Optimal treatment for ovarian cancer: taxoids and beyond

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Introduction

Surgery and chemotherapy are the major contributing features to the management of ovarian cancer. The role of surgery is twofold [1,2], i.e., for diagnosis (staging or diagnostic laparotomy) and for treatment (radical, cytoreductive or debulking surgery). Nowadays, comprehensive surgical staging [3] is considered essential to adequately determine the stage of the disease [4] and to define a subset of early ovarian cancer patients that does not require additional therapies [5]. The role of debulking surgery in patients with advanced disease is further discussed in the section on “Best timing and applications of debulking surgery” in this educational session.

Good evidence based on sound randomised clinical trials has indicated which drugs should be used to obtain the best results in this disease in terms of response and survival. This is particularly true for patients with advanced disease, but less clear in patients with early-stage disease. It is the purpose of this review to summarise the data on what should be considered optimal therapy for ovarian cancer, with emphasis on the potential future role of systemic therapies.

Early-stage ovarian carcinoma

In early-stage ovarian cancer (FIGO stages I–IIA) the tumour is confined to the ovaries, fallopian tubes or uterus. Malignant washings or ascites in stage I is permitted, but no adherences to other pelvic structures are allowed (which would denote stage IIB). Grade, histologic type, dense adhesions, large volume ascites, age, and FIGO substage have been identified as independent prognostic factors that predict for relapse and survival in earlier studies. Vergote et al. [6] in a meta-analysis of five studies comprising 1287 patients with FIGO stage I ovarian carcinoma showed that, using a Cox regression analysis, grade is the strongest prognostic factor. However, also the completeness of staging has shown to be an important and independent prognostic factor [7]. Based on these observations early-stage ovarian cancer patients can be categorised to have low-risk disease or high-risk disease. Those at low risk exhibit all the following characteristics: one or both ovaries involved, grade 1 (well-differentiated), intracyclic (i.e. no tumour on the external surface of the ovary), no ascites, negative peritoneal cytology, and no extraovarian disease [5]. Patients at high risk have any of the following: grade 2 or 3 (moderately or poorly differentiated), extracyclic (i.e. tumour on the surface of the ovary), ascites, positive peritoneal cytology, or extraovarian (stage II) disease [5].

Management

Several randomised trials have been performed in the past to test the value of post-operative adjuvant therapies in early-stage disease (radiotherapy, instillation of $^{198}$Au or $^{32}$P, single alkylating agent therapy, or a combination of these). The majority of these trials suffered from a number of shortcomings, such as the omission of a therapy-free arm in the high-risk categories, the inclusion of borderline tumours, incomplete surgical staging or inclusion of patients with stage II or III disease who had minimal residual disease. Moreover, sometimes no data were given on the distribution of important prognostic factors [8].

More recent trials in patients with stage I and II disease [9–15], including some non-randomised studies in the low-risk categories [10,11] and one randomised study with disease stages I through III (without residual disease) also allowing borderline tumours [12], but all applying comprehensive surgical staging, have demonstrated that (a) careful surgical staging is important to establish the patient’s risk for recurrence, (b) low-risk patients with stage I A or IB disease have a favourable outcome (5-year disease-free survival in excess of 90%), do not need any additional treatment and could, if retention of reproductive function is strongly wished, even qualify for conservative surgery, (c) high-risk patients have a risk of relapse of 30% to 40% and a 25% to 30%
chance of dying within the first five years after initial surgery, with uncertainty about survival benefit from any of the applied adjuvant therapies.

