Over the past 2 decades, we have seen major progress in the management of women with ovarian cancer, with improvements in both overall survival and quality of life. To truly appreciate this progress, it is important to understand the state of affairs regarding the treatment of ovarian cancer in the early 1980s. This paper will discuss that historical background, describe the increasingly favorable impact of evolving treatment paradigms in ovarian cancer, and note future directions for clinical research in this complex disease process.

In a 1981 review article published in the Annals of Internal Medicine discussing "current strategies" in the management of ovarian cancer, the authors noted the controversies regarding the role of a single agent vs combination chemotherapy, and single-agent chemotherapy vs radiation therapy in stage III disease, as well as the lack of a clearly established role for the "new" cytotoxic drug cisplatin. This paper further noted that the "age-adjusted death rate from ovarian cancer has remained unchanged over the past 20 years despite attempts at earlier diagnosis and more aggressive treatment." In commenting on the data regarding the risk of secondary alkylating agent-associated acute leukemia, the authors stated, "clearly, the benefits of adjuvant chemotherapy and prolonged chemotherapy in ovarian cancer patients need closer scrutiny." Finally, although the article described the "significant" toxicities of chemotherapy (including cisplatin)—which "may include troublesome nausea and vomiting, renal impairment, ototoxicity, and peripheral sensorimotor neuropathy, and unusual side effects such as anaphylactic reactions and clinical tetany from hypomagnesemia"—there was no discussion regarding the impact of these effects on either overall short-term or long-term quality of life.

It is important to understand the state of affairs regarding the treatment of ovarian cancer in the early 1980s to truly appreciate the enormous changes in disease management since that time, and evidence for substantial improvement in both the duration of survival and quality of life for patients with the disease. This paper will briefly discuss the increasingly favorable impact of evolving treatment paradigms in improving these critical parameters, and note future directions for clinical research in this complex disease process.

Primary Treatment of Ovarian Cancer

Central Role of Platinum Agents

Multiple randomized trials and several meta-analyses have clearly established the role of platinum agents (cisplatin and carboplatin) in the primary chemotherapeutic management of ovarian cancer.[4-7] The most recent phase III study, which directly compared single-agent cisplatin to single-agent paclitaxel as front-line treatment of advanced ovarian cancer, demonstrated that cisplatin produced a substantially higher objective response rate, compared to what many consider to be the "second-most-active drug" in the malignancy.[8]

Based on this extensive experience revealing the critical role of platinum agents in ovarian cancer,[4-7] it is difficult to see a justification for future front-line chemotherapy trials in this malignancy to attempt to find substitutes for this class of cytotoxic drugs. Rather, research efforts should be focused on discovering agents that can add to the activity of platinum agents. Of course, if a well conceived and conducted prospective phase III randomized trial demonstrates that a pretherapy "in vitro diagnostic test" can reliably determine that the ovarian cancer in a particular patient is highly resistant to platinum drugs, it would be appropriate to consider treatment with alternative strategies.[9]

Studies have now convincingly shown that carboplatin is equivalent to cisplatin when combined with either cyclophosphamide[10,11] or paclitaxel[12] in the primary treatment of advanced ovarian cancer, with the carboplatin-based regimen generally being preferred by most oncologists (and patients) due to its more favorable toxicity profile (eg, less emesis, neuropathy, nephrotoxicity). However, it remains uncertain whether this same statement can be made for the equivalence of cisplatin and carboplatin when delivered by the intraperitoneal route as primary treatment of small-volume residual advanced ovarian cancer.
Based on the results of a series of excellent phase III clinical trials, it is appropriate to conclude there are three intravenous platinum-based primary chemotherapy regimens acceptable for use outside the setting of a clinical trial (Table 1).[12-15] As previously noted, the carboplatin-based programs are more likely to be employed in routine practice, not because of superior efficacy, but due to less toxicity and ease of administration (eg, when given with cisplatin, a 24-hour paclitaxel infusion is required to reduce the risk of severe neurotoxicity).[16]

