available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

NEWS. . .NEWS. . .NEWS

New CONSORT statement released

New guidance intended to improve the reporting of trial findings has been published. The updated Consolidated Standards of Reporting Trials (CONSORT) statement was first published in 1996 and revised in 2001. It includes a checklist to help authors write reports of randomised controlled trials so that others can judge the reliability and validity of the results.

Speaking on behalf of the co-authors, Kenneth Schulz (Family Health International, North Carolina, USA) said that CONSORT is an evolving guideline. 'In the future we will further revise the CONSORT material considering comments, criticisms, experiences, and accumulating new evidence. We invite readers to submit recommendations via the CONSORT website (*www.consort-statement.org*).'

Research published to coincide with the new statement compared all primary reports of randomised trials indexed in PubMed in December 2000 (519) and in December 2006 (616). Reporting of several aspects of trial methods – such as details of the primary outcome, sample size calculation and methods of random sequence generation – improved during the period (*doi:10.1136/bmj.c723*).

'WITHOUT COMPLETE REPORTING, IT IS DIFFICULT FOR READERS TO ASSESS A TRIAL'S VALIDITY'

However, the quality of reporting remains well below an acceptable level, the researchers conclude: 'Without complete and transparent reporting of how a trial was designed and conducted, it is difficult for readers to assess its conduct and validity.'

Mastectomy versus breast conserving surgery

Women carrying the BRCA1 and BRCA2 mutation may not need the most radical surgery, delegates at the 7th European Breast Cancer Conference (Barcelona, Spain; March 24–27, 2010) were told.

A study conducted in the US, Australia, Spain and Israel compared outcomes after breast conserving therapy (BCT) or mastectomy in 655 women carrying either BRCA mutation. At 15 years, BCT patients had significantly higher rates of cancer recurring in the breast than those who had mastectomy (23.5% versus 5.5%). However, the risk was reduced to 11.9% among BCT patients who received adjuvant chemotherapy.

Despite the higher rates of local recurrence in the BCT group, other risks – metastasis, breast cancer-specific survival, and overall survival – were similar, the researchers found.

Presenting the results, Professor Lori Pierce (University of Michigan, Ann Arbor, USA) said the study 'will provide important data to patients trying to decide what will be the best treatment for their hereditary breast cancer, as well as to the doctors advising them.'

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):55 #7N*]

See over for more reports from EBCC7

No-go for azacitidine in UK

The UK's National Institute for Health and Clinical Excellence (NICE) has issued a Final Appraisal Determination (FAD) which means that azacitidine (Vidaza) will not be generally available through the National Health Service to UK patients with bone marrow diseases.

The FAD applies to patients with the following conditions and who are not eligible for haematopoietic stem cell transplantation: intermediate-2 and high-risk myelodysplastic syndromes; chronic myeloproliferative leukaemia with 10–29% marrow blasts without myeloproliferative disorder; or acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia.

Patients with these conditions who are currently receiving the drug are able to continue treatment until they and their clinicians consider it appropriate to stop.

Professor Ghulam Mufti (King's College Hospital, London, UK) said, 'These drugs are in routine use in the USA following the approval by the FDA, and most, if not all, the countries in the EU. It is disconcerting to note that we seem to be always last in licensing effective medications, particularly in relatively rare disorders. It should be noted that Vidaza is the only effective drug for these patients, who have a high risk of considerable morbidity and mortality.'

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

doi:10.1016/j.ejca.2010.04.001

7th European Breast Cancer Conference March 24–27, 2010; Barcelona, Spain

Chemotherapy in pregnancy

Women who discover they have breast cancer while they are pregnant can be treated with chemotherapy without endangering their unborn baby, a German group says.

A registry study conducted by the German Breast Group included data on 235 patients prospectively (119) and retrospectively (116). Women were aged between 23 and 46 and breast cancer was diagnosed, on average, at 23 weeks into the pregnancy.

Interim analysis on 151 women found that babies exposed to chemotherapy during pregnancy were born weighing slightly less than babies who were not (2636mg vs 2791mg). However foetal outcomes did not differ significantly between the groups.

Dr Sibylle Loibl (University of Frankfurt, Germany) said, 'We would like to generate more robust data to confirm this and so the registry is continuing and we are updating and completing the data.'

