Novel Approaches to Improve the Treatment of Rare Gynecologic Cancers: Research Opportunities and Challenges

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OVERVIEW

More than 50% of all gynecologic cancers can be classified as rare tumors (defined as an incidence of fewer than six per 100,000). Improved understanding of the molecular pathogenesis of tumors increases the proportion of rare tumors and creates challenges in optimizing the design of clinical trials. Novel trial designs are needed to take forward the development of new treatments in rare tumors. This requires international partnerships, harmonization of treatment, and collaboration to overcome the regulatory barriers to conducting international trials. Although randomized trials can be done in many tumor types, there are some for which conducting even single-arm studies may be challenging. For these tumors, robust collection of data through national and/or international registries could lead through audit to improvements in the treatment of rare tumors.

It is estimated that globally gynecologic tumors account for approximately 19% of tumors in women.¹ This relatively high figure is largely accounted for by the high incidence of cervical cancer in the developing world. However, in the United Kingdom uterine and ovarian cancers account for only 5% and 4% of female cancers, respectively, (www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers) and the frequency of tumors of the vulva and vagina is much lower. Carcinosarcomas, germ cell, gestational trophoblastic, and stromal ovarian tumors are even less common (Sidebar), but as a group rare gynecologic tumors are quite common.² Until recently the three most common types of gynecologic cancer (epithelial ovarian, cervical, and uterine) have been treated as individual entities with few adjustments for histologic subtype. The term “rare tumor” was mainly reserved for nonepithelial tumors. However, oncologists have become increasingly aware that there are distinct pathologic behavior patterns of histologic epithelial subtypes of ovarian, endometrial, and cervical cancers, placing many more of these tumors into a rare category, defined as an incidence of six or fewer per 100,000 (www.rarecare.eu). In total, rare gynecologic cancers represent more than 50% of the total number of gynecologic tumors, with about 80,000 new cases per year in Europe, involving more than 30 different histologic diagnoses, with a very limited number of patients in each diagnostic category.² The group of rare tumors is becoming larger as molecular classification further subdivides common tumors. Here we will look at the challenges faced in introducing new treatments for rare gynecologic cancers and will discuss the strategies being developed to study novel therapies.

SIDEBAR. The “Commonest” Rare Gynecologic Tumors

- Cervical adenocarcinoma
- Papillary serous tumors of the endometrium
- Clear cell cancers of the gynecologic tract
- Carcinosarcomas
- Gynecologic sarcomas
- Tumors of the vulva and vagina
- Sex cord tumors
- Small cell tumors of the gynecologic tract
- Germ cell tumors
- Gestational trophoblastic tumors

BIOLOGIC VARIATION: META-ANALYSES AND RANDOMIZED TRIALS BASED ON HISTIOTYPE

Until recently clinical trials and therapeutic guidelines for epithelial ovarian cancer have not distinguished the clinical behavior of the four main histopathologic subtypes: serous, endometrioid, clear cell, and mucinous tumors. Pooling knowledge in meta-analyses from large-scale clinical trials has shown that the outcome of rarer types of ovarian cancer, especially clear cell and mucinous subtypes, is very different from the more common serous ovarian cancers and that spe-
cific therapies need to be developed.\textsuperscript{3,4} The pathogenesis of ovarian cancer is now more clearly understood, and the distinct origins of low- and high-grade serous tumors\textsuperscript{5} explain the considerable variation seen in responsiveness to conventional chemotherapy.\textsuperscript{6,7}

Differences in clinical behavior are also seen among subtypes of adenocarcinoma of the uterus (e.g., serous papillary, clear cell, and carcinosarcoma). Together they represent less than 10% of endometrial cancer, and little is known about how they should be treated compared to the more common endometrial adenocarcinoma.\textsuperscript{8} We are beginning to understand more about the different origin of squamous and adenocarcinoma of the cervix, but have not devised different treatments directed to their different biologic behavior.\textsuperscript{9,10}

