Design Issues in Clinical Trials of Ovarian Carcinoma

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Ovarian carcinoma is the second most common invasive malignancy of the female genital tract. Because it is the only one of the three common gynecologic cancers without an effective early diagnostic test, it is the leading cause of death as a result of gynecologic cancer and the fourth leading cause of cancer death in women in the United States. Ovarian carcinoma has been studied extensively over the last three decades with the result that significant progress has been made in the management of the disease. For progress to continue, investigators must understand specific significant issues in clinical trial design. The following review will analyze these issues.

Overview of Management of Ovarian Carcinoma

Cancer of the ovary includes cancers that arise from celomic epithelium that invests the ovary during development to form a capsule, germ cell cancers, cancers arising from the ovarian stroma, and a variety of rare cancers of the ovary. The celomic epithelial cancers account for 90% of all ovarian cancers and will be the focus of this review. In this regard, it is important to note that celomic epithelial cancers arise not only on the ovary but also throughout the peritoneal cavity which is lined by the same celomic epithelium. Studies of ovarian cancer typically focus on celomic epithelial cancers exclusively and include these primary peritoneal neoplasms that arise from other parts of the peritoneal cavity. These celomic epithelial carcinomas as a group comprise the focus of the studies under discussion.

Management of these celomic epithelial cancers (hereinafter referred to as ovarian carcinoma) depends on the extent of disease and prior therapy that the patient has received. The FIGO staging system provides the basis for classifying the extent of disease (Table 1). Patients with newly diagnosed disease that is stage III or IV have advanced ovarian carcinoma, those with stage I or II disease have limited ovarian carcinoma, and those who have recurrent or persistent disease after prior therapy are referred to as having recurrent or persistent disease.

Advanced Disease

The international standard of care for patients with advanced disease includes an aggressive attempt at surgical bulk reduction followed by chemotherapy consisting of paclitaxel 175 mg/m^2 as a three hour infusion followed by carboplatin AUC 6-7.5 administered every three weeks for six cycles.[1] Results with this approach depend on the volume of residual disease. Those with large-volume residual disease (nodules larger than 2 centimeters in diameter remaining after surgery) will achieve a clinical complete remission in 40-50% of cases and will have a progression-free survival of 17 months at the median and a survival of 30 months at the median. Those with small-volume residual disease (no nodule larger than 2 centimeters in diameter remaining after surgery) have a

95% probability of ending initial therapy with no clinical evidence of disease and will exhibit a progression-free survival of 25 months at the median and a survival of better than 50 months at the median.

Limited Disease

Patients who present with stage I or II disease are categorized as having disease at either low risk or high risk for recurrence. Those at low risk for recurrence have grade 1 cancers which arise from invaginated portions of celomic epithelium and hence are located within the substance of the ovary. In addition, they must exhibit no extraovarian disease, no ascites, and negative peritoneal cytology. When all of these features are present, management is surgical resection followed by observation. The patient typically undergoes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and careful surgical exploration and is then closely followed with an expected five-year disease-free survival of more than 90%. Patients with any one of the following are considered to be at high risk for recurrence: grade 2 or 3 disease, disease on the surface of the ovary, extraovarian disease, ascites, or positive peritoneal cytology. With surgery alone, these patients have a risk of recurrence which approaches 40%. Studies[2-3] have shown that adjuvant platinum-based chemotherapy will improve both recurrence-free and overall survival.

Recurrent/Persistent Disease

A majority of patients will develop either recurrent or persistent disease and require further therapy (Table 2). Management of these patients requires that the patient first be classified as having either chemosensitive disease (response to first-line therapy leading to a treatment-free interval of at least six months) or chemoresistant disease (progression during first-line therapy or best response to first-line therapy stable disease or recurrence within six months of completing first-line therapy). Those with chemosensitive disease respond well to retreatment with platinum-based therapy and usually receive paclitaxel/carboplatin like that given as first-line treatment.[4] Those with chemoresistant disease are usually treated with alternative agents capable of inducing responses in patients with chemoresistant disease. Active agents for use in this setting include a number of drugs (Table 3).

