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NICE: New criteria for end-of-life medicines

The UK's National Institute for Health and Clinical Excellence (NICE) is to allow its Appraisal Committees to consider expensive medicines licensed for terminal illnesses. The supplementary advice, issued in January 2009, covers medicines which have so far been considered too expensive to be a cost-effective use of NHS resources.

The advice covers medicines with a cost-effectiveness ratio higher that that normally considered by NICE's Appraisal Committees to represent a good use of NHS resources (UK £30,000 per quality adjusted life year or QALY). But further conditions apply. Medicines must be licensed for treating a patient population not normally exceeding 7000 new patients each year. They must be indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months. There must be sufficient evidence to indicate that the treatment offers a substantial average extension to life compared to current treatment. No alternative treatment with comparable benefits should be available through the NHS.

'THE PUBLIC VALUES TREATMENTS WHICH EXTEND LIFE WHEN PATIENTS ARE CLOSE TO DEATH'

Commenting on the move, Chief Executive, Andrew Dillon, said that NICE's thinking on how best to approach decisions on life extending medicines had evolved over recent months: 'The Institute is aware that patients, and the public, place considerable value on treatments which offer the possibility of extending life when we are close to death. We believe that we should reflect that view when we are asked to make recommendations on the use of medicines that are designed to extend life, at the end of life.

'The new advice we are giving to our Appraisal Committees will help them to take account of this and will better enable them to decide when to recommend the use of life extending treatments.'

NICE stated that, subject to agreement with the UK's Department of Health, medicines recommended for use on the basis of the criteria set out in these proposals would be subject to a programme of evidence development to ensure that the anticipated survival gains are evident when used in routine practice.

NICE's move was criticised in a commentary in the British Medical Journal (*BMJ 2009;338:b67*). Professor James Raftery (Health Technology Assessment, University of Southampton, UK) said that the high price of new drugs for cancer 'is not always accompanied by commensurate improvements in health and their cost effectiveness (usually measured as cost per QALY) is consequently poor.'

Professor Raftery examined NICE's technology appraisals from 1999 to November 2008. During this period, 11 cancer drugs were refused on the grounds of cost effectiveness. The prices of these drugs were high, particularly for those it provisionally refused. 'These drugs included the 5 most costly that NICE has ever appraised,' he said.

NICE's decisions not to allow these drugs sparked ethical, legal and political dilemmas, and led to NICE's current change of heart. But Professor Raftery found that the new arrangements would be unlikely to improve availability of expensive cancer treatments. 'Few of the rejected drugs would qualify under the new criteria, with much depending on the interpretation of the criterion that no alternative treatment with comparable benefit is available through the NHS.'

'FEW OF THE REJECTED DRUGS WOULD QUALIFY UNDER THE NEW CRITERIA'

A further problem arises from making an exception for one group of patients on the upper cost per QALY: 'The main attraction of the cost per QALY measure is its universal applicability. Making an exception for any group – such as life extending treatments for terminally ill patients – limits that universality and sets a precedent for other groups.

'In addition, setting the threshold higher for some groups within a fixed overall budget results in other patient groups being denied treatment,' he said.

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doi:10.1016/j.ejca.2009.01.025

Hormones and cancer

Obese women who have never used menopausal hormone therapy, are at an increased risk of developing ovarian cancer compared with those of normal weight, US researchers say (*doi:10.1002/cncr.24086*).

Dr. Michael Leitzmann (National Cancer Institute, Bethesda, Maryland) and colleagues studied 94,525 US women aged 50–71 years. There were 303 cases of ovarian cancer during the 7 years of the study.

Obese women who had never taken hormones after the menopause had an 80 percent increase in risk of ovarian cancer, compared to those of normal weight. By contrast, no link between body weight and ovarian cancer was found for women who had ever used menopausal hormone therapy.

Dr. Leitzmann said the findings support the hypothesis that obesity may enhance ovarian cancer risk in part through its hormonal effects. Excess body mass in postmenopausal women leads to an increased production of oestrogen, which may in turn play a role in the development of ovarian cancer.

A possible mechanism was suggested by a British-Spanish research group, who demonstrated that a gene normally involved in the immune response can be triggered by hormones to ignite and drive breast, ovarian and possibly prostate cancer (*doi:10.1084/jem.20080521*).

They showed that oestrogen is able to activate the AID (Activation Induced Deaminase) protein. Oestrogen binds to the AID gene, which then produces higher levels of AID protein and ultimately mutations in some of the growth controlling genes. This could lead to cancer.

