

# Chemotherapy for Advanced or Recurrent Gynecologic Cancer

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Studies of chemotherapy in advanced or recurrent gynecologic cancer have focussed on ovarian, cervical, and endometrial carcinoma. For celomic epithelial carcinomas of the ovary, a large number of cytotoxic agents have been shown to be active. Dramatic improvement in frequency of response with lesser improvement in survival has been noted with the use of cisplatin-based combination chemotherapy as compared to single alkylating agents. More recent studies have evaluated alternative ways to employ cisplatin: higher dose schedules, intraperitoneal administration, and platinum compounds with a potentially better therapeutic index. None has yet been shown superior to a combination of relatively low-dose cisplatin plus an alkylating agent with or without doxorubicin. Cisplatin remains the best studied and most active single agent in patients with squamous cell carcinoma of the cervix. While a number of other agents have demonstrated moderate activity, no combination of drugs has as yet proved superior to single-agent cisplatin. In endometrial carcinoma, progestins and doxorubicin are the most active agents. Tamoxifen, cisplatin, and hexamethylmelamine appear to have moderate activity. No combination has yet been shown to be superior to single agents. Information on chemotherapy for less common gynecologic malignancies is largely anecdotal. Two observations are of note. Cisplatin-based combination chemotherapy is highly active against germ-cell neoplasms of the ovary. Cisplatin also has definite activity against mixed mesodermal sarcoma of the uterus.

*Cancer* 60:2104-2116, 1987.

THE ROLE of systemic therapy in patients with gynecologic malignancies has received increasing scrutiny in the last ten years. This effort has focussed on the more common lesions: celomic epithelial cancers of the ovary, squamous cell carcinoma of the cervix, and carcinoma of the endometrium. To a lesser extent, studies have evaluated systemic therapy for patients with endometrial sarcomas, carcinomas of the vulva and vagina, and germ cell neoplasms of the ovary. This review will concentrate on the three most common neoplasms and will mention briefly those other lesions for which some data exist.

## Celomic Epithelial Carcinoma of the Ovary

Systemic therapy has long been a central part of the management of advanced epithelial carcinoma of the

ovary. Stage or extent of disease is the single most important determinant of the application of this management.<sup>1</sup> For patients with Stage III disease, however, another consideration becomes very important: the volume of residual disease present at the time of initiation of treatment.<sup>2-10</sup> The definition of such minimal residual (optimal) disease varies from no gross residual disease to nodules as large as 3 centimeters. Regardless of the definition, studies consistently show that patients with minimal residual disease both respond more frequently to chemotherapy and demonstrate significantly better survival than those with bulky Stage III or Stage IV disease. Conclusions drawn from any trial of advanced ovarian carcinoma must take into account the percentage of patients with minimal residual disease in order to assure that differences reflect treatment, not simply the bulk of disease.

## Single Agents

A number of systemic agents are active against ovarian carcinoma (Table 1).<sup>11-16</sup> Traditional single-agent therapy is a single alkylating agent, usually l-phenylalanine mustard (melphalan, alkeran). Reported response rates with oral melphalan vary widely from 12%<sup>17</sup> to 54%.<sup>9</sup> Results obtained by the Gynecologic Oncology Group (GOG) from three separate studies of patients

Presented at the American Cancer Society National Gynecologic Conference, Atlanta, Georgia, September 17-19, 1986.

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Supported in part by the following National Cancer Institute grants: CA 13633 (University of Mississippi) and CA 37517 (Gynecologic Oncology Group Statistical Office).

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Accepted for publication March 10, 1987.



TABLE 3. Dose and Schedule of the Combination\* Developed by Indiana University<sup>26†</sup>

Drug	Dosage
Cisplatin	50 mg/m <sup>2</sup> IV
Doxorubicin	50 mg/m <sup>2</sup> IV
Cyclophosphamide	500 mg/m <sup>2</sup> IV

GOG: Gynecologic Oncology Group; IV: intravenously.

\* Regimen is repeated every 3 weeks for eight cycles or until evidence of progression of disease, whichever comes first. Second-look laparotomy was performed in patients achieving clinically complete response or in those thought to be resectable after eight cycles of therapy.

† Evaluated by the GOG<sup>28</sup> in patients with bulky advanced celomic epithelial carcinoma of the ovary.

regimen yielded a significantly greater percentage of clinical complete responses.

