ELSEVIER

European Journal of Cancer 41 (2005) 1495–1499

European Journal of Cancer

www.ejconline.com

NEWS...NEWS...NEWS

Adjuvant potential of trastuzumab

New evidence that trastuzumab may be effective as an adjuvant therapy was presented at this year's annual meeting of ASCO (American Society of Clinical Oncology, 13–17 May 2005, Orlando, Florida, USA). Research suggested that the drug may reduce risk of recurrence by up to 52%.

Three trials – the HERA (Herceptin Adjuvant), NCCTG-N9831 and NSABP-B31 trials evaluated the effects of trastuzumab as adjuvant therapy on breast cancer recurrence. The HERA study included 5090 patients with invasive, early-stage HER2-positive breast cancer, with or without the involvement of the lymph nodes. Patients had previously undergone a range of surgical, chemotherapy and/or radiotherapy regimens and were randomly assigned to receive trastuzumab for 12, 24 months or no treatment. Interim analysis showed a highly significant 46% reduction in risk of recurrence. The drug was well-tolerated with only a 0.5% increase in congestive heart failure in trastuzumab patients compared to those without treatment.

Trastuzumab is a humanised monoclonal antibody directed against tumour cell protein markers. It blocks the function of human epidermal growth factor receptor 2 (HER2), which is a key component in cellular growth and proliferation. Breast cancer cells that over-express HER2 are often clinically more aggressive.

Dr. Martine Piccart (Jules Bordet Institute, Brussels, Belgium), lead author of the HERA trial said, ''In the advanced breast cancer setting, Herceptin has already demonstrated that it prolongs patients' lives. To see such impressive results with Herceptin in early-stage breast cancer, already at the interim analysis, is a major breakthrough in the treatment of this aggressive disease. These results now add to the growing body of evidence that Herceptin should be considered the foundation of care for HER2-positive breast cancer patients, regardless of the stage of their disease''.

A joint interim analysis of NCCTG and NSABP trials by Dr. Edward Romond (University of Kentucky, Lexington, USA) and Dr. Edith Perez, (Mayo Clinic, Florida, USA) echoed the results from the HERA study and showed a remarkable 52% reduction in cancer recurrence and a 33% decrease in risk of death in the trastuzumab arm. The NCCTG and NSABP recruited 3406 and 2085 patients, respectively, with early-stage HER2-positive breast cancer who were initially on adjuvant therapy with doxorubicin and cyclophosphamide. Patients were then randomly treated with either paclitaxel alone or in combination with trastuzumab. As in the HERA trial, trastuzumab was tolerated without any unexpected adverse events.

The full analysis of these trials when completed could, finances allowing, change the treatment of HER2-postive breast cancers and have a significant positive impact on the lives of the 20–30% of women who have this type of breast cancer.

Lekshmy Balakrishnan
Orlando

Renewed interest in angiogenesis prevention

The molecular targeted cancer drug, bevacizumab (Avastin) may improve survival of patients with breast and non-small cell lung cancer (NSCLC), according to research presented at ASCO, 2005.

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). The anti-angiogenesis drug is currently approved for use against metastatic colorectal cancer.

The E2100 randomized phase III trial, led by Dr. Kathy Miller (Indiana University Cancer Centre, USA), included 715 patients with locally recurrent or metastatic breast cancer without prior treatment. They received paclitaxel, with or without bevacizumab. Patients in the bevacizumab arm had significantly increased progression-free survival from 6.11 to 10.97 months, and a higher response rate (14.2% *vs* 28.2%). A trial of bevacizumab in the adjuvant setting for breast cancer is being designed by the same research group.

A second study, presented by Alan Sandler (Vanderbilt University Medical Centre, Nashville, USA) looked at disease progression and survival in NSCLC patients. Patients (878) with untreated stage IIIb/IV NSCLC were treated with either bevacizumab and standard regimen (paclitaxel and carboplatin) or standard treatment alone. After a median follow-up of 9.4 months, those on bevacizumab had significantly increased survival (12.5 *vs* 10.2 months), higher response (27% *vs* 10%) and longer progression-free survival (6.4 *vs* 4.5 months), compared to those on standard treatment.