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):205 #499*]

'Cooling off' period before mastectomy

Giving women counselling and time to think may lead to a reduction in the numbers of prophylactic mastectomies, a UK surgeon told the meeting.

Mr Ajay Sahu (Frenchay Hospital, Bristol, UK) questioned 27 consecutive patients with breast cancer and found that they overestimated their risk of contralateral breast cancer by a factor of 5 to 10.

At 6 and 12 months, 23 of the 27 chose not to have the prophylactic operation.

Mr Sahu cautioned that the study is small, but said 'the important message is that patient's choice may be based on inaccurate overestimation of risk at the time of diagnosis and, given time, they may not have the same risk perception later on.'

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):126 #233*]

PARP expression 'in all subtypes'

Contrary to the widespread belief that the poly (ADP-ribose) polymerase (PARP) protein is associated with a limited number of tumours, its expression occurs in all breast cancer subtypes, research from the German Breast Group suggests. PARP provided more accurate prognostic information than the grade of differentiation, and predicted response to chemotherapy.

Professor Gunter von Minckwitz (University of Frankfurt, Germany) presented the data: 'We believe that we may be on the verge of a major change in the way breast cancer is treated,' he said.

The team examined tissue from 646 patients in a neoadjuvant phase III trial (GeparTrio). They found that PARP was present in all tumour subtypes, but it occurred most frequently in HER2 positive and triple negative tumours. It correlated with most known prognostic factors, except HER2. Tumours with a high level of PARP expression had a total response in 26% of cases, whereas those tumours which did not express PARP had a total response in only 9%. 'The relationship to total response was remarkable,' Professor von Minckwitz said.

The group intends to follow up these initial findings with a trial randomising patients to either chemotherapy alone, or chemotherapy plus a PARP inhibitor.

'Particularly in triple-negative tumours, there is a great need to improve treatment options. Apart from chemotherapy, there is no other treatment such as endocrine or anti-HER2 therapy available for this aggressive form of breast cancer,' Professor von Minckwitz said.

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):20–21*]

Specific lymph node radiotherapy

Women with early breast cancer 'will probably benefit' from additional radiotherapy to the lymph nodes behind the breast bone and above the clavicle, following mastectomy or breast conserving surgery, EORTC researchers told the meeting.

Radiotherapy is routinely given to breast, chest wall and axilla after surgery, in order to reduce the risk of local recurrence. There is no consensus on the optimal management of internal mammary and medial supraclavicular lymph nodes, and whether additional radiotherapy to these nodes has an impact on survival.

Initial findings from the 4,004-patient, multi-centre study imply no increased toxicity to the heart at 3 years' follow-up among patients who received the additional radiotherapy. Longer term follow up will assess possible long term damage to the heart or lungs.

Trial coordinator Dr Philip Poortmans (Dr Bernard Verbeeten Instituut, Tilburg, The Netherlands) said the primary endpoint of the study – overall survival at 10 years – was intended to be performed in 2012. 'However, thanks to the actual survival estimate that is even higher than expected, this might have to be postponed until 2014,' he said.

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):54 #6N*]

New marker for anthracycline response

An abnormality on chromosome 17, called CEP17, is a highly significant indicator that the tumour will respond to anthracyclines, an international team has found.

A meta-analysis of four large breast cancer trials including nearly 3,000 patients found that – after adjusting for additional factors relating to the tumour and its treatment – patients with CEP17 who were treated with anthracyclines had a two-thirds increase in overall survival compared with those who did not receive the treatment.

Professor John Bartlett (University of Edinburgh, UK) said the finding is 'entirely novel' and needs to be confirmed, but it could shed light on relevant mechanisms and suggest new targets for drug development.

[*Proc EBCC-7; EJC Supplements 2010; 8 (3):121 #213*]

EUROFILE

Pharmacovigilance changes: For better or worse?

Drastic changes to pharmacovigilance practices in Europe are expected to be adopted by the end of 2010. While policymakers haggle over the fine details, stakeholders are divided on whether they will really improve the situation.

The Commission's proposed revisions to directive 2001/83/EC and regulation EC/726/2004 are intended to improve the monitoring and safety of medicines, cut bureaucracy and grant quicker drug authorisations. They have finally reached the European Parliament.

The revisions were put forward in December 2008 after several stakeholder consultations. They amend which adverse drug reactions (ADRs) need to be reported, where they must be reported, by whom, and how.