Cancer Research UK's Dr. Svend Petersen-Mahrt (London, UK) said it has not been understood how hormones fuel mutations. 'This research shows that AID could be the missing link.'

'But all women produce oestrogen and most of them will not develop a hormone induced cancer, so we now need to find out what other genetic and environmental factors trigger the disease,' he said.

Adjuvant chemotherapy in pancreatic cancer

Adjuvant 5-fluorouracil and folinic acid (5FU/FA) for pancreatic cancer reduces the risk of death by around 30% compared with surgery alone, according to the European Study Group for Pancreatic Cancer (ESPAC).

Researchers pooled the results from three of their trials (ESPAC-1, ESPAC-1 plus, and early ESPAC -3 (v1)), which included 458 randomised patients and 364 deaths. Patients given the adjuvant treatment had a median survival of 23.2 months, compared to 16.8 months among those treated with resection and observation (*BJC 2009; doi:10.1038/sj.bjc.6604838*).

The data 'supports the use of adjuvant 5FU/FA in pancreatic cancer', they wrote. Lead researcher Professor John Neoptolemos (University of Liverpool, UK) said, 'There is still a long way to go before we can really reduce the number of people that die from the disease but this research moves us in the right direction.'

The full results of ESPAC-3(v2) will determine whether or not gemcitabine is superior to this treatment.

Positive opinion for degarelix

The Committee for Medicinal Products for Human Use (CHMP), part of the European Medicines Agency (EMEA) is recommending marketing authorisation for degarelix (Firmagon) for the treatment of advanced hormone-dependent prostate cancer.

Swiss manufacturer Ferring Pharmaceuticals said that in phase III studies, the GnRH receptor antagonist degarelix produced a significant reduction in levels of testosterone within 3 days in more than 96% of study patients.

The phase III study, which was presented at the 23rd EAU Congress, Milan, Italy, 2008 (Abstract #537) compared monthly administration of degarelix with monthly luteneising hormone releasing hormone (LHRH) agonist leuprorelin. The 12 month randomised, open-label, parallel group study found that degarelix suppressed serum testosterone and prostate specific antigen (PSA) significantly faster than leuprorelin. The low levels were sustained throughout the 12 month study.

Both treatments were well-tolerated and showed similar side-effect profiles. The most common side effects of degarelix are hot flushes, injection site pain, injection site erythema, increased weight, nasopharyngitis, fatigue and back pain. No evidence of systemic allergic reactions has emerged in 20 studies, the company said.

MBT 'may be a human carcinogen'

A chemical commonly used in the manufacture of rubber products may cause cancer in workers regularly exposed to it. Workers exposed to MBT (2-mercaptobenzothiazole) had twice the normal risk of dying from cancers of the bladder and large intestine (*doi:10.1136/oem.2008.041400*).

Researchers analysed mortality rates among men who had worked for at least 6 months, between 1955 and 1984, at a rubber chemicals plant in North Wales, UK. They also looked at cancer diagnoses between 1971 and 2005. Among the 2160 employees, 363 had worked in a job that would have exposed them to MBT.

Compared to national statistics, workers exposed to MBT were twice as likely to die of cancers of the bladder and large intestine. They were twice as likely to be diagnosed with bladder cancer, and 4 times more likely to be diagnosed with multiple myeloma.

When compared with 1797 workers who had not been exposed to MBT during their employment, the risks of multiple myeloma and cancer of the large intestine both increased significantly according to the amount of MBT exposure.

Further research in other groups of people expose to MBT should be carried out to see if similar patterns emerge, the authors conclude: 'In the meantime, perhaps MBT should be handled with increased care as it may be a human carcinogen.'

Marker for lung cancer treatment

Patients with neuroendocrine small cell lung cancer (SCLC) may benefit from a blood test which could help determine their treatment, UK researchers say (*Clin Cancer Res 2009;15:274–283*). They identified a molecular marker which may provide a sensitive prognostic biomarker for non-invasive monitoring of this type of lung cancer.

A team led by Cancer Research UK's Dr. Judy Coulson (University of Liverpool, UK), found that a molecule called SCG3 mRNA in the bloodstream is highly associated with neuroendocrine SCLC.

The marker could be developed for use in blood tests to predict how well patients with this type of lung cancer will respond to treatment. There are no other clear biological markers in blood for this cancer.

