Advanced epithelial ovarian cancer: improvements in first- and second-line treatment

The treatment of ovarian cancer and management of advanced ovarian cancer have progressed over the past few decades through several key milestones, including improvements in surgery, the evolution of chemotherapy and the establishment of an organisation of international co-operative groups for clinical trials in gynaecologic cancer.

Five-year survival in ovarian cancer has nearly doubled over the past 30 years, increasing from approximately 25% to 50%. This is clearly a result of developments in approaches to its management. The milestones in epithelial ovarian cancer have been in surgery and chemotherapy:

- Surgery is being performed in accordance with the International Federation of Gynecology and Obstetrics (FIGO) guidelines, which means at least lymph node sampling (LNS) and peritoneal staging. Upfront maximal surgical debulking is the treatment of choice in advanced ovarian cancer.
- Chemotherapy has also evolved over time. The introduction of platinum compounds and taxanes has been of significant importance.
- The setting up of the Gynecologic Cancer Intergroup (GCIG) in 1997 was also a very important milestone. This organisation now consists of eighteen large co-operative groups worldwide, which it brings together to perform trials in such a way that the

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e-grandround

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In this issue, Jan Vermorken, University Hospital Antwerp, Edegem, Belgium, reviews the treatment of advanced epithelial ovarian cancer. He assesses new developments, in both first- and second-line treatment. His presentation was summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

outcomes become available to patients much more rapidly than in the past.

The management of advanced-stage ovarian cancer (stages IIb-IV) has also progressed as a result of the different consensus meetings. Key strategies now include:

- Upfront radical cytoreductive surgery. If this is not possible, for whatever reason, then chemotherapy should be given, and a second attempt should be made. This applies particularly to patients who have shown a response to chemotherapy or who have stable disease with a decrease in CA-125, because a trial in Europe has shown this has an impact on the outcome of the disease. This is an important message and means that a patient should have an attempt to achieve optimal debulking at least once.
- Platinum (taxane)-based chemotherapy. This is standard after surgery. A combination of a platinum compound and a taxane is currently being given in six cycles of chemotherapy, although this number is arbitrary.
- Second-look surgery is not considered a standard approach. However, it can be used in trials, for example as part of second-line treatment protocols or maintenance therapy.

Standard chemotherapy currently being used in advanced ovarian cancer is a combination of paclitaxel and carboplatin (TC). This was judged as the generally agreed standard at a consensus meeting in Germany in 2004, and no other regimen has been shown to outperform it. It is being used as the control arm in recent randomised trials looking for superior combinations. However, the outcome with this so-called standard treatment is still far from optimal, with a median time to progression of 15–18 months, and median overall survival of less than three years. There is still a lot of work needed in order to improve on this.

Advanced ovarian cancer

There is a range of approaches that could be used to improve outcomes. First, we need to look for an increase in the rate of optimal cytoreduction, which may provide a role for interval debulking and also raises the concept of neoadjuvant chemotherapy. Another option is to increase the efficacy of cytotoxic chemotherapy, by adding a third drug, using maintenance/consolidation therapy or using dose-dense therapy.

A third approach is to modulate resistance, focusing on modulating agents or increasing dose and exposure to systemic/regional chemotherapy. Finally, there is the use of targeted therapies.

There is a clear relationship between chemosensitivity, successful debulking and survival. We do not know whether the biology of the disease is playing a very important role, whether it is the chemotherapy, or if it is the tumour that is ultimately defining the outcome.