The Commission proposes expanding the definition of ADRs to include adverse reactions caused by medication errors, misuse and abuse. It also wants to enlarge the role of pharmaceuticals companies to receive ADRs from patients and healthcare professionals.

All ADRs occurring in the EU, whether serious or not, would be reported by national authorities and pharmaceutical companies within 15 days. At present, this rule applies only to serious ADRs. All other ADRs are covered by periodic safety update reports (PSURs) required from companies once their product is on the market. Instead of the raw ADR data companies currently present, they would be required to undertake its analysis and provide a risk-benefit summary in the PSURs.

In addition, the proposal seeks to abolish the complex set of rules governing where companies must report ADRs, which can currently result in reports being sent to all EU countries. Companies would instead, submit a single report to the Eudravigilance database at EMEA, which could then be accessed by competent authorities. The database would become the central hub for all ADR information in Europe.

Patient groups, health professional groups and research organisations would be granted access to Eudravigilance ADR data which is not commercially sensitive.

Currently, few member states allow patients to report ADRs directly to their national authorities. Under the proposal, the authorities would create a national internet portal for patients (and clincians) to do so.

The Commission proposes changes to applications for new drug authorisations. Companies would only need to supply key elements of their pharmacovigilance system, and not the detailed description currently required. However, they would be obliged to maintain a detailed master file on site, have a risk management system in place, and conduct regular internal audits of their system. The main audit findings would be noted in the master file for inspection by authorities.

Companies would have to pay EMEA for all pharmacovigilance assessments. The Commission estimates that this would earn EMEA an additional annual income of 10.6 million Euros.

Stakeholder groups unhappy with the provisions have been lobbying the European Parliament, which began refining the proposal in March 2010.

Many are concerned about revisions entrusting pharmaceutical companies with the responsibility for receiving ADRs and reporting them directly to a central database. According to the European Public Health Alliance (EPHA), whose members include ECCO, the Association of European Cancer Leagues, and the European breast cancer coalition, Europa Donna, 'This arrangement provides an opportunity for drug companies to manipulate the data before independent analysis.'

It is also against the proposal under which companies provide their own risk-benefit analysis in PSURs. 'In this case, pharmaceutical companies would be defendant and jury charged with assessing the change, if any, in their products' risk-benefit balance,' it states. '[It] would further endanger patients by stripping health authorities of their authority, expertise, credibility and autonomy.' It finds that the private funding of assessments would also compromise the credibility and independence of authorities.

The Medicines in Europe Forum which has 70 members including cancer patient groups, agrees: '[The revisions] will dismantle the system and delay the detection of adverse effects as well as decisions that are required to protect public health - at least until drug companies have earned the anticipated 'return on their investment'.'

Linda McAvan, the UK Socialist MEP steering the proposal through the European Parliament argues current dysfunctions are already detrimental to patient safety. 'There have been cases of companies breaking the law and submitting misleading reports. But competent authorities are swamped by PSURs and don't have time to look at them,' she explains. She will ask MEPs to vote for further safeguards on non-compliance, including independent external audits of company findings.

She will also propose the disclosure of commercially sensitive data if it is in the public interest; provisions allowing patients to report ADRs by phone or letter; and a blame-free system for reporting ADRs due to medication errors. McAvan supports the private funding measures but the Green MEP, Michele Rivasi, from France, will be urging MEPs to vote against them.

The European Federation of Pharmaceutical Industries and Associations is displeased by the internal audit disclosures. It is lobbying for the proposed company master file to include only information on the procedures for internal pharmacovigilance audits (for the previous 5 years and the future) rather than the findings themselves.

The proposal can only be adopted by the EU Council of Ministers. However it is a co-decision procedure, obliging ministers to incorporate at least some of the Parliament's amendments into the final text. The process involves the proposal being passed between the institutions until a clear consensus emerges.

Saffina Rana
Brussels

New hope for melanoma

Like a sibling trying on cast-offs, no treatment that has worked for other cancers has been a proper fit for melanoma. 'Drug therapy for metastatic melanoma or adjuvant therapy for those who have had surgery with curative intent has severe limits with regard to efficacy', says Keith T Flaherty (Massachusetts General Hospital Cancer Center, Boston, MA, USA). On average, patients with stage IV disease survive for 6–10 months, with fewer than 5% surviving beyond 5 years. The melanoma research community, intent on extending that window significantly, has been struck with infectious optimism fuelled by a growing understanding of the molecular underpinnings of melanoma, the identification of new genetic and immune-system targets, and encouraging results from clinical trials.

