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Translational research in clinical trials: the only way forward

Translational research in early clinical trials is not only feasible and desirable, but it is an essential and integral aspect of the development of the new generation of cancer drugs. Translational research in late (phase II and III) clinical trials can also be essential in defining different patient populations that may benefit to differing degrees from new treatment regimens, and thus provide us with further insight and refine clinical practice in an increasingly patient-tailored approach.

The EORTC is formally committed to the concept of translational research being a part of all clinical trials, and held a meeting (The 1st EORTC Translational Research Meeting, Palais des Congrès, Brussels, 7–8 June 2001) to bring together basic researchers and clinicians to promote such studies.

Translational research is part and parcel of contemporary drug development. Historically, we have not paid the attention we should have done to understanding why good drugs work and why unsuccessful ones do not. In modern drug development, the action of a new drug at the molecular level needs to be defined not only during the pre-clinical phases of development, but also as part of clinical trials. Only when we have this information can we be sure that the effects of the drug on the patient are taking place through the intended mechanism. A mechanistic understanding of both activity and toxicity in patients allows the optimisation of therapy at an early stage as well as providing important feedback to pre-clinical drug developers. Early clinical trials should be seen as part of both the development and the clinical trials phases of drug discovery.

Conventional phase I studies on what were mainly antiproliferative agents have been carried out using normal tissue toxicity as a surrogate marker for antitumour activity, i.e. damage to proliferating cells in the gastrointestinal tract or bone marrow. However, most of the new generation of drugs are directed at specific molecular targets, which may not be present in normal proliferating tissues, and hence this approach is no longer applicable.

In formulating approaches to the development of the new generation of cancer treatments, it is useful to consider the hierarchy of conditions that must be met for successful therapy. First, a potentially effective plasma level must be achieved. Then the drug must get to the site of the intended target, usually the tumour in cancer therapy, at the required concentration and for the required duration. Next, drug–target interaction must take place, and finally the drug–target interaction must have the desired biological effect. All of these conditions must be met before we can say that a new drug is actually being evaluated in patients, and translational research as part of new drug development seeks to establish whether or not this is the case.

Involving patients in drug development through translational research raises logistical and ethical questions. Whilst laboratory researchers can stick a pipette in a test tube as many times as they want, there is a limit to the number of samples which can be taken from a patient. A balance has to be struck between what the laboratory researcher wants in terms of the size, frequency and number of samples taken; what the clinician feels is justified and technically feasible; and what an ethics committee will accept in terms of patients' interests and well-being.

New, non-invasive techniques such as functional imaging will help but every technique has its limitations as well as its advantages. The most appropriate tools will depend on the drug being tested, and is important to realise that the tools required for translational research can take as long to develop as the drug itself. The assays needed, for example a functional imaging technique to measure whether a drug has interacted with its target, should be thought about very early on in the drug development process, i.e. at the stage of target validation, and developed in parallel with the drug.

Translational research requires a formidable team effort. It involves not only the clinical team looking after the patient, but also functional imagers, pharmacologists, molecular biologists and biochemists. Whilst daunting, the logistical, ethical and practical barriers are not insurmountable. Many presentations at the EORTC Translational Research meeting demonstrated that translational research can be done, and that the information derived is of practical value in the development of a drug and the management of patients. Over the past 5 years it has become apparent that translational research is no longer an optional extra in the drug development process, but is now a mandatory component.

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Thalidomide is back

Thalidomide is active against the lymphoma Waldenstrom's macroglobulinemia (WM) say researchers in Greece (*J Clin Oncol* 2001, **19**, 3596–3601) and it may be 'a lifesaver' for patients with other advanced plasma cell malignancies.

The Athens-based researchers treated 20 elderly patients with WM, all of whom were symptomatic. They increased the dose fortnightly from 200 mg daily to a maximum of 600 mg. The prospective phase II study found that 5 achieved a partial response and experienced at least a 50% reduction of serum monoclonal protein. This was accompanied by a reduction of tumour infiltration at all involved sites, an increase in haemoglobin levels and a decrease of elevated B2-microglobulin levels.

