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Cancer management 'should be top priority'

Access to quality cancer treatment should head the European health agenda, according to speakers at the European Health Forum (Bad Hofgastein, Austria, 7th October, 2004). They called on the UK and Luxembourg Governments to put access to the latest advances at the top of the health agenda during their Presidencies of the EU in 2005.

Lack of such access means that the real progress made over recent years is not appreciated, said Prof. John Smyth, *EJC*'s editor-in-chief and President-Elect of the Federation of European Cancer Societies (FECS). 'Availability of treatment is as much a political as a medical decision', he said.

The Health Forum brings together experts from the medical profession and from patients' organisations, policy makers from European Institutions, representatives from national health ministries, Members of the European Commission and Parliament.

The different roles of academia and industry, and the current threat to academic research need to be addressed, said Prof. Smyth, and the amount of bureaucracy associated with clinical research reduced. 'Increased numbers of European citizens would survive cancer if the overall community and politicians would support health infrastructure development, allowing the implementation of multidisciplinary cancer care, and provide the funding to ensure that proven treatments are made available without restriction', he said.

Ms. Susan Knox, Executive Director of Europa Donna, the Breast Cancer Coalition, pointed to the Breast Cancer Resolution, passed by the European Parliament in June 2003. It outlined breast services that should be provided across the EU and included recommendations on screening, patients' rights, treatment and training.

The Resolution has not yet been implemented across the EU. 'We would call on the authorities to continue to press for the Resolution to be adopted across Europe to ensure that all European women have access to high quality breast services and screening programmes', said Ms. Knox.

Mr. Christian Ligensa, Steering Committee member of Europa Uomo, said it was 'disgraceful' that treatment of prostate cancer is a low priority for European governments. Ms. Catriona Moore, on behalf of UK charity CancerBACUP, said that huge variations in access to cancer treatments exist in the UK. 'At present there is no mechanism for ensuring that national guidance on cancer treatments is implemented at local level. European governments must… ensure that patients are given the best choice of treatments available for their illness and that funding gets through to the front line of cancer care'.

Networks of cancer care have been introduced in Scotland over the last five years and have increased access to treatment irrespective of where patients live. 'This demonstrates how politicians, responding to calls by health professionals, supported by patients, can modernise and improve cancer care in a dramatic manner', said Prof. Smyth.

Shorter chemotherapy regimens for Wilms' tumour

Chemotherapy for Wilms' tumour can be given for 4 weeks rather than the standard 18, with no reduction in effectiveness, researchers say. The shorter regimen reduces side effects and inconvenience for patients, and is cheaper (*Lancet* 2004, **364,** 1229–1235).

The International Society of Paediatric Oncology (SIOP)'s Nephroblastoma Trial Committee conducted a pan-European study including 410 patients aged between 6 months and 18 years. They had stage I intermediate-risk and anaplastic Wilms' tumours.

All received pre-operative vincristine and dactinomycin, followed by resection of the tumour. They then received the same drugs either as a standard 3-course strategy, or the experimental single course.

There were no significant differences between the groups in 2 year event-free survival (about 90%) or 5-year overall survival (about 95%). 'Reduction of post-operative chemotherapy is feasible for patients with stage I intermediate-risk or anaplastic Wilms' tumour', the researchers said.

Contraception for young adults with cancer

Contraception needs to be discussed with young adults with cancer, say researchers in this issue of EJC (*see page 2705*). Adolescents usually take on board the risk of infertility, but many are not aware that if they are sexually active, they are more likely to need protection against pregnancy and sexually transmitted infections.

Many cytotoxic drugs, as well as radiotherapy, are teratogenic and mutagenic, 'thus emphasising the need for effective contraception in sexually active young people', they say. However, many methods are not recommended for those undergoing chemotherapy. 'A dual method with the condom plus another method with better contraceptive effects would be ideal and has to be discussed whenever medically possible', they conclude.

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Indian group challenges rights granted for leukaemia drug

A patient-support group, Cancer Patients Aid Association (CPAA, Mumbai, India) has challenged the exclusive marketing rights (EMR) granted by the Indian patent office to Novartis for imatinib for treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours. The EMR were granted as part of the Indian government's commitment to shift to product-patent regimens in 2005.

CPAA contends that the drug's price in the Indian market has rapidly increased by over ten times since generic manufacturers have had to stop making it. 1 month's supply of the drug costs around Rs 110 000, compared with Rs 8000 for generic versions.

