Improving Platinum Therapy for Ovarian Cancer Patients

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Executive summary

Less than half of women diagnosed with ovarian cancer in the UK survive for five years following their diagnosis. Platinum therapy is important in the fight against this, but unfortunately patients often develop resistance to this treatment. A team of scientists at Imperial College London believe they may have identified a way to overcome this resistance, and improve the quality of life and survival prospects and for thousands of ovarian cancer patients.

Who will benefit from this project

This project will help the 7,000+ women each year who are diagnosed with ovarian cancer in the UK. Survival rates for these women depend on the stage their cancer has reached by the time they have been diagnosed. For those British women presenting a stage IV cancer, their survival prospects are only a shocking 5%. The overall five year survival rate is 46% for British women with ovarian cancer.

As has been often noted, ovarian cancer patients in the UK have a poorer chance of survival than women in other countries. The detailed in-depth comparison study published by the International Cancer Benchmarking Partnership (ICBP)[1] indicates that this is not because of a failure to spot the disease early in the UK, as was assumed for some time. Instead the results suggest that when the disease is spotted late, the UK seems to be worse at managing these patients than other countries. By improving platinum therapy, the project outlined in this paper aims to improve the survival prospects and quality of life for ovarian cancer patients in the UK, and hopefully worldwide.

Background to project

Platinum-based chemotherapy is an important treatment in ovarian cancer. However, whilst it is usually effective at the onset of treatment, resistance often develops and the response to chemotherapy becomes significantly diminished. Maintaining platinum sensitivity and understanding the mechanisms to overcome platinum resistance is key to improving survival of this disease.

A team based at Imperial College London, and partly funded by Action Against Cancer, have been working in this field of research. These scientists believe they may have identified a novel approach to overcoming platinum therapy resistance, and now require the funding for a new project to continue the exploration of this poorly understood area.

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[1] Maringe, C. et al (2012). Stage at diagnosis and ovarian cancer survival: Evidence from the International Cancer Benchmarking Partnership, *Gynecologic Oncology, 127* (1) 82. DOI: 10.1016/j.ygyno.2012.06.033 & http://scienceblog.cancerresearchuk.org/2012/10/03/treating-late-stage-ovarian-cancer-why-does-the-uk-do-so-badly/

Progress to date

The team have been conducting experiments on RNA, a molecule similar to DNA but single stranded. MicroRNAs (called miRNAs) are small pieces of genetic code crucial for regulating cancer genes. In a recently published paper, the team demonstrated a previously undescribed mechanism of the regulation of miRNAs by a tumour protein called TP53.[2] This has relevance to the process of how normal cells turn into cancer cells and the tumour response to DNA-damaging agents. In this work, it was shown that TP53 binds to a protein coding gene and regulates the association of a number of miRNAs. This has an important effect on the co-ordination of the cells response to chemotherapy. Interestingly, the BRCA genes were shown to be targeted. Women with harmful mutations in a BRCA gene have a risk of breast cancer that is about five times the normal risk, and a risk of ovarian cancer that is about ten to thirty times normal.[3]

The intention is to use tumour samples from a study (SCOTROC4[4]) conducted by another team in which ovarian cancer patients were treated with platinum therapy alone. These samples provide a unique translational resource for assessing predictive and prognostic biomarkers of response to platinum therapy in patients with high grade ovarian cancer.

Project objectives

1) Improve understanding of the role of RNA and miRNAs in response to platinum chemotherapy.
2) Define the differing effects of various TP53 mutations on the RNA signatures of ovarian cancer. This will allow:
    - Better identification of patients who will or will not respond to platinum therapy early in their disease.
    - Toxicity to be reduced and quality of life improved for those women in whom platinum therapy alone may be sufficient without the need for combination chemotherapy.
    - More appropriate treatment for patients who would not respond well to platinum therapy, as doctors would know to use platinum sensitising agents from the outset or to treat them with drugs such as taxol. This would improve progression free survival in this patient group and help to avoid toxicities associated with drugs that will not be effective.
3) Derive novel drug targets for overcoming platinum resistance, which will improve survival outcomes for ovarian cancer patients.

It will be demonstrated that the objectives have been achieved by the dissemination of findings in publications in high impact factor peer reviewed journals, presentations at national and international conferences and in articles in the press.

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[2] Krell J, Stebbing J, Carissimi C, Dabrowska AF, de Giorgio A′ Frampton AE, Harding V, Fulci V, Macino G, Colombo T, Castellano L.TP53 regulates miRNA association with AGO2 to remodel the miRNA-mRNA interaction network. Genome Res. 2015 Dec 23.

[3] "BRCA1 and BRCA2: Cancer Risk and Genetic Testing". National Cancer Institute. 29 May 2009.

[4] Banerjee S[1], Rustin G, Paul J, Williams C, Pledge S, Gabra H, Skailes G, Lamont A, Hindley A, Goss G, Gilby E, Hogg M, Harper P, Kipps E, Lewsley LA, Hall M, Vasey P, Kaye SB. A multicenter, randomized trial of flat dosing versus intrapatient dose escalation of single-agent carboplatin as first-line chemotherapy for advanced ovarian cancer: an SGCTG (SCOTROC 4) and ANZGOG study on behalf of GCIG. Ann Oncol. 2013 Mar;24(3):679-87. doi: 10.1093/annonc/mds494. Epub 2012 Oct 5.

Project activities

1. Perform RNA and miRNA sequencing on non-microdissected samples from patients treated in the SCOTROC4 trial.
2. Perform RNA and miRNA sequencing on a smaller selected cohort of patients treated in the SCOTROC4 trial after microdissection of the samples has been performed.
3. Perform DNA sequencing for TP53 and BRCA mutations in patient samples.
4. Use a bioinformatic and statistical approach to assess a relationship between:
    a. RNA and miRNA signatures and outcome
    b. Specific TP53/BRCA mutation and outcome
    c. TP53/BRCA mutation and RNA and miRNA signatures
    d. Markers in the tumour microenvironment and their correlation with outcome.

Budget and funding

Item	Cost
Research Technician salary (12 months)	£53,000
Bioinformatics support	£15,000
DNA & RNA extraction	£10,000
DNA sequencing	£25,500
RNA sequencing	£74,500
cDNA library prep kits	£9,400
Desktop computer	£1,000
Laptop	£1,000
	£189,400

Some indirect costs will be covered by the Imperial Centre for Translational and Experimental Medicine at Hammersmith Hospital in London where the project will be undertaken, for example, performance monitoring and evaluation. The NHS and Cancer Research UK will also indirectly support this project, as they jointly fund the Experimental Cancer Medicine Centre at Imperial College, which will provide technical support for obtaining samples and providing them on slides.

Timetable

Preparing samples comprises the initial activities of this project, and as this will be done by the staff at the Experimental Cancer Medicine Centre at Imperial College, this can commence in Summer 2016 whilst recruitment begins for the required Research Technician. That person would be required for 12 months. Following this there may be further analyses and validations of data required for up to six months, to be undertaken by the scientists overseeing the work. Thus, the project in its entirety will take up to two years.

Conclusion

There is highly promising preliminary data to suggest that TP53 and its effect on miRNAs has a significant role to play in the efficacy of treating ovarian cancer with platinum therapy. The overall aim of this research is to improve survival rates of patients with ovarian cancer.