J Gynecol Oncol Vol. 19, No. 4:218-222, December 2008 DOI:10.3802/jgo.2008.19.4.218

Review Article

Gynecologic oncology group trials in uterine corpus malignancies: recent progress

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The Gynecologic Oncology Group (GOG) has conducted multiple trials related to malignancies of the uterine corpus. Recently, several of these trials have been presented and/or published. Areas of focus included the feasibility of laparoscopic staging for endometrial cancer, the adjuvant management of locally advanced endometrial cancer, whole abdominal irradiation in maximally resected advanced endometrial carcinoma, and combination chemotherapy regimens for stage I and II carcinosarcoma after primary surgery and for advanced or recurrent carcinosarcoma. This article will discuss the background and details of each of these important advances.

Key Words: Endometrial neoplasm, Carcinosarcoma, Clinical trial

INTRODUCTION

The Gynecologic Oncology Group (GOG) charges its Committee on Cancer of the Uterine Corpus to design, conduct, and monitoring of phase III trials in cancer of the endometrium, uterine sarcomas, and gestational trophoblastic neoplasia; phase II trials of hormonal therapy in cancer of the endometrium and chemotherapy in gestational trophoblastic neoplasia. Recently, several of these trials involving uterine malignancies have been presented and/or published.

LAPAROSCOPIC SURGERY FOR UTERINE CANCERS

GOG9402 previously described the feasibility of laparoscopic staging of gynecologic cancers.[1] That study led to GOG LAP2, the first multi-center randomized trial of laparoscopy to be conducted in gynecologic cancer (Fig. 1). This study addressed the important question of the equivalency of conventional surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and periaortic lymph node dissection versus laparoscopic pelvic and periaortic lymph node dissection, bilateral salpingo-oophorectomy, and vaginal hysterectomy for clinical stage I and IIa endometrial carcinoma. The parameters that were evaluated include adequacy of the specimen, operative time, operative and postoperative morbidity, length of hospital stays, progression-free interval, and survival. Additionally, 600 patients were evaluated for quality of life objectives. The study was amended to enroll an additional 1,900 patients to monitor subcutaneous abdominal wall recurrences and recurrence rates during the first 5 years following surgery. Laparoscopy patients had similar rates of intraoperative injuries as laparotomy patients (9% vs. 8%, $p=0.11$), fewer adverse events (27% vs. 37%, $p<0.001$), fewer moderate to severe (>CTC grade 2) complications (14% vs. 21%, $p<0.001$), and had shorter length of hospital stay (median 3 days vs. 4 days, $p<0.001$). Eight (0.5%) deaths within six weeks occurred in laparoscopy arm and six (0.7%) in the laparotomy arm ($p=0.579$). This study showed that laparoscopic staging is feasible with longer operative times, comparable complications, shorter hospital stay, and better quality of life at six weeks than laparotomy. Of note, GOG LAP2 did not assess cost, which may be significantly higher for laparoscopy. Data reflecting survival analysis is not yet mature. At this time, therefore, laparoscopy cannot be considered standard of care, although it should be considered a feasible alternative for appropriate patients.[2,3]

The current staging protocol is GOG0210 "A Molecular Staging study of Endometrial Carcinoma." This is a molecular and Surgico-pathological staging study of endometrial carcinoma. The overall goal of this pilot protocol is to improve outcome and/or quality of life for patients with endometrial cancer. This fundamental goal will be accomplished through the development of more accurate models of risk, identi-

Received November 21, 2008, Revised November 28, 2008, Accepted December 9, 2008

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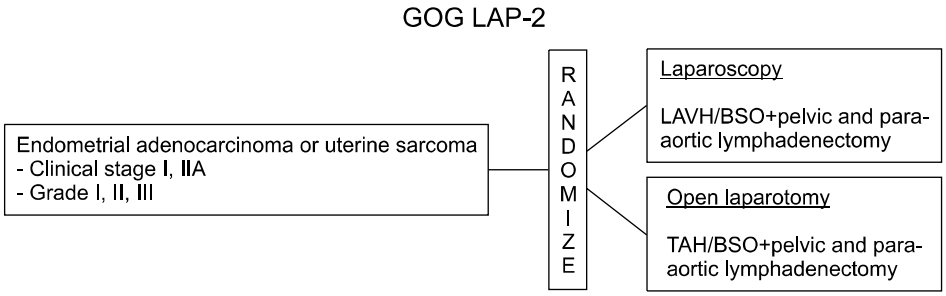

Fig. 1. A phase III randomized clinical trial of laparoscopic pelvic and para-aortic node sampling with vaginal hysterectomy and BSO versus open laparotomy with pelvic and para-aortic node sampling and abdominal hysterectomy and BSO in endometrial adenocarcinoma and uterine sarcoma, clinical stage I, IIA, Grade I, II, III.

