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The last hurdle for erlotinib

In April, 2010, the US's Food and Drug Administration (FDA) went against the advice of its own advisory committee to approve erlotinib (Tarceva) as a maintenance therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

The move follows the positive opinion issued by the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP). The opinion – announced on 18th March – was expected to be accepted by the European Commission within 44 days.

CHMP has recommended – and the FDA has approved – erlotinib as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC who have stable disease after 4 cycles of standard platinum-based first line chemotherapy. It is also indicated for second-line treatment of locally advanced or metastatic NSCLC; and as first-line treatment of locally advanced, unresectable or metastatic pancreatic cancer.

The outlook for erlotinib appeared difficult in December, 2009, when the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 12-1 against the maintenance indication for erlotinib. ODAC members were concerned about the modest effect achieved by the drug in the study submitted by the manufacturer for approval.

According to a report on *OncoStat* (*http://www.oncologystat.com/news-and-viewpoints/news/FDA_Explains_Erlotinib_Approval_After_ODAC_Advised_Against_It_12-1_US.html*), the ODAC's recommendation was carefully considered in extensive discussions within FDA.

A key issue was regulatory precedent. Bevacizumab and pemetrexed had both previously been approved based on similar reductions in risk of death (bevacizumab in combination therapy compared with chemotherapy alone for nonsquamous NSCLC; pemetrexed as maintenance therapy).

The SATURN (Sequential Tarceva in Unresectable NSCLC) trial was another issue, and regulators said that the optimal design would have been erlotinib maintenance versus erlotinib at progression of disease (rather than placebo).

Speaking to *OncoStat*, Dr Robert Justice said that, in the US, the absence of an FDA comparative effectiveness standard played a role in the agency's decision: 'Once safety and effectiveness have been demonstrated, it is up to patients in consultation with their physicians to determine the treatment that is most appropriate for them.'

Immunotherapy approved for prostate cancer

The US' Food and Drug Administration (FDA) has approved sipuleucel-T (Provenge) for the treatment of asymptomatic or minimally symptomatic metastatic prostate cancer which is resistant to standard hormone therapy.

Sipuleucel-T is the first in a new therapeutic class known as autologous cellular immunotherapy and is designed to stimulate a patients' own immune system to respond to their cancer. Each dose is made by obtaining a patient's immune cells from the blood, and then enhancing their response to the cancer by exposing the cells to prostatic acid phosphatase, an antigen expressed in 95 percent of prostate cancers. The patient's own cells are returned to the patient intravenously to treat the cancer.

The treatment was studied in 512 patients with metastatic hormone treatment refractory prostate cancer in a randomised double-blind, placebo-controlled trial. Median survival for patients receiving sipuleucel-T was 25.8 months, compared to 21.7 months for those on placebo.

Almost all of the patients receiving the active compound had some type of adverse reaction, including fatigue, fever, back pain and nausea. Serious adverse events were reported in one quarter of patients on sipuleucel-T and included acute infusion reactions and stroke.

Professor Philip Kantoff (Harvard Medical School, Boston, Massachusetts) said the approval 'represents a significant scientific and clinical advancement for the treatment of prostate cancer.

'Cancer immunotherapies that use the patient's own immune system will likely create an entirely new treatment paradigm for patients with cancer.'

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

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CXCR4: a new target?

Patients with non-small cell lung cancer (NSCLC) whose tumours over-express a cell surface molecule called CXCR4 have a significantly worse outcome than those whose tumours do not, Canadian researchers found. They say the molecule could become a new target for therapy.

The CXCR4 receptor normally plays a role in immune system signalling between cells. Evidence that it is involved in the growth and metastasis of cancer has been growing.

Researchers from the Tom Baker Cancer Centre (Calgary, Canada) studied tumour samples from 103 patients with stage IV NSCLC on the Glans-Look lung cancer database between 2003 and 2006.

They found that 10.7% of the tumours over-expressed CXCR4. Over-expressers had a median overall survival of 2.7 months; significantly lower than the 6.1 months among low-expressers.

If confirmed in an expanded series of 170 patients from the same database, the results will suggest that strategies to block CXCR4 should be tested in patients whose tumours over-express the molecule.

