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The American Society of Clinical Oncology held its Annual Meeting in Orlando, Florida (May 29–June 2, 2009). Robert Day-Webb reports

PARP inhibitors 'active' in advanced breast cancer

Two drugs from a new class of targeted agents called poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated significant activity against hard-to-treat breast cancers, according to findings from two separate phase II trials.

The PARP enzyme is used by cancer cells to repair DNA damage, including damage inflicted by chemotherapy drugs. Drugs that inhibit PARP might therefore diminish this self-repair mechanism, making cancer cells more sensitive to treatment and promoting cancer cell death.

The larger trial tested PARP inhibitor BSI-201 in combination with conventional chemotherapy in 116 women with metastatic triple-negative breast cancer (tumours lacking expression of oestrogen and progesterone receptors and without overexpression of HER2). They were randomly assigned to receive standard treatment (gemcitabine and carboplatin) with or without BSI-201 (*J Clin Oncol 2009;27: June Suppl. Abstract #3*).

Approximately 62 percent of patients receiving BSI-201 showed clinical benefit, compared with 21 percent in the group receiving chemotherapy alone. Tumour response (complete or partial) was observed in 48 percent of patients who received BSI-201, which was significantly greater than in the patients receiving chemotherapy alone (16 percent).

Women who received BSI-201 had a median overall survival of 9.2 months and a median progression-free survival of 6.9 months compared with 5.7 months and 3.3 months, respectively, in women who received standard treatment alone.

BSI-201 was well-tolerated and did not add to the toxicity associated with the chemotherapy. 'The progression-free survival and overall survival data demonstrate significant clinical benefit with little or no added toxicity, which hopefully will lead to BSI-201 becoming a first-in-class treatment option for patients with metastatic triple-negative breast cancer,' said lead author Dr. Joyce O'Shaughnessy (Baylor-Charles A. Sammons Cancer Center, Dallas, Texas).

In the second trial, an oral PARP inhibitor called olaparib was used as a single agent in women with advanced breast cancer whose tumours had mutations in the BRCA1 and BRCA2 genes and whose disease had persisted despite prior treatment (*J Clin Oncol 2009;27:June Suppl. Clinical Review Abstract #501*).

This study is the first to evaluate olaparib when used alone in women with BRCA-deficient breast cancer. A prior phase II study showed that some women with BRCA-deficient ovarian cancers responded to olaparib.

Tumours that arise in patients with BRCA mutations have a defect in their ability to repair DNA. Olaparib blocks an alternative DNA repair mechanism, PARP, and might therefore lead to cancer cell death.

In this study, 27 patients received olaparib continuously at the maximum tolerated dose of 400 mg twice a day in 28-day cycles. A second cohort of 27 patients, received the lower dose of 100 mg twice a day (a previously-identified PARP inhibitory dose).

Better outcomes were seen with the higher dose. Forty one percent of patients in this group responded to olaparib (experienced tumour shrinkage) compared to 22 percent of women receiving the lower dose. The drug was well-tolerated with the most common side effects being mild fatigue, nausea and vomiting.

'The findings of our study provide very promising evidence that the potent PARP inhibitor olaparib may be useful for treating BRCA-deficient breast cancers,' said lead author Dr. Andrew Tutt (Kings College, London, UK). 'However, this drug is in a very early stage of development, and additional clinical trials are necessary to determine the best way to use olaparib in women with BRCA-deficient breast cancer. We are actively discussing the design of future PARP inhibitor studies for women with BRCA1 and BRCA2 mutations.'

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

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ASCO *continued* Robert Day-Webb reports

Cancer vaccines 'show promise'

Two novel therapeutic vaccines have performed well in clinical trials, providing some of the first positive data on the effectiveness of therapeutic cancer vaccines.

In one study, a patient-specific therapeutic vaccine, BiovaxID, prolonged disease-free survival of follicular lymphoma, delaying relapse by 14 months (*J Clin Oncol 2009;**27**:June Suppl. Abstract #2*). In a second study, it was reported that the addition of a novel targeted cancer vaccine, gp100:209-217(210M) peptide, to standard therapy, doubles treatment response rates and increases progression-free survival in patients with metastatic melanoma (*J Clin Oncol 2009;**27**:June Suppl. Clinical Review Abstract #9011*).

BiovaxID is an individualised treatment manufactured from a tissue biopsy from a patient's own tumour which targets a unique protein expressed only by cancerous B cells in follicular lymphoma, thereby sparing healthy cells.