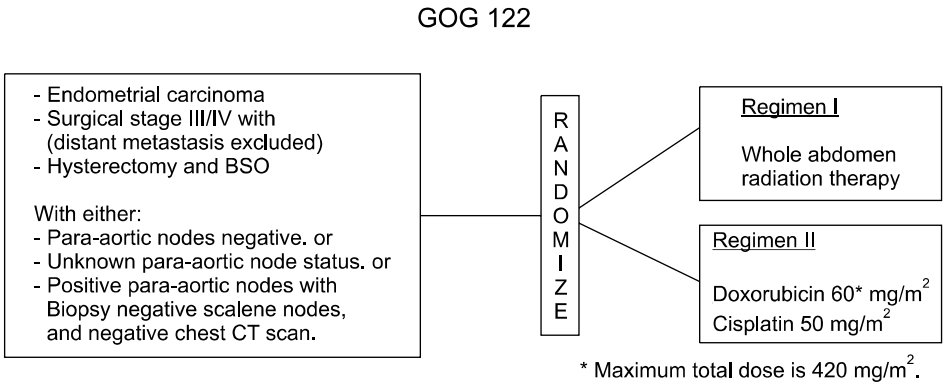

Fig. 2. Whole abdominal radiotherapy versus combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma (phase III).

fication of candidate targets for therapeutic intervention and utilization of individualized treatments based on molecular characteristics identified in tumor tissue, normal tissue and/or in readily accessible biological fluids, like serum and urine. Specifically, a repository of clinical specimens (tissue, urine, and serum) with detailed clinical and epidemiologic data from patients with surgically staged endometrial carcinoma has been established. It will utilize genomic, proteomic and immunoassay results from these specimens for the purpose of class prediction and class discovery to identify and validate molecular characteristics associated with risk of endometrial cancer recurrence, clinical and histological characteristics, and epidemiologic factors. The study will seek to improve the accuracy and resolution of the risk assessment models for predicting endometrial cancer recurrence using informative genomic, proteomic and immunoassay results *in combination with* clinical, pathological, and epidemiologic factors. Mining the genomic, proteomic and immunoassay results along with the clinical, histological and epidemiologic data obtained for this research study should identify candidate characteristics to target or exploit that would help prevent and/or treat endometrial carcinoma, and to expand the current understanding of the biology, progression, metastasis and responsiveness of endometrial carcinoma. As technology advances, other laboratory and translational proposals are being sought to fulfill the aims of GOG0210.

IRRADIATION AND COMBINATION CHEMOTHERAPY IN MAXIMALLY RESECTED ADVANCED ENDOMETRIAL CARCINOMA

Previously, GOG0094 showed that whole abdominal irradiation (WAI) in maximally resected advanced endometrial carcinoma has tolerable toxicity, and that the outcome may be improved in patients with completely resected disease.[4] In addition, GOG0107 reported that adding cisplatin to doxorubicin (AP) in advanced endometrial carcinoma improved response rate and progression free survival.[5]

GOG0122 was a phase III comparison of abdomino-pelvic radiotherapy versus standard combination chemotherapy (AP) for small volume (less than 2 cm) endometrial cancer confined grossly to the abdominal cavity (Fig. 2). Two hundred and two patients were randomly allocated to receive WAI. Irradiation dosage was 30 Gy in 20 fractions, with a 15-Gy boost. One hundred and ninety four patients were allocated to receive chemotherapy. Although WAI was previously considered the standard therapy, GOG0122 showed for the first time that combination chemotherapy given adjuvantly in this group of patients significantly improved survival and disease-free survival compared to WAI. At 5 years, approximately half the patients receiving chemotherapy were without evidence of recurrence compared to 38% of those who received WAI. It was concluded that combination chemotherapy with AP significantly improves progression-free survival and overall survival when compared with WAI. However, acute toxicity is significantly increased with AP che-

motherapy compared to WAI. The most common grade 3 to 4 toxicities were hematologic and included neutropenia, leukopenia, and thrombocytopenia. The percentage of patients who developed at least one grade 3 or 4 hematologic toxicity of any type was significantly greater for AP chemotherapy than WAI (88% as compared to 14%). Other grade 3 or 4 toxicities were also more common in AP than in WAI and included gastrointestinal (20% vs. 13%), cardiac (15% vs. 0%) and neurologic (7% vs. 1%). By contrast, hepatic toxicity was reported in 3% of WAI patients and 1% of AP chemotherapy patients. Finally, the authors note that treatment probably contributed to eight deaths in the AP chemotherapy arm and five deaths in WAI arm. In sum, GOG0122 showed that the addition of AP chemotherapy significantly improved survival and disease-free survival but at the cost of significant increase in acute toxicity.[6,7]