Presenting the data, Dr Gwyn Bebb said CXCR4 could become a therapeutic target 'but we need to learn more about its role in each specific malignancy.'

The molecule has been well-studied in HIV/AIDS patients; where it is a portal for the virus' entry into immune cells. Drugs that block CXCR4 have been developed and could be tested in the cancer setting.

Dr Bebb said, 'This is an exciting possibility. It seems very likely that a better understanding of the role of CXCR4 in lung cancer will lead to new treatment strategies and might allow us to meaningfully improve treatment for some lung cancer patients in the very near future.'

[*Jnl of Thoracic Oncology 2010; 5 (5): S39 #90*]

Closer co-operation essential for personalised therapy

Sweeping changes to the structure of diagnostic services will be needed before personalised therapy can become a reality, Professor Robert Pirker (Medical University of Vienna, Austria) warned the meeting.

Personalised therapy, in which treatment is based on the characteristics of an individual patient's tumour, promises to improve outcomes for patients, as well as being more cost-effective and less toxic than existing treatments. It means that testing for mutations in tumours will become routine, he said, but there are currently many obstacles to be overcome.

Molecular analysis of biopsies 'changes the whole diagnostic workup and requires some change in the thinking of oncologists, including closer co-operation between the various disciplines: interventional pulmonologists, pathologists, biologists, oncologists.

'The obstacles include the fact that too few doctors are trained in invasive tumour sampling, that mutation analysis is not yet readily available, and that there are reimbursement issues which might vary from country to country,' he said.

[*Jnl of Thoracic Oncology 2010; 5 (5): S79 #201*]

Targeting anti-angiogenesis treatment

Early clues that angiogenic profiles could define subgroups of patients who will benefit most from anti-angiogenic therapies have been uncovered by Spanish researchers.

In an analysis of 135 lung cancer specimens, researchers evaluated the expression of 8 different genes related to vascular endothelial growth factor (VEGF), a key target for anti-angiogenic drugs. They correlated gene expression levels with clinical outcomes, including overall survival and time to tumour progression.

The expression of VEGF-A and VEGFR-1 was related to outcome, Dr Eloisa Jantus (General University Hospital, Valencia) said: 'The subgroup of patients with high levels of expression of VEGF-A and VEGFR-1 showed a 30% shorter time to progression and overall survival, when compared to those with low expression levels.'

This suggests that angiogenic profiles could define subgroups of patients who will better benefit from the use of anti-angiogenic therapies.

'We think that it seems improbable that a single angiogenic marker will provide all of the relevant clinical information because one biomarker cannot reflect the complexity of the angiogenic process. However, when the markers were considered in combination, they provided a more comprehensive pattern or profile, significantly improving their prognostic value,' Dr Jantus said.

[*Jnl of Thoracic Oncology 2010; 5 (5): S55 #135 and #136*]

Finding 'cold spots' may minimise side-effects

Fine-tuning radiotherapy to take into account the parts of a tumour which are most active could improve cancer control while subjecting patients to lower doses of radiation, Dutch researchers said.

Dr Christian Siedschlag (Netherlands Cancer Institute, Amsterdam) said, 'The underlying question that motivated this study was: can we give less radiation to these cold spots?'

His group used FDG PET scans in a preliminary group of 61 patients and identified cold spots in the tumours of 7 patients. Surgical examination showed that in 5 cases, the spots were comprised of dead cells.

'By decreasing the doses given to the cold spots, one might be able to increase the dose given to the rest of the tumour, while keeping the normal tissue dose constant,' Dr Siedschlag said.

[*Jnl of Thoracic Oncology 2010; 5 (5): S71 #181*]

Palliative care for children

Governments, pharmaceutical companies, hospitals, academic institutions and individual caregivers should make a united effort to develop palliative care programmes for children with cancer worldwide, US researchers say in a forthcoming issue of *EJC*. They call for new approaches to increase the availability of palliative care to children, especially in low income countries.

'Creative, bold solutions are needed to overcome the impact of economic factors on the availability and quality of important elements of palliative and end-of-life care for children suffering from the devastating effects of cancer and other life-threatening conditions,' they write (*doi: 10.1016/j.ejca.2010.05.006*).

