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Chemotherapy in Rectal Cancer

Preoperative chemotherapy should be considered for patients with stage T3 or T4 rectal cancer, according to European researchers. An EORTC Radiotherapy Group Trial found that a fluorouracil/leucovorin combination significantly improved local control.

Preoperative radiotherapy is recommended for selected patients with rectal cancer. The EORTC Trial (22921) investigated whether the addition of chemotherapy would further improve outcomes.

The trial (*N Engl J Med* 2006; 355:114–23) was conducted in centres throughout Europe. It included 1011 patients with clinical stage T3 or T4 resectable rectal cancer, randomised into 4 groups. All received preoperative radiotherapy but some also received chemotherapy, either before or after surgery, or both.

The timing of chemotherapy appeared to make little difference to outcomes, and there was no evidence that giving chemotherapy both before and after surgery was beneficial. However, while adherence to preoperative chemotherapy was excellent, less than half of the patients assigned to postoperative chemotherapy received it according to protocol.

The cumulative incidence of local recurrence as a first event at 5 years was 17.1% in the preoperative radiotherapy group, compared with 8.7% in the group also receiving preoperative chemotherapy.

However, the addition of chemotherapy had no significant effect on survival. The 5-year cumulative incidence of distant metastases was about three times that of local recurrences. The researchers said this indicates that "future trials should focus on eradicating micrometastases."

They concluded that chemotherapy "provides a significant benefit with respect to local control.

"The role of postoperative chemotherapy is not yet defined and adherence to it is poor. We believe, therefore, that preoperative chemotherapy is an option worth considering for some patients."

Antifungal Prophylaxis Approved in US

Posaconazole has been approved by the US' Food and Drug Administration (FDA) for the prophylaxis of invasive aspergillus and candida infections. It can be given to severely immunocompromised or immunosuppressed patients 13 years of age and older.

Patients undergoing haematopoietic stem cell transplant or chemotherapy for haematological malignancies such as acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) who develop invasive fungal infections (IFIs) have a mortality rate of between 60–90% (*Clin Inf Dis* 2003; 36:9–15).

Manufacturer Schering-Plough says that posaconazole (Noxafil) is the first antifungal agent approved by the FDA for the prevention of IFIs caused by aspergillus. Its application for use of posaconazole in certain refractory IFIs received an approvable letter from the FDA in June 2005 and is pending review of additional data.

Posaconazole is approved in the EU and Australia for the treatment of IFIs including invasive aspergillosis and fusariosis, in adults with disease that is refractory to, or in patients intolerant of the commonly-used antifungal agents, amphotericin B and itraconazole. A new drug application for posaconazole prophylaxis is currently under review by the European Medicines Agency (EMEA).

Jury Still Out on Erythropoietin

The use of erythropoietin to treat anaemia induced by cancer treatment is to be reassessed in the UK. An appeal against National Institute for Health and Clinical Excellence (NICE) guidelines has been upheld.

NICE issued a Final Appraisal Determination (FAD) on treatment induced-anaemia – not cancer-related anaemia – in March, 2006. It stated that erythropoietin should be used only as part of ongoing or new clinical trials constructed to address the gaps in the currently available evidence. Patients who were receiving erythropoietin at the time were given the option to continue therapy.

Appeals against the FAD were submitted by Amgen, International Myeloma Foundation and Leukaemia Care (joint appellants), Janssen-Cilag Ltd, Ovacome, Roche, and the Royal College of Pathologists.

The independent appeal panel, which reported in September, 2006, upheld the appeal on the grounds that the institute failed to act fairly and in accordance with its own procedures. Several other aspects of the appeal were dismissed.

The appeal panel asked the appraisal committee to review the FAD, and to publish revised guidelines "in due course".

A spokesperson for Roche welcomed the appeal panel's findings and said: "We are looking forward to working with NICE to ensure UK patients do not have to suffer the effects of cancer treatment-related anaemia unnecessarily."

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Obesity and ovarian cancer

Obesity may lead to more aggressive types of ovarian cancer, say US researchers. They found a significant association between body mass index (BMI) and cellular characteristics of the cancer. For women with advanced disease, increasing BMI was associated with decreasing survival "in a fairly 'dose-dependent' fashion".

Researchers at Cedars-Sinai Medical Center, Los Angeles, USA reviewed data on 216 women with ovarian cancer, 35 of whom were obese and 108 of whom were of ideal weight. They found that the obese women were more likely to have mucinous and non-serous tumour types.

