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Radiotherapy 'as good as surgery' for bladder cancer

Radiotherapy may be as effective as surgery in treating invasive bladder cancer, according to British researchers. They found that survival rates were similar, whether patients were treated with radiotherapy or radical cystectomy.

Radiotherapy could therefore become the treatment of choice, the researchers suggest, because of the potentially severe impact on quality of life associated with surgery.

Cancer Research UK scientists examined the medical records of 169 patients treated for invasive balder cancer between 1996 and 2000 (*International Journal of Radiation Oncology Biology Physics doi:10.1016/j.ijrobp.2007.06.030*). 97 were treated with radiotherapy, 89 underwent surgery.

There were no significant differences in survival at either 5 or 8 years. This was despite the radiotherapy group being older, with an average age of 75.3 years compared with an average of 68.2 for the surgery group.

Surgical removal of the whole bladder along with the prostate in men and, in some cases, the uterus and ovaries in women, is the current 'gold standard' treatment for invasive bladder cancer.

Lead author Dr Anne Kiltie (University of Leeds, UK) said, 'Although radiotherapy carries its own long term side effects, the interesting finding in our study was that the older, less fit patients did as well as the younger, fitter patients who had surgery to treat their disease.

'Since bladder cancer is a disease of older people, radiotherapy will play an increasingly important role as the population ages, and this study encourages us to believe that such elderly patients will not be disadvantaged by having an alternative curative treatment to surgery.'

'Small benefit' from chemotherapy in colorectal cancer

Patients with colorectal cancer at low risk of recurrence may benefit from adjuvant chemotherapy, researchers say. Among patients with stage II disease, they found a 'small but definite benefit' from chemotherapy with fluorouracil and folinic acid.

The QUASAR trial included 3239 patients who had undergone apparently curative resections of colon or rectal cancer. They were enrolled between 1994 and 2003 from 150 centres in 19 countries. Patients were randomly assigned to receive chemotherapy with fluorouracil and folinic acid, or to observation.

After a median follow-up of 5.5 years, there were 311 deaths in the chemotherapy group versus 370 in the observation group; the relative risk of death from any cause with chemotherapy versus observation alone was 0.82 (*Lancet 2007;370:2020–29*).

'The small but definite benefit from well-tolerated chemotherapy found here should provide helpful new information for discussions between patients and physicians on the potential benefits of chemotherapy and allow the patient to make a better informed decision to proceed with, or refuse, the offer of chemotherapy,' the authors conclude.

An accompanying editorial (*Lancet 2007;370:1980–1*) points out that most patients with resected stage II colorectal cancer have a good prognosis: 'The continued development of genomic platforms might assist in identifying new prognostic/predictive molecular markers and signatures which, with ongoing randomised trials of novel adjuvant therapies and assessment of shorter duration of therapy, will help to refine the treatment of stage II and III colorectal cancer', it concludes.

New indication for bevacizumab

Bevacizumab (Avastin) has received European approval for the first-line treatment of patients with advanced renal cell cancer (RCC), when used in combination with interferon, the current standard of care.

The approval was based on data from the phase III Avoren trial, which included 649 patients with advanced RCC. They were randomised to receive standard interferon α-2a, with or without bevacizumab. Those in the bevacizumab group had progression free survival of 10.2 months (compared to 5.4 months among those receiving the interferon alone). Data on overall survival are still pending.

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Pharmaceutical downsizing and oncology drug development

In mid December, 2007, Novartis became the latest pharmaceutical giant to announce major financial cutbacks. More than 2500 jobs will be cut in the next 2 years in Europe, in addition to 1260 redundancies in the company's US-based sales and marketing operation. Bristol Myers Squibb, Merck, and Pfizer are also downsizing, with Pfizer cutting a massive 10 000 jobs. 'The pharmaceutical industry has regularly earned profits at a rate two to three times higher than most other global businesses. It is, therefore, major news when it seems to be falling on hard times', says Howard Brody (University of Texas Medical Branch, Galveston, TX, USA).