The research group, from St Jude Children's Research Hospital (Memphis, Tennessee) surveyed paediatric oncologists who use the English-language Cure4kids website. They evaluated responses from 242 physicians from 58 countries, categorised as low-, middle- and high-income [LIC, MIC, HIC] countries.

They found, not unexpectedly, that access to adequate palliation is associated with national income. 'Our respondents' perception of the quality of palliative and end-of-life care was related to the economic status of the country,' and they call for strategies and collaborations that are less dependent on a single country's economy.

Governments are a major source of funding at all economic levels, but additional support is needed in low-income countries, they say: 'Potential sources include non-profit organisations, international networks and international funding agencies. Institutional 'twinning' programmes, such as those implemented to treat paediatric cancer, may also be used to improve the quality of paediatric palliative and end-of-life care in impoverished nations.

'International collaboration may also promote the implementation of clinical practice guidelines, palliative care education and research.'

In the survey, communication, including patients' and families' participation in decisions, was seen in HIC as an important determinant of the quality of end-of-life care. The survey found that parents participate less in decisions in LIC 'where poverty, limited resources, cultural norms and the absence of laws safeguarding self-determination may be factors.'

Almost one third of respondents indicated a lack of access to ethics committee consultation. 'Development of ethical practice norms and elimination of legal roadblocks would be a priority area for programme development,' the authors state.

Clinical practice guidelines will require not only adequate infrastructure and comfort care drugs 'but also an aggressive effort to change attitudes and promote palliative care competencies.

'Children with incurable cancer require palliative care, particularly at the end of life, and all clinicians must recognise the moral and ethical obligation to attend to this need,' the researchers write.

Misconceptions about end-of-life drugs

Misconceptions about the life-shortening effects of opioids 'seem to persist', Belgian and Dutch researchers say.

They identified the physicians who issued a representative sample of death certificates (6927) for patients who died in Flanders between June and November 2007. There were 208 certificates for deaths involving the use of life-ending drugs.

An explicit patient request had been made for 142 of the deaths; there was no request for 66 of the deaths. The researchers found that – where there was no explicit request – physicians had most often used opioids, alone or with benzodiazepines.

'The use of opioids for ending life [is] discouraged because the patient may regain consciousness and because the procedure can take longer than expected,' the researchers write (*Canadian Medical Association Journal doi:10.1503/cmaj.091876*).

'Furthermore, the life-shortening effect of opioids is subject to speculation.'

European paediatric research network is set to go

An organisational structure has been agreed for the European Paediatric Research Network at the European Medicines Agency (EnprEMA). Networks interested in becoming partners have until the end of July, 2010, to perform a self-assessment against recognition criteria.

'The agreement on the recognition criteria and the operational structure represents a milestone in getting this network off the ground,' said Agnès Saint-Raymond, who is responsible for medicines for children at EMA. 'We have a clear idea now what expertise and experience we are looking for in this network and how it is going to be run.

'What we have seen from working with the existing networks, investigators and clinical trials centres so far, has given us a lot of reasons to be confident that EnprEMA with its emphasis on inter-network and stakeholder collaboration will help fostering high-quality, ethical research of medicines in children.'

Networks will have to provide evidence of their research experience and their scientific competencies, their organisational structure and quality management processes, their training and education programme and the involvement of patients, parents and their organisations in their work. The results of the self-assessments will be made publicly available by the networks and EMA.

EnprEMA will have an operational centre, the 'Coordinating Group' responsible for the long- and short-term strategy of the network. The Group will have up to 20 members, representing as many types of networks as possible. Its tasks will include facilitating access of the pharmaceutical industry to paediatric clinical study centres and experts; identifying new networks not presently included; and developing common educational tools for children and parents to increase their willingness to participate in clinical trials.

In principle, membership of the Coordinating Group will be for three years only to ensure sufficient renewal and involvement of the various members. Initially, however, only some members will be replaced, to ensure continuity.

Over-diagnosis in thyroid cancer?

People with papillary thyroid cancer that has not spread beyond the thyroid gland appear to have favourable outcomes regardless of whether they receive treatment in the first year of diagnosis, US researchers say. 'Clinicians and patients should feel comfortable considering the option to observe for a year or longer cancers that fall into this category,' they say (*Arch Otolaryngol Head Neck Surg 2010;136(5):440–444*).

