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The need for cardio-oncology

A new generation of cardio-oncologists is needed to overcome communication gaps between cardiologists and oncologists, according to Italian researchers. 'There is a need for cooperation between these two areas and for the development of a novel discipline, which could be termed cardio-oncology or onco-cardiology,' they write (*doi:10.1093/jnci/djp440*). 'Cardiotoxicity is becoming one of the most important complications of cancer chemotherapy and, sometimes, of cancer chemoprevention.'

In an aging population, it is increasingly probable that a patient may have both cancer and cardiovascular disease. Combination therapy often amplifies cardiotoxicity, and radiotherapy can cause heart problems, particularly when combined with chemotherapy. But despite a growing number of clinical trials into the long-term side effects of anticancer therapy 'a clear understanding of what cardiotoxicity is and how anticancer therapy stresses the cardiovascular system is lacking,' they write.

One key strategy will be to identify patients at higher risk, but 'current screening methods are cumbersome and lack sufficient predictive power.' The discovery of new biomarkers to identify high risk patients 'is a high priority.'

The authors, led by Dr Adriana Albini (Research Institute MultiMedica, Milan, Italy) call for guidelines for cancer treatment that take cardiologic conditions into account, and for the identification of new compounds such as antioxidants that can prevent cardiotoxicity. Furthermore, they say, 'assessment of cardiotoxicity should become part of phase I trials to develop agents with less risk.'

The approach of cardiologists to the definition of disease is quite different from that of the oncologist, and there is a risk that many concepts and observations may be 'lost in translation', the researchers write. Cardio-oncologists could overcome such communication gaps.

'Today's oncologists must be fully aware of cardiovascular risks to avoid or prevent adverse cardiovascular effects, and cardiologists must now be ready to assist oncologists by performing evaluations relevant to the choice of therapy.'

Cardiac outcomes in survivors of childhood cancers

Adult survivors of childhood cancer are at 'substantial' risk of cardiovascular disease as late as 30 years after their cancer therapy, US researchers say. The risk of complications – heart failure, myocardial infarction, pericardial disease and valvular abnormalities – was apparent at lower exposures to anthracyclines and radiation therapy than previously thought.

The researchers identified 14,358 adults diagnosed with cancer before the age of 21 between 1970 and 1986. The control group was comprised of 3899 siblings.

The retrospective cohort study relied on participants or their parents to complete a questionnaire. It found that the cancer survivors had a five or six fold increase in their risk of various cardiac outcomes compared to their siblings: risk of congestive heart failure was increased (hazard ratio, HR = 5.9), myocardial infarction (HR = 5.0), pericardial disease (HR = 6.3), and valvular abnormalities (HR = 4.8).

Exposure to 250 mg/m^2 or more of anthracyclines increased the relative hazard of congestive heart failure, pericardial disease and valvular abnormalities by 2 to 5 times compared with survivors not exposed to these drugs. Cardiac radiation exposure of 1500 centigray or more increased the relative hazard of the four complications 2- to 6-fold compared to non-irradiated survivors. The cumulative incidence of adverse cardiac outcomes continued to increase up to 30 years after the diagnosis of cancer (*doi: 10.1136/bmj.b4606*).

'Young adults who survive childhood or adolescent cancer are clearly at risk for early cardiac morbidity and mortality not typically recognised within this age group,' the researchers conclude.

An accompanying editorial (*BMJ 2009; 339:b4691*) suggests that, with rising numbers of adult survivors, a cost effective approach may be a network of specialists that collaborate across age boundaries to optimise care pathways for patients with complex problems.

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Late diagnosis in England

Later diagnosis in England compared with other countries in Northern and Western Europe has been a major factor in the poorer survival rates, according to the National Cancer Director, Professor Sir Mike Richards.

In *Cancer Reform Strategy: Achieving local implementation – 2nd annual report*, Professor Richards notes that cancer mortality has fallen by 19.3% among people under 75 from the 1995–97 period to 2006–08. 'We are well on track to achieve the target of a 20% reduction by 2010', he writes in an introductory letter.

He lists progress in specific areas such as vaccination against the human papilloma virus among teenage girls, and roll-out of bowel cancer screening in the 60–69 year age group. But he also highlights the variation in key quality indicators according to the primary care trust (PCT) responsible.

In comparison with other countries, he states that 'significant challenges' remain in the stage of diagnosis of cancer in England. 'Patients in this country are diagnosed later and with more advanced disease than elsewhere in Europe. Addressing this problem could save thousands of lives.'