''The drug has become unaffordable and CML patients are simply going to die'', said Yogendra Kumar Sapru (CPAA). ''This amounts to denial of right to health and life as enshrined in the Indian constitution, and a violation of right to health guaranteed in the International Covenant on Economic Social Cultural Rights, to which India is a signatory.'' The petition seeks to address the issue of whether intellectual property rights can over-ride rights to health and life, and wants the court to ask the government to bring life-saving cancer drugs under statutory price control.

In a bid to mute criticism over high prices, Novartis has been supplying the drug free of charge to ''patients who cannot pay for it'' and to those not insured. Patients referred through a network of 90 medical oncologists and haematologists are considered for free supplies. So far 2900 patients have benefited and 2500 are currently enrolled, according to a company spokesperson.

''CML PATIENTS ARE SIMPLY GOING TO DIE''

Besides price, quality is another concern in both generic and patented drugs sold in India. ''There are instances of generic drugs showing very poor activity in comparison to patented drugs. We also found a multinational firm marketing a haemopoietic growth factor in India without temperature-sensitive strips, while it does so internationally'', said Thangarajan Rajkumar (Scientific Director, Cancer Institute, Chennai). ''Is it because they have added a stabilising agent to the product which other countries do not need? Or is it because the drug acts exceptionally well on Indians irrespective of temperature it is stored or transported at?''

Dinesh C Sharma

This story was originally published in Lancet Oncol 2004, **5**, 583.

Pemetrexed approved

Pemetrexed (Alimta) has received EU approval for the treatment of mesothelioma and non-small cell lung cancer (NSCLC). The drug is expected to be launched in Germany and France by the end of 2004, and in Italy, Spain and the UK next year.

It was approved in combination with cisplatin for the treatment of malignant pleural mesothelioma (MPM) in patients who have not received prior chemotherapy and who are not candidates for surgery. It was approved as single agent therapy for patients with locally advanced or metastatic NSCLC after previous chemotherapy.

Manufacturer Eli Lilly & Co. said clinical research is ongoing into pemetrexed's use as first-line therapy for NSCLC and in combination with radiotherapy.

Expanded indication for oxaliplatin

Sanofi-Aventis has announced that oxaliplatin (Eloxatin) has received European approval for its indication to be extended to include the adjuvant setting.

The drug has been marketed for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil and folinic acid. The new indication covers its use as adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.

The company successfully completed a Mutual Recognition Procedure in Europe. The approval was based on the results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), published recently (*N Engl J Med* 2004, **350,** 2343-2351).

MOSAIC was a randomised phase III trial involving 2246 patients with completely resected stage II/III colon cancer. They received 5-FU/LV with or without oxaliplatin. The addition of oxaliplatin increased disease free survival at 3 years from 72.9% (in the 5-FU/LV alone group) to 78.2%.

The authors admit that the use of disease-free survival as a primary endpoint ''is still under discussion'', and say, ''No conclusion can be drawn about differences in survival between the treatment groups''. The effect of the drug on survival will become apparent within the next 2 years, they say.

On the basis of the MOSAIC results, Sanofi-Aventis has submitted a supplemental New Drug Application to the US' Food and Drug Administration (FDA) to include the use of oxaliplatin for adjuvant treatment of colon cancer. Similar applications have been made in other countries including Switzerland and Australia.

Licence for inhibitor programme

Vernalis plc has licensed exclusive worldwide rights to an anti-cancer Hsp90 inhibitor programme. The company will pay the UKs Cancer Research Technology Limited and the Institute of Cancer Research a signature fee, milestone payments, royalties on sales and a proportion of sublicensing fees. Vernalis has now signed an exclusive collaboration and licence agreement with the Institute of Biomedical Research Inc (Novartis).

Many of the signalling proteins that behave aberrantly in cancer cells require the chaperone protein Hsp90 in order to remain active. Drugs that inhibit Hsp90 simultaneously block several different pathways, and could potentially be used in the treatment of many different types of cancer.

Docetaxel in advanced prostate cancer

Docetaxel may improve survival for men with androgen-refractory prostate cancer, researchers say. Two large randomised trials report that docetaxel-based regimens increase survival by around 2 months. An editorial (*New Engl Journ Med* 2004, **351,** 1488–1490) says they are the first treatments to increase survival in this group of patients.

The TAX 327 trial, a North America–Europe–Australian collaboration, included 1006 men with metastatic hormone-refractory prostate cancer. They received prednisolone, along with either mitoxantrone or docetaxel. The docetaxel was given either weekly, or every 3 weeks.