The study (*Cancer* 2006 DOI: 10.1002/cncr.22194) undermines suggestions that the higher mortality associated with obesity may be caused by delays in diagnosis. It "supports the hypothesis that obesity impacts ovarian cancer mortality by influencing tumour biology," the authors conclude.

Exercise 'Improves Breast Cancer Survival'

Overweight women who exercised regularly in the year before they were diagnosed with breast cancer appeared to have improved survival rates, say US researchers. Obese and overweight women who reported the highest levels of moderate or vigorous recreational physical activity had better 5-year survival patterns than other groups.

The benefit of exercise on survival was not seen in women of ideal body weight; nor among those with more remote histories of physical activity in adolescence or early adulthood.

Exercise has been shown to be a significant factor in preventing breast cancer but its role in prognosis after diagnosis remains unclear. Researchers at the University of North Carolina, USA, investigated the relationship between physical activity levels pre-diagnosis and survival among 1264 women with breast cancer (*Cancer* 2006 DOI:10.1002/cncr.22201).

They concluded: "Given that obesity is relatively well established as a poor prognostic factor in breast cancer, it is hopeful that activity may provide an opportunity to improve survival in this population."

Consensus on Adjuvant Aromatase Inhibitors

Aromatase inhibitors (AIs) are the adjuvant treatment of choice in early breast cancer, according to an expert panel. A round table session involving 24 experts from Europe, the USA, Australia, China and Brazil, concluded that AIs are superior to tamoxifen in the adjuvant endocrine treatment of postmenopausal women.

However, questions about the best way to use AIs – such as the optimal length of treatment and how a sequence of tamoxifen followed by an AI compares with AI monotherapy – "will require further data to resolve."

The International AI Expert Panel reviewed safety and efficacy data from major recent trials investigating tamoxifen and the third-generation AIs in postmenopausal women. The data reviewed came from: the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, Breast International Group (BIG) 1–98 study, National Cancer Institute of Canada MA17 trial, Intergroup Exemestane Study (IES), Italian Tamoxifen Anastrozole (ITA) trial, Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 8 and Arimidex-Nolvadex (ARNO) 95.

The consensus document (*Current Medical Research and Opinions* 2006 22:8, 1575–85) aimed to provide a "rational interpretation of the impact of these data on current practice". Consensus statements included:

- AIs are superior to tamoxifen and are therefore the treatment of choice in oestrogen receptor (ER)-positive breast cancer. In newly diagnosed postmenopausal patients, AIs are considered the preferred therapy, and patients already receiving tamoxifen should consider switching to an AI.
- As yet, there are no data from direct comparisons between a sequence of adjuvant endocrine therapy (ie tamoxifen followed by an AI) compared with 5 years of AI therapy alone.
- There may be advantages to continuing adjuvant therapy beyond 5 years.
- There are no data which confirm that there is any group of patients for whom AIs are not effective adjuvant therapy.
- The risks of tamoxifen treatment with respect to deep-vein thrombosis (DVT), stroke and endometrial cancer are unpredictable in individual patients.
- The relationship of coronary heart disease (CHD) to AI use requires further evaluation... current evidence suggests that AIs have either no or little effect on CHD and the presence of CHD should not impact on the prescribing of AIs for adjuvant use.

"Over the last 3 years there has been an influx of new information about the use of AIs in early breast cancer and while this is great news, it has created a great deal of confusion," said lead author Dr Aman Buzdar (MD Anderson Cancer Centre, Houston, Texas, USA). "We can now be confident that to provide the best care for our patients, we should be using an AI at the earliest opportunity."

Bush "thwarted new prospects for research"

President George Bush's veto of a congressional act on embryonic stem cell research has "thwarted" new prospects for advancing research, according to a US journal. The veto, on July 19, 2006, is the first he has exercised in 6 years in office. It will prevent the use of federal funding to derive embryonic stem cell lines from fertilised eggs which are stored in freezers and already tagged for destruction.

The veto "thwarted new prospects for advancing embryonic stem cell research and will result in a terrible waste: tens of thousands of fertilised eggs will be destroyed without a single one being permitted to contribute to our knowledge of cell differentiation" (*N Engl J Med* 2006; 355:12 1189–91).

The *NEJM* perspective concluded: "The delay of medical advances by theological disputes is not in the best interests of the sick and disabled."

