



# Highlights From the Discussion

Iris Raquin (French). *Spring in Venice*. Oil, 36" × 25".

## Management of Primary Refractory Ovarian Cancer

*DR SPRIGGS*

As a basis for this discussion, I present here a graphic representation of how ovarian cancer is currently being managed in a typical community oncology practice (Fig 2). My purpose is to use this schematic illustration as a structure for our discussion today. To begin, I ask you to review — in the context of this figure — the principles of managing a patient with refractory ovarian cancer during or following initial treatment with a platinum compound and a taxane. Dr Matulonis?

*DR MATULONIS*

A patient with up-front platinum-refractory ovarian cancer is at great risk for rapidly progressive disease because of the inherent aggressiveness of this subtype of ovarian cancer. These patients should be assessed for widespread abdominal disease, pleural effusions, and unusual sites for metastatic disease that include brain and occasionally bone, especially in the case of clear cell cancer. The therapy must be targeted, perhaps with systemic chemotherapy and/or surgery, perhaps neither. Basically, we are talking about palliative care.

*DR HOROWITZ*

I agree. I'm not sure what the role of chemotherapy or surgery would be in this case. What we really need to look at is "quality of life" issues. Quite possibly, neither chemotherapy nor surgery would be appropriate when the patient has a significant amount of intra-abdominal or pleural disease. You have to look at her performance

status, her age, other health issues such as her strength and emotional state. In almost any case the prognosis is likely to be dismal no matter what treatments we offer, and since the ultimate outcome is not likely to change, the quality of her remaining life is most important.

*DR HERZOG*

I agree that the prognosis is dismal in such patients, but we should also note that since standard chemotherapy is of little benefit, the Gynecologic Oncology Group (GOG) has designated these patients as probably the best candidates in which to evaluate novel therapies such as the new biologics and some of the new gene therapy products.

*DR DUNTON*

But from the perspective of the community oncol-

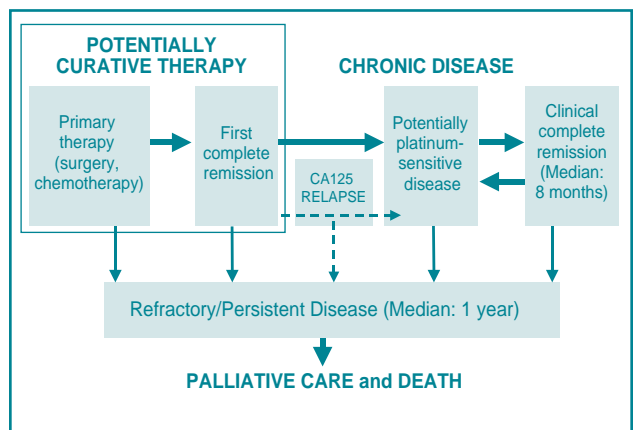


Fig 2. — Disease state model. This schematic describes a new paradigm for the long-term management of chronic ovarian cancer in a community oncology practice.

ogist, these patients need to be counseled carefully. After discussing the nature of their disease and explaining that they have already received our best available primary therapy, one must allow them to determine whether they want to go on to experimental therapy. So, a clinical trial may be one answer but, if not, the treatment goal is palliation.

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### *DR ARMSTRONG*

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And patients need time to consider this. Remember, when you first discussed your treatment options with the patient, prior to starting standard first-line chemotherapy, you were probably fairly optimistic about treatment, and then suddenly, you find that the disease is taking a turn for the worse compared with most patients with ovarian cancer. Most patients need time to make the emotional adjustment — at the very point where there may not *be* a lot of time.

## Consolidation Therapy for the Patient With a Partial Response

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### *DR SPRIGGS*

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How about the patient who has a partial response to primary chemotherapy with a platinum and a taxane? Here, we are discussing the patient with a reduction in CA125, but not down to normal levels, and there is some persistent disease evident by computed tomography (CT) scanning and/or physical examination. How would that patient be treated differently? Should we administer consolidation therapy?

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### *DR DUNTON*

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Even within our own group at Jefferson we debate how best to manage these patients. But I do have some personal guidelines. For example, one must consider the prognosis when such patients don't achieve a complete remission after six cycles of platinum-taxane treatment. We know that cure is not likely so, on that basis, my bias has always been to maintain the current platinum-taxane treatment program. If that combination is working, even partially, keeping the disease in remission or stable, without progression, I prefer to continue it until the patient develops significant toxicity or shows signs that she is no longer responding. My rationale is clear: I cannot guarantee that any second-line agent will produce a better or similar response.