Bevacizumab toxicity was tolerated in both studies. The most significant side effect was bleeding and thromboembolic events.

Many smaller trials with preliminary data on the clinical benefits from bevacizumab therapy were also presented at ASCO this year. As ASCO president Dr. David Johnson said, ''It looks as if angiogenesis is making a comeback''.

LB

EJC News is compiled by:
Helen Saul
Tel: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.com

doi:10.1016/j.ejca.2005.06.001

Adjuvant chemotherapy for stage III colon cancer patients

The addition of irinotecan to standard therapy for patients with advanced colon cancer significantly reduced the risk of recurrence, European researchers said. The results, presented at ASCO 2005, demonstrated the clinical benefit to stage III colon cancer patients.

The PETACC-3 (Pan European Trial Adjuvant Colon Cancer) study, led by Professor Eric Van Custem (University Hospital Gasthuisberg, Belgium), is the largest of its kind and included 3278 patients with stage II or III colon cancer patients. Patients were randomized to receive LV5-FU with or without irinotecan for six months. This study differed from others in that it used only infusional delivery of LV5-FU, which is associated with fewer side effects than bolus injection in metastatic colorectal cancer.

The study found that, after a median follow-up of 38 months, inclusion of irinotecan significantly reduced the risk of colon cancer recurrence in stage III patients when combined with infused LV5-FU. The 3-year relapse-free survival was 66% in the irinotecan/LV5-FU arm compared to 62% in LV5-FU alone.

Irinotecan was also shown to reduce cancer recurrence significantly by 13% when stage II and III patients were pooled and analysed as a group. Patients taking irinotecan had slightly more adverse side effects (low white blood counts and diarrhoea) but overall, toxicity was low and manageable. Toxicity was less than that previously observed with bolus 5-FU injection.

''These findings are encouraging and show that irinotecan plus infused LV5-FU is a valid treatment option in stage III colon cancer patients'', said Professor Van Custem. Further follow-up studies are ongoing and results from analyses examining possible benefits from irinotecan for early stage (stage II) patients are keenly awaited.

Lekshmy Balakrishnan
Orlando

Response confirmation 'is unnecessary'

Confirmation of responses in clinical trials is unnecessary, and may increase the heterogeneity in results, say researchers in this issue of *EJC* (*see pages 1528–1532*). A group led by Dr. Jose Luis Perez-Gracia (Clinica Universitaria de Navarra, Pamplona, Spain) found that response confirmation added no value to assessment using the first best response observed.

The study – the first to systematically compare response rates with and without confirmation – was based on 9 phase II trials of one single cytotoxic drug, including 416 patients selected from a pharmaceutical database. Dr. Perez-Gracia found that agreement between both methods was excellent. Adding response confirmation altered response rates by 0–5% in most studies. ''This seems unlikely to change any decision taken because of the trial,'' he said.

Confirmation is time- and resource-consuming and may increase the heterogeneity of clinical trial results, the researchers found. Confirmation is performed at different intervals depending on factors unrelated to the true activity of the drug, such as the resources available for the study, or the capacity of the site to perform image tests in the minimum interval allowed. Well-resourced studies may obtain better response rates just because the image tests are performed earlier. In addition, it is possible that response confirmation is not performed in every trial reported, which may artificially increase response rates in comparison with other studies.

All response assessment guidelines include the requirement for responseconfirmation, but the rationale is unclear. Some guidelines state that, without confirmation, the drug's effect may be overestimated. ''But in respect to what?'' asked Dr. Perez-Gracia.

Dr. Jose Luis Perez-Gracia

The researchers found no clear rationale for requiring response confirmation. ''The only reason I could come up with is that it has always been performed, and stopping the practice next year, say, could make it difficult to compare the results of future trials with those from older ones. But the differences between confirmed and non-confirmed responses do not seem to be large, and are probably much smaller than differences due to newer techniques for assessing responses.

