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International Childhood Cancer Day

Parent groups in 46 countries united to support the International Childhood Cancer Day on Saturday, 15 February 2003. The day, which was organised by the International Confederation of Childhood Cancer Parent Organisations (ICCCPO) aimed to educate the general public about childhood cancer, raise money through fundraising events and promote the work of local parent organisations.

Parent groups were encouraged to organise their own local fundraising events. In 2002, 30 countries took part and raised US $100 000. In 2003, more countries, including India, Brazil and South Africa, joined in. Fundraising events were held throughout February 2003.

Tony Blair, Shanon Fenlon and Sir Paul Nurse

To highlight the day in the UK, 8-year old cancer survivor Shannon Felon met Prime Minister Tony Blair and Sir Paul Nurse, Chief Executive of Cancer Research UK. Mr Blair said, "Thankfully children like Shannon, who are treated in Britain, stand a very good chance of being cured of their cancer. Seven out of 10 British children with cancer are now successfully treated for their disease. But many children around the world are not as lucky as Shannon. International Childhood Cancer Day is an important time to highlight the inequalities in access to treatments across the globe and help us create opportunities to help improve the situation."

Sir Paul said, "We need to help developing countries benefit from the results of our research as we improve cancer drugs and develop new vaccines. The world's children deserve better."

All clear for acrylamide?

Concerns about cancer risks associated with acrylamide have been overstated, say New Zealand researchers (*Lancet Correspondence*, 2003, **361**, 434). Even people who eat high levels in regular portions of hot chips and potato crisps are consuming amounts three orders of magnitude below that which would have adverse effects. This amount "represents a very low cancer risk," they say.

The conclusion is based on work on rats, which assessed phaechromocytoma, testicular mesothelioma and thyroid adenoma. Levels of acrylamide of 0.1 mg/kg body weight were associated with no observable adverse effects. People eating chips and crisps have levels of about 0.3 μg/kg bodyweight—which is 3 O-M lower.

However, a related commentary points out that UN agencies have conceded that "on present knowledge the human cancer risk, if any, could not be calculated directly".

The Food and Drug Administration (FDA) in the US is engaging in a public debate on acrylamide and European Union experts are saying that the risk from exposure cannot be determined. "Translation of all the acrylamide data into sensible public-health advice is proving very difficult," the commentary states.

Voraxaze receives orphan drug status

Voraxaze (carboxypeptidase G2) has received Orphan Drug Status in the European Union, following a recommendation from the European Medicine Evaluation Agency (EMEA). The drug is a treatment for methotrexate toxicity and manufacturer Enact Pharma says it can reduce elevated serum levels by 98% within 15 minutes.

Orphan drug status in the USA is still pending.

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Urgent need for palliative care expertise in india

The European Society for Medical Oncology (ESMO) held a workshop on palliative care at the Tata Memorial Hospital, Mumbai, India, on 8 February 2003. The workshop is part of a move by ESMO to expand globally, offering requested expertise in collaboration with local oncologists.

One million people develop cancer each year in India. More than three-quarters have advanced cancer before they seek medical help, and half will die. "Eighty percent of the population live in rural areas where the lack of education and a poor health system prevent cancer being detected at an early stage," said Dr Mary Ann Muckaden, an oncologist at the Tata Memorial Hospital. "The stigma of breast or ovarian cancer is a particular issue for women," she added.

The Workshop heard that high-quality palliative care is possible at low cost and many symptoms can be treated, if necessary, with inexpensive drugs that are widely available globally. Caring for dying people does, however, require specialist training, skills and knowledge, as well as collaboration with healthcare workers, support groups and paramedics.

"THE EXTENT OF MISERY IS UNIMAGINABLE"

"Only three percent of the two million people who need palliative care receive it," said Dr M.R. Rajagopal from the AIMS Hospital in Kochi, Kerala. There is no state-sponsored social security system in India. "Medical treatment destroys families financially and the extent of misery is unimaginable."

India has only 20 cancer centres and 13 hospices. Inevitably, many states in India have no palliative care facility. Dr Purvish Parikh, ESMO's regional representative from the Tata Memorial Hospital which sees about 1000 cancer patients each day and 15 000 new patients every year, said, "Palliative care is not part of oncologists' training. ESMO's workshop will help to show how we can help to improve a patient's life and we appreciate the contribution from experts in other countries." Dr Muckaden aims to ensure that in the next 10 years, with the co-operation of members of the Indian Association of Palliative care and the state and centre health ministry officials, every patient who requires it will have access to palliative care within a 50-mile radius. "Palliative care in India is in its infancy," she said. "There are just not enough specialists and we need to promote it in undergraduate education."