Median survival in the group given docetaxel every 3 weeks was 18.9 months, compared to 16.5 in the mitoxantrone group. Serum PSA and pain levels were more often reduced in the docetaxel group and quality of life more often improved. Adverse events were more common in the docetaxel group but were 'bothersome rather than life-threatening', the researchers said. The weekly schedule offered no benefits over the 3 week interval. (*New Engl Journ Med* 2004, **351,** 1502–1512)

'Cytotoxic chemotherapy can significantly prolong survival', the researchers conclude. 'Our data suggest that docetaxel plus prednisolone is the preferred option for most patients with hormone-refractory prostate cancer'.

> *''CYTOTOXIC CHEMOTHERAPY CAN SIGNIFICANTLY PROLONG SURVIVAL''*

The second study (*New Engl Journ Med* 2004, **351,** 1513–1520), a multicentre, pan-American study, included 674 patients. Half received docetaxel and estramustine; the others received mitoxantrone and prednisolone. The increase in survival was similar, up from 15.6 months in the mitoxantrone group, to 17.5 in the docetaxel group. Again the rate of adverse events was increased with docetaxel and the researchers noted that 'these factors must be balanced when one is considering the use of docetaxel and estramustine as first-line therapy'.

The accompanying editorial suggests that docetaxel works by inducing apoptosis (via more than one pathway) and by inducing over expression of the cell-cycle inhibitor p27. 'The mechanisms by which a prostate-cancer cell survives after androgen-ablation therapy are still not entirely understood', the authors write.

However, the search for therapies aimed at decreasing the survival of prostate cancer cells 'is beginning to pay off', they say. 'In the near future, as more cell-survival pathways are defined, the specific targeting of genes involved in such pathways may further increase the chances of survival for patients with androgen-refractory prostate cancer'.

Antioxidant supplements 'increase mortality'

A Cochrane review found no evidence that antioxidant supplements can prevent gastrointestinal cancers. 'On the contrary, they seem to increase overall mortality', the researchers concluded *(Lancet* 2004, **364,** 1219-1228)

A group led by Dr. Goran Bjelakovic (Copenhagen University Hospital, Denmark and University of Nis, Serbia and Montenegro) reviewed 14 randomised trials comparing antioxidant supplements with placebo for prevention of gastrointestinal cancers. All gave the supplements orally and used placebo capsules or tablets as a control intervention. Together, the studies included more than 170,000 randomised participants.

Supplementation with β-carotene, vitamins A, C, E and selenium – either alone or in combination – had no significant effect on the incidences of oesophageal, gastric, colorectal, pancreatic and liver cancer. Selenium, but none of the others, significantly reduced the incidence of gastrointestinal cancers.

Worse, meta-analysis of the high quality trials 'showed significantly increased mortality in the antioxidant-supplement group'. The relative risk of mortality was 1.06; which was 'unexpected'. 'For every million people exposed to toxic combinations or amounts of antioxidant supplements, about 9000 premature deaths could have occurred', the authors say.

Most trials have failed to take the recommended daily allowances into account. 'Indeed most trials have investigated the effects of antioxidant vitamins given at substantially higher doses than those usually found in a balanced diet, and some trials used dosages well above the recommended tolerable upper intake levels', the researchers wrote.

> *''IT MEANS 9000 PREMATURE DEATHS AMONG ONE MILLION PEOPLE ON SUPPLEMENTS''*

Limitations of the analysis include variation in the examined populations. Some of the studies looked at high risk populations, such as smokers, while others examined only healthy participants. Further supplementation lasted 1–12 years, which may be too short given the length of time needed for cancers to develop.

The researchers stress that their results should not be translated to the potential effects of vegetables and fruits, which are rich in antioxidants and other substances. Micronutrients, dietary fibre and phytochemicals might have protective effects and vitamins typically exist at safe levels.

They conclude that their work, along with other meta-analyses and systematic reviews 'collectively suggest that antioxidant supplements might not be beneficial for cancer prevention'.

An accompanying editorial (*Lancet* 2004, **364,** 1193–1194) points out that the mortality analysis in Bjelakovic's study is exploratory, since many more trials of vitamin supplements reporting mortality as an outcome were not included because they did not have endpoints for gastrointestinal cancer. It said the review is a 'work in progress' which 'does not offer convincing proof of hazard'.

More work is needed into the potential benefits of vitamin C (which was only used as a single intervention in one small trial) and selenium. The editorial calls on the researchers to identify which specific interventions are associated with risk. 'It is unlikely that all supplements will exert a similar effect and it will be vital to establish the safety profile for those with demonstrated benefits', it concludes.

