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Accelerated assessment for Herceptin

Herceptin (trastuzumab) is to have its indication extended to include the adjuvant treatment of early breast cancer. The European Medicines Agency (EMEA)'s Committee for Medicinal Products for Human Use (CHMP) has given a positive opinion on the extension.

The positive opinion covers use of the drug to treat early invasive, non-metastatic breast cancer which over-expresses HER2, following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy if applicable.

Herceptin was previously authorised in Europe for the treatment of patients with metastatic breast cancer, either as monotherapy for patients who have undergone at least 2 chemotherapy regimens or in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for the metastatic disease.

CHMP has stressed that excess of HER2 must be demonstrated before treatment with Herceptin can be initiated. The main risk associated with the drug is cardiotoxicity but CHMP concluded that the benefits of Herceptin are greater than its risk in early breast cancer.

Herceptin's extension of indication is the first accelerated assessment by the EMEA under new EU legislation introduced in November 2005. The application was submitted by manufacturer Roche in February 2006.

- The UK's National Institute of Health and Clinical Excellence (NICE) is expected to issue guidance to the NHS on the use of Herceptin, in July 2006.

NICE guidance on colon cancer treatments

The UK's National Institute of Health and Clinical Excellence (NICE) has issued guidance on the use of capecitabine and oxaliplatin for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer, following surgery for the condition.

The guidance suggests the use of capecitabine as monotherapy; or oxaliplatin in combination with 5-fluorouracil and folinic acid.

"The choice of adjuvant treatment should be made jointly by the patient and their doctor. The patient should be informed about the differences between the medicines available and the potential contra-indications and side effects so that she or he can be fully involved in the decision," the guidance states.

Chemoprevention: new agents needed!

Women with BRCA1 mutations are unlikely to benefit from any of the chemopreventive agents currently in development, Dr Ruth O'Reagan (Emory University, Atlanta, USA) says (*Lancet* 2006;**367**:1382–3).

"All the agents currently in development as chemopreventives in breast cancer act through the oestrogen receptor, and are therefore unlikely to affect the incidence of oestrogen-receptor-negative cancers. This is of particular importance in women with BRCA1 mutations, who develop oestrogen-receptor-negative cancers and would be unlikely to benefit from chemoprevention with these agents.

"It is imperative that we identify agents that might decrease the incidence of oestrogen-receptor-negative breast cancers," she concludes.

Positive opinion for sunitinib malate

Sunitinib malate (Sutent) has received a positive opinion for use in gastrointestinal stromal tumour (GIST) and metastatic renal cell carcinoma (mRCC). The European Medicines Agency (EMEA)'s Committee for Medicinal Products for Human Use (CHMP) has recommended conditional marketing authorisation, which means that further evidence is awaited.

The positive opinion is for the treatment of unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance; and for advanced and/or metastatic RCC after failure of interferon alfa or interleukin-2 therapy.

Further evidence is required of the drug's impact on progression-free survival in patients with mRCC. A study is being conducted; the EMEA will review new information within a year and update the product information as necessary.

The positive opinion for sunitinib was the first to be granted under new EU rules which came into force in April 2006. The drug, produced by Pfizer, was approved by the US' Food and Drug Administration (FDA) in January 2006. In the US, it is indicated for the treatment of advanced RCC; and for GIST in patients whose disease has progressed or who are unable to tolerate treatment with imatinib mesylate.

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New explanations for the effect of exercise

Laboratory research has shed new light on the mechanisms by which exercise protects against skin and bowel cancer. Two US studies examined the effect of voluntary exercise among groups of mice.

The first study (Carcinogenesis doi:10.1093/carcin/bg1056) exposed mice to ultraviolet B light (UVB); and gave only some access to running wheels. The mice able to exercise took longer to develop skin tumours, and developed fewer and smaller tumours. The researchers suggest exercise may trigger apoptosis in UVB-induced tumours.

Author Dr Allan Conney (Rutgers University, New Jersey, USA), said, "Preliminary indications from follow-up work in the laboratory suggest that voluntary exercise enhances UVB-induced apoptosis in the skin, and that it also enhances apoptosis in UVB-induced tumours. So although UVB is triggering the development of tumours, exercise is counteracting the effect by stimulating the death of the developing cancer cells."