Patients with neuroendocrine SCLC usually have multiple tumours and are not able to have surgery. This marker may in future help clinicians make more informed decisions about therapy, or recommend that patients take part in trials. Currently, all patients with SCLC are usually treated with the same standard form of chemotherapy.

Dr. Coulson said, 'We found that SCG3 mRNA is an incredibly sensitive marker of these tumours and it could be used to detect circulating tumour cells in patients with this disease.'

The need for better policies on radon

Cheap and basic measures to prevent radon in all new homes would be more cost-effective and have greater potential for reducing lung cancer deaths than policies which focus on the small number of homes with high radon levels, UK researchers say.

About 1100 people each year die in the UK from lung cancer related to radon (about 3.3% of all lung cancer deaths). Across the 27 countries of the European Union, the figures are higher, with around 8% of deaths from lung cancer attributable to radon. The researchers say their conclusions 'are likely to apply to most developed countries, many with higher mean radon concentrations than in the UK' (*BMJ 2009; doi:10.1136/bmj.a3110*).

Radon in the home is a natural air pollutant produced by the decay of uranium in the ground. The gas seeps into buildings through cracks and holes in the foundations and when it decays it produces particles that can enter the lungs and expose them to damaging radiation.

UK policy is to search for homes with high levels of radon and encourage homeowners to take remedial action at their own expense. But the researchers estimate that that less than 5% of radon-related deaths occur from exposure above the current action level. Further, many homeowners refuse to have their home tested, or to spend money reducing radon levels.

Simple preventive measures in new homes are highly effective, the authors say. Installing a gas-resistant membrane in the foundations would halve radon levels and cost only UK £100.

The study also found that 6 out of 7 radon-related lung cancers occur in current or former smokers. The best way for current smokers to reduce risk is clearly to stop smoking, but this group could also reduce their risk by taking radon control measures seriously.

An accompanying editorial (*doi:10.1136/bmj.a3128*) points out that cost effectiveness is context specific, and that policies for preventing lung cancer caused by radon should be tailored to the local or national distribution of radon concentrations in dwellings. 'In areas where a large proportion of homes have high radon concentrations, measuring radon and taking action if the action level is exceeded may still be cost-effective'.

Feasibility of screening

The UK's National Institute for Health Research Health Technology Assessment programme has commissioned a feasibility study on screening trial for lung cancer. If the results are promising, a randomised controlled trial will be set up to assess whether CT scanning is the best way forward. 'Only then would evidence be available to show whether a national lung cancer screening programme should be considered,' said Professor John field (University of Liverpool, UK).

HPV in lung cancer

The human papilloma virus (HPV) is the second most important cause of lung cancer after cigarette smoking, say German researchers. They call for further research on the potential viral carcinogenesis of lung cancer 'in particular its association with HPV' (*Lung Cancer*; *doi:10.1016/j.lungcan.2008.10.003*).

An analysis of 53 papers reporting on 4508 cases found the mean incidence of HPV in lung cancer was 24.5%. In Europe and the US, reported frequencies were 17% and 15%, respectively, but across Asia, it was 35.7%. Frequencies of 80% were reported in Okinawa (Japan) and Taichung (Taiwan).

All lung cancer subtypes were affected; high risk HPV types 16, 18, 31 and 33 were seen along with the low risk types 6 and 11, which were mainly found in association with squamous cell carcinomas.

The authors speculate that regional differences in the association of HPV and lung cancer could be linked to the epidemiology of HPV in different countries. Although there is no data on worldwide incidence of HPV, many viral infections are more prominent in Asia and 'it is not unlikely that HPV is more widely spread in Asia than in the rest of the world,' they say.

They suggest that – since direct mucosa contact can not be the route of infection in these cases – HPV might be transmitted via the air stream carrying infected cell complexes or particles to the periphery of the lung.

Final proof that HPV has a causal role in lung carcinogenesis is still missing, but they point to research that confirmed that the viral DNA is integrated into the tumour genome, which, at least for the high risk types, 'would argue for the case of a cancer-inducing infection and not just a colonisation.'

They conclude: 'There is a need for additional research on the potential viral carcinogenesis of lung cancer and in particular its association with HPV.'

