A Systematic Overview of Chemotherapy Effects in Ovarian Cancer

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Acta Oncologica Vol. 40, No. 2/3, pp. 340–360, 2001

A systematic review of chemotherapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for the evaluation of the scientific literature are described separately (Acta Oncol 2001; 40: 155–65). This overview on chemotherapy for epithelial ovarian cancer is based on a total of 176 scientific reports. Five meta-analyses including 17291 patients, 33 prospective randomised studies including 12340 patients, 36 prospective studies including 3593 patients and one retrospective study including 421 patients. The studies include approximately 33642 patients. The conclusions reached can be summarized into the following points:

- Radically operated patients with low-risk early ovarian cancer (stage IA or IB non-clear-cell well-differentiated carcinomas or borderline tumours) have a very good prognosis and there is no indication for adjuvant therapy.
- Radically operated patients with high-risk early ovarian cancer (clear cell carcinomas or FIGO stage IA or IB moderately or poorly differentiated carcinomas or stage IC) have a substantial risk for micrometastatic disease. However, the role of adjuvant chemotherapy is unclear and such therapy should, thus, only be used within clinical trials.
- The median overall survival for patients with advanced (FIGO stages II–IV) ovarian cancer randomised to paclitaxel/platinum-containing chemotherapy in three large studies ranged between 36–39 months. Compared with historical data, this represents a six to seven times longer median survival time than after surgery only. The probability for long-term survival for patients treated with a paclitaxel/platinum combination is too early to define.
- In two prospective randomised trials in advanced ovarian cancer, paclitaxel in combination with cisplatin has provided a survival benefit over cyclophosphamide/cisplatin. Based on these trials, paclitaxel/cisplatin is considered to be the standard treatment.
- This choice of standard therapy might, however, be questioned based on the results of the hitherto largest randomised study in advanced ovarian cancer, ICON3, which is, as yet only available in abstract form. It compared paclitaxel/carboplatin with carboplatin only or a platinum combination (cyclophosphamide/doxorubicin/cisplatin). There were no statistically significant differences in progression-free or overall survival. The drug regimen in the control arms of the previous studies showing superiority of the paclitaxel-cisplatin combination may not have been the optimal non-paclitaxel platinum-containing regimen.
- Three randomised studies have compared carboplatin/paclitaxel with cisplatin/paclitaxel. All three are hitherto only published as abstracts with short follow-up precluding survival analyses. None of them shows any difference in response rates. All three show less toxicity and one also better quality of life with carboplatin. Thus, there are preliminary data supporting the substitution of cisplatin with carboplatin.
- Intraperitoneal therapy with cisplatin caused improved survival compared with intravenous therapy in one ramdomised study. Further studies have shown trends to better survival and longer progression-free interval with intraperitoneal therapy. The accrual to studies on intraperitoneal chemotherapy has been poor reflecting that it is a cumbersome and not easily accepted treatment.
- In advanced ovarian cancer, no convincing advantage has been shown from more dose-intensive chemotherapy, without cytokines or bone marrow stem cell support, compared with standard doses.
- High response rates are achieved with high-dose chemotherapy with stem cell support in the salvage situation but response duration is short. Phase III studies evaluating high-dose chemotherapy in the first-line situation are ongoing. Until supportive controlled clinical trials are presented, high-dose chemotherapy should be confined to clinical trials.

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 ISSN 0284-186X

- Tumour response is frequently observed on re-treatment with the same drugs as given first-line in patients sensitive to first-line platinum-based chemotherapy with a long progression-free interval. Thus, in these patients treatment with a platinum/ paclitaxel combination might be recommended, albeit based on limited data. In patients resistant to first-line therapy, a number of single agents induce tumour responses in the range of 10–30%. The literature does not permit general treatment recommendations in these patients, which are recommended to be included in controlled clinical trials.

Ovarian cancer has long been the third most common female cancer in Sweden, after breast and colorectal cancer. Recently, however, endometrial and lung cancers have increased in incidence while ovarian cancer has decreased. In 1997, 828 cases were diagnosed in Sweden, which comprised 4% of the 21 558 new cancer cases registered in women (1). Ovarian cancer carries the highest mortality among gynaecological malignant tumours. In 1997, 643 women were registered as having died of ovarian cancer in Sweden (2).

