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New agent shows promise in GIST

Patients with unresectable or metastatic gastro-intestinal stromal tumours (GIST) can expect significant improvement with the new agent STI-571 (Glivec), researchers say. At a plenary session of the 37th ASCO Annual Meeting, they said the rationally developed compound is showing impressive results in solid tumours.

STI-571 is a signal transduction inhibitor, which has already shown encouraging, results in the treatment of chronic myeloid leukaemia. In GIST, it blocks the growth signal of c-kit, a gene that is overexpressed and promotes cell proliferation.

"FOR THE FIRST TIME, STI-571 IS SHOWING TREMENDOUS BENEFIT IN A SOLID TUMOUR."

Professor Allan van Oosterom (UZ Gasthuisberg, KU, Leuven), President of EORTC, presented data from a phase I clinical trial conducted by EORTC's Soft Tissue and Bone Sarcoma Group. The study found that, in 36 patients with GIST, only 4 progressed in the first 8 weeks of treatment. Doses were escalated from 400 mg twice daily to 500 mg twice daily and nearly all patients could tolerate the lower dose for more than 2 months.

Professor van Oosterom said the results of the study were "impressive". An EORTC-co-ordinated international and intergroup phase III trial of STI-571 is now underway. It will compare the clinical activity of STI-571 at two dose levels in patients with GIST, which expresses the KIT receptor tyrosine kinase (CD117). The trial aims to recruit 800 patients.

A larger phase II study from Oregon Health Sciences University, USA, was presented at the same session. It found an 89% clinical improvement in patients with GIST. The trial included 139 evaluable patients, of whom less than 1% had responded to previous therapies. 68 patients experienced a partial response and a further 54 had stable disease. "These results are very exciting and demonstrate the value of therapy that is molecularly targeted at what makes a cell cancerous," said lead author, Dr Charles Blanke. "For the first time, STI-571 is showing tremendous benefit in a solid tumour."

Other cancers such as small cell lung cancer and mast cell leukaemia also express c-kit but it is not yet known whether blocking this pathway will inhibit cell growth or cause responses in these cancers.

"THE QUALITY OF LIFE OF MOST PATIENTS IS EXCELLENT."

Professor van Oosterom said that for patients with GIST, the new drug is important. "In advanced patients treated with classic drugs, only 10% of them improved, whereas with the new drug 70% of them improved and the quality of life of most patients is excellent."

New drugs slow progression of prostate cancer

Preliminary results suggest that oral clodronate delays symptomatic progression of bone metastases from prostate cancer, UK researchers report. A phase III trial included 311 patients with advanced prostate cancer that had spread to the bone. The study found that those who received oral clodronate reported pain after a median of 24 months compared to 19 months in patients who received placebo.

The researchers, from the Royal Marsden Hospital, Sutton, UK, say the trial also suggested an overall survival benefit of 7 months but stressed that confirmatory studies with longer follow-up are needed.

Meanwhile, researchers at Johns Hopkins University, Baltimore, MD, USA, studied 244 men with hormone-refractory prostate cancer that had spread to the bones but who did not yet have associated symptoms. Patients were randomised to receive either atrasentan (ABT-627) or a placebo. Those on the active drug went for 198 days before imaging tests or the onset of pain signalled further bone metastases, compared with 129 days for those on placebo.

The drug also increased the time for prostate specific antigen (PSA) levels to rise by more than 50%, from 10 to 20 weeks. This is another indicator that progression of the disease had slowed down.

Lead study author Michael Carducci (Johns Hopkins University) said, "This is quite exciting because the data suggests this low-toxicity pill leads to clinical benefit and delays time before patients may need additional systemic treatments."

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Implications of human genome project discussed

Clinical and ethical implications of the human genome project were addressed at a symposium held jointly by ASCO and ESMO (European Society for Medical Oncologists).

"Our hope is to apply whole genome expression analysis to patients that will lead to a new taxonomy of cancer," said Dr Jeffrey Trent (National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA). He said identification of genes responsible for genetic and genomic disorders will have clinical applications. Professor Martin Fey (Institute of Medical Oncology, Berne, Switzerland) said the human genome project would also have a clinical impact on the molecular approach to sporadic cancers.