Current Research Directions

Ongoing clinical research efforts currently focus on four areas: intraperitoneal therapy,[5-7] addition of a third cytotoxic agent to first-line therapy, addition of a targeted agent to first-line therapy, and evaluation of maintenance/consolidation therapy.[8]

Unique Features of Ovarian Carcinoma

The overview of current management of ovarian carcinoma points to several unique features of ovarian carcinoma which must be taken into account in the design of clinical trials. Firstly, ovarian carcinoma arises from celomic epithelium which is present not

only on the surface of the ovary but also lines the entire peritoneal cavity. Most trials of ovarian carcinoma include both the ovarian lesions and those that arise elsewhere in the peritoneal cavity. Secondly, the primary route of spread of ovarian carcinoma is via direct seeding of the peritoneum. Thirdly, accurate staging and assessment of the patient with ovarian carcinoma requires a thorough evaluation of the peritoneal cavity. Fourthly, because the disease process is an intraabdominal process throughout much of its natural history, there is no effective early diagnostic test. As a result, most patients have advanced disease at the time of presentation. Fifthly, there are a number of active agents (Table 3). Sixthly, high response rates to initial therapy are reported. In fact, ovarian carcinoma, with reported complete response rates of 50% or better in advanced disease, may be the most chemosensitive solid tumor other than germ cell cancers. Seventhly, because of the large number of active agents and the high initial response rates, further therapy after initial treatment may blur survival differences in clinical trials of first and subsequent line therapy. Finally, the widespread use of serum CA-125 levels as indicators of progression of disease may impact clinical trial end points such as progression-free survival and must be accounted for in the design of trials.

Goals of Therapy

There is a common misconception among non-oncologists that, if a therapy cannot cure a given cancer, there is no point in giving that treatment. This misconception in fact resulted in this statement from a member of the Oncology Drugs Advisory Committee during a March 13, 2006, meeting: "I won't vote to approve anything that doesn't cure ovarian cancer." While cure is a very important goal, another very important goal is the achievement of clinical benefit for the patient. This clinical benefit may manifest as: prolongation of survival, delay in progression of disease, reduction of tumor burden, alleviation of symptoms associated with the disease, and minimization of toxicities associated with the treatment of the disease. In this respect, cancer is no different from a number of chronic diseases commonly treated by physicians including, for example, diabetes mellitus, chronic obstructive pulmonary disease, essential hypertension, congestive heart failure, chronic renal failure, rheumatoid arthritis, systemic lupus erythematosis among many more. Virtually all of these diseases cannot be cured in the vast majority of cases; but therapy affords patients with significant benefit.

Candidate Trial End Points Reflecting Goals of Therapy

Survival is generally regarded as the gold-standard end point for trials of cancer therapy, particularly first-line therapy. Many other end points also reflect clinical benefit for the patient and, in some instances, may serve as a surrogate for survival. These include: progression-free survival, objective response as assessed by the RECIST criteria or by CA-125, pathologic complete response assessed at the time of second-look laparotomy, and quality of life (or patient reported outcomes) as assessed by, for example, the FACT-O or the EORTC QLQ-C30 and QLQ-OV28.

Clinical Settings for Trials

Which of these end points might be appropriate for a particular trial will depend on the clinical setting of the trial. In ovarian carcinoma, there are five clinical settings which must be considered: first-line therapy for advanced disease, first-line therapy for limited disease, maintenance therapy, recurrent/persistent chemosensitive disease, and recurrent/persistent chemoresistant disease.

First-Line Therapy for Advanced Disease

Regulatory approval has generally required demonstration of survival improvement over standard therapy if the therapy is proposed for use in the first-line setting for advanced disease. The Third Consensus Conference on Ovarian Carcinoma of the Gynecologic Cancer Intergroup (GCIG), held September 2004 in Baden-Baden, Germany, focused on issues related to end points for trials of first-line therapy for ovarian carcinoma. The unanimous consensus of the thirteen cooperative clinical trials groups represented at the conference adopted the following four statements:[1]

- "There is an impact of post-recurrence/ progression therapy on overall survival."
- "It is not possible to standardize post-recurrence/progression therapy at present."
- "Although overall survival is an important end point, progression-free survival may be the preferred primary end point for trials assessing the impact of first-line therapy because of the confounding effect of the post-recurrence/progression therapy on overall survival."
- "There should be clear definition of how to determine progression-free survival."