Competition from generic drugs, patent expiration, and high development costs are all cited as contributory factors. Brody points out that, during the 1990s, the global pharmaceutical industry con-centrated its drug development efforts along two lines: mechanised, high-throughput screening

'PARADOXICALLY, THE CUTS MAY IMPROVE INTERACTIONS WITH ACADEMIA'

and the pharmaceutical prospects expected to emerge from the human genome project. 'It now appears that both these gambles failed. Assembly-line screening methods may have done more to depress morale among company scientists than to find useful, new drugs and, although the genome may produce many novel drugs, it will not be anytime soon', says Brody.

Nevertheless, the current research pipeline in oncology medicines is very healthy, according to Richard Ley (Association of British Pharmaceutical Industry, London, UK). 'Some 300 medicines that have a UK input into their development are currently at various stages from preclinical through to pre-registration. This is 11% of the global total of about 2800 such medicines', he reports. Will the current heavy financial cutbacks cause this activity to falter? 'Paradoxically, these cuts may result in companies being leaner and fitter with more effective interactions with academia and [small biotechnology companies]', says John Caldwell, (University of Liverpool, UK). These organisations tend to be more inventive and are increasingly seen as the best way to address new targets, many of which now emerge from patient-focused translational research, he predicts.

Herbie Newell (Cancer Research UK) agrees, 'I am extremely confident that there will continue to be significant activity in the field of oncology drug development'. Newell explains that unmet clinical need and commercial influence from the pharmaceutical industry are still a major force for oncology drug development, but that scientific influences are coming forward to encourage collaboration. 'In the future, predictive, pharma-cological, and surrogate biomarkers will be used to identify drug candidates that should be less likely to falter in late-stage clinical trials', he says. Caldwell also believes that 'prizes in the next few years will go to those with access to patients and patient-derived material in biobanks as well as biomarker-based tools for the staging of disease and the rapid determination of efficacy. Interestingly, this is exactly the path along which research in the UK National Health Service is currently being driven and one hopes that this will indeed be successful', he adds.

Cost-effectiveness should increase through the adoption of such a strategy, but not all cost issues will be resolved easily. 'Some promising drugs are shelved because total sales fall short of initial predictions', says Brody. Eric Nadler (Baylor University Medical Center, Dallas, TX, USA) says that massive profits have been realised as therapeutic drugs broaden beyond their initial indication. Nadler cites Genentech's Avastin (bevacizumab) as an example—its original pricing was based on its indication in metastatic colon cancer. As its market increased to include metastatic non-small-cell lung cancer, its pricing structure remained unchanged. 'Future indications could include other cancers and it will be interesting to see if its pricing schema changes at these future points', comments Nadler.

'SOME PROMISING DRUGS ARE SHELVED BECAUSE SALES FALL SHORT OF PREDICTIONS'

Ley says that pricing and cost effectiveness are big issues in the UK: 'Many new oncology drugs are being turned down on cost-effectiveness grounds by the National Institute for Health and Clinical Excellence and are, therefore, unlikely to benefit the patient', he says. In particular, there is great difficulty in showing the cost-effective benefit of oncology medicines at launch, since clinical trials are, by necessity, carried out in small numbers of patients, who are often in terminal stages of the disease and taking other medicines. 'However exciting new collaborative development may be, this is certainly a strong disincentive to companies to invest the 10–12 years and £500 million that is the average cost of bringing a new medicine to market', he says.

Kathryn Senior

*This story originally appeared in Lancet Oncol 2008;***9**:11.

'Inaccurate' breast cancer websites

One in 20 breast cancer web pages contains inaccurate information, US researchers say. Websites devoted to complementary or alternative medicine were especially likely to carry false information.

Researchers used 5 popular search engines to identify webpages that consumers are likely to use when searching for information on breast cancer. They evaluated a total of 343 separate web pages, and reviewed the accuracy of each with respect to breast cancer guidelines.

They found 41 false or misleading statements on 18 of the webpages (5.2%). Pages containing information on complementary and alternative medicine were 15.6 times more likely to contain inaccuracies than pages without this information. No quality criteria, or website characteristic, singly or in combination, reliably identified inaccurate information (*Cancer 2008 doi: 10.1002/cncr.23308*).

EUROFILE

Research networks look for longer life

The Networks of Excellence established under Framework 6 are starting to think about their future. The Commission's intention in launching the scheme was that the networks should become financially independent after their initial injection of EU funds, on average lasting 4–5 years. But as the oldest networks approach the end of their funding, concerns are growing that this move to independence will not be easy.

