

## Inherited Variation and Clinical Cancer Care

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### Summary

Dr Mackay began by describing BRCA mutations and observations in the laboratory about the susceptibility of BRCA2-null cancer cells to the chemotherapy drug cisplatin. This information is being used to establish a clinical trial based on genetic information into the treatment of breast cancer in BRCA mutation carriers. He then went on to outline the Chemocare Database and its potential in working towards the ultimate goal of individualised cancer care.

Dr Mackay began by outlining the current status of BRCA1 and BRCA2 testing in London. The testing process has two main stages - initially a blood sample is taken from an individual with cancer, DNA extracted and a mutation searched for. If a mutation is identified DNA testing can be offered to other family members. Approximately 3000 patients have had the BRCA test performed on 60% of the gene sequence, in accordance with former NHS practice. Although funding has now been received to test the remainder of these patients' BRCA gene sequence there is currently a large backlog of patients with incomplete test results. The important clinical message is that there are many patients with inconclusive results and their interpretation of this information is unclear.

If a BRCA mutation is identified in an individual they are considered to be at high risk of developing breast or ovarian cancer at an early age. In mutation carriers somatic cells carry one copy of the normal gene and one faulty copy. If this individual goes on to develop cancer, genetic analysis of tumour cells shows that they only contain the faulty BRCA gene (NB - this is not the only change in cancer development, it is a multi-step process).

Research carried out by Alan Ashworth, Andy Tutt and colleagues in the Breakthrough Breast Cancer laboratory at the Institute of Cancer Research has identified that cells lacking BRCA2 (equivalent to cancer cells) are approximately 20 times more sensitive to the drug cisplatin (a platinum analogue) than other chemotherapy drugs. The reason for this sensitivity is thought to be due to the fact platinum causes many double stranded DNA breaks. These breaks can be repaired by two different mechanisms; one pathway is error free but requires an intact BRCA2 pathway and the second pathway works without BRCA2 but allows replication mistakes.

Therefore in BRCA2-null cancer cells DNA breaks are repaired by the BRCA2 independent error-prone mechanism and errors accumulate which will eventually kill the cell.

Important questions must be asked in order to transfer this laboratory observation into information that can be used for cancer therapy in the clinic. For example, are tumours in BRCA2 carriers more sensitive to platinum than other drugs? Is the normal tissue in BRCA2 carriers also more sensitive to platinum than other drugs? This final question is important because if there is a disparity between sensitivity of normal and tumour cells to a chemotherapy drug this offers exciting clinical potential to remove tumour cells without damaging normal tissue.

A study is to be carried out in known BRCA carriers with breast cancer who have relapsed. Patients will be randomised to either taxane or platinum and transferred to the corresponding drug if there is disease progression. It may be difficult to recruit enough BRCA carrier volunteers due to the inconclusive mutation testing described earlier. There is strong international support for this study which is the first chemotherapy trial based upon inherited genetic makeup in the world. The trial has begun in the UK but no international recruitment is yet taking place due to finalisation of international sponsorship arrangements.

Finally Dr MacKay described the Chemocare database which has been designed by Clinisys Oncology Ltd to improve the collection of routine clinical data on cancer therapy. It has information on a) drug dose, prescription and delivery b) over 150 chemotherapy protocols, including information on common and rare side effects and c) all laboratory tests performed on patients since their chemotherapy was started. Currently the database contains information on over 2.4million prescriptions and around 5-600,000 patients. It can be used to identify many variables such as individuals who have had severe reactions to chemotherapy and also those who are relatively stable on a particular treatment.

Any NHS Trust is able to purchase this database and enter their own data. If a single blood sample was to be taken from individuals with consent then genetic data could also be included. Once the data has been anonymised it can be analysed and associations between inherited genetic variation and markers of tumour biology may be identified. This information could be used to predict individuals who are going to respond well to a particular treatment and those who will have severe side effects. The ultimate goal of collating this information is working towards individualised cancer care.