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New cancer care guidelines from ESMO

The European Society for Medical Oncology (ESMO) has released a revised set of clinical recommendations. The Clinical Practice Guidelines provide evidence-based information on incidence, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up.

They include guidelines for breast, colorectal and non-small-cell lung cancer (NSCLC) that have been expanded to include more treatment details and further discussion of the importance of multidisciplinary plans for particular patient settings. One new guideline focuses specifically on the cardio-toxicity associated with some chemotherapeutic agents.

Guidelines on soft tissue sarcoma and bone sarcoma, and one on the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting, have been re-written.

Other guidelines have been reviewed:

- Multiple myeloma: revised according to new drug indications.
- Gastrointestinal stromal tumours (GIST): revised with more treatment-orientated details.
- Cancer, fertility and pregnancy: including more information on treatment, especially surgery and highlighting problems of breast and cervical cancer and myeloma in pregnancy. Further details are included on delivery of chemotherapy, hormonal and targeted therapy, radiotherapy and supportive agents in pregnant women with cancer.
- Endometrial cancer: including a new section of histology and further guidance on treatment options.
- Management of febrile neutropenia: including more detail on treatment assessment and patient management.

Large, multidisciplinary writing groups were involved in the writing of some of the guidelines, in order to ensure optimal input from the profession and a better geographic representation, ESMO said.

"By developing these new guidelines with the assistance of a wide range of clinicians we can help share the joint expertise of the world's best doctors from many disciplines," said ESMO President, Professor David Kerr.

EACR Cancer Researcher Award

Photo: AndrewBinns, EACR

Professor Kevin Ryan (Beatson Institute for Cancer Research, Glasgow, UK) was presented with the EACR Cancer Researcher Award at EACR-21 (Oslo, Norway; 26–29 June, 2010) by the then EACR President, Anne-Lise Borresen-Dale.

The Award is given annually 'in recognition of an outstanding contribu-tion in the field of fundamental research in cancer' to an EACR member with no more than 15 years post doctoral experience.

Professor Ryan discussed his award lecture, 'Interplay between apoptosis and autophagy in the control of tumour cell death' with EJC; see page 2338 for more information.

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News from NICE

Gastric cancer

Draft guidance from the UK's National Institute for Health and Clinical Excellence (NICE) recommends oral capecitabine (Xeloda), in combination with a platinum-based regimen, for the first line treatment of inoperable advanced gastric cancer. These patients currently receive fluorouracil via infusion pump as first line treatment.

NICE estimates that if the 6400 people diagnosed with advanced stomach cancer in the UK each year were to receive capecitabine rather than 5-FU, the NHS would save UK £ 10 million annually.

Final guidance is expected to be published in July, 2010.

- However, NICE did not recommend trastuzumab (Herceptin, also from Roche) in combination with cisplatin and capecitabine or 5-FU. The appraisal covers the treatment of people with HER 2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease.

Preliminary draft guidance has been issued for public consultation. Sir Andrew Dillon, chief executive of NICE, said, "Although clinical trials suggest that trastuzumab can extend life for patients with HER 2-positive metastatic gastric cancer, there is considerable uncertainty about the data on how long this extension would be. The manufacturer and other consultees now have an opportunity to help the Independent Appraisal Committee resolve this uncertainty, to the extent that they can."

Renal cell carcinoma

NICE said it was unable to recommend everolimus (Afinitor, Novartis) for the second line treatment of advanced renal cell carcinoma "because it does not provide enough benefit to patients to justify its high cost".

Commenting on the draft guidance, which is now with consultees, Sir Andrew said, "We have to ensure that the money available to the NHS is used to best effect, particularly when NHS funds, like the rest of the public sector, is under considerable financial pressure."

Evidence suggests that everolimus increased survival by more than 3 months compared with best supportive care. The manufacturer agreed a patient access scheme with the Department of Health in which the first treatment pack is free to the NHS and thereafter, there is a 5% cost discount.

Everolimus was considered under the more generous end-of-life criteria, but even with the patient access scheme, it was not considered a cost-effective use of NHS resources.