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### *DR SPRIGGS*

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What is your definition of “stable disease”?

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### *DR DUNTON*

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A partial response to treatment, stable — but not necessarily low — CA125 levels, no radiographic or clinical evidence of disease progression, no positive pathologic evidence of disease progression, plus of course control of symptoms and reasonable quality of life. And in that setting, if the patient were tolerating the initial therapy, I would probably extend the platinum-taxane treatment so long as the CA125 wasn't rising and there were no signs of disease progression.

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### *DR HERZOG*

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I feel much the same as Dr Dunton, but I rarely treat beyond eight cycles with up-front platinum and taxane in the belief that if eight cycles haven't taken care of the disease, it's unlikely that additional cycles will produce the desired effect. And then you have to couple that concern with the cumulative toxicities associated with platinum and taxanes. For example, there's the cumulative neuropathy associated with paclitaxel as well as the cumulative thrombocytopenia associated with carboplatin. These adverse effects severely limit the physician's ability to administer other potentially useful agents. In other words, after six or at most eight cycles of carboplatin-paclitaxel, I would argue for switching those “stable disease” patients to another agent such as topotecan or liposomal doxorubicin.

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### *DR HOROWITZ*

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I'm somewhere in between. In our clinic, when we observe a partial response to primary therapy — say, for instance, the patient has an elevated CA125 with no radiographic or clinical evidence of disease — we continue with the initial therapy as long as the patient remains in remission. But one must weigh the risks and the benefits of continuing the initial therapy because of the cumulative toxicity, so in that patient we might suspend active treatment temporarily and monitor her closely. If the CA125 start to rise, we would then consider single-agent treatment. We're not likely to re-treat with the platinum-taxane combination.

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### *DR ARMSTRONG*

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That's an important consideration. Even those patients who achieve only a partial response to primary therapy have a substantial likelihood of long-term survival and merit close monitoring — perhaps without active therapy — until they show definite disease progression. In other words, it is not absolutely mandatory that these partial-response patients immediately go on to consolidation treatment or second-line treatment.

As one can tell from the heterogeneity of opinion among the panel here, there is no literature that instructs us — in the post-taxane era — of the optimum way to manage these patients. Yes, three relatively small studies have been reported,<sup>3,5</sup> but none of them were powered to make a statistically significant statement in this regard. This issue of consolidation therapy remains one of the more important unanswered questions in the subject area of primary treatment.

## Consolidation Therapy for the Patient With a Complete Remission Following Primary Treatment

*DR SPRIGGS*

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Now let's look at patients who have had a clinical complete remission to primary platinum-taxane treatment. Dr Herzog, your thoughts on further treatment for these patients?

*DR HERZOG*

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Intellectually, I'm enamored with the concept of consolidation therapy in these patients, because we know that most of them will ultimately relapse; in fact, about 80% of patients who present with advanced-stage disease are going to relapse at some point during their surveillance. But having said that, unfortunately there is very little in the literature to support the concept of consolidation therapy. You've already cited the study out of your institution, Dr Spriggs, by Dr Barakat and colleagues, looking at the benefits of intraperitoneal therapy (IP) vs historical controls, which showed a modest increase in median survival with IP cisplatin and etoposide as consolidation therapy.<sup>3</sup> But most of the literature is discouraging in this respect.

At our institution we do not use consolidation therapy outside of a clinical trial. But again, this issue of consolidation therapy is currently being investigated by several groups in Europe as well as by the Gynecologic Oncology Group (GOG). In Europe, for example, investigators are now performing a phase III randomized trial of single-agent topotecan vs observation following six cycles of standard primary therapy. We should have those data fairly soon.

*DR DUNTON*

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I agree with Dr Herzog. Outside of a clinical trial, we do not administer consolidation therapy because we have no strong data to support it.

What are your views concerning a second-look laparotomy in these patients?

*DR ARMSTRONG*

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For me, that's still a thorny issue. The question is: What benefits derive from the information obtained during a second look? In some series, even those patients who receive treatment based on a positive second-look in most cases do not achieve superior survival compared to those with a negative second look, throwing into question the true validity of the benefits of the surgery. That doesn't mean we don't do the surgery, it just means it needs to be justified.