Randomized trials provide the highest level of evidence to support new treatments for gynecologic cancer and have been key to the approval of new drugs by regulatory authorities. Multicenter national clinical trials, often with international collaboration, are needed to improve the treatment of even relatively common gynecologic cancers. In 1997 several national networks came together to form the Gynecologic Cancer InterGroup (GCIG), which now comprises 24 national gynecologic cancer trials groups committed to developing better treatments through international collaboration.\textsuperscript{11} GCIG has spent much of its time devoted to large studies, looking for small incremental benefits.\textsuperscript{12} Its work has also led to greater harmonization of treatment across the developed world and provided, through meta-analyses of trials, a greater insight into the outcome of specific subtypes of tumors. The value of such collaboration is even greater when researching rare tumors. This has been clearly shown by the Japanese-led GCIG trial in clear cell ovarian cancer, which recruited 650 patients in under 5 years (JGOG 3017; EudraCT number: 2007–007849-13). However, recruitment to the GCIG trial in advanced mucinous cancer has been less successful. The Gynecologic Oncology Group (GOG) and National Cancer Research Institute (NCRI) in the United Kingdom led a randomized trial (consisting of two parallel but identical protocols, GOG 241/mEOC) that closed prematurely because of poor recruitment. It identified the complexities of accessing off-label drugs (oxaliplatin and capecitabine) through health care funders and the regulatory challenges of giving bevacizumab with limited funding for a small-scale multicenter academic study. Furthermore, with careful pathologic assessment, the incidence of the disease appeared lower than previously thought.

An International Rare Cancer Initiative (IRCI) has been established to deal with some of these challenges. It is a consortium established by the National Cancer Institute (United States), European Organisation for Research and Treatment of Cancer, and the National Cancer Research Network and Cancer Research UK (United Kingdom).\textsuperscript{13} IRCI has now approved an adjuvant chemotherapy trial for uterine leiomyosarcoma comparing postoperative observation with gemcitabine and docetaxel followed by doxorubicin (NCT01533207). A second randomized trial in advanced high-grade undifferentiated sarcoma will compare maintenance carboplatin with placebo after chemotherapy (NCT01979393). Both the GOG and GCIG have within their portfolio ongoing trials in rare gynecologic cancers. Most of these have been single-arm phase II studies that have helped to increase the percentage of patients with rare tumors into clinical trials. However, with the exception of germ cell or gestational trophoblastic tumors, these trials have not defined new treatment paradigms for gynecologic cancers. To address this issue, the GCIG Rare Tumor Working Party held a trial-planning workshop in London, United Kingdom, in November 2013. The outcome of this meeting is now being prepared for publication.

**KEY POINTS**

- Novel trial design and international collaboration are needed to improve the management of rare gynecologic tumors.
- Harmonization of treatment and methods to overcome international barriers to clinical trials is an important factor that will benefit such research.
- Partnerships with pharmaceutical companies are important to access novel compounds for studies in rare cancers.
- National funding streams are essential to allow academic intergroup collaboration to proceed.
- National networks should have dedicated data collection mechanisms for rare gynecologic cancers that allow secure international interchange of data to conduct research in areas where clinical trials are not feasible.

**TARGET-SPECIFIC THERAPIES**

Molecular and genetic studies of gynecologic cancers have identified many subgroups within ovarian and endometrial cancer, distinct from simple histopathologic categorization.\textsuperscript{14-16} A number of new targets have emerged, some of which have drugs that specifically interfere with these targets and downstream events. This is already having a major effect on the design of new trials in these tumors (Table 1). The clearest example is the presence of a BRCA mutation in approximately 15% to 20% of patients with high serous or endometrioid cancer of the ovary. The biologic behavior of tumors arising in patients with a germ-line mutation of the BRCA gene is different from sporadic ovarian cancer, and BRCA-mutated tumors constitute a new subgroup that are likely to benefit from PARP inhibitors that exploit defects in DNA repair mechanisms (homologous recombination deficiency [HRD]).\textsuperscript{17} It is estimated that 40% to 50% of patients with high-grade serous tumors may have HRD through germ-line or somatic mutation of BRCA, BRCA gene methylation, and other mutations that interfere with DNA repair, increasing the opportunities for using PARP inhibitors.\textsuperscript{18,19} Tumor response and disease control have been seen with the PARP inhibitor olaparib, given as a single agent to patients with BRCA-mutated and BRCA wild-type tumors,\textsuperscript{20,21} and thus far, it has not been difficult to recruit patients to PARP
TABLE 1. Targets for Therapeutic Strategies in Ovarian Cancer Endometrial Tumors

