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PROGRESS IN GYNECOLOGIC CANCER RESEARCH: THE GYNECOLOGIC ONCOLOGY GROUP EXPERIENCE

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Abstract

Since 1970, the Gynecologic Oncology Group (GOG) has been a leader in clinical research in gynecologic oncology. Currently comprising fifty-nine institutions and their affiliates in the United States, Canada and elsewhere, GOG has defined, principally through phase III randomized clinical trials, the standard of care for several stages and types of female pelvic cancer. This review will briefly summarize, in the context of research done concurrently by other groups and institutions, important GOG trials that have moved the field forward, especially in ovarian, endometrial, and cervical cancer. The role of cisplatin, carboplatin and paclitaxel as well as other drugs and combinations in gynecologic cancer has been extensively studied by GOG, as has chemoradiation in cervical cancer. Surgical staging of cervical and endometrial cancers has provided new insights and guidance for management. The benefits and limitations of radiation therapy in these diseases have been carefully examined. Thus, the stage has been set for further progress in this field.

INTRODUCTION

At the beginning of the 1970s, when the newly established Gynecologic Oncology Group initiated its first controlled clinical trials, a variety of questions existed about the optimal management of gynecologic cancers and the integration of radiation therapy (RT) and other modalities with surgery. For example, progestins were thought by many to have a major role in treating advanced endometrial cancer. Metastatic gestational trophoblastic neoplasia had been one of the very first neoplasms to be cured with cytotoxic chemotherapy, but not everyone was cured, and new regimens proliferated without rigorous testing. While several drugs were being used in advanced ovarian cancer, no combination was consistently better than melphalan alone, and a survival benefit was uncertain. No cytotoxic agents had an established role in the management of cervical or corpus cancer. There were no published, completed, phase III trials of therapy in gynecologic cancer. In that setting, and in parallel with other developments in oncology, the GOG began to ask important and timely questions. The principal focus in this review will be on phase III GOG trials, with a few other GOG studies and non-GOG trials mentioned as appropriate.

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OVARIAN CANCER

Most ovarian cancers arise from the epithelial covering of the ovary, hence the term epithelial ovarian carcinoma (EOC). Typically, a histologic grade can be assigned, with the lowest grade usually being less aggressive. Of note, however, is the so-called 'borderline tumor' or 'low malignant potential' (LMP) neoplasm, a recognized entity, intermediate between benign ovarian tumors, such as serous cystadenoma, and carcinomas. LMP tumors have not reproducibly responded to chemotherapy (1) and generally have a very indolent course (2), underscoring the critical importance of expert pathology review, as is routine in GOG studies.

EOC is usually diagnosed in stage III (intra-abdominal spread) or stage IV (spread outside the peritoneal cavity and/or parenchymal liver involvement), so surgery usually is not able to remove all known disease. Even with 'maximal debulking' the cancer is virtually certain to recur; thus, post-surgical therapy needs to be considered. In stage I (confined to the ovary/ovaries), and to a lesser extent stage II (pelvic extension), there are cures with surgery alone (not only hysterectomy and salpingo-oophorectomy, but omentectomy and meticulous exploration of the abdominal cavity). Nevertheless, a substantial risk of recurrence in stage I and II was evident, implying the need for adjuvant treatment in these cases as well. The non-surgical modalities available in 1970 were single agent chemotherapy, principally nitrogen mustard analogs (for example, melphalan or cyclophosphamide), whole pelvic RT, whole abdominal RT (necessarily limited in dose because of radiosensitive normal tissues in the treatment field), and intraperitoneal radioisotopes such as radioactive chromic phosphate (P32).

Early Stage Ovarian Cancer

The very first GOG trial randomly compared melphalan vs. pelvic RT vs. observation in the adjuvant setting; there was no survival difference among 86 eligible patients but the recurrence rate (6 vs. 30 vs. 17%) favored melphalan (3). There was, however, a high inevaluability rate, and the main value of this trial was a lesson in study management. Subsequent studies in stage I and II EOC confirmed certain features, including stage IC (capsule rupture, surface tumor or positive washings), high grade or clear cell histology, as well as stage II, associated with a higher risk of post-surgical recurrence. In the absence of such features, the 5 year survival comparing melphalan vs. observation in 81 patients was 98 vs. 94% (4) so, after careful staging and pathology review, adjuvant therapy was not indicated for such cases. Careful staging warrants further emphasis, as illustrated in a surgical staging trial of ovarian cancer (5); of those with stage II, 20% actually had positive pelvic nodes and/or positive para-aortic nodes; also, grossly negative omental specimens and random diaphragmatic biopsies were sometimes positive histologically.

In the higher risk early stage cases, P32 had no advantage over chemotherapy (4,6) and was abandoned, especially as more active, cisplatin-based regimens, were being identified in advanced disease. Other groups also evaluated platinum as an adjuvant; a combined analysis of the so-called ICON1 and ACTION trials (7) found that platinum-based therapy significantly improved overall survival (OS) over observation. GOG 157 (8) enrolled stage I high risk and stage II cases; employing a regimen of carboplatin + paclitaxel that had been developed in advanced cases (see below). The question asked in this trial was whether longer treatment (6 cycles) was superior to shorter treatment (3 cycles). The latter, if comparable, would mean less acute toxicity, less risk of late toxicity, and less cost. The result, in 457 women, was a similar death rate. The recurrence rate was 24% lower for 6 cycles, but not significantly ($p=0.18$) (in this review, 'significant' always refers to statistical significance, with $p < 0.05$). Not surprisingly, there was more grade 3 and 4 neurotoxicity with longer therapy. Despite these findings, there remains some sentiment for longer treatment. A subsequent trial, GOG 175, used 3 cycles of carboplatin + paclitaxel in all patients, followed by random assignment to

observation or weekly paclitaxel for 24 weeks, based on phase II activity in GOG 126N when given weekly (9). GOG 175 enrolled over 500 patients, and the data are maturing.