Multiple myeloma

In draft guidance, NICE recommended thalidomide (thalidomide) in combination with an alkylating agent and a corticosteroid for the first line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is inappropriate.

- Bortezomib (Velcade) – also in combination with an alkylating agent and a corticosteroid – was recommended in the same draft guidance where the patient is unable to tolerate or has contraindications for thalidomide.
- The European Medicines Agency (EMA) has approved an update to the bortezomib label to include long term data on overall survival benefit (at 3 years' follow-up) in previously untreated patients with multiple myeloma.

GIST

NICE was also unable to recommend increased doses of imatinib (Glivec) for people with unresectable and/or metastatic gastrointestinal stromal tumours (GIST). This draft guidance applies to those whose disease has progressed after treatment with 400mg/day imatinib. The application was for doses increased to 600 or 800mg/day.

NICE currently recommends 400mg/day for patients with inoperable GIST, with sunitinib (Sutent) as a second-line treatment option. Sir Andrew said: "Since the appraisal [on 400mg/day imatinib] was published in October 2004, there has been no new good quality clinical and cost effectiveness data produced on doses of 600 or 800 mg/day. On this basis, we cannot recommend these higher doses of imatinib for use on the NHS."

- In further draft guidance, NICE did not recommend imatinib as an adjuvant treatment for GIST. The Appraisal Committee said there is evidence that adjuvant imatinib can delay the recurrence of GIST. "However, there is currently a lack of evidence about key aspects of the clinical effectiveness of imatinib, in particular whether adjuvant imatinib extends life expectancy, how long treatment should be continued and whether resistance to imatinib develops.

"If resistance develops as a result of treatment after surgery, that could reduce the benefits of imatinib if a patient needs it at a later stage after their cancer has recurred."

More mature evidence is expected in 2011, and the Appraisal Committee has recommended that the appraisal be considered for review at an early stage.

NSCLC

Final guidance from NICE recommends pemetrexed (Alimta) for the maintenance treatment of non-small-cell lung cancer (NSCLC) – the first drug to be recommended by NICE for this use. It follows NICE's recommendation of the same drug as a first line treatment for NSCLC in September 2009.

- ICE did not recommend erlotinib (Tarceva) as maintenance therapy for people with NSCLC, whose disease has remained stable after first line treatment. In preliminary guidance, the advisory committee suggested that the manufacturer's (Roche) submission underestimated the cost of treatment and concluded that on current evidence, "erlotinib would not be a good use of NHS money."
- Gefitinib was recommended – in draft guidance - as first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation.

This follows NICE's request for more data on the effectiveness and cost-effectiveness of the drug. Manufacturer Astra Zeneca provided the data along with a revised patient access scheme. The drug is provided at no cost for patients who are treated for up to 2 months. For all other patients, gefitinib is available at a single fixed cost to the NHS irrespective of the duration of treatment.

For more detailed information see www.nice.org.uk

EUROFILE

European countries seek to cut drug costs

In May 2010, the Greek Government announced cuts averaging 25% in the price they pay wholesalers for patented drugs. Pharmaceutical companies, already among those to whom Greece owes some €6.5 billion in unpaid hospital debts, were dismayed. Two groups – Novartis and Leo Pharma – said they would prefer to withdraw from the Greek market.

Greece's economic troubles are so profound that it's difficult to draw conclusions from their decision to enact these cuts. But the country is not alone in seeking to reduce its drugs bill. Spain plans similar cuts of 10–16%; Germany proposes raising its mandatory rebate on patented medicines by 10%, which amounts to much the same thing; and Ireland intends to cut the costs of generic drugs by up to 40%. In the UK, the new coalition government talks of instituting a "value-based" approach to drug-pricing when the Pharmaceutical Price Regulation Scheme – a compact with the industry that limits the profits a company can make – expires at the end of 2013.

"We accept that no-one is going to be exempt from the pain of the economic crisis," stressed Colin Mackay (European Federation of Pharmaceutical Industries and Associations); but he cautioned against singling out pharmaceutical companies to bear the brunt of spending cuts. "Cost-containment measures need to reflect all areas you can make savings – efficiency, distribution channels, generics – not just pharmaceuticals."