<table>
<thead>
<tr>
<th>Ovarian Tumor Targets</th>
<th>Mutation</th>
<th>Endometrial Tumor Targets</th>
<th>Amplification/overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA, HRD</td>
<td>PTEN, PIK3CA</td>
<td>DNA methylation</td>
<td>PIK3CA</td>
</tr>
<tr>
<td>KRAS/BRAF (low-grade serous)</td>
<td>AKT</td>
<td>Signal pathway</td>
<td>PI3K-AKT-mTOR</td>
</tr>
<tr>
<td>ARID1A (clear cell/endometrioid)</td>
<td>KRAS</td>
<td>Aurora kinase</td>
<td>PI3K-AKT-mTOR</td>
</tr>
<tr>
<td>PTEN</td>
<td>PS3</td>
<td>Wnt/β-catenin</td>
<td>MAPKinase</td>
</tr>
<tr>
<td>FOX12 (granulosa cell)</td>
<td>FGFR2</td>
<td>PI3K-AKT-mTOR</td>
<td>Angiogenesis pathway</td>
</tr>
<tr>
<td>PIK3CA</td>
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inhibitor trials.21,22 There are now five randomized trials, open or planned, for patients with BRCA-mutated ovarian cancer. It remains to be seen whether a high recruitment rate will be sustained. There is little doubt that the fast recruitment rate has arisen through the very encouraging and unusually positive phase I trial results using an oral drug with low toxicity in a highly motivated population of patients.

Rapid recruitment to trials in advanced low-grade serous cancer (LGSC) may be more challenging. Advanced LGSC represents approximately 3% of ovarian cancers and these tumors respond poorly to chemotherapy.7 They may benefit from treatment with a MEK inhibitor.23 Several MEK inhibitors have been developed by the pharmaceutical industry as their therapeutic potential is believed to be wide-ranging, with activity in many different cancer types. The GOG and NCRI are leading an international trial in advanced LGSC with trametinib (LOGS trial), randomized against a choice of regimens as there is no standard therapy for this disease. There is also a global industry-sponsored study with a MEK inhibitor (MILO trial; NCT01849874) using a similar design and competing for the same (small) group of patients.

A targeted strategy is also being investigated in recurrent clear cell ovarian cancer, a tumor in which angiogenic-driven growth may be considerable. Phase II trials have recently been completed with sunitinib, and GCIG/European Network for Gynecologic Oncology Trials is launching a randomized trial with nintedanib, a triple angiokinase inhibitor against VEGFR, FGFR, and PDGFR. The Nintedanib in Clear Cell Cancer Trial will compare nintedanib to weekly paclitaxel or topotecan meaning comparison to one of three alternatives viz paclitaxel, topotecan, or pegylated liposomal doxorubicin chosen by the physician. This is an academic-sponsored study within Europe, financially supported by a charity, Cancer Research UK, and the pharmaceutical industry. The protocol will include 30 women with clear cell cancer of the endometrium who will not contribute to the main analysis. The results from this group will be in the form of a descriptive analysis, and their inclusion provides a cost-effective opportunity to gain more information about the activity of the drug in more than one (related) tumor type, using a single regulatory and ethics application. This is a model that has been successfully applied to the Australian-led (ANZGOG) single-arm phase II trial of anastrazole in a variety of estrogen receptor-/progesterone receptor-positive gynecologic tumors (PARAGON).

TRIAL DESIGN FOR UNCOMMON VARIANTS OF GYNECOLOGIC CANCERS

Randomized trial design can be challenging where there is no clear lead compound or the disease is uncommon. It is harder for industry to commit financially, so leadership and, to some extent, funding are very dependent on the academic community. However, the pharmaceutical industry has shown interest in targeting the EML4-ALK translocation, occurring in only 6% of non-small cell lung cancer, but numerically this translates to 60,000 patients annually worldwide.24 It is important that gynecologic cancer trials are considered when evaluating the large number of molecularly targeted agents now available. However, finding meaningful targets is not always straightforward. P53 mutations are common in both papillary serous cancer of the endometrium and ovary, but the biologic behavior of these two tumors is different and choosing the right target is challenging.25 Adaptive designs or multiarm multistage trials are options to consider when evaluating multiple new agents in a randomized setting.26,27 The attraction of these approaches is that a simple and commonly used drug regimen, such as carboplatin and paclitaxel, can be compared sequentially with different arms containing an investigational agent, using clearly defined stopping rules. A single protocol can continue with the introduction of substantial protocol amendments. This greatly reduces the administrative cost of a trial and increases efficiency, introducing new agents without stopping and restarting protocols. This has been successfully achieved in a prostate cancer study in the United Kingdom (STAMPEDE trial).28 This approach could be considered for rare variants of the common gynecologic cancers, such as papillary serous carcinoma of the endometrium or carcinosarcomas of the gynecologic cancer tract. These histologic subtypes are usually included in large-scale studies, and although pooled information can through meta-analyses provide prognostic information, it is unlikely that better treatments will emerge unless specific studies are performed.

