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Book Review

Oncogenes in the Development of Leukaemia

Series Editor L. M. Franks, Guest Editor O. W. Witte. Cold Spring Harbor, Cold Spring Harbor Laboratory Press. Cancer Surveys, 1992, Vol. 15.

THE COLLECTION of essays in this volume of Cancer Surveys covers a broad range of concepts that we should consider in the study of leukaemia.

When a patient or experimental animal succumbs to a leukaemia or lymphoma the pathological consequences of an overabundance of a specific blood cell type filling the marrow, peripheral blood or lymph nodes are easy to discern. Normal blood forming capacity of the bone marrow may be blocked, and infiltration of solid organs with leukaemic cells may lead to secondary problems, including infections and bleeding. The end result of hundreds of cell divisions by the leukaemic clone is the global breakdown of the homoeostasis that keeps the bone marrow's production of specific blood cells in balance with the needs of the peripheral organs. What is not obvious is the pathway on which the leukaemic clone travelled. Deciphering the mechanisms that upset the normal equilibrium to initiate the disease can be difficult to separate from the effects of secondary oncogenic changes that accumulate as the disease progresses.

The special properties of the pluripotent stem cell are described by Ihor Lemischka. The remarkable ability of stem cells to rest in a G_0 state, and later display a vast replicative capacity that enables them to repopulate a damaged marrow quickly with differentiated progeny, must involve special control mechanisms that are potential targets for leukaemogenic events. The use of retroviral marking experiments has now permitted a detailed analysis of the behaviour of stem cells that can be used as a basis for comparison with the growth properties of leukaemias and lymphomas.

It is clear that normal haematopoietic development depends on a balance of extracellular factors and cell–cell contacts that regulate autonomous cellular events and the differentiated phenotype. Perturbation anywhere along the signal transmission pathways from extracellular growth factor to nuclear controls on transcription and cell cycle regulators can initiate leukaemic progression. Alan D'Andrea describes the remarkable story of molecular mimicry of erythropoietin by the glycoprotein gene of the spleen focus forming virus (SFFV) component of the Friend strain of murine leukaemia virus. Although this event may seem very specific to this animal virus model, the implications for the role of receptor stimulation in leukaemia in general are important.

Growth deregulation by members of the tyrosine kinase family of oncogenes is a common event in human and animal models of leukaemogenesis. Charles Sawyers describes how the *bcr–abl* oncogene plays a critical part in the genesis of chronic myelogenous and acute lymphocytic leukaemia in man. The intriguing problem of how two different genetic elements fused into a single chimaeric protein can lead to deregulation of their intrinsic biochemical activities is considered. The important model of the avian erythroblastosis virus is discussed by Mike Hayman and Harmut Beug to exemplify the critical synergy between a growth stimulating tyrosine kinase receptor gene and a nuclear regulator of differentiation phenotype.

Signals sent from the cell surface or cytoplasm must eventually reach the nucleus and affect transcriptional regulation and cell cycle events. Tom Gilmore covers the *rel* family of oncogenes and transcriptional regulators. He points out their complex modes of regulation which include the action of specific inhibitors and cytoplasmic to nuclear relocalisation. Changes in the *rel* proteins themselves, as well as their regulators, can be associated with leukaemia. A large number of transcription factor related oncogenes have now been defined. Mike Cleary discusses how they can augment growth through positive or dominant negative mechanisms.

Most oncogenes involved in leukaemogenesis are grouped into the positive acting or growth stimulating class or the tumour suppressor on negative oncogene class. Stan Korsmeyer describes a new type of oncogene that maintains cell viability by blocking programmed cell death. Failure to die can result in the accumulation of unwanted cells and the beginning of the leukaemic phenotype.

All leukaemias, and in fact all cancers, are likely to be the final product of sequential oncogene changes that accumulate and give greater advantage to specific clones of cells. Our understanding of the specific combinations and synergies that work in different types of leukaemia is reviewed by Jerry Adams and Suzanne Cory, who describe the use of transgene technology and related approaches to establish tumour prone animal models for such studies.

The impact of new genetic technologies in the molecular analysis of chromosomal alterations in human haematopoietic disease is exemplified by Michelle LeBeau in her discussion of the role of chromosome 5 deletions in malignant myeloid disorders which includes the complex myelodysplastic syndromes that often precede frank leukaemia.

Progress in understanding human leukaemia has often been limited by our inability to culture or maintain leukaemic cells in the laboratory. John Dick covers the dramatic improvements in the use of immunodeficient rodent models for the propagation of normal and leukaemic cells. Such techniques are likely to have a major impact on the study of leukaemogenesis as well as other cancers.

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News

Towards Professional Training of (Local) Data Managers, an Objective of the EORTC Study Group on Data Management (SGDM)

We would like to introduce the objectives and programme of the EORTC Study Group on Data Management (SGDM) and inform EORTC investigators of the possibilities of support

European School of Oncology

Palliative care in cancer patient management
is an area of increasing importance,
and in response to this,
the European School of Oncology
set up an agreement
with three leading centres in this field.