This is a problem because no provision has been made for continued support under Framework 7. A campaign is now underway among the networks to persuade the Commission that something needs to be done to help them.

Networks of Excellence (NoEs) were set up to tackle fragmentation in European research, bringing together leading academic research groups and industrial scientists to pursue high priority projects. The most important aim was to achieve an integration of their activities, allowing closer collaboration on research and training, and more engagement with the public through dissemination activities.

'THERE IS NO ALTERNATIVE TO EU FUNDING'

Around 170 NoEs were funded under Framework 6, including several that address topics in cancer research. Many of these cancer NoEs emerged from existing collaborations, and despite the demands of creating such large networks the funding is extremely attractive.

'Even with all the challenges and the problems, where else can you get such a large sum of funding to get on with your work, and to do all those things that you don't usually have the staff or the money to do?' asks Paul Affleck of St James' University Hospital, Leeds. He is project manager of an NoE set up by the Melanoma Genetics Consortium, building on its research into the genetics of familial melanoma. It has 21 partners in 13 countries.

NoEs have hit a variety of problems in achieving financial sustainability. Some argue that they need more time to demonstrate their effectiveness to future investors, whether in the public or the private sectors. This is certainly an issue in cancer research where 4–5 years is rarely sufficient to complete a clinical trial or epidemiological study. 'Once you do start to produce those results then people can see the benefit and you might have more luck finding funds to continue,' says Affleck.

But a more serious complaint among the cancer NoEs is that there is no alternative to EU funding for the international component of their work.

'Every country has its grant or funding system, but most of those funds are for national projects,' observes Fatima Cardoso, of the Jules Bordet Institute, Brussels. 'Even the cancer leagues and cancer foundations normally want to use the money for national projects. They don't like the money to go out of the country.'

She is joint coordinator of TransBIG, an NoE with 39 partners in 21 countries, created by the Breast International Group to promote translational research linked to its clinical trials. It is the multinational aspect of clinical trials that makes it so hard to find support. 'For the time being the European Commission is the only central body in Europe that can provide this funding for multinational projects,' she says.

Joakim Dillner, of Lund University agrees. He coordinates the CCPRB NoE, which is investigating cancer control using population-based registries and biobanks, with 18 partners in nine countries. 'I really don't understand how you are supposed to obtain funding for European-wide scientific collaboration from a source other than the European Union,' he says. 'We at least have found no academic or commercial source that is willing to fund a network.'

It's a concern shared by Paul Affleck. 'Part of the problem is finding funds for things like administrative support, database support and dissemination activities,' he says. 'We now have a very large database, but to keep that up to date and to keep the software up to date all requires time and effort, and somebody to do it.'

Sometimes an NoE's research may make industrial support unlikely. The trial being carried out by TransBIG, for example, seeks to identify patients who will and will not benefit from chemotherapy. 'That is not necessarily going to interest the pharmaceutical industry,' says Cardoso.

There is also a concern that while drug companies may sponsor projects with an NoE they will not be prepared to pay to maintain the network. However, Jean-Yves Blay at the University Claude Bernard Lyon 1 is optimistic about possible industry partnerships. He is coordinator of the Conticanet NoE, which brings together researchers working on connective tissue cancers, such as sarcomas, aggressive fibromatosis and hamartomas. It has 19 partners in nine countries.

'We are in the process of building something which is going to be extremely important for companies developing drugs in this area,' he explains. Conticanet started to think about how this industry link was to be achieved early on. 'Our goal is to create a foundation or an administrative structure that will enable us to collect funds from various sources and to continue to work together beyond the first five years.'

'OUR NETWORK WILL BE EXTREMELY IMPORTANT FOR COMPANIES'

The Commission appreciates the problems faced by the networks, and has set up a group of external experts to reflect on the future of the NoEs. This is due to make its first report by the middle of 2008. The cancer networks should at least get a sympathetic hearing, since one of the four academics on the group is Toivo Maimets, a specialist in tumorigenesis who heads Tartu University's Institute of Molecular and Cell Biology.