Advanced Ovarian Cancer

GOG 2 (10) compared whole abdominal irradiation (WAI) versus melphalan versus either treatment sequence in stage III. In retrospect, this trial was overly optimistic in that, although it restricted eligibility to patients with 'optimal' residual disease, 'optimal' was defined as ≤ 3 cm. residual. Such relatively large lesions are, according to current thinking, not amenable to control by RT. At any rate, there was no significant difference in survival in GOG 2. GOG 3 (11) compared one versus 2 versus 3 drugs in suboptimal cases, with no significant difference except toxicity, but the drugs that were added to mustard, namely fluorouracil and dactinomycin, are not highly active, by current standards, in this type of cancer. GOG 25 (12), in 'optimal' stage III, again defined as ≤ 3 cm. residual, studied melphalan with or without *Corynebacterium parvum* as an immune stimulant; there was no improvement in outcome over melphalan alone.

By 1976, two other cytotoxic agents, hexamethylmelamine and doxorubicin, in combination with mustard analogs, were deemed of interest in ovarian cancer. GOG 22 compared melphalan +/- hexamethylmelamine to cyclophosphamide + doxorubicin (CA) in patients with stage III residual disease > 3 cm. and stage IV. There was no significant difference in progression-free survival (PFS) or OS, but there was a higher clinical complete response rate (32%; $p = .04$) with CA (13). On that basis, CA was employed as the control arm of GOG 47, in suboptimal stage III and IV. Cisplatin had been observed to have activity in refractory ovarian cancer (14), and had begun to be used as initial chemotherapy in various combinations in ovarian and other cancers. GOG 47 compared CA +/- cisplatin (P) in 440 women (Table 1). There was a higher clinical CR rate (51%) with CAP, without an increase in hematologic toxicity. PFS was significantly longer, and OS was longer with CAP in the measurable disease subset (15). A subsequent analysis, adjusting for the poor prognosis histologies (mucinous and clear cell), showed a significant advantage in OS for CAP in the entire group; this trial provided a clear demonstration of the importance of cisplatin in ovarian cancer (16).

Although the non-hematologic toxicity of doxorubicin in GOG 47 had not been a major problem, occasional troublesome extravasation of administered drug and the potential for serious cardiotoxicity led GOG to question the role of doxorubicin (in retrospect the role of cyclophosphamide should have been questioned as well). Thus, GOG 52 was a trial in stage III cases, using a new definition of optimal as ≤ 1 cm. residual, instead of ≤ 3 cm. C1000 + P50 were compared to C500 + A50 + P50 (are they mg/m^2 ?) in 349 patients. The hematologic toxicity was comparable. There was a slight but not significant difference in PFS and OS favoring CAP (17). A meta-analysis of this and three European trials revealed a small but significant OS advantage for CAP, but the other CP/CAP trials used somewhat greater doses of CAP, so it was not clear if the difference in OS in the meta-analysis was from dose intensity or from the doxorubicin (18). Subsequent trials by other groups using anthracyclines have not shown a major benefit (19,20), and their use in first line therapy has declined.

GOG 60 attempted to confirm an earlier Southwest Oncology Group (SWOG) report of a survival benefit in ovarian cancer using BCG vaccination. CAP +/- BCG was studied in 411 patients with stage III > 1 cm. and stage IV disease. No significant difference was observed (21).

Dose intensity was a popular concept in oncology in the 1980s, and retrospective reports in ovarian cancer lent support to the idea that higher drug doses would improve outcome. Thus, GOG 97 (22), in suboptimal stage III and IV compared $\text{C500} + \text{P50} \times 8$ vs $\text{C1000} + \text{P100} \times 4$ (are they mg/m^2 ?). Unfortunately, there was no significant improvement with the more dose-

intense regimen but there was more toxicity. The question arose whether the doses were high enough, and uncontrolled trials seemed to support mega-dose therapy with autologous stem cell rescue. GOG was not able to accrue adequately to a randomized study of the question; other groups have also had difficulty accruing to that type of trial (23).

Investigators had been searching for a new drug or class of drugs that might supplement the activity of cisplatin, when paclitaxel emerged as an active agent in cisplatin -refractory ovarian cancer (24). After pilot studies established that cisplatin 75 mg/m² and paclitaxel 135 mg/m² could be safely combined, GOG 111 was initiated in stage III with > 1 cm. residual and stage IV patients, comparing cyclophosphamide + cisplatin versus paclitaxel + cisplatin. The latter regimen proved to be significantly better in response rate, PFS and OS, and represented a new standard of care, albeit not without troublesome toxicity in some patients, and eventual relapses in many (25). The European Organization for Research and Treatment of Cancer (EORTC) and Canadian investigators confirmed these results in their OV10 trial (26).

The question then arose whether paclitaxel might be more active than cisplatin first-line, since it yielded responses in refractory cases. This led to the design of GOG 132 in women with suboptimal III and IV disease, using cisplatin 100 versus paclitaxel 200 mg/m² versus the combination using the GOG 111 doses. The result was that paclitaxel alone was significantly inferior to the other two arms with respect to response rate and PFS (but not OS). Surprisingly, the combination was not better, but had a better toxicity profile than the cisplatin 100 mg/m² alone, and was favored for further study (27).

There was some lively discussion when the results of ICON3 (28) became available; that European collaborative study employed either single agent carboplatin or cyclophosphamide + doxorubicin + cisplatin as the control, versus carboplatin + paclitaxel as the experimental arm in 2074 patients, and found no significant difference. Ultimately, however, the weight of evidence and further follow-up supported the use of platinum + paclitaxel (29).

