozen for > 72 hours. Thus new styropore parts were developed in co-operation with SKUFA, Alveslohe, Germany. A patent application for these new tumor transport containers is in preparation.

To establish 3 tumor tissue banks

Three tumor tissue banks were established in Köln (neuroblastoma, rare tumors, and germ cell tumors since recently), Würzburg (nephroblastoma), Bonn (medulloblastoma/PNET, hepatoblastoma). This was necessary because until now tumor tissues for molecular investigations have been collected only sporadically in clinical institutions (hepatoblastoma, nephroblastoma, medulloblastoma) or were sent to one laboratory for specific analyses (neuroblastoma).

To develop an "informed consent paper" for all pediatric tumors

Proposal of an "informed consent paper" uniform for all pediatric tumors. The paper informs the parents and patients on the scientific use of the collected tissue and requests written consent. The giving no cause for concern has been attested by the ethical committee of the University of Cologne. The informed consent paper has been adopted by the participating clinical trials and is now part of the protocol.

To develop software on Oracle basis for the tissue storage

Software on Oracle basis for the tissue storage with connection to the therapeutical trial data (e.g. stage, risk, date of surgery, resectability, preceding treatment, tumor status) was developed.

To establish an independent board of directors who decide on the use of the collected tumor tissue

Since a central system for tissue storage that could be provided to network partners for serial analyses or to investigators outside the network did not exist, an independent board of directors was established to decide on the use of the collected tumor tissue. Two formal applications have been received by December 31st, 2000 (neuroblastoma, neuroblastoma plus nephroblastoma).

To improve the tissue transport between the Medical Research Network laboratories

Improvement of the tissue transport between the Medical Research Network laboratories (medulloblastoma/PNET: Mannheim, medulloblastoma/ PNET and Hepatoblastoma: Bonn, nephroblastoma: Würzburg, neuroblastoma: Köln, neuroblastoma: Marburg).

Project Status

The compliance of sending tumor material (especially of brain tumors and nephroblastomas) from large pediatric oncology centers needs to be improved.

Immunotherapy and Gene Therapy of Neuroectodermal and Hematopoietic Neoplasias

The aim of the project is to improve the overall prognosis and decrease unwanted effects of mutagenic therapy in malignant diseases in childhood through immunotherapeutic and gene therapeutic strategies.

Aims – Results

The establishment of a Pediatric Immune and Gene Therapy Registry (PIaGeneR)

A registry of all research projects and clinical studies within Germany and Austria in immune and gene therapy has been established. Currently 30 research projects and 5 clinical studies are registered. A total of 158 patients have been treated. 150 patients have been treated with antibodies. 8 patients have received cellular therapies with wild type or gene modified cells. The registry has increased the flow of information between the treatment centers. It has begun to generate synergy effects between research projects and has already decreased the number of redundant activities. It enables the participating centers to focus their activities and to cooperate wherever possible.

To improve communication between the treatment centers on a national and international basis, the documentation of treatment practice

Treatment practices of the participating centers have been documented. Heterogeneity and discrepancies with regard to study design and regulatory issues have been identified. While one institution holds a production license for the engineering of cellular and gene therapeutic agents, many others rely on the license of their blood bank or other institutions. Some centers have not obtained a production license. All research and clinical studies have been approved by the local ethics committees. One study is being processed by the Commission for Somatic Gene Therapy of the BÄK (Federal Medical Board).

To give support for treatment centers in regulatory and legal issues which will help to standardize immuno- and gene therapy procedures and will increase safety and efficacy of these new therapeutic strategies

The project has helped individual institutions to meet regulatory demands to start research or clinical projects. It has improved communication between the clinical centers to establish treatment algorithms and standards for immunotherapy and gene therapy. Overall cooperation and communication has improved.

Perspectives

Functional Genomics

In the project, data obtained with the tools of functional genomics will be made available to all participating centers. The data can then be used for the design of individual immunotherapies (vaccines, antibodies). A data base containing the genetic expression profiles of all screened pediatric malignancies is planned. Again the improvement of cooperation and communication will create significant synergy.

Public Relations

The participating centers wish to increase the acceptance of immunotherapeutic and gene therapeutic treatment strategies in the general public as well as in the medical and legal community with educational campaigns, a national meeting and various public relation activities.

Provision of Information concerning Regulatory and Legal Issues

There is still a significant information deficit concerning the regulatory and legal issues of gene therapy and immunotherapy (publication Burdach et.al enclosed). The project will continue to provide the necessary information to the treatment centers. The heterogeneity documented in the treatment practices of the participating centers calls for standardized approaches to study and research planning, approval and conduction.

