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KRAS status and targeted treatment

The KRAS status of tumours in patients newly diagnosed with metastatic colorectal cancer may determine their response to the targeted therapy cetuximab (Erbitux), according to a presentation at ASCO (44th American Society of Clinical Oncology Annual Meeting, May 30–June 3, 2008, Chicago, Illinois).

Professor Eric van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium) presented data from the CRYSTAL trial, which found that patients whose tumours contain the wild-type KRAS gene are more likely to benefit from the addition of cetuximab to chemotherapy as part of first line treatment, than those whose tumours have a mutation in the KRAS gene.

'While our initial study indicated that cetuximab has the potential to become part of the standard treatment for patients with newly diagnosed metastatic colorectal cancer, this study helps us to identify which patients are most likely to benefit from adding the drug to treatment', said Professor Van Cutsem. 'KRAS testing should be routinely conducted in all colorectal cancer patients immediately after diagnosis to ensure the best treatment strategies for the individual patient.'

'KRAS TESTING SHOULD BE ROUTINELY CONDUCTED IN ALL PATIENTS IMMEDIATELY AFTER DIAGNOSIS'

Cetuximab is a targeted therapy that blocks the epidermal growth factor receptor (EGFR), common in many types of cancer. The original CRYSTAL study showed that adding cetuximab to the chemotherapy regimen known as FOLFIRI increased progression-free survival, compared with chemotherapy alone. The current study sought to determine which subsets of patients benefited most from the addition of cetuximab.

Researchers examined tumour material from 587 of the 1,198 patients in the original trial. They detected KRAS mutations in 35.6% of patients' tumours. Among patients with normal KRAS, 59.3% responded to chemotherapy plus cetuximab (their tumours shrank by more than half), compared to 43.2% who responded to chemotherapy alone. Among those with mutated KRAS, there was no difference in response rates between those who received chemotherapy alone, and those who received cetuximab in addition (Abstract #2).

Among all patients, the addition of cetuximab to FOLFIRI resulted in a 15% decreased risk for progression. When KRAS was evaluated, the normal KRAS gene group had a 32% decreased risk for progression with the addition of cetuximab. The study concluded that patients with a mutant KRAS gene in their tumour did not benefit from the addition of cetuximab to chemotherapy.

Commenting on the study, Dr. Julie Gralow (University of Washington, USA) said, 'Advances in molecular biology are moving the field of personalised medicine forward by helping 'researchers understand the characteristics that determine why individual patients and individual cancers respond differently to anti-cancer drugs'.

Photo courtesy of ASCO

Professor Eric van Cutsem

- The Committee for Medicinal Products for Human Use (CHMP) has given a positive opinion on Merck KGaA's application to broaden the use of cetuximab.

CHMP has recommended the first-line use of cetuximab in the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer, in combination with chemotherapy. It is also recommended as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

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New Director at IARC

Professor Christopher Wild has been elected Director of the International Agency for Research on Cancer (IARC) for 5 years starting January 1st, 2009. He is currently professor of molecular epidemiology and director of the Leeds Institute of Genetics, Health and Therapeutics (LIGHT, Leeds, UK).

Professor Wild is a former head of environmental carcinogenesis at IARC (1995–6), Chair of the UK Molecular Epidemiology Group and a member of the UK Biobank Ethics and Governance Council (London, UK). His research focuses on understanding the interaction of environmental and genetic risk factors in disease.

'We can now fully integrate laboratory science and population-based research in order to achieve the goal of cancer prevention,' he said. 'I would like IARC to develop into a centre for collaborative research efforts, to facilitate international cancer prevention research.' IARC needs to develop further its focus on low- and medium-resource countries, he said.

Dr. Lars Hanssen, Chair of the IARC Governing Council, expressed the Council's appreciation to outgoing director Dr. Peter Boyle for his work and commitment to global cancer control and prevention. Dr. Boyle will remain in office until the end of his 5-year term in December 2008.

Professor Christopher Wild

• Austria has become the 21st State to participate in IARC. The Agency said that, over the past 5 years, there has been a sharp increase in public funding for cancer-related research and development in Austria. It has demonstrated its commitment to building a sustainable and internationally-oriented research policy by joining other international research organisations this year.