As paclitaxel was being developed, questions arose about dose and infusion duration. A National Cancer Institute of Canada (NCIC) study in relapsed patients used 135 or 175 mg/m² and 3 or 24 hour infusion time in a bifactorial design, and reported similar response rates but less neutropenia with the shorter infusion time; PFS but not OS was longer in the higher dose group (30). Dose was also addressed in GOG 134 which compared 175 versus 250 mg/m² given over 24 hours in platinum-pretreated patients; there was no PFS or OS advantage for the higher dose (31). Meanwhile, there had been suggestions that a still longer infusion time might improve results, but 96 hour infusions in GOG 162 did not show an advantage over 24 hours (32).

The cisplatin analog most extensively studied by the GOG has been carboplatin. A pilot study of carboplatin + paclitaxel established safety (33). This combination was easier to give than cisplatin + paclitaxel, but a prospective, non-inferiority comparison was needed. GOG 158 compared these regimens in 792 eligible patients with residual stage III disease ≤ 1 cm. There was no significant difference except more GI, renal and metabolic toxicity and more grade 4 leukopenia with cisplatin + paclitaxel (34). Thus, the carboplatin + paclitaxel regimen became a new standard of care. Second look laparotomy (SLL) had been employed in earlier trials to assess residual disease after initial chemotherapy, but its therapeutic value was controversial. GOG 158 addressed this point prospectively, but not in a randomized fashion. Instead, patients were asked to indicate prospectively whether they would accept a second look operation; about half did. There was no significant difference in outcome (35).

GOG has not done a large scale study of docetaxel, another taxane with comparable activity. Using docetaxel + carboplatin in a randomized comparison, a Scottish group reported similar

PFS, with more neutropenia and neutropenic complications but less neurotoxicity than with carboplatin + paclitaxel (36).

In parallel with the development of the carboplatin + paclitaxel regimen in first line therapy was the emergence of liposomal doxorubicin, topotecan and gemcitabine as active second line agents. How to efficiently introduce these agents into first line trials was a challenge. GOG 182, done in collaboration with other national and international cooperative groups, addressed this problem using triplet and sequential doublet regimens in a single large five-arm trial. Both large and small volume residual cases were eligible. The experimental arms were carboplatin + paclitaxel + gemcitabine; carboplatin + paclitaxel + liposomal doxorubicin; carboplatin + topotecan for 4 cycles followed by 4 cycles of carboplatin + paclitaxel; and carboplatin + gemcitabine for 4 cycles followed by 4 cycles of carboplatin + paclitaxel. Over 4000 patients were accrued in 3 1/2 years. Unfortunately, none of the experimental arms was superior to carboplatin + paclitaxel. Nevertheless, the mechanism succeeded in efficiently evaluating four experimental regimens (20). Conventional cytotoxic regimens including more than two drugs have not, as yet, found a convincing role in treating epithelial ovarian cancer (19,37).

Meanwhile, the importance of angiogenesis in tumor growth and the potential for blocking it with 'targeted' therapy, already appreciated in other areas of oncology, was recognized in ovarian cancer, and GOG 170D, a phase II trial of the angiogenesis inhibitor bevacizumab, showed promising results (38). Thus, GOG 218 studied carboplatin + paclitaxel +/- bevacizumab; completion and analysis of this study are awaited with great interest.

Intraperitoneal Chemotherapy

Since ovarian cancer is principally a disease of the peritoneal surfaces, and since achievable intraperitoneal (i.p.) drug concentrations are dramatically higher with some drugs than what can be safely achieved systemically, this approach has been of long-standing interest. A number of phase II i.p. trials by GOG and other investigators showed the feasibility of this route, and suggested activity, but were difficult to interpret in the absence of controls. Then GOG joined a trial initiated by SWOG (GOG 104), in which i.v. cisplatin + cyclophosphamide were randomly compared with i.p. cisplatin + i.v. cyclophosphamide in stage III patients with 0–2 cm. residual. OS was significantly longer using i.p. cisplatin (49 vs. 41 mo, median, $p = 0.02$), but the smaller volume subset (0–0.5 cm.), which one might predict would be more likely to benefit from i.p. therapy, did not show a significant improvement in OS compared to control (39). Moreover, the advent of paclitaxel raised the question whether the cyclophosphamide-containing regimen was still relevant. A follow-up intergroup study (GOG 114) used i.v. cisplatin + paclitaxel as the control arm. The experimental arm used relatively high dose carboplatin (Area under the curve = 9) i.v. for two cycles in patients with residual disease ≤ 1 cm, hoping to further cytoreduce the tumor before the initiation of i.p. cisplatin + i.v. paclitaxel for 6 cycles. There was a significant improvement in PFS but the increase in OS (63 vs. 52 mo.) was of borderline significance, and the experimental arm was significantly more toxic. Because more than one variable was included, it was not clear how much of the improvement was from the i.p. component (40).

A third i.p. trial (GOG 172) also used the GOG 111 regimen of i.v. cisplatin + paclitaxel as the control, in stage III residual disease up to 1 cm. In the experimental arm, i.v. paclitaxel 135 was given on day 1, i.p. cisplatin 100 (mg/m²?) on day 2, and i.p. paclitaxel 60 mg/m² on day 8 every 3 weeks $\times 6$. PFS and OS (66 vs. 50 mo., $p = 0.03$) were significantly longer with the i.p. arm (41), but it was also more toxic and had more complications (42) and only 42% of patients were able to complete all 6 i.p. cycles. Quality of life (QOL), assessed prospectively, was worse acutely in the i.p. arm, but there was no difference in the arms one year later (43). GOG 172, along with the earlier trials, clearly established a first-line role for i.p. chemotherapy, but it was not without its critics, partly because of the toxicity and complications and partly

because the i.p. regimen had not been compared with the current standard, intravenous carboplatin + paclitaxel (44). GOG is now evaluating modifications of the GOG 172 regimen that might be more tolerable, hopefully without losing efficacy.

