First randomized trial of targeted cancer medicine in all tumor types

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A further step along the road to the personalisation of cancer medicine, where treatment is based on the individual molecular characteristics of tumours rather than their primary site, will be presented at the 2013 European Cancer Congress (ECC2013), which starts on Friday 27 September in Amsterdam, The Netherlands.

Dr Christophe Le Tourneau, Head of the Phase I Programme at the Institut Curie, Paris, France, will tell the congress that the SHIVA trial is the first randomised trial to look at patient outcomes after treatments were chosen according to the individual molecular profiles of each person's tumour. It is also the first trial to do this for all tumour types. About 40% of all those taking part in the trial have molecular abnormalities that can be targeted by existing drugs, he will say.

To date, 320 patients from seven comprehensive cancer centres across France have been included in this phase II trial, of whom 60 have been randomised. In the standard arm, the patients received the chemotherapy they would have received if they had not been participating in the trial. All patients had recurrent or metastatic cancer that was unresponsive to standard treatment for their disease.

"Our goal is to have 200 randomised patients," says Dr Le Tourneau. "Although 40% of the 320 patients have a tumour for which targeted drugs are available, some are still on the chemotherapy that was started at the time of the biopsy and therefore we will have to randomise them later. Because we are looking for an effect in different kinds of tumours,

we have ruled out the inclusion of any particular type of tumour if this brings the number of randomised patients with this type to over 20% of the total. We have also allowed the inclusion of patients with rare tumours."

Preliminary results of the feasibility study, to be presented at the congress, show that this approach works, the researchers say. The ultimate goal of the phase II trial is to see whether the selection of drugs that target the specific molecular profiles of tumours will improve outcomes for patients.

Once the first 100 patients were included, the researchers looked at the feasibility of a biopsy of a metastasis, since the molecular profile of the primary tumour, if tissue is available, may not be the same as that found in a metastasis. They also investigated the quality of available tumour samples, the proportion of the patients for which the necessary analyses could be undertaken, the proportion for which a molecular abnormality can be identified and for which a targeted therapy exists, and the timeframe needed to establish the tumour profile.

"Recent advances in diagnostics have enabled us to ascertain the molecular profile of tumours in a timeframe which is compatible with good clinical care, but we needed to verify this in our study," says Dr Le Tourneau.

Unlike conventional chemotherapy, molecular targeted agents only work in the presence of their targets. Side-effects are lessened and, in principle, efficacy heightened. One of the problems to date, however, is that such drugs have principally been developed based on the primary location and histology (cellular make-up) of the tumour. This has meant that many potentially promising targeted drugs have failed in early clinical trials simply because they have not induced a response in a sufficient number of patients.

"The history of breast cancer changed beyond recognition with the discovery of the role played by the ErB2/HER2 gene, which is amplified in up to 20% of breast cancers. And we now know that trastuzumab (Herceptin), one of the most widely-used targeted cancer therapies, which targets that gene, is effective in several tumour types and not just in breast when the ERBB2/HER2 gene is amplified or even mutated," says Dr Le Tourneau. "We also know that patient outcomes in the few trials to date where the choice of treatment is based on a molecular abnormality are better than those where the treatment is not matched to the abnormality. What was missing to date is a histology-independent randomised trial comparing molecular targeted treatment with conventional therapy, and this is why I decided to set up the SHIVA trial."

Even today, the researchers say, molecularly targeted therapy for cancer patients is initially prescribed according to the location of the primary tumour. At the end of the trial, analysis of progression–free survival will show whether this practice needs to be changed.

A positive finding would imply the need to make major changes in the way cancer drugs are developed and tested in patients. But this would represent a new and difficult challenge.

"At present we have no data on the efficacy of drugs in patients with the same molecular abnormality but different tumour types, and we also suspect that a treatment effect would not depend on the presence of a single molecular abnormality, but, more likely, on several. However, we believe that it is most likely that, in future, tumour location and histology will no longer be the primary criteria for the prescription of molecularly targeted agents; rather, tumour biology will be the deciding factor," says Dr Le Tourneau. "A positive result from our trial would be an important step forward on the road to personalised medicine."

Professor Cornelis van de Velde, President of ECCO, said: "This ground-breaking randomised trial is very exciting since this is the way to individualise therapy. We have already moved from empirical to stratified treatment, and now we can offer patients personalised treatment based on the understanding of the particular molecular profiles of their tumours in order to select drugs that target a specific profile. The means to determine the individual molecular profiles of tumours will be readily available at low cost in the years to come, and the integration of biopsy-based molecular profiles with individual patient characteristics will enable precision diagnosis to be translated into precision personalised therapies. ECCO will have an important role to play in ensuring the incorporation of molecular biology genetics into clinical multidisciplinary meetings."

Provided by ECCO-the European CanCer Organisation