Pergamon

European Journal of Cancer Vol. 33, Suppl. 4, pp. S23–S30, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00143-3

The Challenges and Opportunities of Cancer Clinical Research: EORTC Perspectives

F. Meunier

European Organization for Research and Treatment of Cancer, Avenue E. Mounier, 83, Bte 11, 1200 Brussels, Belgium

While substantial gains have been made in the early diagnosis and successful treatment of cancer, it continues to be the second most common cause of death in European Community countries. It is imperative to develop new preventive and early detection strategies, to evaluate and implement new and more effective treatments, and to disseminate the most current information as rapidly and efficiently as possible to the largest number of clinicians and patients. The most complete and reliable information about a new diagnostic test or state-of-the-art treatment advance continues to come from the progression of laboratory work to early clinical trials to appropriate large, multicentre clinical trials. In order for this process to continue, it has become necessary for research programmes throughout Europe to integrate scientific disciplines, pool available resources, and establish adequate facilities to coordinate, oversee and facilitate high-quality research efforts. An important force in this cooperative movement has been the establishment of the European Organization for Research and Treatment of Cancer (EORTC). The aim of the EORTC is to conduct, develop, coordinate, and stimulate research related to all aspects of the experimental and clinical treatment of cancer throughout Europe. Close cooperation with national research organisations has been created and EORTC objectives are now achieved by multidisciplinary research groups including radiotherapists, surgeons, oncologists, pathologists, immunologists, infectiologists, specialists in quality-of-life assessment, health economists, and other categories of scientists. Currently the EORTC investigators consist of a unique network involving more than 300 institutions working on a voluntary basis. Pre-clinical and early clinical trials are coordinated through the EORTC New Drug Development Office (NDDO) based in Amsterdam, The Netherlands while all other studies are coordinated by the EORTC Data Centre based in Brussels, Belgium. Speciality units (Investigational Agents, Leukaemia, Quality of Life, Health Economics, Meta-analysis, and Quality Assurance) also have been created at the EORTC Headquarters to coordinate all specific aspects of large cancer clinical trials and to increase the efficiency and quality of services. Several new EORTC groups have been formed to address emerging needs and concerns. Additionally, an Education Office has been set up as well as an EORTC Fellowship Programme to provide training to a variety of professionals interested in cancer clinical research methodology, in order to guarantee high quality clinical research in Europe and to promote dissemination of the results, thereby improving quality of cancer care for all patients, not only those treated in research-oriented institutions. © **1997 Published by Elsevier Science Ltd.**

Key words: cancer, clinical trials, diagnosis, EORTC, research, treatment
Eur J Cancer, Vol. 33, Suppl. 4, pp. S23–S30, 1997

INTRODUCTION

SUBSTANTIAL GAINS have been made in the early diagnosis and successful treatment of cancer during the past few decades. Overall, only 40–50% of cancer patients survive and recent data show indeed that the 5-year case fatality from 1950–1954 to 1986–1991 for all forms of cancer declined from 70 to 50% [1]. Moreover, cure rates for some specific cancers have increased tremendously; for example, cure rates have risen from 0 to 70% in children with leukaemia [2], 3 to 30% in adults with leukaemia [3], 5 to 55% in bone cancer [4, 5] and 0 to 80% in testicular cancer [6].

Despite these advances, cancer continues to be the second most common cause of death. In European Community (EC) countries, more than 1.3 million new cancers are diagnosed

every year and an average of 900 000 deaths per year occur as a result of cancer [7]. Cancer incidence may increase given our increasingly larger older population and smoking pattern in women. Therefore, there is a major need for further progress in the management of cancer. Cancer clinical research is not a luxury, it is a necessity. In order to have a positive impact on these cancer statistics, it will be mandatory to develop new preventive and early detection strategies, to evaluate and implement new and more effective treatments, and to disseminate the most current information as rapidly and efficiently as possible to the largest number of clinicians and patients.

Basic and clinical research are complementary; progress in cancer care requires a comprehensive new drugs development programme as well as rapid assessment of optimal strategies. This is achieved by high quality clinical trials to define the safest and most effective treatments, to explore issues related to quality of life, to identify ineffective and redundant tests, diagnostic procedures, and treatments, and to evaluate the cost-effectiveness as well as the availability of these various approaches.

CURRENT ISSUES IN CANCER CLINICAL RESEARCH

In general, the lack of harmonisation of legal requirements and administrative procedures throughout Europe has made international cancer clinical trials difficult to implement, costly to conduct, and viable only for physicians affiliated with larger academic and research institutions. Furthermore, differing methodologies have produced data that are not comparable among studies and inadequate sample sizes have yielded results not applicable to a larger population. Although convincing clinical research is mandatory to establish state-of-the-art treatments and to translate laboratory discoveries into practice, clinical trials have traditionally received less funding and less recognition than basic research activities. Breakthroughs in molecular biology or gene therapy will have no impact on cancer care unless they are carefully evaluated in clinical trials.

