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CLINICAL INVESTIGATION

Developing an international network for clinical research: the Gynecological Cancer Intergroup experience

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International cooperative clinical trials groups are usually evolutionary by nature and their progress and success emanate from compromise, goodwill, hard work, diligence and a vision of improving outcomes in the most scientific and timely way. Practical barriers to success require lateral thinking in many instances and theoretical impediments need to be constantly kept in mind when trials are designed and analyzed.

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The Gynecological Cancer Intergroup (GCIG) evolved out of an ovarian cancer trials intergroup network, which in turn started as a result of European and Canadian cooperative groups recognizing that there was an urgent need for large-scale trials of enough power to answer important clinical questions with accuracy and reasonable speed, particularly following the introduction of new active agents including taxanes [1]. This was especially true following the publication of GOG 111, which was reported in 1993 showing a benefit for the combination of cisplatin and paclitaxel over standard therapy, which at that time was cisplatin and cyclophosphamide [2]. This newly formed group involved the European Organization for Research and Treatment of Cancer, the National Cancer Institute of Canada Clinical Trials Group, the Nordic Gynecological Cancer Study Group and the Scottish Gynecological Cancer Trials Group. This trial really led by example: 680 patients were accrued within 15 months and results were already reported at ASCO meetings in the late 1990s and outcomes published in 2000 [3].

Meanwhile in the UK, cooperative groups – the International Collaborative Ovarian Neoplasm organization and the German consortium of the German Ovarian Cancer Study Group together with the French trials group, GINECO – joined with this embryonic network, which led to the formation of the GCIG in 1997 [4]. Since then the GCIG has blossomed and now consists of 23 member groups, regulatory and national authority agencies including the French and US National Cancer Institutes, and also the International Society for the Study of Trophoblast Disease. Into the bargain there are six pharmaceutical/biotechnology members and four *ex officio* members who have been elected due to their extraordinarily productive individual contributions to the GCIG over a number of years. In 2011 the GCIG became an incorporated body.

Structure

Each cooperative clinical trial group sends six representatives to attend meetings of the GCIG, which are held biannually, always at the American Society of Clinical Oncology Meeting each year and alternating between the biannual meetings of the International Gynecologic Cancer Society and the European Society of Gynecologic Oncology.

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The GCIG is managed by an executive board consisting of a chair, a past chair and chair-elect together with representatives from each of the groups; this executive board oversees the work of the various committees, including harmonization, translational research, ovarian cancer, cervix cancer, endometrial cancer, rare tumors and so on. There is currently also a very active 'Symptom Benefit Working Group.'

The committees and working groups come together to develop new concepts which, in turn, have been brought forward by the various member groups; once these concepts have been matured and are ready for adoption they are passed to the executive board for support. Publication guidelines are determined prior to any study commencement.

Professional support

The administration of the Intergroup is provided by a half-time Executive Officer whose salary originally was provided by the National Cancer Institute of Canada but who is now fully supported by the annual dues from the Intergroup members of US$1500 per group. Supporting the Executive Officer is a web master who is generously provided without direct cost to the Intergroup by the National Cancer Institute (US). In this way the website is continuously updated and includes details of the Membership slate, the Government and statutes, details on GCIG meetings and events, and a list of current and past clinical trials together with a bibliography.

The publications arising out of GCIG studies have risen exponentially over the last 10 years with now over 25 studies having been reported or accepted for publication in the last 3 years.

Cervical Cancer Research Network

Any international or national research cooperative group that performs clinical trials in gynecological cancer can become a member but such cooperative groups have to consist of several centers and must be able to show that they have been part of at least one randomized multicenter Phase III trial in gynecological cancer. All groups are required to follow GCP, to follow the guidelines of the declaration of Helsinki and to ensure as good quality assurance as possible.

By contrast, however, it has been recognized that, particularly in relation to studies in cancer of the cervix, there is a vast need for clinical trials that are relevant to the developing world and, indeed, are ideally best undertaken in the developing world both for validity reasons and also strategically.