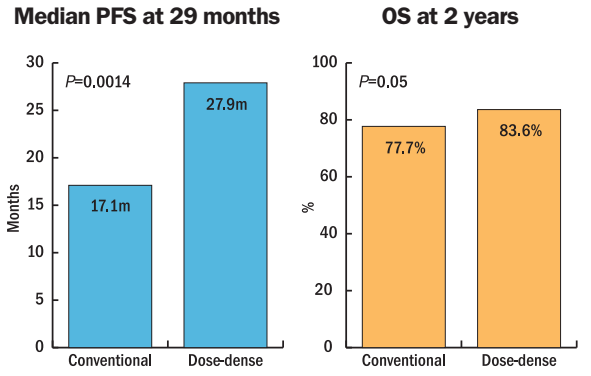
This has been explored in the neoadjuvant setting in a prospective, randomised study of neoadjuvant chemotherapy followed by interval debulking surgery versus surgery followed by chemotherapy, which was performed in New Delhi, India. The study included 128 stage III/IV patients (pleural effusion only). Patients were randomised to primary surgery followed by six cycles of paclitaxel and carboplatin, or they had chemotherapy with three cycles of paclitaxel and carboplatin, then had surgery before three further cycles of paclitaxel and carboplatin.

This trial indicated very clearly for the first time that giving chemotherapy upfront may have some advantages, in that there was a higher optimal debulking rate in the patients given induction chemotherapy ($P<0.001$). This group also had decreased blood loss ($P<0.003$), reduced postoperative infection ($P<0.04$), and their quality of life appeared better ($P<0.001$) (Kumar et al, ASCO 2007, abstract 5531). However, the survival data, both disease-free and overall survival, are not significantly different to date, although firm results on survival are unlikely from a study of only 128 patients.

A very large EORTC trial, conducted with Canadian colleagues, randomised patients with stage IIIc/IV disease to upfront primary debulking surgery or upfront neoadjuvant chemotherapy. This is a crucial trial, and is the only one, at present, that may ultimately give a final answer. Results were reported at the 12th biennial meeting of the International Gynecologic Cancer Society in Bangkok, 2008, but it has not yet been published in a peer-reviewed journal. Nevertheless, the outcome appears to be very interesting.

Results showed that while optimal debulking (lesions ≤1cm) was seen in 46%

DOSE-DENSE CHEMOTHERAPY



The survival gains shown in the early results of this Japanese trial could change the standard of care if confirmed by a further trial

PFS = progression-free survival, OS = overall survival

Source: Isohishi et al, ASCO 2008, abstract 5506

of the patients after primary debulking surgery, it was seen in 82% of the group given neoadjuvant chemotherapy followed by interval debulking surgery. This is not quite twice as high, but is clearly much greater with neoadjuvant chemotherapy than with primary debulking surgery.

In agreement with the Indian trial, the study results showed that postoperative mortality, postoperative sepsis, fistula and bleeding were much less frequent in patients given neoadjuvant chemotherapy followed by interval debulking surgery. However, while patients given neoadjuvant chemotherapy had nearly twice the cytoreduction achieved in those given upfront surgery, the survival curves were the same. The median progression-free survival for both groups was 12 months, and the overall survival was 29 months for patients given primary debulking surgery and 30 months for those given neoadjuvant chemotherapy.

This is a fascinating trial and there has been a lot of discussion among gynaecological oncologists about whether neoadjuvant chemotherapy or primary debulking surgery is the better option. This is likely to remain a topic for discussion, and we should wait until this trial has been published in a peer-reviewed journal before drawing final conclusions.

Chemotherapy for advanced ovarian cancer

The next question is whether we can improve outcomes with chemotherapy beyond those achieved with paclitaxel and carboplatin. Options include adding a third drug, maintenance/consolidation therapy and dose-dense therapy. Randomised trials have compared paclitaxel plus carboplatin with experimental arms looking at the addition of agents such as epirubicin, topotecan, pegylated liposomal doxorubicin and gemcitabine. A Canadian trial reported in 2008 compared eight cycles of paclitaxel and carboplatin with four cycles of topotecan plus cisplatin followed by four cycles of paclitaxel plus carboplatin. Taken together, none of these trials showed any benefit from adding a third drug. This indicates that we have reached a plateau with standard chemotherapy, and we now have to look for other options if we want to improve outcomes.