One-year survival data are used as a proxy for late diagnosis. In breast cancer, one year survival in England was 94.9% overall, with a range of 89.3% to 99% according to PCT. The international good practice benchmark is 97%. In colorectal cancer, one year survival was 70.7% overall (range: 57.9% – 80%); the international benchmark is 79%. In lung cancer, one year survival was 28.1% (range: 15.4% – 43.7%). Only one PCT matched the international benchmark of 37% or higher.

Priorities for 2010 include raising awareness and promoting early diagnosis; improving access to diagnostic tests for GPs; continuing work on comparisons of the use of drugs in different countries; reduction in unnecessary inpatient bed usage.

Obesity 'could wipe out benefits of smoking cessation'

The negative impact of increasing rates of obesity will outweigh the benefits from continued reductions in smoking, US researchers predict. 'The detrimental effect of increased in obesity rates on population health is tempered only somewhat by the decline in the prevalence of smoking,' they say.

Using data on obesity from the National Health and Nutrition Examination Survey, and on smoking from the National Health Interview Survey, they estimate that the combined effect of reduced smoking and increased obesity will be to reduce the life expectancy at age 18 by 0.71 years over the next decade. This is about one quarter of the 2.98 year *increase* in life expectancy that they forecast would have occurred between 1990 and 2004 with no change to either risk factor.

'Our results do not imply that life expectance will fall; more likely, life expectancy will continue to rise but less rapidly than it otherwise would,' (*N Eng J Med 2009; 361:2252–60*).

While acknowledging the difficulty in predicting future trends in smoking and obesity with accuracy, the authors suggest that if past trends continue, almost half the US adult population will meet the WHO criteria for obesity by 2020. There is, however, evidence that the rate of increase in BMI may be decelerating.

Efforts to improve health should focus on stabilisation or reversal of trends in BMI, continued reductions in tobacco use, and better control of the clinical risk factors associated with obesity and smoking.

'Inadequate progress in these areas could result in an erosion of the pattern of steady gains in health observed in the United States since the early 20th century,' the researchers conclude.

Androgen deprivation therapy linked to heart disease

Men of all ages treated for prostate cancer with androgen deprivation therapy (ADT), specifically with gonadotrophin-releasing hormone agonists (GnRH) have an increased risk of diabetes and cardiovascular disease, US researchers say.

Dr Nancy L Keating (Brigham and Women's Hospital, Boston, Massachusetts) and colleagues conducted an observational study of 37,443 men diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration between 2001 and 2004, with follow up to the end of 2005.

Treatment with GnRH agonists was associated with statistically significant increased risk of incident diabetes (159.4 events per 1,000 person years versus 87.5 events for no ADT). (*doi:10.1093/jnci/djp404*). Rates of incident coronary heart disease, myocardial infarction, sudden cardiac death and stroke were all significantly increased.

In an accompanying editorial, Dr Peter Albertsen (University of Connecticut, Farmington) said: 'With the growing number of men wrestling with rising PSA [prostate-specific antigen] values after treatment, we should organise appropriate trials and reflect carefully about the anticipated benefits and harm before initiating ADT treatment.' (*doi:10.1093/jnci/djp427*)

EAU and Europa join hands

The European Association of Urology (EAU) and Europa Uomo, the European advocacy movement dedicated to prostate cancer, have entered into an affiliated partnership. It is 'part of their long-term commitment to increase and improve patient awareness in Europe with regards to urological diseases,' they say.

It is the first time EAU has had such an arrangement with a patient organisation. Both parties are expected to support the goals, objectives and activities of their new partner, although they are not part of each other's organisational structures.

Professor Per-Anders Abrahamsson, Secretary-General of EAU said: 'Ultimately, we strive toward a common goal: to raise the level of urological care in Europe. We can definitely help each other, for instance by exchanging information.'

Professor Louis Denis, Secretary of Europa Uomo, said: 'Both sides, urologists and patients, benefit.'

Time to raise the bar for cancer drug approval?

The recent finding that adding trastuzumab to anastozole improves progression-free survival (PFS) by just over 2 months in postmenopausal women with HER2/hormone-receptor co-positive metastatic breast cancer (compared with anastrozole alone) raised the issue, once again, of how much benefit is sufficient for regulatory agencies to approve new cancer drugs and for health-service providers to agree to pay for them.

The economic reality is that drug regulators must be convinced that the benefit achieved by new drugs – or existing drugs in new indications – justifies their increasingly high costs. And the clinical reality is that drugs must achieve sufficient real benefit to patients to outweigh any side-effects.