All patients who eventually responded showed evidence of the drug's activity with the starting dose of 200 mg, and within 2 months. This means that trials longer than 3 months may not be necessary to assess disease sensitivity. Adverse effects such as constipation, somnolence, fatigue and mood changes were common but reversible, though only low doses of the drug were tolerated.

Thalidomide's mechanism of action is probably complex, researchers say, but the rapid responses "were consistent with a direct cytotoxic effect on tumor cells or with an immunomodulatory effect of thalidomide". They suggest that, since it is not associated with myelosuppression, further studies combining it with chemotherapy or with rituximab "may be relevant".

An editorial (*J Clin Oncol* 2001, **19**, 3593–3595) suggests that thalidomide and dexamethasone combined may act synergistically. ''Preliminary results from a Mayo Clinic study using this combination as initial therapy for previously untreated myeloma indicate promising activity with a response rate of over 75%'', it states. They urge caution until further safety and efficacy data are available, but say that thalidomide ''now seems to be a lifesaver for patients with advanced plasma cell malignancies''.

It suggests that thalidomide should be tested in early-stage plasma cell disorders and the researchers note that preliminary data suggests activity in myelodysplastic syndrome, myelofibrosis, gliomas and renal cell cancer. Further studies should focus on its mechanism of action, ideal dosing schedule, duration of therapy and role in maintenance therapy.

Norway says no to PSA

Norwegian oncologists, urologists and general practitioners have been advised not to offer the prostate specific antigen (PSA) test to healthy men. An information pack sent out by a group of medical societies states: "In accordance with scientifically-based medicine, one can not recommend PSA testing of healthy men".

The brochure

The advice goes on to state that, if the test is given, "The doctor must give information about possible treatment side effects, such as impotency and problems with urination".

The pack was produced by the Center for Medical Technology Assessment, Norwegian Board of Health, Norwegian Medical Association, Norwegian Patient Association, Norwegian Urological Cancer Group and Norwegian Cancer Society. The Norwegian Urological Society also contributed.

The brochure states that no studies so far have documented that PSA screening reduces mortality from prostate cancer and that, although it may disclose disease in the prostate gland, it is not specific for cancer. There is no general agreement that present treatment options, including prostatectomy and high-dose radiation therapy, increase life span, it says, and for many patients, treatment involves considerable side-effects which can reduce the man's quality of life. ''Most become impotent and some incontinent. A close follow-up without treatment may be a satisfactory alternative for a man who has no symptoms. In Norway, men aged 70 years or older will as a rule not be offered any type of radical treatment'', it says.

The report 'Screening for cancer of the prostate. Documentation background for the health effects of routine screening' was produced by the Center of Medical Technology Assessment. Further information on report and brochures is available from smm@unimed.sintef.no

Carbon black and bladder cancer

A study among longshoremen has provided further evidence for a link between carbon black and bladder cancer, say Italian researchers (*Lancet* 2001, **358**, 562). The men unloaded paper sacks containing carbon black at the Genova docks in Italy. Those with the highest exposure had a signficantly increased incidence of bladder cancer.

Between 1947 and 1957, around 10 000 tons of carbon black were unloaded annually at the docks. From 1958, the quantities fell sharply and, from 1960, the paper sacks were replaced with sealed boxes. Some men operated forklift trucks and cranes, others carried the sacks on their shoulders and their skin became covered by a dark greasy substance.

The retrospective study included the 2286 longshoremen employed by three dockside companies between 1933 and 1980. Frequency of cancer between 1986 and 1996 was determined through the Genova cancer registry. The researchers analysed data for 858, 709 and 534 men with, respectively, low, moderate and high exposure to carbon black. Those who died before 1986 were excluded.

Men who had handled the carbon sacks directly had a significantly increased incidence of bladder cancer. Those who were hired before 1958 also had twice the risk compared with those hired later. In 1996, an IARC Working Group classified carbon black as possibly carcinogenic; this study provides further evidence. The researchers conclude, "The increase in bladder cancer in longshoremen is probably related to high exposure to carbon black".