Since response confirmation is a widespread practice, more studies are probably required before making definitive changes. However, even if future studies find significant differences between confirming responses and assessing only the best response, they should point out the advantages of performing the more complex procedure.''

Change in standard treatment for gastric cancer?

Perioperative chemotherapy before and after surgery improves survival in patients with operable gastric and lower oesophageal cancer compared to surgery alone, said UK researchers. Their results should change the standard practice for this cancer.

Professor David Cunningham (Royal Marsden Hospital, London, UK) presented the final results from the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial at ASCO 2005. The study included 503 patients with operable adenocarcinoma of the stomach, oesophagogastric junction or lower oesophagus. Patients were randomised and treated with surgery with or without perioperative chemotherapy. The chemotherapy regimen included three preoperative and three postoperative cycles, three weeks apart of epirubicin, cisplatin and infused 5-fluorouracil.

Comparison of progression-free and overall survival rates at 5 years after diagnosis showed that both were significantly longer in patients who had received perioperative chemotherapy. The five-year survival rate was 36% in the chemotherapy arm and 23% in the surgery alone arm. Furthermore, only 70% of patients in the chemotherapy group experienced progression of disease compared to 80% in the other arm. Median survival was 4 months longer in patients receiving perioperative chemotherapy.

''This clearly shows that, in patients with operable gastric and lower oesophageal cancer, preoperative and postoperative chemotherapy leads to downsizing of the primary tumour, improves progression-free survival and improves overall survival'' said Professor Cunningham. He added, ''This approach should be considered one of the standard treatment options for patients with these cancers''.

LB

EUROFILE

International Tissue Research: The Challenges

International guidelines are urgently needed to ease the burdens associated with conducting tissue-based research at national, European or transatlantic levels, said speakers at a tissue research workshop. Legal, ethical and administrative requirements, coupled with procedures for obtaining informed consent, pose significant barriers, they said.

The workshop, *The Challenges of Conducting International Tissue Research,* chaired by both Professor Anthony Murgo (National Cancer Institute, Rockville, USA) and Professor Françoise Meunier (EORTC), was organised within the framework of the 16th EORTC/NCI/AACR Symposium on Molecular Targets and Cancer Therapeutics (Geneva, September 28 – October 1st, 2004) and concluded that the current lack of international harmonisation results in significant barriers to conducting tissue-based research.

Ms. Caroline Trouet (University of Leuven, Belgium) said tissue research is currently regulated through an amalgam of differing and occasionally conflicting laws and policies throughout the world. The rights of individuals have been reinforced in many countries, while the numbers of regional and national regulations have similarly multiplied, particularly in the area of privacy and confidentiality. Despite adherence to broad general principles on the use of the human body and its materials, national laws and customs still prevail.

The question of ownership of the samples and the associated data remains unresolved. Procedures for the use of archived human biological materials for biomedical research generally consist of obtaining consent from the patient and approval from the competent authorities (usually ethics committees).

Furthermore, transfer of material is only possible if the recipient country has regulations offering a similar level of protection to the country sending the sample. Ms. Trouet called for international guidance on the implementation of the informed consent requirement. Patients should have different options in consent procedures because future research purposes are not always known. There is a need for discussion of how new findings – relevant either to the current patient's management or future health status – should be dealt with.

On a positive note, Dr. Manuel Morente (CNIO, Madrid) said that the Tumour Bank Network in Spain is promoting the establishment of tumour banks in Spanish hospitals, to facilitate molecular studies through the cooperation of a coordinated network of hospital banks.

Associated hospital tumour banks are interconnected through a computer-based network, currently incorporating 20 hospitals and dealing with 80 projects within Spain. Other tumour bank networks are being established in the UK, Italy, Ireland, and on a pan European level within the Tubafrost project, part of the European Commission's 5th Framework and coordinated by EORTC.