Protein degradation research leads to Nobel Prize

The Royal Swedish Academy of Sciences has awarded the Nobel Prize in Chemistry for 2004 for the discovery of ubiquitin-mediated protein degradation. The joint recipients are Aaron Ciechanover (Technion – Israel Institute of Technology, Haifa, Israel), Avram Hershko Technion – Israel Institute of Technology, Haifa, Israel) and Irwin Rose (University of California, Irvine, USA).

At the beginning of the 1980s, the three researchers discovered one of the cell's most important cyclical processes: regulated protein degradation. Cellular proteins are constantly being built up and broken down. The degradation is not indiscriminate, but occurs through a controlled process whereby the proteins to be broken down at any moment are given a molecular label. Labelled proteins are fed into the cells 'waste disposers', the proteasomes, and destroyed.

The label consists of a molecule called ubiquitin. It fastens to the protein to be destroyed, accompanies it to the proteasome where it is recognised as the key in a lock, and signals that a protein is on the way for disassembly. Just before the protein is squeezed into the proteasome, its ubiquitin label is disconnected and may be re-used.

The cell uses ubiquitin-mediated protein degradation to control a number of central processes by breaking down certain proteins and not others. Cell division, DNA repair, quality control of newly-produced proteins and important parts of the immune defence are controlled in this way. Cervical cancer and cystic fibrosis are examples of what may happen when the degradation does not work correctly. Knowledge of ubiquitin-mediated protein degradation provides a target for the development of drugs against these and other diseases.

''CERVICAL CANCER MAY DEVELOP WHEN THE DEGRADATION DOES NOT WORK CORRECTLY''

It was known by the 1950s, that the breakdown of the cell's own proteins requires energy – unlike, for example, the breakdown of proteins in our food by trypsin. After taking his doctorate, Avram Hershko studied energy-dependent protein degradation in liver cells, but in 1977, transferred to a reticulocyte extract. The extract contained large quantities of haemoglobin, which upset the experiments, so he and Aaron Ciechanover attempted to remove the haemoglobin using chromatography.

They discovered that the extract could be divided into two fractions, each inactive on its own. But as soon as the fractions were recombined, the ATP (adenosine triphosphate)-dependent protein degradation restarted. In 1978, they reported that the active component of one fraction was a heat-stable polypeptide with a molecular weight of only 9000, which they termed APF-1 (active principle in fraction 1). This protein was ubiquitin.

Much of the work leading to the Nobel Prize was carried out during a series of sabbatical leaves that Profs. Hershko and Ciechanover spent with Irwin Rose at the Fox Chase Cancer Center in Philadelphia, USA. In 1980, the three scientists reported that APF-1, whose function was entirely unknown at the time, was bound covalently (i.e., very stably) to various proteins in the extract. A second publication the same year showed that many APF-1 molecules could be bound to the same target protein: a phenomenon termed polyubiquitination. This is now known to be the signal that leads to degradation of the protein in the proteasome, the labelling or 'kiss of death'.

These unanticipated discoveries made it possible to concentrate on identifying the enzyme system that binds ubiquitin to its target proteins. Since ubiquitin occurs so generally in tissues and organisms, it was quickly realised that ubiquitin-mediated protein degradation must be of general significance for the cell. The researchers guessed that the energy requirement in the form of ATP enabled the cell to control the specificity of the process.

It is now known that a typical mammalian cell contains several hundred E3 enzymes, whose specificity determines which proteins in the cell are to be marked for destruction in the proteasomes.

Tumour suppressor gene p53 slows the development of cancer and the p53 protein is mutated in at least half of all human cancers. In a normal cell it is continually produced and broken down; the breakdown being regulated through ubiquitination and the E3 enzyme responsible forms a complex with the p53 protein. Following DNA injury, the p53 protein is phosphorylated and can no longer bind to its E3 enzyme. The breakdown stops and the quantity of p53 in the cell rises rapidly.

''IMPROVED UNDERSTANDING OF THE PROCESS WILL HAVE MANY OTHER APPLICATIONS''

The p53 protein binds to and controls genes that regulate DNA repair and programmed cell death. Raised levels of the protein lead first to interruption of the cell cycle to allow time for repair of DNA damage. If the damage is too extensive, the cell triggers programmed cell death.