As the search for melanoma-specific targets continues, however, there is unfortunately no one-size-fits-all approach. 'All tumours look and act differently even within the same patient', says Meenhard Herlyn (Wistar Institute, Philadelphia, PA, USA). 'We are distinguishing between a genetic and a biological cancer signature. If we know the 'drivers', those genetic alterations that drive the malignancy, we can individualise our therapies and tailor them against those mutant proteins–albeit our repertoire is still limited. We hope that the cancer genome atlas will provide more information to distinguish between drivers and passengers. In the biological signature, we find heterogeneity due to different stages of the cell cycle or due to specific sub-populations, some of which may have special survival skills'.

'C-KIT IS PROOF OF PRINCIPLE THAT YOU CAN PERSONALISE TREATMENTS BASED ON THE TUMOUR'S GENOMICS'

Many research centres are exploring potential targeted therapies, such as BRAF and C-KIT inhibitors. 'The most promising are those in which there is a defined mutation in all cancer cells that leads to constitutive activation of the protein and the pathway, and in which a drug is available to inhibit its activity. The newest example is PLX4032 for the mutant BRAF oncogene,' says Herlyn.

BRAF was identified in 2002, and mutations occur in over 50% of melanoma patients. Several BRAF inhibitors are now in clinical testing, although PLX4032 is furthest along, having moved into phase 3 clinical trials in December, 2009. However, Herlyn adds that 'mutant BRAF alone cannot transform melanocytes, it needs cooperating genes. Those need to be found and then targeted. Thus, a BRAF inhibitor alone will not cure, it needs to be used in combinations, except that we do not yet know which other pathways we need to block, nor how many'.

C-KIT comprises a much smaller set of mutations than BRAF, affecting around 1–3% of patients. 'It's a small number of patients but it's the first proof of principle that you can personalise treatments for melanoma based on the genomics of their tumour', says F Stephen Hodi (DanaFarber Cancer Institute, Boston, MA, USA). 'Even though things look the same under the microscope, when you look at genomics, you'll find that a patient has the KIT mutation versus other mutations that can suggest a treatment path'. A number of KIT-active drugs are being tested for this melanoma subtype.

Another broad group of molecules being explored are anti-apoptosis inhibitors, such as ABT-737, which inhibits BCL2 and BCLXL (which stop cells from undergoing cell death). 'The drug binds to these inhibitors, and releases proteins that promote cell death. This is more broad spectrum, but it still needs to hit MCL1', explains Victor Tron (Laboratory for Skin Cancer Biology and Therapeutics, Queen's University, Kingston, ON, Canada). 'More drugs are coming down the pipeline that will target BCL2, BCLXL, and MCL1. Those may be very promising.'

Meanwhile, Hodi is still hopeful that immunotherapy can offer something valuable, the idea that 'by pressing down on the accelerator or taking the brakes off of the immune system, you can very selectively take advantage of that. And by figuring out what those molecules do, you can literally steer the immune system in the right direction to try to fight cancer'. Hodi's team is exploring a cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibody, one of a family of immune checkpoints that can limit the potential therapeutic potency of cancer vaccines by suppressing T-cell function. Hodi reports that additional phase 3 results are expected soon.

'MANY RESEARCHERS BELIEVE THAT MELANOMA MAY NEED TO FOLLOW HIV'S LEAD: COMBINATION THERAPY'

Convinced that no magic bullet will emerge for melanoma, many researchers believe that it may need to follow HIV's lead: combination therapy. That is the idea that spawned the Melanoma Breakthrough Consortium recently assembled by the Melanoma Research Foundation (MRF), which combines the work of ten academic centres with pharmaceutical companies that have a melanoma research focus. 'Its core focus is to do combination studies that aren't being done anywhere else that we are convinced will be relevant for melanoma patients', says Tim Turnham (executive director of MRF), and to accelerate the complicated and slow' drug-development process. Flaherty says that even for the promising PLX4032, they are eyeing combinations for 'attacking other mutated genes and enzymes that happen in the same cells as BRAF and can be targeted with drugs', and moving toward adjuvant therapy trials in the not-too-distant future with single-agent BRAF inhibition with the hope of curing'.