Also, in any given patient, when I'm finishing up the initial therapy and talking to her surgeon about a second look, I always run through all the possible scenarios. What if the second look is grossly positive? What if it's microscopically positive? What if it's negative? What are the actions we would recommend in this particular patient in response to these findings? We often find that patients tell us, "I know what the outcome is going to be even if the surgery is negative. There is still a high risk of relapse. So, I will probably want more treatment beyond the standard six cycles no matter what the results of the second look." As a result, most of our patients decide not to have a second look because they are asking for aggressive chemotherapy whether the surgery is positive *or* negative. My point is, as physicians and surgeons, either we react positively to the findings of the second-look laparotomy, or we shouldn't do the procedure.

*DR HERZOG*

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Dr Armstrong, are you saying that you give some of your patients consolidation therapy?

*DR ARMSTRONG*

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Yes, if we're going to do a second look. We might give, for example, four cycles of topotecan to a patient who normalizes her CA125 after six cycles of standard primary treatment. We are particularly inclined in this direction in the patient who wants to be very aggressive with her treatment, usually someone who knows the data on relapse.

*DR SPRIGGS*

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Dr Matulonis, what's your approach at Dana-Farber?

## *DR MATULONIS*

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Our surgeons do not routinely offer second-look laparotomies unless they are performed within the context of a clinical trial. Currently, we have two open studies. And we do not routinely administer consolidation chemotherapy unless the patient is on a clinical trial.

## *DR SPRIGGS*

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Dr Herzog, where do you come down on this issue?

## *DR HERZOG*

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I am not a huge proponent of second-look laparotomy for the very reasons discussed earlier. We just do not have strong data to justify it. However, there is one subgroup of patients — those with small-volume residual disease following standard primary chemotherapy — in whom second looks can probably be supported. Such patients can be re-debulked and then, perhaps, be successfully re-treated with chemotherapy.

## *DR SPRIGGS*

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What about high-dose chemotherapy as consolidation treatment? Anyone?

## *DR ARMSTRONG*

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If our objective here is to guide the community oncologist, then we are obligated to emphasize that high-dose chemotherapy outside of a well-designed clinical trial is still inappropriate, despite what may have been reported recently in the literature. Any early observations must be allowed to mature so they can be validated.

## Following the Patient in Complete Remission

### *DR SPRIGGS*

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Another issue for discussion is, how do we follow patients who are in clinical complete remission following primary therapy? Dr Horowitz, your approach?

### *DR HOROWITZ*

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I ask my patients to come in quarterly for clinical evaluations for 2 years following completion of chemotherapy, and then semiannually after that for the next 3 years. In other words, I see them periodically for at least 5 years after completion of primary chemotherapy. If the CA125 remains elevated but stable, I contin-

ue to see them periodically. During this time, unless the patient is symptomatic, I do not routinely order any CT scans or other imaging procedures.

## *DR MATULONIS*

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We do almost the same — for the first 3 years, a quarterly physical evaluation with pelvic examination, and a check of the CA125. We then shift to a longer interval for years 4 and 5 and perform physical examinations and CA125s every 4 months. After 5 years, patients are followed yearly. Also, we do not obtain CT scans or other imaging procedures unless prompted by symptoms or signs of disease progression.

## *DR DUNTON*

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My approach is similar. I might add that despite efforts to decrease follow-up *after* 5 years, I have been unable to convince patients to see me less frequently than 6-month intervals, and I do not order CT scans or other imaging procedures unless the patient volunteers the fact that she has symptoms.

## *DR HERZOG*

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Our surveillance strategy is similar, but there is one difficult caveat: We are so tuned in to up-front treatment and to following patients' CA125 values during follow-up, we ought not casually dismiss these patients when they're alive 5 years later. A little patient education goes a long way in trying to allay their fears and also in alerting each patient to possible changes in her health status so she can carefully follow her own medical course.

## *DR SPRIGGS*

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Dr Herzog, since you've raised the subject, how do you manage an asymptomatic patient with a rising CA125?

## *DR HERZOG*

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That's a tough question. However, there are several strategies from which to choose. At our institution, we usually try to postpone active treatment until symptoms or follow-up tests reveal the slope of the CA125 curve. Also, we almost never treat any CA125 value under 100 in an asymptomatic patient with negative physical and imaging exams.

## *DR ARMSTRONG*

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What about imaging procedures to follow the patient?