Ian Mundell
Brussels

49th Annual Meeting of American Society of Haematology Atlanta, Georgia, 8–11 December, 2007

Dasatinib after imatinib in CML

Continued efficacy for dasatinib (Sprycel) in chronic myeloid leukaemia (CML) was demonstrated in the 2-year updated results of the START programme, delegates heard. Hagop Kantarjian (MD Andersen Cancer Center, Houston, Texas, USA) said the results were reassuring: 'It's changing the treatment paradigm in that people who've failed imatinib (Glivec) should not now consider transplantation unless they've also failed a second generation TKI,' he said.

In the stage II START C trial (*Abstract* # 734), 387 chronic phase CML patients with documented resistance (n=288) or intolerance (n=99) to imatinib were switched to 70 mg dasatinib twice daily.

At a median follow-up of 24 months, progression free survival was 80% (compared with 91% at 1 year), and overall survival was 94% (compared with 97% at 1 year). Principal investigator Richard Stone (Dana Farber Cancer Institute, Boston, Massachusetts, USA), said the results were remarkably stable. Of patients who achieved a major cytogenetic response at one year, 88% held that response at the 2-year mark. 'This is an extraordinary achievement in patients who initially had a poor prognosis after failing imatinib treatment,' he said.

Kantarjian presented 2-year data from a second study, START R (*Abstract* # 736) which showed that switching to dasatinib produced better patient outcomes than raising the dose of imatinib in patients experiencing previous imatinib resistance.

The phase II study randomised 150 patients with chronic phase CML resistant to imatinib 400-600 mg/d to dasatinib 70 mg BID (n=101) or imatinib 800 mg/d (n=49). The updated 2 year results show progression free survival was 86% for dasatinib versus 65% for imatinib (P=0.0012).

Janet Fricker

BEACOPP in Hodgkin's lymphoma

NEW data supports the use of escalated BEACOPP as first-line therapy in advanced-stage Hodgkin's lymphoma, researchers say.

BEACOPP is a novel chemotherapy regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone. The phase III trial (*Abstract* # 211) included 1,196 advanced-stage Hodgkin's lymphoma patients randomised to receive either a standard or escalated dose of BEACOPP, or standard chemotherapy (COPP – cyclophosphamide, vincristine, procarbazine and prednisone – alternating with ABVD – doxorubicin, bleomycin, vinblastine and dacarbazine).

Overall survival rates at 10 years were: standard of care (75%), standard-dose BEACOPP (80%) and escalated-dose BEACOPP (86%). Dr Volker Diehl (University of Cologne, Germany) said: 'These results now challenge ABVD as the standard of care for this patient population.'

Rhonda Siddall

'Less is more' with dexamethasone

Low dose dexamethasone confers a survival advantage in multiple myeloma, compared with a high dose of the same drug, researchers announced.

A phase III study by the Eastern Cooperative Oncology Group (ECOG) compared different doses of dexamethasone in patients with newly diagnosed disease. (*Abstract* # 74) A survival advantage was associated with the lower dose. 'The study shows that use of high dose dexamethasone needs to be completely re-evaluated in multiple myeloma,' said principal investigator S Vincent Rajkumar (Mayo Clinic, Rochester, Minnesota, USA).

The phase III study included 445 newly-diagnosed patients randomised to receive either high or low dose dexamethasone in combination with oral lenalidomide (Revlimid). Overall survival at 1 year was 96% with low dose compared to 88% with high dose (p=0.003). Overall survival at 2 years was 87% with low dose compared to 75% with high dose (p=0.009).

Only 10 of the extra deaths could be attributed to toxicity, the remainder occurred as a result of progressive disease. Patients on the lower dose had reduced side effects, stayed on the drug longer, and had significant survival benefits,' researchers said.

Janet Fricker

Consolidation in follicular lymphoma

A single infusion of a radioimmuno therapy agent given to patients with advanced follicular lymphoma who had only partially responded to induction therapy brought three-quarters into complete remission.

Investigator Dr Franck Morschhauser (Centre Hospitalier Regional Universitaire de Lille, France) told EJC: 'This conversion rate from partial to complete response is the best ever achieved by a consolidation treatment in this area of cancer therapy.'

The international randomised phase III First-line Indolent Trial (FIT) trial included patients who had responded to first-line induction therapy (chemotherapy or immunochemotherapy). Half (n=208) received consolidation with a single dose of [^{90}-Y]-ibritumomab tiuxetan (a combination of an anti-CD20 monoclonal antibody and a radioisotope), the control group (n=206) received no further treatment.