The need for education and training in palliative care has been recognised by the World Health Organization for more than 15 years and is endorsed by ESMO. A survey of 900 oncologists in 64 countries, including India, conducted by ESMO in October 2002 revealed that almost all (92%) agreed that patients with incurable cancer should receive end-of-life support as well as antitumour therapy. Less than half, however, routinely co-ordinate the care of cancer patients at all stages of their disease or collaborate with support teams and social workers. "Improving the quality of life is a central part of caring for cancer patients," said Dr Nathan Cherny from Shaare Zedek Medical Centre in Jerusalem, Israel, who coordinated the survey. To this end, ESMO has produced a policy reflecting its commitment to the continuity of care and defining standards of excellence in this area.

Dr Dirk Schrijvers from the Middelheim Hospital in Belgium, on behalf of ESMO's educational committee, emphasised the importance of recognising specific needs in different countries. The organisers expect around 150 delegates to attend the workshop. "We will not be dictating instructions on how to organise a palliative care system in India. Every country has its own structures, so we need to work with existing and functioning systems," he said.

"WE NEED TO WORK WITH EXISTING SYSTEMS"

Prevention is better than cure and Dr Schrijvers further stressed the importance of early diagnosis of cancer. "We must also find ways to encourage people to see their doctors as soon as possible. If cancer is detected at an early stage, it is possible to treat it successfully. Also if a patient needs palliative care, the prevention of complications is of utmost importance."

Dr Purvish Parikh

"In my opinion a medical oncologist must be the leader of this team, because the patient knows the medical oncologist from the beginning of treatment," said Dr Ozgur Ozyilkan from Baskent University Faculty of Medicine in Turkey. "Cancer patients do not die suddenly. They usually live with an advanced and incurable disease for many months. Oncologists also must prepare themselves emotionally to deal with patients at the end of life," he said.

The ESMO Workshop was a two-way dialogue. "India is the motherland of spirituality and psychological understanding of illness," said Dr Marianne Kloke from the West Cancer Centre, Essen, Germany. "We want to learn how people in India manage life-and-death situations. Palliative care is not technical. Its strength lies in good communication between doctors, patients and their families."

"The workshop will enable us to share experience and knowledge with cancer specialists in the Indian sub-continent," said Dr Cherny. "This is another step to enhance ESMO's relationship with oncologists around the world and we look forward to other initiatives and integration of palliative care schemes globally," he concluded.

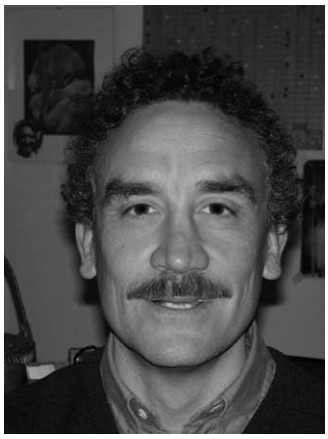
Melanoma: an unexpected decrease in deaths

Italian researchers have found an unexpected decrease in deaths from melanoma among men in central Italy (see *EJC*, this issue—REF). The finding is "difficult to understand," they say, given that incidence rates of the thicker melanomas have remained stable and that there have been no clear-cut advances in treatment.

The registry-based study found a significant increase in invasive and *in-situ* cancers in both sexes between 1985 and 1997. The increase in invasive tumours was mainly due to thin lesions 1.00 mm or less. However, there was a statistically significant decrease in mortality among men from 1985 to 1999. It did not happen among women.

At the beginning of the study period, men were presenting at a more advanced stage than women, and therefore had more scope for improvement. But the finding is still largely unexpected because the incidence of thick forms of melanoma was stable throughout the study.

The paper notes that there has been a preventive campaign in the Florence area since the late 1980s. The authors hypothesise that men—who had double the mortality rate of women at the beginning of the study period—benefited more than women from an increased awareness about melanoma screening. Backing this was the finding that the reduction in deaths was only among only young subjects—who were most effectively targeted by the campaign.



Dr Emanuele Crocetti

Speaking to *EJC News*, lead author Dr Emanuele Crocetti said that the findings are based on relatively few cases: 19 deaths per year among men. However, a similar finding has been observed in both Spain and the US. The Spanish result was partially explained by a decrease in outdoor work and exposure to sunshine, something not applicable to the Italian population, since invasive melanoma in the Florentine population are continually increasing. Any reduction in exposure to sunlight should have produced a reduction in the incidence of melanoma.