Based on the outcome of the Ovarian Cancer Study Group/Gynecologic Oncology Group (OCSG/GOG) protocol 7602 in patients at high-risk for recurrence (i.e. poorly differentiated disease, extracystic tumour, ascites, positive peritoneal cytology, or extra-ovarian lesions), showing a 5-year disease-free survival of 80% with either 12 cycles of melphalan (0.2 mg/kg/d orally) or one administration of $^{32}$P (15 mCi, intraperitoneally) and a 5-year overall survival of 81% and 78% with both therapies, respectively, no further studies with a control arm were pursued in such patients. However, which form of adjuvant therapy had to be preferred was studied in GOG protocol #95. In this protocol high-risk patients were randomised to receive, after comprehensive surgery, intraperitoneal $^{32}$P or three cycles of intravenously administered cisplatin $(100 \text{ mg/m}^2)$ plus cyclophosphamide $(1000 \text{ mg/m}^2)$ (CP), delivered on a 21-day schedule. A total of 251 patients, of whom 205 were evaluable, were entered into this trial. With a median follow-up of six years, the investigators reported an estimated 31% reduction in risk of recurrence with the use of CP (with a relative risk of 0.693, 90% confidence interval: 0.454–1.06, $p = 0.075$). Survival at five years was 84% with CP and 76% with $^{32}$P [14]. The investigators concluded that because of the better progression-free survival with CP and the problems associated with $^{32}$P regarding adequate distribution and bowel toxicities (2 patients had bowel perforation during catheter insertion) platinum-based chemotherapy should be the standard for patients who need adjuvant therapy. It is therefore not surprising that in the current GOG study (protocol #157), indeed all patients receive chemotherapy. Assuming that patients with early-stage ovarian cancer should be treated as if they had advanced ovarian cancer, patients in GOG protocol 157 receive a combination of paclitaxel plus carboplatin (TCb), the combination which is mostly used in the US in the advanced disease setting. Patients are randomised to receive three cycles versus six cycles of TCb. No report on the usefulness of this regimen in early-stage ovarian cancer is available. There are no data that indicates its superiority over single agent platinum treatment alone.

The philosophy in Europe has been somewhat different. There have been some serious doubts about the potential benefit of adjuvant therapies based on the fact that some studies with a control arm in these high-risk categories of patients with early-stage ovarian cancer did not show a survival advantage for those treated in the adjuvant setting over those treated on relapse [13,15]. The results of these studies are summarised in Table 1. Moreover, from retrospective reviews of stage I ovarian cancer patients, some investigators have questioned the value of adjuvant chemotherapy in a rather provocative manner [16]. Therefore, the outcome of the Adjuvant Clinical Trial in Ovarian Neoplasm (ACTION) trial organised by the Gynecological Cancer Cooperative Group (GCCG) of the European Organisation for Research and Treatment of Cancer (EORTC) and the first International Collaborative Ovarian Neoplasm (ICON-1) trial, organised by the Medical Research Council (MRC) in the United Kingdom, the Mario Negri Institute in Italy, and the Swiss Institute for Cancer Research, are eagerly awaited. The ACTION protocol included stages IA and IB, grades 2 and 3, and stages IC and IIA, all grades. After (optimal) surgery, patients were randomly selected to receive either four or more courses of adequately dosed platinum-based

Table 1
Randomised trials of chemotherapy vs. control in early-stage ovarian cancer

<table>
<thead>
<tr>
<th>Study group</th>
<th>Disease stage and grade</th>
<th>Treatment (mg/m²)</th>
<th>No. of patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GICOG (1995)</td>
<td>IA &amp; IB, G2,3</td>
<td>P 50, q 4 wk × 6</td>
<td>42</td>
<td>DFS 83%, OS 88%</td>
</tr>
<tr>
<td>NOCOVA (2000)</td>
<td>I G1 (AN)-NCC</td>
<td>Cb AUC7, q 4 wk × 6</td>
<td>81</td>
<td>DFS 70%, DSS 86%</td>
</tr>
<tr>
<td></td>
<td>I G2,3-NCC, CC</td>
<td>Control</td>
<td>81</td>
<td>DFS 71%, DSS 85%</td>
</tr>
<tr>
<td>EORTC</td>
<td>IA &amp; IB, G2,3</td>
<td>Pt-based × 4–6</td>
<td>448</td>
<td>Not evaluated yet</td>
</tr>
<tr>
<td></td>
<td>IC, IIA (all grades)</td>
<td>Control</td>
<td>448</td>
<td>Not evaluated yet</td>
</tr>
<tr>
<td>MRC</td>
<td>I–II (uncertain risk)</td>
<td>Pt-based × 4–6</td>
<td>470</td>
<td>Not evaluated yet</td>
</tr>
</tbody>
</table>