The second study used APC Min mice, whose genetic mutation predisposes them to develop intestinal polyps. One group of mice were given access to the running wheel and a restricted calorie intake; the others had unrestricted food but no running wheel.

The exercising mice had a negative energy balance and weighed less than the control group, but developed significantly fewer and smaller polyps, and had prolonged survival. This was despite their higher levels of hormones known to be associated with the onset of cancer – insulin-like growth factor-1 (IGF-1) and corticosterone.

Lead author Dr Lisa Colbert (University of Wisconsin-Madison, USA) said the exercising mice ran an average of 3.8km a day, and the further they ran the fewer polyps they had. "These data suggest that voluntary exercise that induces a negative energy balance protects against the onset of cancer in these mice, but that the mechanism is unlikely to be related to body composition, IGF-1 or corticosterone."

Common susceptibility genes "are unlikely to exist"

The hunt for common inherited genetic variants that increase susceptibility to cancer is like the search for the end of the rainbow, say researchers. They point to "important methodological and practical challenges for cancer prevention" and say that, despite the huge resources invested, success is unlikely.

Genetic epidemiologist, Dr Jaakko Kaprio (University of Helsinki, Finland), and biostatistician Dr Stuart Baker (National Cancer Institute, Bethesda, USA) emphasise several problems: "The first is that recent research suggests these genes are unlikely to exist or, if they do, are unlikely to have much of an effect on the incidence of cancer" (*BMJ* 2006; **332**:1150–2).

Early stage carcinogenesis seems to entail alterations in the stroma rather than genetic mutation of the parenchyma or functional tissue. In addition, the rapid changes in cell morphology needed for evolving cancer cells to have a growth advantage over other cells are likely to require large genetic rearrangements rather than single polymorphic changes.

Another reason to play down the role of these genes is the migration studies suggesting that environmental, dietary, or lifestyle changes have a large effect on the incidence of cancer. Further, twin studies suggest that genetic susceptibility made only a small to moderate contribution to the incidence of cancer. "The results support the argument for the primacy of environmental effects," say the authors.

Even if large studies detect true associations between common genes and common cancers, it will still be difficult to show clinical benefit. Studies will have to include between 10,000 and 30,000 people (because cancer is rare in asymptomatic people), and even larger numbers will have to have genetic testing to identify those suitable for randomisation.

Huge resources are being invested in the search for these genes. The US cancer genetic markers of susceptibility project (http://cgems.cancer.gov) will cost Euro 11 million, and large replication studies may still be necessary to confirm generalisability to other populations. But the authors conclude, "Enthusiasm for this new field of research should not precipitate unwarranted expectations."

PGD allowed in UK

The UK's Human Fertilisation and Embryology Authority (HFEA) has ruled that preimplantation genetic diagnosis (PGD) is to be permitted for inherited susceptibility to cancers such breast, ovarian or bowel. These conditions differ from those previously licensed because they are late onset, lower penetrance and potentially treatable.

The decision applies to carriers of BRCA 1 and BRCA2 mutations and to hereditary non-polyposis colorectal cancer (HNPCC).

The HFEA made its decision after gathering public views and having discussions with genetic interest groups, cancer charities, geneticists and clinicians. A Licence Committee will initially consider applications on a case-by-case basis. None has yet been received.

"This is not about opening the door to wholesale genetic testing," said Dame Suzi Leather, Chair of the HFEA. "These genetic tests can still only be used for a minority of people if there is a clear history of cancer across generations of a family.

"Not every family who carries a condition would want to have PGD and the availability of this option should not dictate a woman's treatment. But we feel it would be appropriate that this choice should be available."

The decision was welcomed by the UK's British Medical Association (BMA). Dr Vivienne Nathanson, Head of Ethics and Science, said, "The BMA believes that it is right to use advances in medical technology to reduce suffering and impairment. We do not believe parents will undertake embryo selection for trivial reasons and we do not believe they should be allowed to do so."