An interesting study reported last year at ASCO by the Japanese Gynecologic Oncology Group (JGOG) looked at a dose-dense approach. Patients with advanced-stage ovarian cancer (stages II–IV) were randomised to receive the standard chemotherapy after surgery (paclitaxel 180 mg/m^2 on day 1 and carboplatin, with an area under the curve [AUC] of 6, on day 1, repeated every 21 days for six to nine cycles) or a dose-dense weekly TC regimen (paclitaxel 80 mg/m^2 on days 1, 8 and 15 and carboplatin with an AUC of 6 on day 1, repeated every 21 days for six to nine cycles). To our amazement, progression-free survival was significantly better with the dose-dense weekly TC regimen compared to conventional paclitaxel and carboplatin in patients with advanced epithelial ovarian cancer. Haematologic toxicity was increased with dose-dense paclitaxel and carboplatin. Neurotoxicity was similar in both groups.

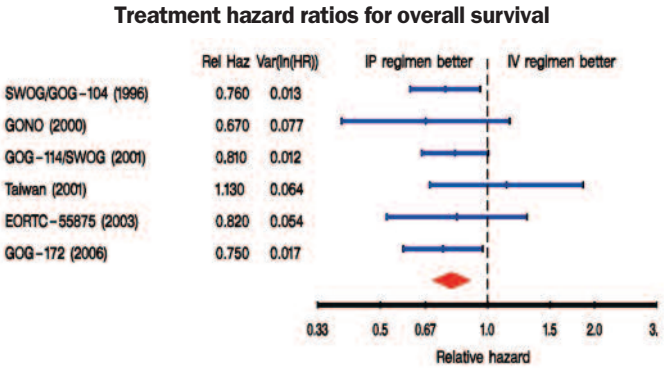
For the first time in ovarian cancer, we saw an improvement in outcome of chemotherapy just by changing the administration of paclitaxel, similar to improvements seen in other cancers including breast. Analysis of overall survival is ongoing, but I think if we can confirm this in another trial this would really change our daily practice.

Intraperitoneal (IP) chemotherapy

A further strategy is to modulate resistance by increasing drug dose and exposure (systemic and regional). I would like to focus particularly on intraperitoneal (IP) chemotherapy in advanced ovarian cancer, which has recently achieved recognition, at last. We have been dealing with IP chemotherapy for years, but initially it tended to be used only in patients with recurrent disease, where its use was sometimes difficult because these patients had undergone several surgical procedures.

In the last 15 years, at least three large US trials have demonstrated the value of IP therapy in the first-line setting (Alberts et al 1996; Markman et al 2001; Armstrong et al 2006). These studies, which included large groups of patients, showed a survival benefit in experimental arms with IP chemotherapy compared to control arms where all drugs were given IV. The first study compared cyclophosphamide, given

INTRAPERITONEAL VS INTRAVENOUS THERAPY



Pooled data from all cisplatin studies show a consistent pattern of better survival using IP regimens

intravenously, plus cisplatin given either IP or IV. Results showed that giving cisplatin IP achieved a survival benefit. This was confirmed in two further studies, which prompted the National Cancer Institute (NCI) to recommend that clinicians should revise the way they look at IP chemotherapy.

The pooled analysis of all available trials where survival data are known makes it clear that there is a significant difference in favour of IP chemotherapy. Overall, the combined use of IV and IP chemotherapy (i.e. cisplatin IP and paclitaxel only IV or IV and IP) leads to a significant survival benefit in women with optimally debulked epithelial ovarian cancer (median 12 months). This is an enormous difference, and we need to inform patients about it. However, it is only for patients who have small-volume disease and where the expected risk of complications is not too high.

The NCI strongly recommends consideration of a regimen with IP cisplatin (100 mg/m^2) and a taxane (whether IV or IP), based on the most recent trials. The toxicities, inconvenience and costs of IP therapy are justified by the improved survival.

Targeted therapies

The targets that are most commonly considered in ovarian cancer are growth factors and growth-factor receptors, extracellular matrix and angiogenic pathways, signal transduction pathways, cell-survival pathways and protein production. Targeted therapy drugs being tested in ovarian cancer include: ErbB kinases, such as gefitinib and trastuzumab, monoclonal antibodies, small molecules targeting angiogenesis, and agents targeting endothelial cells, such as combretastatin. However, the most promising approach currently seems to be with antiangiogenic compounds, particularly bevacizumab and pazopanib.