'Austria is expected to make a significant scientific contribution to global cancer research in joining the World Health Organization's cancer research Agency, as it reflects the growing awareness of the increasing cancer burden around the world. We need this growing political commitment to fight the disease,' said Dr. Peter Boyle, out-going Director.

'Sad irony' of modern radiotherapy

The negative effects of waiting times for radiotherapy are probably sufficient to cancel out the many advances of the last 20 years. This is 'one of the sad ironies of modern radiotherapy', say Canadian researchers (*Radiotherapy and Oncology 2008;87:3–16*).

A meta-analysis of studies in head and neck cancer found that risk of recurrence increased by 3.7% per month of delay, which 'may have a very important detrimental effect on the overall value of a RT program because it potentially affects every patient.'

Shortening waiting lists represents a straightforward opportunity to improve local control rates: a program with chronic waiting lists could expect an absolute increase in local control of between 5% and 10% in head and neck cancer simply by reducing its waiting times by 6 weeks.

Waiting times for radiotherapy 'should be as short as reasonably achievable', they say, and a broad range of stakeholders is needed to 'translate that principle into context specific, operational guidelines'.

Screening compliance and risk of cervical cancer

Women who had not been screened for cervical cancer within the recommended screening interval had an almost 5-fold increase in risk of advanced disease, Swedish researchers found (*JNCI 2008 100 9:622–2*). A nationwide case-control study concluded that participation in screening reduced the risk for all types of cervical cancers in all ages.

Dr. Bengt Andrae (Gävle Hospital, Sweden) and colleagues used data from the Swedish Cancer Registry and Sweden's National Cervical Cancer Screening Registry. They identified 1,230 women with cervical cancer, diagnosed between 1999 and 2001, and matched them for age with 6,124 controls (who were not diagnosed with the disease) from the population register.

Those who had not had a Pap smear within the recommended 3-year interval were 2.5 times more likely to be diagnosed with cervical cancer compared with those who had been screened as recommended. These women were also nearly 5 times as likely to be diagnosed with advanced disease.

The study demonstrated for the first time that screening reduced the risk for all types of cancers including non-squamous cancers; and that it reduced the risk for women aged between 23 and 30 years.

In an editorial (*JNCI 2008 100 9:603*), Professor Jack Cuzick (Cancer Research UK, London, UK) said, further, that 32% of all cancers – and an even greater percentage of late-stage tumours – appeared in women older than 65 years which 'suggests that it might be useful to extend routine screening to women who are older than 60 years' – the current limit in Sweden.

Professor Cuzick welcomed the audit, which 'allows evaluation of routine service screening, as opposed to extrapolation from clinical trials.' He said it 'should be widely emulated for all types of mass screening programs and not only restricted to cervical cancer.'

The authors concluded, 'These results indicated that compliance with screening recommendations and high population coverage of screening are vital for success and that attention should be paid to under-screened older women.'

EUROFILE

Finding platform for translational cancer research

Cancer research in Europe is fragmented and inefficient, according to the Eurocan+Plus project, a two-year consultation whose findings were published in April, 2008. To address this, the project recommends the creation of a translational cancer research platform to coordinate basic, clinical and epidemiological research, establishing formal cooperation agreements between comprehensive cancer centres and basic research laboratories throughout Europe.

In the longer term this platform should evolve into a European Cancer Initiative, modelled on the European Molecular Biology Organisation. Yet Eurocan+Plus also identifies a lack of leadership in cancer research as one of Europe's problems. So who is going to take these recommendations forward?

According to Philippe Autier of the International Agency for Research on Cancer (IARC), who was involved in coordinating the project, leaders will emerge as the next steps are discussed. 'Little by little leadership is arising,' he says, 'it will naturally come from those institutions who are most involved in translational research. They are going to set the research agenda.'

He says that the project itself has taken the edge off the competition between research institutions. 'After the Eurocan project, all of these centres are closer than they were before,' he explains. 'Now they are talking much more and are able to forge projects together with a common vision.'

The next important step in taking the Eurocan+Plus recommendations forward will be a meeting in Paris in September 2008: 'The main idea will be to activate an effective coordination for translational research in cancer'.

