NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Combination therapy improves AIDS-related lymphoma outcome

→ Cancer

Survival rates in HIV patients suffering from aggressive malignant non-Hodgkin's lymphoma improved when treated with a combination of HIV therapy and chemotherapy, according to a new study published in the journal *Cancer*.

The benefits of combining the two therapy treatments were most obvious in HIV patients who did not have severely damaged immune functions. These patients survived just as long as the lymphoma patients who didn't have HIV.

Lymphomas are cancers of the immune system's white blood cells, and are treated with chemotherapy. People with HIV are at an increased risk of developing aggressive, fast-growing lymphomas known as 'AIDS-related lymphomas' (ARL) – these generally have a worse outcome than non-HIV-related lymphomas.

'Highly active antiretroviral therapy' (HAART) has revolutionised the care of HIV-positive men and women by improving their survival and delaying the onset of AIDS and AIDS-related cancers – including lymphomas. Scientists looked at combining HAART with the chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Rudolf Weiss, of the Specialist Practice for Haematology, Oncology and Infectious Diseases in Bremen, Germany, who led the study, treated 72 HIV patients who had ARL. He divided them into high-risk and standard-risk groups and treated both groups with combined chemotherapy and HAART adapted to the risk level. The study found that the combined therapy improved survival rates for patients with ARL and a standard level of risk to rates comparable to lymphoma patients who didn't have HIV and were treated with CHOP, and superior to previously published rates achieved by CHOP alone.

For standard-risk ARL patients, 79% achieved complete remission. By the end of the study, with 47 months' follow-up, more than 50% of patients had survived. Only 40% reported moderate drug toxicity. For high-risk ARL patients, only 29% achieved complete remission and median survival was only 7.2 months; 69% reported moderate toxicity.

The authors concluded that "The present study showed that our risk-adapted strategy for concomitant administration of HAART with CHOP is effective and safe."

■ Acquired immunodeficiency syndrome-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival. Results of the German Multicenter Trial. R Weiss, P Mitrou, K Arasteh, et al. *Cancer* 1 April, 106:1560–1568

Thalidomide should be added to treatment for multiple myeloma

→ The Lancet

Adding thalidomide to the standard combination of drugs used to treat multiple myeloma in elderly patients could improve event-free survival, according to a randomised trial reported recently in *The Lancet*.

Multiple myeloma accounts for about 1% of all cancers diagnosed in Europe. Its incidence increases with age, and more than 80% of cases are diagnosed in people over 60 years old. Since 1960 oral melphalan and prednisone (MP) have been regarded as the standard of care in elderly multiple myeloma patients.

Thalidomide has shown some promise in previous clinical trials when combined with chemotherapy agents. The drug was originally developed to prevent morning sickness in pregnant women; tragically it caused birth defects in the unborn foetus. Researchers discovered that thalidomide interfered with the growth of blood vessels in foetal limbs and reasoned that thalidomide might also interfere with the growth of blood vessels in tumours.

In a trial involving 255 patients, Antonio Palumbo (University of Torino, Italy) and colleagues found that those treated with melphalan, prednisone, and thalidomide had higher response rates and longer event-free survival than those who were treated with MP alone. This benefit, however, must be balanced against increased rates of thrombosis, neurological toxic effects and infection, warn the authors.

Palumbo concludes, "After 50 years of unsuccessful attempts to find new and more effective treatment approaches suitable for most patients with myeloma, our results lend support to the use of thalidomide in the initial treatment of elderly patients with multiple myeloma."

In an accompanying comment, Shaji Kumar (Mayo Clinic, Rochester, USA) states that these results, combined with the preliminary results of a study in France, are enough to change clinical practice. He calls this an 'historic moment in myeloma therapy'.

■ Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma. A Palumbo, S Bringhen, T Caravita, et al. *The Lancet* 11 March, 367:825–831; Progress in the treatment of multiple myeloma. S Kumar, ibid, pp791–792

Patient treatment decisions may be influenced by media coverage

➜ JNCI

A study reported in the *Journal of the National Cancer Institute* has shown that the oral presentation of data from a single study at a national cancer conference changed patient treatment, even before the study's publication or approval by the US Food and Drug Administration (FDA).

