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Overcoming resistance to STI571

Gene profiling may predict whether or not leukaemias will respond to treatment with STI571, according to a joint German/US research group. They were able to discriminate between sensitive and resistant leukaemias "with high accuracy", and say their finding could be relevant in the clinic, (*Lancet* 2002, **359**, 481–486).

STI571 produces durable responses in stable-phase chronic myeloid leukaemia (CML), but most patients with blast-phase CML or Philadelphia-chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) develop drug resistance within a few months.

The researchers identified 95 genes whose expression could be used before treatment to predict the sensitivity of Ph+ ALL cells to the drug. In 25 bone marrow samples taken from 19 patients, expression data from the 95 genes distinguished all sensitive samples from resistant samples. The researchers stress that their observation needs to be validated in prospective clinical trials.

Another German group (*Lancet* 2002, **359**, 487–491) identified five point mutations in 7 patients with Ph+ ALL which was resistant to STI571. All the mutations were at points known to be important for drug binding, within the ATP-binding pocket or activation loop of BCR-ABL. These mutations have conferred resistance *in vitro*. They conclude that leukaemias can develop resistance by acquiring individual point mutations. This "could make it difficult to overcome resistance to STI571 by use of alternative kinase inhibitors," they write.

An accompanying commentary (*Lancet* 2002, **359**, 458–459) suggests that efforts should be focused on preventing resistance from occurring. Useful strategies are likely to include the speedy elimination of leukaemic cells, and combining STI571 with other agents, such as ABL inhibitors with different contact sites, or other signal-transduction inhibitors acting on a critical downstream pathway. Techniques such as immunotherapy, known to be effective at eliminating minimal residual disease, could also be useful in combination.

"Now that specific, targeted, therapies for leukaemias are available, learning how to use them to optimum advantage is the next step," the commentary concludes.

Young people's smoking habits "worrisome"

No European country has managed to reduce smoking among young people since the late 1990s, a new report found. The World Health Organization's (WHO) European Report on Tobacco Control Policy 1996–2001 found that, throughout Europe, around 30% of 15 to 18 year olds are smokers.

The report found that in 10 countries (Belgium, Finland, France, Iceland, Italy, Norway, Poland, Portugal, Sweden and the UK), tobacco-related deaths decreased. In five countries (Finland, Iceland, Italy, Slovenia and Sweden) reported levels of tobacco consumption fell below 25% of the population aged 15 years and over.

However, there were no significant reductions in smoking by young people anywhere in Europe. Rates were similar throughout Europe and the gender gap appears to be disappearing; in 12 countries, teenage girls smoked more or as much as boys.

Dr Marc Danzon, WHO Regional Director for Europe, said, "We see here evidence of a hazardous harmonisation in tobacco consumption by 15–18 year old girls and boys at around 30%. It signals a very worrisome development and we have to be aware of the harm to health it projects."

Comparable data from 13 countries showed that smoking is more common among teenage girls (25.3%) than among adult women (21.5%). Only 5 years ago, teenage girls smoked as much as or less than adult women.

Cancer patients online

Interviews with patients living with breast and prostate cancer have been made available online. The site includes text, audio and video clips and is intended to give other newly-diagnosed patients access to the experience of others.

It was launched by Dr Ann McPherson, GP and researcher at Oxford University Department of Public Health and Primary Care, after she was diagnosed with breast cancer herself. "It helps to know you are not alone. Most people know very little about the disease at the time they are first diagnosed," she said.

The Database of Individual Patient Experiences (DIPEx) is supported by Macmillan Cancer Relief. The interviews cover the impact of illness on patients' daily lives, its effect on their family and friends, treatment choices and the effects they had. Information on the illness itself is included, along with frequently-asked questions and links to support groups and agencies.

It can be found at *www.dipex.org*

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A new era in colorectal cancer?

Developments in all disciplines are coming together to create a new era in treatment of colorectal cancer, say editors of a forthcoming *EJC* Special Issue (*Eur J Cancer* 2002, **38**(7)). Advances in genetics and surgery, together with a variety of new treatments, are changing the outlook for patients, they say.