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*DR HERZOG*

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We do not order them until there are at least two CA125 elevations over 35. Otherwise, the yield is low and they are not cost-effective, in our experience — we have rarely observed anything on imaging when the CA125 is less than 85, even with spiral CT scans, although of course that is likely to change as we develop more sophisticated radiographic techniques. I would also argue that we've already made so many advances in imaging techniques that we are now able to diagnose recurrence earlier than ever before.

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*DR SPRIGGS*

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Do you ever initiate treatment for recurrent disease based solely on an elevated CA125, with no radiographic confirmation?

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*DR HERZOG*

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Yes. Sometimes the patient wants it — *asks* for it — and sometimes not, but this strategy is clearly justified by the literature. The correlation between second-line treatment and disease control is very high.

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*DR DUNTON*

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I agree, and I will treat a rising CA125 after a dialogue with the asymptomatic patient. Usually, she requests it. Still, I prefer to see the CA125 doubling, and I also like to see it over 100 prior to starting treatment. Also, before starting the therapy, I make certain that the patient understands that cytotoxic treatment is the only thing we have to offer, that it's not necessarily going to make her feel better, and that it may or may not influence her quality of life and the length of her life. On the other hand, I have some asymptomatic patients whom I've followed for more than 2 years with persistently elevated CA125s — they do not require treatment, they haven't asked for it, and they are okay with that.

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*DR MATULONIS*

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I typically do not treat elevated asymptomatic CA125s. But obviously patient education is hugely important; patients must understand that the response rates to second-line or third-line treatment — “chronic” treatment, as we have begun calling it — are in the range of 20% to 25%, and to give an asymptomatic patient chemotherapy that is potentially toxic may not be in her best interests.

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*DR HOROWITZ*

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What do you do at Memorial, Dr Spriggs?

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*DR SPRIGGS*

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We try very hard not to treat asymptomatic patients with isolated elevated CA125s. I won't say it never happens, but it is something that we try to avoid because it is very difficult to prove that we are increasing this patient's survival while incurring the risks of toxicity. I also want to mention that for most patients, this is really the entry point into the chronic phase of their disease, a time when any efforts that we make in terms of patient education will really bear fruit through the next several years of management.

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*DR ARMSTRONG*

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And another important point: the longer the interval between primary therapy and second-line therapy, the greater the likelihood of a positive response, which leads us to the next segment of our discussion.

## Managing the Platinum-Sensitive Patient With Recurrent Disease

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*DR SPRIGGS*

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Let's turn to management of recurrent disease. First, let's lay some groundwork. “Recurrent disease” is usually defined as a period of complete remission without clinical evidence of ovarian cancer, followed by unequivocal confirmation of recurrence such as radiographic changes, physical examination, and serologic testing. The recurrent disease population consists of two groups of patients who are stratified by the duration of that complete remission: patients who are “platinum-sensitive,” having achieved a treatment-free interval of 6 months or longer, and patients who are “platinum-resistant,” those who recur in less than 6 months. The duration of the complete response provides a useful guide to treatment for recurrent disease. It's well accepted in the field now that these are two very different patient populations and as such, our various treatment options have very different roles to play in them.<sup>6-13</sup> Dr Armstrong, would you like to begin with a brief review of optimal treatment for the management of the potentially platinum-sensitive patient with recurrent ovarian cancer?

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*DR ARMSTRONG*

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First, the distinction between the early-relapse patient and the late-relapse patient is actually quite important not only in the oncology clinic, but also in clinical trials design in terms of evaluating the potential of new agents and new treatments. Among the reasons for this is the well-documented fact that patients who are platinum-sensitive are generally much more respon-

sive to second-line agents other than platinum, and patients who are platinum-resistant are significantly less responsive to second-line agents other than platinum.

Second, I actually *like* calling it “*potentially* platinum-sensitive,” because there is nothing magical happening at that 6-month interval — it’s just a convenient statistical breakpoint on a continuum in terms of the return of platinum sensitivity. The simple explanation for this is that during primary treatment, under the selective pressure of chemotherapy, resistance develops — and when the course of chemotherapy is concluded, the selective pressure of chemotherapy ends and resistance is gradually lost. We begin to see it clinically at about 6 months. Further out on the continuum, there is less and less selective resistance and then finally, the resistance mechanisms are largely gone. In other words, calling the disease “platinum-sensitive” implies that beginning at 6 months, you may reintroduce a platinum drug, but that’s not necessarily the case.