Before then, meetings will be held to address specific issues, such as the creation of an accreditation scheme for translational research centres and a database of activities, including biobanking and the skills at different European laboratories.

Alex Eggermont, president of the European Cancer Organisation (ECCO), was on the Eurocan+Plus steering committee. He identifies two initiatives which are key to its success.

One is the Network of Core Institutions, an EORTC initiative which links cancer centres committed to coordinating translational research. Eight centres have concluded a legal consortium agreement, and further participants are expected to join in the near future.

The second initiative is the Stockholm declaration, published in March 2008, in which 16 comprehensive cancer centres (including several in the EORTC network) and pre-clinical or basic research organisations announced their intention of creating a platform.

An important target for these emerging networks is the Innovative Medicines Initiative, a programme jointly funded by the EU and the pharmaceutical industry. 'Its clear that IMI will impact quite considerably on applied research and on the possibility of basic and clinical research to work together,' says Autier.

'DOCTORS AND RESEARCHERS ARE FINALLY COMING UP WITH A POLITICAL AGENDA'

'A lot of this innovative medicine will need strongly organised translational research infrastructure,' Eggermont adds.

However, there are questions over how the desire to work together will fare once competition for funds becomes a real issue, both between research centres and nations. 'The thing about a translational research platform is that it's an extremely competitive area between member states, because it's within that translational area that the pharma companies are key,' observes Richard Sullivan, chairman of the European Cancer Research Managers Forum. When it comes to working with industry, governments think national rather than European. 'You can see how a serious national political priority cuts across the idea of a single European platform.'

So far, successful platforms have emerged only in specific areas with a clear common need for collaboration. 'They work because the individuals discover it is in their mutual interest to work together or because there has been a real clinical need,' Sullivan says. 'The difficulty with the common translation platform is what on earth do we mean by this? You've got to be much more specific.'

While creating a translational research platform is in the hands of the research community, the move to a European Cancer Initiative requires government intervention. 'If you like, Eurocan is doctors and researchers finally coming up with some sort of political agenda,' Autier says. 'But the way that the political agenda would be adopted by politicians is out of our hands.'

'WHAT ON EARTH DO WE MEAN BY A COMMON TRANSLATION PLATFORM?'

The ECI would be a permanent, independent organisation of 20–25 people, supported by contributions from cancer research funders across Europe. It would provide a forum for researchers from all backgrounds and from all countries to meet with other specialities (including nurses, clinicians and funders) and develop priority research programmes.

It should become the common voice of the cancer research community. 'If you want to talk to cancer research in Europe, who should you telephone?' asked Peter Boyle, outgoing director of IARC, presenting the Eurocan+Plus findings in April. 'We do not know the answer to that just now, but in years to come it will be this European Cancer Initiative.'

Sullivan is sceptical that governments will put their hands in their pockets to fund the ECI, given the poor performance of similar initiatives in the past and their urge to compete rather than collaborate. 'The best we can hope for, to begin with, is that the major individual centres do talk to each other through whatever structure comes up, and that individual member states start properly funding cancer research activities in their own countries.'

Ian Mundell
Brussels

What are the clinical implications of breast-cancer stem cells?

The number of breast-cancer stem cells expressing the CD44+/CD24–/ low marker decreased in women with primary breast cancer after treatment with lapatinib, reported researchers at the 6th European Breast Cancer Conference (Berlin, Germany; April 15–19, 2008).

'The activity of lapatinib, an epidermal growth factor receptor (EGFR)/ERBB2 tyrosine-kinase inhibitor, suggests that targeting specific signalling pathways responsible for self renewal of these cells could provide a therapeutic strategy for eliminating breast-cancer stem cells', says Jenny Chang (Baylor College of Medicine, Houston, TX, USA) co-author on the lapatinib study. Max Wicha (University of Michigan, Ann Arbor, MI, USA) agrees: 'this is consistent with our findings that ERBB2 is an important regulator of the breast-cancer stem-cell phenotype', he says. 'The breast-cancer stem-cell hypothesis has important clinical implications for breast carcinogenesis, and therefore the prevention and successful therapy of breast cancer', he explains.