The industry fears an increase in arbitrage. Since each nation within the European Union (EU) decides independently how much they will charge for a drug, intermediaries can buy drugs at a lower price in one country and sell them at a profit in another. But this legal activity, known as parallel trading or arbitrage, is not likely to wield influence on policy. As long as a supply of drugs can be guaranteed – and it usually can – many politicians are inclined to consider arbitrage an industry problem, a cost of doing business. Furthermore, some countries such as Belgium use prices abroad as a guide to assigning domestic drug prices. Industry representatives worry that Greece's decision could create a domino effect that leads to a pan-European drop in prices.

Meanwhile, there is increasing consternation across the EU at the costs of pharmaceuticals. France has one of the highest expenditures in Europe – US$554 per head – and sales of expensive new drugs are increasing by 20% a year. This burden, in France and elsewhere, falls overwhelmingly on the state.

Broadly speaking, individual countries either take the manufacturer's price into account when assessing drugs, or else assess the drugs before they negotiate prices. Sweden's Pharma Benefit Board, for example, uses cost-benefit analysis to assess new products. The applicant stipulates the drug's price, but must be careful not to pitch it too high, for this will affect the outcome. The process weighs the direct and indirect costs – such as loss of productivity – against the clinical and therapeutic benefits of the drug. Sweden, incidentally, spends significantly less per head on pharmaceuticals – US$351 – than other European nations.

Like Sweden, Britain uses quality adjusted life years (QALYs) to assess new drugs. The National Institute for Clinical Excellence (NICE), which carries out these assessments, has been criticised for focussing on cost-effectiveness – which is after all its remit – to the detriment of patient well-being. The new government has pledged to establish a £200 million per year Cancer Drug Fund, which will explicitly allow access to drugs "even if they have not been appraised as cost-effective by NICE". The decision illustrates the contradictory nature of healthcare politics. For NICE, cost-effectiveness is the paramount consideration; for the putative Fund, it is ensuring that "patients get the drugs their doctors recommend" So which guiding principle is it to be?

French health care is widely considered to be one of the best in the world. But it comes at a price: a healthcare deficit of some €4.4 billion in 2008. Cancer drugs are entirely covered by mandatory health insurance, itself running a sizeable deficit. The decision as to whether to reimburse drug companies for specific products is taken purely on medical grounds. If a drug is of therapeutic or clinical benefit, it will be approved. There is concern that this will become unsustainable. Some experts moot the idea that drugs that offer marginal benefit for a steep price – a category into which several cancer medications fall – should not necessarily be reimbursed. But the French system is notoriously resistant to change: the status quo should prevail for the foreseeable future.

How can healthcare systems reduce drug costs whilst ensuring an adequate supply? Governments are likely to push for reduced prices from pharmaceutical companies. In which case, companies might choose to focus on emerging markets. In India and Thailand, drugs companies pitch expensive medications at the richest 3% of the population; a high-price, low-volume business model that is unlikely to supplant the European market.

Hans Hogerzeil (WHO, Geneva, Switzerland) insists that the European system for drug procurement and financing – in which big buyers negotiate with suppliers on behalf of patients – can weather the economic storm. He compares it with the unfettered free market arrangement of USA. "The European approach is the right one as far as we are concerned. Europe is always willing to pay a good price for drugs that offer a real improvement on what is already there at a lower price."

Talha Burki

For further information see Appl Health Econ Health Policy (doi: 10.2165/11313900) and http://ec.europa.eu/pharmaforum/docs/pricing_assessing_en.pdf

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Autophagy and the control of cancer cell death

From Professor Kevin Ryan's EACR Award lecture

'Apoptosis is a pro-death mechanism; autophagy in most contexts promotes cell survival. In combination with other pathways, autophagy may contribute to cell death, but it is no longer widely considered a second type of cell death in its own right. Both processes are evolutionarily conserved and genetically defined.

Autophagy degrades cytoplasmic constituents including long-lived proteins and it is the only mechanism for degrading organelles. The breakdown products of autophagy are usually reused to generate more of the same proteins and organelles (in tissue remodelling different proteins may be generated). It is a mechanism for maintaining protein integrity and homeostasis and preserving the normal healthy cell.