EUROFILE

Winners and Losers in Framework 6

With the EU 7th Framework research funding programme (FP7) due to start in 2007, there has been much interest in how medical research projects have fared during the lifetime of FP6. The Framework programmes are Europe's largest publicly funded research programmes – FP6, which finishes at the end of 2006, has an overall budget of €17.5 billion – and are the EU's main instruments for the funding of collaborative research.

So how has cancer research fared? Although the individual calls for proposals under FP6 had a narrower thematic focus than those from previous Framework Programmes, the overall budget available for cancer research in FP6 was much higher than those of previous Framework Programmes. As a result, the overall number of research teams participating in cancer research in FP6 was significantly higher than in previous Framework Programmes, says the Commission.

The DG Research website (http://cordis.europa.eu/lifescihealth/cancer/cancer-pro-calls.htm) lists 65 cancer-related projects approved and funded to date under the various calls for proposals. Among these is INCA – the role of chronic infections in the development of cancer, coordinated by Professor Thomas Schulz from the University of Hanover, Germany. "When we saw the call for expressions of interest in 2002 we thought it gave us a good opportunity to try to put a consortium of tumour virologists together and to suggest to the Commission that investigating the role of viruses in cancer would be worthy of their support. We then found that other scientists were working through their national representatives to have bacterial infections included and we thought, why not? So the final project includes all infections."

''THE RATIONALE FOR THE SELECTION WAS NOT ALWAYS APPARENT''

Although Schulz is generally supportive of the role of the Commission, he would prefer less of a 'top down' approach to the selection of research topics. "In FP6, research topics were selected on the basis of a previous round of 'expressions of interest'. The rationale for this selection was, in my view, not always apparent, and I would prefer a gradual shift to a more 'bottom-up' approach, which allows groups of investigators from different countries to submit collaborative research projects on less narrowly defined research topics," he said.

The Commission is often maligned for its bureaucracy, but in reality it is not much worse than putting in a grant application under some national systems, says Schulz. "In terms of how long it took before we received the funding, it wasn't much different from the German system. The real problem is the contract negotiation process because you are dealing with many different countries with different legal systems."

Mr. Paul Affleck (University of Leeds, UK), project manager of the GenoMEL project – an investigation of familial melanoma – disagrees about time scale: "I have previously been involved in UK projects and was not used to this kind of timescale – it took many, many months before everything was finalised. And then there was the problem of different languages when dealing with so many different countries, and indeed with the Commission, given that often you are dealing with people in a language that is not their mother-tongue. But our contact in the Commission was extremely helpful and made useful suggestions about how we could improve the project. I think the DG Research scientific officers have a very tough job to do and I have a lot of sympathy for them."

What all cancer researchers would like to know, of course, is what projects stand a good chance of being selected for funding under FP7? The Commission says there are neither hidden agendas nor magic formulae: "Of course each application is different and each evaluation is different, so it's difficult to be too hard and fast. But I would certainly say that the most important criteria are scientific and technical ones, rather than 'European' ones. The scientific quality and approach of projects, together with their management, are the main reason why some applications succeed and others fail," said a source at DG Research.

''THE MOST IMPORTANT CRITERIA ARE SCIENTIFIC, RATHER THAN 'EUROPEAN' ''

Some scientists criticise the emphasis on the spread of partners which they see as necessary to a successful application. The source says this is a myth that has grown up without any foundation. "Of course, if a project came to us and it had five Italian partners, four Spanish, and three Portuguese, let's say, although such a proposal would formally comply with the minimal requirements and therefore be eligible for evaluation, it seems unlikely that the external peer reviewers would consider such a project as balanced in terms of Member State participation. The Commission encourages the inclusion of new Member States strongly, but there is no formal requirement to include them. Indeed, to do so just for the sake of it might well do more harm than good."

FP7 will have strong elements of continuity, says the Commission. "In addition to the types of collaborative projects already known from FP6, there will be major novelties of high relevance for cancer research, such as the availability of funding managed by the European Research Council for individual research teams performing basic research.

"Of course, budgets are not unlimited, and people will have to try to find a good balance between being scientifically ambitious and financially realistic, but this is not impossible, as the FP6 projects have already shown," the Commission source says.

Mary Rice
Brussels

Tobacco control – mixing health and advocacy

Scientists are beginning to practice what they preach. The US National Cancer Institute (NCI) announced in July, 2006 that its meetings will be held only in cities and towns that have adopted comprehensive smoke-free policies. The move comes in the wake of a new report from the US Surgeon General, saying that more than 126 million Americans are exposed to second-hand smoke. The NCI directive aims to raise public awareness about the importance of protecting adults and children from environmental tobacco smoke.