GICOG = Gruppo Italiano Collaborativo Oncologica Gynecologica; NOCOVA = Nordic Ovarian Cancer Study Group; EORTC = European Organisation for Research and Treatment of Cancer; MRC = Medical Research Council (in cooperation with Mario Negri and SAKK); AN = aneuploid; NCC = non-clear cell; CC = clear cell; G = grade; DFS = disease-free survival; DSS = disease-specific survival; OS = overall survival; P = cisplatin; Cb = carboplatin; Pt = platinum. The year of publication is indicated in parentheses.
chemotherapy (i.e. cisplatin at 75 mg/m² or carboplatin at 350 mg/m²) per cycle) or observation. The trial was closed in the beginning of 2000 after 448 patients had been accrued. The ICON-1 trial had a more liberal approach in that it randomised all early-stage disease patients for whom the responsible physician was "uncertain" about the need for chemotherapy. The advised dose of cisplatin, if used, had to be at least 70 mg/m² when used as a single agent and 50 mg/m² when used in combination. If carboplatin was used, a glomerular filtration rate (GFR)-based area under the curve (AUC) dose schedule was recommended with an AUC of 5 when used as a single agent and an AUC of 4 when used in combination. The recommended number of treatment cycles was six. Also this trial was recently closed after a total of 470 patients had been entered. ACTION and ICON-1 will be analysed both separately and together. A first report can be expected in 2001.

Based on the available literature to date it is difficult to draw a final conclusion as to whether high-risk patients should be treated with adjuvant chemotherapy after comprehensive surgery. It is defendable to do so, because of the fact that such patients have a significant risk of relapse and 25% to 30% mortality within five years and there is a suggestion from at least two studies that platinum-based chemotherapy might have an impact on the disease-free survival. Indeed, a majority of clinicians also in Europe make use of this approach. However, when applying this one should realise that the proper drugs, doses, and duration of treatment are unknown at this time, as is the risk-benefit ratio compared with no therapy [17]. Therefore, those who consider the overall survival data not in balance with overtreating a large proportion of patients have all the arguments not to treat them. Hopefully, the larger ACTION and ICON-1 trials will give an answer to this burning question. It is evident that, next to better treatment options, more refined methods are needed to define what’s good-risk and what’s high-risk based on a better understanding of the 'natural/clinical' history/biology of this disease.

Advanced-stage ovarian carcinoma

The recommended treatment strategy for patients with advanced ovarian cancer is upfront radical cytoreductive surgery followed by combination chemotherapy with a taxoid and a platinum compound [18]. This recommendation is based upon level one evidence of two large prospective randomised trials which established that a combination of paclitaxel plus cisplatin (TP) was superior to cyclophosphamide plus cisplatin (CP) in patients with advanced ovarian cancer and applied to both optimally and suboptimally debulked patients [19,20].