While most physicians recognise the importance of clinical research, less than 10% of medical doctors have ever participated in clinical trials (Professor G. McVie, Cancer Research Campaign, London, U.K.). Many doctors are either unwilling or not encouraged by hospital administrators to invest the time necessary to initiate or take part in these studies, and most physicians, even those anxious to participate in studies, are not adequately trained in the methodology of clinical research. Similarly, less than 5% of cancer patients are currently enrolled in clinical trials (Professor G. McVie, Cancer Research Campaign, London, U.K.) because, at least in Europe, most patients are still unaware and uninformed of the potential benefits that can come from involvement in clinical research trials. Obviously, there are major variations among the European countries; as an example, in France, 50% of patients with cancer are treated in private practice, 30% in public hospitals, and 20% in one of the cancer centres affiliated with the 'Fédération Nationale des Centres de Lutte Contre le Cancer' (Professor Horiot, Centre G-F Leclerc, Dijon, France). However, among all French patients entered in EORTC clinical trials, 37% are treated in these cancer centres.

In addition, cancer is mainly a disease of the elderly and until rather recently, patients older than 65 years were almost uniformly excluded from most clinical trials. This approach is not adequate, taking into account the current challenges of cancer care for these specific groups of patients which are still too often undertreated [8] and also facing significant ageing of the population.

Treatment of cancer is, in and of itself, a complex undertaking requiring a multidisciplinary team including surgeons, radiotherapists, medical oncologists, pathologists, immunologists, infectious disease specialists, pharmacists, and nurses, among a variety of other healthcare professionals including general practitioners. This comprehensive approach is necessary not only to control the underlying disease, but to provide the supportive care needed to deal with concurrent issues such as pain management, infection control, quality of life, and adequate nutrition. Cancer clinical research involves all these interactions, in addition to partnering with the pharmaceutical industry, academic institutions, national and international research organisations, and a variety of governmental and regulatory agencies.

Advances in biology have opened doors to innovative and provocative new therapies. This profusion of technologies, treatments, and preventive measures, while creating numerous clinical research opportunities, makes a scientifically rigorous and medically sound system of validation more important than ever. The established progression from laboratory work to early clinical trials, to appropriate large, multicentre clinical trials still provides the most complete and reliable information about a new diagnostic or state-of-the-art treatment advance.

The art and science of high-quality clinical trials is complex and highly dependent on good operation design, statistical techniques and analyses, rigorous quality assurance programmes, effective computer technology, and most importantly, upon medical knowledge. The last few decades have seen increased sophistication of the technologies used for protocol design, data collection, analysis, quality assurance procedures, and medical monitoring. As a result, present day cancer research is characterised by the necessity for rapid interdisciplinary exchanges. Researchers also must investigate the economic impact and efficacy of various diagnostic procedures and treatments to ensure the greatest health benefits from available budgets, and by eliminating unnecessary, ineffective, and redundant tests or strategies, to conserve resources and enhance the overall quality of care.

Cooperative solutions from the research community

Comprehensive cancer research encompasses epidemiological, basic, and clinical research with efficient and effective translation into clinical application. Medical research and medical practice are synergistic and complementary, with the common aim of decreasing the mortality rate of cancer and improving the quality of life of cancer patients using the best available therapeutic modalities. Independent and objective evaluation of all facets of diagnosis and treatment must be the cornerstone of cancer clinical research. However, such research has become more and more expensive and is often beyond the means of individual laboratories and hospitals. It is apparent that research programmes need to integrate scientific disciplines, pool available resources, and establish adequate centralised facilities to coordinate and oversee research efforts.

The research community itself has long recognised the advantages of multicentre clinical trials. The Commission of the EU has taken this one step further with the initiation of

international programmes on cancer that could synchronise the efforts of clinical and basic research groups throughout Europe [9]. Multinational and multidisciplinary approaches already established in Europe have produced important benefits, allowing complex therapies to be evaluated even in rare cancers and identifying in a reasonable time frame small but medically important differences in large scale clinical trials that can ultimately affect many patients. For example, a 5% improvement of survival demonstrated in 5000 clinical trial patients with breast cancer can translate to saving the lives of 7000 patients throughout Europe each year. An important force in this cooperative movement has been the establishment of the European Organization for Research and Treatment of Cancer (EORTC).

EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)

The EORTC is an international research association founded in 1962 by leading cancer specialists of the Common Market countries and Switzerland. The aim of the EORTC is to conduct, develop, coordinate, and stimulate research related to all aspects of the experimental and clinical treatment of cancer, with the ultimate goal of improving the standard of cancer care throughout Europe.

