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New hope for RCC patients

Treatment regimens for kidney cancer – which have not changed in more than 2 decades – look set to be overhauled by a new class of targeted agents. Delegates at the 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Atlanta, Georgia (June 2–6th, 2006) heard promising results from several trials.

The studies presented concluded that sunitinib (Sutent), used as a first-line treatment, improved progression-free survival in metastatic kidney cancer, compared with interferon-α, the standard of care. The experimental therapy temsirolimus improved overall survival in patients with advanced, high-risk kidney cancer, again when compared with interferon-α. Lapatinib (Tykerb) slowed cancer growth and improved survival among a subset of patients whose cancer continued to grow despite standard therapy.

Sunitinib, from Pfizer, is a tyrosine kinase inhibitor, which acts through multiple targets known to be involved in both tumour cell proliferation and tumour angiogenesis. Results from a randomised phase III trial demonstrated a statistically significant improvement in both progression-free survival and in objective response rate.

The study (*Am Soc Clin Onc 2006, Late-Breaking Abstract # 3*) included 750 patients with advanced clear cell carcinoma. They were randomised to receive either sunitinib or interferon-α. Progression-free survival (the endpoint of the trial) was 47.3 weeks for the sunitinib group, compared with 24.9 weeks for the interferon-α group. Response rates were 24.8% for sunitinib, compared with 4.9% for interferon-α.

Dr Robert J Motzer (Memorial Sloan-Kettering Cancer Center, New York) led the study and said he believes sunitinib will become the new standard of care for advanced renal cell cancer. "There were some side effects, including fatigue and reduced blood counts, but because of the overwhelming superiority and efficacy of this drug, and the fact that the side effects were very well tolerated, the benefits clearly outweigh the costs," he said.

Researchers will continue to follow the patients in the study to determine the difference in overall survival.

The experimental drug temsirolimus, from Wyeth, is a targeted inhibitor of mTOR, a signalling protein that regulates cell growth and angiogenesis. It was tested on patients with advanced, metastatic renal cell carcinoma (mRCC), and with a poor prognosis (*Am Soc Clin Onc 2006, Late-Breaking Abstract # 4*).

"SEVERAL DRUGS ARE LOOKING VERY GOOD IN CLINICAL TRIALS"

The 626 patients included were randomised to receive either interferon-α, temsirolimus, or a combination of the 2 drugs. Median overall survival was 7.3 months, 10.9 months and 8.4 months, respectively. Progression-free survival was 1.9 months, 3.7 months and 3.7 months, respectively.

Lead author Dr Gary Hudes (Fox Chase Cancer Center, Philadelphia, Pennsylvania), said that several drugs are "looking very good" in clinical trials. "Temsirolimus is the first of these agents to show an overall survival advantage for kidney cancer. In addition, this was the first study focusing exclusively on patients whose cancer was so advanced they would not qualify for most other clinical trials."

The goal for research on the emerging new class of targeted agents for kidney cancer is to determine the optimal way to administer them, either in combination or sequentially, to provide patients with the maximum benefit, he said.

A third agent, lapatinib (Tykerb) improved survival in the subset of patients whose RCC produced the greatest amounts of epidermal growth factor receptor (EGFR). Lapatinib inhibits 2 tyrosine kinase enzymes which are part of the EGFR pathway, responsible for tumour proliferation and growth.

A phase III study (*Proc Am Soc Clin Onc 2006 # 4502*) included 416 patients whose advanced RCC continued to grow despite treatment with immunotherapy. They were randomised to receive either lapatinib or hormonal therapy (megestrol acetate or tamoxifen). In the group as a whole, neither overall survival nor time to progression differed significantly between the 2 treatment groups.

However, among the 241 patients whose tumours produced the highest amounts of EGFR, time to progression was longer in the lapatinib group (15 weeks versus 10.9 weeks for the hormonal therapy group). Overall survival was 46 weeks versus 37.9 weeks, respectively.

Lead author Dr Alain Ravaud (University Hospital of Bordeaux, France) said, "Our findings suggest that lapatinib could be a new treatment option along with immunological therapies and anti-angiogenesis agents, for patients with advanced renal cell carcinoma that produced high levels of EGFR".

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STAR trial reports

The Study of Tamoxifen and Raloxifene (STAR) trial found that the two drugs are equally effective in preventing invasive breast cancer in postmenopausal women at high risk of the disease. Tamoxifen was more effective in reducing non-invasive breast cancers but raloxifene was associated with fewer endometrial cancers, deep vein thromboses and pulmonary emboli.