To this end, following a meeting in Manchester on 'state of the science in cervix cancer' in 2008, a Cervix Cancer Research Network has been established as a subsidiary of the GCIG with the aim of recruiting centers and patients from resource-constrained countries. Site visits to India have already been undertaken and Eastern Europe and Thailand are next on the list. A demonstration project (TACO), which is a randomized clinical trial of weekly versus triweekly cisplatin-based chemoirradiation in locally advanced cervical cancer is about to commence with the mentoring group being the Korean Gynecologic Oncology Group and the Cervix Cancer Research Network Group the Thailand Society of Gynecological Cancer. Robust discussion about the protocol and quality assurance has been part of the process with fruitful results. Compromise has been present in abundance. This project is extremely important and should be the flagship for further research.

Progress

Apart from numerous publications emanating from randomized trials, the GCIG has generated a number of meta-analyses and has supported a number of topic-related scientific meetings including state of the science workshops in endometrial and cervix cancer in Manchester, a full day's workshop on clear cell carcinoma of the ovary in Vancouver and four consensus conferences around ovarian cancer with the last being in Vancouver in 2010 [5]. Into the bargain, CA 125 response criteria have been established [6]. An updated bibliography of GCIG trials can be accessed online [101].

Challenges with large-scale clinical trial organization

Despite an impressive list of recent publications, there is little doubt that there are number of barriers to first of all getting international trials up and running and secondly ensuring first-class quality in the design, conduct and analysis of such studies.

Given the fact that there are 23 different groups at the table presently with more membership applications being continually received, the actual functioning of the GCIG as an identity is challenging. It is acknowledged that there are multiple demands on clinical trial specialists in other areas and that the generation of clinical trials would be enhanced if more time was available. Thus the meetings of the GCIG have traditionally had to center around other large-scale international meetings and because of this, members of the group often have different and competing responsibilities to the current scientific meetings along which the International Gynaecogical Cancer Society is held. This poses some challenges since it is obviously best that the best people are present at the GCIG to represent the views of their own groups and also to provide their not inconsiderable expertise.

The six working groups face geographical challenges; even setting up teleconferences across the globe is difficult with time zones often being a challenge to Korean

and Japanese colleagues who are often asked to join in very early in the morning.

Since a realization that the GCIG should probably function better, a strategic planning meeting was held in Milan in October 2011 just before the European Society of Gynecologic Oncology meeting and it was agreed that one of the 2 days of every second meeting would be tumor site specific and would consist of concept development and trial design together with brainstorming the most important questions which need to be answered.

Owing to the large number of groups involved with the GCIG, there is an ongoing tension between so-called 'academic' trials and pharmaceutical-driven trials. This inevitably comes down to funding, with some countries providing large infrastructure grants and per patient payments for academic trials and other countries not, the latter depending on pharmaceutical-driven trials and the 'soft' money generated through such trials to provide infrastructure support for their groups. As a result of this tension a set of principles governing the clinical trials undertaken by the GCIG was posted on the website in January 2011. These are principals of independence encompassing the topics of trial development, trial review, sponsorships and funding, conduct/control of trials, data management, and trial analysis and reporting.

Another area of dysfunction relates to the fact that with so many member groups, immediate commitments to trials proposed at GCIG meetings are not possible since the protocols have to be taken back to the various groups to finalize the trial design and estimate potential trial populations. Feasibility surveys are then generated within the member groups. This inevitably leads to delays and these delays may vary from months to years. Into the bargain, commercially available drugs without licensing indications for specific gynecological cancers cannot be prescribed in many settings and furthermore experimental agents with different pharmaceutical sponsors between countries make it very difficult to have quality control and uniform funding.

As a result of differences in practice patterns, achieving uniformity and consensus in relation to trial design can be a major undertaking. For instance, the standardization of radiation treatment in cervical cancer has been a major challenge to the GCIG, taking a number of years to finally resolve. In addition, surgical trials (which will be dealt with in more detail later) depend on different practice patterns including tumor bulk reduction for ovarian cancer and the use of lymphadenectomy in endometrial cancer. Such differences in practice patterns also relate to such scenarios as the use of neoadjuvant chemotherapy for cervix cancer and the use of intraperitoneal chemotherapy for ovarian cancer.