The first study, performed by the GOG (protocol #111) in the US, included 410 suboptimally debulked stage III or IV epithelial ovarian cancer patients. Patients were randomised to receive either 24-hour paclitaxel given at a dose of 135 mg/m² followed by cisplatin at a dose of 75 mg/m² or 750 mg/m² of cyclophosphamide plus 75 mg/m² of cisplatin. Both regimens were given at 3-week intervals for six cycles. Because of the restricted availability of paclitaxel at the time, only 8% crossed over to paclitaxel on first progression of the disease in that study [19]. Early (positive) results were presented at the 29th annual meeting of the American Society of Clinical Oncology in 1993. Although the data on response and progression-free survival were impressive, they were not considered conclusive enough to adapt TP as a new standard [2]. For that reason investigators from Europe and Canada planned a confirmatory phase III trial. This large intergroup trial, including 680 patients, differed from the GOG trial with respect to: (a) patient selection (i.e. also patients with optimally debulked stage III or IV disease could enter the study as well as those with FIGO stages IIB and IIC), (b) a flexible centre policy concerning secondary surgery, (c) the introduction of interval debulking surgery as an option for patients who could not be optimally debulked upfront [21], (d) the paclitaxel infusion schedule (i.e. 3-hour paclitaxel instead of 24 hours), (e) paclitaxel dose (i.e. 175 mg/m² instead of 135 mg/m² and with a possible escalation to 200 mg/m²), (f) the number of treatment cycles (i.e. up to nine cycles were allowed). Moreover, in case of substantial neurotoxicity cisplatin could be replaced by carboplatin. This proved to be of importance as indeed a 14% rate of grade 3 neurotoxicity was observed during the time of the first six treatment cycles with TP (vs. 4% observed in the GOG study). A relative low proportion of patients (12% in the TP arm and 9% in the CP arm) had cisplatin replaced by carboplatin during the course of their chemotherapy. The results after a median follow-up of 38.5 months were recently reported [20]. Indeed, because of the wider availability of paclitaxel when this second study was performed 48% crossed over to paclitaxel on first progression in the CP arm. Nevertheless, again a significantly longer progression-free survival (primary trial endpoint) and overall survival were obtained in the TP arm (see Table 2). The trial did not have the power to compare the chemotherapy regimens in the subsets of patients having optimal...
Table 2
Progression-free survival and overall survival data of various randomised trials studying the role of paclitaxel in first line for patients with ovarian cancer

<table>
<thead>
<tr>
<th>Trial group</th>
<th>Treatment arm</th>
<th>Overall resp. (%)</th>
<th>Median PFS (mo.)</th>
<th>Median surv. (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-111</td>
<td>CP (750/75)</td>
<td>60</td>
<td>13.0</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>TP (135–24 h/75)</td>
<td>73</td>
<td>18.0</td>
<td>38.0</td>
</tr>
<tr>
<td>INT</td>
<td>CP (750/75)</td>
<td>67*</td>
<td>11.5</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td>TP (175–200–3 h/75)</td>
<td>78*</td>
<td>15.5</td>
<td>35.6</td>
</tr>
<tr>
<td>GOG-132</td>
<td>P (100)</td>
<td>67</td>
<td>16.4</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>T (200–24 h)</td>
<td>46</td>
<td>11.4</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>TP (135–24 h/75)</td>
<td>67</td>
<td>14.1</td>
<td>26.6</td>
</tr>
<tr>
<td>ICON-3</td>
<td>CTR (CAP or Cb)</td>
<td>NA</td>
<td>16.2</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>TCb (175–3 h/AUC6)</td>
<td>NA</td>
<td>16.7</td>
<td>38.7</td>
</tr>
</tbody>
</table>

GOG = Gynecologic Oncology Group Study; INT = European-Canadian Intergroup Study; ICON = International Collaborative Ovarian Neoplasm Study; NA = not available; PFS = progression-free survival.

* Including unconfirmed responses.

or suboptimal residual disease. However, treatment effects observed in both categories looked alike in the same direction.

GOG protocol 132 compared single agent cisplatin (100 mg/m²) with single agent 24-hour paclitaxel (200 mg/m²) and with the combination of both (as used in GOG-111). This trial confirmed again the importance of cisplatin, and showed a significantly higher response rate than that obtained with paclitaxel (67% vs. 46%). The median survival of all three regimens was the same (see Table 2). This study was complicated in its evaluation as result of the fact that many patients treated in the single drug arms changed to the other arm before clinical progression based on persistent disease radiographically or findings of residual disease at second-look laparotomy or otherwise (i.e. clearly differing from the policy followed in the European-Canadian intergroup trial). Therefore, protocol GOG-132 has been interpreted (rightly or wrongly) as a comparison of using the two drugs sequentially versus concomitantly. The balance was in favour of the combination because of a better tolerance, and this trial in that sense was not felt as contradictory to GOG-111 and the Intergroup trial.