Post-Remission Therapy (“Consolidation” versus “Maintenance”)

Most women with stage III or IV ovarian cancer who achieve a complete response to chemotherapy (either clinically or at second look operation, SLL) will subsequently relapse. Longer treatment with the initial regimen or switching therapy has not improved survival. For example, GOG 93 used i.p. P32 versus observation in stage III patients after negative second look; there was no significant difference; of note, 61% of those patients relapsed within 5 years of a negative second look (45). However, a SWOG/GOG trial (GOG 178) compared 3 versus 12 monthly courses of paclitaxel after a clinically defined complete response to platinum + taxane therapy. At a planned interim analysis, there was a significant increase in PFS (the primary endpoint), and the study was closed; the question of a possible difference in OS was not answered (46). Recently, GOG 212 was activated, comparing, in clinical complete responders to initial therapy, pegylated paclitaxel vs. paclitaxel vs. observation, with OS as a primary endpoint. The pegylated drug is being studied, in part, for the possibility that neuropathy might be lessened.

Surgical Studies

GOG 41 and the second look aspect of GOG 158 have already been referred to (5,35). GOG 152 was a randomized study of secondary surgical cytoreduction in stage III cases with residual tumor > 1 cm. This trial was prompted by an EORTC report showing a significant survival benefit for chemotherapy followed by secondary debulking. In the GOG trial, there was an initial attempt at aggressive debulking, followed by chemotherapy, with half of the patients randomly assigned to secondary debulking between the third and fourth of six cycles of cisplatin + paclitaxel. There was no significant difference in OS (47). QOL was prospectively assessed in this trial (48); the interval cytoreduction resulted in no notable long-term difference. An initial effort at maximal debulking was required for GOG 152, but not for the EORTC trial; thus, it appeared that if primary cytoreduction was thought to be maximal, secondary surgery would not improve outcome over chemotherapy alone.

Rare Ovarian Cancers

Although the timely conduct of phase III trials has not been feasible, the GOG has generated useful information about several of these cancers.

Germ cell tumors: Early trials (GOG 10, GOG 11) employed dactinomycin-based therapy (principally vincristine + dactinomycin + cyclophosphamide, or VAC), with some success in endodermal sinus tumor, embryonal carcinoma, immature teratoma and mixed tumors. These trials showed the importance of complete tumor resection, and suggested that grade 2 or 3 immature teratoma had a better prognosis than other histologies (49). Extrapolating from brief reports and the experience with testicular cancer, later trials used platinum-based regimens, first bleomycin + vinblastine + cisplatin (50), and more recently BEP, substituting etoposide for vinblastine. BEP was also very active in dysgerminoma (51). Patients with incompletely resected tumors containing teratoma sometimes benefited from resection after chemotherapy (52).

Granulosa cell tumors and other stromal malignancies: BEP was employed in GOG 115 (53) in 57 evaluable patients; 14 of 38 with a SLL had negative findings. BEP was considered an active regimen.

Ovarian carcinosarcoma: In GOG 50, a phase II trial, doxorubicin was not highly active (54). Cisplatin (GOG 26) had a 20% response rate, similar to uterine cancers of this cell type (55).

CORPUS CANCER

The situation in 1970 with respect to endometrial carcinoma was that the staging system was 'clinical' with its inherent uncertainties, and the armamentarium other than surgery was largely limited to pelvic RT, assumed to be beneficial but not rigorously studied, and progestin therapy, not likely to be useful in those cases that recurred, most of which were high grade and/or hormone-receptor negative. In that environment, and after a pilot study (56) confirmed the feasibility of surgical staging in such patients, GOG 33 was carried out, involving 895 evaluable women with clinical stage I (corpus) or II (corpus plus cervix) disease (57,58). Grade was a highly significant predictor of recurrence. Para-aortic node metastases, although uncommon, were almost always associated with grossly positive pelvic nodes, adnexal metastases, or outer-third myometrial invasion. Cervical invasion by itself did not appear to decrease survival. This large data base allowed grouping of patients as low, intermediate or high risk for recurrence. The intermediate risk group, with findings such as deep myometrial invasion, high grade, or lymphovascular invasion, might be studied after surgery with or without adjuvant therapy. Those with positive nodes or other extra-uterine disease (high risk) were candidates for more intensive intervention.

Laparoscopic Staging

Laparoscopy has been shown to be feasible for staging of endometrial cancer (59) and is now being compared in a randomized trial with open laparotomy. Safety, efficacy and cost are being evaluated.

Radiation Therapy

Adjuvant post-operative pelvic RT versus observation was studied in early stage, intermediate risk cases (GOG 99). Recurrence was significantly reduced, but survival was not improved (60).

Whole abdominal irradiation (WAI) has also been studied in endometrial cancer, since upper abdominal recurrence may be seen, especially in high risk cases, and stage III or IV may present with such involvement. GOG 122 (61) was a phase III trial comparing WAI with doxorubicin + cisplatin, a regimen that had been studied in GOG 107 in advanced disease (62). Stage III (loco-regional spread) and intra-abdominal stage IV were eligible for GOG 122 without gross residual or with macroscopic residual up to 2 cm. Actually, very few with macroscopic disease (14%) were enrolled. PFS and OS significantly favored the chemotherapy, although it was more toxic (61). In particular, cisplatin had an adverse impact on QOL with respect to peripheral neuropathy, so the important increase in survival came at a price (63). Future studies will consider chemotherapy plus tumor-directed RT, rather than WAI. An Italian study of a slightly different population (stage IcG3, IIG3 with myometrial invasion >50% and stage III) did not find a survival difference between whole pelvic RT and cisplatin/doxorubicin/cyclophosphamide given every 4 weeks (64). Perhaps with more localized disease the RT provides better control.