Sweden has the highest incidence of ovarian cancer in the world (3), the reasons being unknown. During the 20th century the age-corrected incidence has steadily increased. In 1975 this trend was broken in Sweden and since then (1975 to 1991) the incidence has decreased. This decreasing trend was first noticed in younger age cohorts (4) and it is probably an effect of the wide spread use of oral contraceptives (5), which is the best known protector against ovarian cancer. In a co-operative project, the Nordic Cancer Registries recently made a prognosis for the development of cancer incidence in the Nordic countries up to the year 2010 (6). A continuing decrease in incidence is foreseen for ovarian cancer and the prognosis for Sweden is a 10% decrease up to 2010. However, most patients with ovarian cancer are elderly and with a progressively increasing proportion of elderly women in the population, the prognosis is that the absolute number of cases will be virtually unchanged.

The relative five-year survival (the observed survival divided by the expected survival for the general Swedish female population during the same period and with the same age distribution) can be interpreted as a measure of the excess mortality associated with the cancer diagnosis under study. For women with ovarian cancer the relative survival has increased in Sweden during recent decades (7). During the period 1960 to 1969, the five-year relative survival was 30% (95% confidence interval, CI, 29–32%) for all patients with ovarian cancer registered in the Swedish Cancer Registry, while for patients registered during 1980 to 1989 it was 38% (CI 37–39%). This increase in relative survival is especially notable in younger women. The relative survival has increased from 55% (CI 51–58%) to 69% (CI 65–72%) for patients aged 45 or less at diagnosis. Also in elderly women ($>$ 64 years) improvements have been seen, albeit less impressive. Importantly, the increases in relative survival are still evident at ten years; from 28% (CI 27–29%) to 35% (CI 33–36%) from the 60s to the 80s for all ages.

It is possible that part of the increase in relative survival depends on earlier diagnosis. Information about staging is missing in the Swedish Cancer Registry. However, clinical materials from different time periods in Sweden do not support the hypothesis of earlier diagnosis (8–11). Another possibility is that the proportion of cases misdiagnosed as malignant, when the true histology was actually borderline tumour, has changed during the period. As patients with borderline tumours have about 95% five-year survival, this would affect the survival figures. However, the proportion of borderline tumours has increased from 5% to 13% from the 60s till 80s (7). It is thus more likely that this factor leads to an underestimation of the survival improvement. Yet another possibility is that the biology of the disease has changed.

The improvement in relative survival has occurred during the period chemotherapy has been used in the treatment of ovarian cancer. However, surgery has also been improved during the same period. The relative contributions of the two modalities are not possible to differentiate. It could be hypothesised that more aggressive cytoreductive surgery affects short-term survival while long-term survival depends more on chemotherapy. From Norway the same survival trends have been seen, both in a population-based material from the whole country (12) and in the hospital-based material from the Norwegian Radium Hospital (13).

Controlled prospective randomised clinical studies are today considered a prerequisite for the documentation of treatment effects. However, in a survey of randomised chemotherapy studies that had been performed in advanced ovarian cancer during 1975–1988 (14), i.e. during the early era of chemotherapy use in ovarian cancer, it was found that the largest study included 374 patients. With that number of patients, a difference from, e.g. 25% to less than 40% in survival would be undetectable. Many of the studies might well have missed a small but important treatment effect (type II error).

Evaluation of quality of life (QoL) is, unfortunately, entirely missing in most of the cited studies. In some of the most recent studies on advanced ovarian cancer QoL has, however, been measured, at least in subsets of the patient populations. The realistic goal of treatment in most cases of advanced ovarian cancer is palliation, i.e. to obtain or prolong a more or less symptom-free period. This has been termed clinical benefit. This concept has been hard to quantify and thus more easily quantifiable and established variables have been used, e.g. tumour response rate (RR), progression-free survival (PFS), overall survival (OS), and toxicity.

It is the definitive, albeit subjective, common opinion among gynaecological oncologists that patients with ad-

vanced ovarian cancer nowadays have a better QoL and that this better QoL has been obtained mainly with the help of modern chemotherapy. Cachectic patients, with abdomens distended by enormous amounts of ascites, are rarely seen today. Thus, modern treatment seems not only to have bettered the survival but also altered the course of disease. However, scientific evidence documented in the literature for this improvement is lacking.