Generic problems

■ Translational research

It is mandatory that every clinical trial patient should have tumor samples stored for further analysis and that there has to be some harmonization of methodology of tumor access, site of tumor sampling (e.g., primary and metastatic disease in ovarian cancer) preparation of samples (to ensure that samples truly contain malignant tumor and not just stromal components, necrotic tumor and inflammatory infiltrates) and that there is an agreement that multiple tumor samples be taken during the time course of treatment so that recurrent disease samples are available for studies of drug resistance and molecular signatures. Such uniform tumor collection approaches have still not been used in any GCIG studies.

■ Surgical trials

The number of surgical trials in the literature lags enormously behind pharmaceutical trials. Surgical trials pose particular practical and methodological challenges not only in relation to funding but in particular to surgical learning curves and trial design issues including blinding and timing of randomization together with outcome assessments [7]. Most healthcare systems currently provide little funding for randomized surgical trials, largely because of lack of commercial stimulus or the academic support to ensure good quality surgical trials are undertaken. Because of reasonable criticism that the experience of surgeons differs across surgical techniques and that this has a resultant negative effect on the potential acceptance of the results of randomized surgical trials, it has been suggested that a minimum number of cases be required for each surgeon taking part in surgical trials and even that a 'mentor' assesses each surgeon's approach. This approach lends itself well particularly to laparoscopic and robotic investigations, which can be videotaped.

The number and type of cases that are referred to a specific center impacts enormously on surgically experience, and furthermore, the definition of what constitutes appropriate surgery still eludes us in many areas of gynecological cancer. For instance, the practice of debulking surgery varies enormously across centers and indeed the term 'optimal' in relation to ovarian cancer debulking has only recently been accepted as, ideally, no macroscopic residual disease or, at worst, less than 1 cm remains at the end of the operation. The different training required for subspecialization in many aspects of our surgical care together with different approaches to cancer, particularly of the ovary, such as diaphragm spread stripping, pleurectomy or video-assisted thoracoscopy procedures mean that surgical trials still face an uphill battle to become accepted and it is up to trial

groups to urgently address how best to run surgical trials and how quality assurance around surgical trials can be optimally achieved.

Routine versus research investigations

There is little doubt that one of the barriers to clinical trials in resource-constrained countries relates to the use of 'routine imaging' in the follow-up of patients in clinical trials so that progression-free survival can be accurately ascertained. There is very little discussion in the literature on the 'ethics' of such potential 'over-investigation,' which is pharmaceutical driven rather than perhaps being in the best interest of the patient or of the cancer center. The advent of metabolic imaging, such as the use of PET/CT scanning, is going to provide perhaps more accurate ways of assessing any benefits in randomized trials but such techniques have their own inherent problems and harmonization is obviously mandatory in this regard. There are no guidelines available to ascertain what are acceptable limits regarding the number of scans per patient. Radiation dose must be an important issue in patients being treated in the hope of a cure.

Even simple things like biochemical estimations are all too often regarded as 'routine' when in fact they offer little in the way of improving patient care. Also the variability of assay kits for measurements of tumor markers is enormous and in some way needs to be standardized when tumor markers are used as the only measurement of disease.

Finally, the use of maintenance therapies, which are being increasingly trialed across the spectrum of gynecological cancers, means that patients will be expected in some cases to have ongoing imaging and blood tests for a number of years and we have to ask ourselves just how necessary these investigations are in trial analysis and assessment of any differences in randomized studies.

Choice of imaging

Options for imaging are rising exponentially and currently include CT, MRI, DW-MRI, MRS, bold MRI and USG. All these options have their own problems for both the investigators and the trial participants, including radiation exposure, spatial resolution, cost, reproducibility and data interpretation [8].