**Clinical Research Efforts in Advanced Disease**

For more than a decade investigators have explored methods to improve the primary treatment of advanced ovarian cancer. The substitution of paclitaxel for an alternative second agent (eg, cyclophosphamide), when combined with cisplatin, has been shown to substantially (and statistically significantly) improve both progression-free and overall survival in the malignancy.[13,16] When combined with carboplatin, docetaxel has been demonstrated to be equivalent to paclitaxel in the treatment of advanced ovarian cancer (Table 1), but the two taxanes have different toxicity profiles.[14] The docetaxel-containing regimen is associated with a greater risk of potentially clinically relevant neutropenia compared to paclitaxel, while the paclitaxel program is more likely to produce a sensory peripheral neuropathy. The decision regarding which taxane to employ as a component of primary chemotherapy in ovarian cancer should be based on the experience of the oncologist with the agents, unique clinical characteristics (eg, preexisting neuropathy from diabetes, elderly patient with a concern for bone marrow suppression), and patient choice.

Unfortunately, other attempted modifications of the "established" ovarian cancer treatment program, examined in prospective phase III randomized trials, have not been shown to favorably affect outcome in the disease. These changes include (1) "doubling" platinum dose intensity (eg, cisplatin, from 50 to 100 mg/m²; carboplatin, from AUC 4 to AUC 8; or AUC 6 to AUC 12).[17-19] (2) extending the paclitaxel infusion schedule from 24 to 96 hours; and (3) adding a third drug to a platinum/taxane program (eg, topotecan [Hycamtin], epirubicin [Ellence]). Of note, the preliminary results of a large (4,000-patient) international phase III ovarian cancer primary chemotherapy trial directly comparing several three-drug combination regimens to a carboplatin/paclitaxel program should be available within the next year.

**Duration of Primary Chemotherapy in Advanced Disease**

Several research groups have explored the concept of extending the duration of primary cisplatin-based chemotherapy regimen, from a standard 5 or 6 treatment cycles, to as many as 10 to 12 courses.[20-22] Unfortunately, prospective phase III trials have failed to reveal any additional benefits from this approach, but toxicity was clearly increased.

Despite this outcome with extended platinum-based primary chemotherapy in advanced ovarian cancer, interest was generated for examining a consolidation, or maintenance, strategy using paclitaxel, a cycle-specific agent that had previously been shown to exhibit a relatively acceptable
Management of Ovarian Cancer
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toxicity profile when delivered for prolonged time periods (> 1-2 years) in the second-line treatment of the malignancy.[23-26] In a somewhat controversial phase III trial, the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG) randomized women with advanced ovarian cancer who had achieved a clinically defined complete response to primary platinum/paclitaxel chemotherapy to receive either 3 or 12 additional cycles of single-agent paclitaxel (175 mg/m2) delivered on an every-28-day schedule.[27]
The study was discontinued by its Data Safety and Monitoring Committee when approximately one-half of the intended patient population had been entered, because of a highly statistically significant difference in progression-free survival in favor of the 12-cycle arm (28 vs 21 months; P = .002).[27] Although the monitoring committee has the absolute prerogative to independently assess the ethical justification for continuing any randomized study, the decision to close the trial has been criticized, as it essentially eliminated any possibility that the trial would reveal an overall survival benefit associated with this novel strategy, if one truly exists.

For the present, it is reasonable to conclude that women with advanced ovarian cancer who achieve a clinically defined complete response to primary platinum/taxane-based chemotherapy (eg, normal physical exam and computed tomography scan of the abdomen and pelvis, normal serum CA-125 antigen level) should be informed of the results of this trial and be given the option of receiving this therapy, in the absence of clear treatment-related contraindications (eg, prior chemotherapy-induced neuropathy). In this discussion, the possible benefits (ie, extended time to disease relapse, improvement in overall survival) will need to be balanced against the potential harms (eg, development of treatment-related peripheral neuropathy).