EUROFILE

EU 'Could do Better' on Orphan Drugs

Orphan drugs – those medicines used for the diagnosis, prevention or treatment of rare and serious conditions, or intended for conditions where, without incentives, revenues would not justify investment – had little encouragement in the EU until 2000, when the first regulations were introduced. They covered incentives for research, development and marketing. Five years on, the Commission has produced a staff working document looking at progress so far.

In terms of the legal framework, the EU started out late. The US has had an Orphan Drugs Act since 1983, and Japan a similar regulation since 1993. Australia and Singapore also beat Europe to the post. So it was important that significant incentives to develop drugs for rare diseases were given if European patients were not to lose out. Among the incentives offered in the series of Commission regulations which came into force in 2000 are scientific advice to optimise development; 10 years' market exclusivity for companies that produce such drugs; help and guidance in preparing the regulatory dossier for the authorities; fee reductions for marketing authorisations; and the eligibility of those developing the drugs for EU and Member State research grants.

At first glance this may seem quite generous. But when compared with what is available in the US, it looks less so. There, companies are able to receive large tax credits – up to 50% – against the cost of clinical trials. Similar fiscal benefits are available elsewhere. Of course, these other countries have national tax systems, and the EU does not, so in the current circumstances it would be impossible for such a benefit to be introduced. But looking at the Commission report, it is easy to see that some kind of additional incentive is needed if the European orphan drugs programme is to prosper.

''EU INCENTIVES NEED TO BE SUPPLEMENTED BY MEMBER STATES''

"Of the 268 designated orphan medicinal products between April 2000 and April 2005, 49 (19%) have applied for a marketing authorisation. Of these, 44 have filed through the centralised route and 5 via national procedures. During the same period, 22 orphan medicinal products have received a marketing authorisation," says the working document. However, they acknowledge that this is clearly not enough. "Incentives at the European Union level need to be translated into rapid access of patients to the new products throughout the entire Community and they need to be supplemented by incentives at Member States level. In this regard, the past experience was not entirely satisfactory". Given the limited competence of the EU in healthcare issues, and the lack of a co-ordinated approach between Member States, the granting of marketing approval does not mean that a drug will available in all countries, and this makes patient access to orphan drugs far more difficult and complex.

''SEVERAL THOUSAND RARE DISEASES ARE STILL AWAITING THERAPY''

A recent paper, "Orphan drug development is progressing too slowly" (*British Journal of Clinical Pharmacology*, Joppi et al, 2006;**61**(3):355–360), looked at the impact of the EU orphan drug regulations. "The paucity of European incentives... and the poor documentation underpinning the applications may have limited the number of new orphan medicinal products" say the authors. "There is an urgent need to establish programmes setting aside a special fund and providing tax relief for sponsors producing orphan medicinal products. The fact that it took 4 years to develop 18 drugs and that there are still several thousand rare diseases awaiting therapy is a public health issue that cannot be neglected."

With many cancers qualifying as rare diseases, this subject is clearly of interest to oncologists. "Nearly all drugs currently used to treat children with cancer were developed for adult cancers and then found effective in children", said Professor Mike Stevens, head of the Paediatric Oncology and Haematology unit at the University of Bristol, UK. "But most common types of childhood cancer are distinct from adult cancers clinically, pathologically, and in their associated molecular characteristics. If we could harness knowledge of these defining characteristics to develop new agents for childhood cancers there is every reason to believe that cure rates could be further improved for all paediatric cancers, perhaps particularly those for which current survival is still too low, for example, many types of brain tumour and advanced stages of tumours like neuroblastoma, and soft tissue and bone sarcoma."

Improved incentives would be one way to generate the willingness to address the issues involved in the development of new agents for these cancers, many of which fall into the category of rare diseases, says Stevens. "However, we need to remember that most orphan drugs would be evaluated in a clinical setting through an academic clinical trial, and the requirements of the Clinical Trial Directive will not aid this process, but rather increase both costs and the time taken to undertake the trial."

Mary Rice
Brussels

Scientific meetings might affect prescribing

A study by US researchers suggests that presentation of medical research at conferences affects prescription of drugs by physicians and community treatment patterns (*J Natl Cancer Inst* 2006;**98**:382–88).