These projects aim to establish a framework for a central tissue repository, complying with different national legislations. Optimal tissue collection is influenced by the diversity in national legal requirements, and also by pathologists' reluctance to provide material for central storage. A further problem is the ability of patients to fully understand the difference between research conducted on tissue samples removed during standard therapeutic procedures, or research conducted later on, which is not directly linked to the patient's management.

Researchers in the US face a parallel predicament. Dr. Sheila Taube from the National Cancer Institute (NCI), USA said that, again, the requirements for specimen handling and associated data depend on the type of research that will be performed using the specimens.

The NCI has developed different resource models to serve the varied research needs. A virtual bank has been established for archival collections of breast cancer and prostate cancer, for example. Tissue used for basic research has different data needs from translational research, which requires collection of clinical and follow-up data.

Addressing the ethical and legal issues associated with the various resources requires implementation of personnel training, data use agreements and firewalls. An honest broker model has been developed that interposes a tissue bank trustee between patients and biomedical researchers and enables strict control of the flow of information associated with research using banked tissues.

Evolving science creates new challenges: for example, in certain circumstances, fresh frozen samples are needed, in addition to those obtained during surgery at the time of diagnosis. Legal and ethical requirements are designed to ensure the best outcome for the patient.

The NCI has developed a web-based system, the Shared Pathology Informatics Network (SPIN) to help researchers find the specimens they need. Other resources include tissue micro-arrays and national biospecimen networks. All models need to consider specimen preparation, data acquisition and data security in addition to legal and ethical issues.

Dr. Richard Schilsky (University of Chicago, USA) said the CALGB Cooperative Group has specimen repositories that collect, store and distribute samples as paraffin blocks, frozen tumour, bone marrow, oral smears and biological samples including whole blood for DNA/RNA isolation.

CALGB's banking of solid tumour specimens, blood and plasma is coordinated through a Pathology Coordinating Office established in 1999. CALGB has a web-based pathology review system and a Leukemia Tissue Bank. However, obstacles remain. Specimen handling can vary across multiple sites; there is a lack of uniform standards for specimen processing and storage; variability in Institutional Review Board (IRB) protocols for specimen banking and a lack of consensus on specimen ownership and intellectual property.

The ultimate goal is to minimise variability in tissue procurement, processing and storage to produce research-quality specimens. Yet specimen collection in multi-centre studies remains universally complex and expensive. The problems faced by researchers in the US and Europe remain essentially the same, but in recent years, where European countries have introduced regulations, they have been more restrictive than US law. The general trend is towards increasing the individual rights of citizens and especially the right to privacy.

Quality specimens, coupled with annotation of patient characteristics, treatment and outcomes, provide outstanding opportunities for correlative science research. The barriers to successful tissue transfer and tissue research need to be addressed if the tremendous potential held by this research is to be realised.

Françoise Meunier
Director-General, EORTC

Raloxifene: the safer tamoxifen?

Raloxifene may dramatically reduce the risk of endometrial cancer, researchers say. Compared to non-users, the risk of endometrial cancer development was reduced by 50% among women prescribed raloxifene.

The results, presented at ASCO 2005, come from a new population-based, case-control study. It showed that – in contrast to the encouraging results found for raloxifene – tamoxifen users had an increased risk of the cancer compared with non-users (50% increase).

Raloxifene and tamoxifen use was compared in 547 women with endometrial cancer and 1412 control cases without cancer. After adjustment for confounders including body mass index and previous history of breast cancer, the odds ratio associated with developing endometrial cancer among raloxifene users was 0.5, while the odds ratio among tamoxifen users was 1.50. The benefit of raloxifene on endometrial cancer risk remained among those with short-term use for less than three years.

Tamoxifen, a selective oestrogen receptor modulator (SERM), is known to reduce breast cancer recurrence in women with oestrogen receptor-positive tumours and to be chemopreventive in women who are at high-risk from developing breast cancer. However, this study and others have shown that treatment with tamoxifen also increases the risk of endometrial cancer.