Many investigators, academics, and clinicians have started to evaluate patients in terms of 6-month blocks of time following the conclusion of initial platinum-based chemotherapy. This is quite helpful because the therapeutic options tend to change in each of those 6-month blocks. For example, I prefer *not* to use a platinum compound during the 6-to-12-month time block. During that period I prefer single-agent non-cross-resistant therapy such as topotecan or liposomal doxorubicin. For patients who recur during the 12-to-18-month time block, I still prefer single-agent therapy, but I will consider carboplatin. During the 18-to-24-month time block or later, I consider using platinum-based combination therapy such as carboplatin-paclitaxel, but I also might prefer single-agent treatment.

For single-agent treatment, the choice frequently depends on the patient’s toxicity profile during prior treatment. And there are several possible options — not only carboplatin and paclitaxel, alone or together, but also topotecan, liposomal doxorubicin, gemcitabine, oral etoposide. Unfortunately, at 24 months and beyond, we really do not have a lot of clinical trials data on these drugs to guide us except for topotecan, which is the most-studied of these drugs in this setting.

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### DR SPRIGGS

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What is your preference for therapy in the recurrent platinum-sensitive patient, Dr Horowitz?

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### DR HOROWITZ

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One of my concerns is that if I reintroduce carboplatin alone or with paclitaxel too early, I am not only

fighting potential platinum-resistance, but also possibly elevating the risk of myelosuppression and compromising my ability to give another useful but myelosuppressive drug, topotecan, at a later point. Therefore, quite often I will treat the relapsing patient with topotecan first, and reserve the carboplatin for later. Meanwhile, I’m extending the platinum-free interval and diminishing the risk of platinum resistance.

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### DR DUNTON

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I agree with Dr Horowitz. My cutoff for the reintroduction of carboplatin is 24 months. Prior to that point I prefer one of the non-cross-resistant agents. Incidentally, after the 24-month interval, a patient with recurrent disease in my clinic is regarded as a potential surgical candidate, especially if there is evidence of bulky disease on CT scan. Frequently we will surgically debulk them and then, in effect, treat them with platinum-based combination chemotherapy as if they were new cases.

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### DR MATULONIS

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We also consider surgical intervention after a treatment-free interval of 12 to 24 months followed by chemotherapy but not necessarily platinum-based chemotherapy, especially in the patient who has experienced severe neuropathy. In that case, neither carboplatin nor paclitaxel would be the best choice; one of the other drugs makes more sense. We also worry about the potential hypersensitivity reactions to carboplatin, that occur with repetitive treatment.<sup>14</sup>

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### DR HERZOG

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You know, this discussion really emphasizes the concept of managing ovarian cancer as a chronic disease, and emphasizes the importance of a treatment-free or a platinum-free interval. Certainly the literature raises the issue of the biologic relevance of this interval as demonstrated by the data from Kavanagh and colleagues.<sup>9</sup> For instance, they used a non-platinum compound at first relapse to extend the platinum-free interval beyond 12 months; later, they came back with a platinum and were able to show a 21% response rate in patients who were previously platinum-resistant (Table 2). This clearly demonstrates a useful role at first relapse for something other than a platinum, with a novel mechanism of action and a different toxicity profile. And, equally important, there are significant rates of response to these non-platinum therapies. In fact, most of our patients are going to be treated with a series of these non-platinum drugs so that, over time, they are likely to receive multiple single-agent therapies before re-

Table 2. — Response of Patients to Platinum Reinduction After Failure or Relapse With a Taxane (n=33)

Clinical Response	Total Response	Platinum-Free Interval
Partial Response	7 (21%)	≥12 months
Stable Disease	6 (18%)	8-33 months
Progressive Disease	20 (61%)	<12 months
Data from Kavanagh et al. <sup>9</sup>		

treatment with carboplatin. We clearly need some rational basis as to how to best use these agents and in what order.

## Other Treatment Considerations in the Platinum-Sensitive Patient With Recurrent Disease

### *DR SPRIGGS*

In the relapsed platinum-sensitive patient, once you've started second-line single-agent therapy, when do you stop?

### *DR ARMSTRONG*

We tell our patients, "There are two criteria for continuing therapy: Your disease is not getting worse and you're tolerating the treatment well."

### *DR HOROWITZ*

I try to develop a partnership with my patient, discussing these and related issues. One of the points I make is that the prospects of cure are dim, but that years of survival with good quality of life are achievable goals. I also make the point that a sequence of single-agent therapies will be required. Having said that, in the patient with measurable disease I will try to maintain the treatment program as long as the disease remains in remission — stable. This may be for quite a prolonged period of time. Unfortunately, quite often we must discontinue the therapy when the toxicity is such that we need to pull back or stop.