The third major trial in the GOG sequence was based on a pilot study at Indiana University which evaluated the combination of cisplatin, doxorubicin, and cyclophosphamide.<sup>26</sup> The pilot suggested that the addition of cisplatin to combination chemotherapy yielded a higher response rate and longer survival than had been noted with regimens not containing cisplatin. The frequency of clinical complete response was 41% (23 of 56 patients). The pilot also used second-look laparotomy at 12 months after initiation of chemotherapy to demonstrate that 40% of clinical complete responses (10 of 23 patients) were in fact pathologically complete responses. A recent update of these data<sup>27</sup> documented the durability of these pathologically complete responses with six of the ten patients still free of disease at 7 years.

These pilot results led to the third major GOG study which compared cyclophosphamide to the best arm of the second trial, the combination of cyclophosphamide and doxorubicin.<sup>28</sup> This large trial again included only patients with bulky disease, about half of whom had measurable disease. For this measurable-disease population, results demonstrated superiority for the cisplatin-containing combination in regard to response rate, duration of response, and survival. For the overall patient population, the cisplatin-containing combination yielded a significantly better progression-free interval but not a superior survival. The frequency with which patients achieved a pathologically complete response also favored the cisplatin-combination (25 of 205 patients or 12% versus nine of 215 patients or 4%).

Although there are still those who would argue that single-agent therapy<sup>29</sup> or the use of sequential alkylating agent and cisplatin<sup>30</sup> is preferable, the prevalence of opinion favors the use of cisplatin-based combination chemotherapy.<sup>31</sup> The most extensively studied regimen is the combination of cisplatin, doxorubicin, and cyclophosphamide<sup>26,28</sup> (Table 3). The addition of hexamethylmelamine<sup>32-34</sup> or BCG<sup>35-36</sup> to a cisplatin combination

has produced no evidence of any advantage. Other studies have evaluated the role of doxorubicin in the combination with inconclusive results to date.<sup>37-39</sup> Based on these results, it is reasonable to regard the three-drug combination of cisplatin, doxorubicin, and cyclophosphamide in the dose and schedule reported by the GOG<sup>28</sup> to be the chemotherapy of choice for advanced ovarian carcinoma.

### New Directions

A number of new alternatives are under investigation. These include: the role of cytoreductive surgery, intraperitoneal chemotherapy, and combinations using extremely high-dose platinum compounds.

With regard to the role of cytoreductive surgery, interest was generated by observations of improved response to chemotherapy and improved survival in those who had minimal residual disease.<sup>2-5,8-9</sup> The GOG recently completed a large trial in patients with only minimal residual disease<sup>39</sup> and observed a high frequency (>30%) of pathologically complete response to cisplatin-based chemotherapy. Two questions remain, however, regarding whether initial cytoreductive surgery is truly of benefit. First, is the advantage observed for optimal disease a result of cytoreductive surgery or a reflection of patients who have less aggressive disease that is already optimal at the time of surgery? Secondly, if surgical cytoreduction is of benefit, can a sufficient number of patients be successfully cytoreduced to justify laparotomy as an initial step in the management of a majority of patients? A current study of the GOG addresses these questions by randomizing patients to receive either cisplatin-based chemotherapy initially or cytoreductive surgery followed by the same chemotherapy.

The second of these, intraperitoneal chemotherapy, has attracted interest because of the propensity of ovarian carcinoma to spread by intraperitoneal seeding. Basic studies demonstrated the feasibility of and pharmacologic advantage for administering such agents as cisplatin, methotrexate, 5-fluorouracil, and doxorubicin in the peritoneum.<sup>40-42</sup> Studies using intraperitoneal chemotherapy, principally cisplatin, have shown that patients who have failed prior chemotherapy including cisplatin will respond and that, particularly in patients with minimal residual disease, some of the responses will be durable pathologically complete responses.<sup>43-46</sup> No data are available on the use of intraperitoneal chemotherapy in patients with no prior therapy, but the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) are conducting an intergroup study comparing intravenous cisplatin plus cyclophosphamide to intraperitoneal cisplatin plus intravenous cyclophosphamide.