It also has a role in cell survival in starved conditions: yeast in nutritionally-depleted conditions leads to autophagy. Protein is broken down to its constituents and used as an ATP source that bridges feeding hiatuses. Similarly, if a tumour lacks blood supply, it lacks nutrients and oxygen, and autophagy may be activated to try to keep the cell alive so in this context it is most likely an oncogenic process. Further – to extrapolate from studies in mice which are deficient in autophagy genes – it's critical for keeping up ATP levels in newborns when they switch from umbilical cord feeding to suckling.

Autophagy protects against multiple forms of disease. It removes protein aggregates in the brain and protects against diseases such as Huntington's and Parkinson's; mice studies have shown that if autophagy isn't happening in the brain, there will be neurodegeneration even without any other genetic event. It's important in inflammatory disease – mutation in a key autophagy gene contributes to Crohn's disease – in diabetes, and in innate and acquired immune responses. Autophagy has multiple roles in response to different cellular states; different aspects of the cell are digested and the outcome changes according to the stimulus.

'AUTOPHAGY IS NO LONGER WIDELY CONSIDERED A SECOND TYPE OF CELL DEATH'

There are three different types. Macro-autophagy involves relatively large vesicles called autophagosomes which encapsulate the cargo destined for digestion and deliver it to the lysosome where it is hydrolysed. In micro-autophagy, small invaginations pinch off little bits of cytoplasm. Chaperone-mediated autophagy involves binding of the damaged protein, and its delivery to an individual docking protein on the lysosome membrane.

We've been working on macro-autophagy and hypoxia in drosophila. We wanted to identify signalling pathways that might be applicable to tumour-associated autophagy but not to other forms. We believed it could allow us to target tumour-related autophagy selectively while leaving those other beneficial forms alone. We chose hypoxia because – apart from advanced cardiovascular disease – it is largely a tumour-associated state. We've identified a signalling pathway, an autonomous loop by which cells produce growth factors that engage receptors on the same cell. It doesn't occur in normal cells, only in tumour cells; it means that they become autonomous and don't require neighbouring cells to deliver growth factor. Basically, the loop is required to induce hypoxia-induced autophagy.

The pathway was known to be activated in tumour cells and it involves members of the platelet-derived growth factor receptor family. It's was thought to promote growth and cell survival but the link to autophagy had not been previously recognised.

Our finding won't necessarily be developed therapeutically – we're a long way from having a molecule that can modulate this loop in a specific fashion – but it suggests that tumour-associated autophagy can be targeted in a selective manner, while leaving other, beneficial, forms of autophagy alone.

Some broad spectrum autophagy inhibitors already look quite promising, and it may well be that in the short term inhibition of all forms of autophagy will give therapeutic benefit; only time will tell if it's detrimental in other ways. Chloroquin, for example, an agent which disturbs lysosome function, is racing ahead because it is already clinically approved for treatment of malaria.

My laboratory's remit is to identify new cell death regulators. Cell death pathways are inactivated in tumour development, removing the cell's natural protective mechanism against proliferation of damaged cells. But many standard forms of chemotherapy either target or utilise the same cell pathways that are inactivated during development of the disease. We've been looking for cell death regulators that are still intact in tumours – they may be somehow perturbed – and may be useful in diagnosis, therapy choice or ultimately novel targets for therapy intervention.

'WE'RE TRYING TO ESTABLISH WHEN TO TARGET AUTOPHAGY POSITIVELY, NEGATIVELY, OR PERHAPS NOT AT ALL'

A few years ago we identified an unknown protein in the lysosome – we called it DRAM1 – which we thought might regulate autophagy. It did, and now there is a family of DRAM proteins. We're working on them to understand what they do in cells.

We're also trying to establish the contexts in which autophagy is pro-survival, or pro-death, and when it may be beneficial to target it positively or negatively or in some cases perhaps best not to target it at all.