The vaccine is administered as a subcutaneous injection along with granulocyte-monocyte colony stimulating factor and keyhole limpet haemocyanin, which together enhance the potency of the immune response induced by BiovaxID. This phase III trial included 117 patients who had a sustained complete response to standard chemotherapy. They were randomised to receive vaccination or no further treatment. After a median follow-up of almost 5 years, the median disease-free survival in the vaccine arm was 44.2 months compared with 30.6 months among controls, which was significant. BiovaxID also demonstrated a favourable safety profile.

'With this vaccine, we've now moved into an era where we can safely use a patient's immune system to effectively fight follicular lymphoma and enhance the response to conventional chemotherapy,' said lead author Dr. Stephen J. Schuster (University of Pennsylvania School of Medicine, Philadelphia). 'Because this vaccine uniquely recruits the patient's immune system to seek and destroy only tumour B cells, this approach may be applicable to the treatment of other B-cell lymphomas.'

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Delegates at ASCO 2009

Dr. Schuster said that when the trial started, chemotherapy was the standard of care for previously untreated patients. Since then, standard care has evolved to include chemotherapy plus the antibody rituximab. Dr. Schuster therefore believes a clinical trial should be launched to test whether adding a personalised vaccine to the current standard of chemotherapy plus rituximab will improve patient outcome.

'If indeed our trial is right that this approach leads to improvements in progression-free survival, then adding it to even more effective therapies like chemotherapy plus rituximab might result in even greater benefit,' he said.

In the second trial, a peptide-based vaccine, gp100:209–217(210M), was used to treat patients with metastatic melanoma.

The vaccine stimulates T cells to multiply and seek out and attack melanoma cells by locating a specific antigen, gp100, on the surface of melanoma cells.

In this multi-institutional phase III trial, the vaccine was combined with interleukin-2, the standard therapy for advanced melanoma that boosts the immune response to the vaccine. Eighty six patients were randomly assigned to the vaccine plus interleukin-2 or interleukin-2 alone.

Among the patients treated with the vaccine plus interleukin-2, 22.1 percent had their tumours shrink compared to 9.7 percent of patients receiving interleukin-2 alone. There was a slight improvement in progression-free survival, 2.9 versus 1.6 months, and a non-significant trend towards improved overall survival. The vaccine was well tolerated with few side effects.

'This study is one of the first to show positive, promising results for a cancer vaccine in melanoma,' said lead author Dr. Douglas Schwartzentruber (Center for Cancer Care, Goshen, Indiana). 'Metastatic melanoma is a very difficult disease to treat successfully and is very resistant to most therapies. These results will give patients and the oncology community hope that we are making some progress against the disease.'

Follow-up is continuing to see how long the vaccine remains effective and to assess its value in various patient subgroups. 'Right now, the vaccine can only be given to half of those with melanoma because it has to match a patient's tissue type, or human leucocyte antigen. A major priority for us is to figure out ways to broaden our approach and use mixtures of peptides so that more patients are eligible,' said co-investigator Dr. Patrick Hwu (M.D. Anderson Cancer Center, Houston, Texas). 'We would also like to improve upon it by including other immune-stimulatory agents, such as anti-CTLA4, an antibody that can take the brakes off the immune cells.'

ASCO *continued* Robert Day-Webb reports

HRT link to lung cancer death

Menopausal hormone therapy increases the risk of dying from non-small cell lung cancer (NSCLC) in women with the disease, researchers said (*J Clin Oncol 2009;27:June Suppl. Clinical Review Abstract #1500*).

Secondary analysis of data from the Women's Health Initiative showed that women who took hormones (conjugated equine oestrogen (CEE) plus medroxy progesterone acetate (MPA)) for relieving symptoms of menopause had a higher mortality rate from NSCLC than women who did not take hormones.

Although previous research has suggested that hormones play a role in NSCLC, this is the first study to examine this relationship in a randomised, controlled clinical trial.

The study looked at NSCLC incidence and mortality during 5.6 years of intervention with hormone therapy or placebo and 2.4 years of follow-up. While there was no significant difference in NSCLC incidence between the two groups, mortality after a NSCLC diagnosis was significantly higher for those who received hormones compared with those who did not (67 versus 39 deaths, respectively).

Hormone-taking women who smoked had a further increase in mortality risk. Among smokers, 3.4 percent of hormone users died from NSCLC, compared to 2.3 percent in the placebo group.