Hormone Therapy

GOG 81 showed no advantage for medroxyprogesterone at 1000 mg over 200 mg/day; in fact, the response rates, 15% vs. 25% seemed to favor the low dose; poorly differentiated tumors not expressing progesterone receptors were more common in the metastatic/recurrent setting, but had very low response rates, less than 9% (65). Although tamoxifen alone has little activity in this disease, tamoxifen sequenced with medroxyprogesterone (GOG 119) (66) or with

megestrol acetate (GOG 153) (67) has provided provocative phase II results, possibly by increasing progesterone receptor expression. Randomized control trials will be required to assess this approach.

Chemotherapy

Early GOG phase III trials (Table 2) did not suggest a major role for nitrogen mustards or 5FU (68,69) nor for single agent doxorubicin as an adjuvant (70). The activity of doxorubicin, cisplatin and paclitaxel in advanced endometrial carcinoma led to further studies. GOG 107 showed superiority of doxorubicin + cisplatin over doxorubicin alone in response rate and PFS (62). In GOG 139, spacing the administration of these drugs during the day (“circadian timing”) did not improve results (71). A comparison of doxorubicin + cisplatin vs doxorubicin + paclitaxel + filgrastim showed no significant difference (72). In contrast, GOG 177 used doxorubicin + cisplatin vs. those two + paclitaxel+ filgrastim (TAP), and yielded a superior response rate, PFS and OS for TAP (73), but more neurotoxicity. Subsequently, the importance of doxorubicin was questioned, so GOG 209, comparing TAP vs carboplatin + paclitaxel, was initiated; results are pending. In the meantime, GOG 184 compared TAP with doxorubicin + cisplatin in the ‘adjuvant’ setting; patients with stage III or IVA disease with less than 2 cm. residual disease after surgery received tumor-directed irradiation followed by either drug regimen; results are pending.

Uterine Sarcomas

These tumors comprise 5% or less of uterine cancers. Carcinosarcoma (previously called malignant mixed mullerian tumor or mixed mesodermal sarcoma), leiomyosarcoma (LMS), and the even rarer endometrial stromal sarcoma are the main categories. Carcinosarcoma (CaSa) frequently recurs, both intra-abdominally and at distant sites, while LMS has more lung metastases (74). In the early 1970s, doxorubicin was considered the most active agent for soft tissue sarcomas, and doxorubicin combinations were thought by some to be better still, but had not been proven. GOG 21 randomized doxorubicin +/- dacarbazine in advanced or recurrent uterine sarcomas; there was no significant improvement with the combination, but there was a hint that LMS was more responsive to doxorubicin-based therapy than CaSa (75)(Table 3). In that setting, GOG 20 was one of the first randomized adjuvant sarcoma trials, enrolling stage I and II uterine sarcomas post-operatively, with doxorubicin every 3 weeks for 8 cycles versus observation as the control. There was no agreement about the possible role of adjuvant pelvic RT, and it was allowed as an option in GOG 20. There was no significant improvement in survival with adjuvant doxorubicin in either CaSa or LMS (76). Of interest, a meta-analysis of adjuvant doxorubicin-based chemotherapy in soft tissue sarcomas from all anatomic sites, and including data from GOG 20, suggested an improvement in recurrence-free interval ($p < .05$) but no increase in OS (77). A retrospective analysis of GOG 20 regarding the optional pelvic RT showed fewer pelvic recurrences with RT, but with no impact on survival (78).

A subsequent trial of doxorubicin +/- cyclophosphamide in advanced disease did not favor the combination (79). The activity of ifosfamide, cisplatin and paclitaxel in CaSa emerged in that sequence, leading to randomized comparisons; GOG 108 evaluated ifosfamide +/- cisplatin and found a small improvement in PFS (80). GOG 161 studied ifosfamide +/- paclitaxel in this tumor type; survival was improved ($p = 0.03$) with the combination (81). Before the results of GOG 161 were available, GOG 150 was initiated, with all stages of CaSa being eligible, after debulking to ≤ 1 cm residual; it compared WAI 30 Gray, with a pelvic ‘boost’ up to 50 Gray, vs ifosfamide + cisplatin for 3 cycles. Although OS was not significantly different, the results did favor the chemotherapy (82). Based on this observation plus the possibility that longer treatment and/or the introduction of paclitaxel into the regimen would be more effective, GOG will move forward with further adjuvant drug trials in CaSa.

Gestational Trophoblastic Disease (GTD)

Most hydatidiform moles are successfully treated with uterine evacuation or hysterectomy. Those that persist are usually cured with chemotherapy, but there have been very few randomized trials. It was thought that oral contraceptives (OCP) were contraindicated after evacuation of a mole because trophoblastic tissue might be stimulated, but a randomized trial (GOG 55) showed that OCP were actually preferable after molar evacuation (83).

For a number of years, complex, effective but inconvenient regimens of methotrexate (MTX) or dactinomycin had been widely used for nonmetastatic cases. GOG 174 compared weekly intramuscular MTX vs i.v. dactinomycin once every two weeks for low risk cases; the results are pending. For high risk metastatic disease, increasingly complicated multi-drug regimens became popular but had not been rigorously evaluated, until GOG 57 randomly compared a regimen of MTX, dactinomycin and chlorambucil (MAC) versus the so-called CHAMOMA regimen (cyclophosphamide, hydroxyurea, dactinomycin, MTX, vincristine, melphalan and doxorubicin); the more complex therapy was more toxic and less effective than MAC (84).

CERVICAL CARCINOMA

Surgical Studies

GOG 49 enrolled 1003 women with stage IB (clinically visible lesion) cervical cancer in a prospective surgical-pathologic study (85,86). At exploratory laparotomy, pelvic and para-aortic nodes were resected; if para-aortic nodes were not involved by frozen section examination, a radical hysterectomy was done. Careful pathologic study and clinical correlation indicated that even without positive nodes, large primary tumors, deep stromal invasion or capillary-lymphatic space involvement increased the risk of relapse and death. This analysis directed the planning of subsequent studies of stage IB disease. GOG 71 randomly compared extrafascial hysterectomy to observation in bulky (>4 cm.) stage IB cancers following definitive RT; the combined approach (RT + surgery) provided greater local control, but contrary to some uncontrolled reports, there was no survival advantage (87).