"The mortality reduction in the male Florentine population is a very promising—though unexpected—finding in the fight against melanoma," said Dr Crocetti, who added: "A fully convincing explanation for mortality reduction is still to be found."

Increase in adult brain tumours

Primary lymphomas of the central nervous system (CNS) have increased seven- to ten-fold in the past 20 years, in both immunocompromised and immunocompetent populations. While the Epstein-Barr virus is probably a key factor among the former, the cause of the immunocompetent form remains unknown.

In a Seminar on primary brain tumours in adults (*Lancet* 2003. **361**:232-31), Professor Jean Yves Delattre (Pitié-Salpêtrière, Paris, France) and colleagues expand on advances in treatment for primary lymphomas of the CNS. In immunocompetent patients these are chiefly due to the addition of methotrexate chemotherapy to radiotherapy. However, the combined treatment exposes elderly patients in particular to severe delayed neurotoxic effects: up to 80% of those over 60 years develop progressive leucoencephalopahy and cognitive dysfunction a year after treatment.

Alternative strategies are being investigated.

The other frequent adult primary tumours are gliomas and, again the incidence of malignant gliomas is increasing in elderly people "for unclear reasons". New developments are on the horizon. "There is a growing consensus that molecular genetic analyses will soon become as important as morphological criteria to improve classification of gliomas."

Low-grade gliomas mainly affect young adults and treatment options include anticonvulsant therapy, surgery, radiotherapy and chemotherapy. The most appropriate sequences and timing are unclear.

Substantial progress has been made in the understanding of the biology of primary brain tumours and in the management of some, particularly oligodendrogliomas and primary CNS lymphomas. The seminar concludes, "The challenge in the next decade will be to translate pathophysiological advances into efficient therapeutic strategies."

Research training in Bari

Internet teaching is a valid approach for developing competence in scientific writing, Italian researchers say. More than half the participants in a course thought it was a good idea and had no problems with distant teaching.

The Internet teaching was part of a modular course run by the National Cancer Institute in Bari, Italy in 2001. The Institute employs 60 doctors managing 150 beds, and it was observed that only a minority of investigators were publishing scientific material. The course was designed to cover organisation, funding, writing and publication of medical research.

Aside from the Internet course, other modules included a course on the theory of medical research, including literature analysis and revision; hands-on teaching with the University of Edinburgh; and a face-to face editorial meeting with editors-in-chief of the *British Medical Journal and International Journal of Oncology*. Participants presented posters and abstracts for comment and criticism. At the end of the course, 80% were able to write a scientific manuscript.

Fighting cancer in the developing world

Oncologists from the developing world had the opportunity to meet and exchange medical, social and cultural experiences at a conference in Abu Dhabi (United Arab Emirates, 15–16 December, 2002). The meeting attracted almost 100 participants from 33 different countries' half from developing countries and the others from UAE.

Issues addressed by the meeting included screening for breast and cervical cancers, and clinical issues raised by several different developing countries. A special session was dedicated to information and communication in the emerging world and the final panel discussion to international co-operation in the fight against cancer in developing countries.

Participants drew up 'The Abu Dhabi Statement' (printed in full, *EJC*, this issue, p. xx), which is an eight-point plan setting the agenda for the future. It includes pledges to promote innovative approaches to diagnosis, treatment and prevention of cancer appropriate to the emerging world; and to prepare a set of minimum clinical recommendations with priority given to those cancers relevant to the developing world.

The Second International Conference on 'The Fight Against Cancer in the Emerging World' was organised by the Challenge Fund (London and Cairo) and the European School of Oncology (Milan). It was held under the Patronage of H.H. Sheikh Khalifa Bin Zayed Al Nahyan, the Crown Prince of Abu Dhabi, who generously sponsored the conference.

H.H. Sheikh Khalifa Bin Zayed Al Nahyan, Crown Prince of Abu Dhabi

Conference Chair Professor Indraneel Mittra (Director-General of Bhopal Memorial Hospital and Research Centre)

"No advantage" for intrahepatic arterial chemotherapy

Use of intrahepatic arterial (IHA) chemotherapy should not be routinely used for patients with metastatic colorectal cancers, researchers say. "The regime improves neither progression-free nor overall survival compared with the standard intravenous treatment," they said.

The randomised trial was conducted jointly by the European Organization for Research and Treatment of Cancer (EORTC) and the UK's Medical Research Council (MRC). It included 290 patients with metastases confined to the liver, who received fluorouracil and folinic acid, either intravenously or by IHA (*Lancet* 2003, **361**, 368–73).