Cisplatin-Based Intraperitoneal Chemotherapy of Small-Volume Residual Advanced Disease

For more than 50 years, researchers have been interested in the intraperitoneal delivery of cytotoxic agents in the management of ovarian cancer, largely based on the anatomic location of the malignancy and its propensity for malignant ascites formation.[28] In the late 1970s, a solid pharmacokinetic rationale for this strategy was presented by Dedrick and his colleagues at the National Cancer Institute (NCI), which led a number of research groups to systematically explore the approach.[29]

Table 2

<table>
<thead>
<tr>
<th>Study Arms</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: cisplatin 100 mg/m2 IV + cyclophosphamide 600 mg/m2 IV</td>
<td>—</td>
<td>IP: 49 mo</td>
</tr>
<tr>
<td>Experimental: cisplatin 100 mg/m2 IP + cyclophosphamide 600 mg/m2 IV</td>
<td></td>
<td>IV: 41 mo (P = .02)</td>
</tr>
<tr>
<td>Control: cisplatin 75 mg/m2 IV + paclitaxel 135 mg/m2 IV over 24 h</td>
<td>IP: 28 mo</td>
<td>IP: 63 mo</td>
</tr>
<tr>
<td>Experimental: carboplatin (AUC 9) x 2, followed by cisplatin 100 mg/m2 IP + paclitaxel 135 mg/m2 over 24 h</td>
<td>IV: 22 mo (P = .02)</td>
<td>IV: 52 mo (P = .05)</td>
</tr>
<tr>
<td>Control: cisplatin 75 mg/m2 IV + paclitaxel 135 mg/m2 over 24 h</td>
<td>IP: 24 mo</td>
<td>IP: 66 mo</td>
</tr>
<tr>
<td>Experimental: cisplatin 100 mg/m2 IP + paclitaxel 135 mg/m2 IV over 24 h</td>
<td>IV: 18 mo (P = .027)</td>
<td>IV: 50 mo (P = .017)</td>
</tr>
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</table>

IP = intraperitoneal; IV = intravenous.

These efforts culminated in three multicenter NCI cooperative group-based randomized phase III trials (Table 2),[30-32] which have unequivocally demonstrated the superiority of intraperitoneal...
cisplatin compared to intravenous cisplatin, when employed as primary chemotherapy of small-volume residual advanced ovarian cancer (variously defined as the largest residual tumor nodule being < 1-2 cm in maximal diameter following initial cytoreductive surgery). The randomized trials have revealed that cisplatin-based intraperitoneal chemotherapy programs are associated with somewhat greater acute toxic effects compared to an "all-intravenous" regimen, but the studies also showed no increase in treatment-related mortality. Further, a finding of great importance emerged from the most recently reported phase III trial, which compared a regimen of intravenous cisplatin/paclitaxel to a program of intraperitoneal cisplatin plus both intravenous and intraperitoneal paclitaxel: While there was a greater decline in formally assessed quality of life during treatment with the regional strategy, when examined at 12 months' follow-up, there was no difference between the two study arms.[32] Thus, it is reasonable to conclude that all women with small-volume residual advanced ovarian cancer who do not have contraindications to intraperitoneal drug delivery (eg, extensive abdominal adhesions, infectious peritonitis) should be considered for management by this approach.

Several options for primary intraperitoneal chemotherapy may be considered, including the exact regimen utilized in the most recent GOG trial.[32] However, it is also rational to argue that the tolerability of regional treatment could be enhanced without compromising the major survival advantage of this approach, by reducing the dose of cisplatin from 100 mg/m2, as employed in each of the three randomized trials, to a dose of 75-80 mg/m2.[29-33]

Future research efforts in this area will hopefully build upon current experience and explore other agents for regional delivery. Ongoing studies designed to improve the technology of drug delivery (eg, by optimizing catheter insertion or developing strategies to prevent adhesion formation) have the realistic potential to further enhance the efficacy of this novel management approach.

'High-Risk' Early-Stage Disease
It has been known for more than a decade that the administration of cytotoxic chemotherapy could delay the time to disease progression in women with "high-risk" early-stage (eg, stage IC or II) ovarian cancer, but data were not available to document whether such "adjuvant" treatment would favorably impact overall survival.