New imaging techniques and improved computer software mean that virtual colonoscopy is now a "promising new method for assessing the colon", according to researchers from Leiden University Medical Center in The Netherlands. Helical CT generates two-dimensional axial images of the abdomen and pelvis. The data can used to reconstruct three-dimensional images, comparable with those obtained from conventional colonoscopy. The process is safe, highly acceptable to patients and provides a full structural evaluation of the entire colon. Recent results are "extremely encouraging", the researchers write. "The challenge remains to reproduce these favourable results in clinical practice and to evaluate the use of virtual colonoscopy in a purely screening population."

Novel therapies that specifically target malignant processes are progressing to phase III clinical assessment, says a joint group from Birmingham University and the Royal Marsden Hospital, Sutton, in the UK. For example, inhibition of the enzyme (farnesyl transferase) involved in posttranslational processing of the ras genes could result in targeted treatment of ras-oncogene dependent tumours. A multicentre double-blind placebo controlled phase III trial of the farnesyl transferase inhibitor R115777 for patients with metastatic colorectal cancer who have failed conventional chemotherapy has recently completed accrual.

Other potential targets discussed by the UK group include COX-2, the EGF receptor, metalloproteinases and CEA, a glycoprotein tumour-associated antigen over expressed in 85% of colorectal cancers.

Developments in surgery could reduce mortality and morbidity for patients. Transanal endoscopic microsurgery, a minimal invasive technique for the local resection of rectal tumours, should be re-evaluated for local excision with curative intent, say surgeons from The Netherlands. Early results were associated with inferior tumour control, but the Dutch group presents data which suggest that, in early rectal cancer, local recurrence and survival rates are comparable with total mesorectal excision.

New minimally invasive techniques may also complement surgical resection for patients with limited hepatic tumour involvement. Methods include laser, microwave and radio-frequency ablation.

The editors conclude that developments, such as those in the genetics of colorectal cancer, will have far-reaching public health consequences. "We hope that this issue will provide the reader with state of the art knowledge at the brink of this fascinating era," they say.

Reproductive factors and breast cancer risk

A study involving 91000 French women confirms that late child-bearing and early menarche increase risk of breast cancer. Spontaneous abortion has no significant effect on breast cancer risk at any age (*Br J Cancer* 2002, **86**, 723–727).

The prospective study tracked women over a 10-year period, during which 1718 were diagnosed with breast cancer. The women answered detailed questionnaires sent by post.

Reproductive factors had complex effects on breast cancer risk. For example, women who completed their first full-term pregnancy in their 30s were 63% more likely to develop premenopausal breast cancer than those who had their first child before the age of 22 years. However after the menopause, their risk was increased by only 35%.

Each additional year that menarche was delayed, between 11 and 15 years, decreased risk of premenopausal breast cancer by 7%. Risk of postmenopausal breast cancer was delayed by only 3% for each of these years.

Spontaneous abortion had no significant effect on either pre- or postmenopausal breast cancer risk. Study author Dr Francoise Clavel-Chapelon (Institut Gustave-Roussy, Villejuif, France) said that fear of breast cancer has added to the anxiety already felt by women who have miscarried. "I'm very glad to be able to allay those fears."

However, Dr Jan Willem Coebergh (Erasmus University Medical School, Rotterdam, The Netherlands) said he was very surprised that the paper made no mention of work carried out at the Netherlands Cancer Institute in the late 1980s and early 1990s (Rookus MA, van Leeuwen FE, *J Natl Cancer Inst* 1996, **88**, 1759–1764). The population-based, case-controlled study included 918 women and found no link between spontaneous abortion and risk of breast cancer. "This was already a non-issue," he said.

He added that the French work had research implications. "This study really should focus research interest on the window between menarche and first pregnancy," he said.

New approach for rare blood cancer

Arsenic trioxide shows "great promise" for the induction, consolidation and maintenance of complete remission in relapsed patients with acute promyelocytic leukaemia (APL), says an American researcher (*Acta Haematol* 2002, **107**, 1–17).

Presenting a treatment algorithm, Dr Dan Douer (University of Southern California, Los Angeles, USA) states that arsenic trioxide (Trisenox) exerts its effects by mechanisms complementary to all-trans retinoic acid (ATRA), the first-line treatment for APL. This potentially allows for combination therapies "with additive or even synergistic results," he said. Bone marrow transplants may also be complementary to arsenic trioxide in post-remission treatment. In future, he suggests that molecular monitoring of patients after initial therapy "may predict relapse risk and permit more effective intervention before overt clinical relapse occurs".

