Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Improving Outcomes for Patients with Gestational Trophoblastic Disease (GTD)

1. Summary of the impact (indicative maximum 100 words)

GTD is a group of pre-malignant and cancerous conditions that affect pregnancy occurring in 1800 women annually in the UK. The Charing Cross GTD centre at Imperial College is a world leader in this disease area and since 2008our impacts include the health and welfare benefits associated with the development of new combination chemotherapy regimens which have been recognised in national and international guidelines and the refinement of patient stratification to a particular treatment. Imperial researchers have taken a leading educational role both nationally and internationally on the disease and its management to help others to develop new centres in their own countries.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Edward Newlands, Professor of Cancer Medicine (1989-present), Honorary consultant medical oncologist (1975-present) and Head of the GTD Service from 1991-2004
Professor Michael Seckl, Professor of Molecular Oncology (2002-present), Honorary consultant medical oncologist (1995-present) and Head of the GTD Service (2004-present)

GTD affects 1800 women in the UK each year and comprises the premalignant conditions of complete and partial hydatidiform moles through to the malignant invasive mole, choriocarcinoma and rare placental site trophoblastic tumours. The Charing Cross GTD service at Imperial College is the world's largest centre for managing this group of illnesses and plays an international leading role in establishing effective treatment and management protocols.

Development of new treatments
The Charing Cross centre under Professor Newlands (Head of Service, 1991-2004) developed an effective salvage chemotherapy called EP/EMA (a combination chemotherapy of **e**toposide and cis**p**latin with **e**toposide, **m**ethotrexate, **a**ctinomycin) for women relapsing after EMA/CO chemotherapy (a combination chemotherapy of **e**toposide, **m**ethotrexate and **a**ctinomycin with **c**yclophosphamide and vincristine [**o**ncovin]), also developed at Charing Cross by Professor Newlands). EP/EMA was piloted in a non-randomised phase II study between 1980 and 1997 and our results published in 2000 (1) showed a 75% cure rate for women failing EMA/CO chemotherapy. However, the treatment was associated with frequent side-effects often requiring delays, dose reductions or even cessation of therapy and was quite difficult to administer so a new less toxic alternative was required (1). Professor Seckl (1995 onwards) therefore developed and introduced a regimen called TE/TP (a combination therapy of paclitaxel (**T**axol) and **e**toposide, followed by paclitaxel (**T**axol) and cis**p**latin) in 1999. This was used both to rescue patients with testicular germ cell tumours who had failed one or more types of chemotherapy as a prelude to high dose chemotherapy and also to treat women with GTD who had failed EMA/CO or subsequent EP/EMA chemotherapy. Our Phase II trial results were published in 2004 in men with testicular cancer and in 2008 (2) in the GTD patients. TE/TP was much better tolerated than EP/EMA and cured at least 70% of women failing EMA/CO chemotherapy (2).

Refinement of patient stratification
The commonest form of GTD is the premalignant condition of a hydatidiform mole or molar pregnancy. About 10% of affected women develop cancer following a molar pregnancy and require chemotherapy. Patients used to be stratified to one of 3 types of chemotherapy (low, medium and high-risk) depending on their risk of developing disease resistance to single agent treatment with methotrexate or actinomycin D. The low risk patients received single agent therapy whilst the

medium and high risk patients received two different types of combination agent chemotherapy both of which were more toxic than single drug treatment. In 2002 we published the results of a long term study investigating a novel algorithm for managing patients in which the low and medium risk groups were merged into a new larger low risk group. This enabled more patients to start treatment with the least toxic single drug chemotherapy, methotrexate. In addition, using the novel algorithm, those patients who became resistant to methotrexate instead of automatically changing to combination agent chemotherapy were instead only given this if their tumour burden was higher than a certain amount assessed by the level of the pregnancy hormone hCG. Those women with an hCG less than 100 IU/L simply received anther single agent actinomycin D. Our results (3) showed that following this protocol, 100% of women in this new low risk group could be cured and that fewer women needed exposure to the more toxic combination agent therapies.

Education
Nationally, we and the Sheffield GTD centre have been running annual training days to facilitate awareness and understanding of this rare group of diseases amongst UK health professionals. This has been lead by Professors Newlands, Seckl (Imperial College) and Hancock/Coleman (Sheffield) since 1995. In addition, we regularly host national trainees in our centre and help to shape national guidelines. Internationally, Newlands/Seckl impart their experience in managing GTD at numerous meetings/conferences and in Europe Seckl played a founding role in establishing the European Organisation for the Treatment of Trophoblastic Disease (EOTTD). The Imperial GTD centre is frequently visited by doctors from other countries that spend time with us to learn how we manage GTD and to re-import this experience to their own countries. Thus, we have helped others to establish GTD centres in their own countries. For example, in 1998-2000 Seckl was visited on several occasions and paid a return visit to a medical team from Lyon as they created their own centre. Similarly we have been visited by medical teams from Switzerland, Australia, Brazil, Norway, Ireland and elsewhere to learn from our experience and adopt/adapt this in their own countries.

