Discovary

A consortium of researchers dedicated to the understanding and treatment of Ovarian Cancer

LAY PROGRESS REPORT 2011 FOR

THE Emer Casey FOUNDATION

The difficulty in diagnosing and treating ovarian cancer in 2004/2005 in Ireland

Ovarian cancer is the 4th leading cause of cancer deaths among western women. Ovarian carcinoma has remained the most challenging of all the gynaecological malignancies for two reasons. First, early-stage disease that has a good prognosis cannot be detected easily. Early stage ovarian cancer has up to a 90% 5-year overall survival rate whereas late stage cancers have less than a 30% 5-year survival rate. The lack of a sensitive screening test results in patients being diagnosed with advanced cancer (cancer that has spread beyond the ovary).

Second, standard chemotherapy approaches such as paclitaxel and carboplatin often fail and patients develop recurrent chemoresistant disease. Patients with ovarian cancer are treated with a combination of surgery and/or chemotherapy. The common scenario is that a patient will first have surgery and then receive chemotherapy (usually carboplatin and paclitaxel) after this. About 25% of patients will not respond to this chemotherapy and their tumours continue to grow. A further 50-60% will respond initially and within 18-24 months the tumour may re-grow and no longer respond to chemotherapy. There is a limited understanding of the mechanisms of why the tumours grow back and no longer respond to the chemotherapy.

How is the research being done by DISCOVARY focused on dealing with these different challenges, and progress realised to date;

The two major challenges in ovarian cancer is diagnosing the disease at an early stage (still confined to ovary) and to overcome the problem of tumours no longer responding to chemotherapy.

The DISCOVARY consortium is committed to addressing these problems, however, a cure will not be found overnight and while biomarkers have been identified that may aid in diagnosis and determine prognosis, these have to be validated before they can be used in the clinical setting. Validation of such markers is currently being performed.

Research is ongoing internationally on the challenges posed by ovarian cancer so why does DISCOVARY think they can do better?

Firstly, the consortium has established a well characterised bioresource of matched blood and tissue from patients undergoing surgery for ovarian disease and there is detailed follow up and survival data for all patients. This is an invaluable resource for any ovarian cancer study and it has been a limiting step for some of the research performed to date in other ovarian cancer groups. We also obtain blood samples for any patients undergoing chemotherapy for ovarian cancer at intervals throughout their treatment and on completion of treatment. Analysis of these samples will allow us to identify markers in the blood that will tell us how the patient is responding to treatment.

Secondly, the DISCOVARY consortium has the expertise and infrastructure to address the challenges posed by ovarian cancer. The acquisition of the SOLiD 2nd generation sequencing machine is allowing us to characterise the precise genetic content of patients' samples. This acquisition was made possible by a donation of €75,000 from the Emer Casey Foundation and other donations received through Matheson Ormsby Prentice. Running a sample on SOLiD generates an enormous amount of data. Each sample typically takes months to analyse so the findings from this will not be available immediately. That said this is the most comprehensive way to map genetic changes in patients' samples and by detecting variations common among samples we stand the best chance of making real inroads into better understanding the disease and confirming the utility of markers.

The key findings of the consortium to date

1. **Identified an antibody signature in early and late ovarian cancer which could be used a blood test for the disease [novel findings]**

   This is work carried out by one of the Emer Casey PhD fellows, Mairead Murphy. Serum samples from patients in the bioresource with ovarian cancer, benign ovarian disease and healthy controls have been screened to determine if they express different patterns of autoantibodies. Panels of autoantibodies have been identified that can distinguish early and late ovarian cancer and these are currently being validated. Once validated these markers could then be examined in a clinical trial.

2. **We have identified a chemical inhibitor [MMP9i] that may be able to restore chemosensitivity [novel findings]**

   Using tumour tissues from our bioresource we have identified a gene that is higher in the tumours that grow back and no longer respond to chemotherapy. We have grown ovarian cancer cells in the lab and added a chemical that blocks this gene and found that we can make a tumour respond better to chemotherapy. We are currently trying to work out how this chemical inhibitor exerts this effect.