Funding for the EORTC comes primarily from national cancer organisations (through the EORTC Foundation), the European Commission (DGV, DGXII, DGXIII), the National Cancer Institute (NCI) of the United States, and from other contributors (private or corporate), as well as from specific research projects performed in collaboration with the pharmaceutical industry.

There will be no further progress in cancer care without high quality clinical research and there is no research without adequate financial support. Currently, collaboration with the pharmaceutical industry represents approximately 30% of all research activities conducted by the EORTC. It must be emphasised also that the EORTC mission is to provide scientific and administrative support for specific studies of high interest to the public and to healthcare providers, not necessarily involving new drugs but, instead, innovative and/or more effective therapeutic strategies leading to better use of current knowledge, already available means and within the limits of budgets. Such important issues for cancer patients and for health authorities will never be answered by clinical studies conducted only under the auspices of the pharmaceutical industry aiming at registration of new drugs. Such clinical research is important to guarantee administration of state-of-the-art treatment to all cancer patients, but the research organisations and universities are still lacking adequate financial support for these tasks. There is an urgent need for healthcare providers to allocate scarce resources and to invest more than ever in high quality and independent academic research. Indeed, using state-of-the-art treatment reduces inefficient use of money, and economic evaluations performed alongside clinical trials provide insight into the cost and benefits of treatments; therefore, healthcare providers can greatly benefit from well-conducted, relevant clinical trials.

A major difficulty has been the independent large pivotal studies concerned with issues not directly related to the evaluation and marketing of a particular drug, but on therapeutic strategies using a combination of modalities. Questions such as duration of treatment, optimal choice of therapeutic modality, sequence of treatment in relation to surgery, radiation, combination therapy, etc., are important issues for the survival of patients but also for their quality of life, and can have a direct financial impact on the healthcare budgets of countries worldwide. The EORTC Foundation has been established to provide support to those 'non-sponsored' trials which are crucial for optimal management of cancer patients.

The EORTC is now active in the entire range of cancer research from new drug development to advanced clinical trials, and plays a major role in maintaining Europe's important contribution to biomedical research. Clinical research is mainly accomplished through large, prospective, randomised, multicentre cancer clinical trials. This multinational, multidisciplinary, cooperative approach to cancer research decreases the time needed to evaluate new therapeutic or prevention modalities, improves the quality of data, and allows for the rapid dissemination of information to the greatest number of people. In this way, the EORTC facilitates the translation of experimental discoveries into state-of-the-art treatment. The EORTC is in fact the only comprehensive organisation which coordinates cancer clinical trials on a true European level. Therefore, the results of those trials are widely applicable and have a maximal impact for all European countries.

Currently, the EORTC network includes more than 2000 physicians located in more than 300 university hospitals or affiliates in 31 countries. Clinical trials are conducted by groups of investigators focused either on a specific tumour type or centred around a certain discipline (such as radiotherapy). All groups comprise experts from various disciplines in oncology, as well as from more basic disciplines, such as pharmacology, pathology, and biochemistry.

Since 1991, several new EORTC groups have been created to focus on increasingly important issues including: Biological Therapeutic Development, Continuing Medical Education, Invasive Fungal Infections, Chronotherapy, Ophthalmic Oncology, Positron-emission Tomography (PET), Pathology, Pain and Symptom Control, Boron Neutron Capture Therapy and Treatment Outcome Group. A Radiation Technologist group has also been formed. Another important addition has been the establishment of the Cancer in the Elderly Group because oncological treatment and management in this population will be a major issue facing clinicians in the future.

All EORTC groups work together to address the issues related to cancer in a comprehensive and co-operative manner. There are more than 100 clinical trials open to patient entry at any time and all the EORTC activities are described in the manual '*Organisation, Activities and Current Research*', published annually [10]. All practical procedures involved in the conduct of EORTC clinical trials are published in a manual entitled '*Practical Guide to EORTC Studies*' [11].

The research conducted by the EORTC is supervised by different committees including the Protocol Review Committee (which asseses the scientific validity and priority of specific investigations), the Quality Control Committee, the Scientific Audit Committee (which evaluates the global scientific output and functioning of the various divisions, offices and groups), and the New Drug Development and Coordinating Committee.

In 1972, the United States National Cancer Institute (US NCI) also created a liaison office next to the EORTC Headquarters in Brussels, Belgium to coordinate research conducted simultaneously in the U.S.A. and in Europe, with

the goal of accelerating the development of new and effective treatments without duplication of efforts.