The STAR trial is one of the largest breast cancer prevention trials ever conducted. Run by the US' National Surgical Adjuvant Breast and Bowel Project (NSABP), it includes 19,747 postmenopausal women at more than 500 centres in the United States and Canada. The women had a 5-year predicted breast cancer risk of 1.66%, as determined by the modified Gail model.

The women were randomised to receive 60 mg of raloxifene or 20 mg of tamoxifen, once daily for 5 years, starting in July 1999. After a median follow up of 4 years, the double-blind study found no significant difference in the number of invasive breast cancers between the two groups. Both drugs are known to increase the risk of blood clots but the risk was 29% lower in the raloxifene group compared with the tamoxifen group (*Am Soc Clin Onc 2006, Late Breaking Abstract # 5*).

The women are continuing to be followed and those taking tamoxifen have been given the option to switch to raloxifene.

Dr D. Lawrence Wickerham, Associate Chair of the NSABP, and the study's lead author, said, "These findings show that raloxifene represents an effective alternative for breast cancer prevention in postmenopausal women at high risk for this disease."

The decision to choose one drug over another is based on a woman's medical history, and that woman with certain cardiovascular problems or uncontrolled diabetes may not be able to take raloxifene, he said.

Tamoxifen is approved in the USA for 2 indications: to reduce the risk of breast cancer recurrence, and to reduce the risk of developing the disease in both pre- and postmenopausal women at high risk. Raloxifene has US approval for use in the prevention of osteoporosis. This is the first head-to-head comparison of these drugs.

- Professor V Craig Jordan (Fox Chase Cancer Center, Philadelphia, Pennsylvania) received the American Cancer Society Award at the ASCO meeting. It was given for his translational research demonstrating the chemopreventive effects of tamoxifen and raloxifene.

Considered the "father of tamoxifen" Dr Jordan was one of the first researchers to analyze and describe the drug's preventive properties. His abstract (*Jnl of Steroid Biochemistry and Molecular Biology, 1974*) was the first to report that tamoxifen could prevent rat mammary carcinogenesis and block oestradiol binding to the human oestrogen receptor in breast tumours. The abstract led to proper evaluation of the drug which became the standard of therapy for patient with breast cancer.

Dr Jordan said the main challenge he faced in championing widespread adoption of tamoxifen was a "lack of interest in the 1970s in developing a new anti-hormone therapy", coupled with unpromising clinical results before the correct patient populations were treated (ie oestrogen receptor-positive women).

"The question of overcoming [these] challenges really involved a passionate desire to help people with breast cancer and a relentless commitment to target the right patients with the right treatments," he said.

Photo Courtesy © ASCO/Scott Morgan 2006

Anti-apoptosis agents "may halt cancer"

Novel agents which encourage apoptosis may halt the growth of advanced cancers, while remaining well-tolerated, researchers say.

One agent, Apo2L, is recombinant human Apo2L/TRAIL, a protein involved in the regulation of apoptosis. The agent is thought to target 2 receptors, called DR4 and DR5, and selectively induce apoptosis in cancer cells, while sparing most normal, health cells.

A phase I clinical trial (*Proc Am Soc Clin Onc 2006 # 3013*) included 58 patients with different advanced cancers. They received varying doses of the drug. Among the 37 patients whose tumours have been assessed so far, 22 (60%) had stable disease after 4 cycles, while 4 (10%) had stable disease after 8 cycles.

Lead author Professor Roy S Herbst (University of Texas MD Anderson Cancer Center) said, "Although these are early data, this new class of agents targeting receptor pathways that promote cell death is showing itself to be safe and may have activity in patients with advanced cancer, potentially giving us a new weapon to combine with other targeted agents in the treatment of this disease".

A second agent, YM155, is designed to inhibit survivin – a protein that suppresses apoptosis in cancer cells – thereby paving the way for the normal destruction of cancer cells, is also showing promise (*Proc Am Soc Clin Onc 2006 # 3014*). Of 5 patients with non-Hodgkin's lymphoma, 3 experienced a partial response. 2 of 9 with prostate cancer showed more than a 50% reduction in prostate-specific antigen levels.

Glivec and beyond

Five year data from the landmark IRIS study – presented at ASCO (Proc Am Soc Clin Onc 2006 # 6506) – show overall survival for imatinib (Glivec) in Chronic Myeloid Leukaemia (CML) is greater than for any other CML therapy, and that disease progression is slowed for patients on the drug.