This controversy has now been resolved to the satisfaction of most ovarian cancer clinical investigators with the publication of results from a combined analysis of two large randomized phase III trials (N = 1,000), which directly compared adjuvant platinum-based chemotherapy to an observation strategy until disease relapse in women with high-risk early-stage cancer.[34,35] The studies revealed an improvement in both 5-year disease-free survival (76% vs 65%; P = .001) and, most importantly, 5-year overall survival (82% vs 74%; P = .008), associated with the early (adjuvant) treatment approach.[34,35]

The optimal number of platinum-based chemotherapy cycles to be delivered in this setting remains somewhat unsettled.[36] Nevertheless, a strong argument can be made (both on theoretical grounds and considering limited existing data) that the same number of courses routinely employed in advanced disease should be utilized in this patient population, in the absence of excessive toxicity experienced by an individual patient (eg, early development of platinum-induced peripheral neuropathy).

'Second-Line' Therapy
Despite the substantial improvement in the outcome of patients with ovarian cancer, demonstrated both in individual randomized trials and in population-based studies,[37] the majority of women who present with advanced disease ultimately die as a result of complications of progressive cancer. Before discussing the treatment of individuals whose malignancy has "failed to respond completely" to primary chemotherapy, or those in whom this state has been attained but the "cancer has recurred," it is relevant to note an evolving conceptual change in the general management of this population—that of viewing ovarian cancer as a chronic disease process.[38] In this somewhat complex, and unquestionably controversial analysis, it is argued that an increasingly large percentage of patients with persistent/recurrent ovarian cancer can be anticipated to live for extended periods of time (often measured in years), despite the fact that the cancer can only be "controlled" and never eliminated.

Considered in this light, it becomes critically important to focus not only on the short-term side effects of treatment, but also on the longer-term toxicities. These effects may not only substantially interfere with a patient's quality of life, but may also impair her ability to subsequently receive drugs that might further delay the development of symptomatic disease progression. This is far from a trivial matter, as there are an increasing number of antineoplastic agents with documented activity in well-defined "platinum-resistant" ovarian cancer, and it is not uncommon for a patient to receive
five or more regimens during the course of her illness. Thus, for example, if aggressive dosing of a particular treatment program has a reasonably high probability of producing persistent peripheral neuropathy—such that it may be impossible to administer other neurotoxic agents in subsequently delivered regimens—it is difficult (if not impossible) to understand the justification for such an approach, in the absence of evidence-based data (prospective phase III randomized trials) revealing the superiority of an aggressive strategy, compared to more modest dosing programs.

Recurrent 'Potentially Platinum-Sensitive' Disease

It has been recognized for more than a decade that ovarian cancer patients who initially respond to a platinum-based chemotherapy regimen, and who subsequently experience a recurrence of the disease process, can respond a second, third, or even fourth time, to re-administration of a platinum-based chemotherapy regimen.[39-41] In considering patients for entry into research protocols, ovarian cancer clinical investigators have decided that the appropriate study population to be included in the category of platinum-sensitive ovarian cancer consists of individuals whose disease has recurred more than 6 months after the completion of primary platinum-based chemotherapy.[42] It is important to note, however, that this is nothing more than an acceptable operational definition for the purpose of determining trial eligibility.

In fact, the opportunity for a patient who experiences recurrent ovarian cancer to achieve a "second response" to a platinum-based regimen is a continuum, with the statistical probability of observed biologic activity (and hopefully, clinical benefit) increasing as the duration of the time away from chemotherapy (or at least platinum therapy) lengthens.[39-41] Thus, while approximately 20% to 30% of patients with a treatment-free interval of 6 to 12 months may respond to "second-line" platinum-based therapy, for individuals with a treatment-free interval greater than 24 months, the objective response rate will be predicted to exceed 40% to 50%.[39-41]