More puzzling is the outcome of the only randomised trial which compared a paclitaxel–carboplatin combination with two non-taxoid-containing regimens. This trial performed under the sponsorship of the British Medical Research Council was recently updated and presented at the 36th annual meeting of the American Society of Clinical Oncology in New Orleans by Colombo on behalf of the ICON collaborators [22]. In this very large trial 2074 patients with ovarian cancer stages I–IV were randomised to an experimental arm consisting of paclitaxel plus carboplatin (TCb) versus either of two control arms, which could be carboplatin alone (n = 1421) or the traditional CAP regimen (n = 653). All treatments were given every three weeks for six cycles. Paclitaxel dose was 175 mg/m² (3-hour infusion), carboplatin was given at a minimum dose of 6 (calculated GFR + 25) mg, cyclophosphamide 500 mg/m², doxorubicin 50 mg/m² and cisplatin 50 mg/m². After a median follow-up of 29 months 925 of the 2074 patients had died and 1293 had progressed; so the data were considered secure to three years. The study showed no difference in progression-free survival (1% at 1 year) and no difference in overall survival (2% at 2 years). Thirty percent of the patients in the control arm had received a taxoid-containing regimen on progression. There was no evidence of different effects in different subgroups. The exploratory subgroup analysis included the randomising group, the number of patients randomised by a centre, age, FIGO stage, residual bulk, histologic type and differentiation. The reason for the confusion is evident from Table 2, in particular taking into account that only 6% seemed to have received a taxoid-containing regimen prior to documented progression in the control arm. Although criticism has been expressed related to the non-random selection of the control arm, the unusual high number of institutions involved and the seemingly paradoxical effect in patients with small volume disease, these are not strong enough to refute the outcome of the study. The simple fact remains that this very large trial, the only one comparing a carboplatin/paclitaxel combination vs. a non-taxoid containing regimen, did not show superiority either over optimally dosed carboplatin alone or the CAP
Table 3
Randomised trials of paclitaxel–cisplatin versus paclitaxel–carboplatin

<table>
<thead>
<tr>
<th>Study group</th>
<th>Stages of disease</th>
<th>Study arms</th>
<th>No. of patients</th>
<th>RR (%)</th>
<th>Median PFS (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch/Danish</td>
<td>IIIB–IV</td>
<td>TP (175–3 h/75)</td>
<td>208</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCb (175–3 h/AUC5)</td>
<td></td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>AGO</td>
<td>IIIB–IV</td>
<td>TP (185–3 h/75)</td>
<td>798</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCb (185–3 h/AUC6)</td>
<td></td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>GOG 158</td>
<td>optimal</td>
<td>TP (125–24 h/75)</td>
<td>840</td>
<td>NA</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>TCb (175–3 h/AUC7.5)</td>
<td></td>
<td>NA</td>
<td>95</td>
</tr>
</tbody>
</table>

AGO = Arbeitsgemeinschaft Gynaekologische Onkologie; GOG = Gynecologic Oncology Group; TP = paclitaxel plus cisplatin; TCb = paclitaxel plus carboplatin; NA = not available; RR = response rate; PFS = progression-free survival.

regimen. In that respect it is of importance to recall that a meta-analysis, using individual patient data, has indicated that CAP is superior to the CP combination at a cisplatin dose of 50–60 mg/m² [23], while the control arm in GOG-111 and in the European–Canadian intergroup study used CP at a cisplatin dose of 75 mg/m². Moreover, if indeed better results could be achieved with carboplatin alone at an optimally tolerated dose than with the CP combination and survival curves with carboplatin (or for that matter cisplatin) at an optimally tolerated dose would be no different from those obtainable with CAP then a lot of rethinking would be necessary.