Clinical research and the EORTC Data Centre

The EORTC Data Centre provides the scientific and administrative support for all clinical groups conducting EORTC clinical research, i.e. late phase II and phase III trials including speciality services such as Quality of Life and Health Economics Evaluation. The Data Centre oversees all stages of trials from conception to publication of final results. It provides the optimal infrastructure to rapidly evaluate, in a rational, objective, and independent manner various treatment strategies administered to cancer patients in Europe. The Data Centre comprises more than 60 professionals including physicians, statisticians, data managers, health economists, scientists specialising in quality-of-life issues, computer analysts, administrative personnel, and research fellows. Therefore, it provides data management, computer, statistical, and medical expertise to cooperative groups at a central, economical site. In addition, the Data Centre offers assistance and direction with issues dealing with the legal and administrative aspects of international clinical trials, compliance to Good Clinical Practice (GCP) guidelines, quality control procedures, and insurance coverage. The EORTC provides insurance, according to local regulations, for all trials not sponsored by pharmaceutical companies.

Overall, the Data Centre coordinates a database of more than 90 000 cancer patients, with approximately 7000 new patients added each year. The activities of the EORTC Data Centre are reviewed and re-evaluated every 3 years by a committee of the US NCI. These reviews have resulted in continuous financial support to the Data Centre from the NCI since 1974.

Speciality units at the EORTC Data Centre

Six speciality units have been created in the EORTC Data Centre to coordinate specific aspects of large cancer clinical trials and to increase the efficiency and quality of the services provided.

Investigational Agent Unit. This unit was created to improve the efficiency of data management for phase II trials, as well as trials conducted in cooperation with the pharmaceutical industry, using non-registered therapeutic modalities but performed in a totally independent manner. Standard operating procedures for trial management, statistical guidelines for writing protocols, a master protocol for phase II trials with new cytostatic agents, and a standard set of case report forms with a detailed coding guide have been developed to implement GCP guidelines in these EORTC trials and to fulfil the requirements of authorities and sponsors for trials used in new drug applications. The Investigational Agent Unit also is concerned with drugs not yet registered or drugs that require special monitoring.

From January 1994 until December 1996, this unit has handled 1528 patients from 29 studies conducted by eight EORTC cooperative groups. A site visit programme has been established and 183 site visits (in 67 institutions) have been carried out by the Data Centre staff since September 1993.

Leukaemia Unit. This unit provides support to all studies initiated by the leukaemia groups (adults and children) in various haematological malignancies including acute lymphoblastic leukaemia, acute myelogenous leukaemia, myelodysplastic syndrome, chronic lymphocytic leukaemia, multiple myeloma, chronic myelogenous leukaemia, and hairy cell leukaemia. New approaches, such as the study of multidrug resistance, minimal residual disease, growth factors, and quality-of-life issues have been developed. Specialised databases have been created for immunology and cytogenetics and for the documentation of infectious complications. The entry rate into studies managed by the Leukaemia Unit is approximately 900 new cases each year.

Quality-of-Life Unit. The Quality-of-Life Unit was created to permit a more comprehensive evaluation of treatment outcomes, to include the physical, psychological, and social aspects and function of patients entered in cancer clinical trials, and to increase the clinician's awareness of quality-of-life issues in cancer treatment. This unit is working in close cooperation with the EORTC Quality of Life Group as well as with the various disease-oriented groups. The EORTC Quality-of-Life Group has developed a validated questionnaire (available in 23 languages) to evaluate quality-of-life issues within clinical trials [12].

Health Economics Unit. Researchers have been called upon to integrate economic efficiency measures into their research, in addition to efficacy and safety parameters. These economic issues can impact how priorities are set and can directly affect healthcare budgets. This unit, created with financial support from the European Commission, evaluates within prospective clinical trials the cost-effectiveness of different therapeutic approaches to cancer treatment. Data on cost issues related to various cancer treatment modalities all over Europe are evaluated and analysed in tandem with efficacy and safety data. These economic assessments are made available to clinicians and various governmental bodies as well as healthcare providers.

Meta-analysis Unit. In order to draw valid conclusions from a clinical trial, a large number of patients must be treated. When this is not possible, the results from similar trials can be combined using a statistical technique called 'meta-analysis'. The Meta-analysis Unit provides the scientific means and expertise required to identify, process, and analyse the data from trials to be included in meta-analyses conducted by the unit which also receives support from the European Commission. Several meta-analyses have already been completed with others underway including: prognostic factors in three EORTC testicular cancer trials; epirubicin toxicity in seven EORTC phase II/phase III trials; assessment of bone marrow transplantation in acute myelogenous leukaemia (AML) (with the Medical Research Council (MRC) in Oxford, U.K.); the role of intravesical chemotherapy in patients with superficial bladder cancer (with the MRC in Oxford); and perioperative chemotherapy in early-stage breast cancer.