The authors found that use of taxanes increased after the May 1998 annual meeting of the American Society of Clinical Oncology (ASCO). At the conference preliminary data were presented suggesting that the use of taxanes as adjuvant therapy could improve survival in women with lymph-node-positive breast cancer. The research was covered by key media, including the *New York Times, Wall Street Journal,* and *U.S. News and World Report.*

Researchers from the University of Texas MD Anderson Cancer Center set out to investigate the impact of the ASCO taxane presentation. One of the taxanes they looked at was the drug paclitaxel. This did not receive FDA approval for adjuvant breast cancer until October 1999, and the final study report was not published until 2003.

The researchers studied chemotherapy use in 3,341 women older than age 65, identified in the Surveillance, Epidemiology, and End Results Medicare database, who were diagnosed with stage 1–3 breast cancer between 1994 and 1999 and received adjuvant chemotherapy within 1 year of diagnosis.

The percentage of women receiving adjuvant chemotherapy who received taxanes such as paclitaxel remained at around 10% from 1994 to early 1998, and after early 1998 the rate of increase over time increased more than seven fold.

Rates of taxane use increased primarily in women with node-positive breast cancer in early 1998, and it also increased in women with node-negative breast cancer by the end of 1999, even though such women were not included in the taxane study.

The authors suggest that the increased use resulted from publicity at ASCO and consequent media coverage.

They caution that medical decisions based on premature data from a meeting presentation may pose a risk for patients who could be exposed to drugs that may have toxic effects before the drug's benefits have been definitively established.

The authors write, "Although in many ways this example represents a best-case scenario, in which the meeting report of a multicenter randomised trial turns out to have stimulated the adoption of a treatment that has eventually become part of evidence-based practice, it also illustrates the enormous power of highly publicised meeting presentations.

"Investigators should be aware of the potential impact of their presentations and exercise appropriate caution and judgement in their interpretation of research findings."

■ Impact of a scientific presentation on community treatment patterns for primary breast cancer. SH Giordano, Z Duan, Y-F Kuo, et al. *Journal of the National Cancer Institute* 15 March, 98:382–388

Treatment duration may be critical for best results in pre-leukaemia disease

➜ Cancer

According to a new study, longer courses of a mild form of chemotherapy may help patients with a pre-malignant form of leukaemia called myelodysplastic syndrome (MDS). Patients with MDS have been shown to benefit from a new DNA hypo-methylating agent: decitabine. Researchers, led by Michael Lubbert of the University of Freiburg Medical Centre, Germany, assessed the efficacy of retreating on relapse high-risk MDS patients who had already received initial treatment with the drug. Patients had a median of three further courses of decitabine, and 45% of patients responded, but had a poorer response than was shown after the first treatment. As a result of the study, researchers believe that longer initial treatments of decitabine may be more beneficial to patient outcome.

Ten out of 22 patients responded to decitabine when given an average of three courses of the drug. Three patients achieved a partial or complete response in red cells, white cells and platelets. The other seven patients experienced at least a 50% drop in blood transfusion requirements and higher cell counts in one or two of the blood cell lines. All patients had an average survival of 28 months. Patients who were retreated with decitabine had a median survival of 13 months after their relapse.

The authors conclude, "Results of the present analysis point to the importance of extending therapy with low-dose decitabine beyond the point of first response, and strongly support institution of a maintenance treatment."

■ Superiority of prolonged low-dose azanucleoside administration? Results of 5-Aza-2'-deoxycytidine retreatment in high-risk myelodysplasia patients. B Ruter, P Wijermans, M Lubbert, et al. *Cancer* doi: 10.1002/cncr, published online 13 March

Action is needed to safeguard cancer research in Europe

➜ British Medical Journal

Research looking at clinical trials has found a dramatic drop in the number of new trials undertaken since the EU clinical trials directive came into force in 2004. The clinical trials directive was intended to protect patients and improve research standards. But many investigators warned at the time that the labour-intensive, bureaucratic, and expensive endeavour of running a clinical trial would become worse under the new rules.