Trisenox (arsenic trioxide) has just been approved in Europe for treatment of APL.

EUROFILE

European cancer patients remain disunited

This autumn's 'Europe Against Cancer' week will be devoted to 'Patients' Rights', in recognition of the rise of empowered and informed patient advocates. But how far does the image reflect reality? Are cancer patients in Europe organised, and are they really fighting for their rights?

Currently, Europa Donna, the Milan-based breast cancer organisation, is the only patient group to operate at European level. Susan Knox, its director, said: "It is important to encourage former cancer patients to speak out and get involved in advocacy movements, and this is not always easy to do."

In some regions, there is still a stigma attached to having cancer, she said. "The most important thing we can do to overcome this is for those of us who have had cancer to speak out wherever and whenever possible so that others will feel empowered to do so, so that people will see that there are survivors of breast cancer who continue to live normal lives."

"PATIENT NETWORKS ARE MORE COMMON IN CHRONIC DISEASES"

It's an admirable sentiment, but other cancer patients have yet to follow the same path.

Andrew Hayes represents the Association of European Cancer Leagues in Brussels, and is also President of the influential European Public Health Alliance (EPHA), which lobbies on EU health policy. He is not sure that increased organisation of cancer patients at European level would necessarily bring tangible benefits. "Much could be achieved just by making models of good practice, and the necessary resources, more available around the Community, for standards are exceedingly patchy even within countries, let alone between countries. If your chances of survival depend on where you live, rather than the severity of diagnosis, something is clearly wrong", he says.

This is clearly a matter for healthcare professionals, providers and policymakers, but surely pressure from patients would help to bring this about faster? Of course, says Hayes, but the problem is finding representative patient groups. Most cancer patients hope that they will be treated effectively, and become ex-patients as soon as possible, he says. Patient networks are much more common among people with chronic diseases who will need continuing care, long-term medication, and treatment for the rest of their lives.

An additional problem may be that the physical and emotional demands of cancer, at least in the early stages of treatment, leave patients with little stamina to commit themselves to any kind of support group, let alone one which aims to influence European health policy. It is those who survive and have to live with the threat of a possible recurrence who continue to be active.

Europa Donna's members are mainly drawn from such survivors. A relatively young organisation, it has already shown what can be done with determination and enterprise. The group acts as secretariat to the newly formed European Parliamentary Group on Breast Cancer, and is planning a week-long poster exhibition on breast cancer in the European Parliament in June. Its members are among the first to join the European Health Policy Forum set up by the European Commission. The Forum was instituted by Health Commissioner David Byrne to enable patients to become more involved in policy development, and to provide a means of consulting with a wide range of interests on health issues. "We are keeping breast cancer on the European health care agenda", says Knox. There are plenty of similar opportunities for other cancer groups to do the same for their diseases, but up to now these have not been taken up.

A previous column pointed out that effective patient power can help push drug authorisation through. The EMEA exceptional circumstances procedure was used to licence eight anti-HIV/AIDS drugs as opposed to only two for cancer during the period 1995–1999. Cancer patient groups are just as organised as the European HIV/AIDS patient community. With 5-year survival on the increase, it is possible that more cancer patients will find the energy and enthusiasm to pursue their cause, but much needs to be done.

"SURVIVORS ARE IN THE BEST POSITION TO FIGHT FOR BETTER FACILITIES"

"I don't take much notice of any industry which comes to see me with a problem when I have not heard a word from the consumer side," said a leading UK MEP recently. "I want to know how this affects people, not just companies." Keeping independence from industry is a must, he said. "I do not want my views to be used as an excuse for the pharmaceutical industry to buy up patient groups." Andrew Hayes agrees that there are problems of credibility when industry is seen to be too close to patient advocates. Transparency about funding sources and relationships to industry is absolutely essential, he says, as are publicly-available ground rules about sponsorship.

So is it worth negotiating the minefield of funding and sponsorship, and the problems of setting up and running an organisation for cancer patients at European level? Yes, absolutely, says Susan Knox. "As breast cancer survivors, we are in the best position to fight for and insist on better screening, diagnostic and treatment facilities as well as continued research to find a cure for this disease."