Quality Assurance Unit. This unit was created to support the activities of the EORTC Quality Control Committee and to guarantee the quality of data within the clinical trials, but also to ensure that all patients in EORTC studies receive uniform, high quality treatment and that all participating institutions follow established guidelines for patient selection, treatment protocols, and data management. Since the quality of treatment administration and of patient care has a direct influence on survival, all patients should receive adequate treatment, in the correct form, at the appropriate time. Medical monitoring (both at the Data Centre and in the participating institutions) is performed under the supervision of physicians based at the Data Centre.

New drug development program and the EORTC New Drug Development Office (NDDO)

Series of groups were established to strengthen the impact of basic research on the clinically oriented activities of the EORTC. A primary aim is to promote project-oriented cooperation between groups involved in basic research and clinical oncology and to identify promising new scientific approaches that can be pursued more effectively at a European level. Particular attention is paid to new developments in the area of molecular biology, including gene therapy, molecular genetics, basic developmental and differential processes and apoptosis, immunology and vaccines, and advances in molecular design and genetic engineering.

Phase I and early phase II trials are performed mainly by the Early Clinical Study Group working with the support of the NDDO in Amsterdam, The Netherlands.

The Early Clinical Study Group is aiming at effective new drug development in order to promote rapid access to innovative cancer modalities. Multicentre trials on vaccines in patients with various types of tumours have been initiated with the cooperation of groups belonging to the EORTC Research and Treatment Divisions. The standard operating procedures of the EORTC NDDO and the Early Clinical Study Group have been filed at the United States Food and Drug Administration (Drug Master File no. 11609) [13].

Education and training

In order to guarantee that all cancer patients, even those treated outside of research-oriented institutions, receive state-of-the-art treatment through the rapid dissemination of knowledge and expertise to all healthcare professionals, four groups have been created: The Continuous Medical Education Group, The Study Group on Data Management, The Oncology Nurses Study Group, and The Radio Technicians Study Group.

The Data Centre has also taken a lead in education by producing manuals on methodology of clinical research and by offering various courses on procedures related to cancer clinical research. Training courses on clinical trial methodology or other topics such as Quality of Life and Health Economics are organised on a regular basis with the support of the EORTC Education Office based in Brussels.

SELECTED EORTC RESULTS AND ACHIEVEMENTS

In the past few years, EORTC clinical trials have produced improved treatment strategies for almost all types of cancers. Speed and quality are needed in the complex process of the development of more effective treatment approaches, which only result from close cooperation of this unique network of investigators.

The EORTC new drug development programme is now recognised as an important European resource for screening compounds and beginning the essential preclinical and early clinical studies with new drugs and biological agents.

In recent years, the EORTC has contributed substantially to the clinical development of important new anticancer drugs such as docetaxel, topotecan, gemcitabine and others.

The adoption of European standards, contrasted with longer American standards, for toxicology studies of new agents, significantly accelerates drug development without compromising safety. This European toxicology package is used routinely to establish a starting dose for phase I clinical trials in cancer patients. More than 50 new drugs have been successfully introduced into clinical trials on this basis. Agreements signed by the EORTC, the US NCI and the U.K. Cancer Research Campaign (CRC) facilitate collaboration in this drug development programme. In addition, EORTC large clinical studies performed by the various groups serve the public health.

The EORTC melanoma group has made an important contribution in the evaluation of risk of melanoma associated with the use of both regular and psoralen sunscreens [14]. The melanoma group is also addressing adjuvant therapy with interferon alpha.

The EORTC Radiotherapy and Breast Groups have conducted a large trial including more than 5000 patients with breast cancer. This trial investigates the effect of adding a booster dose of radiotherapy, after breast-conserving surgery and radiotherapy, on the survival and on the cosmetic outcome of patients with small breast tumours [15].

More recently, a new large trial requiring more than 4000 patients has been initiated to evaluate internal mammary chain irradiation. A 5% improvement in survival at 10 years which could be expected from irradiation would benefit around 7000 patients per year in Europe.

Another significant contribution of the EORTC Breast Group has been provided for patients with locally advanced breast cancer, demonstrating after long-term follow-up evaluation the improvement in survival attributable to hormonal therapy [16].

The EORTC Radiotherapy Group has also pioneered the field of quality assurance programmes and recently carried out an evaluation of the structures and human resources of 50 participating centres, providing a unique database for establishing guidelines for minimum recommendations for European radiotherapy departments involved in clinical research [17–19].

A head and neck cancer study conducted by the Radiotherapy Group has shown improved local control of tumours using a radiotherapy scheme with a reduction in overall treatment time by increasing the number of fractions given per day while maintaining the same total dose [20].