The IRIS trial (International Randomized Study of Interferon versus STI571) – which started in June 2000 – recruited 1106 treatment naïve patients in chronic phase CML from 117 centres in 16 countries. Patients were randomized to imatinib or interferon-alfa plus Ara-C (cytarabine) – then the standard treatment.

Prior to imatinib, about 50% of patients progressed to the more advanced stages in 3 to 5 years. In the IRIS study, overall survival at 5 years was 89% for patients given imatinib. The annual rate of progression of imatinib-treated CML patients to accelerated phase or blast crisis decreased over time – 0.6% at 5 years, compared with 0.9% for year 4 and 1.6% for year 3.

Due to tolerability reasons, or lack or loss of response to treatment, 69% of patients in the interferon arm crossed over to imatinib (only 3% of patients in the imatinib arm crossed over). As a result, there is no figure for overall survival for the interferon arm.

Of the 553 patients given imatinib, 69% of patients remained on therapy after 5 years, 11% of patients receiving imatinib withdrew from therapy due to either disease progression or lack of efficacy, and 5.8% withdrew due to either side effects or death not associated with CML.

"Prior to this [analysis], we had to project what the 5-year survival data would be and worried that the risk of relapse might increase. With this data, we have increased confidence in this targeted therapy," said principal investigator Brian J. Druker (Oregon Health and Science University).

At the European Hematology Congress (15–18 June, Amsterdam, the Netherlands), much of the debate shifted to the treatment of imatinib-resistant CML, and reviewed second generation tyrosine kinase inhibitors developed to be more selective inhibitors of BCR-ABL, the aberrant protein driving CML.

Resistance to imatinib is often due to acquired mutations in the BCR-ABL coding region affecting binding of imatinib to its ATP binding pocket. Insights into the mechanisms responsible for the acquisition of resistance resulted in development of 2 second-generation tyrosine inhibitors – dasatinib and nilotinib. Both demonstrate pre-clinical activity against 18 of 19 imatinib-resistant BCR-ABL mutants, with the exception of the T315I mutation. In addition, dasatinib also inhibits SRC protein kinases, which may provide real benefits since these enzymes play a role in the proliferation of CML cells.

In the first phase II head-to-head comparison of imatinib versus dasatinib (abstract 0465), 150 chronic phase CML patients resistant to imatinib were randomised in a 2:1 ratio to either start treatment with dasatinib at 140 mg/day (n = 101) or to receive escalated imatinib doses of 800 mg/day (n = 49).

"WE HAVE INCREASED CONFIDENCE IN THIS TARGETED THERAPY"

Results show that at 12 weeks a major cytogenetic response was achieved by 35% of dasatinib patients (35/101) compared with 29% (14/49) patients in the imatinib arm. "I think once patients are treated early with dasatinib we are going to see the emergence of very little resistance," said Dr Hagop Kantarjian, from MD Anderson Cancer Center (Houston, USA), who presented the data.

Michele Baccarani (University of Bologna, Italy) said, "Over the next few years there are a number of questions that need to be answered, such as whether the new tyrosine kinase agents should be used front-line to prevent resistance or second line to treat it. And whether these drugs should be used in combination."

Janet Fricker

European Union ruling on medicines in children

The European Union has reached an agreement to improve regulation of drugs for children. New rules, which could be in place by the end of 2006, include: a 6-month patent extension in return for data on safety and efficacy studies of drugs in children; more funding for the study of off-patent drugs; and marketing of appropriate formulations.

The high proportion of drugs not authorised for use in children is a particular issue in paediatric oncology.

"I welcome the recognition that much more research needs to be done", says Gareth Veal, UK Children's Cancer Study Group (UKCCSG) and University of Newcastle, UK. "There is certainly a widespread issue of cancer drugs not being tested in children. Although the use of these drugs has developed over many years of clinical experience, for many agents there is not sufficient pharmacological evaluation to support current dosing strategies." He adds that the availability of appropriate drug formulations, particularly in infants, is also an important issue.

Nicholas Andre, University of Marseille School of Medicine, France, says: "This is a crucial issue. We do not really know what are the optimum [doses for older] drugs such as cyclophosphamide, vincristine, or [dactinomycin] for infants. In Europe, pharmacology groups from the UKCCSG and [the French Society for Paediatric Oncology (SFCE)] are doing studies together to increase our knowledge regarding how to better dose anticancer agents in infants".

