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Single jab for testicular cancer

A single injection of carboplatin could replace radiotherapy as a cure for a common type of testicular cancer, UK researchers say. They found that men with early stage seminoma who were given carboplatin endured fewer side effects, were able to return to their normal lives earlier, and had a marked reduction in cancer of the other testis, compared to those given standard radiotherapy.

Presenting the results at the UK's National Cancer Research Institute (NCRI) conference (Birmingham, UK, 5–8 October, 2008), Dr. Ben Mead (University of Southampton, UK) said, 'The initial results of the trial looked encouraging, but we needed to follow patients for another 4 years before we knew for sure that they had been cured. These follow up results are very reassuring and have already changed practice in Europe.

'A particular advantage with this treatment is that follow up beyond three years is not necessary.'

In the study, 573 men with early stage seminoma were given a single carboplatin injection. A further 904 received the current standard treatment of 2–3 weeks of daily radiotherapy. Of those who received the carboplatin, 5% relapsed, almost all within 3 years, and after further successful treatment, none died from the disease.

Nobel Prize for the discovery of HPV

Harald zur Hausen (Professor emeritus, German Cancer Research Centre, Heidelberg, Germany) has won the Nobel Prize in Physiology or Medicine, 2008, for his discovery of human papilloma viruses (HPV) causing cervical cancer. He won half of the prize, with the rest shared between Françoise Barré-Sinoussi (Institut Pasteur, Paris, France) and Luc Montagnier (World Foundation for AIDS Research and Prevention, Paris, France) for their discovery of the human immunodeficiency virus (HIV).

In the 1970s, Professor zur Hausen went against the prevailing view, and postulated that oncogenic HPV caused cervical cancer. He assumed that tumour cells containing an oncogenic virus would harbour viral DNA integrated into their genomes. The HPV genes promoting cell proliferation should therefore be detectable by searching tumour cells for such viral DNA.

He pursued this idea for more than 10 years by searching for different HPV types, a search made difficult by the fact that only parts of the viral DNA were integrated into the host genome. He found novel HPV-DNA in cervical cancer biopsies and discovered the tumourigenic HPV-16 type in 1983. In 1984, he cloned HPV types 16 and 18 from patients with cervical cancer.

A statement by the Nobel Assembly at the Karolinska Institutet said that Professor zur Hausen 'demonstrated novel properties of HPV that have led to an understanding of mechanisms for papilloma virus-induced carcinogenesis and the predisposing factors for viral persistence and cellular transformation. He made HPV available to the scientific community. Vaccines were ultimately developed that provide $\geqslant$ 95% protection from infection by the high risk HPV16 and 18 types. The vaccines may also reduce the need for surgery and the global burden of cervical cancer.'

Photograph by DKFZ

Professor Harald zur Hausen

On HIV, the Assembly said, 'Never before has science and medicine been so quick to discover, identify the origin and provide treatment for a new disease entity. Successful anti-retroviral therapy results in life expectancies for persons with HIV infection now reaching levels similar to those of uninfected persons.'

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Computer-aided detection of breast cancer

Single reading of a screening mammogram along with computer-aided detection (CAD) could be an alternative to double reading, UK researchers say. Use of the technology could also improve the detection rate where single reading is standard practice.

In the trial, 31,057 women undergoing routine screening by film mammography at one of 3 English centres were randomly assigned to double reading; single reading with CAD; or both (*N Eng J Med* 2008;**359**:1675–84).

The proportion of cancers detected was similar in both approaches: 199 of 227 (87.7%) for double reading, and 198 of 227 (87.2%) for single reading with CAD. Recall rates were higher in the latter group: 3.9% compared with 3.4% for double reading. There were no significant differences between the groups in the pathology of the tumours detected.

The readers in the trial all read more than 5000 mammograms per year, and were breast radiologists, breast cancer clinicians or film-reading technologists. The researchers stress that their conclusion 'applies only if the single reader with CAD has experience similar to that of a first reader in a double setting.'

Double reading is recognised as the best method for the detection of small invasive cancers, they write, but is often difficult to achieve in practice because of costs and the need for 2 readers.