The following three candidates have now been chosen
to follow a 2-month training period
in palliative care:

Dr. Mariela Bertolino (AR) at the
Hôpital Dieu, Paris, France.
Programme Director: Prof. R. Zittoun

Mrs Marianne Kerpel (NL) at the
Memorial Sloan-Kettering Cancer Center, New York, U.S.A.
Programme Director: Dr. J. Holland

Dr. Vladimir Bryuzgin (CIS) at the
Istituto Nazionale Tumori, Milan, Italy.
Programme Director: Prof. V. Ventafridda

This educational programme was made possible by a special grant from

Upjohn

which may be obtained from our Group for the training and education of data managers in the conduct of EORTC clinical trials.

Performing clinical trials becomes more and more complex with increasing costs and considerable demands of regulatory authorities. Also, the EORTC is continuously working to improve the quality of its trials and therefore imposes more responsibilities on its investigators. The EORTC Data Center Quality Control Measures approved by the Board in 1989 regarding the quality and the timeliness of the data provided are being more and more vigorously applied. Consequently, investigators increasingly realise that carrying out clinical trials with a high level of quality nowadays becomes almost impossible without the support of an efficient and professional group of medical and paramedical staff.

Presently, people with a great variety of backgrounds (secretaries, nurses, research assistants, residents, paramedics, etc.) are actually involved in certain aspects of carrying out clinical trials (documentation of disease and therapy, data collection and transfer), having received an "on the job" training. Lack of specific training programmes implies that each centre involved in clinical trials spends considerable time and effort in providing "in house" training.

The definition of an EORTC local data manager which we would like to put forward, is as follows: "an appropriately trained person, whose work consists of coordinating the technical aspects of the protocol, the related data collection and quality control within the hospital".

The EC Guidelines on Good Clinial Practice call such a person a local Study Coordinator with the following definition: "an appropriately experienced person nominated by the investigator to assist in the administration of the trial at the investigational site".

What can be the tasks of a local data manager?

An EORTC local data manger is mainly involved in the organisation of data collection for clinical trials within the hospital. This may include verification of the patients eligibility to enter a study, registration of the patient in a protocol, ensure pre-treatment and follow-up investigations, ascertain the presence of the necessary documentation in the patients clinical records, data extraction from the patients clinical records onto the case report forms (CRF), collection of biopsy material, serum samples, X-rays, and so on, for central review, assistance in audits and/or site visits.

But, it is evident that depending on the structure of the department or institution where the local data manager is located, more responsibilities can be added, especially towards support in the development of the technical aspects of protocol based studies and CRF development and reporting for in house trials.

One of the main goals of the EORTC SGDM is to support these tasks through the following objectives: provide and stimulate education and training of data managers involved in EORTC trials, improve the quality of local data management in EORTC studies and increase contacts between European data managers through their national organisations.

Presently the EORTC SGDM counts 235 full members from Australia, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Luxemborg, The Netherlands, Norway, Saudi Arabia, Spain, Switzerland, U.K. and U.S.A. The activities of the EORTC SGDM are supported by 10 sponsoring members from the industry.

What are the activities of the EORTC SGDM?

The EORTC SGDM is interested in education of its members through training projects organised at three levels.

Starting courses for new data managers are planned as of 1993 in the form of a 1 day workshop at the EORTC Data Centre. The aim is to give enough background concerning protocols, CRF and the functioning of the Data Centre to make people confident in the starting up of EORTC trials in the hospital.

A basic training course "Data Monitoring in Cancer Clinical Trials" has been developed for persons with a minimum experience in the field. The first course was held in Leuven in 1991 in collaboration with the ESO. It is evident that advanced level courses are indispensable for the multidisciplinary team involved in the conduct of cancer clinical trials. The first such course will be held in Brugge in 1993 in collaboration with the EORTC Oncology Nurses Study Group, the ESO and various national organisations.

Annual EORTC SGDM meetings are organised consisting of a 2 day programme including formal scientific lectures, practical workshops and poster sessions and plenty of opportunity to make contact with data managers from other centres.

Quality assurance programmes are set up to assess the accuracy of data collection in the hospital and the quality of data transfer onto the EORTC CRF. In order to increase the efficiency of these tasks, the EORTC SGDM is in the process of developing a manual which will be available in the course of 1993. Finally, a group of local data managers from various countries has been assigned to review and comment on the EORTC CRF at the design stage before submission to the EORTC Form Review Committee.

A joint effort of the EORTC SGDM together with the investigators who conduct EORTC clinical trials, towards training and education of local data managers, will certainly be beneficial for all parties involved:

— the investigators will be able to rationalise their time and effort spent in conducting clinical trials;
— the institutions will be supported by an efficient multidisciplinary team performing clinical trials at the highest level;
— the EORTC will remain competitive and increase its reputation through the high standard quality of its clinical trials;
— the data manager will improve in ability and enthusiasm.

If you are interested in contributing to this effort then kindly inform your relevant personnel of the activities of the EORTC SGDM and especially *support* them in following training programmes. For further details, please contact one of the Group's officers.

We look forward to receiving your comments and suggestions.

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