The third of these, the use of extremely high-dose intravenous cisplatin, was first reported in a series of patients who had failed prior chemotherapy including cisplatin.<sup>20</sup> An observed response rate of 32% in this series of 19 patients receiving cisplatin 40 mg/m<sup>2</sup>/d in hypertonic saline for 5 days every 4 weeks suggested that the use of this regimen was not only feasible but also potentially highly active. A subsequent trial of this high-dose regimen in combination with cyclophosphamide in patients with no prior chemotherapy confirmed a high order of activity for this regimen.<sup>47-48</sup> The results in the first 24 patients, however, show a pathologically complete response rate of 14% (two of 14) in patients with bulky disease and 50% (five of ten) in patients with minimal residual disease. These results are not strikingly different from the results of the GOG using a far less toxic dose of cisplatin of 50 mg/m<sup>2</sup> in combinations (12% pathologically complete response in patients with bulky disease<sup>28</sup> and 34% in patients with optimal disease<sup>39</sup>). The concept of the importance of dose intensity to the success of cisplatin-based combinations is being tested in a current GOG trial, but the highest dose of cisplatin in either regimen is 100 mg/m<sup>2</sup>.

#### Other Alternatives

Two other alternatives of potential value in the management of ovarian carcinoma include hormonal therapy and the use of the *in vitro* human tumor stem cell assay to direct the choice of cytotoxic agents for a particular patient. Collected data from the last decade confirm the presence of estrogen and progesterone receptors in over half of cases of ovarian carcinoma (74% positive for estrogen receptor and 51% positive for both receptors).<sup>49</sup> Although there are insufficient data at the present time to draw a correlation between receptor status and response to hormonal manipulation, collected data do document modest activity for progestins in ovarian carcinoma (12% of 176 patients).<sup>49</sup> What role, if any, hormone receptor assays and progestins will have in the treatment of ovarian carcinoma remains to be determined.

The status of the *in vitro* human tumor stem cell assay is similar. Ovarian carcinoma cells, especially those taken from malignant ascites, can be grown in culture in more than half of cases.<sup>50</sup> The assay predicts for drug resistance reasonably accurately, but identification of drugs to which the cells are sensitive is less accurate. Whether the assay is of value in determining the appropriate drug regimen for any given patient remains to be seen.

#### Squamous Cell Carcinoma of the Cervix

Over 80% of carcinoma of the uterine cervix is squamous cell carcinoma. The trials of the GOG, which rep-

TABLE 4. Single-Agent Activity of Commercially Available Agents in Patients With SCC of the Cervix

Drug	No. of patients	Responses	
		No.	Percent
Alkylating agents			
Cyclophosphamide <sup>51,55</sup>	251	38	15
Chlorambucil <sup>51</sup>	44	11	25
Melphalan <sup>51</sup>	20	4	20
Methyl CCNU <sup>51</sup>	94	7	7
CCNU <sup>51</sup>	63	3	5
Antimetabolites			
5-fluorouracil <sup>51</sup>	142	29	20
Methotrexate <sup>51</sup>	96	17	18
6-mercaptopurine <sup>51</sup>	18	1	5
Plant alkaloids			
Vincristine <sup>54,56</sup>	55	10	18
Vinblastine <sup>57</sup>	20	2	10
VP-16-213 <sup>58</sup>	31	0	0
Antibiotics			
Adriamycin <sup>51</sup>	205	33	16
Bleomycin <sup>51</sup>	172	17	10
Mitomycin-C <sup>51</sup>	18	4	22
Hydroxyurea <sup>52</sup>	14	0	0

SCC: squamous cell carcinoma; CCNU: lomustine.

resent a majority of information on chemotherapy in cervix cancer, separate squamous cell carcinomas from other histologic types. The following discussion will focus on GOG investigations of squamous cell carcinoma and on certain other data which are comprised, for practical purposes, of patients with squamous cell carcinoma.

In patients with squamous cell carcinoma of the cervix, the most significant prognostic factor is extent of disease at time of diagnosis. Chemotherapy has for the most part been reserved for those patients with advanced (Stage IVB) or recurrent disease no longer amenable to surgery or radiotherapy. Such patients present several problems. First, most of these patients have had prior radiotherapy which impairs the bone marrow and interferes with vascular supply and hence, delivery of drug to tumor in the pelvis. Secondly, renal impairment present in many of these patients because of ureteral obstruction restricts tolerance to chemotherapeutic agents which are nephrotoxic or which are excreted by the kidney.