Pelvic Irradiation

The role of adjuvant RT had been controversial. GOG 92 studied stage IB cancers with 'intermediate risk' factors. After radical hysterectomy and pelvic lymphadenectomy, eligible patients without node involvement received adjuvant pelvic RT or were observed. RT improved local control and PFS but not OS (88,89).

Chemoradiation in Locally Advanced Disease

Although pelvic RT was standard therapy of stage IB2 and IIB-IVA (i.e. locally advanced) cancers, the results were not optimal. The possibility of enhancing irradiation with chemicals was intriguing, and GOG 4 (90) sought to assess the contribution of hydroxyurea (HU) in stage IIB and IVA cases, randomly assigning patients to pelvic RT +/- concurrent HU. The combined approach improved PFS and OS (Table 4). Although there were concerns about methods and execution in this early trial (91), concurrent HU was accepted by GOG as a standard for comparison with new approaches. GOG 56 compared HU vs. the hypoxic cell sensitizer, misonidazole, concurrent with pelvic RT; the outcome favored HU ($p=0.066$) but not significantly (92).

In the meantime, cisplatin had been identified as an active agent in advanced/recurrent cervical cancer, and pilot studies established a tolerable dose schedule with RT. GOG 85 was an intergroup trial (93) that compared cisplatin + 5-fluorouracil vs. HU with concurrent RT in surgical stage IIB-IVA cases. GOG 109 (94) was another intergroup trial (with GOG the largest contributor) using RT +/- cisplatin + 5FU infusion in IA2, IB and IIA cases, after radical

hysterectomy, if nodes or margins were positive. GOG 123 (95) in 'bulky' stage IB cases gave RT +/- concurrent cisplatin (all patients were to have adjunctive hysterectomy). All of these trials, as well as an RTOG study in 403 stage IIB-IVA patients using cisplatin + 5FU (96), significantly favored cisplatin-containing chemoRT.

GOG 120 was a three-arm trial comparing RT + HU vs. RT + cisplatin vs. RT + HU + FU + cisplatin; RT + HU was inferior in OS and the 3 drug arm was more toxic (97). A Canadian trial, reported later, failed to show an advantage for chemoRT; the sample size was relatively small (253 patients) and surgical staging was not used, but why its results were at variance with the others was not clear (98). At any rate, the weight of evidence favored chemoRT. Thus, RT + concurrent cisplatin was adopted as a new standard for locally advanced carcinoma of the cervix. Cisplatin +/- 5FU hasn't been studied, but cisplatin vs. prolonged FU infusion had no advantage for 5FU in GOG 165 (99). Current efforts to improve chemoRT are directed at new agents, new combinations and extended field RT. GOG 219 assesses tirapazamine, a hypoxic cell sensitizer, in patients receiving cisplatin + RT.

Chemotherapy for Advanced/Recurrent Cervical Cancer

GOG 23 was a three-arm trial of doxorubicin alone vs. with vincristine or with cyclophosphamide (100) that showed, at best, a 20% response rate for doxorubicin and no improvement with the combinations (Table 5). Although cisplatin had been identified by GOG as an active agent in carcinoma of the cervix, the optimal dose and infusion time were not clear, so GOG did two studies to clarify these issues. GOG 43 randomly compared 50 mg/m² vs. 100 mg/m² every 3 weeks vs 20 mg/m² × 5 days every 3 weeks in 497 evaluable cases. There was no significant improvement in OS with the higher doses, but more toxicity (101). GOG 64 studied 50 mg/m² infused at 1 mg/minute vs. a 24 hour infusion every 3 weeks; although nausea and vomiting were less with the prolonged infusion, there was no other advantage. Parenthetically, this trial antedated potent anti-emetics (102). A randomized trial of two platinum analogs, carboplatin and iproplatin (GOG 77), with carboplatin dosed by body surface area rather than AUC, enrolled 394 patients. There was no difference in OS and the response rates seemed low, 15% and 11% respectively, in relation to the historical experience with cisplatin of at least 20% (103). Also, some patients later responded to cisplatin, so carboplatin has not gained as much favor in cervical cancer as in ovarian and corpus cancer.

Based on phase II activity for ifosfamide and for mitolactol (dibromodulcitol), and phase I combination trials, GOG 110 compared cisplatin vs. cisplatin + ifosfamide vs. cisplatin + mitolactol in 438 eligible patients. Cisplatin + ifosfamide had a significantly higher response rate ($p = .004$) and PFS ($p = .003$) compared with cisplatin alone, but no improvement in OS; the combinations were more toxic (104). This was the first evidence of an impact of chemotherapy on PFS in this disease. Since uncontrolled reports suggested that bleomycin + ifosfamide + cisplatin were very active, GOG 149 studied cisplatin + ifosfamide again, +/- bleomycin (105); unfortunately, there was no difference in response or survival.

With the recognition of paclitaxel as active in cervical cancer, it was combined with cisplatin, with promising results in phase II, and then randomly compared with cisplatin alone in GOG 169 (106). The response rate and PFS were significantly better with the combination, but not OS. The combination was more toxic, but this did not decrease prospectively assessed QOL (107). GOG 179 took note of the clinical activity of topotecan, in vitro synergy with cisplatin, as well as reports that methotrexate + vinblastine + doxorubicin + cisplatin (MVAC), widely studied in bladder cancer, was also very active; patients received cisplatin alone, cisplatin + topotecan, or MVAC; the latter regimen was closed early because of excessive toxicity, and the trial was completed as a 2- arm study. The topotecan combination had a significantly higher response rate, PFS and OS than cisplatin (108). QOL was not significantly decreased, despite more toxicity (109). This was the first randomized phase III trial to show a survival benefit in

advanced cervix cancer. More recently there has been interest in vinorelbine and gemcitabine combinations with cisplatin. GOG 204 randomly compared cisplatin + paclitaxel, cisplatin + topotecan, cisplatin + vinorelbine, and cisplatin + gemcitabine; QOL assessments are included; results are pending.