Carboplatin was developed as a less toxic alternative to cisplatin and since its introduction into clinical practice its advantages over cisplatin in terms of toxicity became evident. Considering the fact that carboplatin in some curable diseases such as testicular cancer has shown to be inferior to cisplatin concern has been expressed as to whether this drug could replace cisplatin in the treatment of patients with ovarian cancer, in particular those with optimal stage III disease [24]. However, a series of studies demonstrated equivalent activity, and a recently updated meta-analysis confirmed this lack of difference, for patients overall and in any specific subgroup [25]. Nevertheless, the fact that the equivalence of carboplatin and cisplatin has been suggested from trials without a taxoid does not automatically mean that this is also true for carboplatin/paclitaxel combinations vs. cisplatin/paclitaxel combinations. For the interaction between carboplatin and paclitaxel on the megakaryocyte leads to less carboplatin-induced thrombocytopenia when given combined than when given alone and why would this effect not be present also at the level of the tumour cell. It is therefore reassuring to know that so far three prospective randomised trials, including one in patients with only optimal stage III disease (GOG protocol 158), comparing cisplatin plus paclitaxel versus carboplatin plus paclitaxel, have shown no difference in response rates or progression-free survival ([26–28], see Table 3).

All three studies have concluded that carboplatin plus paclitaxel is the preferred regimen in terms of (less) toxicity and, where studied, in terms of quality of life. However, more mature data on overall survival are required before there is certainty about the equivalence of the two regimens [29].

Intravenous paclitaxel/platinum and what next?

Intraperitoneal chemotherapy

The preferred regimen for the treatment of ovarian cancer should not only provide the best long-term survival rates but also meaningful palliation and acceptable quality of life for the majority of patients with a less favourable prognosis [29]. For patients with suboptimally debulked disease paclitaxel/carboplatin might well be the treatment of choice if long-term survival data from the randomised trials show equivalent results. But what about the patients with optimally debulked disease? GOG protocol #158 indeed demonstrated a reduction in the hazard ratio for patients treated with paclitaxel/carboplatin (0.91, with 95% confidence limits 0.76–1.10) which makes it very unlikely that the paclitaxel/carboplatin arm will ever be inferior to the paclitaxel/cisplatin [30]. Still, it needs to be awaited. In that same category of patients another form of therapy deserves further attention, i.e. intraperitoneal chemotherapy. There is ample data to suggest that intraperitoneal chemotherapy may be of benefit to advanced ovarian cancer patients with no gross residual disease or small volume residual disease after initial surgical tumour debulking. At least three randomised trials have indicated a striking risk reduction of dying when treated with intraperitoneal chemotherapy compared to intravenous chemotherapy ([31–33], see Table 4).
Table 4
Results of randomised trials of first-line i.p. versus i.v. chemotherapy in advanced epithelial ovarian cancer

<table>
<thead>
<tr>
<th>Study group</th>
<th>No. of patients</th>
<th>Disease stages</th>
<th>Survival evaluation</th>
<th>MDS (mo)</th>
<th>P value</th>
<th>Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>i.p.</td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td>GONO</td>
<td>113</td>
<td>II–IV</td>
<td>PFS</td>
<td>42</td>
<td>25</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>67</td>
<td>51</td>
<td>0.14</td>
</tr>
<tr>
<td>INT-1</td>
<td>546</td>
<td>III</td>
<td>PFS</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>49</td>
<td>41</td>
<td>0.02</td>
</tr>
<tr>
<td>INT-2</td>
<td>523</td>
<td>III</td>
<td>PFS</td>
<td>27.6</td>
<td>22.5</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>52.9</td>
<td>47.6</td>
<td>0.056</td>
</tr>
</tbody>
</table>

GONO = Gruppo Oncologico Nord-Ovest; INT-1 = Intergroup Trial [32]; INT-2 = Intergroup Trial [33]; MDS = Median Duration of Survival. Modified from Vermorken [34].

* Calculated with Log OR = (O - E)/ V and x² = (O - E)²/V (kindly provided by M. Buyse).

