Academic Network for Gynecologic Oncologic Trials

The Nordic Society for Gynecologic Oncology (NSGO) was founded in 1987 and is celebrating its 25 years anniversary this year. One of the main tasks has been to perform clinical trials. The gynecologic cancer population is relative small, so multinational cooperation is needed to be able to perform relevant clinical trials. Some 15 years ago, NSGO together with the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) took the initiative to build an international network for research in gynecologic cancer. This network was named Gynecologic Cancer Intergroup (GCIG) and is today a global network with representatives from all the major cooperative academic groups around the world working in gynecologic cancer. The aim is to promote and conduct high quality clinical trials in order to improve outcomes for women with gynecologic cancer. In addition to coordinate international clinical trials, GCIG has also organized consensus meetings to discuss and set rules for standard of care for patients participating in clinical trials and further to pinpoint areas in need of further research. These statements have been published.

In 2007 the European cooperative groups decided to work more closely together and founded the European Network of Gynecological Oncological Trials Groups (ENGOT) where currently 17 European gynecological trials groups are members. The spectrum of activity for this kind of international cooperation is broad. A number of purely academic studies have been performed leading to important results, but to achieve progress it is also important to work together with the industry on testing of new drugs. Cooperation between academy and pharmaceutical companies can be fruitful for both parties. The ENGOT groups can provide clinical knowledge and expertise and access to patients. However, such cooperation demands a set of rules to ensure the integrity of academia and a high quality of the trials. For this reason, ENGOT has set up and published requirements for trials between the academic ENGOT and pharmaceutical companies. NSGO works primarily within the framework of ENGOT and GCIG.

Important achievements have been obtained through this networking. The studies leading to marketing of paclitaxel in the treatment of ovarian cancer was conducted by cooperative groups participating in GCIG. NSGO, EORTC and the Italian group MANGO have published results from studies showing that the addition of chemotherapy to the traditional radiotherapy after surgery for endometrial cancer improves survival. A number of studies have been performed in ovarian cancer to find the optimal combination and scheduling of chemotherapy. It has been found that intensification through addition of a third drug or by increasing the dose of drugs above common standard does not improve survival. The backbone in first line treatment of ovarian cancer is still the combination of carboplatin and paclitaxel. A study performed by a Japanese cooperative group found that weekly administration of paclitaxel was superior the traditional 3 weekly administration. This is now being tested on a western patient population. The survival of patients with advanced ovarian cancer is still unsatisfactory despite good surgery and standard chemotherapy. It is clear that new treatment
modalities are needed. Targeted treatment has become increasingly important. With this kind of treatment, biologic mechanisms important for tumor growth and spread are blocked. Good results have already been obtained in other tumor types. Some important studies have been performed and more are planned.

Academic trials groups within GCIG have performed 2 studies on the use of bevacizumab in first line treatment of ovarian cancer. The studies were named GOG218 and ICON7 and were performed in cooperation with the industry. Bevacizumab is an antibody blocking a growth factor that stimulates formation of new blood vessels. Formation of new blood vessels is important for tumor growth. Treatment with bevacizumab would thus be able to inhibit growth of a tumor. In both studies, it was shown that addition of bevacizumab to chemotherapy, followed by continued treatment with bevacizumab for a total treatment time of 12 to 15 months delayed relapse of the tumor (figure 1 and 2). In ICON7 it was shown that the effect was greatest in patients where tumor greater than one cm in diameter was left at surgery (figure 2).

A study performed by the US study group GOG on patients with a relapse of ovarian cancer showed a substantial benefit by giving bevacizumab in addition to chemotherapy followed by continued treatment with bevacizumab until progression.

European cooperative academic groups have been quite successful in performing clinical studies leading to improvement of treatment for patients with gynecologic cancer. In addition to already mentioned studies, we have studied the importance of surgery in ovarian cancer. It is obvious that good surgical skill is mandatory and it is recommended that the surgical treatment of patients with advanced ovarian cancer is centralized to cancer centers with the needed surgical resources. In first line treatment of ovarian cancer, surgery is usually the first step. In case the tumor is located in places inaccessible with surgery, the treatment may start with chemotherapy. In case the tumor relapses, the most usual treatment is chemotherapy. A study performed by a German cooperative group (AGO-OVAR) indicated that surgery may benefit a subgroup of patients where complete removal of the relapse is possible. A study has been initiated to evaluate the benefit of such surgery.

In endometrial cancer a previous NSGO led study showed benefit of chemotherapy together with radiation after surgery. Radiotherapy gives good protection against relapse in the pelvis, but does not influence survival. The benefit of radiation has thus been questioned. Additional treatment after surgery (so called adjuvant treatment) is clearly indicated in patients with spread outside the uterus detected during surgery or by histologic evaluation of lymph nodes removed by surgery. It is an open question whether adjuvant chemotherapy is beneficial to patients with tumors with aggressive features but no metastases outside the uterus at time of surgery. A Scandinavian led study has been initiated to evaluate this question.

In cancer of the vulva, treatment consists of surgical excision of the tumor with ample margins together with evaluation of the inguinal lymph nodes. This has usually been performed by removing these lymph nodes. Unfortunately, this leads to uncomfortably edema of the legs in a number of patients. An international study is ongoing to evaluate the safety of
the sentinel node technique in this situation. By sentinel node technique, only a single lymph node directly draining the tumor is removed, thereby removing the risk of leg edema.

In the coming decade innovative Phase I and II trials and large Phase III trials will be needed to establish the role of new treatment modalities in gynecological cancer. With the structure for cooperation between academia and industry previously mentioned, we foresee an important role of academic groups in order to safeguard the scientific rationale and appropriate accrual of these trials.

We have already performed several important trials and are presently either running or planning several new studies to be conducted in cooperation between academic groups and industry partners. Ongoing ENGOT trials are listed on the web:
http://www.esgo.org/engot/Pages/ENGOTTrials.aspx

Ongoing GCIG trials are also listed on the web:
http://www.gcig.igcs.org/ClinicalTrials.html

Some studies will be listed on both places. This is due to the fact that European cooperative academic groups working together in the ENGOT Network also belong to the GCIG Network.