Late Effects and Quality of Life (1)
A Vertical Network for Pediatric Oncology (2)

(1) Aims – Results

To evaluate prospectively in a standardized fashion somatic, neuropsychological and psychosocial long term effects together with Quality of Life (Qol) in children and adolescents with brain tumors and leukemia

Until June 2001, 90 patients with brain tumors (n=20) and leukemia (n=70) have been registered prospectively and tested within the project. Four time points were scheduled to compare the influence of the different treatment phases on long- term effects and QoL. Therefore, in about one third of patients results on 2 tests are already available. Compliance to the testset and to the participation in the project is satisfactory. 18 institutions all over Germany are participating, and a close network has been established between psychological and medical caregivers.

To promote a set of instruments for baseline evaluation for broader use

Until the end of 2001, it s planned to create a first concept of a reduced testset to select the instruments that showed most valuable results in measuring problematic areas concerning long- term effects and QoL in the prospective setting. By the end of 2001, first results of comparing long- term effects and QoL data are expected to highlight specific areas of correlation of both issues.

Summary

The project is well integrated in Pediatric Oncology in Germany. Cooperation is satisfactory and proposed aims will be reached in time.

(2) Aims – Results

To identify and support health care providers responsible for long-term survivors of childhood cancer in order to develop an integrated network of continuous and disease specific follow-up and care.

To establish a structured follow-up by designing and implementing respective guidelines in collaboration with the GPOH and to develop case report forms for similar disease entities

The first year of the project aimed at establishing contacts between the involved institutions and professions and developing standardized follow-up recommendations for leukemias and embryonal tumors. These guidelines have been integrated as amendments into the respective treatment protocols. Modalities for presentation (internet, mailings etc.) have been discussed within the Medical Research Network and the GPOH.

Project Status

The project is in line with the schedule.

Second Malignant Neoplasms (SMN)

Considerable progress was made in the treatment of children with cancer in the last 25 years. The data of the German Childhood Cancer Registry shows that more than 70% of all children with cancer still live 5 years after diagnosis. Most of these survivors can presumably be considered cured. For some diseases cure rates are 90% or above.

Since patients with cancer survive their disease longer, secondary tumors are increasingly being observed. The risk seems to differ considerably by primary malignancy. Currently it is not possible to differentiate clearly which SMN have to be regarded as a consequence of treatment for the primary malignancy and which ones have to be attributed to a general genetic predisposition.

Further research is warranted to clarify this question, in particular with regard to the design of treatment protocols and the structured follow-up for future patients.

Aims – Results

To identify risk factors responsible for the etiology of secondary malignant neoplasms

In spring 2000, an expert meeting with principal investigators of clinical trials and other interested clinicians was held in Mainz in order to further optimising the recording of SMN and coordinating further steps. We agreed to run all our cases again by the relevant GPOH study centers in order to guarantee optimal data quality. This retrospective assessment is finalized now and all so far known 500 cases were validated.

To this end, we record details on the primary therapy and molecular biological and cytogenetic factors. It is ensured that all new SMN cases will continuously be validated prospectively in close collaboration with the GPOH therapy optimisation studies. Along with this we further try to improve the organization of the long-term follow-up for the currently recorded 22,000 surviving registered patients.

We worked out an agreement with the Cooperative Pediatric Registry for Stem Cell Transplantation to compare the data bases on stem cell transplantation and secondary malignancies. Thus, both registries will further complete their data bases.

To prepare the intended epidemiological case-control study

The preparations for the intended epidemiological case-control study have proceeded satisfactorily. We developed questionnaires specifically for the recording of data on patients with SMN and the controls to be selected. A study design has been worked out including hypotheses related to treatment modalities and genetic predisposition.

To improve long-term follow-up beyond childhood

Long-term follow-up beyond childhood has been improved to ensure high completeness not only for children but also for individuals who develop their second malignancy in adolescence or in adulthood.

To establish a consultant board of principal investigators

The GPOH established a consultant board of four principal investigators of clinical trials in March 2001. This board met for the first time in May 2001. It was agreed to set up a compilation of hypotheses on possible potential risk factors to be investigated.

Project StatusThe project proceeds according to schedule. The initiation of a consultant board has increased the pediatric and oncological competence. To perform molecular genetic investigations we require further competent counselling, e.g. by a human genetics expert. We are currently finalizing the set of hypotheses for the case-control study.