These statements effectively recommend the adoption of progression-free survival as the most appropriate end point for randomized phase III trials of ovarian carcinoma. The statements reflect two basic reasons for regarding progression-free survival as the optimal primary end point. Firstly, progression-free survival avoids the confounding effect of post-recurrence/progression therapy. The efficacy of chemotherapy in ovarian carcinoma in general and the plethora of active agents available mean that this post-recurrence/progression therapy will certainly have a major impact on survival and may well blur survival differences that otherwise would have been seen in trials of first-line therapy. Secondly, progression-free survival in and of itself provides a measure of clinical benefit to the patient: delay in progression with a consequent increased time free of the adverse effects of therapy before recurrence/progression.

In addition, improvement in progression-free survival predicts for improvement in overall survival. The literature includes fifteen large randomized trials of chemotherapy for advanced ovarian carcinoma which report both progression-free and overall survival. Thirteen of these studies (Table 4) show that the results of comparison of progression-free survival predicts for the results of comparison of overall survival;[6-7,9-19] whereas two do not exhibit such a concordance (Table 5).[20-21] In the two which are not concordant,

progression-free survival suggests superiority of one regimen over the other; whereas survival is similar between the two arms of each study. In each study, the drug under study (and hence used in one arm but not the other) was commercially available and was extensively employed in patients failing the regimen not containing the drug in question (in both cases, the drug is cisplatin). GOG 47 compared doxorubicin/cyclophosphamide with or without cisplatin.[20] Although the study showed no survival advantage for the cisplatin-containing regimen, that regimen became the standard of care for ovarian carcinoma in the mid-1980s I part as a result of GOG 47. GOG 132 compared paclitaxel/cisplatin to paclitaxel and showed a significant progression-free survival advantage for the combination without a survival difference.[21] Almost 85% of patients assigned to paclitaxel received cisplatin or carboplatin after progression; and this accounts for the failure to observe a survival difference. Paclitaxel plus a platinum compound became the standard of care for advanced ovarian carcinoma shortly after completion of GOG 132. These two trials are examples of the blurring of survival differences which otherwise would have been identified in each trial.

These studies support the fact that improvement of progression-free survival predicts for an improvement in survival. The use of progression-free survival as the primary end point of a trial, however, requires two important additional steps. Firstly, follow-up in the study must be defined such that patients in each arm are followed in a uniform way and at intervals that are less than the expected difference in progression-free survival. Secondly, the role of CA-125 in determining progression must be defined since common practice in the United States with regard to rising CA-125 may otherwise contaminate this determination.[22-23]

First-Line Therapy for Limited Disease

There have been no approvals of drugs specifically for the management of limited ovarian carcinoma. Appropriate end points for studies of limited disease were considered by the GCIG Consensus Conference with the following three statements adopted unanimously:[1,24]

- "There is an impact of post-recurrence/ progression therapy on overall survival."
- "It is not possible to standardize post-recurrence/progression therapy at present."
- "Early ovarian cancer: recurrence-free survival"

Because limited disease is a relatively uncommon finding, there have been only a small number of trials and only one trial sufficiently large to permit appropriate conclusions to be drawn.[3] This trial is a combined analysis of two studies conducted in Europe. The study included 925 stage I-II patients, most of whom had high-risk limited ovarian carcinoma. Patients were randomized to either observation or adjuvant platinum-based chemotherapy. The study demonstrated both a recurrence-free survival advantage for treatment (76% recurrence-free with treatment versus 65% recurrence-free with surgery alone after 5 years, HR=0.64, p=0.001) and a survival advantage for treatment (82% alive

with treatment versus 74% alive with surgery alone, HR=0.67, p=0.008). This suggests that improvement in recurrence-free survival predicts for improvement in overall survival and forms a major part of the basis for the GCIG recommendation. As with progression-free survival, recurrence-free survival requires a careful definition of the criteria for determination of recurrence and an accounting of the role of CA-125.

Maintenance/Consolidation Therapy

The overall clinical complete response rate for patients with stage III-IV disease is 75%. If nothing further is done after initial therapy, however, 75% of these clinical complete responders will recur. A number of studies over the years have investigated consolidation and maintenance therapies; but only one of these trials has produced a positive results. This study, an intergroup effort by the Gynecologic Oncology Group (GOG) and the Southwest Oncology Group (SWOG), randomized patients in a clinical complete response after initial paclitaxel/platinum treatment to either 3 or 12 monthly courses of paclitaxel alone.[8] The study was closed as a result of an interim analysis that showed a highly significant reduction in recurrences and prolongation of progression-free survival in those patients receiving 12 cycles of monthly paclitaxel. The difference in progression-free survival has been maintained well beyond the cessation of therapy; but no survival analysis has yet been published. An ongoing GOG study seeks to confirm these observations by randomizing patients in a clinical complete response after 5-8 cycles of paclitaxel/carboplatin to either no further therapy, 12 cycles of paclitaxel monthly, or 12 cycles of a polyglutamated paclitaxel which may cause less neurotoxicity.