Radiological Society of North America 94th Annual Meeting Chicago, Illinois, USA November 29–December 5, 2008

Whole body MRI for children

Whole body MRI scans are more effective for assessing cancer in pediatric patients than whole body PET scans. Hyun Goo (Seoul, South Korea) and colleagues analysed 26 pairs of MRI and PET scans in 19 patients (mean age 8 years, range 2–17 years) with various oncological diseases. On the basis of pathological proofs, clinical, and imaging data, five of the 26 pairs of scans were in agreement. MRI gave more accurate information about the tumours than did PET in 18 studies, and less accurate information than PET in six studies. Use of diffusion/perfusion MRI reduced the number of inaccurate lesions detected in three studies and increased diagnostic confidence in two studies.

Gd-BOPTA is safe and effective

Gadobenate dimeglumine (Gd-BOPTA) is safe and effective as an MRI enhancing agent for children. Cesare Colosimo (Chieti, Italy) and colleagues assessed Gd-BOPTA and gadopentetate dimeglumine (Gd-DTPA) in 151 children with brain or spinal lesions. Adverse events, most of which were mild and consisted of fever or headaches, were reported in 11 patients receiving Gd-BOPTA and 13 patients receiving Gd-DTPA. Visualisation of tumour changes was significantly better for Gd-BOPTA than Gd-DTPA at the lesion (p=0.011) and the patient (p=0.008) level. In a second study, Giovanni Morana (Verona, Italy) and colleagues reported that hepatobiliary phase imaging after Gd-BOPTA can improve lesion characterisation and differential diagnosis of benign tumours. The researchers retrospectively assessed results of 534 patients who had 947 hypervascular liver lesions, and underwent T1-weighted MRI before and after administration of Gd-BOPTA. The images were compared with pathology results which identified 384 cases with benign masses and 563 with either malignant or borderline pathology. By comparing images with histology findings, sensitivity (91.4%), specificity (88.8%), accuracy (90.1%), positive predictive value (84.9%), and negative predictive value (94.2%) for identification of true benign tumours were calculated.

Tongue cancer brachytherapy

Brachytherapy is effective as primary therapy in stage T1 early invasive cancer of the tongue, or as a boost therapy in patients with stage T2 tongue cancer. In a study done by Ahmed Akl (Flint, MI, USA) and colleagues, one patient with T1 cancer was given high-dose rate brachytherapy (eight×50 Gy radiation treatments delivered to the tumour with a minimum 2.5 cm margin) and nine patients with T2 cancer were given external beam radiation to the neck. Complete responses were observed in all patients. One patient with a T2 tumour relapsed locally after 12 months and underwent surgery. Mean follow-up for the 10 patients was 32.7 months (range 8–84 months). Dry mouth and tongue pain persisted for about 3 months. Taste was regained after 4–6 months and all patients regained total tongue function.

Pituitary gland radiation

The pituitary gland receives unintended, high doses of radiation when patients are treated for nasopharynx and paranasal sinus cancer, reported Vishal Gupta (Sacramento, CA, USA) and colleagues. The study included five patients with nasopharynx cancer and five patients with paranasal sinus cancer who were treated with 70 Gy delivered in 2 or 2.12 Gy daily fractions. Using CT images obtained at the time of stimulation, the average mean dose to the pituitary was 40.5 Gy (SD 23.4), and about 33% of the gland received as much as a 50 Gy dose. Long-term follow-up with hormonal assessment is needed to investigate the clinical importance of exposure of radiation to the pituitary gland.

New mammography system

Slot scan mammography with a photon-counting detector system allows visualisation without motion artifacts, and might improve digital mammography results. Felix Diekmann (Berlin, Germany) and colleagues tested slot-scan mammography with plexiglass phantoms created to simulate tumours ranging in size from 2.5 mm to 10 mm. Using this system, the minimum iodine concentration required to visualise the 10 mm phantom was 1 mg/mL, and a minimum concentration of 4 mg/mL was needed to visualise the 2.5 mm phantoms. Contrast-to-noise ratios were at least equal to results with flat panel detectors.

Experimental radiosensitiser

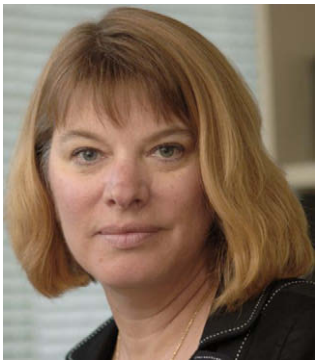
James Clarke (Columbus, OH, USA) and colleagues reported on an in-vitro study of poly (ADP-ribose)polymerase inhibitor, ABT-888, to increase the effects of irradiation on head and neck cancer cell-lines. Clonogenic survival assays showed that, compared with radiation alone, pre-treating cells with 5 μmol/L ABT-888 led to a radiation dose-dependent decrease in DNA-repair proteins on SCC4 and SCC15 tongue cancer cell-lines. These results indicate ABT-888 is an active radiosensitiser in head and neck cancer cells, and could be useful in clinical applications.