'Our results suggest that single reading with CAD is an alternative to double-reading; whether to adopt this technology is a question of cost-effectiveness,' they conclude. The additional costs of CAD equipment and those associated with an increase in recall 'must be balanced against the potential savings in reader time.'

Furthermore, they state that comparisons between the performance of CAD in full-field digital mammography and in the film mammography used in this study 'will be required.'

Quality of surgery in colon cancer

The quality of surgery for colon cancer is associated with patient survival, UK researchers say. They found that improvements in the plane of dissection in stage III disease could double the number of patients who are alive at 5 years.

There is extensive evidence that the quality of surgery for rectal cancer has an impact on local disease recurrence and patient survival. The new data, from Leeds, UK, suggests for the first time that the same is true in colon cancer.

The retrospective study used a regional cancer registry to identify all patients who had resections for primary colon adenocarcinoma between January 1997 and June 2002. Digital images of the excised tissue were retrieved from computerised pathology archives, and used to grade the plane of dissection.

Of 521 cancers identified, 122 were excluded because of inadequate images. That left 399 for grading according to the plane of surgery. One in three (127) were carried out in the mesocolic plane; 95 (24%) specimens were mucularis propria, and 177 (44%) were intramesocolic plane (*Lancet Oncol* 2008;**9**:857–65).

The study found a 15% overall survival advantage at 5 years with mesocolic plane, as compared with muscularis propria plane, surgery. The finding was stronger in patients with stage III cancers (hazard ratio 0.45; p = 0.014).

The Leeds group suggest that, if the finding is confirmed by clinical trial data, 'improvement of the plane of dissection might be a new cost-effective method of decreasing morbidity and mortality in patients with colon cancer.'

'ONLY A MINORITY OF COLON CANCERS WERE TREATED WITH GOOD QUALITY RESECTION'

An editorial (*Lancet Oncol* 2008;**9**:815–7) described the findings as 'alarming'. Only a minority of colon cancers were treated with good quality resection: 'The fact that two of three resections are not done in the mesocolic plane shows the need for renewed and continuous training in colon cancer surgery, especially if the present findings are confirmed in large prospective studies,' it stated.

Vitamin C 'may antagonise cancer therapy'

Vitamin C supplements may reduce the efficacy of a range of cancer therapies, US researchers say. Laboratory work on cell lines revealed that vitamin C could reduce the impact of anti-cancer drugs, and the researchers suggest that their finding could have implications for patients on chemotherapy.

The therapeutic efficacy of doxorubicin, cisplatin, vincristine, methotrexate and imatinib were compared in leukaemia (K562) and lymphoma (RL) cell lines, with and without pre-treatment with dehydroascorbic acid (*Cancer Res* 2008; **68**(19):8301–8).

Pre-treatment with vitamin C caused a dose-dependent attenuation of cytotoxicity after treatment with all of the agents tested. It led to a 'substantial reduction' of the therapeutic efficacy of doxorubicin in mice with RL cell-derived xenogeneic tumours. Furthermore, pre-treatment caused a dose dependent decrease in apoptosis in cells treated with the anti-neoplastic agents.

Vitamin C is an antioxidant that has been hypothesized to antagonize the effects of reactive oxygen species (ROS)-generating anti-neoplastic drugs. However, this study found it had only modest effects on intracellular ROS, and the researchers suggested that its mechanism of action 'is not mediated by ROS.'

All of the neoplastics agents tested caused mitochondrial membrane depolarization that was inhibited by vitamin C and the researchers suggest that the vitamin has its impact by preserving mitochondrial membrane potential in the cell lines.

The New York group concludes: 'These results support the hypothesis that vitamin C supplementation during cancer treatment may detrimentally affect therapeutic response.'

Drug development: No risk, no fun

Strengthening the partnership between clinical researchers and the pharmaceutical industry could save time and money in early drug development, according to Professor Jaap Verweij (Erasmus University Medical Center, Rotterdam, The Netherlands).