3. **Identified hypoxia as having a major role in the chemo response in ovarian cancer, particularly contributing to chemoresistance [novel findings]**

   This is work carried out by another of the Emer Casey PhD fellows, Lynda McEvoy. Lynda has found that ovarian cancer cells which are grown in a low oxygen environment (hypoxia) don't respond as well to chemotherapy. Low oxygen is common in ovarian cancer as the tumour usually grows in a large mass so the inner part of this mass wouldn't be receiving as much oxygen. Lynda is currently trying to work out how this low oxygen concentration can have this effect on the response to chemotherapy and she will be using SOLiD to do this.

4. **Hypoxia appears to drive cross chemoresistance in ovarian cancer [novel findings]**

   An additional finding by Lynda was that this low oxygen concentration can also make the cells resistant to one drug but sensitive to another. This cross resistance pattern was seen with the two drugs used to treat ovarian cancer; platinum and paclitaxel. This could have important implications in the treatment of ovarian cancer as both drugs are given in combination. Lynda is currently looking at tens of thousands of genes on a slide known as a microarray and analysis of this should give important insights into how this cross resistance occurs.

5. **Somatic mutations in BRCA-1 and BRCA-2 genes may play a pivotal role in chemoresistance in ovarian cancer [novel findings]**

   BRCA1/2 are the genes involved in inherited breast and ovarian cancer. Certain mistakes in these genes (known as mutations) can predispose a woman to breast or ovarian cancer. Women who inherit a faulty BRCA1/2 gene are at higher risk of developing breast or ovarian cancer. But now it has been shown that there are mistakes in these genes that are not inherited so mistakes in this gene can be responsible for a greater number of ovarian cancers than previously thought and a clinical trial is about to begin using a drug (PARP inhibitors) that targets the mistakes in these genes. This work is being done in collaboration with Prof Bryan Hennessy of RCSI and MD Anderson in Texas.

6. **Successfully able to isolate cancer stem cell populations from ovarian cancer which have the capacity to regenerate cancer stem cell and non-stem cell phylogenies [novel findings]**

   Cancer stem cells are believed to be the cells responsible for starting the tumour and within very tumour it is believed there is a population of these "starting cells" as well as the bulk of the tumour. It is believed that these cells are the ones responsible for the tumour growing back and not responding to treatment. Brendan Ffrench, an Emer Casey PhD fellow is investigating these "starting cells" in ovarian cancer. Brendan is working on techniques to separate these cells from the main bulk of tumour and he has successfully done this. He now needs to show that these cells are capable of starting a tumour in an animal model as this is one of the characteristics of cancer stem cells. He will then use SOLiD to examine these cells and this will give us information on the genetic make up of these cancer stem cells and will have huge implications in ovarian cancer and other cancers.

7. **We have demonstrated that ovarian cancer creates a pro-thrombotic environment by the production of PDGF [novel findings]**

   Ovarian cancer patients are at high risk of developing a clot both before and after surgery and we are trying to understand why this happens. One of the factors that could be responsible for this is platelet derived growth factor and a high level of this could identify patients more at risk of developing clots. This can have important implications in the treatment of these patients as they could be prescribed anti clotting drugs to prevent this.

8. **Ovarian cancer cells utilize platelets to form 'platelet cloaks' so as to avoid the natural immune system. This forms the basis of the SFI CSET Onc-1 Programme [novel findings]**

   Cancer cells can spread to other parts of the body and it is this process called metastasis that can lead to the death of the patient. One method used by the cancer cells to spread is for them to enter the blood system and travel around to another site. Usually the body's immune system can recognize foreign bodies in the blood and get rid of them. So why does this not happen in cancer? It is thought that a component of the blood known as platelets can stick to the tumour cells and prevent the immune system from recognizing the tumour cells. How this happens is now the subject of the Onc-1 programme which is a 5 year study. The acquisition of SOLiD and the funding from the Emer Casey foundation were crucial factors in obtaining this funding.