Ursula Creutzig, University Children's Hospital, Muenster, Germany, says: "We hope that our phase III trials, which ensure close observation, adverse-event monitoring, and quality control in the total group of patients with a specific form of cancer will be supported".

She adds: "Due to the small number of patients it will not be possible to do phase I or II studies in a reasonable timeframe for each off-label drug, which has been in use for many years".

Emma Wilkinson

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Identification of Mismatch Repair Genes

A new method of identifying patients with colorectal cancer who carry mutations in DNA repair genes has been described by scientists in Scotland, UK (*Barnetson et al, NEJM 2006 354:2751–63*).

The new algorithm draws on clinical features to estimate the likelihood that a patient with colorectal cancer is a carrier of germ-line mutations in the DNA mismatch repair genes MLH1, MSH2, and MSH6. It was developed using a population-based approach among patients under the age of 55 years with newly diagnosed colorectal cancer.

The 870 patients in the study were not preselected and family history was not taken into account. The 2-stage predictive model incorporates only clinical variables in the first stage; the second is comprised of analysis of the tumour by immunohistochemical staining and tests for microsatellite instability. It gives a quantitative prediction of the chance of finding a mutated mismatch-repair gene.

The model was tested on a separate group of patients diagnosed at a younger age. The researchers found, as expected, a higher number of cases with the faulty genes in the younger group.

Identifying groups of patients who carry these genetic mutations could improve their treatment and survival. The model could in future also allow family members to be monitored to ensure the disease is detected early.

Co-author Professor Malcolm Dunlop (University of Edinburgh, UK) said, "The model we developed is easily accessed on our website for clinicians who can then use the prediction to determine who needs genetic blood tests. Our method also shows that a higher proportion of bowel cancer patients fulfilled the criteria for having genetic faults than the current methods would suggest.

"The findings will also help determine the best treatment for patients with gene faults," he said.

(The website is at *www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php*)

NICE gives go-ahead to Herceptin ...

The UK's National Institute for Health and Clinical Excellence (NICE) is set to recommend the use of trastuzumab (Herceptin) for women with early stage breast cancer. Unusually, NICE issued its draft guidance just 2 weeks after the drug was licensed for this indication by the regulatory authorities.

The draft guidance recommends the drug for women with early stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). The exception is where there are concerns about the woman's cardiac function. Cardiac function should be assessed prior to the initiation of therapy, and assessments repeated every 3 months during treatment.

The draft recommendations were subject to an appeal period, and the final guidance was expected to be issued in July, 2006.

... docetaxel in advanced prostate cancer ...

NICE has also recommended the use of docetaxel (Taxotere) for men with hormone-refractory metastatic prostate cancer. The guidance recommends the drug as a treatment option where the patient is well enough to care for himself with occasional assistance. It should be stopped at the completion of planned treatment of up to 10 cycles, or if the disease progresses.

Professor Peter Littlejohns, NICE's Clinical and Public Health Director, said, "Unfortunately, hormone-refractory metastatic prostate cancer cannot be cured, however our assessment showed that docetaxel is a cost-effective way to offer patients additional months of life."

... and guidance in CNS tumours

NICE, together with the UK's National Collaborating Centre for Cancer, has issued guidance aimed at improving delivery of services for patients with brain and other central nervous system (CNS) tumours.

The guidance acknowledges that care of patients with brain tumours can often be fragmented and uncoordinated; and that the management of less common tumours often requires access to highly specialised services. The aim of the guidance is to improve the organisation, and consistency, of care.

Recommendations include that all patients' care should be co-ordinated through a designated multi-disciplinary team (MDT); that diagnostic investigations should be provided within national waiting times targets; that patients should have face-to-face contact with healthcare professionals at critical points in their care pathway; all should have a clearly defined key worker; and that clinical nurse specialists and palliative care specialists should be core members of the MDT.

The document, "Improving Outcomes in Brain and other CNS Cancers" is the final publication in NICE's Cancer Service guidance series. Publication of the documents should allow the identification of gaps in local provision.

Professor Mike Richards, UK's National Cancer Director, said, "The 'Improving Outcomes Guidance' reports on cancer services have been an essential component of the drive to improve the quality of care for cancer patients over recent years. I am very grateful to everyone who has been involved in this process and to NICE for overseeing it."

Positive opinion for dexrazoxane

Dexrazoxane (Savene) has received a positive opinion in Europe for the treatment of extravasation accidents. The European Medicines Agency (EMEA) has recommended that the European Commission (EC) grant marketing authorisation.