Speaking to *EJC* in advance of his Michel Clavel lecture at the 20th EORTC-NCI-AACR symposium on Molecular Targets and Cancer Therapeutics (Geneva, Switzerland, 21–24th October, 2008), he paid tribute to the dedication on both sides of the partnership, but underlined the value of experience: 'Everyone involved in drug development is devoted and committed, but on the industry side, they are not always experts in oncology; experts in other fields of medicine may be shifted across. It's crucial that they understand that drug development is quite different in oncology from those other fields.'

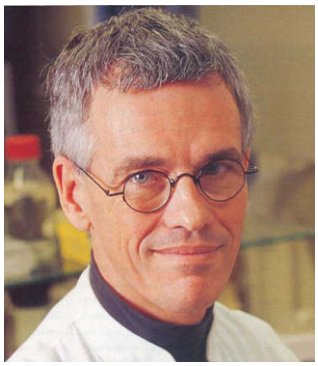
'The person in charge of the trial may not have appropriate full knowledge of the field and will need to make use of the expertise of clinical investigators. If they fully exploit this experience, it will save time in the long run,' he said.

He stressed that, despite the title of the lecture – No risk, no fun – he was not advocating taking risks with patient safety. However, there may be creative ways of speeding up these early trials.

'WE SHOULD NOT OVER ESTIMATE THE POTENTIAL OF BIOMARKERS'

Straightforward steps, such as ensuring the availability of multiple tablet strengths, and defining flexible dose escalation steps in advance, may put back the start of the study slightly, but can prevent larger delays later on.

'Cut and paste' happens too often from one protocol to the next, Professor Verweij said. 'If the principle of the protocol is the same in two trials, people say, 'Why re-invent the wheel? Just cut and paste.' For a large part, that is acceptable, but for some crucial parts it is not. Every drug is different, every situation is different, and without the right experience, cutting and pasting anything is likely to lead to problems.'



Professor Jaap Verweij

Similarly, serious consideration needs to be given to site selection. Companies may believe that adding sites to the study will speed up the trial, but researchers have found the opposite to be true (*J Clin Oncol* 2008;**26**:1926–31). Professor Verweij: 'A phase I cohort may consist of 3 patients. One enters the study and after 1–2 weeks, another two follow. If this happens at a single site, you have total control, and you know what is happening with the patient. If a patient for some reason becomes ineligible, you can quickly find another.

'With 2 sites, you have to communicate and it is slower and more complex. With 3 sites, it is even more so, and can mean that one of the sites is unable to enter a patient into the study for weeks or months. In that case, momentum is lost, other projects take priority and this study may get forgotten. Accrual will be slower. Adding sites wastes time and money and puts more patients at risk than necessary.

'It is an example of where taking a small risk – the chance the chosen site may not perform – is likely to pay dividends and speed up drug development.'

Eligibility criteria should be considered more carefully: 'Sometimes the criteria are so conservative that the eligible patient hardly ever exists,' said Professor Verweij. Even top investigators struggle to predict whether patients will survive for 90 days – which is often demanded – and where they are wrong, patients have to be replaced and delays occur. He called for the development of prognostic scores in multi-institutional, multinational trials in a large sample of patients. 'This could lead to a much more focused selection of patients for phase I studies,' he said.

Furthermore, the potential of biomarkers in phase I trials should not be over-estimated: 'Biomarkers are an example of where we have to be humble. Even fantastic fundamental research can get it wrong. If a drug works in an animal model, it tells you that it has anti-tumour activity, but not how it works. There are examples of drugs which were active, but through an unexpected mechanism. If we had selected patients on the basis of the mechanism we thought was involved, we would never have detected the drugs' activity.

'The problem is that biomarkers are only validated by survival data in phase III trials, and by definition, that's too late. I'm not saying we shouldn't use biomarkers, but we should not overestimate their potential,' said Professor Verweij.

'ADDING SITES LEADS TO SLOWER ACCRUAL'

Highly defensive legal procedures are a major cause of lost time, he said. 'The pharmaceutical industry is very defensive; their legal departments check every sentence and it takes a tremendous amount of time. We were once sent a 132 page protocol and asked for our reply in 24 hours. We sent back 5 pages of comments – in the required time – and the company then took a year to incorporate our changes. After such delays, industry may then pressurise investigators to make up lost time, and this threatens the balance in the relationship.

