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EDITORIAL

Workshop on Minimal Residual Disease

9th Expert Meeting for Pediatric Oncology and Hematology, funded by the Kind-Philipp Foundation, Germany

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In October 1998, the Kind-Philipp Foundation asked Martin Schrappe (Hannover) and Claus R Bartram (Heidelberg) to set up an organizing committee to invite a faculty of experts for a special workshop on minimal residual disease (MRD) in malignant disease. The intention of this workshop was not only to bring scientists together from different backgrounds, but to have them teach a small group of young researchers and to foster scientific discussion and exchange. The organizing committee (M Schrappe, CR Bartram, JJM van Dongen, M Kneba, G Henze) assembled an international faculty of 30 basic scientists and clinical researchers from 10 different countries and similarly sized group of young fellows, mainly from Germany, Austria and Italy.

Initially, the workshop covered the issues of leukemia etiology (fetal origin, deletion of parental genes as potential risk), the detection of leukemia at birth (Guthrie cards), and the impact of gene rearrangements of 11q23 in childhood ALL. Subsequent speakers coming from research in solid tumors (neuroblastoma, breast cancer) focused on new technologies of detecting minimal amounts of disseminated tumors cells or tumor cell DNA, thus raising important questions about how to define clinical stages of malignant disease at diagnosis as much as during follow-up. The second day was devoted to new technological aspects for the detection of minimal residual disease in leukemia and disseminated cancer. Most important were the issues of quantification, in particular due to the introduction of new more automated technology (LightCycler, Taqman). This discussion raised the question of whether results generated by different techniques are comparable. In particular for the leukemias, the comparison of RT-PCR for fusion genes, clonospecific PCR for immunoglobulin and T cell receptor (TCR) genes, and immunophenotyping for leukemia-specific antigen detection were debated.

The third major part of the workshop illustrated the important results of the clinical application of MRD detection in various clinical settings and in different biological subtypes. New data were presented with regard to the prognostic impact of MRD in adult and pediatric leukemia protocols (including stem cell transplantation), as well as in the treatment of non-Hodgkin's lymphoma and Ewing's sarcoma. Some of the new data indicate that not only the level of MRD at a certain point in treatment, but also the type and intensity of treatment before material for MRD detection is obtained, is important for its interpretation. This implies that (semiquantitative) MRD results have not only to be taken with caution with regard to the detection technique, but also with respect to treatment applied. The final session focused on some fundamental issues arising from the arrival of the new detection techniques in the clinical setting. First of all, the prognostic impact of MRD needs to be evaluated in prospective clinical trials whenever such technology is being introduced into the treatment of a new disease entity, and with predefined conditions for quality control of the method. The high sensitivity available today requires new definitions for 'response', 'remission', and 'relapse' which up to this point are based on morphology in cytology and histopathology, or on imaging techniques in the management of solid tumors and their metastases. Most participants agreed that an uncontrolled introduction of new definitions for remission and relapse would be detrimental for clinical trials. Also, the introduction of this kind of detection technology would not necessarily help the patient, as the clinical behavior of minimal disease is not known for various tumor entities. With regard to cost/benefit aspects it is mandatory to prove first in well-designed clinical trials that any new stratification of treatment according to new MRD detection technique will benefit the patients.

This issue of *Leukemia* comprises several contributions of this workshop published as Synopses and chosen by the organizing committee. The coordinator wishes to thank the Kind-Philipp Foundation, Essen, Germany, for its generous support, the members of the organizing committee for their input, and the participants for their contributions.