Detecting sporadic mutations can help physicians distinguish one form of cancer from another he said, for example, acute myeloid leukaemia from acute lymphoblastic leukaemia: "Chip technology shows whether specific genes are highly expressed or not expressed in these leukaemias and helps distinguish clinically separate disorders," he said.

However, Dr James Mackay (Addenbrook's Hospital, Cambridge, UK), said testing for inherited mutations can sometimes cause undue anxiety in patients, even where the tests are negative. A woman found not to have *BRCA* mutations may still feel uncertain about her health, wonder whether a technical mistake has been made or about other gene mutations in her family.

New trial methods needed for anti-angiogenic drugs

Traditional phase I clinical trials may not be appropriate for testing anti-angiogenic compounds, EORTC researchers say. While testing an agent that blocks the action of vascular endothelial cell growth factor (VEGF), they found that even separate tumours within the same patient react differently to the drug.

The researchers, from across Europe and the US, performed biopsies in 20 patients taking HuMV833. Side-effects never appeared in patients and so dosing of the drug was not limited by safety concerns. Lead author Dr Gordon Jayson (Christie Hospital, Manchester, UK) said "We have seen significant variation within and between patients in how their tumours take up the drug and respond biologically. We need to redesign trials for cytostatic agents to compare escalating doses within each patient, not between patients."

However, he said that HuMV833 "shows promise" in its ability to reduce the permeability of blood vessels, and thus slow cancer growth.

Improved survival in aggressive NHL

Monoclonal antibody ritumab, used in combination with standard chemotherapy, significantly improved survival in patients with aggressive non-Hodgkin's lymphoma NHL, researchers said. Ritumab (MabThera) is currently indicated only for the treatment of relapsed or chemoresistant low grade or follicular NHL.

The results presented at ASCO were from an interim analysis of 328 patients included in a European trial, Groupe d'Etude des Lymphomes de l'Adulte (GELA). Those receiving ritumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) had an 83% survival at 1 year; for those receiving the chemotherapy alone, it was 68%.

Professor Bertrand Coiffier (Hospices Civiles de Lyon, France), principal investigator, said "This is the first new drug combination in 20 years to show an improvement in overall survival in aggressive NHL."

Based on this data, an application to expand the indication of ritumab to include aggressive NHL has been filed with the European drugs authority (CPMP).

EGFR inhibitors 'show promise'

Inhibitors of the Epidermal Growth Factor Receptor (EGFR) are now a clinical reality, according to speakers at an Integrated Symposium at ASCO. The inhibitors have shown antitumour activity, increased effectiveness and decreased toxicity of chemotherapy.

A selective EGRF inhibitor, OSI-774, has shown overt antitumour activity in several types of cancer including metastatic head and neck cancer and non-small cell lung cancer (NSCLC), according to Dr Eric Rowinsky (Cancer Therapy and Research Center, San Antonio, TX, USA). The effects were demonstrated by PET studies. At a dose of 150 mg/day, the most common side effect was an acneiform skin rash. Another study conducted by Dr Neil Senzer suggested that OSI-774 offers similar survival rates for head and neck cancer compared to other chemotherapy regimes, but with lower side-effects. Dr Senzer said that overexpression of EGFR does not appear to be a prerequisite to antitumour activity by OSI-774.

Another tyrosine kinase inhibitor, ZD 1839 (Iressa) may be effective for treatment of certain breast tumours, according to Dr Stacy Moulder (Vanderbilt University Medical Center). *In vitro* experiments which involved exposing multiple HER2-overexpressing human breast tumour cell lines to ZD 1839, demonstrated that the drug blocks the transactivation of HER2 by inhibiting the EGFR tyrosine kinase. Dr Moulder suggested that Herceptin plus ZD 1839 may be effective for the treatment of breast tumours that express EGFR and overexpress HER2. Iressa is in phase III trials for NSCLC and in phase II trails in gastric, hormone refractory prostate and breast cancers.

Dr Carlos Arteaga (Vanderbilt University Medical Center) said the studies presented at the symposium highlighted the need to determine better predictors of clinical response to EGFR therapies; the side-effects of prolonged chronic inactivation of EGFR and to find safer chemotherapy drugs to use in combination with them. Dr Arteaga questioned whether EGFR therapies would be more appropriately used for chemoprevention than adjuvant therapy.