The limited number of positive studies and the incomplete reports on the one such positive study leave insufficient information on which to base a recommendation for a primary end point other than overall survival. As a result, the GCIG Consensus Conference adopted the following:[24]

- "Maintenance following first-line: OS"
- "Since trials involving maintenance by definition have longer treatment on the experimental arm as compared with the control, the real question is whether the prolonged therapy improves survival."

For the present, overall survival is considered to be the preferred primary end point for trials of maintenance or consolidation therapy.

Recurrent/Persistent Disease

Approvals of drugs in the setting of recurrent or persistent disease have been based on a variety of criteria including response rate and overall survival and have included approval on the basis of studies which missed their stated primary end point of progression-free survival. This situation has created a confusing situation characterized by moving targets for approval. Recently, approval was refused despite the fact that the randomized study met its primary end point of progression-free survival on the basis that an improved

progression-free survival unassociated with an improvement in overall survival was insufficient for approval (see ODAC reports for March 13, 2006). The GCIG Consensus Conference considered this situation and adopted the following, the only one of the consensus statements not approved unanimously:[24]

- "The choice of the primary end point needs to be fully justified with appropriate power calculations. Symptom control/quality of life (for early relapse) and OS (for late relapse) may be the preferred primary end point although PFS should still be used in the assessment of new treatments."

Despite these considerations, the reasons for strongly considering progression-free survival as a valid primary end point for regulatory approval of an agent in the recurrent/persistent disease setting are essentially the same as those cited above in regard to first-line therapy for advanced disease: to avoid the confounding effect of additional therapy after progression, to provide a measure of clinical benefit by delaying an increase in tumor burden, and, as will be shown, to predict for survival improvements. To demonstrate these points, the three large randomized trials in this setting will be examined: ICON 4, AGO OVAR 2.5, and a comparison of pegylated liposomal doxorubicin (PLD) and topotecan.

The first of these trials, ICON 4, randomized patients with chemosensitive disease to a platinum regimen with or without paclitaxel.[4] The study demonstrated an improved response rate (66% versus 54%, p=0.06), an improved progression-free survival (50% progression-free at one year versus 40%, HR=0.76, p<0.001), and an improved overall survival (57% alive at 2 years versus 50%, HR=0.82, p=0.023) with the paclitaxel/ platinum regimen.

The second of these trials, AGO OVAR 2.5, randomized patients with chemosensitive disease to carboplatin versus gemcitabine/carboplatin.[25] The study demonstrated an improved response rate (47% versus 31%, p=0.0016), improved progression-free survival (8.6 versus 5.8 months, HR=0.72, p=0.0038), and no difference in survival (18.0 versus 17.3 months, HR=0.96, p=0.7349). In this particular trial, 75% of the patients received additional active therapy as an explanation for the lack of a survival difference. This study was labeled as insufficient to justify approval of gemcitabine in combination with carboplatin in chemosensitive recurrent ovarian carcinoma.

The third of these trials randomized both chemosensitive and chemoresistant patients to either PLD 50 mg/m^2 every four weeks or topotecan 1.5 mg/m^2 days 1-5 every three weeks.[26-27] PLD had previously been given accelerated approval based on response rate in phase II trials. Progression-free survival was the primary end point in this phase III trial. The initial analysis showed no difference between the two arms with regard to response (20% versus 17%), progression-free survival (16 versus 17 weeks), and survival (60 versus 57 weeks). In a later analysis of long-term results, an overall survival advantage for PLD was identified (63 versus 60 weeks, HR=1.216, p=0.05). A subset analysis revealed this to be entirely a result of a marked advantage for PLD in the

chemosensitive subset (108 versus 71 weeks) which was predicted by the progression-free survival in that same subset (29 versus 23 weeks). In the chemoresistant subset, no differences were observed (PFS 9 versus 14 weeks, OS 36 versus 41 weeks with the trends favoring topotecan). Because of the overall survival advantage, full approval was granted.

