OVER HALF OF ALL GYNAECOLOGIC CANCERS ARE RARE: BARRIERS AND CHALLENGES TO IMPROVING OUTCOMES

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Abstract

Evidence-based medicine is the bedrock for optimal clinical practice and relies on using the best available evidence from randomised controlled trials to guide management for an individual patient. Over 50% of gynaecological cancers are classified as 'rare', which creates additional challenges in carrying out clinical trials and establishing a robust evidence-base for treatment. It is now clear that epithelial ovarian cancer, one of the most common gynaecological cancer types, is not a distinct entity, but is comprised of multiple distinct subtypes which differ in their biological behaviour and response to treatment. Simply treating all patients with epithelial ovarian cancer as a uniform entity in large clinical trials will be a legacy of the past and this is applicable to most other types of gynaecological cancers as well. As we move rapidly into the era of genomic profiling, there will an exponential increase in the number of patients identified with 'rare' gynaecological cancers. Standard clinical trial design and traditional endpoints will have to change and international collaboration will be essential if we are to develop better treatments for our patients. Additional challenges, including funding, as well as regulatory requirements, will need to be overcome. This review will focus on national and international efforts to advance our understanding and management of patients with rare gynaecological cancers.

Over 50% of gynaecological cancers are classified as 'rare'.[1] There is a disparity in the outcome of patients with rare cancers, compared to patients with more common cancers, where there is often a large body of evidence from clinical trials. This is well illustrated by the inferior outcomes of patients with rare subtypes of epithelial ovarian (e.g. clear cell and mucinous) and endometrial (serous and carcinosarcoma) cancers, compared with the more common subtypes of high grade serous ovarian cancer and endometrioid cancer of the endometrium.[2-6] Establishing the best treatment for patients with rare gynaecologic cancers is difficult, due to a paucity of clinical trials designed to establish outcomes for patients with rare cancers.

Ideally, all patients with rare gynaecological cancers should have their pathology reviewed by a gynaecological pathologist and managed within a multi-disciplinary framework, with access to clinical trials and rare cancer registries. However many patients are not referred to a tertiary centre for management with demographics often dictating where patients receive care.

There is an international effort to meet the challenge of research in rare cancers, including rare gynaecological cancers, and this has laid the groundwork for multi-centre and international trials and registries.

Gynaecological Cancer InterGroup Rare Cancer Tumour Working Group

The Gynaecological Cancer InterGroup (GCIG) established a Rare Cancer Tumour Working Group, which includes representatives from each of the international gynaecological trials groups, including The Australian and New Zealand Gynaecological Oncology Group (ANZGOG). This group meets on a biannual basis with the aim to develop consensus guidelines for management of women with rare gynaecological tumours, address the national and international barriers to rare cancer research, identify key priorities for research and develop and conduct clinical trials. The GCIG Rare Cancer Tumour Working Group has discussed establishing an international rare gynaecological web-based cancer registry. However, barriers such as patient confidentiality and data security, inherent in international registries, have delayed this initiative progressing.

The Rare Cancer Working Group has developed a number of novel strategies to provide clinical support for clinicians treating patients with rare cancers. The GCIG website includes a clinical question and answer forum, where members can request advice on the management of rare cancers. This allows clinicians to obtain second opinions from international experts. A range of such consensus

statements has recently been published to help in the management of patients with rare gynaecological cancers (table 1) and these will be updated on a regular basis.[7] Clinical trial development is underway for a number of rare cancers, which will be discussed below.

Table 1: *GCIG Consensus Review Topics*

Ovarian and uterine carcinosarcoma
Low malignant potential tumours
Low grade serous carcinoma
Sex cord tumour
Germ cell tumour
Squamous ovarian carcinoma
Small cell carcinoma cervix
Small cell ovarian carcinoma
Vulva and vaginal melanoma
Ovarian carcinoid tumour
Mucinous carcinoma
Clear cell carcinoma ovary
Clear cell carcinoma cervix and uterus
Trophoblastic disease
Low grade endometrial stromal sarcoma
High grade uterine sarcoma
Uterine serous carcinoma
Adenosarcoma
Uterine and ovarian leiomyeosarcoma
Glandular carcinoma of the cervix

International Rare Cancers Initiative

The International Rare Cancers Initiative was established in early 2011 as a joint initiative between National Institute for Health Research, Cancer Research Network, Cancer Research UK, National Cancer Institute and the European Organisation for Research and Treatment of Cancer. Recently, the Institut National du Cancer in France and other national bodies have joined/initiated joining. The primary objective of The International Rare Cancers Initiative is to facilitate international clinical trials in rare cancers with a focus on diseases where there is no or very limited clinical trial data.