Edward Susman

This report originally appeared in Lancet Oncol 2009;10:18

PODIUM

Metastasis suppression: the way ahead



Dr. Patricia Steeg is Chief of Women's Cancers at the Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute (Bethesda, MD, USA). Her research has focused on molecular and translational aspects of tumour metastasis and she gave a well-received Brinker award presentation at the recent San Antonio Breast Cancer Symposium.

You have shown that metastatic cells are quite different from those in the primary tumour?

This is not just my work; it has now been supplemented by multiple lines of research. I discovered the first metastasis suppressor gene, *nm23*, in melanoma and breast cells 20 years ago. Unlike a tumour suppressor gene, a metastasis suppressor gene has no effect – or a very limited effect – on the primary tumour. Instead, it reduces the number of metastases. Tumour suppressor and metastasis suppressor genes work in very different ways.

There are now 20 known metastasis suppressor genes and they all have the same function: to inhibit the ability of the tumour cell to make a new home in a distant organ, to prevent its interaction with local micro environment and subsequent proliferation.

Further, others have shown clearly that some compounds have qualitatively different effects on primary tumours than they do on metastases.

Third, while gene expression profiling studies show that primary tumours and metastases are closely related, they are not identical. Studies of matched primary tumours and metastases have been conducted at the RNA, DNA and protein levels and show important differences.

What changes are needed in drug development?

Most studies have not used the right pre-clinical models. In pre-clinical studies in mice, researchers inject tumour cells under the skin, and examine whether the drug slows growth of the tumour over a few weeks. A few studies have done a better job and looked not only at the effect on the primary tumour but also on metastases; some drugs have a dramatic effect on one but not the other. There are good pre-clinical models of metastatic cancer – mostly xenografts. We need to use these to get data we can believe in.

We also need to develop drugs that target metastatic colonisation, the outgrowth of tumour cells in a distant organ. The question is how to test these drugs in the clinic? Typically, in phase I trials we test the drug on patients with advanced metastatic disease. But drugs which suppress the formation of metastases wouldn't melt metastases that have already formed.

We need fundamental changes and it will take time. Cancer researchers have done a good job in targeting proliferation and tumour growth, but we haven't targeted the metastatic process. There is more to tumour progression than growth. We need to find the important molecular changes in metastasis.

It's been argued that drugs can't alter the metastatic process?

That's true to some extent – the horse is already out of the barn – but not completely. A woman with lymph node positive breast cancer is at risk of metastatic disease. The first step of metastasis has been done; the cells have already gone through the circulatory system and are sitting as micrometastases in distant organs. If left, there likely will be metastatic colonisation and progressive growth of cells in a distant organ.

But these cells are not autonomous; they have to survive in a new environment. Metastatic colonisation is not just about growth and it should be perfectly druggable if we can figure out how it works. After surgery, 94% of breast cancer patients have no distant metastases, so maybe we can attack metastatic colonisation in the vast majority. It gives us a whole different set of targets.

When we find agents we will have to do clinical trials differently. We usually only start the big adjuvant trials when we have responses and improvements in patient survival in the metastatic setting. But if we're targeting metastatic colonisation, we won't have this data in an already metastatic population. Maybe we can do smaller adjuvant trials, or find new ways to determine which agents to take further. Could early clinical trials use biopsies to determine that the drug hit its intended target?

Why has it taken so long to get this far?

Twenty years ago, the hallmark of metastases was thought to be instability. My discovery of *nm23* suggested that underneath the instability a series of consistent genetic changes were occurring, and this went against the prevailing view.

Metastasis work is also difficult. There is no in vitro assay; we have to use complex mouse models. But clinical trials based on the discovery of *nm23* and the other metastasis suppressors are starting; in fact data on metastatic colonisation is coming in from all angles: metastasis suppression, drug development, expression profiling. Different groups of people are coming to the same conclusion – that this is a good therapeutic target – and it's very helpful.

At San Antonio, the audience was mostly clinicians who are using drugs and don't know why they're not working. They understood the relevance of this work.

Helen Saul