Bladder cancer: survival rates almost double

Pre-operative chemotherapy almost doubled the median survival of patients with locally advanced bladder cancer, compared to the standard treatment of surgery alone, US researchers found. In a phase III randomised trial of 317 patients, those receiving neoadjuvant chemotherapy had a median survival of 6.2 years, compared with 3.6 years for those receiving surgery alone.

Study leader Dr Ronald Natale (Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA, USA) said, "Although the results of a single clinical trial alone do not change the standard of care, the striking results of this study requires that patients should at least be informed that preoperative chemotherapy might significantly change their survival."

The study indicated that chemotherapy alone may be effective in some patients. In 38% of patients who received the chemotherapy regimen of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) there was no pathological evidence of cancer in removed bladder. Dr Natale said, "The question of whether we can preserve the bladder or at least defer cystectomy can now be considered."

ASCO 'should support tobacco control'

ASCO should restate its position on tobacco control, says a Lancet editorial (*Lancet* 2001 **357**, 1459). It noted that the American Medical Administration has urged the Bush administration to continue the Justice Department's lawsuit against the tobacco industry. It states, ''Given its influence, ASCO should follow suit by restating its position on tobacco control, starting by using its muscle to counter the influence of the tobacco industry in the Bush administration, and by publicly supporting the FCTC''. (World Health Organisation's Framework Convention on Tobacco Control.)

The editorial notes that British American Tobacco has just signed an agreement with China to build a large plant in western Szechuan Province which "challenges efforts so far to control the use and spread of tobacco".

Further fraud in South African breast cancer trials

The scientific misconduct by a South African researcher uncovered in 2000 was not limited to a single study, according to ASCO. A new audit of Dr Werner Bezwoda's work concluded that a study conducted in 1995 was also deeply flawed. It has now been officially retracted by the *Journal of Clinical Oncology*.

The 1995 study was purportedly the first randomised, phase III trial to find a benefit from high-dose chemotherapy in metastatic breast cancer. It reported that high-dose CNV (cyclophosphamide, mitoxantrone and vincristine) offered a significant advantage over conventional therapy.

However, the audit, published online (www.asco.org/ascoindex.htm) found ''substantial evidence of scientific misconduct''. Researchers trawled through 15 000 patient records, numerous research files and meeting minutes. They found:

- No signed informed consent forms for patients in the trial;
- The trial had not been approved by the University's Institutional Review Board, despite statements to the contrary;
- Little evidence of randomisation;
- The study protocol was written 9 years after the study was started and only after the investigation into Bezwoda's 1999 study had begun;
- The paper stated ''no treatment-related deaths'' but the auditors found at least three;
- No records for 29 of 90 patients;
- Insufficient records for many patients and some were treated with regimens and hormonal agents not consistent with the published information.

Dr Raymond Weiss (Georgetown University, USA) led the audit and said the findings were disturbing. ''Not only did our research uncover scientific misconduct in the 1995 study but we also discovered untrue statements in eight other publications involving authorship by Dr Bezwoda,'' he said.

ASCO advises that the remaining large ongoing trials of high-dose chemotherapy be completed before a final recommendation can be made about the appropriate use of the treatment. It says women should only undergo high-dose chemotherapy and bone marrow transplantation in the context of a carefully controlled clinical trial.

Smoking, obesity, infections and cancer

Smoking causes 60% of all cancer deaths in smokers and as many deaths again from other diseases, according to Professor Julian Peto. "It is absurd for smokers in the West to worry about anything except stopping smoking," he said.

In a review of cancer epidemiology over the past 50 years (*Nature* 17 May 2001) he found that being overweight caused 10% of cancer deaths among American smokers, and about 7% in Europe where obesity is less common. The only substantial environmental carcinogens in developed countries are sunlight and indoor radon, which further increases lung cancer among smokers.

Viruses are particularly important in the developing world and hepatitis B infection causes almost as many cancers as smoking does in China. About 5% of cancers in the US are due to infections, and 7% in Europe. The main risk is the bacterium that causes stomach cancer.

Cancers of the lung, colon, rectum, bladder and prostate (but not breast) are increased by immunosuppression. This suggests, Professor Peto said, that unidentified viruses may be important in these cancers as well. He said it would be an important field for future research.