Furthermore, a breakthrough in cancer treatment has come about through a large, landmark EORTC clinical trial conducted by the EORTC Head and Neck Cancer Co-operative Group comparing a larynx-preserving treatment with chemotherapy and radiotherapy with the standard treatment of surgery and irradiation [21, 22].

In 1996, the results of a trial conducted by the Radiotherapy and Genito Urinary Cancer Cooperative Groups in prostate cancer have shown improved survival and better control of cancer with hormonal agents added to radiotherapy [23].

The role, dose, and schedule of postoperative radiotherapy in patients with low grade glioma remains controversial. The EORTC is currently conducting a large trial on this topic; more than 300 patients have already been included and the results are keenly awaited by the whole scientific community as well as by patients.

The EORTC Gynaecological Group has shown that one-third more women with advanced ovarian cancer survived if a debulking surgery was performed after induction chemotherapy [24].

EORTC clinicopathological research conducted by the lymphoma group has identified a new clinical entity of non-Hodgkin's lymphoma through an analysis of data from two

large trials involving more than 600 patients [25, 26]. One of these publications [26] has been selected by the *Journal of Clinical Oncology* to be reprinted in the '*Classic Paper and Current Comments: Highlights of Clinical Lymphoma Research*'.

Among rare tumours, the EORTC Sarcoma Group has been able to enroll approximately 200 patients a year and has thereby accumulated one of the largest databases on sarcoma in the world. The studies conducted by this group have established state-of-the-art treatments for these patients [27].

Euroscan, a major chemoprevention trial (to prevent secondary tumour) in patients with either lung cancer or head and neck cancer has closed with a total of 2542 patients. The preliminary results of the study will be available in 1997.

Specific progress data and contributions in the field of leukaemia resulting from EORTC trials are described in the enclosed paper by Willemze and associates.

A combined analysis of EORTC and MRC randomised clinical trials for the prophylactic treatment of stage $T_A T_1$ bladder cancer has recently shown that the use of adjuvant prophylactic treatment has little apparent effect on the long-term results [28].

A large phase III trial (310 patients) performed by The EORTC Gastrointestinal Tract Cancer Cooperative Group recently showed that low-dose methotrexate effectively modulated high-dose infusional 5-fluorouracil in patients with advanced or metastatic colorectal cancer with a favourable safety profile [29]. In resectable gastric cancer patients, the same group reported that FAM2 (modified fluorouracil, doxorubicin and mitomycin) did not significantly improve survival [30] and started a new phase III trial investigating the value of adjuvant FAMTX with respect to survival.

Other recent developments within the EORTC

The education and training of healthcare professionals to ensure a supply of highly skilled clinical investigators is a fundamental concern of the EORTC. An EORTC Fellowship Programme was established in 1973 to foster the exchange of physicians and scientists involved in research within institutions of the EORTC membership countries and with the US NCI. Since 1991, a new fellowship programme, specifically dedicated to healthcare professionals involved in cancer clinical research, has been created at the EORTC Data Centre. This fellowship programme has been expanded to provide training in clinical research methodology for professionals interested in cancer clinical research. Over the past five years, more than 40 research fellowships have been awarded to medical doctors, biostatisticians, health economists, quality-of-life specialists, computer scientists, and other scientists from 14 countries within the EC, as well as from Eastern and Central Europe. Funding for this fellowship programme comes from various sources (EORTC Foundation, several European cancer leagues, Fondation Cancer, the European Commission and pharmaceutical industries).

It is also the responsibility and task of the EORTC research community to share information with the public in general and cancer patients in particular, and to inform and educate healthcare professionals regarding all possible cancer treatment options. An EORTC Education Office was established in 1994 within the EORTC Central Office in Brussels, Belgium to promote the dissemination of the results of EORTC trials. The goal of this office is to organise training courses (in collaboration with the European School of Oncology (ESO) in Milan, Italy to improve the treatment of all cancer patients, including those treated outside research-oriented institutions.

The EORTC has also been at the forefront of efforts to simplify and harmonise the procedures involved in ethics committee reviews and in insurance coverage for large clinical trials (particularly for strategy trials not directly involving the pharmaceutical industry). Presently, France has a system in place whereby one central review committee can give approval for a clinical trial to be conducted within the entire country; other countries require review and approval from each individual research site. In addition, the EORTC is involved with the various regulatory agencies within the 15 EC countries, as well as with the EMEA (European Agency for the Evaluation of Medicinal Products) Office in London, U.K. (the EORTC is an official observer to EMEA), with the ultimate goal being the harmonisation of legal and administrative obligations of clinical investigators throughout Europe, as well as the development of guidelines for drug development.

In 1995, the EORTC Board created a position for the Director General to coordinate and administer all EORTC activities in order to promote the EORTC as a major European resource in the field, and to represent the EORTC in its relations with the European Commission, the US NCI, the various European cancer leagues, the EMEA in London, and the pharmaceutical industry.