In particular, grant-funded academic researchers, who performed most cancer trials, raised concerns that their resources might not suffice to meet the requirements of the new directive.

An analysis of research undertaken since the directive was implemented suggests that many of those fears have been realised. For example, the number of new trials fell from 19 in 2004 to 7 in 2005 (a 63% decrease), and a third fewer patients were enrolled.

Simultaneously, trial costs increased by 85% and insurance costs from 70 mn to 140 mn euros. Trial initiation took about five months longer than in 2004, while paperwork and documentation increased.

Instead of benefiting patients, the analysis suggests that the directive has hindered their access to new treatments.

"Our own experiences are in accordance with these findings," say the authors Akseli Hemminki and Pirkko-Liisa Kellokumpu-Lehtinen, from Helsinki University Central Hospital and Tampere University Hospital, in Finland. The number of approved applications for both academic and company-sponsored cancer trials in Helsinki steadily decreased, from 120 in 2002 to 70 in 2005 (42% decrease), but the workload of the ethics committee increased.

These numbers seem to confirm the initial worries about the future of investigator-initiated clinical cancer research, conclude the authors, adding that new directives on clinical research are in preparation, and physicians, patients, universities, and politicians need to take action to ensure that academic research can continue in Europe.

■ Harmful impact of EU clinical trials directive. A Hemminki and P-L Kellokumpu-Lehtinen. *British Medical Journal* 4 March, 332:501–502

Advocates, clinicians and researchers call for action on breast cancer

➜ EBCC – Nice

Organisers of the European Breast Cancer Conference (EBCC) – Europa Donna (the European Breast Cancer Coalition), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society of Mastology (EUSOMA) – have issued a manifesto in order to highlight what needs to be done to support breast cancer research and improve patient outcomes. The Nice Manifesto highlights seven areas for action:

1. *Improve the number and quality of European screening programmes.* Population-based screening programmes carried out in accordance with EU guidelines for quality assurance in mammography screening help to detect early breast cancer and save lives. Increasing the number of screening programmes free at the point of access and improving their quality would save the lives of many European women. Women should be encouraged to participate in screening programmes.

2. *Support breast cancer research.* Independent academic research is under threat due to insufficient funding in many European countries. It is a driving force in improving our knowledge of cancer and developing tailored, potentially cost-saving therapies. Studies which answer important clinical questions and which have the potential to increase our knowledge of the biological and genetic basis of the disease should be given priority.

3. *Rethink the breast cancer staging system.* Researchers and clinicians should be creative in designing new quality-assured diagnostic and staging systems which improve prediction of outcome. The genetic make-up of the tumour, for instance, should be defined in greater detail to identify the natural history of the disease in each individual patient, and the likelihood of response to standard therapies and molecular targeted treatments.

4. *Define metastatic breast cancer guidelines.* Most women still die from metastatic breast cancer. The general criteria on how to manage metastatic breast cancer need to be defined. Specific guidelines can help the patient and the clinician make the right choice.

5. *Increase the number of breast care nurses.* In most European countries today there are no breast care nurses. Breast care nurses can improve the treatment and management of breast cancer for patients. Greater involvement will improve patient care and quality of life.

6. *Expand the Breast Unit accreditation process.* Breast units should be accredited to ensure that they meet guideline requirements for standardisation of best care. Accreditation guidelines for carrying this out should be developed not only by professionals, but also by patient advocacy groups. Women should have equity of access and the choice to select appropriate facilities for diagnosis and treatment and be sure they are getting gold standard care.

7. *Give recognition to the essential role played by charities in independent breast cancer research.*
Encourage those charities to realise the potential benefits of their effort for all European patients and to expand their work even further.

Cooperation on medicines regulation intensified

➜ European Medicines Agency

The European Commission, the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) have agreed to increase the degree to which they cooperate on different aspects of drug regulation. Under the EU–FDA confidentiality agreement, the two agencies are providing parallel scientific advice in order to facilitate the development of safe and effective medicines, as well as sharing information about pharmacovigilance so as to enhance patient safety. The agencies have agreed to intensify transatlantic cooperation in the area of medicinal products, with particular focus on vaccines (including preparedness for an influenza pandemic), medicines for children, medicines for rare diseases ('orphans'), oncology and pharmacogenomics.