GOG0122 was followed by GOG0184 where, after surgery with optimal debulking (diameter $\leq$2 cm) and tumor directed radiation, patients were randomized to cisplatin and doxorubicin with or without paclitaxel (Fig. 3).[8] Participating patients had advanced endometrial carcinoma of any histological type. Six hundred and fifty nine patients were enrolled after surgery and 552 were eligible after radiation for randomization to chemotherapy. Adverse events were significantly more frequent and more severe in the paclitaxel arm ($p < 0.01$). Specifically, there were more instances of grade 3 and 4 leukopenia (77% vs. 51%), neutropenia (68% vs. 47%), thrombocytopenia (24% vs. 10%), anemia (15% vs. 12%), infection/fever (8% vs. 1.5%), febrile neutropenia (5% vs. 0), sensory neuropathy (9% vs. 2%), pain (10% vs. 7%) and myalgia (3% vs. 0) in the cisplatin and doxorubicin with paclitaxel arm (CDP) versus the cisplatin and doxorubicin arm (CD) respectively. Approximately 80% of enrolled patients completed the six cycles of chemotherapy. The proportion of patients alive and recurrence free at 36 months was 62% for those in the CD arm and 64% for those in the CDP arm. There was no statistically significant improvement in recurrence-free survival between the two regimens ($p=0.21$). Overall, the addition of paclitaxel had little impact on recurrence free survival and was associated with increased morbidity. Of note, subset analysis revealed a 50% reduction in the risk of recurrence or death for patients with gross residual disease in the CDP arm when compared to the CD arm. This subset analysis suggests that if there is any benefit due to paclitaxel, it is primarily observed among those patients with gross residual tumor.[8]

The recent NCI sponsored Endometrial Cancer State of the Science meeting recommended that further trials be conducted in this group of patients. A follow up trial, evaluating the role of tumor directed radiation, UC0704 "A Randomized Phase III Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Advanced Endometrial Cancer", has been approved and is planned to open when GOG0209 closes.

UTERINE CARCINOSARCOMA: SUPERIOR OVERALL SURVIVAL FOR COMBINATION CHEMOTHERAPY

After a decade of persistent and patient study, significant progress in the treatment of uterine carcinosarcoma was published in 2007. GOG0108 previously showed that ifosfamide plus cisplatin offers a slight prolongation of progression-free survival but no significant overall survival benefit.[9] GOG0117 showed that adjuvant ifosfamide and cisplatin after primary surgery for stage I or II carcinosarcoma of the uterus was tolerable.[10]