Generalizability

Most studies report that only between 1 and 2% of all eligible patients actually end up in clinical trials. This potential influence on the external validity of clinical trial results is one area of major concern to clinicians who are ultimately going to be responsible for the management of patients based on the results of Phase III trials as level 1 evidence. One of the main areas of concern relates to the inclusion and exclusion of patients depending on age, sex and ethnicity and, furthermore, whether the results of trials in one racial group are readily transferable to that of another racial group [9]. Moreover, it has been recognized that if there are major prognostic differences in trial participants compared with the population as a whole then the general community may be disadvantaged by the results rather than achieve a benefit. A good example of this is a cohort of over 62,000 patients with newly diagnosed malignancy who presented between 1990 and 1997 to the MD Anderson Cancer Center. An analysis to ascertain differences in the 19,000 patients who entered clinical trials and those who did not reveals that trial participants with localized solid tumors had a shorter survival compared with nonparticipants, whereas in patients with metastatic solid tumors, trial participation resulted in a significantly longer survival. It was noted that trial participants were younger and had a better performance status but were more likely to have locally advanced disease, to have liver metastases, positive lymph nodes, high-grade tumors and multiple metastatic sites [10].

Quality assurance in international multicenter clinical trials

From 1990 to 1999, the number of non-US clinical investigators on investigational new drug applications to the US FDA increased from 271 to 4458 but during the same time period there was only an increase of FDA inspections from 22 to 64. The Inspector General of the Department of Health and Human Services in the USA at that time suggested that since the FDA was unable to assure the same level of human subject protection in 'foreign' trials and that key entities including the pharmaceutical industry itself, national regularity agencies, the National Bioethics Advisory Commission and WHO had all raised concerns about the experience of institutional review boards at some sites, it was recommended that drug sponsors obtain more information from foreign investigators to ensure greater sponsor monitoring and that there should be a database to track the growth and location of foreign research. Almost 10 years later it was noted that 80% of approved marketing application for drugs and biological data came from foreign clinical trials with half of clinical trials subjects and sites located outside the USA. It was noted that the FDA inspected less than 1% of 'foreign' sites. It was recommended that the FDA should require sponsors to submit clinical trial data in a standardized electronic format to enable the FDA to improve its review processes and to create an internal database to systemically monitor clinical trial information and more effectively select sites for inspection.

It is not inconceivable that major international trial groups across all tumor sites could come together to try and improve quality assurance around trials by harmonizing much of the templates for the conduct of trials and also for their quality assurance. Major regulatory agencies should be challenged to facilitate this.

Future perspective

The GCIG is now over 15 years old. It is a productive, effective and smoothly run organization that still faces a large number of challenges to increase its trial portfolio, ensure quality assurance and expand translational aspects of randomized clinical trials in gynecologic malignancy. The current membership of 23 groups, which generates nearly 200 participants at its biannual meetings, is perhaps close to optimal. Any less may reduce trial numbers and participation, whilst any more will make the practical aspects of group communications and meetings somewhat unwieldly. Most trials will continue to be funded by the pharmaceutical industry and constant surveillance will be required to ensure independence of trial design, analysis, publication and ownership of data. Global harmonization needs to be a key aim of all international cooperative groups whilst attention to the generic problems inherent in all multicenter clinical trials will ensure the best outcomes for our patients. The collaboration of more groups from the developing world will be a key factor in the GCIG's continuing success.

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Executive summary

- The Gynecological Cancer Intergroup (GCIG) mission is to promote international cooperation in clinical research, to perform studies in rare tumors, to stimulate evidence-based medicine and to support educational activities in trial design and analysis, all with the aim of improving outcomes for women with gynecological cancer.

The GCIG contribution to advancing international gynecological cancer research

- The GCIG has ensured the uniformity of the control arm in all major ovarian cancer research using randomized trials over the last 15 years.
- It has developed standard criteria for response using CA125 and has contributed to the modification of RESIST criteria.
- By promoting partnerships across national groups, large-scale trials have become possible, involving in some cases over 3000 patients. Time frames have been shortened and answers achieved more quickly.

Future perspective

- With the development of the Cervical Cancer Research Network to engage clinicians and promote trials in resource-constrained areas, a substantial impact on the more than 400,000 women who develop cervical cancer in these areas is envisaged. Expertise in surgical trials will expand and international translational research projects will become a standard part of every trial.

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Website

101 GCIG: Gynecologic Cancer Intergroup. www.gcig.igcs.org