Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Systemic therapies for ovarian cancer

1. Summary of the impact

University of Glasgow research has led to the adoption of first-line chemotherapy for ovarian cancer, which has improved patient survival by 11% and has been used to treat 66% of women with ovarian cancer since January 2011 in the West of Scotland Cancer Care Network alone. These therapies are recommended by guidelines for ovarian cancer treatment in the USA, Europe and the UK. The USA guidelines are disseminated to 4.3 million people worldwide and the European guidelines reach 15,000 health professionals. The UK guidelines are used to identify those drugs that are funded by the NHS and used in NHS hospitals.

2. Underpinning research

Since 1993, University of Glasgow investigators have conducted a series of large-scale randomised clinical trials, in association with the Scottish Gynaecological Clinical Trials Group and the Gynecologic Cancer InterGroup, proving the clinical value of taxane-based drugs (such as docetaxel and paclitaxel) in combination with other anti-cancer agents (such as cisplatin and carboplatin) for the treatment of primary ovarian cancer.

Docetaxel

In the early 1990s, taxanes were a new class of anti-cancer agents with a novel mechanism of action (microtubule stabilisation). Advanced ovarian cancer is a fatal disease in most cases, so any agent that offered a potential treatment for this disease was significant. In 1993, one of the first phase I trials in the development of the taxane-based drug, docetaxel, identified the type and reversibility of drug toxicities at different doses.[1] This was led by a University of Glasgow team including Professor Stan Kaye who subsequently, as Chair of EORTC (European Organisation for Research and Treatment of Cancer) Early Clinical Trials Group, led Glasgow's contribution to phase II clinical trials of the drug, in several diseases including ovarian cancer.

In 1995 Dr Paul Vasey led a study to establish the optimum dose of docetaxel in combination therapy, initially with cisplatin, a platinum-containing anti-cancer agent.[2] This work established that cisplatin and docetaxel can each be administered at a dose of 75 mg/m^2, every three weeks. As it became apparent that carboplatin has a very similar efficacy to cisplatin, but with less toxicity, a subsequent dose escalation study was conducted with carboplatin by researchers at Glasgow.[3] This study demonstrated that docetaxel and carboplatin could be combined safely and effectively. Moreover, the study aimed to study the pattern of toxicity of docetaxel in terms of neurotoxicity (nerve damage) and neutropenia (reduction of a key type of immune cell). Among the 139 patients in the trials, the incidence of significant peripheral nerve damage for patients treated with docetaxel-carboplatin was very low (less than 6% of patients), but with the caveat of neutropenia being relatively high (86% of patients), yet tolerable.

This study led to an international large scale phase III trial with 1077 patients, led by Vasey in 1998, demonstrating that docetaxel-carboplatin was as effective as paclitaxel-carboplatin, with a different toxicity profile. Fewer patients experienced nerve damage with docetaxel compared with paclitaxel (11% versus 30%), although slightly more patients experienced neutropenia (94% versus 84%).[5] These studies were led, designed, co-ordinated and analysed by the Glasgow Clinical Trials Unit (CTU).

Paclitaxel

In 1995, a key study in the USA (GOG-111) had shown that paclitaxel-cisplatin treatment was significantly more effective for ovarian cancer than the previous standard treatment (cyclophosphamide-cisplatin). However, the results were not conclusive enough to establish paclitaxel-cisplatin as a new standard; more data were needed, particularly to establish the optimum dosage and to determine how the quality-of-life and economic impacts of the paclitacel-

cisplatin regimen compared with those of the cyclophosphamide-cisplatin regimen.

Researchers from the University of Glasgow were instrumental in the subsequent OV-10 study,[4] which began in 1995. OV-10 had wider patient recruitment eligibility than GOG-111, as it included women with both early and advanced cancers and longer intervals between their first surgery and chemotherapy, and also used surgical guidelines more closely aligned to common clinical practice. These inclusion criteria enabled 680 patients to be enrolled in 15 months, and gave the study an 80% probability of detecting an increase in average progression-free survival – the period of time during and after treatment in which the cancer does not get worse – and represented a turning point in the history of conducting ovarian cancer trials. The UK contribution to this phase III initiative was led from the Glasgow CTU initially by Kaye and latterly by Professor Jim Cassidy.