Long-term survival with advanced ovarian cancer

There are rather few reports with long-term observations of survival. Between 1979–1981 the Netherlands Joint Study Group for Ovarian Cancer randomised 186 patients aged less than 70 years with FIGO (International Federation of Gynecology and Obstetrics) stages II or IV (see below) epithelial ovarian cancer between hexamethylmelamine (H), cyclophosphamide (C), methotrexate, 5-fluorouracil (F) (Hexa-CAF) vs C + H + doxorubicin (A) + cisplatin (P) for five days (CHAP-5). A reanalysis was made with a median follow-up of 9.5 years (15). Of 92 patients treated with CHAP-5, 32% survived five years and 21% ten years. The Swedish Cooperative Ovarian Cancer Study Group (16) included 295 patients with FIGO stages III or IV epithelial ovarian cancer between 1981–1983 and randomised between melphalan (M) + A (MA) vs the same combination with the addition of P (MAP). One hundred and forty-three patients entered the MAP arm. The five- and ten-year OS were 25 and 18%, respectively. In both studies, the survival was worse for patients that did not receive platinum-containing chemotherapy.

Randomised studies are performed in selected patient materials, and it may be difficult to know if the results can be generalised to everyday clinical practice. Three hundred and eighteen consecutive patients with advanced ovarian cancer were treated with A or epirubicin (E) + P and registered in the patient registry at the Department of Gynaecologic Oncology, University Hospital in Lund between January 1987 to March 1993. All registered patients were included regardless of performance status or age at diagnosis (27–85 years; median 62), while in randomised studies there are usually restrictions as regards age and performance status. The OS at five-years was 26% (CI 21–31%) and ten-year OS was 15% (CI 10–20%). It thus seems that in everyday clinical practice with an unselected patient material about the same survival can be obtained as in randomised studies with selected patients.

Staging, histology and prognostic factors

Ovarian cancer is staged on the basis of surgical and pathological findings according to the FIGO rules from 1986 (17) (Table 1). The stage of the disease is an important prognostic factor. Some of the studies cited use the 1973 FIGO staging rules preceding the present ones (18) (Table 2). When discussing treatment, ovarian cancer is often separated into early (FIGO stage IA–IIA) and advanced (FIGO stage IIB–IV) ovarian cancer.

Several cell types are contained in the ovary and consequently a rich variety of tumours can develop. The epithelial tumours are, however, strongly dominating. They arise from the surface epithelium of the ovaries and constitute around 90% of all ovarian tumours. This report solely discusses epithelial tumours. The borderline tumours form a group between the benign and the malignant epithelial varieties. They have been recognised lately. Patients with

Table 1

Staging of epithelial ovarian cancer according to FIGO 1986

Stage I	Growth limited to the ovaries
Stage IA	Growth limited to one ovary; no ascites, no tumour on the external surface, capsule intact
Stage IB	Growth limited to both ovaries; no ascites, no tumour on the external surfaces, capsules intact
Stage IC*	Tumour either Stage IA or IB, but with tumour on surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIA	Extension and/or metastases to the uterus and/or tubes
Stage IIB	Extension to other pelvic tissues
Stage IIC*	Tumour either Stage IIA or IIB, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
Stage III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumour limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
Stage IIIA	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIB	Tumour involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces none exceeding 2 cm in diameter. Nodes are negative
Stage IIIC	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV

*In order to evaluate the impact on prognosis of the different criteria for allotting a case to Stage IC or IIC it would be of value to know, if the source of malignant cells detected was 1) peritoneal washings or 2) ascites; if rupture of the capsule was a) spontaneous or b) caused by the surgeon.