Mary Rice
Brussels

Time for a campaign on melanoma

Calls for a European campaign to reduce sun exposure among children are expressed in this issue of *EJC* (pp. xxx). Researchers found that young children on sunny holidays were much more likely to use sunscreen than to wear clothes or reduce their time in the sun. "There is an urgent need in Continental Europe for educational campaigns targeting families with young children in order to change children's behaviour when in the sun," they said.

The study included 631 young children from Belgium, Germany, France and Italy. Parents gave detailed information on sun exposure and the child's behaviour and researchers found that, in the first 6 years of life, sun exposure increased steadily, while sun protection decreased. Over the whole period, only 8% of the children always wore trousers and a shirt in the sun, compared with 25% who always wore sunscreen.

A working group from the International Agency for Research on Cancer (IARC) concluded that sunscreens should not be the first choice for skin cancer prevention and should not be used as the sole agent for protection against the sun. However, the researchers found that as children got older, sunscreen use remained stable, while the wearing of trousers, shirts and hats decreased dramatically. "Sunscreens are not used as an adjunct to clothing, but as substitutes for clothing," they said.

Lead researcher Dr Gianluca Severi (European Institute of Oncology, Milan, Italy) said there is general agreement among those working in public health that sunscreens should only be used in combination with clothes—shirt, trousers and hat—and with use of shade and a reduction in sun exposure. This message is not getting across to parents. "There is evidence now that what is really important in the development of melanoma, is exposure at early ages in childhood. Children don't sunbathe, but you often see them playing on the beach for hours, and they get the same exposure," he said.

Dr Gianluca Severi

Awareness of the dangers of sun exposure is much lower in Europe than in either the States or Australia, he said. Even within Europe, there are big differences, with the UK and Nordic countries more aware than elsewhere in central and southern Europe.

Strong campaigns in Australia have had striking results, he said. There was an epidemic of melanoma, but mortality rates have now stabilised. Rates in Europe have always been lower than in Australia, particularly in central and southern Europe. However, in the last decade, melanoma mortality rates in central and southern Europe, even though still lower than in the UK, Nordic countries and Australia, increased steadily. "Neither the single nations nor the European Union have thought it necessary to tackle the problem," said Dr Severi. "It is now time for them to do something."

Fingerprick test for ovarian cancer

Mass screening for ovarian cancer could be carried out with a simple fingerprick test, say American researchers. The technique, based on mass spectroscopy, relies on a computer-generated algorithm to a identify proteomic patterns in the blood which are associated with cancer. Early results suggest the test is 100% sensitive and 95% specific (*Lancet* 2002, **359**, 572–577).

Mass spectroscopy sorts proteins and other molecules according to their weight and electrical charge and provides a snapshot of thousands of proteins at the same time. Initial assessment based on 50 women with ovarian cancer and 50 women without disease allowed the algorithm to create key diagnostic patterns which distinguish cancer from non-cancer.

The researchers, from the National Cancer Institute and Correlogic Systems Inc, Bethesda, Maryland, then used the technique on 116 masked blood samples: 50 from women with ovarian cancer and 66 from unaffected women. It identified all cases of cancer, and of the rest 63 of the 66 were recognised as not being cancer. If the sensitivity remains at 100% on further trials, a negative value could be used for reassurance, whereas a positive value might be sufficient to warrant further investigation, they suggest.

"Cost-effective, high-throughput screening is feasible," they say. Raw spectra could be sent via the internet to a central site housing the analytical software. "The pattern itself, independent of the identity of the proteins or peptides, is the discriminator, and might represent a new diagnostic paradigm," they say.

Cancer magazine launched

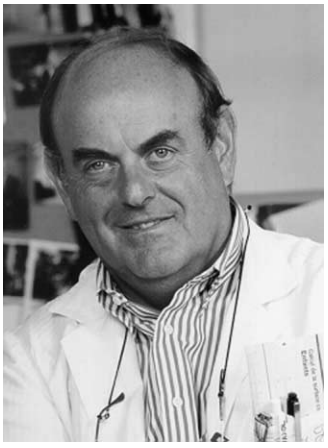
'Cancer Futures', a new multidisciplinary magazine, has been launched by the European School of Oncology (ESO). It aims to be a forum in which cancer specialists and patient advocacy groups can exchange ideas and information. It will contain cancer news, analysis and predictions for the future.