A phase II trial with bevacizumab in patients with recurrent disease showed an astonishing 17.7% response rate with bevacizumab given every three weeks at a dose of 15 mg/kg IV. In comparison to all the trials previously in the GOG, a progression-free survival of six months or longer was seen in 24 cases out of the 62 treated (38.7%) (Burger et al, ASCO 2005, abstract 5009). These are promising data that need to be confirmed.

Another study showed an overall response rate of 16%, but warned of the high rate of complications in patients with ovarian cancer who have undergone surgery: 11% of patients experienced gastrointestinal perforation; 11% bowel obstruction; 9% arterial thromboembolic events; and 5% delayed wound healing (Cannistra et al, ASCO 2006, abstract 5006). This shows that this course of treatment is not without side-effects. Care needs to be taken in patient selection for treatment with bevacizumab, and it is imperative that we stick to patients meeting the criteria of those included in trials and do not go outside these before we know the full benefits.

Bevacizumab is being incorporated into the treatment of patients with advanced disease in different ways. In the GOG trial 218, patients with stage III or stage IV disease are being randomised to paclitaxel/carboplatin followed by placebo, or bevacizumab (15 mg/kg q 3 weeks) given during chemotherapy with TC for six cycles followed by placebo, or TC plus bevacizumab and then continuing bevacizumab in the maintenance setting.

The GCIG trial is comparing paclitaxel/carboplatin with TC plus bevacizumab (7.5 mg/kg every 3 weeks), followed by bevacizumab maintenance therapy.

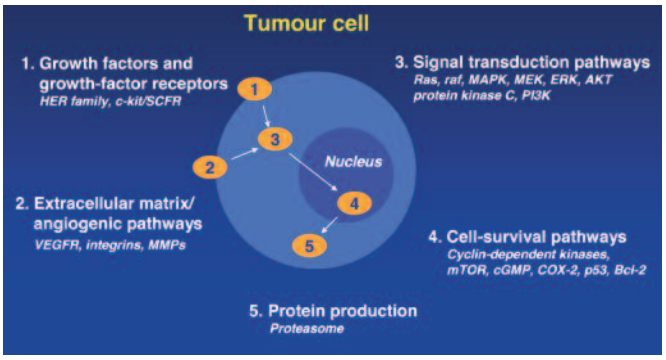
Recurrent ovarian cancer

Recurrent ovarian cancer is an important topic to discuss, because it is clear to us that ovarian cancer is changing to a more chronic disease because of the new treatment options that are available.

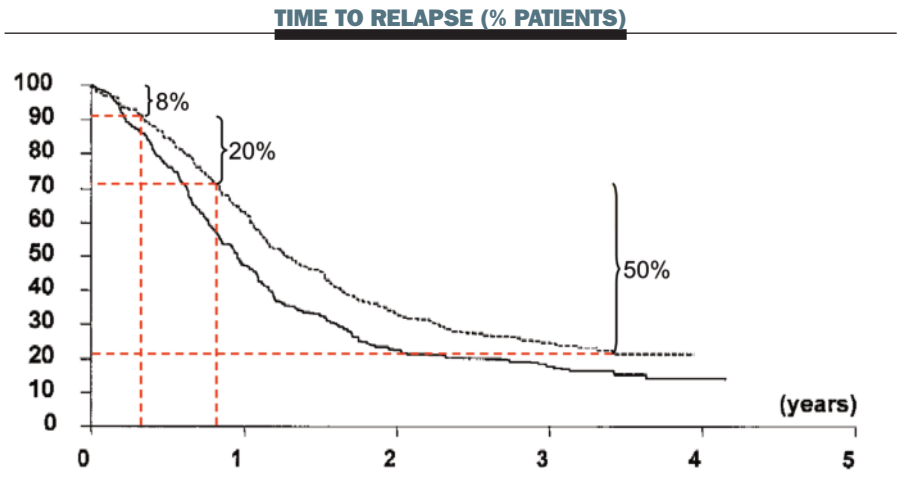
Surveillance options for monitoring disease activity after first-line treatment include: second-look laparotomy, physical examination (particularly pelvic examination), following the serum tumour marker (CA-125), and different forms of imaging, including radiography, MRI, CT and, more recently, positron emission tomography.