Table 2

Staging of epithelial ovarian cancer according to FIGO 1973

Stage I	Growth limited to the ovaries
Stage IA	Growth limited to one ovary; no ascites
i)	No tumour on the external surface; capsule intact
ii)	Tumour present on the external surface and/or capsule ruptured
Stage IB	Growth limited to both ovaries; no ascites
i)	No tumour on the external surface; capsule intact
ii)	Tumour present on the external surface and or capsule(s) ruptured
Stage IC	Tumour either stage IA or Stage IB, but with ascites or positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIA	Extension and/or metastases to the uterus and/or tubes
Stage IIB	Extension to other pelvic tissues
Stage IIC	Tumour either stage IIA or IIB, but with ascites or positive peritoneal washings
Stage III	Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis and/or positive retroperitoneal nodes; tumour limited to the true pelvis, with histologically proven malignant extension to small bowel or omentum
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV; parenchymal liver metastases equals stage IV

early FIGO stage borderline tumours experience a very good survival with surgery only. Borderline tumours can, however, metastasise, but also in the advanced stages the prognosis is much better than for invasive carcinomas of the same FIGO stage. The best treatment of this tumour type, however, is still a matter for discussion (19).

Classical prognostic factors in early ovarian cancer are FIGO stage, age at diagnosis, histology, grade of differentiation, tumour rupture, growth on the outside of the ovarian capsule, dense adhesions, large volume ascites, and ascites containing malignant cells. DNA ploidy has more recently been identified as a strong prognostic factor (20). In advanced ovarian cancer also the amount of residual tumour after primary surgery and performance status are strong prognostic factors (20).

Overview of surgical treatment of ovarian cancer

Patients with early ovarian cancer can practically always be radically operated. Most patients have localised disease without micrometastases and are cured by this procedure.

Advanced ovarian cancer is primarily treated with cytoreductive surgery, which means that as much tumour as possible is extirpated even if that is accomplished by cutting through tumours and leaving parts of unresectable tumours. Most likely this approach works because surgery is followed by chemotherapy and ovarian cancer is a fairly chemosensitive malignancy as opposed to, e.g. colon cancer.

The result of cytoreductive surgery has traditionally been dichotomised as optimal or non-optimal depending on the size of the largest remaining tumour nodules. The cut-off value has varied over time and in different studies. Today the usual value is one cm. Everyone with experience of ovarian cancer surgery knows that these measurements are rather subjective. The total volume of remaining tumour may be more important but is difficult to estimate and has seldom been used in prognostic scoring. The ultimate goal of cytoreductive surgery is total clearance of macroscopic tumour, which results in the best survival figures.

An unresolved question is if the better survival for patients with small tumour burdens achieved by cytoreductive surgery merely reflects that biologically less aggressive tumours are easier to resect. Only randomised studies between cytoreductive surgery followed by chemotherapy vs up-front chemotherapy can answer this. The European Organisation of Research and Treatment of Cancer (EORTC) has published a randomised trial on interval debulking surgery (21). Patients who were non-optimally debulked at primary surgery were randomised to chemotherapy only vs three courses of chemotherapy and interval debulking surgery followed by further chemotherapy. The use of interval surgery led to a significantly better OS, from 46% to 56%, and a prolongation of median OS by six months. In a multivariate analysis, debulking surgery was an independent prognostic factor ($p = 0.012$). Overall, after adjustment for all other prognostic factors, surgery reduced the risk of death by 33% (CI 10–50%; $p = 0.008$). This randomised study thus demonstrates an effect of cytoreductive surgery even though it was not performed up-front.

ADJUVANT CHEMOTHERAPY IN EARLY OVARIAN CANCER

Early ovarian cancer signifies localised disease and is equivalent to FIGO stage IA, B, and C (sometimes also including stage IIA). Truly localised disease is curable by surgery alone.

In a population-based study from the South-Eastern Health Care Region of Sweden, FIGO stage I accounted for 20% of epithelial ovarian cancer (10). For Sweden, this would correspond to around 180 cases per year.

Two problems are encountered as regards adjuvant therapy in early ovarian cancer: The first is to find prognostic

factors that can predict the presence of micrometastases (the disease is no longer localised), the second is to find adjuvant therapies that are both effective in controlling micrometastatic disease and with tolerable short- and long-term side-effects.

Patients with a statistical risk for having persistent disease will be treated with adjuvant therapy. This means that only a fraction of the patient population treated actually has micrometastatic disease and could potentially benefit from the treatment.