VULVAR CARCINOMA

Although randomized trials in this disease have proven difficult to execute, GOG 37 was able to show (110), in a trial of 114 patients with squamous carcinoma and positive groin nodes, that RT yielded a survival benefit over pelvic node resection ($p=.03$).

DEVELOPMENTAL THERAPEUTICS

A number of new agents, new combinations, and drugs plus RT have been screened by GOG; several active drugs and combinations have been identified by this mechanism. In addition to the traditional two stage, response-rate driven approach in phase II trials, GOG has begun to draw on its growing data base to use the historical experience with PFS, for example at 6 months, in several tumor types, to assess treatment effects for biologic agents, etc., where disease stabilization may be a more likely early indicator of activity than regression (111).

TRANSLATIONAL RESEARCH

Among the goals of the translational research effort of GOG are: identifying women at risk, identifying early disease, predicting response, predicting recurrence, and understanding why cancers become resistant to a given treatment. With regard to risk, germ line mutations in BRCA1 and BRCA2 and the mismatch repair families of genes are now known to account for the majority of inherited risk of ovarian and endometrial cancers, so germ line DNA can be screened for mutations in these genes and inherited risk determined. Reports from GOG 143 on BRCA1 (112), GOG 144 on BRCA1 and BRCA2 (113) and GOG 172 regarding CHEK2 gene (114) and BRCA1 (115) have contributed to the understanding of this subject.

In support of selected GOG protocols, molecular pharmacology, clinical pharmacology and hormone receptor core laboratories have been established, in addition to a large GOG Tissue Bank. Relevant publications include, for example, reports from GOG 114 concerning prognostic significance of p53 mutation and overexpression (116), GOG 136 concerning a multidrug resistance protein in ovarian cancer (117) and GOG 148 regarding soluble tumor necrosis factor receptors and CA125 in ovarian cancer (118).

PREVENTION

GOG 137 was a randomized double blind trial of estrogen replacement for 3 years or placebo in stage I and II endometrial carcinoma, assessing recurrence and survival after surgery (hysterectomy and bilateral oophorectomy, with or without pelvic and para-aortic node sampling). By January 2003, 1240 women were enrolled. In the meantime, the Women's Health Initiative stopped estrogen plus progestin replacement because the risk/benefit assessment was no longer favorable; the risk for invasive breast cancer was increased. Enrollment in GOG 137 fell, and it was closed prematurely with 1236 eligible patients when it became clear that the accrual goal of 2108 patients was no longer feasible. Although the study was not completed, the absolute recurrence rate (2.3%) and the incidence of new cancers (1.3%) after estrogen were similar to the controls (119).

GOG 167 studied atypical endometrial hyperplasia (AEH); cases with that diagnosis by the initial pathologist were eligible, and had 2 layers of GOG pathology review. Of 289 cases submitted as AEH, 74 biopsies (26%) were interpreted by the GOG panel as less than AEH,

and 84 (29%) as carcinoma. In hysterectomy specimens with carcinoma, 19% had a study panel biopsy consensus of less than AEH, 39% had AEH, and 64% had a study panel biopsy diagnosis of carcinoma (120,121). The high rate of concurrent cancer was of note.

Among ongoing studies, GOG 199 should be of great interest when completed. This is a prospective study of risk-reducing salpingo-oophorectomy (RRSO) and longitudinal CA125 screening among those at increased genetic risk of ovarian cancer. Those who decline RRSO can enroll in a screening study of CA125 and additional studies based on a risk algorithm. Over 2000 women have been enrolled so far, with about 800 in the RRSO group.

CONCLUSION

Since 1970 the GOG has been in the forefront of clinical research regarding female pelvic cancer. In ovarian cancer, the key role of cisplatin, the enhanced activity of cisplatin plus paclitaxel, the improved therapeutic index of carboplatin plus paclitaxel and the success of intraperitoneal chemotherapy, are major accomplishments of GOG. In endometrial cancer, combination chemotherapy has shown a survival advantage over whole abdominal irradiation in locally advanced disease. With respect to carcinosarcoma, the survival benefit is less clear, but the potential for further improvement in combination chemotherapy favors it over WAI for future study. GOG has clarified the management of gestational trophoblastic disease. The management of endometrial and cervical cancers has benefited from surgical staging studies. Chemoradiation in locally advanced cervical cancer was established as a new standard of care largely through GOG studies. The first demonstration of a survival benefit from combination chemotherapy of cervical cancer and the importance of drugs other than cisplatin resulted largely from GOG trials. In short, GOG, with the collaboration of multiple investigators and institutions in the United States and elsewhere, has provided important answers and new standards of care for gynecologic cancers.