HPV virus may cause skin cancer

➜ JNCI

A study published in the *Journal of the National Cancer Institute* has found that the human papilloma virus (HPV) may cause a common form of skin cancer known as squamous cell carcinoma (SCC).

HPVs are a group of more than 70 different types of virus. They are given numbers to distinguish them. Strains of the HPV virus have been associated with other epithelial cancers such as cervical cancer (particularly numbers 16, 18, 30 and 33) and oesophagus cancers. HPV types 5 and 8 have been detected in skin tumours and previous studies have suggested they may play a role in the development of these cancers. Several vaccines are in development to help prevent infection from the two most prevalent cancer-causing types of the human papilloma virus, HPV 16 and 18, which together are responsible for over 70% of cervical cancers.

Margaret Karagas, of Dartmouth Medical School, and colleagues searched for antibodies to 16 different HPV types in plasma samples from 252 patients with squamous cell carcinoma, 525 patients with basal cell carcinomas (BCC), and 461 control subjects.

The authors detected genus beta type HPV antibodies in patients diagnosed with SCC more frequently than in control subjects, particularly HPV 5. No difference was found in the presence of HPV antibodies in patients with BCC compared to control subjects.

The authors write, "Although sun exposure and sun sensitivity are the major risk factors for [skin] cancers, our data support a role of HPV, particularly beta HPVs, in the development of SCC."

It may be possible in the future to produce a vaccination that can help prevent some cases of squamous cell carcinoma.

■ Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. MR Karagas, HH Nelson, P Sehr, et al. *Journal of the National Cancer Institute* 15 March, 98:389–395

EMEA reveals names of scientific advisors

➜ European Medicines Agency

EMEA has published a new section on its website that provides an overview of the CHMP (Committee for Human Medicinal Products) working parties, scientific advisory groups and other groups. Scientific advisory groups provide advice in connection with the evaluation of specific types of medicinal products or treatments. They consist of European experts selected according to the particular expertise required, on the basis of nominations from the CHMP or EMEA.

The current members of the scientific advisory group for oncology are: Jonas Bergh, Lothar Bergmann, Steen Hansen, Michel Marty (Chair), José Maria Moraleda, Jan Schellens, John Smyth, Patrick Therasse and Allan van Oosterom (Vice Chair).

Breast cancer risk and HRT

➜ EBCC–Nice

Recent research from the 'million women study', presented at the European Breast Cancer Conference in Nice, found that taking hormone replacement therapy (HRT) increased the risk of some types of breast cancer, but not others. The research found that women who took HRT had an increased risk of developing lobular cancer (affecting the cells in the ducts of the milk-producing glands) and tubular cancer. There was not such an increased risk of developing ductal breast cancer, the most common type of breast cancer that affects the cells lining the milk duct. There was no increase in the risk of medullary breast cancer, a kind of cancer that is common in women with a genetic predisposition to breast cancer.

The study demonstrated that women who had taken combined HRT (oestrogen and progesterone) had an even greater risk of developing lobular and tubular breast cancer than women on oestrogen-only HRT. The researchers also discovered similar findings for women with breast cancer in situ – when the cancer has not spread to the surrounding tissues in the breast or other parts of the body. Women who took HRT had a significantly greater risk of developing lobular cancer in situ than ductal carcinoma in situ.

Gillian Reeves, who presented the findings, comments, "One possible explanation for the findings is that certain types of breast cancer are more likely than others to be hormone receptive. Further research into this topic could greatly help our understanding of the biological mechanisms underlying the development of breast cancer."

Breast tissue changes may cause pregnancy-associated breast cancer

➜ Nature Reviews Cancer

A study by scientists from The University of Colorado Cancer Center has found that pregnancy-associated breast cancer may be linked to changes in the breast, when the mammary gland regresses to its pre-pregnancy state.