Angela Pirisi

*This story originally appeared in Lancet Oncol 2010; **11**:317.*

PODIUM

Halting metastasis: a new possibility in the clinic

Dr Patricia Steeg is Chief of Women's Cancers at the Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute (Bethesda, Maryland, USA). She has studied the molecular mechanisms of tumour metastasis for 20 years, and she discovered the first metastasis suppressor gene, Nm23. Dr Steeg is a guest editor of a forthcoming EJC Special Issue, 'Stopping cancer in its tracks: metastasis as a therapeutic target' (EJC 2010; 46(7)).

Your work challenges the idea that metastatic cells are the same as those in the primary tumour?

Yes it does. There is now evidence from multiple sources – mutational analysis, gene expression analysis, genomic amplification and deletion analysis – that metastases and primary tumours share similarities, but they also have important differences. *Nm23* has been demonstrated to inhibit metastasis (but not primary tumour formation) in 11 independent model systems. And more than 20 metastasis suppressor genes have now been found.

What implications does this have for drug development?

Most new drugs are validated in primary tumours but are then tested in the metastatic setting, in stage four cancer patients in whom all standard therapies have failed. Perhaps if we validated drugs in the metastatic setting, we'd get different answers and take different drugs forward for development.

How difficult would this be to implement?

Probably all it would take – after initial testing of a drug in primary tumour xenografts – is to then try it in metastasis model systems. It's unclear whether regulatory agencies are going to ask for this data, but there's enough evidence in the literature to say that this step should be done.

How are pharmaceutical companies reacting to the proposal?

I believe they will come round to it. Some of our work on brain metastases in breast cancer led us to say to companies: if you have 5 leads for a target, please consider brain permeability when choosing a candidate. The pharmaceutical industry has embraced this and it means that successful agents could potentially work on brain metastases – an unmet medical need. So the drug could be approved for treating brain metastases ahead of other indications and thus speed up the drug approvals process.

What success has there been in halting metastasis in the clinic?

We're optimistic that proof of principle is just around the corner with denosumab. It's a human monoclonal antibody which binds to a ligand that inhibits the RANK receptor on osteoclasts. In healthy bone, there's a tightly controlled balance of bone formation and resorption, but the system breaks down when cancer cells invade the bone micro-environment. One of the papers in the Special Issue tackles this in detail (REF) but, in essence, there's a vicious cycle in which cancer cells and osteoclasts stimulate each other, and bone is lost. Denosumab neutralises the RANK ligand, inhibits osteoclast formation, function and survival and preserves the bone.

In early phase testing it slowed the progression of bone metastases and we're hoping that clinical, phase III data will be presented at ASCO this year. Denosumab could be the first marker-directed therapy for metastatic bone disease.

Is a clear picture of metastasis beginning to emerge?

Far from it! There are still controversial questions. Christoph Klein (Regensburg, Germany) has shown that breast cancer cells disseminate early, even in the premalignant phase. Yet we know that ductal carcinoma in situ has a low mortality rate. So if the cells have disseminated, they don't appear to cause lethality. Not all disseminated tumour cells are alike but we don't yet know how to distinguish those that mean trouble.

A researcher might devote a whole career to coming up with an inhibitor to metastatic colonisation of a distant organ. But the tumour may have 3 or 4 more pathways it can use. In the end, a combination of therapies will be needed to treat metastasis.

You even suggest that controlling the growth of the primary tumour could promote metastasis?

Literature on anti-angiogenesis agents in model systems suggests that, though they inhibit growth of the primary tumour, they also promote metastasis. We don't know if this occurs in humans, but with bevacizumab, for example, there's clinical data showing high response rates and tumour shrinkage but survival for patients is either increased by a few weeks or not at all. That is consistent with the idea that the drug is increasing invasion and colonisation, so that the disease becomes more aggressive. There could be other explanations, but it's provocative.

You call for more data on metastasis to be collected.

Clinical trials typically only gather data on the first site of progression. If data on metastases in brain, liver, bone, lung, and so on, were routinely recorded, trends might emerge. Obviously it would take additional funding, but we're wasting opportunities by not doing it.

What do you hope the Special Issue will achieve?

I'm hoping the Special Issue will get the word out that metastasis is relevant to drug development. It has the potential to really improve the situation and to be more than an incremental step forward.

Helen Saul