All these studies made use of cisplatin, being the platinum drug of choice for intraperitoneal use [34]. Because the beneficial effect of intraperitoneal chemotherapy has not been confirmed in a second trial with the new accepted intravenous standard in the control arm, it seems realistic to await the outcome of protocol GOG #172 (study limited to patients with optimal stage III, randomised to receive TP as in GOG-111 or to receive paclitaxel i.v. and i.p. and cisplatin i.p.) and to consider intraperitoneal chemotherapy for that indication still investigational [34].

Optimizing dose, schedule and duration of treatment
Many questions remain related to these three issues and studies both in the US and in Europe have been done or are ongoing. With respect to dose, there is no consensus regarding the optimum dose of carboplatin when used in combination with 3-hour paclitaxel. The optimal dose of paclitaxel in combination with a platinum compound in first line also is unclear [30]. Ultra-high doses of chemotherapy, as used with autologous stem cell support do not have an established role in patients with ovarian cancer [35]. With respect to schedule, there is an indication that the weekly regimen of 3-hour paclitaxel (67 mg/m²/week) might be as active as the three-weekly 3-hour paclitaxel (200 mg/m²) regimen. This was suggested from a randomised trial comparing these two schedules in 208 patients who had been previously treated with platinum-based therapy [36]. Response rates, progression-free survival and overall survival were all comparable between the two arms. However, in terms of safety profile there was a preference for the weekly regimen; grade 3–4 neutropenia, neuropathy, alopecia and arthralgia/myalgia occurred more frequently with the three-weekly regimen. Only severe nail changes were observed with the weekly regimen (9%). The issue of treatment duration is not closed and in particular with respect to the anti-angiogenic properties of paclitaxel, this might be an interesting field of research. The value of consolidation therapies in patients with clinical complete response or maintenance therapy in patients with at least stabilisation after induction chemotherapy has been either disappointing or uncertain to say the least [34,37–39].

The use of alternative platinum compounds or taxoids
Oxaliplatin is an interesting platinum analogue because of its lack of any significant bone marrow suppression and lack of nephrotoxicity. Anti-tumour activity so far observed in phase II studies, in which oxaliplatin was mainly given at the dose of 130 mg/m² as a 2-hour infusion, ranged between 15% and 30%, and confirmed preclinical data. A peculiar sensory neuropathy is the most important side effect. The importance of oxaliplatin was shown in a first-line randomised study which was recently updated and presented at ASCO 2000. It concerned a French study, in which oxaliplatin plus cyclophosphamide (OXC) was compared with cisplatin plus cyclophosphamide (PC) in 177 advanced chemonaive ovarian cancer patients. A similar efficacy was found in terms of response rate (both clinically and pathologically), progression-free survival and overall survival. However, OXC was favoured in terms of toxicity, i.e. less grade 3–4 anemia, less red blood cell transfusions, less grade 3–4 vomiting and less grade 3–4 leukopenia. Moreover, less nephrotoxicity was observed with OXC. Of course this regimen seemed somewhat outdated, but the role of oxaliplatin should be further explored in combination with other platinum compounds, taxoids, and other promising new agents.

Docetaxel, although less extensively studied in ovarian carcinoma than paclitaxel, is of particular interest because of its comparable activity in patients
with refractory disease and because of its somewhat lower neurotoxicity. Combinations with cisplatin in first-line (both drugs given at a dose of 75 mg/m²) showed activity (overall response rate 70%), but one third of 100 patients in a Scottish trial were not able to complete the planned six cycles of therapy [40]. In contrast, 90% of 141 patients could tolerate six cycles of docetaxel (75 mg/m²) plus carboplatin (AUC 5) in a successive study, at the cost of very little neurotoxicity. For that reason a large international trial has been performed, comparing docetaxel–carboplatin with paclitaxel–carboplatin. Early results are expected in 2001.