Prospective observational studies on patients with early ovarian cancer without adjuvant treatment

Three prospective observational studies have been published where patients did not receive adjuvant therapy after surgery (22–24). These studies demonstrate the natural disease course for patients with early ovarian cancer.

Ten Canadian institutions recruited 82 patients (68 eligible) with FIGO stage I epithelial ovarian cancer (23). With a median follow-up time of four years, three patients with disease progression were identified. One died of disease while two patients, both with clear-cell tumours, were disease-free after salvage chemotherapy. The other two patients had clear-cell tumours. Patients with FIGO stage IC disease and with poorly differentiated tumours were under-represented, presumably because of reluctance to withhold treatment.

Trimbos et al. (24) demonstrated the excellent prognosis with surgery only, provided surgical staging is performed according to state-of-the-art. They recruited 67 surgically staged patients with well-differentiated FIGO stage IA–IIA disease. Follow-up ranged between seven months to eight years and 4/67 patients had disease progression and died within a short time therafter (88% 5-year PFS). All 4 were incompletely surgically staged. A PFS of 100% were registered in patients properly surgically staged according to the FIGO recommendations.

The third study from Royal Marsden, London included 194 consecutive patients with FIGO stage I disease (22). After a median observation time of 54 months the five-year OS was 84–94% according to FIGO substage. Five-year PFS was 62–87% according to substage and 90, 85, and 45% for patients with well, moderately and poorly differentiated tumours, respectively. In a multivariate analysis, grade of differentiation, ascites, and cancer vegetations on the tumour surface were identified as significant independent factors that predicted progression.

Treatment trials

Sixteen studies randomising 3130 patients have been published (25–40) and are summarised below. Seven of the studies (26, 27, 29, 30, 32, 33, 35) either have methodological flaws, are small, randomised patients to three arms, or deal only with radiotherapy and will not be further commented on.

Observation vs chemotherapy in low-risk early ovarian cancer

A collaborative study performed by the Ovarian Cancer Study Group (OCSG) and the Gynecologic Oncology Group (GOG) was reported by Young et al. (39). Ninety-two patients (81 eligible) with low risk well or moderately differentiated FIGO stage IA/B invasive carcinoma were randomised to observation vs M. After a median follow-up period exceeding six years no significant differences in OS (98 vs 98%) or PFS (91 vs 94%) could be seen. One patient in the M arm died of aplastic anaemia. The study included few patients and a large part of them, 39% in the observation arm and 28% in the chemotherapy arm, had borderline tumours.

Bolis et al. (25) reported a randomised Italian trial comparing observation vs P in 85 consecutive patients with FIGO stage IA/B well or moderately differentiated disease. With a median follow-up of 76 months a significant reduction of progressions was found in patients treated with P (relative risk 0.35; CI 0.14–0.89; $p = 0.028$). There was, however, no difference in five-year OS (82 and 88%), but few events had occurred at the time of analysis. It was observed that once a progression had occurred, the risk of dying was greater for patients treated with P up-front.

Observation vs chemotherapy in high-risk early ovarian cancer

The Nordic Co-operative Ovarian Cancer group (NOCOVA)-study (37) was closed prematurely because of slow randomisation. Between 1992 and 1997, 175 radically operated patients (162 eligible) with FIGO stage I invasive epithelial ovarian cancer, moderately or poorly differentiated, or well differentiated and aneuploid, or with clear cell histology were randomised to observation vs postoperative carboplatin (cP) for six courses. With a median follow-up of 46 months, progression was registered in 39 patients, 20 in the treatment group and 19 in the control group. The estimated five-year disease-specific and PFS rates were 86% (CI 78–94%) vs 85% (CI 75–95%) and 70% (CI 58–82%) vs 71% (CI 59–83%) for treatment and control groups, respectively. The hazard ratio (HR) was 0.98 (CI 0.52–1.83) in favour of the treatment group regarding PFS while the HR was 0.94 (CI 0.37–2.36) also in favour of the treatment group regarding disease-specific survival. The wide confidence intervals emphasise the inconclusive nature of the study.