Finally, the EORTC is now pursuing, more than ever before, its coordinating role with numerous national research organisations and close cooperation as well as joint

Table 1. *Collaboration of EORTC with other cancer research organisations*

Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC)
Medical Research Council (MRC)
United Kingdom Coordinating Committee on Cancer Research (UKCCCR)
Swiss Institute for Applied Cancer Research (SAKK)
World Health Organization (WHO)
Société Internationale d'Oncologie Pédiatrique (SIOP)
Gruppo Italiano Malattie Ematologiche Maligne dell' Adulto (GIMEMA)
Dutch Children Leukemia Study Group (DCLSG)
Hemato-Oncologie Volwassenen Nederland (HOVON)
Scottish Gynaecological Cancer Study Group
Scandinavian Gynecological Cancer Study Group (NOCOVA)
USA: NCI-SWOG-ECOG
NCIC (Canada)
Cochrane
Various Meta-analysis Trialists Groups

ventures (intergroup studies) have been either initiated or formalised. A list of all collaborating organisations is provided in Table 1.

Telematics developments to facilitate cancer clinical trials

Computer and electronic networks have changed the way modern clinical research is conducted. Applying these tools to promote the enrolment of patients in clinical trials and to improve the quality of the trial is a major challenge. With the support of the European Commission, the EORTC has a number of telematics projects including the development of a remote data entry system for clinical research (MACRO), quality assurance for diagnostic and treatment (CONQUEST) and remote support for pathology (EUROPATH).

Inherent in the effort to provide quality and speed of clinical trials is the use of telematics, for example, for data entry and management. Long-term telematic goals of the EORTC are to document cancer patient data in a standardised electronic chart so as to reduce variability in care and complication rates, to improve treatment efficacy by advanced image processing, to demonstrate interoperability between European cancer centres, and to use telematic tools to improve Quality Assurance (QA) programmes in daily clinical practice.

Already in place for the EORTC is a home page available on the Internet enabling randomisation of patients 24 h a day, as well as improving communication among European oncologists by providing general information on EORTC training courses, ongoing studies, and conferences. Physician Data Query (PDQ), the NCI's electronic database of cancer treatment information, is also available.

DIRECTIONS FOR FUTURE RESEARCH

To ensure the continued success and growth of European cancer research, several important components must be improved and expanded including: standardisation and coordination of research activities, encouragement and support of cooperative efforts among clinical investigators involved in multidisciplinary and multinational groups, the availability of highly trained professionals from a variety of specialised fields, research opportunities available and accessible to interested physicians, and adequate funding to promote the rapid assessment of state-of-the-art cancer diagnostic and treatment procedures. Comprehensive, large-scale trials, with stringent QA programmes and efficient, widespread dissemination of results, need to be conducted to preserve capacities for medical excellence in Europe.

Patients must be made aware of the potential advantages associated with involvement in cancer clinical trials including better care, comprehensive follow-up, and better outcomes. At the very least, patients should be assured of benefit from standard treatments in a randomised setting. Likewise, healthcare professionals throughout Europe need to be encouraged to become members of the research community and to understand the value of participating in clinical trials. They should have proper training in all aspects of research methodology, have access to the resources necessary to perform high-quality clinical research, and be able to rely on continuing support for data collection, management, and analyses, and finally, be assured that results of their studies will be disseminated.

Furthermore, the evaluation of innovative treatments such as vaccines, anti-angiogenic agents, and gene therapies will require specific endpoints and evaluation means. Procedures to measure the broader biological effects of treatments and the efficacy of maintenance therapies will also need to be investigated. Over the past 20 years, cancer research has brought progress, but it is vital that clinical research continues to be supported at the European level. Such an objective also requires a sufficient supply of highly qualified clinical investigators to maintain the competitiveness of European academic and industrial research. Through the combined efforts of the EORTC, the European medical community, the European Commission and the various governments, the US NCI, and researchers worldwide, cancer patients can be assured that the safest and most effective treatments are available to them today and that this cooperation will ultimately achieve the long-term goal of better cancer care in the 21st century.