Is this a reasonable treatment strategy? One of my patients is making me a believer. She has clear cell carcinoma of the cervix with metastasis, and she is now on her 88th course of paclitaxel. She has persistent but stable disease. Right or wrong, I've extrapolated my experience from that patient and brought it to ovarian cancer. I am now a proponent of continuous therapy in relapsed patients as long as the toxicity is acceptable and the disease remains stable. When I discuss this with my patients, I describe it as a "peaceful co-existence."

### *DR MATULONIS*

My approach is similar, and I find that topotecan is a good drug in the relapsed platinum-sensitive patient, as well as in long-term treatment of stable disease, because there is so little cumulative toxicity, especially peripheral neurotoxicity or even myelosuppression as seen with some of the other drugs.

### *DR HERZOG*

That is an important concept. In ovarian cancer, stable disease is not an irrational surrogate endpoint for evaluating the effectiveness of second-line therapy. In this tumor type, as well as in small cell lung cancer, patients with stable disease do just as well from a statistical standpoint as do those with a partial response. This was shown by Cesano and colleagues, who suggested that in this population, stable disease may represent a potential benefit of chemotherapy and may be a useful predictor of survival.<sup>15</sup>

### *DR SPRIGGS*

Does anyone administer combination chemotherapy in this setting?

### *DR HOROWITZ*

I have no qualms treating a patient with a doublet if she is on a protocol, but otherwise, the data to justify this do not exist. Moreover, if we are going to treat recurrent ovarian cancer as a chronic disease, we need to keep some agents in reserve. To administer combination therapy with no documented survival advantage doesn't really make sense because I may want to use one of those drugs later on, extending the platinum-free interval with the objective of reintroducing platinum later.

### *DR SPRIGGS*

But we all see some patients who have rapidly progressive disease and in whom perhaps there is just one more opportunity to give this patient aggressive chemotherapy, knowing that if she does not respond,

there will not be a chance to do anything more. In this kind of patient, is combination chemotherapy appropriate? Do these desperate circumstances require desperate measures?

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*DR HERZOG*

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I would agree that you should take your best shot at that point.

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*DR MATULONIS*

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We contribute to the phase II trials literature by using combination chemotherapy in this setting. We have observed that the response rates are a little higher to doublets than to single-agent therapy, and perhaps doublet therapy is more appropriate if the patient is particularly ill from her cancer and really needs a prompt response. But I agree, there is no survival benefit yet reported, and single agents are far less toxic. For most patients, the most appropriate therapy is single-agent therapy.

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*DR HERZOG*

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I agree. Remember our goals of therapy: extension of survival for as long as possible with good quality of life. We don't lose a lot by treating with monotherapy compared to combination therapy, and clearly, there is less toxicity and better quality of life with monotherapy.

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*DR DUNTON*

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Outside of a clinical trial, my general approach is single-agent therapy. It's important to note, however, that a randomized trial of single-agent vs combination therapy in relapsed ovarian cancer is now nearing completion in Europe. It may provide the definitive answer to your question, Dr Spriggs.

## Managing the Platinum-Resistant Patient With Recurrent Disease

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*DR SPRIGGS*

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Let's now turn to the medical management of the patient with platinum-resistant ovarian cancer, the patient who relapses within 6 months of completing induction treatment with paclitaxel-carboplatin, or who has relapsed within 6 months of platinum re-treatment. Specifically, let's review the sequencing of our newer individual drugs — topotecan, vinorelbine, gemcitabine, and liposomal doxorubicin — as well as some of the older agents like oral etoposide, 5-fluorouracil, and ifosfamide. As Dr Herzog suggested earlier, we

clearly need a rational basis for selecting which drug to use first, not only in platinum-resistance but also in platinum-sensitive patients. Dr Horowitz, how do you decide which agent or agents should be administered?