#### Single Agents

Despite these difficulties, data are available on a large number of commercially available drugs<sup>51-58</sup> (Table 4). These data are not, in many instances, of optimal quality since they represent material collected from multiple series. The conclusion can be drawn, however, that several of these agents have moderate activity.

In addition, a number of investigational agents have been evaluated<sup>59-76</sup> (Table 5). The majority of these pa-



TABLE 5. Activity of Investigational Drugs as Single Agents in SCC of the Cervix

Drug	No. of patients	Response	
		No.	Percent
Hexamethylmelamine <sup>51</sup>	64	12	19
Porfiromycin <sup>51</sup>	78	17	22
AMSA <sup>59,60</sup>	20	0	0
	25	1	4
Baker's antifol <sup>61</sup>	32	5	16
Dianhydrogalactitol <sup>62</sup>	36	7	19
Dibromodulcitol <sup>63</sup>	47	7	15
ICRF-159 <sup>64</sup>	28	5	18
Maytansine <sup>65</sup>	29	1	3
Mitoxantrone <sup>66</sup>	25	2	8
PALA <sup>67</sup>	33	0	0
Piperazinedione <sup>68</sup>	43	2	5
Spirogermanium <sup>69</sup>	14	0	0
Vindesine <sup>70,71</sup>	49	5	10
Yoshi 864 <sup>72</sup>	18	0	0
Idarubicin <sup>73</sup>	18	0	0
AZQ <sup>74</sup>	26	0	0

SCC: squamous cell carcinoma; AMSA: acridinyl anisidide; AZQ: aziridinybenzoquinone.

tients had received prior chemotherapy with a cisplatin-containing regimen. Moderate activity of possible further interest was observed for vindesine, Baker's antifol, dianhydrogalactitol, dibromodulcitol, ICRF-159, hexamethylmelamine, and porfiromycin.

Most attention, however, has been directed to the investigations of the drug cisplatin (Table 6). Despite an

TABLE 6. Studies of Single-Agent Cisplatin in SCC of the Cervix by the GOG and Other Groups

Study and regimen	No. of patients	Response	
		No.	Percent
GOG protocol 26C <sup>75</sup>			
50 mg/m <sup>2</sup> at 1 mg/min every 3 wk	34	13	38
GOG protocol 43 <sup>79</sup>			
50 mg/m <sup>2</sup> at 1 mg/min every 3 wk	150	31	21
100 mg/m <sup>2</sup> at 1 mg/min every 3 wk	166	52	31
20 mg/m <sup>2</sup> for 5 d at 1 mg/min every 3 wk	128	32	25
GOG protocol 64 <sup>80</sup>			
50 mg/m <sup>2</sup> at 1 mg/min every 3 wk	164	27	16
50 mg/m <sup>2</sup> over 24 h every 3 wk	158	29	18
Totals for GOG	800	184	23
Other studies—prior chemotherapy			
120 mg/m <sup>2</sup> every 3–4 wk <sup>81</sup>	11	5	45
75 mg/m <sup>2</sup> every 3 wk <sup>77</sup>	4	0	0
5 mg/m <sup>2</sup> for 5 d every 3–4 wk <sup>83</sup>	1	1	100
0.75 mg/kg every 4–6 wk <sup>82</sup>	2	0	0
Other studies—no prior chemotherapy			
75 mg/m <sup>2</sup> every 3 wk <sup>77</sup>	4	0	0
3 mg/kg every 3 wk <sup>83</sup>	3	3	100
50 mg/m <sup>2</sup> every 3 wk <sup>83</sup>	8	3	38

SCC: squamous cell carcinoma; GOG: Gynecologic Oncology Group.