The overall median progression-free survival (PFS) was 37 months in the consolidation group compared to 13.5 months among controls. For those in-partial remission, median PFS was 29.7 months versus 6.3 months (p<0.0001). (*Abstract* # 643).

Rhonda Siddall

Janet Fricker was sponsored by Bristol-Myers Squibb; Rhonda Siddall by Bayer Schering Pharma.

PODIUM

Keep taking the tablets!

Dr Ron Mathijssen (Erasmus Medical Center, Rotterdam, the Netherlands) is completing his oncology training, having previously studied the pharmacokinetics and pharmacogenetics of irinotecan for his PhD. He is the corresponding author of an EJC paper, 'Lifestyle habits as a contributor to anti-cancer treatment failure' (Eur J Cancer 2008;44(3): 374–382), which discussed – among other subjects – patients' non-adherence to anti-cancer treatment regimens.

What do you mean by non-adherence?

Adherence is the extent to which a patient's behaviour corresponds to that agreed with the healthcare professional. Non-adherence can mean that the patient is not taking the prescribed medicine but it can also mean that they are taking alternative or complementary medicines alongside it, or are ignoring other parts of advice from the healthcare provider. The definition is wide and it is difficult to say at what point the patient is not adhering.

It has been traditionally assumed that non-adherence was not a problem with cancer treatments. Was this a false assumption?

The problem may be more widespread in other medical specialties, but it is serious in oncology. Adherence rates vary between 20% and 100%. The drugs we use have a narrow therapeutic range and are only active if they are given at the recommended dose. If a patient on an oral anti-cancer drug takes only half the dose recommended, we know it will not work. In other areas of medicine – such as statins for high cholesterol levels – it is probably less serious if people take less of their medicine.

Is non-adherence an increasing problem?

Probably. Patients' attitudes to doctors are changing, they are more likely to question the advice they receive and this probably leads to more non-adherence.

We are also increasingly using oral drugs. Intravenous therapies are given in hospital and we know that the correct dose has been given. Sometimes when patients are at home, they take much less of the drugs.

Is it a problem in the evaluation of drugs?

New (oral) drugs are being studied in phase I–IV trials. Patients in trials are probably more compliant than those taking medicines in a regular home setting. That's only an assumption but patients in clinical trials are followed up more closely and have better social support from the pharmacist and the family doctor during the study period than would be usual afterwards, once the drug has been registered.

Why don't patients adhere to advice?

It may be an active decision, or carelessness. Some believe that they are better able (than the doctor) to listen to their body and won't take pills if they don't feel like it; if they are nauseous, for example. But non-adherence also occurs when patients don't understand a complex regimen, with too many pills each day. Difficult schemes may lead to patients taking more or less than is required.

Is it a hidden problem?

Patients may believe that it has nothing to do with the doctor, that it's their decision whether or not to be treated. Patients may also feel ashamed that they aren't taking pills and be reluctant to admit it. Age, attitude, ethnicity and socio-economic class all play a role. Adolescents for example tend not to adhere because they are in a phase of life where they don't want to follow strict rules.

Does educational level make a difference?

Yes, in that it is easier to explain to an educated person what the disease involves and why it's necessary to take pills, especially in the adjuvant setting. But educated people tend to take alternative medicines and do not adhere in that way. They make up their own rules for becoming healthy which may put them in danger of non-adherence.

How widespread is non-adherence?

One study found that patients taking adjuvant tamoxifen were only 50% adherent in the 4th year of therapy (*J Clin Oncol 2003*;**21**:602–6). We need to recognise this as a major problem. Use of alternative medicines can be dangerous. We found that patients on irinotecan who were also taking St John's Wort had a 42% reduction in levels of the active drug. That's an enormous drop. We shouldn't assume that patients are adherent. If a drug isn't working, we should consider non-adherence as a possible explanation.

How should clinicians approach the subject?

Asking patients if pill-taking is difficult, or about their expectations of therapy, may reveal non-adherence. A direct question - do you take your pills in the right way? - will seem confrontational. But the subject needs to be explored with patients; every one could be non-adherent in future. This problem is set to get worse as we use more oral drugs, as patients have shorter periods in hospital and less involvement with oncologists. Clinicians need to be aware of the possibility and look out for it. Most cases of non-adherence are not recognised.