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News & Views

Tailoring cancer therapy – Validating basic science with the ‘supertrial’

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ABSTRACT

A paradigm shift in research culture is needed in order to set up the large ambitious trials needed to make personalised medicine a reality. Emma Wilkinson talks to the experts about the hurdles they face and what needs to change.



Figure 1 – EORTC president, Martine Piccart.

It is clear to even the casual observer that recent years have seen impressive advances in knowledge of the molecular biology of cancer.

From identifying molecular targets within tumours to finding predictive biomarkers and profiling molecular signatures, basic science is striding forward quickly.

But translating those advances into patient care, reaching the ultimate goal of providing personalised tailored treatment – avoiding undertreatment, overtreatment or wrong treatment – is proving to be a stumbling block.

And one major obstacle is the difficulty of setting up and carrying out the ambitious scale of clinical trial needed to provide definitive answers.

Breast cancer is a good example – according to EORTC president, Professor Martine Piccart, there have been great advances in understanding the molecular biology underlying

the disease, yet there is still a great deal of controversy among breast cancer experts about the right treatment.

With no validated tools to select the best chemotherapy regimen the fall back position is to go for the most recent, most aggressive and most expensive therapy.

What is urgently needed, she believes, is a shift in research methodology and culture.

Instead of just comparing new drug B to old drug A, large-scale ambitious trials need to be able to answer questions around how tumours displaying a given “molecular signature” will respond to drug A, drug B, a combination or neither.

In breast cancer, there are impressive research networks, yet few “supertrials” to date.

There is the ALTTO trial looking at women with HER2 positive breast cancer to look at a double hit of lapatinib and trastuzumab in addition to whether biomarkers can predict whether lapatinib helps prevent cancer from returning.

But other examples are few and far between.

Fátima Cardoso, assistant professor at the Jules Bordet Institute’s medical oncology clinic in Brussels, and scientific advisor of TRANSBIG – the translational research network that grew out of the Breast international Group, says there are major hurdles to overcome.

She is leading the MINDACT trial that will recruit 6000 patients, from across the EU to compare a 70-gene prognostic signature with traditional methods for assessing the risk of breast cancer recurring in women with lymph-node negative disease (Cardoso et al., 2007).

It is hoped that ultimately 10–20% of will be able to avoid chemotherapy and its associated harms.

Setting up this crucial study – which is vital for patients – was fraught with problems, she explains.

“To my knowledge there are no other trials based on a specific test – true translational research – other have the translational bit added in trying to understand the benefits of a specific drug,” says Cardoso.

Logistically, MINDACT is hard to coordinate – frozen tissue has to be collected sent to a central laboratory.

And the sample collection and technology itself is very expensive at around \$3000 for a test that’s not yet fully validated.

The EU provided about a third of the funding for the trial but in order to find the additional resources a “drug question” had to be built in, says Cardoso.

“We had to complicate the trial by including a drug-related question so we could have help from the pharmaceutical industry.”

“It was quite sad because if we’re right we would be prescribing 15% less chemotherapy,” she says.

A combination of the fact that national funding sources are not interested in stumping up the cash for international projects, that many of the questions to be answered by translational trials and not “drug” questions but “management questions”, adequate resourcing becomes almost impossible.

And that is without even considering bureaucratic barriers.

“We need to collaborate at the international level but it’s very complicated because every country has its rules – which are not in the interest of the patient.”

“The EU directive made it almost impossible to run investigator led trials – in the past you could set up these management trials because it’s not expensive as there was no drug involved but now we can’t do that because of a layer of complexity of paperwork and insurance,” she adds.

From the regulatory point of view, the European directive on clinical trials, due to be reviewed by the European Commission in 2010, has a lot to answer for in slowing up the progress of translational research.

Jacques Demotes-Mainard, programme co-ordinator at the European Clinical Research Infrastructures Network, says one fundamental issue is that the directive was largely designed with the needs of the pharmaceutical industry in mind – and the traditional model for testing medicinal products.

“It doesn’t take into account the other types of clinical research.”

“The European Commission should pay attention and develop processes to harmonise with a system that would be convenient for clinical research.”

What is needed, he argues, and it is worth pointing out that this seems to be a fairly commonly held view, is a risk-based approach.

“The distinction should be between high risk and low risk not between commercial and non-commercial trials.”

“This should be independent of whether the study has a commercial or non-commercial objective.”

He adds that there needs to be greater support for academic institutions acting as the sponsor and ultimately the ability to run clinical trials across member states with a single competent authority to provide authorisation.

Multiple sponsorship also needs to be far easier and insurance requirements need to be harmonised across Europe.

“What is also lacking in the EU is funding that can cross borders.”

“There is money at the national level but almost no money for international trials so it is almost impossible to get funding.”

“What we would like is to coordinate the national funding so each country gives some money from national funding, say 5–10%, to a multinational single scientific body which can make clinical judgements.”