9. **Platelet cloaking of metatstatic cancer cells is not confined to ovarian cancer and is a fundamental process in the metastatic highway in all cancers [novel findings]**

   The platelet cloaking process which helps cancers spread throughout the body is not confined to ovary and is important in all cancers. Understanding this with the help of SOLiD could pave the way for cancer treatment in the future.

10. **Epithelial mesenchymal transition [EMT] is fundamental to the metastatic process and is supported by platelet cloaking of metastatic cancer cells [novel findings]**

    For cancers to get out into the blood stream they have to change some of their properties and undergo a process called EMT. To come back out of the blood stream and invade another organ they have to reverse those properties and undergo MET. We have shown that platelets help this process. This supports the evidence for platelets helping the cancer to spread and the exact way this happens is being examined.

11. **Fabricated a novel hypoxia lab-on-a-chip device which allows near patient testing of ovarian cancer cells from patients to assess the efficacy of various chemotherapeutic agents.**

    In collaboration with Dublin City University we have developed a device which will allow us to take some of the patient's tumour sample and treat it with chemotherapy to see what drugs can kill the tumour. This has important implications for the treatment of ovarian cancer.

For a patient seeking treatment now, identify advances which have occurred, and how they improve the treatment of ovarian cancer.

Currently a woman with suspected ovarian cancer will have a blood sample taken and a trans vaginal ultrasound performed. Addition radiological imaging including CT scan and an MRI will also be performed. While different characteristics seen on the scan may indicate whether an ovarian mass is malignant or benign; this is not conclusive until a biopsy is obtained or the mass removed and examined by a pathologist.

The standard of diagnosis and treatment for ovarian cancer has not changed over the past 15 years. The same drugs are being used despite their lack of effectiveness. There is an unmet clinical need to improve the diagnosis and treatment of this disease and the DISCOVARY consortium are striving to do this. With the help of the SOLiD 2nd generation sequencing platform and the infrastructure and expertise we have built to date we are in a prime position to address the challenges posed by this dreadful disease. However, this will not happen overnight and ovarian cancer has a complex biology but we have made some novel findings detailed above which has given us a deeper insight into the biology of this disease.

The DISCOVARY consortium now enrols any patient coming in to St James's Hospital Dublin for surgery for ovarian disease. The various studies are explained to the patient and they are asked for their permission to take a blood sample and some of the tissue removed from surgery. This is placed in the bioresource and allows us to identify markers that have not previously been described and which may be used in the future to diagnose the disease or tell us which chemotherapy a patient should have and how they will respond. We have identified diagnostic markers and markers which will tell us the outcome a patient will have (prognostic). These are currently been validated. To bring such markers into the clinical setting rigorous validations need to be performed to ensure the optimum performance. Many groups have identified potential markers but none of these have reached the clinic as they have failed the validation step. So it is extremely important that we have full confidence in the marker brought forward for this step. Our internal validations are ongoing and we anticipate a validated biomarker panel by the end of this year.

To illustrate the qualitative patient benefits from the SOLiD next generation sequencing platform. In addition, how many patients are benefitting from SOLiD, and are the benefits available to patients country wide.

SOLiD is helping us to understand the biology of ovarian cancer so the patient benefit will not be seen instantly. We see this as a 5 year programme where important genes and markers are identified and validated in a clinical setting.

We envisage SOLiD being incorporated into the clinical setting for the role of personalised medicine. Everyone's tumour is different but current treatment treats all similar cancers the same way and this is based on clinical trials that have been performed. However, medical evidence is telling us we need to treat every patient differently and design a treatment for each individual. When this happens then SOLiD will be crucial to analyse every sample and work out what treatment that patient needs. Currently SOLiD would be very expensive to use routinely. However, we are using the platform as a research tool at present to comprehensively map patients' samples. Once we have a training set of data completed it will be possible to refine the analysis to focus on just the areas of a person's DNA that are specifically altered in ovarian cancer and this will make the analysis more affordable and faster to run.

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