Regulating environmental tobacco smoke is mandatory for countries signing the Framework Convention on Tobacco Control (FCTC). Although the USA has not yet ratified the treaty, FCTC is fast gaining acceptance as the first such pact in public health. 168 countries have signed the treaty, of which 137 (about 80% of the world's population) have ratified it. "It is undoubtedly one of the most rapidly embraced UN treaties of all times", says Yumiko Mochizuki-Kobayashi (Tobacco Free Initiative [TFI], World Health Organization [WHO], Geneva, Switzerland).

All countries ratifying the treaty are legally bound to ban all forms of tobacco advertising, enforce pictorial health warnings on tobacco products, and regulate contents of tobacco products by fixed deadlines. The USA's delay in ratification has been criticised widely. "The US failure to ratify the convention undermines the treaty's effectiveness and will hurt public health," comments Henry A Waxman, member of the US House of Representatives.

"Every country is a different case", comments Mochizuki-Kobayashi. "In some countries, the influence of the tobacco industry is very strong and the resources for tobacco control are very limited. In such situations, it is very difficult to be able to put in place mechanisms that would achieve a reduction of tobacco consumption."

The implementation of FCTC seems to be difficult for many reasons. Clauses of the pact emphasise reduction of both demand and supply. To fulfil their obligations under the treaty, countries must develop national tobacco-control policies, laws required to implement them, and mechanisms to monitor progress. The first stage in this process is the availability of data for different aspects of tobacco control.

However, many countries have no data for tobacco control. By the end of 2006, WHO plans to publish a Global Tobacco Control Report that will act as a reference for global surveillance for tobacco control and provide research for policymaking and surveillance at the country level. It will feature country-wide data for key indicators such as exposure, tobacco use, and second-hand smoke exposure, as well as data for morbidity and mortality due to tobacco, economic effects, legislation, control measures, and industry data. Existing databases such as the Global Information System on Tobacco Control and the Global Tobacco Surveillance System will be consolidated in this report.

"It is likely this report will expose the paucity of data in many countries, lending weight to the need for greater investment in infrastructure for surveillance," says Gemma Vestal, legal officer and scientist at TFI. "It will help build technical infrastructure at a national level to enable contracting parties to report on their implementation of the treaty."

"MONEY ALWAYS UNDERLIES THE POLITICS OF TOBACCO CONTROL"

Enforcement of FCTC clauses will need monitoring to measure its effectiveness. Members have agreed on a graduated reporting system, to enable them to "learn from each others' experience in implementation". Many commentators have thought this reporting system very weak. "Governments have the responsibility to implement and enforce effective, evidence-based life-saving policies, and not merely do the minimum under their FCTC obligations," points out Laurent Huber (Framework Convention Alliance [FCA], Geneva, Switzerland).

For example, the Indian health ministry has banned advertising of all tobacco products and is pursuing a ban on smoking scenes in Bollywood films and television serials. But the advertising expenditure of tobacco companies has gone up. "The exception granted for point of sale advertising has made the ban much less effective. Every street has many kiosks selling tobacco products and they have all been converted into points of billboard advertising," explains Prakash C Gupta (Healis-Sekhsaria Institute of Public Health, Mumbai, India).

Although FCTC applies to tobacco control at the country level, the problem is actually across borders, because of growing trade liberalisation, direct foreign investment, internet marketing and sales, and trade in contraband and counterfeit cigarettes. Some aspects of FCTC directly contravene non-tariff provisions of free-trade agreements.

Robert Weissman (Essential Action, WA, USA) says, "In Canada, Brazil, Thailand and elsewhere, tobacco companies have argued that large health warnings, plain packaging rules, and bans on the use of misleading descriptors (eg, light, mild, and low) violate their trademark rights under trade agreements, while ingredient disclosure rules violate their trade secret rights. At the 13th World Conference on Tobacco or Health (Washington, DC, USA; July 12–15, 2006), Weissman suggested such conflicts can be avoided if tobacco was excluded from international trade agreements, just as military products and fissionable materials are not covered under WTO agreements.

The FCTC has provided a framework for governments, voluntary groups, and anti-tobacco advocates to work towards stringent rules and regulations to control the spread of the tobacco epidemic. It has provided an opportunity and time frame to address previously neglected issues. Tobacco control is not merely a health or science issue, but a political, economic, and business one. As Patricia Lambert, legal adviser to the health minister of South Africa, concluded at the Tobacco Conference: "Tobacco control, and particularly the implementation of the treaty, has an unquestionable political dimension, and underlying the politics of tobacco control there is always the question of money".