Effective identification of breast-cancer stem cells in tumours is not currently possible, but is the focus of intense research. 'Whereas breast-cancer stem cells can currently be identified in patient samples, it is not feasible to perform quantitative analysis', says Lyuba Varticovski (National Cancer Institute, Bethesda, MD, USA). She explains, quantitative analysis cannot be done because of both the variability in the fraction of tumour cells after their isolation from solid tumours and because of the rigorous procedure needed to generate a cell suspension before analysis by flow cytometry.

Jonathan Sleeman (University of Heidelberg, Mannheim, Germany) agrees that identification is still at an early stage and the commonly used marker combination CD44+/CD24 –/low merely enriches the breast-cancer stem-cell subpopulation. 'Additional marker combinations need to be defined to allow precise identification of breast-cancer stem cells', he adds.

Aldehyde dehydrogenase and CD133 have been identified recently as possible additional markers, but Wicha cautions that there might be some heterogeneity in marker expression in different breast cancers. 'This may reflect different cells of origin in these tumours', he says. The microarray data (stem-cell signature by hierarchical cluster analysis and resulting different breast-cancer subtypes) obtained by Achim Rody and colleagues (JW Goethe-University, Frankfurt, Germany) show that the resulting different phenotypes are clinically meaningful. 'The classification of breast cancers according to stem-cell-like features might be helpful in analysing the interaction of endocrine responsiveness and proliferative activity', explains Rody.

But why are breast-cancer stem cells so resistant to treatment? Daniel Birnbaum (Laboratory of Molecular Oncology, Marseilles, France) highlights several potential mechanisms. 'Stem cells remain quiescent; since they don't divide they remain unharmed by chemotherapy and radiotherapy', he says. Jesús Pérez Losada (University of Salamanca, Salamanca, Spain) believes that breast-cancer recurrence a decade after apparently successful treatment might be explained by quiescence: 'these quiescent cells are resistant to therapy and remain in a dormant state for long periods, only to become active much later', he says. Breast-cancer stem cells, he explains, are also resistant to drugs and toxins, because they express drug efflux pumps.

Several studies show that breast-cancer stem cells also possess high DNA repair activity. 'Still a possibility, though controversial, is the proposal by John Cairns that stem cells have a specialised way of replicating DNA, a so-called immortal strand', says Alan Ashworth (Institute of Cancer Research, London, UK). He also thinks that cells respond differently to DNA damage because of differences in the cell cycle or apoptotic response. CD44 could play a crucial role. 'This is a multi-task protein that participates in many cellular functions, including resistance to apoptosis', says Varticovksi. She predicts that elucidating the function of CD44 in breast-cancer stem cells might be crucial for our understanding of breast-cancer stem-cell drug resistance.

'A CONTROVERSIAL PROPOSAL IS THAT STEM CELLS HAVE A SO-CALLED IMMORTAL STRAND OF DNA'

'There is no doubt that curing breast cancer in the long term necessitates elimination of all breast cancer stem cells', says Birnbaum. He is encouraged by the sensitivity of breast cancer stem cells to lapatinib, and suggests that other expressed proteins should be investigated as potential therapeutic targets.

Pérez Losada predicts, 'once we can completely characterise breast-cancer stem cells in individual tumours, and gain the ability to study the drug sensitivity profiles of those cells, we could be in a position to develop specific treatment regimes for each patient to specifically target their cancer cells, stem cells, or otherwise'

Kathryn Senior

This story originally appeared in Lancet Oncol 2008;9:514.

Survival extended in mRCC

Metastatic renal cell cancer (mRCC) patients treated with first-line sunitinib malate (Sutent), are likely to survive 2 years, according to data from a 750-patient phase III randomised study presented at ASCO (Abstract 5024). Specialists say the outcome breaks new ground in mRCC, doubling survival time expected from the previous standard therapy, interferon (IFN) alpha.

Dr. Robert Figlin (City of Hope National Medical Center, Duarte, California), presented data showing sunitinib achieved a median survival of 28 months among patients adhering strictly to study protocol compared to 14 months for patients receiving only IFN alpha (p=0.0033). Most IFN-treated patients, however, were permitted to cross over to sunitinib when their disease progressed, and some sunitinib patients also crossed to other therapies, resulting in an overall median survival of 26.4 vs 21.8 months favouring sunitinib (p<0.05).