More than 20 000 copies of the pilot issue were distributed and a high level of interest was received from the US, the publisher says. Dr Alberto Costa, Director of ESO and Chairman of the Editorial Board of *Cancer Futures*, said, "We are thrilled by this demand and are confident that *Cancer Futures* will be internationally recognised as a leading oncology publication."

Cancer Futures is published six times/year by Springer, France, and will be available at key oncology congresses or via mail order.

INTERVIEW

Dr Hernán Cortés-Funes is head of the Medical Oncology Division at Hospital Universitario '12 de Octubre', Madrid. He is a former president of ESMO and former chairman of FECS, the Spanish Society for Medical Oncology, Spanish Society of Cancer Research and Federation of Spanish Cancer Societies. His special interest is the use of chemotherapy for the treatment of lung and breast cancers, lymphomas and germ cell tumours.



Dr Hernán Cortés-Funes

Where did you train?
I completed my postgraduate training and internal medicine residency in Madrid and then went to the National Cancer Institute in the States to study medical oncology.

Who inspired you?
I can't pick out a specific physician, but towards the end of my training I was treating young people with lymphoma with chemotherapy. Seeing tumours respond was the inspiration behind my decision to take a PhD in Hodgkin's lymphoma and to work in oncology.

Why did you choose to work in the field of cancer?
Cancer is a medical challenge, and you can see the results of progress. Also, when I started out, many physicians did not want to work with cancer patients and there seemed to be a gap in the care on offer, especially for patients with advanced disease.

Did any other branch of medicine appeal?
Surgery, which I loved and thought was a practical solution in medicine. But I was only 21 when I finished my training and I decided to study internal medicine and cancer first. As soon as I started this, I felt it was much wider than surgery.

Might you have done something else altogether?
My family are all lawyers and expected me to consider studying law. But I hated the look of it. The books were all heavy and had no pictures!

After my training, in the early 1970s, I worked for a time as a medical advisor to a pharmaceutical company. It taught me about the industry's goals and the power of marketing. It was useful information as my career developed.

What has been the highlight of your career to date?
When I came back from the States, medical oncology was in its infancy in Spain. There were cancer hospitals in France and the UK, but only a small cancer unit in Spain. I and a group of other physicians formed the Spanish Society of Chemotherapy, now the Spanish Society of Medical Oncology. At the time, specialities in Spain were being re-validated and re-organised and, as a result, Spain was the first country in Europe to recognise medical oncology as an independent speciality.

Also, when I was president of European Society of Medical Oncology (ESMO), we created a certification in medical oncology which was important to the development of the speciality in other countries. It is still a weak speciality in many countries; the UK for example has only 200 oncologists, compared to 500 in Spain.

. . . and your greatest regret?
That medical oncology is still not as developed as it I would like across Europe. We probably need a European Cancer Plan; it will come.

If you could complete only one more task before you retire, what would it be?
To ensure that young people have a clear idea about cancer and understand that it is a chronic disease. We may never cure cancer, but we are learning to handle it, so that patients live longer and better lives. People are afraid of cancer because it is incurable, and it gets a low priority, for young doctors choosing their speciality, and for health authorities funding treatments. It is a medical problem but there is a lot we can do for patients at all stages of the disease.

What is your greatest fear?
Of war. Historically, it's something we know a lot about in Europe but the possibility has increased since the terrorist attacks on the States last September. The creation of a single European state, comparable with North America and Canada is good, but I am afraid that its development will slow down in the current political climate.

What impact has the Internet had on your working life?
It's incredible, as important an invention as the telephone or radio. It creates problems, of course, but it also simplifies life.

How do you relax?
Reading, listening to music, and playing golf.

Who is your favourite author?
Oscar Wilde. It's deep, it's interesting, and it's about a different way of life.

What do you wish you had known before you embarked on your career?
I'm not sure I would have wanted to know more than I did. It could have sent me off in a different direction or into a different career.

What piece of advice would you give someone starting out now?
Young oncologists need a good training in internal medicine. Oncology is very specific and you need to be a good physician first. Take the time to get well trained.

What is your greatest vice?
Playing golf. I know other oncologists who play and we always check to see if there is a golf course near to oncology meetings. I would spend all my free time playing if I could, and my wife objects to me going off with my clubs on wonderful Saturday afternoons!