Raloxifene, also a SERM, is used in the treatment of osteoporosis and shows some promise in breast cancer chemoprevention. The STAR (Study of Tamoxifen and Raloxifene) trial is currently underway to compare the two drugs in preventing primary breast cancer development. Results are expected in 2006.

Dr. Angela DeMichele (University of Pennsylvania, Philadelphia, USA) led the current study, and said, ''It's important to start thinking about strategies to reduce risk (of endometrial cancer). If raloxifene proves effective at treating both breast cancer and endometrial cancer, that information could weigh heavily on a women's decision about which drug to choose''.

LB

Chemoprevention for prostate cancer

A drug used for treating advanced breast cancer may also reduce the incidence of prostate cancer in men who have precancerous prostatic intraepithelial neoplasia (PIN). Lead investigator, Dr. David Price, (Louisiana, USA) said, ''This is the first time that a drug has shown promise for lowering the incidence of prostate cancer in men with PIN.''

While PIN does not always lead to tumours, 39.5% of men with PIN develop prostate cancer at one year after diagnosis and this rises to 80% after five years. Currently there is no effective treatment for PIN and men with this condition receive periodic biopsies to catch the first signs of malignancy.

Dr. Price presented the results of a randomised multicentre phase IIb trial of the selective oestrogen receptor modulator, toremifene, at ASCO 2005. In the study, 514 men with high-grade PIN with no evidence of prostate cancer were randomly assigned to 20, 40 or 60 mg daily dose of toremifene or placebo for a year. The men underwent prostate biopsies at 6 and 12 months after the start of the trial.

Prostate cancer was diagnosed among significantly fewer patients taking 20 mg toremifene compared to placebo. Cumulative incidence of prostate cancer was 31.2% in the placebo group compared to 24.4% in patients taking 20 mg toremifene. Patients treated with 20 mg toremifene for six months had a 22% risk reduction in cancer. Those who took the drug for the entire year had a 48% risk reduction. There was no statistically significant reduction in cancer incidence among men who received the 40 or 60 mg dose. Toremifene was tolerated at all doses but more patients (5%) experienced fatigue compared to the placebo group (3%).

The 60 mg dose is already approved by the US Food and Drug Administration for breast cancer treatment. Instead of increasing the dose as is customary, Dr. Price and colleagues decided to reduce drug dose based on animal studies suggesting that lower doses are more effective in preventing prostate cancer.

Lekshmy Balakrishnan
Orlando

Statins lower risk of breast cancer

The statins, widely-used cholesterol-lowering drugs, may reduce the risk of breast cancer by more than half. Presenting data at ASCO 2005, Dr. Vikas Khurana (Louisiana State University Health Sciences Centre, Louisiana, USA) said, ''Statins may have a role in breast cancer prevention''.

Statins are already known to suppress tumour growth in several animal models but a chemopreventive function for this drug in breast cancer is controversial. Some studies have shown increased risk with lipid lowering agents. However, basic research has also shown that some statins can induce apoptosis and could potentially have a pivotal role in stopping tumours from forming. Statins work by inhibiting HMG-CoA reductase, an enzyme involved in the synthesis of intermediates in many signalling pathways that are important in cell proliferation and cancer development.

This retrospective study included 40 421 female veterans from the South Central United States, of whom 11.8% were statin users. Breast cancer was seen in 1.38% (556) women. After controlling for age, smoking, alcohol use and diabetes, statins were associated with a 51% risk reduction in breast cancer. The type of statin, dose and length of use were not factored into this analysis but this work is ongoing.

Other researchers at ASCO also linked fat metabolism and cancer occurrence. Dr. Rowan T Chlebowski (Los Angeles Biomedical Research Institute, USA) presented phase III randomised clinical trial data. It showed a significant decrease (relapse-free survival improved by 24%) in breast cancer recurrence in 975 early-stage, surgically-treated, postmenopausal women from switching to a low-fat diet. Dr. Khurana and colleagues also presented preliminary results from 2 other studies showing the potential of statins to prevent both prostate and lung cancer.