3. References to the research (indicative maximum of six references)

(1) Newlands, E.S., Mulholland, P.J., Holden, L., Seckl, M.J., Rustin, G.J.S. (2000). Etoposide and Cisplatin/Etoposide, Methotrexate, and Actinomycin D (EMA) Chemotherapy for Patients With High-Risk Gestational Trophoblastic Tumors Refractory to EMA/Cyclophosphamide and Vincristine Chemotherapy and Patients Presenting With Metastatic Placental Site Trophoblastic Tumors. *J. Clin. Oncol*, 18; 854-859. Times cited: 102 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 18.03

(2) Wang, J., Short, D., Sebire, N.J., Lindsay, I., Newlands, E.S., Schmid, P., Savage, P.M., Seckl, M.J. (2008). Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol*, 19 (9), 1578-1583. DOI. Times cited: 28 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 7.38

(3) McNeish, I.A., Strickland, S., Holden, L., Rustin, G.J.S., Foskett, M., Seckl, M.J., Newlands, E.S. (2002). Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinic acid, 1992-2000. *J Clin Oncol*, 20 (7), 1838-1844. DOI. Times cited: 93 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 18.03

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, practitioners and services, public policy
Main beneficiaries include: patients, practitioners, international policy makers

Our findings on EP/EMA and TE/TP were presented at national, international meetings and published as above. Our colleagues in Sheffield, various medical groups around the world and associated organisations (International Society for the Study of Trophoblastic Disease [ISSTD], European Organisation for the Treatment of Trophoblastic Disease [EOTTD], Federation

Internationale for Gynaecolgic Oncology [FIGO]) benefitted from this research, started to use and/or recommend the regimens and they are now widely but not solely employed to treat women who relapse following EMA/CO chemotherapy. Moreover, colleagues in other countries have started to publish with these regimens. In the UK these therapies have been used to treat about 50 women since 2008. World-wide we estimate several hundred women have received EP/EMA or TE/TP since 2008. Most of these women will likely have been saved as a consequence.

The regimens are now recommended in the following guidelines: the Royal College of Obstetricians and Gynaecologists 2010 [1; see pages 6 and 7], the Dutch guidelines 2010 [2], International Society for the Study of Gestational Trophoblastic Disease 2012 [3], and the Australian 2009 guidelines [4].

The results of our work (research reference 3) were presented at national and international meetings. The concept of a merged low and middle risk group was adopted by the FIGO committee and went into the new FIGO scoring system used in national and international guidelines published since 2008 [5]. The step wise use of either another single agent actinomycin D or the introduction of combination agent chemotherapy (EMA/CO) depending on the level of hCG at the point of resistance to methotrexate was adopted initially in the other UK centre in Sheffield but then also in the Netherlands [2], Australia [4], Lyon [6], and elsewhere. In the UK this policy has impacted on the management of about 130 women per year and lead to a further refinement as the hCG cut-off was then increased to 300 IU/L and following a recent audit in which overall cure rates are still running at 100% we will likely increase the cut-off to 1000 IU/L. With the present hCG cut-off, we have saved about 15 women per year in the UK from more toxic combination agent chemotherapy. If this is replicated across the world we will spare about 1700 women per year from unnecessary toxicity. A further increase in the hCG cut-off to 1000IU/L will potentially spare 30 women per yr in the UK from combination agent chemotherapy. The latter has not only short-term side-effects such as hair loss, increased risk of infections and lethargy but in the longer term brings forwards the date of the menopause by 3 years and can minimise the incidence of second cancers in later life [3].

Our on-going research and large national experience has enabled us to play a leading role in teaching practitioners how to manage GTD [3]. The Charing Cross GTD centre (Seckl, Newlands) have been heavily engaged in both international organisations (ISSTD and EOTTD) [3, 7]. We have encouraged approximately 40 exchange visits since 2008 with medical teams from various hospitals around the world which has helped to stimulate the development of new centres in these countries. We continue to advise the centre on how to manage difficult cases, they have adopted our new treatments and we provide them with genetic diagnostic support [8]. Moreover, after 2008 and visits to our centre from a group in Geneva, a new Swiss GTD centre has been established in Jan 2009 [9]. Our impact is therefore not just through development of new treatments but through education events and hosting of international visitors in our centre and/or visits to other centres to share best practice.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] RCOG Green-top guideline 38
http://www.rcog.org.uk/womens-health/clinical-guidance/management-gestational-trophoblastic-neoplasia-green-top-38. Archived on 7th November 2013.

[2] Dutch working group guidelines
http://www.oncoline.nl/persisterende-trofoblast-en-choriocarcinoom. Archived on 7th November 2013.

[3] International society for the study of trophoblastic diseases book
http://www.isstd.org/isstd/book.html. Archived on 7th November 2013.

[4] Australian guideline for NSW GTD patients.
http://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0010/154549/go_clinical_guidelines.pdf.

Archived on 7th November 2013.

[5] Ngan, H.Y., Kohorn, E.I., Cole, L.A., Kurman, R.J., Kim, S.J., Lurain, J.R., Seckl, M.J., Sasaki, S., Soper, J.T. (2012). Trophoblastic disease. (FIGO cancer report). *Int J Gynaecol Obstet*, 119 (Suppl 2), S130-6. DOI.

[6] Lyon centre for trophoblastic disease. http://www.mole-chorio.com/ (archived on 7th November 2013). Can also contact the Head of Obstetrics and Gynaecology, Centre Hospitalier Lyon Sud

[7] http://www.eottd.com/

[8] Bolze, P.A., Weber, B., Fisher, R.A., Seckl, M.J., Golfier, F. (2013). First confirmation by genotyping of transplacental choriocarcinoma transmission. Am J Obstet Gynecol, 209 (4), e4-6. DOI.

[9] Rougemont, A.L., Pelte, M.F., Béna, F.S., Paoloni-Giacobino, A., Petignat, P., Finci, V. (2011) Trophoblastic diseases: a multidisciplinary approach, a first Swiss center. *Rev Med Suisse*, 7 (303), 1496-q501.