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Table 1
Randomized GOG Platinum Trials in Advanced Ovarian Carcinoma

Study	Stage	Comparison	Eligible	OS*	Comment	Reference
47	III ≥ 3cm, IV	Cyclo/Dox ± Cisp Every 3 wks x8	440	P<0.05	-	15,16
52	III ≤ 1cm	Cyclo/Cisp ± Dox x8	349	NSD	-	17
60	III > 1cm; IV	Cyclo/Cisp/Dox ± BCG	411	NSD	-	21
97	III > 1cm; IV	Cyclo 500/Cisp 50 × 8 vs Cyclo 1000/Cisp 100 × 4	458	NSD	Dose intense more toxic	22
104	III ≤ 2 cm	I.V. Cisp/Cyclo vs I.P. Cisp + I.V. Cyclo x6	546	P=0.02	I.P. better	39
111	III > 1 cm; IV	Cisp/Cyclo vs Cisp/Pacl x6	386	P=0.001	-	25
114	III ≤ 1cm	Cisp/Pacl vs I.V. Carbo x2, Cisp 100 I.P. + Pacl 135 I.V.	462	P=0.05	I.P. more toxic	40
132	III > 1 cm, IV	Cisp 100 vs Pacl 200 vs Cisp 75 + Pacl 135 I.V. x6	614	NSD	Pacl RR, PFS lower	27
158	III ≤ 1 cm	Cisp/Pacl vs Carbo/Pacl x6	792	NSD	Toxicity less with Carbo	34
162	III > 1 cm, IV	Cisp+24 vs 96 hour Pacl x6	293	NSD	-	32
172	III = 1 cm	Cisp 75/Pacl 135 I.V. vs I.V. + I.P. Pacl + I.P. Cisp x6 (see text)	415	P=0.03	I.P. more toxic	41

* OS = Overall survival, I.P. = Intraperitoneal, NSD = No significant difference, Cyclo = Cyclophosphamide, Dox = Doxorubicin, Cisp = Cisplatin, BCG = Bacillus Calmette-Guerin, Pacl = Paclitaxel, Carbo = Carboplatin, RR = Response rate, PFS = Progression-free survival

Table 2
Randomized GOG Drug Trials in Endometrial Carcinoma

Study	Comparison	Eligible	OS*	Comment	Reference
28	PAM/5FU vs Dox/Cyclo/5FU	358	NSD	All received medroxyprogesterone	68
34**	Dox x8 or Observation	181	NSD	-	70
48	Dox ± Cyclo x8 cycles	356	NSD	Combination more toxic	69
107	Dox ± Cisp x8	281	NSD	PFS, p = 0.014	55
139	Dox + Cisp, standard vs circadian x8	342	NSD	-	71
163	Dox/Cisp vs Dox/Pacl + GCSF x7	317	NSD	-	72
177	Dox/Cisp ± Pacl + GCSF x7	263	P=0.037	□ response, □PFS	73

* OS = Overall survival, NSD = No significant difference, PFS = Progression-free survival, PAM = Melfalan, 5FU = 5-Fluorouracil, Dox = Doxorubicin, Cyclo = Cyclophosphamide, Cisp = Cisplatin, Pacl = Paclitaxel, GCSF = Filgrastim

** Adjuvant trial in early stage high-risk; all other trials in advanced/recurrent disease

Table 3

Randomized GOG Trials in Uterine Sarcomas

Study	Stage	Comparison	Eligible	OS*	Comment	Reference
20	Adjuvant (I,II)	Dox x8 vs Observation	156	NSD	All cell types	76
21	Adv/Rec	Dox ± Dacarbazine x8	240	NSD	All cell types	75
42	Adv/Rec	Dox ± Cyclo x8	104	NSD	All cell types	79
108	Adv/Rec	Ifx ± Cisplatin x8	194	NSD	CaSa Only; PFS, P=0.02	80
150	Adjuvant (I →IV)	Cisplatin/Ifx x3 vs WAI	206	P=0.085	CaSa Only; Chemo better	82
161	Adv/Rec	Ifx ± Paclitaxel x8	179	P=0.03	CaSa Only; Combo better	81

* OS = Overall survival, NSD = No significant difference, Dox = Doxorubicin, Cyclo = Cyclophosphamide, Ifx = Ifosfamide, WAI = Whole Abdominal irradiation, Adv/Rec = Advanced or Recurrent, CaSa = Carcinosarcoma, PFS = Progression-free survival

Table 4
Randomized GOG Chemoradiation Trials in Cervical Carcinoma

Study	Stage	Concurrent Pelvic RT	Eligible	OS*	Reference
4	IIIB, IVA	HU vs Placebo	97**	P<0.05	90
56	IIIB to IVA	HU vs Misonidazole	294	P=0.066 favors HU	92
85	IIIB to IVA	HU vs Cisp/5FU	368	P=0.018 combo better	93
109	IA2, IB, IIA	± Cisp/5FU infusion	243	P=0.007 chemo-RT better	94
120	IIIB to IVA	HU vs Cisp vs Cisp/5FU/HU	526	P<0.001, HU inferior	97
123	IB2	± Cisp (all had hysterectomy)	369	P=0.008	95
165	IIIB to IVA	Cisp vs 5FU infusion	316	5FU not superior	99

* OS = Overall survival

** Evaluable HU = Hydroxyurea, Cisp = Cisplatin, 5FU = 5-Fluorouracil

Table 5
Randomized GOG Trials in Advanced/Recurrent Cervical Carcinoma

Study	Comparison	Eligible	OS*	Comment	Reference
23	Dox vs Dox/Cyclo vs Dox/Vcr	174	NSD	All received medroxyprogesterone	100
43	Cisp 50 vs 100 vs 20 × 5 days	497	NSD	50: Inferior response rate	101
64	Cisp 1 mg/min vs 24 hour	331	NSD	More vomiting with faster infusion	102
77	Carboplatin vs Iproplatin	361	NSD	-	103
110	Cisp vs Cisp/Ifx vs Cisp/DBD x6 cycles	438	NSD	- □RR, □PFS, with Cisp/Ifx	104
149	Cisp/Ifx ± Bleomycin	287	NSD	-	105
169	Cisp ± Paclitaxel × 6	264	NSD	□RR, □PFS, with combination	106
179	Cisp ± Topotecan × 6	294	P=0.017	-	108

* OS = Overall survival, PFS = Progression-free survival, RR = Response rate, NSD = No significant difference, Dox = Doxorubicin, Cyclo = Cyclophosphamide, Vcr = Vincristine, Cisp = Cisplatin, Ifx = Ifosfamide, DBD = mitolactol