Addition of Paclitaxel—Until relatively recently, there was little evidence to support the administration of one treatment regimen over another in recurrent ovarian cancer, except in that there was little justification to not employ a platinum drug (given its known activity in this setting and that patients will already be familiar with the side-effect profile of this class of drugs).[39-41] For the first time, however, a large (N = 800) but somewhat controversial trial has demonstrated that the combination of a platinum agent plus paclitaxel results in superior overall survival compared to a platinum agent without paclitaxel in the setting of recurrent platinum-sensitive ovarian cancer.[43]

The controversies regarding this trial relate to the failure of the study to precisely specify the exact experimental or control chemotherapy regimens, the fact that this was really a meta-analysis of several trials, and the observation that this "favorable" outcome was made by the same research group that had declared the combination of carboplatin plus paclitaxel to not be superior to carboplatin alone in the primary treatment of advanced ovarian cancer.[44] Of perhaps greater concern is the fact that the "superior" platinum/paclitaxel combination regimen was associated with substantially more clinically relevant peripheral neuropathy (grade 2/3: 20% vs 1%) than the non-paclitaxel-containing platinum program.[43]

Thus, although on the basis of existing data it is reasonable to conclude that the combination of a platinum agent (probably carboplatin) and paclitaxel improves survival (compared to carboplatin alone) in recurrent ovarian cancer, this strategy may not be appropriate for patients who have previously experienced treatment-associated neuropathy, or when the patient (or oncologist) is concerned about the potential for developing this toxicity.

Other Alternatives—Possible alternative strategies in this clinical setting include the planned sequential administration of carboplatin and paclitaxel (or perhaps docetaxel), or the combination of carboplatin and an alternative agent to paclitaxel (eg, gemcitabine [Gemzar], liposomal doxorubicin [Doxil], docetaxel).[44,45] For a patient with recurrent platinum-sensitive ovarian cancer, when it is inappropriate to consider further administration of a platinum agent (eg, due to documented platinum hypersensitivity or significant neuropathy), alternative single agents may be considered, as might be employed in the patient with "platinum-resistant" disease (see below).

Platinum-Resistant Disease
As previously noted, ovarian cancer patients with recurrent disease, or those in whom initial treatment has failed to achieve a complete remission, will likely receive multiple chemotherapeutic agents and regimens over an undefined period of time. Thus, it is something of a misnomer to state that such treatment is "second-line," or to describe treatment of "platinum-resistant" ovarian cancer as if it is a single event.[44,45] Furthermore, an ever-increasing number of antineoplastic agents have been shown to possess a reasonable degree of "biologic activity" in resistant ovarian cancer (Table 3). In the absence of data from prospective randomized trials revealing the superiority of one drug (or treatment regimen) over another, defining an optimal management paradigm in such patients becomes increasingly difficult. In this clinical setting, the oncologist must continually monitor the status of the patient's disease, the side effects experienced by the individual, and rapidly accumulating data in the peer-reviewed medical literature, to appropriately advise the woman regarding the most reasonable future management approaches (Table 4).
Surgery
Including a discussion of surgery near the end of a review of ovarian cancer management may appear somewhat unusual. The intent in doing this is to acknowledge the well-established, critically important role of this modality (eg, staging, primary cytoreductive surgery), which has changed little over the past 20 years, but also to note the need for more definitive evidence-based data supporting its use.

For example, while secondary surgical cytoreduction is employed by many gynecologic oncologists as a standard component of their practice in patients with recurrent (or even platinum-resistant) ovarian cancer, no prospective data from a randomized phase III trial support the routine use of this strategy. Although not quite an identical situation, a recently reported GOG randomized phase III trial exploring a possible role for a "secondary" attempt at surgical cytoreduction (undertaken after three cycles of platinum-based chemotherapy in women who had already undergone a primary "debulking" surgery performed by a gynecologic oncologist) failed to reveal any evidence for the benefits of this secondary surgery.[46]