Pelvic radiotherapy (PR) + whole abdominal radiotherapy (WAR) vs pelvic radiotherapy + chemotherapy

During the late 60s it was realised that the whole abdomen was to be the target if radiotherapy should be used. External irradiation of the entire abdominal cavity or intraperitoneal instillation of radioactive isotopes could accomplish this. Since the liver and kidneys are included in the field and a large volume is treated when giving

WAR, only a low dose of radiation can be delivered. Usually the pelvis is given a higher dose (PR + WAR).

Dembo et al. (27) addressed if WAR could be substituted by chemotherapy that might be more effective and less toxic. Seventy-six patients were randomised to PR + WAR and 71 to PR + chlorambucil. In an update (28), the five-year OS was statistically significantly better in the PR + WAR-arm (78% vs 51%; $p = 0.006$). Two patients receiving chlorambucil later died of acute leukaemia. The study has been criticised because of unusual patient classification and suboptimal dose of chlorambucil.

Klaassen et al. (31) randomised 284 (257 eligible) patients to PR + WAR vs PR + intraperitoneal instillation of radioactive phosphorus (32P) vs PR + M and the Danish Ovarian Cancer Group (DACOVA) (34) randomised 412 (406 eligible) patients with FIGO stage IB–IIC to PR + WAR vs PR + C. Neither of the studies could lend support to any of the treatment alternatives. A long-term follow-up of the Klaassen study (42) with a median follow-up time of 13.5 years could still not reveal any difference in survival between the arms (OS 45% PR + WAR, 50% PR + 32P, 49% PR + M; $p = 0.30$, PFS 50% PR + WAR, 51% PR + 32P, 62% PR + M; $p = 0.15$). Twenty-nine women had developed secondary malignancies, while 18.7 would have been expected ($p = 0.018$). Twenty-four were solid tumours. PR + M appeared to be associated with an increased risk of developing acute myelogenous leukaemia (four patients) and myelodysplastic syndrome (one patient) compared to the PR + WAR arm (0 patients; $p = 0.06$).

Whole abdominal radiotherapy vs chemotherapy

Smith et al. (36) randomised 156 (149 eligible) patients with FIGO stage I, II, III disease and also one patient with stage IV disease between WAR vs M. The five-year OS was similar for the two arms; 71 and 72%. In FIGO stage I the five-year PFS was 85 and 90% and the OS 100 and 86% for WAR ($n = 14$) and chemotherapy ($n = 28$), respectively. The differences were not statistically significant. It was concluded that chemotherapy was the preferred treatment since it was as effective as irradiation, but less toxic and less costly. In a later update (28) two deaths from treatment complications in the radiotherapy arm were reported and two patients from the chemotherapy arm had developed acute leukaemia. There was an imbalance between the randomisation arms in that there were more early FIGO stage patients in the chemotherapy arm. The balance of residual disease and grade of differentiation between the arms was not reported. The irradiation was not true WAR since the diaphragm was not included and liver shielding was used. Right or wrong, this study had great impact in that most institutions in the US abandoned postoperative radiotherapy of ovarian cancer in favour of chemotherapy.

A collaborative study performed by OCSG-GOG (39) randomised 145 (141 eligible) patients with high-risk FIGO stage I (poorly differentiated) or stage II tumours between 32P vs M. The GOG-group later randomised 251 patients (205 eligible) with FIGO stage I or II (high risk) ovarian epithelial cancer after comprehensive surgical staging to 32P vs CP (40). Vergote et al. (38) at the Norwegian Radium Hospital randomised 347 patients (341 eligible) with FIGO stage I (low- and high-risk) and radically operated FIGO stage II and III to 32P vs P. Two of these studies (38, 39), could not disclose any difference in treatment results between radiation or chemotherapy. The GOG-study (40) showed that, after adjusting for grade of differentiation and histology, the estimated progression rate was 31% lower on CP than 32P (HR 0.69, 90% CI 0.46–1.06; $p = 0.075$, one tail test). Two patients in the M-arm died of leukaemia in the OCGS-GOG-study (39). Two patients in the GOG-study (40) had bowel perforations in connection with the administration of 32P and two patients died of treatment complications, one in each arm. Vergote et al. (38) reported that bowel obstruction not caused by malignancy occurred significantly more often after 32P.