What seems clear is there is agreement on what barriers exist to taking bench-top discoveries to the bedside but there are several ideas about the best model for translational research – and the idea of the massive supertrial is not the only way forward.

Professor Mitch Dowsett, head of breast cancer translational research, at the UK Institute of Cancer Research, says the key is standardisation of tissue collection.

Within five years it will be possible to sequence and individuals genome for £500 so imagine what information can be gleaned from a tumour, he says.

“We need to use the knowledge we have gained in the structure of these trials – using knowledge up front to select the population you’re confident will respond.”

This will, he believes, change the landscape of the clinical trial.

But it is not just about setting up large ambitious trials – although that will be part of it.

“If measurement of tissue markers in different trials was identical, if there was some international standardisation, then sub-group analysis could be easily done from data across many studies.”

“One of the ways around the sub-group issue is bringing local trials together but the problem is over the years we haven’t been measuring these biomarkers in a standardised fashion. It’s extremely frustrating.”

Professor Dowsett has been tasked with producing a standardisation checklist by TRANSBIG but that is just one hurdle.

Funding for tissue collection within trials is lacking and it will require a “sea-change” in how diagnostic clinics are run, and how surgeons and pathologists work.

He says that in the neoadjuvant setting there is much scope for speeding up the identification of effective new drugs and groups of patients who will benefit.

POETIC, a 4000-participant trial he launched in 2006, is one of the first peri-operative trials to have a biological endpoint at the core and will test whether levels of Ki67 following two weeks treatment with an aromatase inhibitor prior to surgery can predict long-term outcome.

“It allows close alignment between changes in the molecular biology of the tumour in that women and the nature of her disease and that way we identify groups that are more or less sensitive to particular agents before we go into the adjuvant setting.”

He gives the example of the ATAC – Arimidex, Tamoxifen, Alone or in Combination – trial.

Analysis of a similar smaller trial done by his team showed a correlation between biomarker measurements at two weeks and outcome of the three arms.

“In the ATAC trial in over 9000 women the combination of anastrozole and tamoxifen was worse than anastrozole alone.”

“Had we had these data prior to the launch of the ATAC trial, I think it’s possible we would not have gone forward with the combination arm and we would have saved 3000 women from being recruited and got answers much more quickly.”

“It gives you a flavour of what we’re trying to do.”

Of course these issues do not just relate to breast cancer.

Professor Matt Seymour leads clinical and translational research in gastrointestinal cancer at the University of Leeds, UK and agrees there are significant hurdles to carrying out translational research but says there’s a “very strong commitment” to making it work.

“With colon cancer, we have a disease with quite a lot of drug therapies that are effective but without exception all of the drug therapies we have or are trying out are helpful for a sub-group of patients – maybe at most 50% and at worse 10% will have received any particular drug benefits from it.”

“Even if you stopped drug development today and didn’t bring any single new drug out I would say you could make substantial progress simply by identifying who benefits from it.”

He said there had been reluctance in the pharmaceutical industry to move away from the traditional model of a marketing study but they were slowly coming round to the “new world”.

“Trials need to be big if we want to start selecting patients for treatment we need to demonstrate that we have found a statistically valid predictive biomarker – typically over 1000 patients which is a step up from the size of trials we are used to dealing with.”

“We need to set it up so markers are being measured in a way which is reproducible and we need enough of these trials to make sure it’s not just a random result.”

He cites the recent example of K-ras – a biomarker discovered consistently in several trials to predict non-response to treatment with EGFR inhibitors.

That finding made it into the guidelines without a prospective trial.

But that is not a realistic model for future work, says Seymour.

“Normally we would want to do a prospective study and we never did that with K-ras – we went straight for retrospective licensing.”

“I don’t think we’re going to be able to do that for every marker that comes along, we’re definitely going to have to do prospective research and that’s something we don’t have a lot of experience with.”

He is just about to launch FOCUS a trial testing a couple of biomarkers that have been found retrospectively.

“We’re going to need 3000 patients and that’s a tall order – we don’t normally do trials quite that big.”

Professor Thomas Hudson, director of the Ontario Institute of Cancer Research agrees that the numbers are daunting.

“In many cases it will be a five to ten times bigger trial and the funding agencies are not quite used to this.”

“People are tackling it, there are efforts, it has been going on, but every time you speak to committees of funding agencies they say it’s tough.”

He said they are very keen on using their research budget to fund molecular tests.

“We see ourselves as co-sponsor – companies do care about getting the right drug for the right person.”

“But still I see there’s not enough people willing to put up the dollars for the tests which is why we are funding them.”

Speaking at “A Platform of European Cancer Research Centers for Translational Research” meeting in UNESCO in Paris last year (Brown, 2009), Professor Piccart called for a “paradigm shift”.

“We need a change in culture. We are working too much in isolation.”

“We need to go for an early sharing of all non-protected biomarker data. We have started to dream about personalised cancer therapy, but it is not there yet.”

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