Along similar lines, it is known that a highly aggressive approach to primary surgical cytoreduction can result in a greater proportion of patients having only microscopic or minimal residual macroscopic cancer present prior to the subsequent administration of chemotherapy. However, it remains unknown if such an approach is superior to an alternative strategy whereby women with biopsy-confirmed advanced "bulky" epithelial ovarian cancer receive three to four cycles of neoadjuvant chemotherapy, followed by the subsequent performance of an interval surgical cytoreduction (where appropriate).[47,48]

Over the past several decades, substantial improvements in surgical techniques (eg, laparoscopy) and postoperative management (eg, antibiotics, prophylaxis for thrombotic events) have resulted in impressive reductions in morbidity associated with surgery for ovarian cancer. Further, these changes have permitted invasive procedures to be performed in the setting of palliative care (eg, large and small bowel obstruction), where the goals of therapy are as much to enhance the individual's quality of life as they are to improve the duration of survival. It is hoped that ongoing and future research exploring surgical questions in ovarian cancer will permit the role of this fundamentally important modality to be better defined through the results of prospective phase III randomized trials, rather than solely based on the retrospective experience of excellent individual surgeons.

Radiation Therapy
The role of radiation in the management of ovarian cancer has been substantially reduced from that described in the previously noted 1981 ovarian cancer review paper.[1] Today, the modality is uncommonly employed as a component of a primary treatment program, but women with platinum-resistant disease and clinically isolated recurrences (eg, painful pelvic wall mass) may exhibit impressive short-term palliation and delay in symptomatic disease progression when treated with external-beam radiation.[49]
In the uncommon setting of a patient with a "high-risk" early-stage ovarian cancer who experiences an early surgically confirmed, isolated pelvic recurrence (despite the delivery of adjuvant platinum-based chemotherapy), there may be a legitimate role for aggressive secondary surgical cytoreduction (to completely remove all visible tumor), followed by the delivery of "curative" whole-pelvic radiotherapy.[49]

Future Research
Despite the substantial improvements in the treatment of women with ovarian cancer achieved over the past 2 decades, much remains to be done. Although they are living longer lives of improved quality, the majority of individuals presenting with advanced disease still die as a result of progressive cancer. The development of new and novel antineoplastic agents, perhaps "targeted" to favorably influence biologic factors increasingly recognized to be of relevance in sustaining the growth and progression of ovarian cancer, will hopefully be shown to further improve survival in the malignancy.

Numerous investigators (and manufacturers) have undertaken efforts to develop simple in vitro assay systems designed to assist oncologists in the optimal selection of cytotoxic treatment, particularly in the setting of platinum-resistant disease. However, there are no data from prospective randomized phase III trials to support the superiority of this strategy compared to the empiric selection of therapy by an oncologist with detailed knowledge of a specific ovarian cancer patient.[9] It is reasonable to speculate that either a currently available, or future diagnostic test, will ultimately be shown to be of clinical utility in this setting, but this determination can only be made after appropriately designed prospective clinical trials are carried out.[9]

In particular, we need further research focusing on the development of agents that can prevent or reverse chemotherapy-associated peripheral neuropathy in ovarian cancer.[12-16] Since the platinum drugs will almost certainly remain prominent components of any future treatment paradigm in ovarian cancer, any antineoplastic agent that can potentiate this toxicity (eg, taxanes) may substantially reduce the quality of life for patients undergoing treatment, most notably in the "second-line" setting. New drugs that are active in ovarian cancer and do not affect the function of the peripheral nerves will be important additions to the armamentarium of the oncologist caring for patients with this disease.

Conclusions
The past 20+ years have brought undeniable progress in the management of women with ovarian cancer, resulting in not only improved overall survival, but survival that is of good, if not excellent, quality. It is reasonable to speculate that information generated from future innovative phase I/II clinical trials and definitive phase III studies, as well as data available through the ongoing and accelerating revolution in our understanding of the fundamental molecular events associated with the development and progression of ovarian cancer, will result in profoundly important, highly favorable changes in the management of this disease over the next 2 decades.

Disclosures:
The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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1._management of ovarian cancer


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