Different types of recurrence are seen depending on the type of follow-up adopted. Many patients (55%–70%) are asymptomatic and just show an increase in CA-125. This may precede symptomatic relapse by approximately three months, but it can be quite variable and it could be more than a year before the patient has any symptoms,

TARGETS FOR NEXT-GENERATION THERAPY



A wide variety of targets are currently under investigation in ovarian cancer



Disease is defined as refractory, resistant or TC-sensitive according to the time to relapse, and treatment is tailored accordingly

Source: Modified from Piccart et al (2000) *JNCI* 92: 699–708, reprinted by permission of Oxford University Press

which follow a different pattern depending on where the disease is located.

The recurrences are defined and treated in specific ways. When a patient has progressive disease during first-line chemotherapy, or stable disease as best response, it is considered refractory disease. If a patient has a partial response to first-line treatment, on the basis of radiologic examination, clinical symptoms or a marker, it is termed persistent disease – the disease is detectable, but is partially reduced in size. Patients who have a clinical complete response with first-line therapy, with no evidence of disease, but who relapse within six months, have TC-resistant disease (because therapy is generally paclitaxel/carboplatin). Patients with a relapse beyond six months after an initial complete response have TC-sensitive disease. Nowadays we can go even further, with TC-sensitive disease extending to relapse beyond 12 months, and patients relapsing between six and 12 months having 'intermediate sensitive' disease.

The majority of patients recur later than six months. Approximately 8% of patients have refractory disease, 20% resistant disease, and 50% are TC-sensitive. A large trial comparing cisplatin/paclitaxel with cisplatin/cyclophosphamide showed the proportion of patients relapsing at different time points (see figure above).

Realistic goals of second-line therapy in ovarian cancer are to:

- Improve cancer-related symptoms
- Optimise overall quality of life
- Delay time to symptomatic disease progression
- Prolong overall survival
- Achieve an 'objective' response.

The key question is when to treat patients. Do we need to treat early or wait until later? Too late may have a poor outcome, but too early may cause the patients to suffer side-effects of treatment when you are not certain that treatment will prolong their survival.

Should we treat all the patients the moment they show an increase in CA-125, or should we wait until they have symptomatic disease? Nobody knows at present. A randomised trial (MRC/EORTC) is looking at this question, but results have not yet been reported. The disadvantage of assessing CA-125 and reporting this at regular intervals is that patients tend to get hooked on these data, and the first thing they say when they come to see you is 'How is my CA-125?' because they consider this more important than how they feel. On this basis, it may not always be the best approach.

Treatment options in recurrent epithelial ovarian cancer include hormonal therapy, single-agent and combination chemotherapy, non-cytotoxic chemotherapy, surgery, radiotherapy and palliative care. There are now many chemotherapy drugs available. It is quite clear that patients with TC-sensitive disease have a higher chance of response than patients who are treated when they have resistant or refractory disease.

What have we learned from randomised trials? Some dose schedules or routes of administration are better than others for a specific drug. Intravenous administration of a drug can sometimes be better than oral administration; some drugs are better than others in terms of efficacy; and in specific circumstances, some drugs are to be preferred with respect to toxicity. Combination chemotherapy is superior to single-agent chemotherapy in certain situations.

Patients who have been treated first-line often have remaining side-effects that have previously escaped notice. For example, patients may still have neurotoxicity, which may become unacceptable if you treat with neurotoxic drugs again on recurrence. It is important to be aware of any side-effects left from the first treatment and the side-effects of the drugs that you are going to select for relapsed disease.