TABLE 7. Activity of Platinum Analogues in SCC of the Cervix

Regimen	No. of patients	Response	
		No.	Percent
Carboplatin 400 mg/m <sup>2</sup> every 4 wk <sup>84,86</sup>	29	6	21
	27	6	23
CHIP 300 mg/m <sup>2</sup> every 4 wk <sup>85,86</sup>	22	5	23
	28	10	36

CHIP: iroplatin; SCC: small cell carcinoma.

earlier negative report of the activity of this agent,<sup>77</sup> the GOG was able to demonstrate a high order of activity for the drug at 50 mg/m<sup>2</sup> every 3 weeks in patients with no prior chemotherapy (11 responses among 22 patients) and even some responses in patients with prior chemotherapy (two responses among 12 patients).<sup>78</sup> A subsequent GOG trial compared the low dose regimen to two higher dose schedules: 100 mg/m<sup>2</sup> every 3 weeks and 20 mg/m<sup>2</sup> daily for 5 days every 3 weeks.<sup>79</sup> While the sought-after 15% improvement in response rate with one of the higher doses was not seen, there was a statistically significant 10% improvement with the 100 mg/m<sup>2</sup> regimen as compared to the 50 mg/m<sup>2</sup> regimen. Whether the smaller improvement is clinically significant is not clear. A third study evaluated a 24-hour continuous infusion of the 50 mg/m<sup>2</sup> regimen versus the standard 1 mg/min infusion rate of the same dose with no observable difference in response but a significant increase in the percentage of patients experiencing no nausea and vomiting (33% with the 24 hour infusion versus 18% with the standard infusion).<sup>80</sup>

The sum of the GOG experience with cisplatin as a single agent in squamous cell carcinoma of the cervix shows 184 responses (23%) among 800 patients treated. An additional 33 patients have been reported by other investigators with 12 responses.<sup>81–83</sup> These studies document the significant activity of cisplatin as well as the independence of response from dose and schedule of drug.

Because of the significant activity of cisplatin and the prevalence of renal problems in these patients, interest in certain platinum analogues with less nephrotoxicity has developed. The GOG is currently conducting a randomized comparison of two of these analogues, CBDCA and CHIP (Table 7). The initial experience with each drug reveals definite activity (six responses among 29 patients with CBDCA<sup>84</sup> and five responses among 22 patients with CHIP<sup>85</sup>), but insufficient data are available to allow comparisons to be made as yet. One other trial comparing these two analogues<sup>87</sup> shows a slight but not significant advantage for iroplatin in terms of response rate (36% of 28 patients versus 23% of 27 patients) in a preliminary report. Both drugs appear to be both less



TABLE 9. Studies on the Relationship Between the Status of Estrogen and Progesterone Receptors and Response to Progestin Therapy\*

Series	ER+ PR+ Response		ER- PR- Response	
	No.	Percent	No.	Percent
Creasman <sup>116</sup>	3/5	60	1/8	12
Ehrlich <sup>117</sup>	7/8	88	1/16	7
Benraad <sup>118</sup>	5/6	83	0/5	0
Martin <sup>119</sup>	13/13	100	1/7	14
McCarty <sup>120</sup>	4/5	80	0/8	0
Thigpen <sup>114</sup>	4/10	40	3/25	12
Total	36/47	77	6/69	9

ER: estrogen receptor; PR: progesterone receptor.

### Chemotherapy

Experience with the use of cytotoxic drugs in endometrial carcinoma is virtually limited to data generated in the last decade (Table 10).<sup>124-137</sup> Doxorubicin has definite activity which has been confirmed in three separate trials.<sup>125-126,138</sup> Cisplatin has been evaluated in five series.<sup>127-131</sup> In patients with no prior chemotherapy, there is definite activity confirmed in three series.<sup>128,130-131</sup> In patients with prior treatment, the largest of two Phase II trials suggests little activity.<sup>127</sup> The only other cytotoxic drug which appears to possess activity

TABLE 10. Activity of Single Cytotoxic Drugs in the Treatment of Endometrial Carcinoma