In the TAnDEM study, patients who received anastrozole and trastuzumab, without chemotherapy, showed a small but significant increase in PFS of around 2 months compared with anastrozole alone (hazard ratio 0.63; median PFS 4.8 vs 2.4 months; p=0.0016). Overall survival was similar, but 70% of women in the anastrozole alone group crossed over to receive trastuzumab after their disease progressed (*J Clin Oncol 2009; **27**: 5529–37*). A second study, in a similar population of patients, showed that a combination of the dual tyrosine-kinase inhibitor lapatinib with the aromatase inhibitor letrozole also increased PFS, by around 5 months (hazard ratio 0.71; median PFS 8.2 vs 3.0 months; p=0.019; *J Clin Oncol 2009; **27**:5538–46*).

'RAISING THE BAR FOR APPROVAL WOULD STIMULATE THE DESIGN OF TRIALS WITH STRONGER RATIONALES'

Alberto Sobrero (Ospedale San Martino, Genova, Italy) and Paolo Bruzzi (Instituo Nazionale per la Ricerca sul Cancro, Genova, Italy) argue that the incremental advances gained with many of these targeted agents are not enough to justify their costs: 'Many of these new agents carry a very high price tag, especially considering the relatively modest gain in overall survival offered in the palliative setting' (*J Clin Oncol 2009; **27**: 5868–73*).

They found a median hazard ratio for PFS of 0.57, and for overall survival of 0.73, in phase 3 trials used for registration of new biological agents approved for many solid tumours, including advanced colorectal cancer, breast cancer, and hepatocellular carcinoma. These values translate to a median PFS gain of 2.7 months and an increase in median overall survival of 2.0 months.

Sobrero and Bruzzi propose that only treatments achieving paradigm-changing targets should be approved in advanced cancers. 'We believe that raising the bar for approval would stimulate the design of trials with stronger biological and clinical rationales, accelerating the development of new clinically meaningful treatments for cancer and ensuring that patients benefit as early as possible from very effective new therapies,' they conclude.

Drug regulatory agencies are taking steps to review the evidence they require to approve new cancer drugs. The US Food and Drug Administration (FDA) has approved a range of cancer therapies on the basis of improved PFS, moving away from its previous requirement for demonstration of improved overall survival.

Richard Pazdur, director of the FDA's Office of Oncology Drug Products has announced plans to convene an advisory committee meeting to clarify standards for the use of PFS in cancer drug approvals (OncologyStat, The Pink Sheet Daily, Sept 16, 2009). What is disheartening, he said, is that the FDA 'is detecting a progressive decrement in what one considers a large effect. Some people think 6 weeks is a large effect.'

The National Institute for Health and Clinical Excellence (NICE) in England and Wales has had several major battles with physicians and patient organisations over decisions not to recommend cancer drugs for which the benefits were considered insufficient to justify the costs. NICE recently ruled that sorafenib should not be used in the treatment of advanced liver cancer because the increase in median survival, from about 8 to 11 months, was not found to be 'a cost effective use of NHS resources'.

Peter Johnson, chief clinician with Cancer Research UK, said that the drug is too expensive for the effect it achieves. 'NICE has been too harsh on the drug in its decision making, but the company making it has not been as liberal as it could be on the price.' He advocates a system of value-based pricing, in which drug price is set according to the benefit it achieves.

Johnson considers a 'one size fits all' approach to trial outcome targets for drug approval too simplistic. What seems to be a relatively small increase in PFS with a new drug in an advanced cancer may be clinically meaningful: 'When you are testing a drug in patients who may have already received several lines of treatment, even a quite effective drug might show only a small effect, ' he said. 'We can't be too proscriptive about what outcomes regulators will accept or we risk losing valuable cancer treatments.'

'A DRUG'S PRICE COULD BE SET ACCORDING TO THE BENEFIT IT ACHIEVES'

In a keynote speech for a workshop on PFS in oncology (Oct 7–9, 2009, Bethesda, MD, USA) cosponsored by the Drug Information Association, the FDA, the National Cancer Institute, and the Pharmaceutical Research and Manufacturers of America, Pazdur remarked that PFS is sometimes an appropriate endpoint for registration trials, but argued that the extent of the PFS is most important. Acknowledging the controversy surrounding the issue, he said, 'A lot of it has to do with magnitude. Just demonstrating a statistically significant difference in PFS is not enough. It has to be clinically meaningful.' (*J Natl Cancer Inst 2009; **21**: 1439–41*)

Susan Mayor

*The full version of this story appeared in Lancet Oncol 2010; **11**:16–7*

51st Annual Meeting of American Society of Hematology December 5–8, 2009; New Orleans, Louisiana

Bendamustine 'superior to CHOP'

The combination of bendamustine-rituximab (B-R) has the potential to become the new standard of care in first-line treatment of patients with advanced follicular, indolent and mantle cell lymphomas, according to a phase III study (*Abstract #405*).