1. Cole P, Rodu B. Declining cancer mortality in the United States. *Cancer* 1996, **78**, 2045–2048.
2. Henze G. Childhood acute lymphoblastic leukaemia. *Eur J Cancer* 1997, **33A**, 8–9.
3. Willemze R. New trends in the treatment of adult acute myeloid leukaemia. *Eur J Cancer*, this issue.
4. Meyers PA, Heller G, Healey J, *et al.* Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan–Kettering experience. *J Clin Oncol* 1992, **10**, 5–15.
5. Jurgens H. Recent advances in childhood cancer. *Eur J Cancer*, this issue.
6. International Germ Cell Cancer Collaborative Group. The international germ cell consensus classification—a prognostic factor based staging system for metastatic germ cell tumours. *J Clin Oncol*, 1997, **15**, 594–603.
7. EUCAN 90. Cancer in the European Union. *IARC Cancer Base* No. 1, 1996.
8. Monfardini S, Sorio R, Hoctin Boes G, Kaye S, Sarraino D. Entry and evaluation of elderly patients in European Organization for Research and Tretament of Cancer (EORTC) new-drug development studies. *Cancer* 1995, **76**, 333–338.
9. Gahrton G, Graessmann A, Meunier F, Schmitt M, Van Dongen JJM, Baig SS. Meeting Highlight. Cancer Research in the European Community—Report from a meeting in Stockholm in 1995. *Eur J Cancer* 1996, **32A**, 1300–1302.
10. EORTC (European Organization for Research and Treatment of Cancer). *Organizations, Activities and Current Research: 1996–1997*, Brussels, EORTC, ISBN no. 2-930064-07-2.
11. EORTC (European Organization for Research and Treatment of Cancer). *A Practical Guide to EORTC Studies.* February 1996, Brussels, EORTC, ISBN no. 2-930064-06-4.
12. Aaronson N, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993, **85**, 365–376.
13. Henrar REC. Filing of EORTC SOP's at FDA will speed approval of drugs from Europe. *Eur J Cancer* 1996, **32A**, 389.
14. Autier P, Dore J-F, Schifflers E, *et al.* Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. *Int J Cancer* 1995, **61**, 749–755.
15. Bartelink H. The need for boost doses in breast conserving therapy. 7th EORTC Breast Cancer Working Conference, Bordeaux, France, 10–13 September 1996.
16. Bartelink H, Rubens RD, van der Schueren E, Sylvester R. Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer randomized phase III trial. *J Clin Oncol* 1997, **15**, 207–215.
17. Bernier J, Horiot J-C, Bartelink H, *et al.* Profile of radiotherapy departments contributing to the cooperative group of radiotherapy of the European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol* 1996, **14**, 953–960.

18. Gallagher MJ. International quality control/quality assurance. *Int J Radiat Oncol Biol Phys* 1996, **34**, 965–967.
19. Dusserre A, Garavaglia G, Giraud JY, Bolla M. Quality assurance of the EORTC radiotherapy trial 22863 for prostatic cancer: the dummy run. *Radiother Oncol* 1995, **36**, 229–234.
20. Horiot J-C, Bontemps P, Begg AC, *et al.* EORTC trials on hyperfractionation and accelerated radiotherapy: results and impact on standard practice in head and neck cancers. Balkan Congress of Oncology, Athens, Greece, 3–7 July 1996.
21. Lefebvre J-L, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst* 1996, **88**, 890–899.
22. Forastiere A. Another look at induction chemotherapy for organ preservation in patients with head and neck cancer. *J Natl Cancer Inst* 1996, **88**, 855–856.
23. Bolla M, Gonzalez D, Warde P, *et al.* Immediate hormonal therapy improves locoregional control and survival in patients with locally advanced prostate cancer. Results of a randomized phase III clinical trial of the EORTC Radiotherapy and Genito-Urinary Tract Cancer Cooperative Groups. *Proceedings of ASCO*, 1996, 238.
24. van der Burg M, van Lent M, Buyse M, *et al.* The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *N Engl J Med* 1995, **332**, 629–634.
25. Pittaluga S, Bijnenes L, Teodorovic I, *et al.* Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the revised European–American classification of lymphoid neoplasms: a comparison with the working formulation. *Blood* 1996, **87**, 4358–4367.
26. Teodorovic I, Pittaluga S, Kluin JC, *et al.* Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. *J Clin Oncol* 1995, **13**, 2819–2826.
27. Verweij J, Mouridsen HT, Nielssen OS, *et al.* The present state of the art in chemotherapy for soft tissue sarcomas in adults: the EORTC point of view. *Crit Rev Oncol/Hemat* 1995, **20**, 193–201.
28. Pawinski A, Sylvester R, Kurth KH, *et al.* for the members of the European Organization for Research and Treatment of Cancer, Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Party on Superficial Bladder Cancer. *J Urol* 1996, **156**, 1934–1941.
29. Blijham G, Wagener T, Wils J, *et al.* Modulation of high-dose infusional 5-fluorouracil by low-dose methotrexate in patients with advanced or metastatic colorectal cancer: final results of a randomized EORTC trial. *J Clin Oncol* 1996, **14**, 2266–2273.
30. Lise M, Nitti D, Marchet A, *et al.* Final results of phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin and mitomycin regimen in resectable gastric cancer. *J Clin Oncol* 1995, **13**, 2757–2763.