Paclitaxel was administered as a 3-hour infusion at 175 mg/m^2, instead of a 24-hour infusion at 135 mg/m^2 as used in the GOG-111 trial, and the trial end-point was progression-free survival time.[4] This study provided strong confirmatory evidence (in terms of both progression-free survival and overall survival) that paclitaxel-cisplatin therapy was superior to cyclophosphamide-cisplatin therapy. A long-term follow-up study in 2003 involving the same University of Glasgow team showed that patients who had been treated with paclitaxel-cisplatin had an 11% improvement in survival, i.e. 11% more of them were still alive after 6.5 years compared with those treated with cyclophosphamide-cisplatin, thereby establishing paclitaxel-cisplatin as a new standard regimen for treatment of patients with advanced ovarian cancer.[6]

Key researchers: (Glasgow): Professor Stan Kaye (Professor of Medical Oncology, 1985-2000), Dr Paul Vasey (Clinical Research Fellow, 1992-1996; Senior Lecturer in Medical Oncology, 1996-2003; Reader in Medical Oncology, 2003-2004; Director of Glasgow CTU, 2001-2004), Professor Jim Cassidy (Reader in Clinical Oncology, 1993-1994; Professor of Oncology and Head of the Division of Cancer Sciences and Molecular Pathology, 2001-2011), Mr Jim Paul (Senior Statistician, 1988-present). ***Key external collaborators:*** (refs 4 & 6): European Organisation for Research and Treatment of Cancer –Profs Martine Piccart (Free University of Brussels ULB) and Sergio Pecorelli (University of Brescia). National Cancer Institute of Canada Clinical Trials Group– Profs Gavin Stuart and Keith James (Queen's University, Kingston, Canada).

3. References to the research

1. Bissett, D. *et al*. Phase I and pharmacokinetic study of Taxotere (RP 56976) administered as a 24 h infusion. *Cancer Res.* 1993; 53, 523–527 (no doi available)
2. Vasey, P.A. *et al*. Docetaxel and cisplatin in combination as first-line chemotherapy for advanced epithelial ovarian cancer. Scottish Gynaecological Cancer Trials Group. *J. Clin. Oncol.* 1999; 17, 2069–2080 (no doi available)
3. Vasey, P. A. *et al.* and on behalf of the Scottish Gynaecological Cancer Trials Group. Docetaxel-carboplatin as first line chemotherapy for epithelial ovarian cancer. *Brit. J. Cancer* 2001; 84, 170–178 doi: 10.1054/bjoc.2000.1572
4. Piccart, M. J. *et al.* Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. *J. Natl. Cancer Inst*. 2000; 92, 699-708 doi:10.1093/jnci/92.9.699
5. Vasey, P. A. *et al.* Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J. Natl. Cancer Inst.* 2004; 96,1682–1691 doi:10.1093/jnci/djh323.
6. Piccart, M. J. *et al.* Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. *Int. J. Gynecol. Cancer* 2003; 13, 144–148 doi:10.1111/j.1525-1438.2003.13357.x

4. Details of the impact

Ovarian cancer is the fifth most common cancer in women, affecting 6,500 individuals per year in the UK and 22,000 in the USA. Surgery and chemotherapy are both used to treat ovarian cancer, and most patients are considered for both treatments. At least 55% of women are diagnosed with stage III or IV cancer. The survival rate five years after diagnosis is 20% for stage III and only 6%

for stage IV ovarian cancer (Cancer Research UK), although if ovarian cancer is diagnosed early (in stage I) the survival rate after five years is 90%. University of Glasgow research has helped to develop chemotherapy treatment for ovarian cancer, and is cited in current guidelines around the world, which include:

- The establishment of paclitaxel as a key chemotherapy component in ovarian cancer, which led to an 11% gain in survival rates over previous drugs;
- The establishment of docetaxel as an alternative to paclitaxel with a different toxicity profile

Adoption of paclitaxel in clinical guidelines

The OV-10 study[4], which was co-led by researchers at the University of Glasgow, established paclitaxel as the most effective chemotherapy treatment for ovarian cancer, and since publication of the results, the use of paclitaxel as the preferred chemotherapy for women with ovarian cancer has been adopted by international clinical guidelines that influence the treatment of patients throughout the UK and Europe. These include guidelines written by the European Society for Medical Oncology (ESMO), The Scottish Intercollegiate Network (SIGN) and the National Institute for Clinical Excellence (NICE).

The membership of the European Society for Medical Oncology (ESMO) includes 7,000 oncologists in 100 countries internationally; its biennial congresses are attended by over 15,000 medical professionals worldwide. ESMO has published guidelines entitled 'Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' each year since 2005. Since 2008, these recommended paclitaxel with carboplatin for advanced ovarian cancer, as described University of Glasgow's collaborative OV-10 study, and cite the long term follow-up (2003) survey.[a] This follow-up study confirmed that paclitaxel-carboplatin conferred a survival advantage when compared to cyclophosphamide-cisplatin. EMSO guidelines are followed extensively throughout Europe and by oncologists around the world.