Within gynaecological cancers, sarcomas have been identified by The International Rare Cancers Initiative as a priority for trial development, with several studies under consideration. The first phase III study is underway in uterine-confined leiomyosarcomas, randomising patients to adjuvant docetaxel and gemcitabine, followed by doxorubicin versus observation (NCT01533207). This study opened in June 2012 and aims to enrol 216 patients. A second phase II trial is soon to open randomising patients with high-grade uterine sarcoma to maintenance carbozantinib or placebo after chemotherapy with doxorubicin +/- ifosfamide (NCT01979393).

Clinical trials in rare gynaecological cancers

When designing a clinical trial, a primary statistical consideration is powering the study adequately in order to answer the clinical question. This is the central challenge in rare gynaecology cancer research. In addition to difficulty in recruitment, there can be challenges in estimating power calculations. Phase III trial data is often used to estimate treatment effect sizes, but for rare gynaecological cancers this information is usually not available. Limited information from phase II trials or historical controls may have to be used, reducing the likelihood of a successful trial outcome.

Billingham et al have proposed a novel approach for clinical trials in rare diseases. They propose that a reverse philosophy is used in rare diseases where the design starts with the number of patients that is feasible to collect within a sensible time frame and then, based on a Bayesian analysis, show that this amount of data could provide useful information on which to make clinical decisions in the future.[8] For example, given a predicted number of events, the design is evaluated by: (i) demonstrating the information that the trial could provide for a range of possible observed results and prior distributions; and (ii) given a pre-specified decision criteria, using simulation to determine the probability that the trial will make the correct decision under different underlying true scenarios.

Phase III clinical trials in gynaecological cancers have commonly allowed the inclusion of patients with rare subtypes. For example, in advanced ovarian cancer trials, patients with mucinous and clear cell cancers are included, but are poorly represented and typically account for only <5% of patients accrued.[9-13] Recently, the Japanese Gynaecological Group successfully completed the first phase III clinical trial focusing on clear cell cancer of the ovary. This trial randomised 650 patients with stage I-IV clear cell ovarian cancer to six cycles of carboplatin and paclitaxel or cisplatin and irinotecan. Recruitment was completed in less than five years. There was no difference demonstrated in two-year progression free survival or overall survival.[14] This was a remarkable effort and made possible by the higher incidence of clear cell cancer of the ovary in the Japanese population and the dedication of the investigators and patients. A phase II trial of sunitinib in recurrent clear cell cancer of the ovary has just been completed and based on the high frequency

of PIK3CA mutations in clear cell cancer, a first line trial of temsorolimus in combination with carboplatin and paclitaxel is now underway (NCI-2011-02653).

Less successful was the GOG-mEOC trial (NCT01081262), which closed in August 2013 due to poor recruitment, with only 10% of the target 332 patients. This was the first phase III clinical trial for mucinous ovarian cancer which was investigating the standard regimen for all epithelial ovarian cancer, or carboplatin and paclitaxel versus oxaliplatin and capecitabine with or without bevacizumab as first-line therapy for stage II-IV or recurrent stage I (chemo-naïve) mucinous ovarian or fallopian tube cancer. The number of eligible patients with advanced stage mucinous cancers was lower than anticipated and many centres did not open the trial due to the rarity of these tumours and the costs of opening a trial which may recruit only one or two patients. This is an ongoing challenge with rare tumour trials.[15-16] This study also encountered funding problems with the use of off-label drugs, standard for one tumour type (for example, bowel cancer) but not approved for another (for example, ovarian cancer), another common barrier for rare cancer research.

There are ongoing studies for patients with low-grade serous ovarian cancer, which is quite distinct from high-grade serous ovarian cancer. Low grade serous ovarian cancer is difficult to treat with a poor response rate to chemotherapy.[17-18] Documented mutations in BRAF or KRAS oncogenes have driven interest in MEK inhibitors, with two phase III trials underway. The MILO trial (NCT01849874) is testing MEK162 versus physician choice and the LOGS trial (NCT02101788) is testing the MEK inhibitor, trametinib versus physician choice.

For the treatment of low-risk gestational trophoblastic disease, GOG0275 opened in June 2012. It is a phase III randomised trial of Actinomycin-D versus multi-day Methotrexate. In addition to the primary outcome of complete response, this trial also has several secondary endpoints, including quality of life assessments (NCT01535053). This trial will be important in defining standard care for this highly curable malignancy.