LB

PODIUM

Rest and refreshment on the way

In 1978, Sister Frances Dominica befriended a toddler, Helen, who was in hospital for removal of a brain tumour. After leaving hospital, Helen was looked after at home but Sister Frances occasionally ''borrowed'' Helen to give her exhausted and grieving parents a break. Helen House, the world's first children's hospice, in Oxford, UK, grew out of the experience and was opened in 1982. Douglas House, for adolescents and young people, was opened in 2004.

Sister Frances Dominica

What is the concept behind Helen House?

It starts with the small, homely building. Staying with us should be like visiting friends from time to time. We offer friendship and practical support to the whole family, including well brothers and sisters, and grandparents. They can all come on every visit if they choose. We have only 8 beds but we can be available to 150 families at any one time, because many visits are brief. Our support carries on for as many years as the family wishes after the death of the child. We try to help the family live through the bereavement.

Is it exclusively for children with cancer?

No, it's for all those with life-limiting and life-shortening conditions. The word hospice is misleading; its original definition was a place of rest and refreshment for people on a journey. We have called Douglas House a Respice, to reflect that. We provide long term support for families, networking with other agencies that either are or could be involved, and try to provide joined-up care.

What is your philosophy?

We accept that the child is going to have a shortened life, but there is lots of living to do before they die. We have celebrities willing to do anything and everything for the children, which is wonderful, but it is often the little things that make a difference. We take some of the burden away from the family if only for a brief time so that they can rest and relax, either to do their own thing or to be part of the caring team. Some families do all of the caring; some children come unaccompanied – they may crave the independence that normally is impossible because of their condition.

What was the situation for sick children and their families in 1982?

Many of the families who came to us had never been offered anything else. The first little girl was 11 years old and had Batten's Disease, which is progressive with symptoms including blindness and epilepsy. The only other respite care she had ever been offered was an unaccompanied stay in a psychogeriatric ward.

Have things changed?

They have improved. There are now 36 other children's hospices in the UK alone and a number in different countries; in Japan for instance, there is a keen interest in the kind of paediatric palliative care we offer.

The demands on parents have increased over the years: they are now expected to give quite mind-blowing, high-tech care to their children after discharge from hospital. Parents' expectations of us have also changed: emergency resuscitation was not a feature of hospice care; we would give oxygen and cuddles. Now – especially in the early stages of our relationship with a family – many will expect us to dial 999 in the event of their child collapsing. As trust builds between us, they sometimes change their mind but it isn't easy.

How similar is Douglas House?

It is run along the same lines as Helen House but for young people aged 16–40, whose needs, if anything, are greater. Their parents are often still the main carers and are not getting younger; there is less provision from the education system or social services. They are well aware of the implications of their condition; many will have seen friends progress and die. With so few services available, it can feel like everybody is waiting for them to die too.

What specific issues are raised by this group?

The main one is autonomy. Understandably, parents have often become very protective, and find it hard to accept that their young adult has a right to autonomy. Inside a disabled body may be an able mind with all the emotions and desires of anyone of their age. Sometimes our role, between the two, can be a delicate one.

It must be gratifying to see both Helen and Douglas Houses becoming role models?

It's exciting, but it's important for us not to sit back and enjoy it. We, the professionals involved, are always going to be on a steep learning curve with the real expertise coming from the families. You may have seen the same condition in 105 children, but the next to come along may be different from all the others.

Do you have a message for cancer professionals?

The family of a little boy with neuroblastoma met numerous professionals through his diagnosis, treatment and admissions. But the doctor they will never forget is the one who broke down and cried when he had to accept that the boy would die. This doctor heard what they were saying, he felt deeply with them and for them.

We can't always have the results we wish for but each of us can make a huge difference simply by listening and empathising. Paediatric oncology makes huge demands on professionals, but their way of being can make all the difference in the world to the families concerned.