Dinesh C Sharma

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PODIUM

Other Ways in Palliative Care

Professor Marie Fallon

Professor Marie Fallon (St Columba's Hospice Chair of Palliative Medicine, University of Edinburgh, UK) is a consultant in palliative medicine who specialises in the management of complex symptom/psychological problems which exist in 20% of patients with cancer. Her research programme focuses on bone pain, neuropathic pain and barriers to cancer pain control. She is fully trained in medical acupuncture.

Do you use acupuncture in your normal practice?
Very much so; I use it in an integrated way alongside traditional orthodox medicine in both outpatients and inpatients. I don't have a separate acupuncture clinic.

How does it compare with other complementary and alternative medicines (CAM)?
It is a complementary therapy – like aromatherapy massage, reflexology, and hypnotherapy – and is used in conjunction with orthodox medicine. Alternative therapies imply that they are used instead of orthodox treatment. They include crystal therapies, iridology, radionics, ayervedic medicine; and some have as a prerequisite that orthodox medicines are put to one side.

How effective are CAM therapies?
The evidence base is poor, because there is little appropriate research of sound methodology. Designing trials is a challenge while the traditional randomised controlled trial is the gold standard. Complementary therapies are complex interventions and non-specific effects – such as the time spent explaining it, and the therapeutic touch involved – may be integral to the therapy, increasing relaxation, confidence and trust. In traditional medicine these would be considered confounding factors.

There is a small but growing evidence base for acupuncture; there have been randomised controlled trials using dummy needles. At an anecdotal level, acupuncture can work exceedingly well for some patients and in some indications: musculoskeletal spasm; menopausal symptoms associated with breast cancer treatment; pain associated with mastectomy and thoracotomy scars; general anxiety; chemotherapy-induced nausea and vomiting.

How far might good outcomes be explained by the placebo effect?
We are interested in making objective assessments of nerve pain. We test areas round the painful scars in the skin before and after acupuncture using quantitative sensory testing. In many patients who get a good response, there is an objective difference.

Our translational research programme uses animal models of cancer pain. Recently, we found that a compound which helps nerve pain dramatically in the laboratory is the base of some aromatherapy oils. It's fascinating.

How important is it for cancer patients to feel in control of their treatment?
Having CAM can empower patients, can increase their feeling of control and help them towards better psychological equilibrium and emotional well being. Having a life threatening illness, particularly one not responding to treatment, robs most people of any feeling of control. Using CAM is a practical way of restoring some control.

Can alternative therapies be harmful?
Most probably aren't. Patients often resort to alternative therapies at the end, when they feel that orthodox medicine has nothing left. I wouldn't expect crystal therapy or ayervedic medicine to be harmful. Some strict dietary regimens, though, deprive patients of balanced nutrition in the hope of starving the tumour. These clearly can be harmful; the patient can become weak, fatigued and fragile. St John's Wort, the herbal remedy for depression, can interact with warfarin, a medication prescribed by oncologists. All therapies need evaluation in the same way as any medicine, and clinicians should encourage more openness in consultations to get a better feel for what therapies their patients are receiving.

Are patients too nervous to discuss it?
Patients are keen to receive the optimum treatment that orthodox medicine has to offer and don't want to divert attention from this. Some actively hide the fact that they are seeking alternative treatments as they don't want the clinician to feel they don't have confidence in what the clinic is providing, but many just feel inhibited about discussing it. Studies have shown that a lot of patients are using CAM treatments but this doesn't come across in standard consultations.

What are the cost implications of providing CAM within the NHS?
There obviously is a cost involved, but for example, patients with a painful mastectomy scar, who have failed drug treatment, often have associated psychological morbidity, resulting in more visits to the GP and hospital. A helpful treatment could actually save money and this economic equipoise needs to be included in any research.

Integrating complementary treatments alongside orthodox medicine reduces cost issues. Using acupuncture, my clinics run just as efficiently: I can put needles in and leave the patient with a nurse for 20 minutes, or use the time to evaluate other problems. It does not add a large burden to my workload.

What needs to happen for the integrated approach to become widespread?
Once there is a critical mass of practitioners practicing an integrated approach, we could set up proper clinical studies, which would help make the case to providers. Integration would increase acceptability of the whole range of CAM, and would allow patients to be more relaxed about discussing them with clinicians.