EUROFILE

The EU and cancer research: the defence

Pious expressions of sympathy for cancer research and treatment have multiplied over recent years within European Union institutions. The goodwill has been matched—although to a lesser extent—by support in terms of funding, and this has led to some achievements in advancing the fight against cancer. The following account of where the EU has made a contribution, and what further support is on offer, represents, as it were, the case for the defence in an assessment of the EU's avowed good intentions.

Most of the funding has come either through the EU research programmes or through its programmes on public health. Overall, during the last decade, the EU has provided €260 million to cancer research—and typical funding levels for individual projects range around €2 million. €150 million has been made available under the current cycle of the research programme which runs from 1998 to 2002.

The research support has ranged from assistance to cancer-related organisations and prevention campaigns through to the hard edge of novel treatments. For instance, the EU has supported the EORTC Data Center since its establishment in 1978, as a focus for teams testing new cancer treatments and a source of advice on trial design and data management. It has backed the European Cancer Resources Bank, which grows living cancer cells and supplies them through a catalogue to cancer teams all over Europe. Communication networks between researchers, hospitals and general practitioners which have made new types of study possible have been assisted by the EU: a European project to identify causes of clustering in childhood leukaemia is collecting statistics from a wide geographical area; prevention of colon cancer is being investigated through another cooperative project.

Among innovative treatments, the first clinical trials of boron neutron capture therapy, in particular for malignant brain tumours, were the result of European co-operation and the technical and scientific support of the EU's Joint Research Centre establishment at Petten in The Netherlands. Other recent EU-backed advances include the use of umbilical-cord blood to treat leukaemia in children, studies on mycotoxins, novel concepts in using 'cell factories' to treat cancer, and genome-based projects targeting cancer.

New methodology and software for the storage of electronic data from multiple sites participating in studies have been developed by EU-backed researchers. In diagnostics, another EU-funded project has provided highly sensitive new techniques for identifying cancerous cells at low concentrations. Prostate cancer diagnosis and monitoring has been improved through use of reference material which allows detection of subtle changes in patients' enzyme levels.

"THE EU PROVIDED €260 MILLION OVER THE LAST DECADE"

A new cycle of this so-called R&D Framework Programme is currently under preparation within the EU, to run from 2002 to 2006, with a budget of €17.54 billion. It identifies cancer as one of the key topics for research, particularly the integration of new genomics-based tools with more conventional approaches to treatment, but the share that cancer research will get—against competition from sectors as diverse as aeronautics or nuclear science—is still unclear. The outline is couched in terms of "integrating and strengthening the European Research Area" or "benchmarking and mapping Europe's excellence in science and innovation"—which offers very little handhold to anyone trying to plan a research grant application.

Under the EU's health programmes, an action plan against cancer has been running since 1996. It was due to expire at the end of 2000 but is being extended to 2002, with a budget of €13.3 million a year. This plan ranges widely across data collection, public information, education, cancer training for healthcare workers, early detection and systematic screening, studies on the quality of care, and research. Its key achievements so far have been the establishment of large networks on areas such as cancer and nutrition, quality measures in breast and cervical cancer screening, cancer registries with standardised data and discouraging smoking in adults and young people.

A new EU public health programme is also in the final stages of agreement, to run from 2001–2006, with a budget of €280 million, which will subsume the current programme to combat cancer. Meanwhile, a call for proposals for 2002 under the current programme was issued during the summer, with a submission deadline of 30 October.

"THE SHARE THAT CANCER RESEARCH WILL GET IS UNCLEAR"

The EU has also supported cancer research through other programmes, such as on food, nutrition and health or on radiological sciences. So it would not be true to say that the EU has not put its money where its mouth is in its backing for the fight against cancer. What does remain open to question is whether the money is enough, whether it is sufficiently accessible and whether it is aimed at the right targets. That is a matter for the case for the prosecution—which will be the subject of future articles.