'Most phase I studies are now performed by the pharmaceutical industry in conjunction with clinical researchers. To be most effective in translating the commitment on both sides into results, we need a true working partnership.'

PODIUM

NOCI set to launch first major trial

Professor Martine Piccart-Gebhart is professor of oncology at Université Libre de Bruxelles, and director of medicine at Institut Jules Bordet, Brussels, Belgium. She is co-founder and chair of BIG, the Breast International Group (which brings together 44 collaborative groups from around the world) and of TRANSBIG (40 institutions in 20 countries). As EORTC President since 2006, she has spearheaded the formation of NOCI (Network of Core Institutions) in order to conduct highly technical translational research.

Why was it necessary to set up NOCI?

Most of the institutions have belonged to EORTC for many years, but we thought it was important to create a network of centres of excellence in order to be able to conduct the most challenging trials in oncology today, the clinicogenomic trials. These trials are trying to answer important questions in terms of tailoring treatment strategies or drugs to individual patients. The technology is available but these new translational trials have to be organised in the right way, so that technology is used correctly, tumour samples are collected in a standardised fashion, and so on.

I know from experience at TRANSBIG, in setting up the MINDACT trial, that as soon as you start doing research involving tumour samples and gene expression analysis, and gathering information on thousands of genes expressed by tumours, you generate problems associated with intellectual property rights. This is why I pushed for a consortium agreement between centres. The agreement must be signed by the directors of institutions and be approved by the scientists who play a key role, such as the pathologists who are responsible for specimens. We need to have them as partners, to make it work.

Under the consortium agreement, where a discovery is made in the course of a NOCI trial, part of the intellectual property rights are assigned to the individual scientist or clinician, part to their institution, and part to the EORTC. Most people accept the need for collaboration to move science on, and if a discovery is made during a collaborative trial, it is logical that something goes back to EORTC to invest in future research.

Why has it taken so long to set up the network?

It took almost two years to put the agreement together and to get signatories' comments, but now 21 centres have signed the consortium agreement. It sets the rules for performing clinical trials, addresses issues of intellectual property, access to data, and publication. It also covers the collection of samples from trials run by the network; it set rules for the collection and availability of high quality bio-samples, and the attached clinical data set.

It is a thoughtful agreement. Pathologists need to make sure that patient samples are not completely used; they are obliged to keep a tumour specimen for years in case a new test becomes available that could benefit the patient. This is not easy to put into words, but with time and much consideration, the agreement was drawn up. Now that most centres have signed the agreement, we can start running sophisticated modern trials. I am confident that many other centres will join in the near future.

We could have set up the network in a month, and embarked on the first trial, but we would have immediately run into all sorts of problems. I was responsible for saying we are not doing it in this way, even if it takes a year or two. We needed a fundamental binding agreement between our core institutions. They will be working with patients' blood, DNA, tumour samples, circulating tumour cells and so on; each trial may use 4 or 5 different technologies and involve a number of people in imaging, data analysis, making observations and so on.

How long before the first trial is set up?

We are discussing among other possibilities an innovative trial looking at circulating cancer cells in early breast cancer. It is still to be confirmed but this is a typical trial which can only happen with a high level of organisation: we will need clinicians who are enthusiastic about an interesting research question, laboratory experts who will collect the circulating tumour cells and analyse them, and so on.

The study will need a few highly motivated centres. Blood will be sent to the lab where various techniques to look at circulating tumour cells will be used and compared. I am really excited by this; we will be testing in real time whether the network really can perform this sort of work.

This study is in fact the second NOCI trial. The first looked at a new drug in 5 tumour types. A company had a drug but didn't know which tumour type to investigate it in because the pre-clinical data had not come up with clear indications. We wrote one protocol in 5 indications and used the network to establish the tumour types in which the drug showed interesting activity.

But the consortium is not really necessary for trials like this. It is intended more for studies in which we collect and analyse material, use sophisticated high throughput technology or modern

PODIUM

imaging techniques, generating amazing amounts of data which need to be analysed and used to test the hypothesis. It is for molecularly-driven studies.