Dr. Figlin concluded that the data confirm sunitinib as the reference standard first-line therapy for advanced renal cancer.

Olwen Glynn Owen was sponsored by Pfizer to attend the meeting.

PODIUM

Learning to communicate with dying parents

Dr. Jane Turner, senior lecturer in psychiatry (University of Queensland, Australia), works with multidisciplinary teams in oncology. With colleagues, she devised an educational manual to help professionals respond to dying patients with dependent children (see EJC 2008 doi: 10.1016/jejca.2008.02.045 and editorial comment on doi:10.1016/j.ejca.2008.05.009).

Why are professionals' feelings routinely ignored?

We have developed a culture in which students learn that being strong is the way to get through. When you scratch the surface, almost everyone would admit that it's difficult, but students worry that they will not be seen as professional if they get upset and they go to great lengths to avoid attachment to dying patients.

Professionals feel overwhelmed, helpless, and afraid of upsetting patients. They are trained to fix and cure, and find it difficult when this is not possible. They often focus on practical activities such as checking chemotherapy doses rather than providing emotional support in a medical culture where this is not encouraged.

How do nurses and clinicians differ?

They are similar in their capacity to communicate, and struggle with the same issues. Until recently, nurses tended to be female and it was assumed they would therefore know instinctively how to offer emotional support, which was not always justified. Patients make excuses for doctors, but may expect psychosocial support from nurses; nurses themselves expect to give it, but often receive little training.

How does training help?

It allows us to challenge common responses. Professionals need to reflect on why it is so difficult to give this support, and how the issues resonate with their own experiences of loss and grief.

Training can lead to a dramatic shift in nurses' ability to provide empathetic communication and support. One scenario we use involves a single mother with advanced breast cancer. She keeps shouting at her 16 year old daughter who won't help at home. Pre-training, nurses are pragmatic and task-focussed, discussing practical solutions to getting help at home. Post-training, there is almost none of that. Nurses say that the daughter is scared, frightened her mother will die and they urge the patient to negotiate with her daughter. The change is dramatic.

Nurses are more confident after training, and more likely to encourage patients to sort things out themselves. Pre-training they would assume that they had to 'fix it' for the patient. .

Would clinicians benefit in the same way?

Yes. Clinicians are respectful of patients, and can be helped by knowing the words to say. Our society downplays regret and grief; but when a patient says they regret something, answering 'That's tough. Really hard' rather than 'Of course you did the right thing' allows them to talk.

Listening is an intervention. If I can be with a patient who is distressed, and not rush to reassure them, I am modelling to them that I can bear the pain, and maybe they can too.

Reassurance is unhelpful?

It is natural to want to reassure, but you don't have to fix patients' feelings – they don't want you to – they just want their feelings validated. I see a lot of people with early cancer and a good prognosis, who are worried they might die. When I say I guess they could, they are relieved. Everyone has been telling them they will be fine, and it has closed down all discussion.

Parents tend to reassure. When a 10 year old asked whether his (dying) mother was going to be alright, his father told him that she would be fine because he didn't want to take away the child's hope. But it's possible to say both. He could say that he wants her to get better but that sometimes he also gets scared. Using the word 'if' keeps situations hypothetical. Professionals can say to parents: 'Let's hope you do fabulously and surprise us all. But if that doesn't happen, what would your family need?' The 'if' liberates them to think about it.

How can children be helped?

They need to understand that bad things happen by chance – not because of something they did. It's also good for the surviving parent to help them develop the capacity to relate to the dead parent.

Children do not necessarily suffer irreparable damage when they lose a parent. The literature on resilience is exciting. Children cope with enormous adversity and their loss is modified by good relationships with the surviving parent and with friends, having a particular talent recognised, and so on.

Assumptions are always being challenged?

People frame things differently. A patient with 3 young children had a long and painful death with her husband sitting by her bed. I said to him, 'That must have been difficult', but he said that her struggle was her final gift to her family, showing them her desire to be with them.

We don't know how people will react. Glen Gabbard said, 'When in doubt, act human'. It's excellent advice.

Helen Saul