Sharon Giordano (MD Anderson Cancer Centre, Houston, TX, USA) and coworkers analysed the effect of presentation of the Cancer and Leukemia Group B (CALGB) study 9344, at the American Society of Clinical Oncology in May, 1998.

The study showed that paclitaxel, a chemotherapeutic drug from the taxane family, could be used for chemotherapy in lymph-node-positive primary breast cancer. The researchers used the Surveillance, Epidemiology, and End Results—Medicare database to study use of chemotherapy in 3341 women aged 65 years or older who were diagnosed with stage I–III breast cancer in 1994–99.

''PHYSICIANS WANT TO PROVIDE THE MOST UP-TO-DATE CARE''

They found that after presentation of CALGB data, use of taxanes for primary treatment of breast cancer increased substantially before the study was published or approval was gained by the US Food and Drug Administration.

Absolute taxane use before and after May, 1998, was 5.2% and 23.6%, respectively. Patients treated in May, 1998, or later were more likely to receive taxanes than were those who were treated earlier (relative risk 6.84 [95% CI 5.71–8.07]). Taxane use was limited initially in patients with lymph-node-positive breast cancer, but is gradually beginning to be used in patients with lymph-node-negative disease.

''PRESENTATIONS OFTEN FAIL TO UNDERGO RIGOROUS PEER-REVIEW''

"After presentation at scientific meetings, the results of studies may receive widespread media coverage. Physicians want to provide the best and most up-to-date care for their patients, and patients may request new therapies. All of these influences can lead to rapid adoption of new therapies", says Giordano.

"Early adoption of new therapies can be associated with some risks and further research may disprove the results of earlier studies or new toxicities of drugs may become apparent", Giordano cautions. "Practicing physicians must be cautious in applying the results of preliminary research, and carefully weigh the risk [to] benefit ratio of adopting new therapies.

"Diptendra Sarkar (Institute of Post Graduate Medical Education and Research, Calcutta, India) comments, "Physicians should remain careful about the studies presented at conferences. Compared to the studies published in peer-reviewed journals, studies presented at conferences often fail to undergo rigorous peer-review procedures. Organisers of conferences should address this problem seriously and strengthen their peer-review machineries."

Sanjit Bagchi

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Paclitaxel researcher wins Award

Professor Susan Band Horwitz (Albert Einstein College of Medicine, Yeshiva University, New York) has won the 29th annual Bristol-Myers Squibb 'Freedom to Discover' Award. She was chosen for "her pioneering discoveries of the mechanism of action of paclitaxel", the selection panel said.

Paclitaxel, found in the bark of the Pacific yew tree, was known to have anti-tumour activity in the early 1970s, but it took the identification of its mechanism of action by Dr Horwitz and her colleagues to persuade the US' National Cancer Institute to undertake clinical trials. Dr Horwitz showed that paclitaxel binds to microtubules and stabilises them, thereby interfering with their normal function in cell division. Paclitaxel can therefore can halt or impede uncontrolled cancer cell growth.

In the decades since this discovery, she has worked on the mechanisms of action of anti-tumour agents, especially complex natural products, and on the molecular mechanisms that lead to drug resistance.

Professor Susan Band Horwitz

Dr Horwitz is a past-president of the American Association for Cancer Research, and has received numerous honours and awards for her work. She was selected to receive the Distinguished Achievement Award by an independent panel of her peers; and will receive a US $50,000 cash prize and a silver commemorative medallion.

New EONS Course on Caring for Older People

The European Oncology Nursing Society (EONS) launched its Curriculum for Cancer in Older People at the 5th Spring Convention (Innsbruck, Austria, 20–22 April, 2006). It is intended to help nurses to optimise older people's care.

The course is designed to facilitate post basic training for nurses caring for older people with cancer; to improve health care management; enhance multi-professional working between oncology and gerontology teams; to empower nurses to offer input into the multidisciplinary cancer team; and to foster strategic capability for nursing older people with cancer in any setting.

The course, which is at a more basic level than the Post-basic Curriculum in Cancer Nursing, is comprised of 5 modules, including practical and theory, and lasts 300 hours.

Copies of the curriculum can be obtained from the EONS office by completing a request form on the EONS website (www.cancerworld.org/eons) or by emailing eons@village.uunet.be

PODIUM

Myeloma: Progress at last!