The German Study Group on Indolent Lymphoma (StiL) found that, in comparison with CHOP-rituximab (CHOP-R), the B-R combination significantly improved progression free survival (PFS) and complete response rates and was better tolerated.'While CHOP plus rituximab is the current standard of care, it is frequently associated with serious adverse events and more side effects,' said principal investigator Mathias Rummel (University Hospital, Giessen, Germany).

The study randomized 549 patients, with a median age of 64, to either B/R or CHOP-R. At 34 months, overall response rates were nearly identical for the two treatments: 92.7% for B-R and 91.3% for CHOP-R. The complete response rate, however, was 39.6% for the B-R combination and 30% for CHOP-R combination (p=0.0262). This translated to significantly better PFS: a median of 54.9 months for B-R versus 34.8 months for CHOP-R (p = .00012).

'In a median observation period of 34 months you could not expect to see any survival differences,' said Rummel. Serious adverse events occurred more frequently in the CHOP-R group (74 vs. 49 in the B-R group). Patients treated with B-R also had a lower rate of alopecia, infectious complications and paresthesias.

The bendamustine dose used in the current study was considerably lower than the 120 mg/m^2 dose currently approved in the U.S. for lymphoma. 'With the higher dose there is a danger that you will lose the big advantage of the beneficial toxicity profile,' Rummel said.

Nilotinib 'more effective than imatinib'

Nilotinib (Tasigna) was significantly more effective as first-line treatment for chronic myeloid leukaemia (CML) than imatinib (Glivec) in the phase III ENESTnd study (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients).

Imatinib is currently the only tyrosine kinase inhibitor (TKI) approved for first line treatment in CML. Nilotinib, a second generation TKI, is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) for treatment of CML in patients who have failed on imatinib.

The ENESTnd study was a head-to-head study of nilotinib against imatinib as initial therapy. Giuseppe Saglio (University of Turin, Italy), and colleagues randomised 846 CML patients, from 220 sites, to two different doses of nilotinib or imatinib.

At one year, major molecular responses were seen in about 44% of patients receiving nilotinib compared with 22% of patients receiving imatinib (p<0.0001). There was little difference in the two doses of nilotinib. Complete cytogenic response occurred in 79 % of patients receiving nilotinib compared to 65 % receiving imatinib (P< 0.001). Rates of progression to accelerated phase disease or blast crisis occurred in three out of 563 patients on nilotinib, compared with 11 of 283 patients on imatinib (P<0.01) *(Late Breaking Abstract #1)*.

Omacetaxine 'shows promise in T135I-mutated CML

The novel drug omacetaxine produced durable responses in chronic myeloid leukaemia (CML) patients with the T315I mutation who had failed imatinib.

Tyrosine kinase inhibitors (TKIs) targeting the Bcr-Abl protein (such as imatinib and dasatinib) are standard treatment for CML, but around 5% patients have T315I mutations that prevent these drugs from binding. Omacetaxine, a drug originating from the Chinese evergreen tree *Cephalotaxus Harringtonia*, has a different mechanism of action, inhibiting protein elongation and inducing apoptosis.

In a phase II study, Jorge Cortes (M.D. Anderson Cancer Center, Texas) and colleagues analysed data from 81 CML patients with confirmed T135I mutations, who had failed at least one TKI. They self-administered subcutaneous omacetaxine.

At a mean of 9 months, complete haematologic response was achieved in 85% (42) of the chronic phase patients, 35% (6) of the accelerated phase patients and 47% (7) of the blast phase patients. Of the chronic phase patients, 27% (13) achieved a major cytogenetic response and 18% (9) a complete cytogenetic response *(Abstract # 644)*.

Rituximab 'produces overall survival advantage'

Adding rituximab (MabThera) to chemotherapy in previously untreated patients with chronic lymphocytic leukaemia (CLL) significantly improved overall survival, according to the German CLL Group.

In the CLL8 study, 817 patients with untreated active CLL and good prognostic factors were randomised to receive fludarabine/cyclophosphamide with rituximab (R-FC) or without (FC).