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Workshop on Minimal Residual Disease: Scientific Program

Session I

Opening remarks — P Beck, Kind-Philipp Foundation, Essen; G Henze, Chairman, Society of Pediatric Hematology and Oncology (GPOH), and Member of the Board, Kind-Philipp Foundation

Origin of malignant systemic disease (1)
Chair: CR Bartram, P Ambros

Fetal origins of childhood leukemia	M Greaves
Deletion of parental GST genes as possible susceptibility factor in the etiology of infant leukemia	A Biondi
The promiscuity of 11q23/MLL – the story goes on	A Borkhardt
Rapid isolation of chromosomal breakpoints from patients with t(4;11) ALL: implications for basic and clinical research	R Marschalek
Detection of leukemia specific antigen receptor gene rearrangements in Guthrie cards	K Fasching

Distribution of malignant disease (2)
Chair: M Greaves, A Biondi

Minimal detectable disease in patients with solid tumors: diagnosis and surveillance	P Ambros
Biological characteristics of diesseminated carcinoma cells in bone marrow and lymph nodes	K Pantel
Detection of circulating tumor DNA in the blood (plasma/serum) of cancer patients	P Anker
A lesson from MRD in leukemia	L Foroni

Session II

Detection of minimal malignant disease: technological aspects (1)
Sensitivity/time effort/limitations
Chair: JJM van Dongen, AA Morley

Flow cytometry for immunphenotypic detection of MRD	D Campana
Ig/TCR gene rearrangements – PCR	R Panzer-Grümayer
Chromosomal aberrations/Fusion genes	J Harbott
Single cells (CGH)	M Speicher
Strategies to overcome the limitations in MRD detection	P Ambros

Detection of minimal malignant disease: technological aspects (2)
Quantification
Chair: D Campana, EA Macintyre

The use of monoclonality and sensitive quantification for study of MRD in acute leukemia	AA Morley
Light cycler technology using IgH and Ig markers	T Flohr
Strategies for quantification of MRD	JJM van Dongen
Quantification of leukemia-specific immunophenotypes and prospective utilization in childhood ALL	D Campana
CML: Surveillance of bcr/abl positive progenitor cells	A Hochhaus

Session III

Clinical implications of MRD detection (1) in leukemia and sarcoma
Experience from clinical studies
Chair: H Riehm, K Pantel

Differences in MRD-kinetics between T-ALL and precursor-B cell leukemia	M Willemse
Early response in ALL: MRD *vs* morphology	R Panzer-Grümayer
MRD in APL	A Biondi
MRD in Ewing sarcoma	A Zoubek
Multiparameter flow cytometry for detection of ALL in trial ALL-BFM 95	MN Dworzak
Clinical significance of MRD monitoring in TEL/AML1-positive ALL patients	J Trka
Results from the NOPHO ALL trials: impact of MRD	K Schmiegelow

Outcome prediction by MRD at end of induction depends on therapeutic regimen	U z Stadt
MRD detection in the cooperative Ewing trials	KL Schäfer
Clinical implications of MRD detection (2)	
Rational prospective application of MRD in clinical studies	
Chair: G Henze, M Kneba	
Clinical applications of MRD in adult ALL	EA Macintyre
Adult NHL: significance of MRD	M Kneba
Pediatric ALL: stratification and endpoints	M Schrappe
TEL/AML1 in relapsed ALL	K Seeger
Clinical implications of MRD detection (3)	
BMT and prognostic impact of leukemia surveillance	
Chair: A Reiter, T Klingebiel	
Approaches for MRD detection after allogeneic BMT	T Lion
Residual leukemia and outcome of BMT	C Steward/N Goulden
MRD in ALL patients prior to allogeneic SCT	P Bader/T Klingebiel
Special lecture: Etiology of acute leukemia	M Greaves

Session IV

Minimal requirements for adequate use of MRD techniques (1)	
Chair: L Foroni, T Lion	
Open discussion	A Biondi A Morley D Campana M Kneba JJM v Dongen
Future perspectives (2)	
Chair: M Schrappe, C Steward	
New definitions required for 'diagnosis', 'response', and 'relapse' based on new detection techniques of minimal disease?	
MRD monitoring: quality control	
Cost/benefit analysis:	
Impact on cure?	
Application in countries with limited resources	
Open discussion	CR Bartram L Foroni P Anker JJM van Dongen EA Macintyre J Harbott H Riehm