Regimen	Prior Rx	No. of patients	Response	
			No.	Percent
Doxorubicin				
Collected data <sup>124</sup>	Mixed	18	7	38
ECOG 50 mg/m <sup>2</sup> q3wk <sup>125</sup>	Mixed	21	4	19
GOG 60 mg/m <sup>2</sup> q3wk <sup>126</sup>	No	43	16	38
Cisplatin				
GOG 50 mg/m <sup>2</sup> q3wk <sup>127</sup>	Yes	25	1	4
GOG 50 mg/m <sup>2</sup> q3wk <sup>128</sup>	No	39	10	26
Deppe 3 mg/kg q3wk <sup>129</sup>	Yes	13	4	31
Seski 50-100 mg/m <sup>2</sup> q3wk <sup>130</sup>	No	26	11	42
Trope 50 mg/m <sup>2</sup> q3wk <sup>131</sup>	No	11	4	36
Cyclophosphamide				
Collected data <sup>124</sup>	Mixed	33	7	21
ECOG 666 mg/m <sup>2</sup> q3wk <sup>125</sup>	Mixed	19	0	0
Other				
HMM 8 mg/kg/d <sup>132</sup>	No	20	6	30
VP-16 100 mg/m <sup>2</sup> qod × 3 q4wk <sup>133</sup>	Yes	29	1	3
Galactitol 60 mg/m <sup>2</sup> /wk <sup>134</sup>	Yes	17	1	6
Piperazinedione 9 mg/m <sup>2</sup> q3wk <sup>135</sup>	Yes	20	1	5
ICRF-159 2.5 g/m <sup>2</sup> <sup>136</sup>	Yes	23	0	0
Vinblastine 1.5 mg/m <sup>2</sup> × 5 d CI q3wk <sup>137</sup>	Yes	36	2	6

CI: continuous infusion; ECOG: Eastern Cooperative Oncology Group; GOG: Gynecologic Oncology Group; Rx: treatment; HMM: hexamethylmelamine.

TABLE 11. GOG Studies of Combination Chemotherapy of Endometrial Carcinoma

Study and regimen	Response		
	No.	Percent	Survival
Pilot Studies			
Cyclophosphamide + doxorubicin + 5-FU + medroxyprogesterone acetate <sup>140</sup>	15/20	75	—
Melphalan + 5-FU + medroxyprogesterone acetate <sup>141</sup>	14/15	93	—
GOG Protocol 28 <sup>142</sup>			
Melphalan + 5-FU + medroxyprogesterone acetate	29/77	38	10.6 mo
Cyclophosphamide + doxorubicin + 5-FU + medroxyprogesterone acetate	28/78	36	10.1 mo
GOG Protocol 48 <sup>138</sup>			
Doxorubicin	22/97	22	6.8 mo
Doxorubicin + cyclophosphamide	34/105	32	7.6 mo

5-FU: 5-fluorouracil; GOG: Gynecologic Oncology Group.

ity is hexamethylmelamine,<sup>132</sup> but this result will require confirmation from a current GOG trial.

Combination chemotherapy trials have been for the most part uncontrolled and consequently do not permit conclusions regarding the value of the combination under investigation.<sup>139-144</sup> Two GOG trials are exceptions to this (Table 11).<sup>138,142</sup> The first of these<sup>142</sup> was based on pilot results suggesting a high order of activity for a combination of cyclophosphamide + doxorubicin + 5-fluorouracil + medroxyprogesterone acetate<sup>140</sup> (15 responders among 20 patients) and a combination of melphalan + 5-fluorouracil + medroxyprogesterone acetate<sup>141</sup> (14 responders among 15 patients). The randomized trial comparing these two regimens not only showed no difference between the two combinations but also resulted in response rates of 36% and 38% respectively, rates not different from the 38% response rate reported for doxorubicin in the initial GOG phase II trial.<sup>126</sup>

The second large GOG trial<sup>114,138</sup> approached the development of combination chemotherapy more logically. The study required that all patients receive oral medroxyprogesterone acetate initially. Upon progression, they were randomized to receive doxorubicin 60 mg/m<sup>2</sup> with or without cyclophosphamide 500 mg/m<sup>2</sup> intravenously every 3 weeks for eight cycles. An interim report showed no difference between the two cytotoxic regimens.<sup>138</sup>

There is little evidence at present to support the use of combination chemotherapy in the management of endometrial carcinoma. Efforts on the part of the principal group conducting chemotherapy trials of endometrial carcinoma, the GOG, are currently directed to the identification of additional active agents from which logical



combinations might be devised. In the interim, single agent doxorubicin should probably be considered the chemotherapy of choice.

### Other Gynecologic Neoplasms

There is relatively little information on the use of systemic therapy in other, less common gynecologic neoplasms. Sufficient data do exist for a brief discussion of uterine sarcomas, germ cell neoplasms of the ovary, non-squamous carcinomas of the cervix, and squamous cell carcinomas of the vulva and vagina.