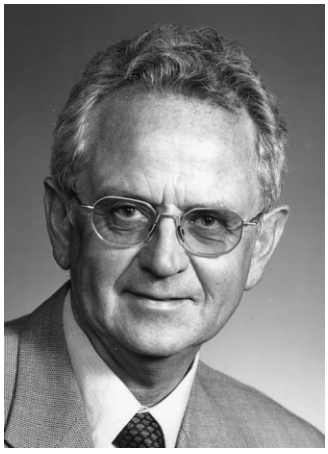
AWARDS AND APPOINTMENTS

ASCO Award for Scientific Achievement

Professor Heine Hansen (National University Hospital, Copenhagen, Denmark) received the ASCO Distinguished Service Award for Scientific Achievement at the opening ceremony of the annual meeting. ''I am deeply honoured and cannot ask for a more gratifying award in my career,'' he said. The award was given in recognition of his work in lung cancer.

After initial training at the University of Copenhagen, Professor Hansen completed his residency and fellowships in haematology and oncology at Montefiore Hospital in New York and the National Cancer Institute Veterans Administration (NCI-VA) in Washington, DC. The incidence of lung cancer in men was rising dramatically at the time, the late 1960s, and was a priority research area. Small cell lung cancer was recognised as a special disease entity in the early 1970s and combination therapy was introduced. New agents such as nitrosoureas and bleomycin, cisplatin and L-asparaginase became available.

Professor Hansen returned to the Finsen Center in Copenhagen in 1976, where he has been Head of Chemotherapy, Head of Oncology and overall Director of the Center from 1994 to 1997. There, he continued his research in small cell lung cancer and with colleagues, conducted clinical trials into prognostic facts and metastatic patterns of the disease, and new treatments. They demonstrated the activity of vincristine, etoposide and teniposide, among others, in small cell lung cancer. ''The disease was transformed from being basically a noncurable disease to a curable disease, albeit only in a small group of patients,'' he said.



Professor Heine Hansen

He has been a member of ASCO since 1972. At EORTC, he co-founded and chaired the Early Clinical Trials Group, and chaired the New Drug Coordinating Committee. He is a past president and now Executive Director of ESMO.

A statement from ASCO said, "Dr Hansen's work has contributed significantly to the staging and treatment of lung cancer, especially small cell lung cancer. The ASCO Distinguished Service Award aptly acknowledges his scientific achievements over the past 30 years."

ASCO's other special awards were presented to Nancy Brinker, founder of the Susan G. Komen Breast Cancer Foundation (Special Recognition Award); Nancy L. Johnston, Chair of the Health Subcommittee of the House Ways and Means Committee (Public Service Award); Dr Charles A. Colman Jr., President of the Cancer Therapy and Research Center, San Antonio, TX (David A Karnofsky Memorial Award); Dr Sidney J. Winawer, Memorial Sloan-Kettering Cancer Center (American Cancer Society Award).

Achievement in Cancer Research

Professor V. Craig Jordan (Northwestern University, Chicago, IL, USA) has been presented with the 24th Annual Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research. He received a US $50 000 cash prize and a silver medallion at a dinner in his honour in New York City on 10 April 2001.

Professor V. Craig Jordan

"With persistence and a faith in anti-oestrogens, the research efforts of Dr Jordan have extended the lives of, literally, hundreds of thousands of women with breast cancer, or who are at high risk of developing the disease," said Robert Kramer, a Vice-President of the company. "He has opened the door for other scientists working toward effective and molecular targeted therapies for cancer."

Professor Jordan trained in pharmacology at Leeds University, UK, and took his doctorate there on the interaction of anti-oestrogens with the oestrogen receptor. At the Worcester Foundation for Experimental Biology, Massachusetts, he conducted the first systematic laboratory study of tamoxifen as a cancer chemopreventive agent. He also worked in Madison, Wisconsin, before taking up his current post in Chicago in 1993. He is the principal investigator of a National Cancer Institute-sponsored Specialized Program of Research Excellence (SPORE) in breast cancer.

Dr Jordan developed the concept of selective oestrogen receptor modulators (SERM) and was the first to identify SERM activities in classes of anti-oestrogens for bone, uterus and breast. This led to the successful development of raloxifene, the first SERM to be used to prevent osteoporosis. It is currently in clinical trials as a preventive agent for breast cancer.