Randomised trials in relapsed ovarian cancer

Some drugs are better than others

A study comparing treosulfan with hormone treatment (leuprorelin) in patients with refractory and resistant disease showed progression-free survival was clearly in favour of the chemotherapeutic agent. Another study of topotecan versus treosulfan showed that topotecan was superior. Two randomised studies showed pegylated liposomal doxorubicin (PLD) was superior to topotecan or gemcitabine, with the benefit seen mainly in TC-sensitive disease.

Differences in safety profiles

Side-effects, whether haematological or non-haematological, are quite variable. With vinorelbine, neutropenia occurs in more than 20% of cases in grade 3 and 4, alopecia in 6%–20% of cases, and nausea and vomiting in 53% of cases. PLD (Caelyx) is associated with hand–foot syndrome. It is important to know the side-effects to decide what is best for the patient, taking into consideration what has remained from first-line chemotherapy.

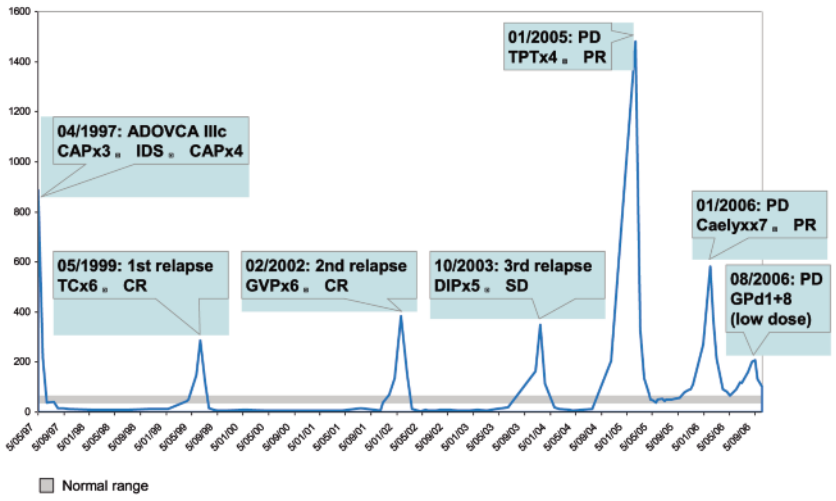
RESPONSE RATES IN RECURRENT OVARIAN CANCER

Agent	Response rates (%; range)		
	Refractory	Resistant	Sensitive
Platinum	< 10	27-34	59-77
Paclitaxel	3-22	11-37	22-55
Topotecan	6-11	15-18	19-33
Gemcitabine	15-20	19-27	34
Epirubicin	11 [a]	14	36
Liposomal dox	11	9-15	18-37
Vinorelbine	15-30	21-33	29
Etoposide	27	27	34
Altretamine	10-14		40
Trabectidin	7		37

A variety of chemotherapy drugs can be used in recurrent ovarian cancer. The best response by far is seen in patients with TC-sensitive disease, when treated with platinum or paclitaxel

[a]Progression-free interval < 3 months. *Source:* Conte 2000; Vermorken 2000; Johnston and Gore 2001; Stebbing and Gaya 2002; Monk et al 2008

DISEASE PROGRESSION IN PATIENT VBH



This patient was treated with a variety of chemotherapies over a nine-year period. CA-125 levels show intervals between recurrences starting at two years, but becoming progressively shorter (horizontal shaded line indicates normal CA-125 levels)

Source: JB Vermorken *Int J Gynecol Cancer* 18 (suppl 1):59–66

Combination versus monotherapy

A meta-analysis that included all the important trials comparing combination with monotherapy showed that combination chemotherapy is important in patients who have TC-sensitive disease (Orlando et al, ASCO 2007, abstract 5524). However, there is no indication of benefit in patients with platinum refractory disease or resistant disease. On this basis, combination therapy should be considered in patients who have TC-sensitive disease, who have a relapse after 12 months of first-line chemotherapy. There is some debate about patients who relapse between six and 12 months after first-line therapy.