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*DR HOROWITZ*

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In any patient who relapses after standard first-line treatment, the first thing I look at is performance status. If she has good performance status and is willing and able to visit our clinic frequently for treatment, I routinely start with topotecan. Topotecan requires a daily office visit for 1 week out of every 3 weeks. My starting dose is low — 1.0-1.25 mg/m<sup>2</sup> × daily × 5 every 21 days, which minimizes the risk of myelosuppression without obviously compromising efficacy. If she has poor performance status or is unwilling or unable to come in for a daily × 5 schedule of topotecan, I'll consider either liposomal doxorubicin or oral etoposide. Their schedules are more convenient than that of topotecan, with response rates comparable to topotecan in platinum-refractory disease,<sup>16</sup> although of course their toxicity profiles differ. With liposomal doxorubicin, for example, palmar-plantar erythrodysesthesia, so-called hand-foot syndrome, could be a problem; this skin toxicity is characterized by erythema, peeling, and pain involving the hands and soles. With oral etoposide, the primary toxicities are mucositis, diarrhea, and myelosuppression. All of these adverse effects are reversible, but they are troublesome in patients for whom we are trying to maintain good quality of life, so the choice of therapy is based primarily on the patient's history and how she tolerated prior chemotherapy.

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*DR SPRIGGS*

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Also, with oral etoposide, there is a 2% to 4% risk of secondary leukemia after 1-2 years. Until this risk is better identified, it may be best to defer using oral etoposide until later in the course of the disease. Please continue, Dr Horowitz.

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*DR HOROWITZ*

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Depending on the patient's response to the first choice, I'll then move her through the queue of the available drugs, knowing that we are very likely to eventually use all or nearly all of them sooner or later. At this point it's a toxicity issue, a quality of life issue, a performance status issue: Which drug is she most likely to tolerate, based on her tolerance of previous therapies?

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*DR MATULONIS*

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My practice is very similar, but I also try to incorporate the patient's wishes into the decision. Does

she prefer an oral medication to infusions? Does she live far away or nearby? Some of my patients, having spoken to others, come in and actually ask for a particular drug.

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### *DR DUNTON*

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In patients who progress on first-line treatment, I prefer oral etoposide or topotecan initially. Oral etoposide is of course more convenient, but in Philadelphia, for patients who live within reasonable distance but cannot get to us for infusional therapy, we will do home infusions. Since there are essentially no acute complications associated with topotecan infusions, that is an attractive therapeutic option which is also convenient.

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### *DR HOROWITZ*

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It's important to also note that the three principal drugs in this setting — topotecan, liposomal doxorubicin and oral etoposide — show fairly comparable response rates. And gemcitabine and vinorelbine are not far behind.

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### *DR ARMSTRONG*

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I agree, and we emphasize this point when we talk with patients. We discuss the notion of long-term therapy and explain that it is not unlikely that several or all of these drugs will be used eventually, one after the other, over a period of several years. The question is, in what sequence should we use them? As is apparent here, we are not certain yet which is the absolute optimal sequence — assuming there *is* an optimal sequence — following platinum-based initial chemotherapy. But in one recent study of relapsed patients, it was at least determined that topotecan should be used earlier in the series rather than later because of the potential for severe myelotoxicity associated with topotecan in heavily pretreated patients; when used early in the sequence, as you suggested, Dr Horowitz, the topotecan-related myelosuppression was easily avoided or managed with modest dose reductions.<sup>14</sup> And in our clinics, we find that using topotecan prior to other single-agent therapies in relapsed patients minimizes the risks of thrombocytopenia, especially in patients with renal insufficiency and decrements in creatinine clearance as a result of extensive prior treatment.

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### *DR SPRIGGS*

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To summarize this portion of the discussion, it appears that we have a consensus: For patients with platinum-resistant disease, topotecan, liposomal doxorubicin, oral etoposide and probably gemcitabine and vinorelbine have similar response rates, and among

them, the physician's choice should be based on patient considerations as well as toxicity considerations. Also, as was mentioned earlier, the myelosuppression associated with topotecan is a motivating factor to administer the topotecan earlier in the queue simply because the later topotecan is used, the more difficult it is to give adequate doses without the risks of myelosuppression, to a patient who might otherwise benefit.

## Management Issues in Palliation Therapy

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### *DR SPRIGGS*

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Now let's turn to palliation therapy — therapy that is administered near the end of life. The first issue I want to address is the role of radiation therapy in this setting.

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### *DR MATULONIS*

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We have used it a number of times, but very specifically: for isolated recurrences such as an isolated enlarged lymph node or a small pelvic mass following surgical resection. It can be very effective in these situations, but we do not use total abdominal radiotherapy for ovarian cancer.

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### *DR DUNTON*

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I agree. Recently we saw two relapsed patients with fairly long disease-free intervals. In both cases we resected the bulk of the pelvic tumor but couldn't get it all — we left some small-volume disease in the abdomen. This was followed by pelvic radiotherapy and single-agent chemotherapy. The results were quite satisfactory. That's an unusual approach, but it illustrates that there are some specific instances when radiation therapy can be beneficial. Also, radiation therapy may be able to palliate a small, well-defined site of pain in the patient for whom you have no other good therapy. Overall, however, we do not administer a lot of radiation in our practice.