The study on circulating tumour cells is exactly what we'd envisaged. It has received the green light to be developed further. We are in discussions with a pharmaceutical partner, and still have to go through the external review process – the protocol review committee has to approve it – but it's on the way. It will give us proof of principle for the consortium agreement.

What will the network mean for centres that are not included?

NOCI is not at all a 'closed' network and will work in collaboration with the well established EORTC groups. NOCI will collaborate with other EORTC centres which are active in specific disease areas. So if we run a complicated study in breast cancer, we will collaborate with centres which belong to the EORTC breast cancer group; a study on colorectal cancer will include centres belonging to the EORTC gastrointestinal tract group. But we need the expert centres to carry out the most sophisticated analysis, laboratory work or imaging.

The creation of NOCI initially caused some tension, until the centres which were not included realised that this network is complementary, not antagonistic or in competition with the EORTC groups. Everybody is talking about individualised tailored oncology but we are not there at all. If we want to get there one day, we have to admit that we need to put in a lot of effort to bring about a cultural change in the way we do research. Some trials need a very high level of expertise in imaging, pathology, surgery, and so on is not available at every centre.

These sophisticated trials will identify new drugs that have real potential within a subpopulation of patients with a disease; and this can only be concluded after extensive translational research performed by a number of highly qualified centres. But to demonstrate that the drug makes a difference, we will still need clinical trials involving large numbers of patients, and the research will then encompass NOCI EORTC plus the relevant disease-oriented group.

Are you saying that NOCI benefits the non-participating centres?

It will. The initial NOCI trials will probably include 100 to 150 patients, who are studied in exhaustive detail, and should establish whether the hypothesis is solid. This work should allow us to identify the subgroup of patients, with a particular biological profile, in whom the drug is likely to represent real progress.

But the findings from this sophisticated translational research still have to be validated in a larger study, the type of clinical trial we carry out all the time, and we will need the whole organisation to do that. The difference in future is that we will have a higher chance of matching the right subpopulation with the right drug. Another important difference is that the confirmatory trial may need fewer patients. In the circulating cancer cell trial, for example, the first step will include 135 patients, and if it goes on to the second step, we will need around 900 patients rather than, say 6,000 as we have been used to. This is an interesting new development.

A further benefit to EORTC researchers is that the NOCI trials will help build a biobank. Material that is not needed to answer the research question, or by the pathologist, will be held in a biobank. EORTC researchers – and possibly others – will be able to apply to use the material to answer research questions: the review committee and ethical committee will look at the proposal.

How many trials do you expect NOCI to run?

In March 2009, at the annual EORTC strategy meeting, an entire afternoon will be devoted to NOCI projects. From 20 proposals submitted 10 will be pre-selected by the EORTC Board for presentation. At the meeting, they will be discussed in the presence of outside experts from Europe, the US, and Canada, and afterwards the EORTC Board will select the five winning projects. We want this to be an open process and hope to generate competition between the disease-oriented groups, to prompt them to come up with interesting ideas. We hope that by the end of 2009, we will have five NOCI trials ready to go.

Anybody in the organisation is free to submit ideas and we want to encourage young researchers with brilliant ideas. We will allocate funding to these projects, though funding from elsewhere may also be necessary. The NOCI trials reflect the strong desire at EORTC to encourage innovative translational research.

All of the trials will be prospective. In the last few years, many people involved in translational research have conducted retrospective analyses, but too often as a sideline. At the end of a clinical trial they look back, see how many tumour blocks there are in the bank, and examine them to test an hypothesis. There are all sorts of problems with these retrospective studies. The only thing to come out of them is publications; they very rarely benefit patients.

Lessons learnt in clinical trials haven't quite got through in translational research. Where we have a question related to a gene or protein which we think could be important in explaining the success or failure of a drug treatment, we need to design a prospective trial in conjunction with a statistician. Translational research studies have to be statistically powered to answer question, otherwise they are useless.

The NOCI network is a major and unique opportunity to address this and carry out a new generation of trials. I'm very enthusiastic about it because this initiative clearly shows that EORTC is changing and is able to tackle the challenges of modern molecular oncology.

Helen Saul