Peter O'Donnell,
Brussels

AWARDS AND APPOINTMENTS

All change!

Professor Odd Søreide has been appointed the new chairman of the Norwegian Cancer Society. He is a gastro-intestinal surgeon, and a professor at the University of Oslo. He is also a senior scientist at the Norwegian Center for Health Technology Assessment in Oslo.

He was, until recently, professor and clinical director of the department of surgery at the National Hospital in Oslo. He trained in Bergen, Norway and London, UK and is a fellow of the American College of Surgeons and the Royal College of Surgeons (England).

Professor Odd Søreide

Professor Søreide, who will be chairman until April 2002, takes over from Professor Stener Kvinnsland. Professor Kvinnsland will continue as a special consultant to the Society. He will become Secretary General in the autumn of 2002 when Mrs Lilly Christensen retires.

By then, Mrs Christensen will have worked for 30 years to improve cancer control efforts in Norway. She will have been Secretary General for 20 years, first of the Norwegian Society for Fighting Cancer and, after 1988 when the two Norwegian cancer societies amalgamated, of the Norwegian Cancer Society.

Professor Kvinnsland, who has chaired the Society since 1992, is an oncologist specialising in breast cancer. He was professor of medicine at the University of Oslo and head of oncology at the Norwegian Radiumhospital until 2000. He is heavily involved in the International Union Against Cancer (UICC) and has been a member of council since 1994. He became Secretary General of UICC in September 2000 and will be President of its next International Cancer Congress, due to be held in Oslo in the summer of 2002.

Professor Stener Kvinnsland

Further information on the Norwegian Cancer Society can be found at www.kreft.no.

Outstanding International Physician

Sir Richard Doll, epidemiologist at University of Oxford, UK, has received the 2001 Dr Nathan Davis International Award for Outstanding International Physician. The Award, which was presented by the American Medical Association (AMA), aims to honour physicians and health initiatives that further health information and medical practice worldwide.

Sir Richard is recognised as one of the world's leading epidemiologists, a senior statesman of cancer research and a great influence in training a generation of world-class scientists dedicated to the eradication of cancer, said the AMA. He was one of the first physicians to link cancer to tobacco use, and his research has provided valuable insight into the role of diet, asbestos, radiation and other factors in the development of cancer. He is also credited with helping develop the randomised medical trial.

Dr Gro Harlem Brundtland, Director-General of the World Health Organisation, said, "For 50 years (he has) been a global leader in the broad field of epidemiology and public health."

"A GLOBAL LEADER IN EPIDEMIOLOGY FOR 50 YEARS"

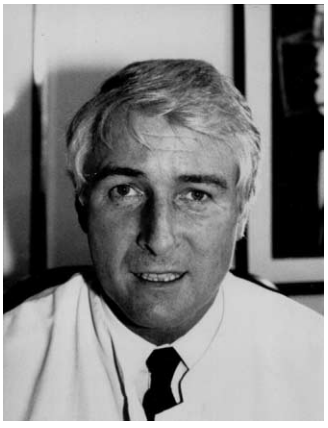
Sir Richard was nominated for the award by Dr Ronald Davis, on behalf of the American College of Preventive Medicine in Washington DC. He received a grant of US$ 50 000 administered through the AMA Foundation, to further the work for which he was recognised. The awards were presented during the AMA 2001 Annual Meeting in Chicago, US, June, 2001. Sir Richard underwent emergency surgery in Oxford, UK and was unable to attend the presentation. He has now recovered.

The Bill & Melinda Gates Foundation Global Health Program received the Dr Nathan Davis Award for Outstanding Global Health Initiative for its efforts to help immunise populations against infectious diseases; provide funds for AIDS vaccines, prevention and awareness programmes; improve women's access in developing nations to reproductive care; and back innovative ways to combat nutrition-related illness.

The Gates Foundation was nominated by Dr Donald Palmisano (Metairie, Louisana) and accepted only the non-cash portion of the award.