At a median observation time of 37.7 months, overall survival rate was 87.2% for patients on R-FC compared to 82.5 % for patients on FC (HR 0.664, p=0.012). Progression free survival was 51.8 months in the R-FC arm versus 32.8 months in the FC arm (HR 0.563, p<0.001). The main adverse event was neutropenia, which occurred in 33.7% of those on R-FC and 21% of those on FC (p<0.0001).

Subgroup analysis showed that the rates of complete remission varied according to genetic subgroup.

Janet Fricker
(who was sponsored by Roche to attend the meeting)

PODIUM

Taking the long term view

Professor Andrew Lister has worked in medical oncology at St Bartholomew's Hospital, London, UK, since the early 1970s, when he trained under Professor Gordon Hamilton Fairley, one of the founding fathers of the discipline in Europe. At the ECCO 15–34th ESMO Congress in Berlin (September 2009), Professor Lister was presented with ECCO's Hamilton Fairley Award – which commemorates his former mentor – and which recognises his own lifetime achievements in science and clinical/laboratory work. Professor Lister devoted his Award Lecture to research into haematological malignancies at St Bartholomew's and spoke later to EJC.

How lasting has Professor Hamilton Fairley's influence been?

His contribution was quite remarkable. He was the first Professor of Medical Oncology in the UK and was instrumental in setting up a national network of academic centres. He was only in post for 5 years before he was murdered in error by the IRA (in 1975) and it's difficult to conceive of what more he might have achieved.

His legacy at St Bartholomew's was to establish a philosophy of patient-orientated research including what is latterly known as the lab-clinical interface, applied and translational research. His interest applied across the spectrum of malignant disease.

How did his philosophy translate into practice?

He appreciated the need to record in a hospital database the details of all the patients in our care – not just those that had entered trials – so that an in-house registry was established. Longitudinal observations were made throughout patients' lifetimes. A laboratory tissue bank was set up and experiments conducted on material from patients. Clinical trials were conducted and crucially, clinical research fellows ensured that research was patient-orientated. First class pathology, imaging, and radiotherapy, were important as was collaboration with other groups at home and abroad.

The database and tissue bank must have been ahead of their time?

They were both set up in the 1970s, and were of the first. We were treating people with acute leukaemia by immunising them with leukaemia cells. This meant we had a fridge full of leukaemia cells but over time this evolved into a tissue bank.

The initial objective of the database was to allow us to develop longitudinal mathematical models to compare outcomes among patients given a new treatment against historical controls. It was a mathematical, pragmatic, approach established by people who were involved in operational research during the war. It has now fallen from fashion, but it allowed us to generate data with half the number of people you would need if you had to compare a new treatment with the prevailing standard. At the time, there were relatively few major randomised controlled trials.

What use has been made of the database?

Recording all data on all patients may help you see whether a particular treatment has an impact on survival. In my field of follicular lymphoma (FL), the registry helped us establish the pattern of the disease over time, and confirm absolutely that FL in some people is extremely indolent, and that in others it may regress partially or remain stable. It's important because people presenting with FL often look quite well and the choice was between starting treatment immediately or 'benign neglect' in which it was delayed until they had symptoms. We found that patients in the latter group waited a median of 4 years before needing treatment and 25% were still without treatment 10 years later. It did not alter the outcome and importantly, some patients with this disease did not need treatment at all.

How far will the database help to predict which patients need treatment?

Combined use of the tissue bank and data base has contributed to a considerable number of international efforts into prognostic factors in lymphoma. Modern laboratory investigation techniques are now being used to link gene expression with immunohistochemistry, work out the pathways involved as illness develops, and the prognostic significance of genetic mutations.

Having such a well-established tissue bank enables us to study new ideas quickly. To investigate levels of a particular protein in prospective material, you would have to wait 10 years until you had sufficient follow up. But if you have data and material going back 20 years, you can have 20 year follow up in patients whose material is taken out of the fridge.

What is the value of such a localised registry, compared to something similar at national or international level?

For a start, it helps you to know exactly what going on with the patients you are looking after. Our data is more complete than national registries: we carry out biopsies at each relapse, not just at diagnosis, for example. Databanks are only as good as the data in them, and that depends on the people recording it: we are fortunate in having 3 very good data managers. Young researchers here don't know how lucky they are to be able to use this resource.

What is the future for registries such as this?

Biobanks are an expensive enterprise and consent issues have become more complicated. But at a practical level, it has recently become possible to extract DNA and RNA from paraffin. It is much easier to store samples in paraffin, so this is an important advance and on the whole, we can be relatively optimistic.

Helen Saul