Both regimens were well-tolerated and there were few serious side effects. However, there was no difference in either progression-free or overall survival between the groups, with overall median survival just over 14.5 months in both. The study did not find improved quality of life associated with IHA.

The researchers point out that IHA infusions are complicated, expensive and require a laparotomy to insert the arterial catheter. The results are in line with previous experience and suggest, they say, that this IHA regimen in unresectable metastatic colorectal cancer "should not be administered outside a clinical trial."

An accompanying editorial (*Lancet* 2003, **361**, 358–359) points out that the systemic treatment of colorectal cancer has progressed considerably in recent years. "There have not been similar advances with hepatic artery infusion," it notes.

PODIUM

Wanted: new trial designs

Professor Mark Ratain is Associate Director for Clinical Sciences at the Cancer Research Center, University of Chicago, IL, USA and chair of the University's Committee on Clinical Pharmacology and Pharmacogenomics. He is co-directing (with Dr Carl Peck) a workshop 'Clinical Development of Oncologic Agents: Challenging the Tradition' in Washington, DC, USA, on 23–24 April, 2003.

Professor Mark Ratain

What is wrong with current trial designs?
The problem is that drugs have changed but we are still using the same trial designs that oncologists have been using for years. We are not taking advantage of the insights into methodology which have been implemented in trials in other chronic diseases. It's an interesting phenomenon: there is probably much greater participation in cancer clinical trials than in other disease areas and most oncologists think they know something about drug development. But people are still spending a lot of time trying to figure out the right dose of drugs in phase I trials. In many other disciplines, they have recognised that this is not possible. The only way is to do an appropriately controlled, dose ranging, Phase II trial. It's an example of people making assumptions and not recognising the limits of what they know and what they can do.

What are the common mistakes?
Not carefully demonstrating proof of concept before initiating large-scale trials; not carefully identifying the right dose before launching a phase III study. It's quite fundamental. Assumptions are being made about the activity of drugs based on uncontrolled trials. The concept of putting two drugs together and counting the number of patients with stable disease by the end of some period of time, then comparing them to historic controls and making assumptions about what that means—it's a great way to lose money.

Surely the money at stake provides a good incentive to get this right?
Drug development is like poker in many ways. In classic seven-card stud, you start with three cards, two face-down and one face up. You receive one card at a time and have to decide whether to bet or fold; and of course you never know what the next card will be. At some point you may have to decide that the hand is no good and it is time to move on.

In drug development, it is similar, in that you are taking bets on incomplete information. But companies seem to take chances without looking at the cards which are face-down. I get the feeling that a lot of them are not good poker players.

What sort of reactions do you receive when you criticise trial design?
A lot of people recognise the issues but they are not always the ones controlling oncology clinical trials infrastructure. There is a lot of rigidity within the pharmaceutical industry, the US National Cancer Institute and its Cooperative Groups. The Food and Drug Administration (FDA) is very progressive in its thinking about clinical trials but is not proactive in talking to companies about its views and doesn't proselytise. Most companies view the FDA as the enemy and don't talk to them any more than necessary.

Do you mean in terms of accepting surrogate endpoints?
There is too much talk of surrogates; people use the term a lot, but surrogate endpoints aren't surrogates unless they have been proven to correlate with real outcomes. Surrogate development is very complicated, it requires a large investment and has to start at the preclinical stage of drug development. This tends not to happen. Companies are trying to decide which drug should go into the clinic and once that decision is made, they want it there fast. But you can't effectively use a surrogate endpoint unless it has been developed from the beginning. You might need a different surrogate for each drug, or you might have to acknowledge that you don't have one, and then you'd have to develop the drug in a different way.

Historically, we could use toxicity: the optimal dose was the one that produced the most neutropenia while remaining tolerable. So the white cell count was the surrogate and you could say—if this drug is going to work it will work at this dose. But now, with oral drugs, given daily and with little toxicity, that is not where we are going.

Why is cancer different from other chronic diseases?
Because the new drugs coming on stream have changed, and created problems with old-style clinical trial design.

Where does the solution lie?
Part of it is in putting sunshine on the problem; you can't solve a problem until you have recognised you have one. We want to open people's eyes and get them out of the rigid 1970s' oncologists' way of doing things.

What are you hoping the Workshop will achieve?
It will bring together 100 to 140 leaders of thought in trial design. We will try to identify problems and propose action items. We're hoping to produce a set of recommendations—for publication—on trial design for the present and future. This problem can be solved.
Further details on the Workshop can be found at http://cdds.georgetown.edu