INTERVIEW

Early in his career, Professor Volker Diehl transformed B-lymphocytes with Epstein–Barr Virus (EBV) and was first to demonstrate that EBV causes infectious mononucleosis. He was also first to establish Hodgkin's cell lines in culture. He won the German Cancer Society award in 1997, is a former member of ASCO's educational board and is director of internal medicine at the University of Cologne.



Professor Volker Diehl

Where did you train?
I studied medicine in Germany and Austria, in Marburg, Vienna and Freiburg. My clinical training was in Berlin and, after registration, I worked on EBV at the Children's Hospital in Philadelphia, with Dennis Burkitt in Africa, and on lymphomas the Karolinska Institute, Stockholm. I then returned to Hannover.

Who inspired you?
My grandmother. She was one of the most famous theatre nurses in Berlin and went on to have 35 grandchildren, all but two of whom became either doctors or nurses - a really boring family! Professionally, Werner and Gertrude Henle in Philadelphia, who said that, in science, you get 7 meagre years and then 7 fat years and that the meagre years are very hard. In the clinic, you will see someone every day who is grateful for your help and their smile is more rewarding than anything.

Why did you choose to work in the field of cancer?
By chance. As a student, I had no topic for a thesis and asked a doorman at the hospital to suggest doctors I should speak to. My thesis eventually demonstrated that normal cells behave like cancer cells in culture. It led to my scholarship to the US, a relief after Germany which still felt small and insular after the war. I am rather optimistic and something of a missionary, which was necessary when leukaemia patients all died and for solid tumours you could give little more than tender loving care.

Did any other branch of medicine appeal?
I could have continued in basic research into infectious diseases, virology or epidemiology, but I wanted to work with patients. In 1978, I took cells from a lady with Hodgkin's disease. She died, but her cells were cultured and immortalised and she lives on in them.

Might you have done something else altogether?
I have played the violin since I was young. I was one of eight children and every evening we played and sang; music has had an enormous impact on my life. I was also athletic: I ran 100 yards in under 11 seconds which was fast in 1958 before modern shoes and tracks. I played basketball and soccer, and was interested in the ancient languages, Greek and Latin. But I had decided early on to be a doctor.

What has been the highlight of your career to date?
Having the opportunity to work with famous and talented people, to travel round the world and to have seen cure rates for Hodgkin's disease rise from less than 40% to 90%.

. . . **and your greatest regret?**
I have none.

If you could complete only one more task before you retire, what would it be?
My greatest desire is to find the infectious agent that causes Hodgkin's disease in people who also have a genetic predisposition. We are now able to cure it but we still don't know why it occurs.

What is your greatest fear?
Losing contact with my scientific friends all over the world after my retirement.

What impact has the Internet had on your working life?
Enormous. In communication, writing papers and being able to continue working regardless of location, Brazil, Africa, anywhere.

How do you relax?
Playing the violin, especially as a quartet with my daughter and grandchildren. I have a farm in the mountains where we go to ski, golf and look after the animals, and when I retire I'd like to write books, poems and paint a little.

Who is your favourite author?
Max Frisch, who is wonderfully nosy and always observes life with a twinkle in his eye. Thomas Mann, who summed up what thousands of others said or thought and put together paradigms which predicted many things which happened under Hitler. And the poems of Hermann Hesse. A few beautiful words, put together artistically, tell a whole story and can transform you just as music can.

What do you wish you had known before you embarked on your career?
How far doctors and scientists envy each other and how much misery this can cause. In the States, I was asked, "Are you brilliant?". When I returned to Germany, I was warned by an old professor, "Don't be too brilliant". The same word, but it is applauded in the States and derided here.

What piece of advice would you give someone starting out now?
Try to think positive, do your best, work hard, enjoy the success of your colleagues and be happy. Life is sometimes much easier than you think.

What is your greatest vice?
You should probably ask my wife this one, but I'd say it's impatience. If someone doesn't want to learn, is lazy or just doesn't grasp it, I can explain something 19 times but not 20!