Nearly every thyroid gland might be found to have a cancer if examined closely enough and the authors, from the Department of Veterans Medical Center (White River Junction, Vermont, US) say that the advent of ultrasonography and fine-needle aspiration biopsy has changed the epidemiology of the disease: 'Over the past 30 years, the detected incidence of thyroid cancer has increased three-fold, the entire increase attributable to papillary thyroid cancer and 87% of the increase attributable to tumours measuring less than 2 cm.'

The researchers identified 35,663 patients with papillary thyroid cancer that had not spread at the time of diagnosis. Of these cases, 440 did not undergo immediate, definitive treatment. Over an average of 6 years' follow up, six died of their cancer, which was not significantly different from the rate among the 35,223 individuals who did undergo treatment (161 deaths in an average of 7.6 years' follow-up).

They estimated the 20 year survival rate from cancer as 97 percent for those who were not treated, and 99 percent for those who were. The data put management decisions in perspective, they say: 'Papillary thyroid cancers of any size that are confined to the thyroid gland, have no lymph node metastases at presentation and do not show extraglandular extension, are unlikely to result in death due to the cancer,' they say.

European workshop on stem-cell research

The European Medicines Agency (EMA) held its first international workshop on the regulatory challenges associated with therapies based on stem cells. On 10th May, 2010, it brought together experts from academia, regulatory authorities and the pharmaceutical industry.

'Today's discussion will pave the way for the first European marketing authorisation application for a stem cell-based product,' Thomas Lönngren, EMA's Executive Director, said.

The workshop was part of the public consultation process on a draft reflection paper (*see www.ema.europa.eu/pdfs/human/cat/57113409en.pdf*) on regulatory guidance on stem-cell research and development. The paper was drawn up by EMA's Committee for Advanced Therapies (CAT), together with the Cell-based Products Working Party and Biologics Working Party.

Research into stem cell-based therapies has increased dramatically in the past few years with ongoing clinical studies in adult stem cells and exploration of embryonic stem cells and induced pluri-potent stem cells (artificially reprogrammed adult cells) for possible future clinical applications.

Christian Schneider, chair of the CAT, said, 'Stem cells hold the promise of an unlimited source of cells for therapeutic applications to treat patients who have no or only unsatisfactory treatment options. However, these therapies bear certain risks, such as tumourigenicity and immunorejection, and hence need to be carefully regulated with the input from multi-disciplinary expertise.'

Within the European Union, 40 clinical trials are exploring the use of stem cells in regeneration of lost or damaged tissue, and in haematological or solid-organ malignancies. Most of the trials are using mesenchymal cells derived from adipose tissue, bone marrow, stromal cells and connective tissue; a small proportion of the trials are using haemopoietic stem cells.

EMA's committees have been advising pharmaceutical companies on stem-cell research for several years, on quality, pre-clinical, and clinical development of seven stem-cell products. The CAT is currently evaluating quality and non-clinical data for stem-cell ATMPs (advanced therapy medicinal products) being developed by small and medium-sized European companies.

Consultation on the draft paper, 'Reflection on stem cell-based medicinal products', ends on 30 June, 2010.

Stereotactic radiotherapy in brain cancer

Hypofractionated stereotactic radiotherapy (H-SRT) in patients with recurrent brain cancer extended survival by 11 months without the side effects associated with chemo- or targeted therapies, US researchers say.

Researchers at Thomas Jefferson University (Philadelphia, Pennsylvania) used a stereotactic linear-accelerator-based radiosurgery unit to deliver tightly focussed beams of radiation, while sparing surrounding normal tissue. It uses both magnetic resonance imaging (MRI) and computerised tomography (CT) images to create a three-dimensional representation of a tumour, and then delivers radiation doses that conform precisely to the tumour. The technique allows physicians to use higher doses over shorter periods of time than standard radiotherapy.

The study included 147 patients with recurrent high grade gliomas. H-SRT was used after the cancer progressed and median survival was 11 months (*Jnl of Clin Onc doi:10.1200/JCO.2009.25.6941*). The researchers compare this with targeted therapies which provide survival of about 6 months after cancer recurrence.