The human papillomavirus (HPV) avoids the p53 protein control function. One of the HPV proteins activates and changes the recognition of an E3 enzyme, which is tricked into ubiquitinating the protein p53, and it is totally destroyed. So the infected cell can no longer repair DNA damage or trigger programmed cell death. DNA mutations increase and can ultimately lead to the development of cancer.

Improved understanding of the process will have many other applications, notably in cystic fibrosis and immune and inflammatory reactions. The Nobel Prize awarding committee said, 'This year's Laureates have explained the molecular background to a protein regulation system of great importance for all higher cells. New cell functions controlled by ubiquitin-mediated protein degradation are being discovered all the time and this research is being conducted in numerous laboratories all over the world'.

PODIUM

Where is the evidence?

Prof. Benjamin Djulbegovic (H Lee Mott Cancer Center, University of South Florida, USA) is a founder and editor of Evidence-based Oncology, which recently merged with Cancer Treatment Reviews. His research incorporates evidence-based medicine, decision-analysis, systematic reviews and the ethics of clinical trials. He has taught on the subject extensively.

Professor Benjamin Djulbegovic

How strong is the evidence base in oncology?

The great irony of contemporary medicine is that, despite the tremendous growth of medical knowledge, data on the benefits and risks of available treatment options are often controversial or even nonexistent. We screened more than 12,000 oncology papers published in 108 journals over a 6 month period, and found only 1–2% papers were reliable enough to inform treatment decisions.

What was wrong with the rest?

Studies need to pass criteria for potential usefulness and for validity. By implication, you cannot say that 99% of studies reliably answer the question they posed.

Why is this happening?

Our finding is based on the quality of the reporting – we were making a judgement on the basis of what was available to us. Studies may be properly performed and then badly written up. But we cannot read minds and policy-makers, physicians and patients can only go by what's reported.

Is the situation improving?

The CONSORT (Consolidated Standards for Reporting of Trials) Group was formed to improve the quality of reporting and issued a statement to that end. It is applied by a handful of journals – though none of the specialist cancer journals – and initial data shows it is slowly having an impact.

What else could be done?

I welcome the recent move by International Committee of Medical Journal Editors (ICMJE) requiring researchers to register trials at inception (see *EJC News* 2004, **40**, 16). Protocols which are publicly available – preferably on the web – and which explicitly state the hypothesis a priori will help ensure that research adheres to the original plan. It could even provoke helpful feedback on the study design. I would absolutely like to see this extended to the big cancer journals.

Publication of every randomised prospective trial is the only way to stop publication bias and should be mandatory. If only those trials showing favourable effects are published, we risk falsely concluding that a treatment works when in fact it does not, and basing decisions on a distorted body of evidence.

Failure to publish is a breach of contract with patients who expect their participation to benefit future patients; and with sponsors who expect results to be disseminated.

Is your point of view widely accepted?

Yes, but conflicts of interest are blocking wider acceptance of mandatory trials registration. Big Pharma pours millions of dollars into sponsoring trials and a lot of money hangs on the results. If the results aren't favourable to their drug, will they publish? Trials are done to answer existing uncertainty, and if properly done, you cannot predict the outcome.

Are health professionals sufficiently critical of what they read?

Probably not. Doctors are busy and they are not well trained in scientific methodology. They just need to know whether they can trust what they are reading. They may have to rely on secondary publications which collect high quality evidence, critically appraise it and put it in context within the available knowledge.

Is the lack of available research having an impact in the clinic?

Yes. Reliable good quality information is often difficult to track down within the time-frame when it is needed. Physicians should ideally have valid information within 15 seconds when speaking with a patient; or within 2–5 min when reflecting on a patient in the decision-making process. Practicing physicians need to instantaneously recall more than 2 million facts but cannot process more than 7 (±2) pieces information at any one time.

Our information needs in every-day clinical practice are not being met. Studies suggest that for every 3 patients seen, there are 2 unanswered questions. By implication, for about 60% of cancer patients, decisions may have been different if reliable evidence had been available to the physician at the time when they saw the patients. We must deliver high quality evidence to practitioners at the time when they need it.

Can all decisions be informed by high quality evidence?

We estimate that up to a quarter of decisions relating to the management of most cancer patients can be supported by reliable (randomized) evidence. It will be impossible – and unethical – to produce empirical randomized data on every decision, but more can be done. Medicine has been around as long as humans have existed but little of what we practice has been subjected to critical evaluation.

Randomised clinical trials have only been around for 50 years as the most reliable way of proving that a particular intervention works. Its only in the last decade or so that we have been asking questions related to the quality and reliability of our knowledge.