'Many women entering menopause have symptoms that make them consider hormone therapy,' said lead author Dr. Rowan Chlebowski (Harbour-UCLA Medical Center, Los Angeles, California). 'We already know that combined hormone therapy has more risks than benefits, including a higher risk of stroke and breast cancer. The link we describe between hormone therapy with CEE plus MPA and death from NSCLC should influence discussions between physicians and women considering hormone therapy use, especially for those with a smoking history.'

'No benefit' from CA125 testing for relapse

Starting treatment for an ovarian cancer relapse based on CA125 blood levels alone does not improve overall survival or quality of life, compared with delaying treatment until symptoms arise, according to findings from a multinational phase III trial (*J Clin Oncol 2009;27:June Suppl. Abstract #1*).

'Women who've completed ovarian cancer treatment often worry about a relapse, and they undergo frequent blood tests for CA125 in the hope of catching it early,' said lead author Dr. Gordon Rustin (Mount Vernon Cancer Centre, Middlesex, UK). 'We thought that delaying chemotherapy might make overall quality of life worse, due to the symptoms of ovarian cancer, but this was not seen in women on this trial. In fact, if anything, early treatment slightly decreases quality of life because women receive far more chemotherapy.'

EARLY TREATMENT DECREASES QUALITY OF LIFE

Researchers compared overall survival between 265 women with ovarian cancer in remission after initial chemotherapy who began second-line chemotherapy after experiencing a rise in CA125 (a marker of growth for several cancers, including ovarian cancer, measured by a blood test), and 264 women with rising CA125 whose treatment was delayed until symptoms of relapse appeared (such as pelvic pain or bloating).

Even though the early treatment group started second-line chemotherapy 4.8 months before the delayed treatment group, and third-line chemotherapy 4.6 months earlier, overall survival was the same between both groups after 4 years of follow-up.

'For the first time, women can be reassured that there is no benefit from early detection by routine CA125 testing. They can be told that even if CA125 rises, chemotherapy can be safely delayed until they have signs or symptoms of recurrence,' Dr. Rustin said. 'Women now have informed choices to be able to decide'.

Bevacizumab 'unsuccessful' in colon cancer

Adding bevacizumab to standard adjuvant chemotherapy did not improve disease-free survival in early stage colon cancer, according to results from a randomised phase III trial (*J Clin Oncol 2009;27:June Suppl. Late Breaking Abstract #4*).

Despite the failure to significantly prolong 3-year disease-free survival (the primary endpoint), the researchers said that bevacizumab did confer a significant transient benefit while it was being taken.

In the study, 2710 stage II and III colon cancer patients were randomly assigned to receive either a 6 month course of standard adjuvant chemotherapy (mFOLFOX6) or 6 months of adjuvant chemotherapy combined with bevacizumab plus an additional 6 months of bevacizumab after the chemotherapy had ended.

After 3 years, there was little difference in the disease-free survival rate (77.4% in the bevacizumab group versus 75.5% among controls). Nonetheless, there was a marked transient benefit in disease-free survival during the 1 year interval that bevacizumab was given. Afterwards, the benefit tailed off until at 3 years, there was no significant difference between the 2 arms.

Bevacizumab conferred no significant benefit in either stage II or III patients.

'Our overall conclusion is that bevacizumab was not effective as an adjuvant treatment for early-stage colon cancer,' said Dr. Norman Wolmark (Allegheny General Hospital, Pittsburgh, Pennsylvania), 'but the transient benefit we saw in patients who received bevacizumab illustrates that we have more to learn about how this reagent works, and we need to design more clinical trials to determine how it can be used most effectively, with the idea and promise that prescribing it for longer durations may improve its efficacy for patients with these stages of the disease.'

Maintenance pemetrexed extends survival in lung cancer

The use of pemetrexed as maintenance following standard treatment, improves overall survival for patients with nonsquamous advanced non-small cell lung cancer (NSCLC), according to an international phase III study (*J Clin Oncol 2009;27:June Suppl. Clinical Review Abstract #8000*).

Preliminary results presented at last year's ASCO Annual Meeting suggested that maintenance therapy with pemetrexed delayed disease progression. This is the first time a significant improvement in overall survival has been shown.

Patients were randomised to either pemetrexed (441 patients) or placebo (222 patients), along with best supportive care. All patients had stage IIIB or IV NSCLC (both squamous and nonsquamous subtypes) that had not progressed after four cycles of platinum-based chemotherapy.