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### *DR HERZOG*

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I agree, and in addition, I have been very reluctant to use radiation as a treatment modality for large pelvic masses due to the profound toxicity.

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### *DR ARMSTRONG*

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Right. Ovarian cancer is radiation-sensitive. It's just that the area to be treated is usually so large that it makes the treatment fairly ineffective and often quite

toxic. It's a very select group of patients who are appropriate for whole abdominal radiation, and in this country there aren't very many radiation oncologists who have a lot of experience with that. We never use it at our institution, although we do radiate isolated nodal recurrences when we can confirm there is no other intra-abdominal disease.

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### *DR SPRIGGS*

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I concur with most of what's been said. In addition, at Memorial, there's another group of patients in whom we rely on radiotherapy for palliation: those patients with symptomatic pelvic recurrences and/or active bleeding who are *not* candidates for additional surgery. With radiation, we are often able to give patients some additional symptom-free time. Dr Horowitz, another difficult-to-manage problem at this stage of the disease is chronic partial small bowel obstruction. What are your preferred management techniques?

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### *DR HOROWITZ*

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A lot depends on the volume of disease demonstrated radiographically, as well as the patient's history. For example, recently I saw a patient with a small bowel obstruction and what looked like a significant amount of disease in the pelvis, plus a large bowel component. We discussed some supportive measures and symptomatic relief, but she insisted on surgery despite my initial reservations. At surgery, we found minimal disease in the upper abdomen, a small obstruction in the jejunum and the ascending colon, and massive disease down in the pelvis. We resected what we could, and she's done well. Shortly thereafter she asked me when we're going to resume chemotherapy! So you have that group of patients with operable disease for which there may be several therapeutic options. On the other hand, there are patients with massive disease for whom the options are limited. When you see massive disease on the scan, knowing the prognosis is not good and the statistics are dismal, you do the best you can for palliation. When operated, the majority of such patients will die within 6 months, and without surgery, few will survive for 1 year even in the best of circumstances.

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### *DR DUNTON*

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I concur. In most cases, very little can be done for them at surgery other than decompressing the stomach. For most patients, the best thing is a percutaneous gastrostomy tube.

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### *DR HERZOG*

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I agree, but for those patients who have isolated

obstructions surgery can be very helpful. It depends where they are on the treatment continuums. As for those in whom a percutaneous gastrostomy tube is placed, the issue of nutrition becomes critical. Should they be given total parenteral nutrition (TPN) or not?

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### *DR ARMSTRONG*

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It's a very difficult decision not only for patients, but also for their families, but I am pretty hard-nosed about *not* starting patients on TPN. I believe the tumor benefits more from TPN than the patient does, particularly in patients with ascites. What results is much more rapid accumulation of the ascites.

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### *DR HOROWITZ*

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It's really a question of patient selection, Dr Armstrong. Suppose you have a 38-year-old patient with two young children who is doing reasonably well but has progression of disease, and you're still trying to actively treat her with cytotoxic agents? Nutrition is really one of your mainstays of support, in order to get her through this episode. In that case I think TPN would be worthwhile.

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### *DR ARMSTRONG*

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Yes, if she has a chance of responding to systemic therapy. But in someone who has already been through several regimens of chemotherapy and whose predicted response to any further therapy is almost zero, TPN isn't going to help. And that's the situation that we face most often.

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### *DR SPRIGGS*

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One more point: If TPN is started, it's very important to identify at the outset what your endpoint is — for instance, that we're going to give TPN for 30 days and at the end of 30 days if it isn't working we're going to stop and switch to hydration and hospice. Without a plan, without that kind of strategy, stopping TPN turns out to be an extremely difficult ethical problem.

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### *DR MATULONIS*

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I do not like to aggressively hydrate these patients. It increases their ascites and their peripheral edema, and often leads to pleural effusions and shortness of breath. I tend to keep these patients on the dry side.

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### *DR HERZOG*

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We do just enough hydration — maybe a liter a day — to prevent thirst.

This has been an excellent review on a topic of increasing concern. Thank you all, individually and collectively, for sharing your insights, strategies, and personal experiences with long-term management of relapsed patients with chronic ovarian cancer.

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