GOG0150 then compared adjuvant ifosfamide and cisplatin

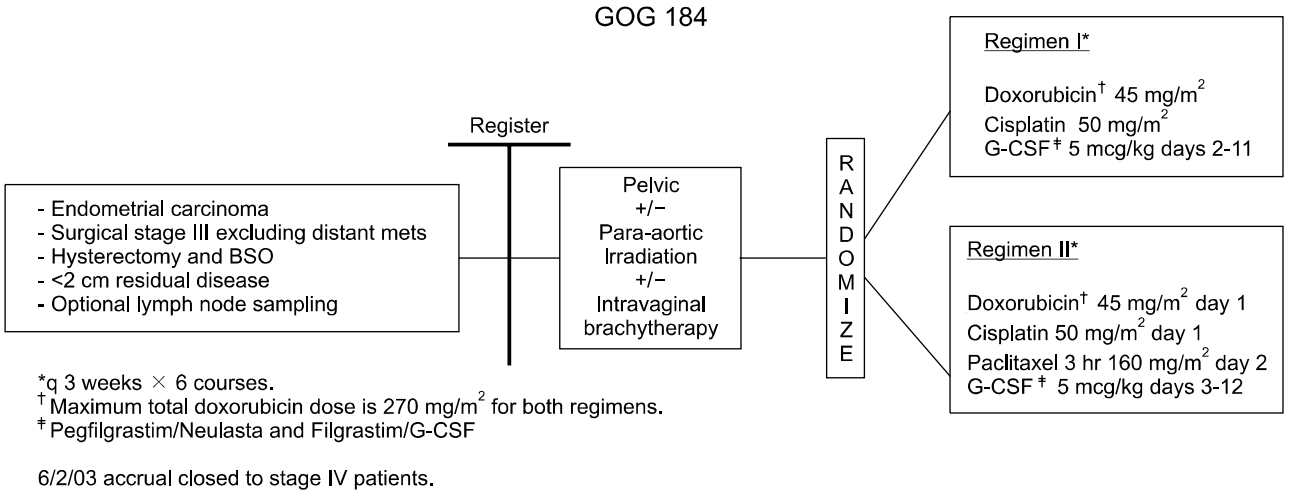

Fig. 3. A randomized phase III study of tumor volume directed pelvic plus or minus para-aortic irradiation followed by cisplatin and doxorubicin or cisplatin, doxorubicin and paclitaxel for advanced endometrial carcinoma.

to whole abdominal radiotherapy.[11] GOG0150 was a randomized study of patients with Stage I-IV carcinosarcoma of the uterus with less than 1 cm residual disease and no extra-abdominal spread (Fig. 4). The study tested if patients treated with systemic treatment or loco-regional treatment differ in failure patterns, progression-free interval, and survival. There were 105 patients in the WAI and 101 in the chemotherapy cohorts, respectively. Out of 206 study patients, there were 112 total recurrences (54%) with 60 (57%) in the radiotherapy and 52 (51%) in the chemotherapy treatment arm. Although patients may have had several different sites of failure, there were more vaginal failures in the chemotherapy (10%) than in the WAI group (4%). However, there were more abdominal relapses in the WAI (28%) than in chemotherapy cohort (19%). Pelvic and distant failures were essentially the same. Although acute toxicities of anemia and neuropathy were more frequent in the chemotherapy arm, there were more severe grade 3/4 gastrointestinal late effects in the WAI group and two patients died as a direct result of radiation hepatitis. The estimated probability of surviving at 5 years was 35% vs. 45%, WAI vs. chemotherapy. After adjusting for stage and age, there is no longer a definite survival advantage but rather now a trend favoring chemotherapy (the estimated death rate was 29% lower for chemotherapy patients than WAI patients (RH=0.712, 95% CI: 0.484-1.048, p=0.085, two-tail test). GOG0150 has shown that adjunctive chemotherapy has less toxic long-term side effects and is more likely than radiotherapy to improve the survival for these patients.[11]

Thereafter, GOG0161 randomized patients with advanced or recurrent carcinosarcoma to ifosfamide versus ifosfamide plus paclitaxel (Fig. 5). Those patients receiving combination chemotherapy experienced more frequent alopecia (grade 1 to 2; 40% vs. 58% for ifosfamide vs. combination chemotherapy respectively), sensory neuropathy (grade 1 to 4; 8% vs. 30%) and thrombocytopenia (11% vs. 46%). Thirty four percent of eligible patients completed all 8 cycles of chemotherapy.