For very rare cancers, conducting phase III randomised clinical trials may not be feasible and clinicians must rely on phase II trials instead. Interpreting results of such trials can be challenging. Appropriate endpoints need to be considered in the design. Response rate may not be the best indicator of activity for some agents. Progression free survival or time without symptoms may be more appropriate endpoints, particularly with targeted therapies. Trials that incorporate early stopping rules can prevent patients receiving ineffective treatment and allow investigators to redirect research efforts. Interpreting the outcome of phase II trials can be difficult in the absence of prior clinical trials or good historical controls, although if the treatment effect size is large, this is less problematic. Randomised phase II trials provide an internal control, however larger patient numbers would be required. Sequential testing of new treatments is another potential way of overcoming this problem.

There is considerable time and cost associated with any clinical trial. Opening rare cancer trials which may only accrue a few or no patients is time-consuming, expensive and often unrewarding. The PARAGON trial, which is being conducted by the ANZGOG, provides one way to overcome this problem.[19] The PARAGON trial is a series of seven individual phase II studies embedded in a single 'umbrella' or 'basket protocol'. It includes a subset of patients with epithelial ovarian cancer, endometrial cancers, uterine sarcomas and sex cord stromal tumours, who all share the common study entry requirement of having an ER/PR positive cancer, which are more likely to respond to hormonal therapies. Patients are treated with the aromatase inhibitor, anastrazole. The novel design of this study has been attractive to a large number of participating centres in Australia and the UK. It is recruiting well and will be successfully completed.

For extremely rare cancers, small case series and case reports may be the only data available. There have been efforts to establish case series for rare gynaecological cancers across institutions both nationally and internationally.[20-21] Case studies provide little more than anecdotal evidence, with a natural tendency for selection bias in cases submitted for publication.

How can we pick molecular targets?

There is much interest in identifying potential treatment targets in gynaecological cancers. PARP inhibitors are the most successful example of the effort to identify a subset of patients with epithelial ovarian cancer most likely to benefit from treatment. Women with high grade serous cancer, who have been shown to have inherited a germline mutation in the breast and ovarian cancer predisposition genes, BRCA1 or BRCA2, have the best outcomes following maintenance therapy in platinum sensitive relapsed disease.[22-23] Several phase III trials are underway for BRCA1/2 mutation carriers and patients with high-grade serous ovarian cancers with Olaparib (SOLO1 NCT01844986, SOLO2 NCT01874353) and Niraparib (NCT01847274). Translational research will be essential to identify potentially actionable mutations and other aberrant signalling pathways in rare gynaecologic cancers. This is an area of intense international effort and the GCIG and International Rare Cancers Initiative have an important role in underpinning these approaches.

Can we use data from similar cancers at other anatomic sites?

Extrapolating from the experience in other more common tumour types has been of value in patients with rare

gynaecological cancers. For example, the management of malignant ovarian germ cell tumours has been based on advances in the management of men with testicular germ cell tumours. Bleomycin, etoposide and cisplatin is the standard chemotherapy regime in males and is equally effective in female patients.[24-25] There are some trials of novel therapies for patients who have failed platinum-based therapies, open to both male and female germ cell patients.

Across the UK and several European countries, centralisation of management of women with gestational trophoblastic disease has improved survival compared with countries that have not adopted this model.[26] Gestational trophoblastic disease and germ cell tumours are good examples of rare cancer subtypes where this should be considered. There is currently no centralisation in Australia for the management of rare gynecological cancers.

Rare cancer registries and gynaecological cancers

CART-WHEEL.org is a web-based rare tumour database which facilitates identification and annotation of rare gynaecologic cancers.[27-28] At present this resource is under-utilised by patients with gynaecological cancers. ANZGOG is committed to developing strategies to promote patient awareness and increase recruitment. This could facilitate pre-clinical research identifying potential actionable aberrations to underpin novel clinical trial design. Ethically approved research projects can apply to access information held by the CART-WHEEL.org, including the entity holding stored tissue for the cases in question. Currently, CART-WHEEL.org research projects are in place for small cell ovarian cancer and high-grade mucinous ovarian cancer.

Conclusion

Over the last decade, there has been significant progress in establishing national and international rare cancer networks, with the specific aim of facilitating research and improving outcomes in women with rare gynaecological cancers. There are many challenges in carrying out clinical trials in these patients, which require national and international collaboration. Registries for patients with rare cancers, such as CART-WHEEL, could facilitate urgently needed research.[27] Translational studies will increase our understanding of rare tumour biology and identify potential drug targets. The number of patients with rare tumours is expected to increase exponentially as genomic profiling divides and subcategorises patients with more common tumours into smaller distinct molecular subsets. Achieving better outcomes for our patients will only be achieved through increased collaboration and improved funding of rare cancer research.

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