Receiving the EACR award is a great bonus! The EACR meetings – and the organisation – are fantastic and the award is recognition not just of what I've done, but what everybody in my lab has done. It's given to people at the cusp of their career, who are in their later 30s, and it gives a boost, along with a lot of recognition which will help them in career development. I'm proud to be added to the list of people who have won this award; they have all gone on to have highly successful careers.'

In conversation with Helen Saul

PODIUM

Rapid learning: a vision for oncology

Professor Sharon Murphy (Scholar-in Residence, Institute of Medicine, Washington DC) won ASCO's Pediatric Oncology Award 2010 and gave her award lecture at the 46th Annual Meeting (June 4–8, 2010; Chicago, Illinois, USA). She discussed her lecture, 'Pediatric Oncology: A Model Rapid Learning Health Care System' with EJC.

What exactly is rapid learning?
It's a notion of gathering as much information as possible from each individual patient, as part of routine patient care, and adding it to a growing database which aggregates all available information. It means that information from all sources – clinical trials, laboratory work, molecular and genetic data, comparative effectiveness studies, registries and so on – is pooled and then made accessible to physicians who can use it to inform the treatment of the patient in front of them.

Is it happening in practice?
It's a vision not a reality but it's within reach because information technology is advancing so rapidly. The difficult part is not the IT but the change in ways and processes involved. In time, it will mean that treatment decisions are truly personalised for every patient.

Are you talking about real-time analysis of data?
Not yet real-time, but much more rapidly than the current slow learning system. Typically it takes years from having an original idea, to setting up a trial and publishing results. It's a really long cycle.

Who benefits from rapid learning?
Researchers, doctors and patients for a start. It would give the public access to the information they need for making smart decisions; it would help governments and politicians to know how valuable certain treatments are. Public demand is going to push the development of rapid learning.

Does it place undue emphasis on observational data?
Challenges exist in trying to draw appropriate inferences from observational data sets, but observational data has strengths, particularly when there's a lot of it. It has limitations, but so do randomised clinical trials data, which exclude people for all sorts of reasons, such as co-morbid conditions, and are therefore not representative of all people with cancer. Grid or cloud computation makes it feasible to analyse observational data along with other, standard, datasets.

How soon will rapid learning become widespread?
There's a momentum behind this; there was a lot of discussion about it at ASCO. At a practical level there's work to be done on standardisation and harmonisation of data collection and storage, governance, data protection and so on. But we also need a new culture of sharing, trust and collaboration. There have been data ownership issues in the past – cooperative groups have historically been in competition with each other – but there's a growing realisation of the large benefits to come from aggregated information. There's no point everyone working on the same question.

You said that paediatric oncology is well set up for rapid learning
Childhood cancer is rare, and because of that a culture of working together, collaborating, and sharing information has developed within the field. A higher proportion of children with cancer are enrolled on protocols, which are tools for rapid learning since data is collected for every patient on protocol. So information on treatment responses, clinical outcome, biomarkers etc, feeds back into the system, and it successively improves as a result. It's a virtuous circle.

In general oncology, treatment according to protocol is increasingly based on consensus guidelines but it is still probably the exception rather than the rule.

Why now?
The field is becoming increasingly complicated, with so many new biologically targeted agents entering practice now. We need the information desperately, to allow us to make the right treatment decisions based on the right evidence. The right underlying information infrastructure will allow us to collect the information efficiently and rapidly, so that every patient encounter is recorded. As we divide cancer into subsets, our need for this type of information is increasing.

How onerous is the data collection?
The ideal situation would be to have data automatically generated from electronic health records so physicians don't have to do any extra work. Asking physicians to enter information over and over again is going to slow things down and be a major impediment to progress. It may be that we have to provide some incentive to physicians for gathering data, so that they are paid more for this higher value care.

Can this really work?
I believe that rapid learning will in the end be of great benefit in clarifying advances, choosing the best treatments and removing inefficiencies. That's not to say there aren't challenges on the way, but this is a real opportunity. There are good models out there – paediatric oncology for one – which demonstrate that it can work.

Helen Saul

For further information, see the Institute of Medicine Workshop Summary, 'A Foundation for Evidence-Driven Practice: A Rapid Learning System for Cancer Care'
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