STUDIES FOR VERY RARE TUMORS: SINGLE-ARM TRIALS AND REGISTRY DATA

Many tumors fall into a category where conducting a randomized trial is difficult. Single-arm phase II trials are usually
criticized, as results may be confounded by selection bias. They continue to be performed but interpretation of results can be difficult.\(^{29}\) Nonetheless, for female germ cell tumors it would be difficult to conduct randomized trials, and progress in treatment has been made by stepwise refinement of single-arm studies. International collaboration is key to accelerating progress in treatment, and currently negotiations are taking place between GOG (United States), the Children’s Oncology Group (United States), and the Childhood Cancer and Leukemia Group (United Kingdom) to develop a joint protocol. For sex-cord tumors, a GCIG randomized trial (Alienor trial), led by the French group Group d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) (NCT01770301) has been launched, but recruitment is challenging for the reasons previously mentioned. Alternative strategies, such as using a historic control, randomized discontinuation design, using the patient as their own control, or comparing progression-free survival results with a previous line of therapy, have all been considered as a means of overcoming the challenge of recruiting patients with rare tumors into clinical trials.\(^{30,31}\)

However, for some tumors it is very unlikely that progress will be made through even single-arm phase II trials. Despite international collaboration, the cost of launching and maintaining a study that could take many years to complete would be prohibitive. International retrospective collection of cases has been tried—for example, in small cell ovarian cancer—but these are subject to collection bias.\(^{32}\) Prospective collection of data through national, or better still, international tumor registries may be the simplest and most cost-effective way forward to learn about rare tumors, harmonize treatments, and improve outcome through repeated audit of data. Clinicians need to work together, both nationally and internationally, to agree to the data elements to be collected and ensure that high-quality information is obtained. Although data collection in this situation is less costly than in a clinical trial, motivation of clinicians at individual sites to collect information on patients they rarely see and for whom there is little academic or financial incentive can make such data collection studies challenging. Nevertheless, registries such as the Global Rare Disease Patient Registry and Data Repository (http://rarediseases.info.nih.gov/research) are now being developed. Established database repositories can be adapted (e.g., http://project-redcap.org), or a customized approach can be developed. GINECO has set up a website for rare gynecologic tumors (www.ovaire-rare.org). Information on a large number of patients has been collected, providing important data to improve clinical management and research at a national level.\(^{33}\) The website also provides information, a bibliography, and a discussion forum dedicated to rare tumors. The website now receives funding from the French National Cancer Institute, and the database has information on more than 3,000 patients with rare gynecologic cancers.

It is particularly important that in addition to collecting clinical data registries to also gain access to tumor and blood samples for molecular analysis. The Center for Analysis of Rare Tumors (CART-WHEEL; http://cart-wheel.org) project is an approach led by an Australian group. Consent can be obtained by patient-driven Web access to studies via diverse routes including social networking sites, using a central secure repository of data managed by BioGrid Australia. There is centralized ethics approval, and patients who give consent can enter some of their clinical information. Investigators are then able to contact individual hospitals to obtain tissue and further clinical data. The Rare Tumor Working Party of GCIG is currently considering how best to take these opportunities forward.

**CONCLUSION**

The rapidly increasing number of targeted therapies provides a great opportunity to improve the treatment of rare gynecologic cancers, but at the same time it leads to the challenge of testing these agents in a growing number of rare tumor types, identified through a better understanding of molecular pathogenesis and pathways. Conducting trials with a small number of patients presents its own challenges: novel trial design, overcoming regulatory barriers for international collaboration, and funding of studies in rare tumors by academic bodies with little, or no, pharmaceutical support. Many of these difficulties can be overcome through the establishment of robust international collaborations that harmonize the approach to clinical trials. However, there remain diseases for which clinical trials are virtually impossible to perform. For these we need robust data collection by national registries that can be merged to form international data sets. Patients with a rare tumor type are only seen occasionally by clinicians and imaginative approaches are needed to engage them to provide information to drive data collection. Evaluation of novel treatments in these very rare cancers may arise through audit, iterative learning, and molecular analyses. Within the GCIG there is a great opportunity to establish a program of trials, guidelines to treat rare tumors, and international registries to increase learning about rare gynecologic cancers that make up over 50% of female genital tract tumors.
References