Overall survival in the pemetrexed group was 13.4 months, compared to 10.6 months among controls. For the nonsquamous subgroup (482 patients), overall survival was 15.5 months for patients on pemetrexed versus 10.3 months for patients on placebo. Patients with the squamous subtype did not benefit with pemetrexed, confirming results seen in previous studies.

Severe (grade 3 or 4) side effects were low but more common in the pemetrexed group, specifically fatigue and low white blood cell count. Side effects did not increase with duration of use, and there were no drug-related deaths.

'This study will change the overall standard of care,' said lead author Dr. Chandra P. Belani (Penn State Cancer Institute, Hershey, Pennsylvania). 'Maintenance therapy with pemetrexed offers a new paradigm for patients who have advanced lung cancer, because it has a low toxicity and can be given on an ongoing basis over a prolonged period of time to extend patients' lives.

The improvement in overall survival of 5.2 months is clinically very significant in patients with nonsquamous histology,' said Dr. Belani.

Trastuzumab improves survival in gastric cancer

The drug trastuzumab (Herceptin), when added to standard chemotherapy, reduced the risk of death by 26 percent in patients with advanced gastric cancer. This is the first time trastuzumab – used to treat HER2-positive breast cancer – has been proven effective in another cancer (*J Clin Oncol 2009;27:June Suppl. Late Breaking Abstract #4509*).

'This is the first phase III study to report improved overall survival with a personalised, targeted treatment for gastric cancer,' said Dr. Eric Van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium), lead author of the study. 'These data indicate that trastuzumab has the potential to have a place in the treatment of a cancer other than breast cancer, and to become a common treatment for gastric cancer patients who are candidates for this drug.'

The trial randomised 594 patients with a locally advanced, recurrent or metastatic HER2-positive gastric cancer to receive standard chemotherapy (5-fluorouracil or capecitabine and cisplatin) plus trastuzumab or standard chemotherapy alone.

Patients who received trastuzumab plus chemotherapy lived 13.8 months, compared with 11.1 months for those who received chemotherapy alone, a difference that was significant. The treatment was generally well tolerated with no unexpected side effects in the trastuzumab group.

While the survival benefit is small, the findings represent a rare advance in gastric cancer, said Dr. Van Cutsem. 'To see this unprecedented survival benefit for patients with HER2-positive gastric cancer is enormously rewarding. There is a high unmet medical need in advanced gastric cancer and the data from this study show that targeted therapy with trastuzumab delivers a major advance in this therapeutic area.'

New standard of care in neuroblastoma?

An antibody-based immunotherapy reduced the risk of relapse and improved overall survival among patients with high-risk neuroblastoma, a difficult-to-treat cancer of the nervous system that largely affects young children, according to a phase III Children's Oncology Group trial (*J Clin Oncol 2009;27:May Suppl. Abstract #10067z*).

The investigational monoclonal antibody ch14.18 stimulates an immune response by binding to a specific glycolipid, GD2, on the surface of neuroblastoma cells. The study found that, 2 years after therapy, ch14.18 produced a 43 percent improvement over standard treatment. It was stopped early due to benefit and, according to lead author, Dr. Alice Yu (University of California, San Diego, USA), 'Treatment with the antibody should now be the new standard of care for patients with high-risk neuroblastoma.'

The study involved 226 patients, all of whom had responded to the standard regimen of intensive chemotherapy, surgery, and a stem cell transplant, followed by radiation therapy. Half were randomised to the standard 13-cis-retinoic acid alone, while the others received 13-cis-retinoic acid plus ch14.18 in combination with the immune-stimulating cytokines, granulocyte-macrophage colony-stimulating factor and interleukin-2.

After 2 years, event-free survival was 66 percent in the ch14.18 group versus 46 percent in the standard treatment group. Overall survival at 2 years was 86 percent for the ch14.18 patients compared to 75 percent for patients in the standard treatment arm. Significant side effects were associated with the immunotherapy, including pain and an accumulation of fluid in the body caused by vascular leakage, but they were manageable and reversible, the researchers said.

'Even though we treat it with aggressive therapy, high-risk neuroblastoma often returns and most patients do not survive,' said Dr. Yu. 'It is very exciting to have a new treatment option for this disease, and we hope to make this immunotherapy available to more children with neuroblastoma.'