Breast cancer associated with pregnancy has a poor prognosis, including an increased risk of metastases. Researchers found that late diagnosis and increased hormone production during pregnancy may not be sufficient to account for increased mortality. There is overwhelming evidence to suggest that pregnancy has a preventative effect on breast cancer. However, some studies indicate that pregnancy may cause a period of tumour promotion before it produces its protective effect. The short duration of increase in breast cancer following pregnancy was found to peak 6 years after pregnancy and to carry on approximately 10 years following childbirth. Breast cancer diagnosis during this period is referred to as pregnancy-associated breast cancer.

After pregnancy and lactation, the mammary gland that produces the milk regresses to its pre-pregnancy state by a tissue remodelling process. The Colorado researchers found that this remodelling, which is associated with pro-inflammatory and wound-healing mechanisms, may help tumour cells spread.

In healthy women, after pregnancy the mammary gland reverts to its pre-pregnancy state and pro-inflammatory pathways are activated, but the balance of pro- to anti-inflammatory signals leans towards preventing inflammation. The authors suggest that, in women with hidden breast tumours, this may aggravate the tumour-promoting micro-environment, by tipping the balance towards overt inflammation. Women with hidden disease after pregnancy might be at an increased risk of tumour cell dissemination. Pepper Schedin, author of the paper, states that, "Effective breast cancer screening in recently pregnant women is warranted immediately."

■ Pregnancy-associated breast cancer and metastasis. P Schedin. *Nature Reviews Cancer* 6:281–291

Teenagers more likely to survive cancer in countries with public health systems

➜ Teenage and Young Adult Cancer Medicine Conference

Countries that have national health services easily accessible to people of all ages are likely to have better survival rates for their teenagers and young adults (TYAs) with cancer than are countries where individuals have to pay for their own medical insurance.

This is the suggestion that arises from new research presented at the 4th International Conference on Teenage and Young Adult Cancer Medicine, in which the health care systems of the United States of America and Australia were compared.

Archie Bleyer, medical advisor at the Cancer Treatment Center, St Charles Medical Center, Bend, Oregon, told the conference that Australia's system of health insurance for all, regardless of age, meant that TYAs were more likely to survive cancer in Australia than they were in the USA.

"Our previous research has shown that the survival of older teenagers and young adults with cancer in the United States has lagged behind progress in younger and older patients. We found that diagnosis was delayed in TYAs who either lacked health insurance or had inadequate insurance, and therefore this lack of progress might be due to the USA health care system, and less expected in countries with national health insurance.

"During the past year we compared survival of TYAs in the USA with those in Australia, a country similar in many demographics to the USA, but with health insurance provided to all citizens regardless of age.

"From 1982 to 1998, the rate of improvement in the 5-year survival from invasive cancer in Australia exceeded that which occurred in the USA, such that by the late 1990s, TYAs in Australia had an overall 5-year cancer survival that was higher than in the USA. The deficit begins at 16 and ends at 55, the same years that national health insurance is not available in the USA. It ranges from 5% for 18 to 25 year-olds to 12% for those aged 30 to 35. This difference suggests that the health care system in Australia, with universal health insurance, was able to provide better cancer care to its TYAs.

"The advantage for Australian TYAs was not apparent in their children or older adults with cancer. This suggests that the need for private health insurance in the USA is responsible for the worse survival of TYAs, in that children and older adults in the USA are more adequately insured than TYAs."

Global pharmaceutical market grew 7% in 2005

➜ IMS Health

New data released by *IMS Health* show that in 2005 global pharmaceutical sales grew 7% to $602 billion. North America accounted for 47% of global sales, while only 30% of sales were in Europe, probably reflecting the strict cost-containment measures adopted by European governments.

There was an 18.6% increase in sales of anti-cancer drugs (cytostatics), with global sales of $28.5 billion. For the first time cancer drug sales overtook anti-ulcerants, and now cancer drugs rank as the second biggest sellers after cholesterol-lowering agents.

In 2005, more than 2,300 products were in clinical development, up 31% percent over the past three years. Ninety-six oncology products are now in Phase III clinical trials or pre-approval stage.