INTERVIEW

Dr Matti Aapro is Director of the Multidisciplinary Oncology Institute at the Clinique de Genolier, Switzerland. He is Secretary-General of EORTC, and holds executive positions in many international cancer organisations, including European School of Oncology and European Society of Medical Oncology. He is also Executive Director of the International Society for Geriatric Oncology (SIOG).

Dr Matti Aapro

Where did you train?
Initially, at the University Hospital in Geneva. I then spent 2 years as a haematology–oncology fellow at the Arizona Cancer Center in Tucson, Arizona before returning to Geneva.

Who inspired you?
I admire many people and am honoured by their support and friendship, but I would shortlist those at the beginning of my career. Professor Alex Muller, Head of Internal Medicine in Geneva when I trained there and a figurehead, a researcher who is also fantastic with patients. Professor André Cruchaud, Head of Immunology in Geneva, introduced me to laboratory work. Syd Salmon and Stephen Jones in Tucson taught me to look carefully and listen to patients rather than just their test results, and Nicolas Odartchenko taught me how to run a journal.

Why did you choose to work in the field of cancer?
Through working with Pierre Alberto during my internship. My mentor then, my friend today, Pierre is a pioneer of clinical research in oncology. He was mainly caring for ambulatory cancer patients and his work appealed to me.

Did any other branch of medicine appeal?
I considered immunology but I got the impression — which might not be correct — that I would not have much contact with patients.

Might you have done something else altogether?
Absolutely. I am a frustrated architect and wanted to study architecture from being a child. My mother says it was because a famous Finnish architect, Alvar Aalto, came to our house when I was young, but I don't think so as I can't remember the visit. But I was born in Brazil and I went back there to see the Rio school of architecture in 1968. The country was under a military dictatorship at the time, and architecture did not seem to be the solution.

What has been the highlight of your career to date?
On my first day at medical school I saw my future wife for the first time, sitting in the front row of the auditorium. It took me a couple of years to convince her that I was right, but that was the best moment of my life.

In 1994, Umberto Veronesi called me and asked me to be the first Head of Oncology at the European Institute of Oncology. It was an exciting and special opportunity to create something that had not existed before. It also allowed me to strengthen my ties with the European School of Oncology and to work closely with Alberto Costa.

. . . and your greatest regret?
I am extremely happy in Switzerland, but at the back of my mind, I still dream of going back to Brazil.

If you could complete only one more task before you retire, what would it be?
I am also a frustrated pianist and when I retire I shall learn to play decently. I have been told it will be difficult but still feasible. Before then, I would like to continue to develop the area of cancer in the elderly and to this end, have set up the scientific society SIOG.

What is your greatest fear?
That patients with cancer might not be getting optimal treatment because of bureaucratic measures which stop oncologists from doing what they think is best. This is happening in Switzerland and all over the world.

What impact has the Internet had on your working life?
I am editor of a website called Cancerworld (www.cancerworld.org), which has links to the websites of other organisations including ESO, EONS, Europa Donna, EUSOMA and Challenge. I hope it will develop links with other societies and become a useful resource both for professionals and the public.

How do you relax?
With my family. My great pleasures are tennis, downhill skiing and siestas. My staff all know that if they phone between 2 and 4 pm when I'm on holiday I will kill them! I also love to sail with my sons and cycle with my daughter. For the time being at least, I can keep up with her.

Who is your favourite author?
I rarely read what is considered good literature — my wife is the intellectual of the family — I prefer history books, spy novels and political fiction. John le Carré is for me the master of the spy novel.

What do you wish you had known before you embarked on your career?
Medical schools devote too much time to diseases that you will never encounter and not enough to what most doctors will actually do: talk and interact with their patients. I had to learn all about strange diseases of young children that will be seen once every 3 years in a paediatric clinic, but there was not much at all about patient psychology.

What piece of advice would you give someone starting out now?
Decide early on whether you want to go for an academic or clinical career. Only a few exceptional people manage to combine both successfully. If you go for academia, link up with an outstanding research group as soon as you can.

What is your greatest vice?
Good food and good wine — and many friends have noticed the effect on my waistline! Unfortunately, my wife is an outstanding cook, we live near the excellent wine-growing regions of France and Italy, and I am a chocoholic in Geneva, home of the best small chocolate producer in the world. Fortunately it is difficult to park nearby, so I don't stop there as often as I would like!