#### Uterine Sarcomas

Uterine sarcomas are comprised of two principal histologic types: leiomyosarcomas and mixed mesodermal sarcomas (heterologous and homologous). Surgical resection of Stage I lesions (confined to the uterus) results in a 50% cure rate, but more advanced lesions (Stages II to IV) recur more than 90% of the time. Since these neoplasms tend to be relatively resistant to radiotherapy, systemic therapy represents the only logical alternative to improve results of treatment. The older literature, however, includes only a small, difficult-to-evaluate experience with a combination of vincristine, actinomycin D, and cyclophosphamide.

The GOG initiated studies (Table 12) of chemotherapy in advanced uterine sarcomas with a trial of doxorubicin 60 mg/m<sup>2</sup> with or without DTIC 750 mg/m<sup>2</sup> every 3 weeks.<sup>145</sup> This trial established the overall activity of doxorubicin with no advantage noted for the combination. A subsequent comparison of doxorubicin at the same dose with or without cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks further confirmed the activity of doxorubicin but again showed no advantage for the combination.<sup>146</sup>

The failures prompted the GOG to begin a series of studies of single agents. Based on an important observation in the first two trials, the differences in response to doxorubicin for mixed mesodermal sarcomas and leiomyosarcomas, trials were geared to accrue a sufficient number of patients of each histologic type to permit separate assessment. Of the three agents studied to date (Table 13), only cisplatin has shown promise of future usefulness.<sup>147-148</sup> In patients who had failed doxorubicin-based chemotherapy, significant activity was observed (five responses among 28 patients) with a cisplatin dose of 50 mg/m<sup>2</sup> every three weeks in patients with mixed mesodermal sarcomas.<sup>147</sup> In patients with no prior chemotherapy,<sup>148</sup> significant activity was once again observed (12 responses among 49 patients). This activity was particularly noteworthy in view of the low response rate of mixed mesodermal tumors to doxorubicin.

TABLE 12. Combination Chemotherapy Studies of the GOG in Patients With Uterine Sarcomas

Study and regimen	Response		Duration (mo)	Survival (mo)
	No.	Percent		
GOG Protocol 21 <sup>145</sup>				
Doxorubicin	13/80	16	3.5	7.7
Doxorubicin + DTIC	16/66	24	5.5	7.3
GOG Protocol 42 <sup>146</sup>				
Doxorubicin	5/26	19	5.1	11.6
Doxorubicin + cyclophosphamide	5/26	19	4.9	10.9

GOG: Gynecologic Oncology Group.

Results of phase II trials of piperazinedione<sup>149</sup> and VP-16<sup>150</sup> failed to show any activity in either major histologic type. Similarly, little activity was observed with cisplatin in patients with leiomyosarcomas.<sup>147-148</sup>

#### Malignant Germ Cell Tumors of the Ovary

Malignant germ cell tumors of the ovary are sufficiently uncommon that the literature on the use of chemotherapy in these lesions is in large part anecdotal. The most commonly reported systemic therapy is a combination of vincristine, actinomycin D, and cyclophosphamide.<sup>151</sup> The combination appears to have activity in patients with advanced disease and to be useful as an adjunct to surgery and radiotherapy in patients with earlier disease.

More recently, the GOG has been evaluating cisplatin-based combination chemotherapy including vinblastine, bleomycin, and cisplatin. Early results indicate a high order of activity for the combination<sup>152</sup> with a potential for cure of even far advanced disease.

#### Non-Squamous Carcinomas of the Cervix

Patients with non-squamous carcinoma of the cervix comprise a small minority of patients with cervix

TABLE 13. GOG Studies of the Activity of Single Agents in Uterine Sarcomas by Cell Type

Cell type	Regimen	Response	
		No.	Percent
Mixed mesodermal sarcomas	Doxorubicin regimens <sup>145,146</sup>	16/92	17
	Piperazinedione <sup>149</sup>	0/6	0
	Cisplatin second-line <sup>147</sup>	5/28	18
	Cisplatin first-line <sup>148</sup>	12/49	25
	VP-16 <sup>150</sup>	2/29	7
Leiomyosarcomas	Doxorubicin regimens <sup>145,146</sup>	16/71	23
	Piperazinedione <sup>149</sup>	1/13	8
	Cisplatin second-line <sup>148</sup>	1/19	5
	Cisplatin first-line <sup>148</sup>	1/27	4
	VP-16 <sup>150</sup>	1/22	5

GOG: Gynecologic Oncology Group.