The figure (left) shows the typical picture for patients with TC-sensitive disease, with the interval between subsequent recurrences becoming shorter over time. The patient (VBH) was initially treated in 1997, with a first recurrence in 1999 and further recurrences until the end of treatment in 2006. Every time, there was an increase in CA-125, which led to

further investigation. The patient was treated initially with platinum-based therapy (consisting of cyclophosphomide, doxorubcin and cisplatin – CAP), then paclitaxel/carboplatin (TC) at the first relapse, gemcitabine in combination with vinorelbine and cisplatin (GVP) at the second relapse, and so on, and responded each time. As long as the patient is motivated and you can administer therapy in a way that it is advantageous to the patient, I believe you should continue.

SUMMARY

The management of advanced ovarian cancer remains upfront surgery followed by six cycles of platinum-taxane-based chemotherapy as standard. Paclitaxel plus carboplatin (TC) is generally the agreed standard. Neoadjuvant chemotherapy followed by surgery for stages IIIc–IV ovarian cancer showed the same overall survival and progression-free survival as primary debulking surgery, with less morbidity in one large randomised Gynecologic Cancer Intergroup trial. The addition of a third drug to TC has no benefit. Intraperitoneal chemotherapy is suitable for selected patients. Targeted therapy is promising (particularly anti-angiogenic approaches) but not yet standard practice.

In the management of recurrent ovarian cancer, the factors that need to be taken into consideration are: platinum sensitivity, toxicity from prior treatment, toxicity of available agents, combinations versus single agents, the patient's preference and costs of treatment.

Sergio Pecorelli, from the Universita degli Studi di Brescia – Ospedali Civili, Brescia, Italy, hosted a question and answer session with Jan Vermorken (JV) on issues surrounding treatment of advanced ovarian cancer.

Question: *Why are so few patients treated with IP chemotherapy even though there is a median benefit of 12 months with this treatment? Is it because we are not choosing the right patients or is it because people are reluctant to treat them?*

JV: I think there is reluctance because some people have experienced complications in the past. Colleagues who do not have experience of IP chemotherapy need to know that you see more complications when you start than when you are very experienced with it. If you do not have experience in your hospital, you should not advise your patient to receive IP chemotherapy and should consider sending her to an institute that has experience.

It is a more difficult treatment to administer than intravenous chemotherapy. There may be drug-induced complications and catheter-related complications. The last trial with IP chemotherapy showed that many patients are not able to tolerate six cycles of chemotherapy, so receive the last cycles intravenously. We should look for new drugs that are less toxic, and some colleagues are using carboplatin instead of cisplatin IP. There are also other options, such as the approach in which chemotherapy is used with hyperthermia during surgery.

Question: *Why was your patient treated with combination chemotherapy when you say that it just adds to toxicity in the recurrent disease setting?*

JV: Nowadays we have more possibilities to combine, with different options for a patient who has platinum-sensitive disease. For example, we now have carboplatin with paclitaxel, and carboplatin with gemcitabine. With the new options, and knowing that there are survival benefits with combination chemotherapy over single-agent chemotherapy, I believe it is something that you should make use of in patients for whom it is suitable.

Question: *You did not mention surgery in recurrent disease. Is there any role for it?*

JV: Absolutely. Recurrent disease that is localised in the abdomen may be suitable for surgery, especially when there is a longer interval between the recurrence and primary treatment. Ongoing studies are looking at the role of surgery.

Question: *You mentioned CA-125, which obviously starts rising much earlier than clinical symptoms. How often should we measure CA-125?*

JV: There are some colleagues who say you should not follow it. However, I think patients with recurrent disease, especially early recurrences, should be included in trials.

I measure CA-125 more frequently in the first six months, but every three months thereafter.

Question: *We have heard about the remarkable results with neoadjuvant therapy versus up-front surgical treatment, and we know that we should perform surgery up-front with the intention of maximum debulking. Has this trial changed our attitude?*

JV: Knowing how important high-quality surgery is in the treatment of ovarian cancer, I have the feeling that, as a general rule, up-front debulking surgery is still the standard of care. But in circumstances where you are absolutely certain that you cannot adequately debulk, then you can consider neoadjuvant chemotherapy.