The SIGN guidelines inform chemotherapy throughout Scotland. From 2003–2013, Guideline No. 75, 'Epithelial ovarian cancer', has recommended the use of paclitaxel-cisplatin over cyclophosphamide-cisplatin, citing Glasgow research[5] as Level 1++ evidence, representing the highest quality data (ref 103, Sections 5.5.3 and 5.5.4).[b] The guidelines describe use of taxane combination therapy as being widespread throughout Scotland.

NICE technology appraisals are the mechanism by which drugs gain approval for funding and use within the UK National Health Service. In 2003, NICE published their recommendation 'TA55 - Guidance on the use of paclitaxel in the treatment of ovarian cancer', which examines the use of paclitaxel and refers to OV-10 as one of the randomised controlled trials that demonstrate clinical effectiveness of paclitaxel in the first-line treatment of ovarian cancer (TA55 Section 4.3.1).[c] In 2009, TA55 was added to the static list; guidance is added to the static list when no new research is available with any material effect on the current guidance, thereby preserving the NHS funding.[c] The NHS funds prescription of drugs that are recommended by NICE and requires that all NICE-recommended treatments be made available within 90 days in their formularies (databases of medicines approved for use on the NHS).[d]

A UK-wide resource for prescription data is not yet launched. For this case study, data were requested from the West of Scotland Cancer Care Network. Taking into account the comparative low incidence of epithelial ovarian cancer, since January 2011, 66% of 490 women treated for newly diagnosed epithelial ovarian cancer within the West of Scotland Cancer Care Network have received a combination paclitaxel-platinum (paclitaxel-carboplatin or paclitaxel-cisplatin) therapy.[e]

Docetaxel as alternative chemotherapy

Studies carried out by the Glasgow CTU demonstrated that docetaxel could be used as an alternative to paclitaxel, was equally effective and had different side effects, making it a valuable alternative treatment for patients who react badly to paclitaxel. The side effects of chemotherapy have serious implications on the quality of life and potential recovery of the patient, and the

existence of an alternative therapy enables more tailored treatment for patients who may react badly to the recommended drug. This 2004 study[5] has enabled oncologists to safely prescribe an alternative, yet equally effective, option for patients for whom the side effects of paclitaxel, particularly neuropathy and alopecia, present major problems.

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 23 leading cancer centres in the USA, dedicated to improving the quality and effectiveness of care. Since 2010, the NCCN 'Clinical Practice Guidelines in Oncology' have recommended docetaxel-carboplatin as an alternative to paclitaxel-carboplatin, citing Glasgow research[5] as Category 1 evidence (the highest evidence level indicating uniform consensus of experts) under Epithelial Ovarian Cancer – Primary Treatment (ref 148, Section MS-8 in v.2.2013).[f] Analysis of the potential side effects of each therapy also cites the Glasgow CTU trial. The 2013 NCCN patient guidelines on ovarian cancer specify prescription of docetaxel-carboplatin as an alternative to paclitaxel with carboplatin or cisplatin in chemotherapy, describing how docetaxel is more likely to increase the risk of infection, whereas paclitaxel is more likely to cause nerve damage.[g]

The NCCN.org website, aimed specifically at clinicians, received more than 1.6 million unique visitors in 2012; the full clinical guidelines (including those for ovarian cancer) are freely available to patients, relatives and health professionals, and in 2012 were distributed to 97,000 people in paper or flash drive format, while 4.3 million copies were downloaded as PDF documents.[h]

5. Sources to corroborate the impact

a. Colombo, N. *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol*. 2010; 21, v23-v30 doi: 10.1093/annonc/mdq244.
b. SIGN, Guideline No. 75: Epithelial ovarian cancer (Sections 5.5.3 and 5.5.4); the peer-reviewed draft of the 2013 update is available on request.
c. NICE TA55: Guidance on the use of paclitaxel in the treatment of ovarian cancer (Section 4.1 and 4.3.1); Review decision in 2009.
d. NICE, GPG1 (2012) Good practice guidance: developing and updating formularies.
e. Audit of WOSCC Network data from Chemocare system provided by NHS Greater Glasgow & Clyde; available on request.
f. NCCN Clinical Practice Guidelines in Cancer: Ovarian cancer v.2.2013 (Section MS-8) [Note: free registration required]; document can also be provided on request.
g. NCCN Guidelines for patients, for discussion with clinical teams.
h. National Comprehensive Cancer Network (NCCN) Annual Report 2012.