Professor Dr Monika Engelhardt

Professor Dr Monika Engelhardt is Head of the Haematology and Stem Cell laboratory at University of Freiburg, Germany, and runs the Autologous Transplant programme. Her research interests include clinical and experimental haematopoiesis and clinical outcomes research. She is co-Guest Editor of EJC's forthcoming Special Issue, "160 years of Multiple Myeloma: Progress and Challenges" (REF).

What is the outlook for patients with multiple myeloma?

It has been poor. Diagnosis is mostly late in the course of the disease; treatment is usually with melphalan and prednisolone and patients do not have prolonged survival. Myeloma patients may not require therapy for months or even years until their disease starts to progress, but in a subset, progress can be aggressive.

Nevertheless, patients with good prognostic factors can now survive more than 10 years, some as if cured. Most, given the best treatment, can expect to survive 5 years, rather than 3 years as it used to be.

Recent advances have been described as historic. Do you agree?

Yes. There has been a dramatic improvement in our understanding of the disease at the molecular level. It has brought significant changes in diagnostic procedures and we have better methods of determining the type of myeloma. Newer treatments - such as the immunomodulatory drugs Thalidomide, Lenalidomide and Actimid, or the proteasome inhibitor bortezomib - are being put through clinical trials and have shown encouraging results.

Why has multiple myeloma proved so difficult?

It has become clear that multiple targeting of a complex signaling network, rather than inhibition of a single pathway or growth factor, is required to efficiently induce myeloma cell death. Researchers are now looking at different molecular pathways and targets (e.g. via genomic and proteomic analysis); and at the genetic signatures that might be typical of various disease patterns. This work may improve identification of prognostic sub-groups.

How important are the newer agents?

They are major advances, but have not so far hugely increased overall survival so there is also some disappointment. Large studies on the use of Thalidomide with or without autologous stem cell transplantation indicate that when patients on the newer drugs relapse, they are even more difficult to treat than those originally given conventional treatments. Further, in trials, patients on the older drugs are sometimes switched to newer therapies, so intention-to-treat analyses struggle to find substantial differences in survival.

What is the aim of treatment?

We want patients to lead a normal life, with few if any symptoms of the disease or its complications. But, despite successful therapy, they may have residual disease or eventually develop active disease again.

The concept of 'indolent and/or persisting disease' is difficult for patients to accept. It feels more rewarding to talk about cure. It is much harder to be more realistic about the disease, and tell a patient that myeloma can rarely (if ever) be cured, but, with appropriate management, is often transferred into an indolent course.

Does the choice of treatment depend on whether cure, or a return to the indolent state, is the aim?

Yes. Some groups have shown that intensive treatments - autologous (auto) transplantation (Tx), tandem-auto Tx or auto-allogeneic transplants, coupled with intensive chemotherapy - may achieve long-term remission or even cure. This can be achieved for possibly 10–20% patients, but most myeloma experts believe that most patients will relapse in the longer term, and that the impressive results are due to careful selection of patients with good prognostic factors early in the disease. The studies appear to show that the myeloma is in long term remission, but most have no follow-up beyond 7–10 years.

With improved understanding of the underlying molecular mechanisms, the aim of targeted therapies is now to identify the patient in whom therapy A, B or C will put their disease back to an indolent phase. We hope to determine which patients need more intensive therapies, including transplants. The dream picture is that all myeloma patients may be cured or transferred to a smouldering myeloma.

What needs to happen for the dream to be realised?

The disease is not common enough for specialists each to run their own trials; the myeloma community needs to work together as a worldwide group and design large trials to answer the most prominent questions in myeloma as soon as possible. We should be using intelligent drug combinations in multicentre trials; but probably do not need to test every conceivable combination.

How important is international collaboration?

Very; accrual is a problem in some myeloma trials. Our patients tend to be elderly and may not be as interested in novel treatments as we would like them to be, especially where the side effect profile is worse than for standard therapies. It's a challenge. You need an excellent doctor-patient interaction so that you get a feel for what might be right for the patient and right for their disease. Good treatment takes some gut feeling, a lot of experience and plenty of reading and understanding of the disease itself.