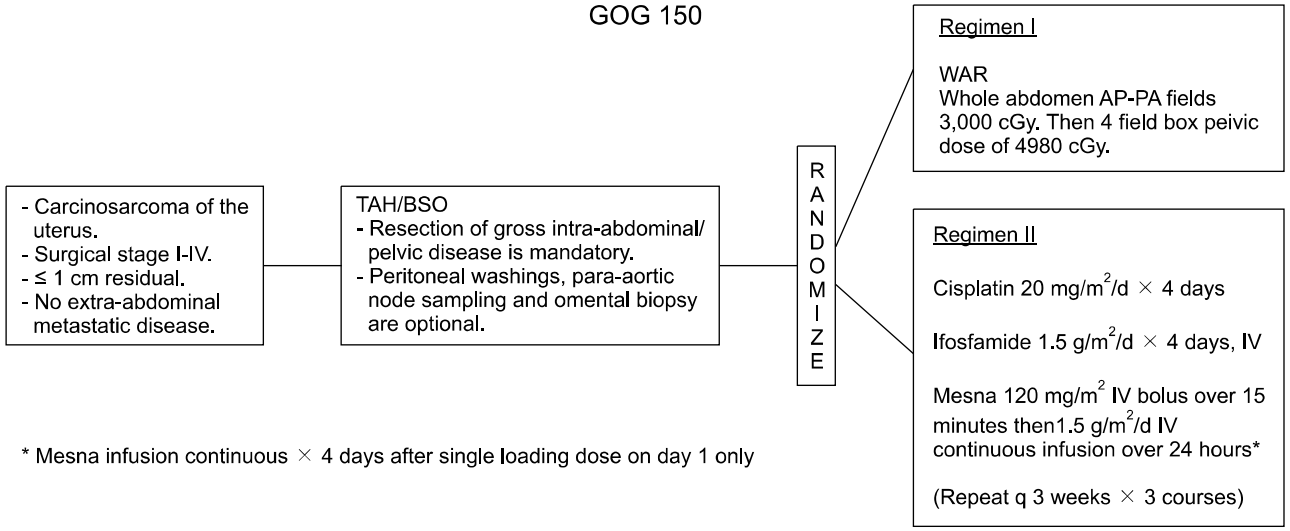

Fig. 4. A phase III randomized study of whole abdominal radiotherapy versus combination ifosfamide-mesna with cisplatin in optimally debulked stage I, II, III or IV carcinosarcoma of the uterus.

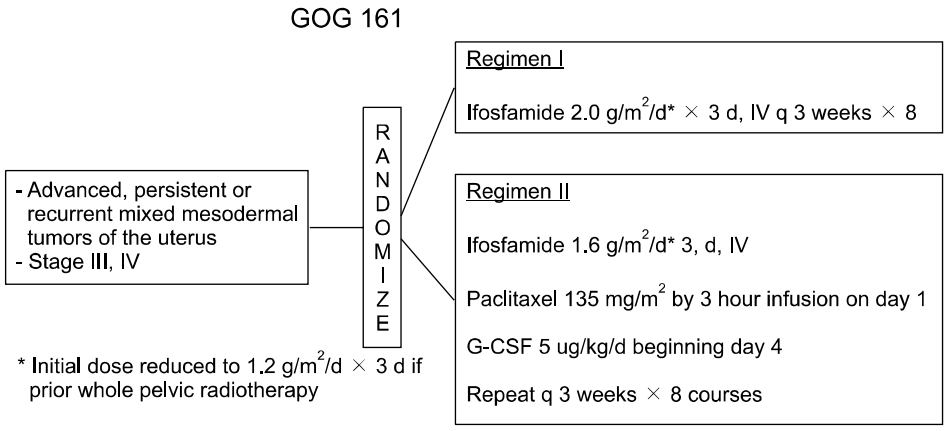

Fig. 5. A phase III trial of ifosfamide versus ifosfamide plus paclitaxel in patients with advanced, persistent, or recurrent carcinosarcoma (mixed mesodermal tumors) of the uterus.

Patients receiving ifosfamide alone were more likely to discontinue therapy early due to progression when compared to those who received combination chemotherapy (54% vs. 33%). There was a survival advantage for combination chemotherapy (13.5 vs. 5.8 months). Thus, GOG0161 is the first randomized prospective trial in uterine carcinosarcoma that clearly demonstrates a superior overall survival for combination (ifosfamide and paclitaxel) chemotherapy compared to single agent treatment (ifosfamide).[12]

The recent NCI sponsored Endometrial Cancer State of the Science meeting recommended that further trials be conducted in this group of patients. Phase II trials are being conducted by the GOG to identify potentially active agents or combinations for incorporation into a future phase III study. GOG0232B, "A Phase II Evaluation of Paclitaxel (Taxol, NSC #673089) and Carboplatin (Paraplatin, NSC #241240) in the Treatment of Carcinosarcoma of the Uterus" has completed accrual. A protocol concept, UC-0701, "Randomized Phase III Trial of Carboplatin (AUC = 6×1 day IV) plus Paclitaxel (175 mg/m^2×1 day IV) versus Ifosfamide (1.6 g/m^2/day×3 days IV) plus Taxol (135 mg/m^2 by 3 hour infusion on day 1) in Patients with Advanced, Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus", has been approved and will open if GOG0232B is a positive trial. Both arms of UC-0701 will repeat chemotherapy doses every 3 weeks for 6 cycles.

SUMMARY

Recent GOG trials have achieved major advances in treatment of uterine corpus neoplasms. Laparoscopic staging when compared to laparotomy is feasible with comparable complications, shorter hospital stay, and better quality of life at six weeks. Combination chemotherapy given adjuvantly for small volume endometrial cancer significantly improves survival and disease-free survival when compared with WAI. Ifosfamide plus paclitaxel confers a considerable survival advantage in the treatment of uterine carcinosarcoma when compared with single agent therapy (ifosfamide alone). In addition, adjunctive chemotherapy has less toxic long-term side effects and is more likely to improve survival when compared with radiotherapy for uterine carcinosarcoma.

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