The addition of other new drugs
An additional way to build on the results obtained with standard paclitaxel/platinum treatment is to incorporate another active agent into the initial chemotherapy approach. Several new cytotoxic agents with activity in relapsed ovarian cancer (see section on “Optimal chemotherapy in relapsed disease”) are being combined with paclitaxel plus platinum as the first step to assess their impact in randomised trials against the standard treatment. Criteria that are used to select drugs for further development include: (1) significant activity in paclitaxel- and platinum-resistant patients, (2) demonstration in randomised patients that the drug added a clinical benefit, and (3) a phase II trial showing a high degree of activity in combination, or in sequence, with paclitaxel and platinum [41]. Promising examples include topotecan, gemcitabine, epirubicin, and liposomal doxorubicin. Because of overlapping toxicities, it has been sometimes difficult to combine some of these agents in full dose with the combination of paclitaxel and platinum. This has been overcome by using the drugs in sequence [42]. As an example the introduction of topotecan (a topoisomerase I inhibitor) in first line in combination with the other two drugs is taken: used as a third drug in combination proved to be difficult [43] because of apparently synergistic toxic effects when combined with either paclitaxel and cisplatin [44,45]. A solution was found in giving the topotecan as part of a couplet with cisplatin followed by therapy with paclitaxel/cisplatin (or carboplatin). In a feasibility study these sequential couplets proved to be feasible and the efficacy encouraging [46]. Another solution is to use single agent topotecan to ‘consolidate’ first-line therapy following standard paclitaxel/platinum. Also this second possibility has been piloted [47] and the study of both approaches in randomised trials is awaited.

Gemcitabine is a novel nucleoside analogue with a mild toxicity profile and a broad spectrum of activity against solid tumours, including ovarian cancer. Preliminary data from phase II studies in chemonaive patients with advanced ovarian cancer showed that the combination of cisplatin and gemcitabine produced an overall response rate of 53% to 72% with an acceptable toxicity profile [48–50]. Hansen recently presented data of a triple regimen (gemcitabine/carboplatin/paclitaxel) in Indianapolis in May 2000 [51]. Doses given were 800 mg/m² for gemcitabine on days 1 and 8, an AUC 5 (⁵¹Cr-EDTA) for carboplatin on day 1, and 175 mg/m² (3-hour) for paclitaxel, also on day 1. This regimen could be repeated every three weeks for a total of 6–8 cycles. In 28 patients (25 evaluable) treated in first line 100% responded (60% CR and 40% PR), with significant, but acceptable toxicity. In order to confirm these single institution data, a multicentre phase II trial in previously untreated patients with stages IIB–IV ovarian cancer was started in November 1998. After the initial 60 patients, who received carboplatin at a dose AUC 5 next patients received an AUC of 4.5 in order to reduce the thrombocytopenia. A first analysis in 27 patients revealed again a high response rate (93% with a 95% confidence interval: 76–99%) and a high clinical complete response rate (70%).

There has been a renewed interest in the use of anthracyclines. Knowing that the addition of anthracyclines to the CP combination has a real impact on survival, and considering the promising interaction between anthracyclines and taxoids in breast cancer, several groups have investigated the addition of an anthracycline (mostly epirubicin or doxorubicin, but recently also liposomal doxorubicin) to paclitaxel plus platinum. So far the combination of epirubicin with paclitaxel and carboplatin has been the most promising since full doses of all three drugs can be given without growth factor support [52]. Two large randomised trials have been launched, in which the three drug combination (TETcb) is compared with the standard-dosed two drug combination (TCb).

Conclusion
There has been a steady improvement in the median survival of patients with advanced ovarian cancer as result of a more skilled surgical approach to these patients and the development of more effective chemotherapy with a better integration of both modalities in first-line treatment. The current optimal chemotherapy approach consists of a platinum compound together with paclitaxel. There is still room for further study how to use and to combine these two classes of compounds in the most optimal manner.
Clinical trials have recently been initiated, whereby the introduction of a third drug either combined or in sequence with the other two is studied. Promising examples are topotecan, gemcitabine, epirubicin and liposomal doxorubicin. Further progress may ultimately depend on the use of novel approaches targeting cell signalling pathways and those aspects of the tumour microenvironment that support cancer invasion, growth and metastasis. In addition, the usefulness of vaccines, gene therapy, and prevention strategies for selected high-risk patient categories are beginning clinical evaluation.

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