Dexrazoxane, which has orphan drug status in both Europe and the US, is a detoxification treatment for anthracycline extravasation. It is believed to act through chelation of iron and/or inhibition of topiosomerase II, and may avoid surgical intervention and to significantly reduce the occurrence or size of the skin wounds caused by anthracycline extravasation.

The most common side effects are dose dependant reactions such as nausea and vomiting, neutropenia, and affected liver function. The EMEA's Committee for Medicinal Products for Human Use (CHMP) considers that there is a favourable benefit to risk balance.

PODIUM

Cancer in the Young: the Baseline

Dr Eva Steliarova-Foucher

Dr Eva Steliarova-Foucher works in the Data Analysis and Interpretation Group at the International Agency for Research on Cancer in Lyon, France. She has a special interest in epidemiology of childhood cancer and is co-ordinator of the Automated Childhood Cancer Information System (ACCIS) project. She is lead guest editor of EJC's forthcoming Special Issue, "Cancer in children and adolescents in Europe".

What does the Special Issue cover?

It describes the incidence and survival from cancer in children and adolescents across Europe over a period of 20 years. The results are interpreted with respect to the geographical and temporal differences in diagnostic methods and registration. It provides reference data for Europe – some of which were non-existent – and outlines the needs for future research. It is the fruit of collaboration between many devoted clinicians and 80 cancer registries organised within the European Network of Cancer Registries.

Why is it essential to have this information?

For successful public health policy, we need to quantify the population cancer burden; the number of children and adolescents with cancer, their treatment requirements, expected survival, and so on. Geographical and temporal differences in cancer incidence may point to underlying risk factors. International collaboration is crucial to collect a sufficient body of information on these rare cancers.

Is the increase in cancer over time real or an artefact?

A part of it is real. Some could be explained by better diagnostic procedures, especially for brain tumours, which are picked up nowadays with non-invasive diagnostic techniques such as MRI scans. Improvements in registration cannot be excluded, although tumours in children were taken seriously and registered carefully throughout the 20 years of the study.

Why do 5-year survival rates vary so widely, from 62% to 77%, according to geographical region?

This has been seen previously in the Eurocare studies (e.g. *EJC 2001 Vol 37 Issue 6*); we confirmed the persistence of variation, despite an overall improvement. The difference may be explained by socioeconomic conditions, such as increased awareness among GPs, likelihood of early referral, access to the right specialists, recruitment into a clinical trial and treatment according to a protocol.

Did your analysis shed light on the aetiology of cancers?

We only had information on broad surrogate risk factors (region of residence, sex, age, period of diagnosis), but we could see where our results are consistent with the findings of previous studies. For example, leukaemia incidence peaks in early childhood, from age 2 to 4 years, and this peak is much more pronounced in the West than in the East. Over the study period, the leukaemia peak in early childhood rose in the East. This corresponds to purported risk factors linked to higher socio-economic status, such as fewer children per family, less/later exposure to viruses, later age of mothers at first pregnancy.

What impact do you hope ACCIS itself will have?

It provides a unique data source for Europe. We hope that the slight but persistent increase in incidence will emphasize the importance of this project and the need for it to continue. The increase could be reversed if specific risk factors were identified and could be prevented. Disparities in survival show the gaps in public health policies and the need for improved access to treatment, or a treatment of better quality.

How would you like ACCIS to evolve in future?

We need the funds to enlarge the database geographically and over time and to enrich its information value. We would like to record more data items per case, for example the tumour stage, participation in a clinical trial, indicators of data completeness etc. With more data we could embark on more sophisticated analyses, and interpret the observed differences with more precision. Data comparability will continue to be the basis of any development of the project. Actually, working on this Special Issue highlighted the importance of complying with international standards of data collection, classification and coding.

What threats does the ACCIS project face?

Lack of good quality data. In countries which have had a recent transition to a market economy, well-established registries often face lack of funds. In addition, stringent data confidentiality rules are imposed in many countries throughout Europe. Yet good quality data may only be obtained if individual cancer records can be linked with national vital statistics, as is the case in the Nordic countries. More should be done in other countries, where the experience of former cancer patients is wasted, because society is not allowed to use it.

What do you hope the Special Issue will achieve?

First, to contribute to the clinical and epidemiological knowledge base. Second, to enhance interdisciplinary collaboration between those involved in the process of data production. Third, to stress that research in this field is based on international data, which is comparable and legally accessible. And finally, to increase awareness of the cancer burden in the young population, and thus inform the decisions of policy-makers. We are grateful to *EJC* for giving us the voice.