Summary

A The coordination and management group is working as a service unit for all partners involved in research in pediatric oncology and hematology. The concept of organising and establishing the FSA in the participating pediatric oncology centers in combination with an education and certification program has shown first promising results. The support for the studies in data management and documentation appears to be helpful and to meet the needs. A greater transparency and an improved workflow between interacting partners has been achieved. Internal and external evaluation measures are underway. Plans were extended to sustain public relation activities and to include structured patient information, for which additional funding is applied for.

B1 The computer based application system for documentation and therapy planning in pediatric oncology is now being tested in several hospitals. The integration into local information systems and the practicability are not yet satisfactory. It appears that more individual support for testing, development of trial specific modules, and immediate troubleshooting are necessary. Additional resources or reallocation of funds is necessary to overcome these problems.

B2 In principle, the problems of data protection and security are recognized and can be solved. In practice, necessary infrastructures and appliances (e.g. chip card readers) are not yet available. An application for funding a public key infrastructure for all medical research networks has been submitted. A central knowledge server has been set up, which receives information from various network participants. Being the central new medium for the emerging vertical networking, it still has to become a help for daily medical practice.

C The survey conducted by the participants of the telemedicine project disclosed the potential areas of optimising inter-institutional consultations but also the legal, technical, and logistic obstacles. In the meantime, additional coworkers have been employed in five major pediatric oncology centers, aiming at establishing pilot set-ups for trial specific purposes such as Hodgkin's disease and Wilms' tumor.

D The project Molecular Parameters of Drug Resistance started to develop an acquisition system for collection of patient material for cellular-, protein-, RNA- and DNA-analysis. Methods for measurement of apoptosis signaling in primary leukemia cells were generated and methods for apoptosis gene mutations inferring drug resistance have been established. Leukemia cell apoptosis in drug response assays has been analysed in leukemia samples and analysis of apoptosis gene expression profiles for prediction of drug resistance is in progress. However, standardization of methods could not be fully completed in time.

E The hematological disorders known to predispose to hematopoietic malignancies were started to be investigated with respect to the acquisition of a number of potential oncogenic changes, development of clonality and apoptosis. The oncogenic changes to study include karyotypic aberrations, mutations of ras, the G-CSF receptor and the Fanconi anemia genes.

F The project Minimal Residual Disease has initiated numerous cooperations. Methodological standards have been developed and first results have been published. MRD has been introduced as a stratification criteria in the largest leukemia trial ALL-BFM 2000, and recent results suggest that the dynamics of MRD is one of the most important prognostic factors in systemic malignant diseases.

G Three tumor banks with a central tumor data base were established. The acceptance of the so-called Biocases is satisfactory, and they are regularly used to send material to the tumor banks and from there to the reference labs. Rules concerning the access to stored tissue have been agreed upon and an independent consortium has been appointed by the board of the GPOH to decide about respective applications.

H A national registry of currently running research projects and clinicals trials in Immuno- and Gene Therapy has been established and treatment modalities of participating centers were documented. Expertise in organizing such trials is offered to interested parties. Cooperative multicentric trials between partners of the Medical Research Network Pediatric Oncology and Hematology but also with other medical networks need to be developed in this still experimental field of medicine.

I The project Long term effects and Quality of Life is well established within the German pediatric oncology. Cooperation is satisfactory and proposed aims will be reached in time. The obtained results will have impact on further optimizing of treatment for the evaluated disease groups as well as to establish a core set for long term effects and QoL in other pediatric oncology patient groups.

K For a nationwide analysis on the frequency and predisposing factors for the occurrence of Second Malignant Neoplasms, a data base has been compiled. This will be continued and serve as a basis for individual counselling and designing future trials.

Despite delays in starting projects, important steps have been done, and in some projects, even substantial results could be obtained and published. The Medical Research Network Pediatric Oncology and Hematology has stimulated physicians and basic scientists who are involved in treatment and research for children with cancer. Extensive exchange of methodology and knowledge has commenced between clinical and laboratory institutions well beyond the previously existing spectrum of Pediatric Oncology in Germany.

Steps have been made in the direction of developing solutions for common demands in several medical research networks as a prerequisite to collaborate and to establish a basis for regular networking between all medical institutions and research facilities. After these initial steps that were made during the relatively short active time of the network substantial progress can be expected in the following time period.

Prof. Dr. med. Dr. h.c. G. Henze	Prof. Dr. med. U. Creutzig	Dr. med. R. Herold
Speaker	Secretary General	Coordinator

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