The Children's Oncology Group study is set to continue as an open-label trial so that children with neuroblastoma can receive the immunotherapy.

The National Cancer Institute produced the ch14.18 antibody and funded the study. The Institute will also sponsor a new ch14.18 clinical trial through the Children's Oncology Group to build up a comprehensive safety profile to help support an application for FDA approval.

PODIUM

A communications network for Europe

Professor Gordon McVie (previously joint director general of Cancer Research UK; former President of EORTC) is founding editor of ecancermedicalscience.com, an online open access journal recently listed on PubMed. The European Institute of Oncology (IEO) and ECCO are founding partners of ecancermedicalscience, and in May 2009, the three groups jointly received a Euro 1.2 million grant from the European Commission (EC)'s FP7 programme to establish a single communications portal for all those involved in cancer in Europe. Professor Umberto Veronesi (IEO) is the Principal Investigator of Europecancercoms; Gordon McVie and Lex Eggermont (ECCO) are managing the project.

What problem is Europecancercoms addressing?

One of the key recommendations from the Eurocan report, which investigated barriers to progress in cancer research, was for an improved communications network. Europe is unbelievably complicated compared to the States; we have numerous societies, each with its own website, perhaps 60-80 ongoing European projects in cancer, and 20 or so different networks, but there is nowhere you can go to find a list. We are building up silos. This doesn't reflect how we look after patients – most centres in Europe have multidisciplinary teams – but our societies are like separate boxes. We do not have the equivalent of clinicaltrials.gov or nci.gov. The EC recognises the issue.

How will the project, Europecancercoms, address this?

We want to establish a 'one stop shop' for people involved in cancer: professionals, patients, politicians, industry – everyone. We're not doing research and we're not creating databases. We're using IT solutions which already exist to coordinate information which is already available. We'll break down the walls of the silos! So we will provide links to clinical trials and research groups, guidelines for clinicians, social networking sites for patients in trials, and so on. The technology is out there but in oncology we are massively behind in its application.

Who is involved?

The partners include IEO and ECCO obviously, but also the ECCO Member Societies EORTC, ESMO, EACR, SIOPE, OECI (Organisation of European Cancer Institutes), and EUSOMA, plus our technical partners. Eurocan had brought together 18 major players in cancer in Europe: charities, governments, research institutes, basic scientists, clinicians, cancer leagues, patient advocacy groups. So these groups had already signed up to the idea.

How will the project be organised?

Basically, ECCO is coordinating the scientific process and ecancer the dissemination of scientific results and publishing. So ECCO is looking after the groups defining the issues (societies, industry, public health, patients) and ecancer is leading the technical team (internet, grid, publishing) and the policy experts. In the first instance, we're looking to provide the model in 5 or 6 languages.

How will the portal be accessed?

We have 2 years to produce a pilot version of the system and it will be freely available on ecancer.eu. We've been aware that patients are visiting the ecancermedicalscience website and we are keen to challenge the notion that people in underdeveloped countries have to wait 6 months or pay money they don't have for online access to journals. We are a charitable organisation and if we make a profit it would be retained by the charity.

Where will you start?

We have to look at the whole process and find the bottlenecks. At present, we don't know who uses what and how each sector accesses the information they use. We have to identify all databases – genomic, proteomic, imaging – and work on making them all accessible. We want to track down all European clinical trials for inclusion; EORTC are behind this, especially because at present all their trials are listed on clinicaltrials.gov. This is being done piecemeal at present – in Italy all clinical trials are included on a data base but most other countries don't do that. And we'll be looking to ESMO and EUSOMA to build a best practice model for anybody writing guidelines.

What knock-on effects do you expect?

Most groups draw up guidelines for treatment and care, but patients aren't consulted, and there's no mechanism for feedback from them. We want to set up social networking sites for patients taking chemotherapy on clinical trials. We want to help them find each other and be able to ask each other how they're getting on. They'll be able to discuss what's worrying them. The whole thing can be done confidentially so that privacy is preserved, but researchers involved in the trial will watch the dialogue for valuable feedback. It will help the interaction between patients and doctors.

What's also interesting is the possibility for setting up phase IV monitoring of licensed drugs – some adverse effects only become apparent once the drug is in the community and we could provide an obvious place for patients to go with information.

It sounds ambitious?

It is a big concept, but we're fulfilling a basic need. It's completely do-able and very exciting!

Helen Saul