TABLE 14. GOG Studies of the Activity of Single Agents in Patients With Carcinoma of the Cervix Other Than SCC

Drug	No. of patients	Response	
		No.	Percent
Piperazinedione <sup>153</sup>	14	2	14
Cisplatin <sup>153</sup>	20	4	20
VP-16-213 <sup>154</sup>	19	1	5
Galactitol <sup>155</sup>	27	2	8
ICRF-159 <sup>156</sup>	26	1	4

GOG: Gynecologic Oncology Group; SCC: squamous cell carcinoma.

cancer. Over the last decade, the GOG has evaluated five new agents in these patients, most of whom have had adenocarcinoma<sup>153-156</sup> (Table 14). Only cisplatin has shown more than minimal activity in these patients, most of whom had received no prior chemotherapy.<sup>153</sup> In 20 patients treated with cisplatin 50 mg/m<sup>2</sup> every three weeks, four responses were noted. No significant activity was noted with VP-16, galactitol, and ICRF-159.<sup>154-156</sup> Modest activity was observed with piperazinedione.<sup>153</sup> There are no reported studies of combination chemotherapy in this patient population.

#### Squamous Cell Carcinomas of the Vulva and Vagina

Carcinomas of the vulva and vagina are uncommon and for the most part are squamous cell carcinomas. In patients with squamous cell carcinoma of the vulva, four drugs have been tested in a sufficient number of cases to permit evaluation (Table 15).<sup>157-158</sup> Although activity was noted for both bleomycin and cytembena, the nature of the data leave questions concerning the true level of efficacy of these two agents. Piperazinedione and cisplatin had no observable activity in GOG phase II trials. Data on combination chemotherapy for vulvar carcinoma are purely anecdotal.<sup>157</sup>

In squamous cell carcinoma of the vagina, only one drug has been adequately tested. A GOG phase II trial of

cisplatin 50 mg/m<sup>2</sup> every three weeks noted only one response among 16 patients (Table 15).<sup>159</sup> All other data on systemic therapy for these lesions is purely anecdotal.

#### Conclusions

Information on the use of systemic therapy for the management of gynecologic malignancies has increased rapidly in the last decade. A number of single agents have been identified as active in celomic epithelial carcinoma of the ovary. Successful cisplatin-based combination chemotherapy has improved response rates, the frequency with which pathologically complete response is achieved, duration of response, and survival. Investigational efforts are now evaluating the roles of cytoreductive surgery, intraperitoneal chemotherapy, platinum analogues, and chemotherapy dose intensity in patients with advanced disease as well as continuing an effort to identify new active drugs.

In carcinoma of the cervix, cisplatin remains the best studied and most active single agent in patients with advanced or recurrent disease. There is no evidence for the superior efficacy of combination chemotherapy over single agent cisplatin. Research efforts are currently directed to the identification of new active drugs.

In endometrial carcinoma, useful systemic therapy includes progestational agents and antiestrogens, doxorubicin, and cisplatin. As in the case of carcinoma of the cervix, no evidence of advantage for combinations of agents exists at present. Research efforts are now directed to the identification of additional active single agents.

Among the less common gynecologic malignancies, two observations are of note. First, uterine sarcomas respond to systemic therapy according to histology with mixed mesodermal tumors sensitive to cisplatin and leiomyosarcomas responsive to doxorubicin. No effective combinations have as yet been identified. Secondly, germ cell tumors of the ovary are very responsive to cisplatin-based combination chemotherapy.

TABLE 15. GOG Studies of Single Agent Therapy in Patients With SCC of the Vulva and Vagina

Disease and drug	No. of patients	Response	
		No.	Percent
Vulvar carcinoma			
Bleomycin <sup>157</sup>	46	27	59
Cytembena <sup>157</sup>	26	4	15
Piperazinedione <sup>158</sup>	13	0	0
Cisplatin <sup>158</sup>	22	0	0
Vaginal carcinoma			
Cisplatin <sup>159</sup>	16	1	7

GOG: Gynecologic Oncology Group; SCC: squamous cell carcinoma.

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