Bolis et al. (25) compared intraperitoneal instillation of ^{32}P with P intravenously in 186 high-risk early stage patients (FIGO 1973 stage IAii/Bii and IC). P reduced the rate of progression with a relative risk of 0.39 (CI 0.19–0.77; $p = 0.007$). There was no difference in OS (79 and 81%). As in the comparison described above between observation vs P in low-risk patients performed by the same group (25), it was observed that once a recurrence had occurred the risk of dying was greater for patients that had been treated with P up-front. A more effective second-line treatment might have affected OS. There are no obvious explanations of the different results between the Italian and the other three studies (38–40). However, the GOG-study (40) has corresponding results, although they did not reach statistical significance.

In conclusion, it has not yet been shown that immediate adjuvant therapy in high-risk early ovarian cancer is better than treatment at the time of progression when OS is the end-point. Two randomised studies addressing this question are at present ongoing in Europe; ACTION organised by the EORTC and ICON1 (International Collaborative Ovarian Neoplasm Study) organised by the British Medical Research Council (MRC). In both studies patients in the control groups receive no up-front adjuvant therapy while those in the experimental arms get adjuvant chemotherapy. The recently published NOCOVA-study (37) has been described above. The first results from ACTION and ICON1 will be presented in April 2001 and data regarding the main question will probably be pooled.

Randomisation between different chemotherapy regimens

The GOG-group randomised high-risk early ovarian epithelial cancer after comprehensive surgical staging and

complete resection (FIGO stage IA or IB poorly differentiated or clear cell histology or IC, IIA, IIB or IIC) between three cycles of cP + paclitaxel (T) vs six cycles of the same chemotherapy (43). By late 1997, 250 eligible patients had been included and 237 were alive and progression-free while 13 had progressed or died. It was too early to report any comparisons between the randomisation groups. This study reflects a difference in attitude between the US and Europe. In the US it has been regarded as ethically and legally impossible not to treat patients with poor prognostic factors with adjuvant therapy. In Europe, on the other hand, ethical committees have approved the ongoing trials with an observation arm because of lack of documentation for the advantage of adjuvant therapy. Currently the GOG is randomising between three cycles of cPT vs three cycles of cPT followed by 26 weekly administrations of T (40 mg/m^2) (40).

The literature shows that:

- There is yet no unequivocal support for a survival benefit from any form of adjuvant therapy in early ovarian cancer. The studies hitherto performed on patients with early ovarian cancer are too small, lacking power to detect or reject expected treatment effects.

Adjuvant chemotherapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	7/1 385	4/626	1/149	12/2 160
P	2/261	1/68	–	3/329
Total	9/1 646	5/694	1/149	15/2 489

*The weight of scientific evidence for each study was graded as described (Acta Oncol 2001; 40: 155–65). M = meta-analysis, C = controlled clinical trial, P = prospective trial, R = retrospective study, L = literature review and O = other studies. The classification of each study is given in the reference list.

CHEMOTHERAPY IN ADVANCED OVARIAN CANCER

There is unfortunately no study that has randomised chemotherapy against no chemotherapy. The absolute therapeutic contribution of chemotherapy by itself is, therefore, unknown. Before the chemotherapy era, postoperative radiotherapy was the treatment of choice. Murphy et al. (44) provided indirect evidence for the contribution of chemotherapy when they randomised between a normal dose of C + cP alternating with doxorubicin (A) + ifosphamide, also at normal doses, given once monthly for six cycles vs half doses given monthly for 12 cycles. The RR was 76% vs 48% (p = 0.009) and with a median follow-up of 26 months the median OS was 21 months and the median PFS was 20 months on the low-dose arm while neither had been reached in the normal-dose arm. Clinical disease progression was 42 vs 8% (p = 0.0003).

The Advanced Ovarian Cancer Trialists Group meta-analysis

In 1991 The Advanced Ovarian Cancer Trialists Group (AOCTG) published a large overview (45) including 8139 patients from 39 published and five unpublished randomised studies (41, 46–83). The study used individual patient data and the follow-up of every patient was updated. Some methodological errors were corrected, e.g. patients excluded after randomisation were re-included in the present analyses. To avoid publication bias, unpublished studies were included as far as they could be identified. Only studies addressing the specific questions asked and where the randomisation procedure was considered proper, were included. An update (84) with prolonged follow-up and addition of a few studies (16, 85–87) has been published.