These three trials are instructive in several respects. Firstly, two of the three show that a progression-free survival advantage predicts for a survival advantage. The third is confounded by the extensive amount of further therapy given after progression on study. Secondly, the overwhelming importance attached to survival improvement, regardless of how achieved, to the exclusion of other parameters is underlined by the decisions in the AGO trial and the trial of PLD versus topotecan. Thirdly, the need for consistent criteria that take into account the confounding effect of additional therapy after progression on study is dramatically illustrated. These points are all arguments in favor of the use of progression-free survival as the preferred primary end point for regulatory approval in the recurrent/persistent setting.

Recommendations

Based on the considerations noted above, the following represent a modest set of recommendations for end points for regulatory approval of new agents and approaches.

First-Line Therapy for Advanced Disease

- First-line therapy, advanced disease
  - Primary end points
    - Survival
    - PFS (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)
  - Supporting end points
    - Response
    - Complete response
    - Quality of life

First-Line Therapy for Limited Disease

- First-line therapy, limited disease
  - Survival
  - Disease-Free Survival (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)

Maintenance/Consolidation Setting

- Maintenance/Consolidation
  - Survival

  - Case for an alternative end point not clear at the present time, but PFS would:
    - Avoid confounding effect of further therapy
    - Reflect clinical benefit in the form of greater time without progressing tumor burden

Recurrent/Persistent Disease

- Recurrence/Persistence
  - Primary end points
    - Survival
    - PFS (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)
  - Supporting end points
    - Response
    - Complete response
    - Quality of life

<u>Issues for Further Discussion</u>

- Issues for further discussion
  - Role for CA-125 in determination of progression and response
  - Clinical trial endpoints for regulatory approval
    - First-line therapy for advanced ovarian cancer
    - Maintenance therapy
    - Subsequent therapy
    - Patient reported outcomes
  - Biomarker and endpoint research priorities

Tables

Table 1. FIGO staging system for ovarian carcinoma

Stage	Description	Incidence	Survival
I	Confined to ovaries	20%	73%
II	Confined to pelvis	5%	45%
III	Spread IP or nodes	58%	21%
IV	Distant metastases	17%	<5%

Table 2. Composition of patient population with recurrent/persistent disease

– Initial status of newly diagnosed disease with probable recurrence rate
  - Large-volume advanced disease: 80-85%
  - Small-volume advanced disease: 60-70%
  - High-risk limited disease: 20%
  - Low-risk limited disease: 10%
– After factoring the frequency of each of the four categories of newly diagnosed disease, calculation shows that an overall 62% will have either recurrent or persistent disease and be candidates for further therapy.

Table 3. Active agents in ovarian carcinoma based on a response rate of at least 15% to treatment with the drug as a single agent

– FDA approved

Cisplatin	Paclitaxel	Carboplatin
Topotecan	PLD	Melphalan
Altretamine		

– Active but not approved

Gemcitabine	Etoposide	Docetaxel
Navelbine	Ifosfamide	Cyclophosphamide
Bevacizumab	5-FU/LV	Tamoxifen
TLK 286		

Table 4. Eleven trials in advanced ovarian carcinoma in which results with progression-free survival predicted for the same results with survival

	PFS (mos)		Survival (mos)	
Study	Control	Exper	Control	Exper
GOG 97 (n=458)	12	13	24	21
GOG 111 (n=386)*	13	18	24	38
GOG 152 (n=550)	11	11	33	32
GOG 52 (n=349)	24	22	42	32
GOG 158 (n=792)	19	21	49	57
GOG 114 (n=462)*	22	28	52	63
GOG 172 (n=416)*	22	28	50	66
ICON 2 (n=1526)	17	15.5	33	33
ICON 3 (n=2074)	16.1	17.3	35.4	36.1
AGO/GINECO (n=1282)	17.9	18.4	41.0	45.8
AGO OVAR 3 (n=798)	19.1	17.2	44.1	43.3
OV 10 (n=680)*	11.5	15.5	25.8	35.6
EORTC Surg (n=278)*	13	18	20	26

*Indicates trial positive for both progression-free and overall survival. All other trials are negative for both

Table 5. Two trials in advanced ovarian carcinoma in which results with progression-free survival are positive in the absence of a difference in survival

	PFS (mos)		Survival (mos)	
Study	Control	Exper	Control	Exper
GOG 47 (n=440)	8	13	16	19
GOG 132 (n=614)	14	11	26	26

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