'We can give a dose that is 50 percent beyond what has been considered the maximum dose of radiation the brain can tolerate,' said co-author Professor David Andrews. 'We have learned over a 15 year experience that this dose is not only safe, but has almost doubled survival for these patients.'

The study found that the patients with the longest survival when treated with SRT after recurrence were those who were younger, with smaller tumours, and, surprisingly, a shorter time between diagnosis and recurrence.

PODIUM

Non-adherence: a new epidemic?

Dr Ann Partridge (Assistant Professor of Medicine, Harvard Medical School, Boston Massachusetts) is the Clinical Director of the Breast Oncology Program, and founded and directs the program for young women with breast cancer at Dana-Farber Cancer Institute. She has a special interest in breast cancer care and survivorship; one aspect of which is non-adherence to therapy.

It's been assumed that people with cancer are conscientious in taking their therapy?

That was the response I got when I was initially considering doing research in this area. We and others have now shown that adherence is a little better in cancer than in heart disease or hypertension, but it's still less than we'd like. Even 'on the ball' people forget.

Adherence wasn't such an issue in oncology when patients had intravenous therapies in the clinic; you knew whether they'd turned up. But more than half of the agents being developed now are oral.

There's a wide range of estimates of adherence?

It depends first on the patient population studied. In breast cancer, people with metastatic disease are more adherent than people with early stage disease and they're both more adherent than those taking hormonal therapy for prevention. If you are taking Glivec for a GIST in your abdomen, you are probably more compliant than if you have early stage breast cancer and are taking adjuvant hormonal therapy for a theoretical risk of recurrence.

It also depends on the methodology; there's no gold standard. Self-report is accurate if patients say they're not taking their drugs but if they say they are, it's not clear. Bioassays measuring end-products have inter-individual variability and other problems and are expensive. Data base studies measuring pharmacy refill rates give the big picture of what a population is doing but they give limited data on why patients are not taking their drugs and how much influence the providers had on this decision.

Nevertheless, such database studies have revealed that among patients taking long-term hormonal therapy for breast cancer, adherence is as low as 50% after 3–4 years.

Does the exact figure matter?

Yes. The WHO has called non-compliance a major public health problem. In breast cancer, if we could fix the non-adherence, we would probably have much improved outcomes. Historically, physicians and providers have said, 'This drug cuts your risk in half – take it.' But we know that human nature is such that people don't always do as they're told, they don't necessarily understand the rationale or hear the outcome. There are lots of reasons for non-adherence; we all know we are not supposed to smoke and that we should exercise every day but plenty of people are not adherent with those recommendations. It's human nature to push things and test the system especially when change or short-term cost or discomfort is required.

Is non-adherence deliberate, rather than carelessness?

There is some carelessness but also, maybe people choose to forget. If you don't have a system that ensures you remember, then you are choosing not to do that. Carelessness implies that you haven't taken on board the gravity of the situation.

What are the consequences for research?

We looked at adherence among women given the experimental oral chemotherapy capecitabine for early stage breast cancer (*JCO 2010 28:14; 2418–22*). It's the first time an all-oral regimen has been used, and the hypothesis was that they would be less compliant. We measured compliance with microelectronic monitoring system (MEMS) caps on pill bottles and the good news was that the majority of women did take the short course, and that adherence was not linked with recurrence. But had we not measured adherence in that trial we'd be left asking why the regimen didn't work.

Should all trials test for adherence?

You should always think about it. Many studies use self-report for oral therapies which is not perfect but it's better than nothing. Further, patients who chose to participate in trials are generally more motivated and educated than the general public and they tend to follow doctors' orders more closely. So anything tested in clinical trials may change in the real world. But you need to assess adherence as best you can in a trial so you at least know whether the therapy administered was actually received.

How can adherence be addressed?

We must continue to look at adherence as we develop drugs, to keep an open mind and measure it as objectively as we can. We need interventions to enhance and improve adherence and some studies are looking at that. In the clinic, there's still too much of the attitude that 'you can lead a horse to water but you cannot make it drink'. There's more to it than that and more that can be done. More patient education – helping patients manage their side effects, and to truly understand the value of their drugs – probably would improve adherence and therefore, cancer outcomes.

Helen Saul