The end-point was OS. This is an indisputable and easily defined end-point. But the use of this end-point does not allow an evaluation of the efficacy of the drug regimen under study. Instead it is an evaluation of a treatment policy that uses the drug regimen under test as first-line treatment. Many claim that the primary chemotherapy mainly determines the ultimate outcome. However, outcome is complicated by the fact that most patients, progressing during or after treatment, receive salvage chemotherapy. Patients in so-called non-platinum arms were thus initially treated with non-platinum-based chemotherapy but at progression many received platinum or a platinum-based combination. If the salvage therapy also influences survival, this might impair detection of a survival benefit from the first-line treatment.

Non-platinum-based single-drug chemotherapy was compared with non-platinum-based combination chemotherapy. This comparison is mainly of historical interest and has not been updated. It consisted of 3146 patients from 16 studies (two unpublished) (41, 46, 52–54, 58, 66, 67, 69, 72, 74, 76, 77, 79). Totally, 2817 deaths were registered and the median follow-up time was ten years. There was no evidence for any difference between the two treatment alternatives. Only one study showed significantly better result for the combination treatment. This was the first Swedish Cooperative Study comparing M with MA (76).

Non-platinum based single-drug chemotherapy was compared with combination chemotherapy containing platinum. The comparison included 1 329 patients from 11 studies (two unpublished) (50, 57, 61, 65, 74, 80, 81, 88, 89). As discussed above, many patients randomised to

single-drug non-platinum therapy received platinum at progression. The total number of registered deaths was 1169. Totally there was no statistically significant difference between the treatment arms ($p = 0.23$) but the platinum combination therapy survival curve is above the single-agent curve especially early on. The HR is 0.93 (CI 0.83–1.05) equivalent to a 7% reduction in the overall risk of death that translates to a suggested increase in OS from 44 to 48% at two years and from 25 to 28% at five years (CI 2% detriment to 7% benefit).

Data on the importance of addition of platinum to a regimen were originally obtained from eight studies (two unpublished) (57, 61, 65, 68, 71, 80). The second Swedish randomised study (16) was added in the update. Five compared an alkylating agent as single-drug chemotherapy with the same drug plus P; these studies were thus a part of both comparisons two and three. This comparison comprised 1704 patients and 1428 deaths were registered. There was a significant difference ($p = 0.02$) between the curves. There is a suggested 12% reduction in the risk of death from the addition of P to a non-P-containing drug regimen, which translates to an increase in OS from 45 to 50% at two years, and 25 to 30% at five years (CI 1–8% benefit).

Data on single-drug chemotherapy with platinum vs a platinum combination originally were obtained from 925 patients from six studies (two unpublished) (55, 60, 75, 83). In the update, two new trials were added to the comparison (85, 87). The number of patients in the comparison was 1095 with 894 events. Overall, the results favour the use of combination chemotherapy with a HR of 0.91 (CI 0.80–1.05; $p = 0.21$) although this is inconclusive. This equals a 3% increase in OS from 45 to 48% at two years and from 25 to 28% at five years (CI 2% detriment to 8% benefit). One study (83) compared high-dose P (100 mg/m^2) as single-drug treatment with a lower dose (20 mg/m^2) in the combination. The other studies had the same dose of platinum in both arms. After exclusion of the high-dose/low-dose study there was a significant difference ($p = 0.02$) between the OS curves for platinum combination trials with HR 0.80 (CI not given; $p = 0.02$).

P has been compared with cP, either as single-drug chemotherapy or in combinations. Originally there were data from 11 studies (one unpublished) (47–49, 51, 56, 59, 62, 64, 73, 82). The update has added one new trial (86) and the comparison comprised a total of 2219 patients and 1745 deaths. There is no significant difference between the OS curves when P or cP were given either as a single drug (HR 1.01; CI 0.81–1.26; $p = 0.92$) or in combination (HR 1.02; CI 0.92–1.13; $p = 0.74$). Overall the HR was 1.02 (CI 0.93–1.12; $p = 0.66$). This could be consistent with improvements in OS of 3% for P or 4% for cP. In the update subgroup analyses were performed using data from 11 of the trials included in the cP/P comparison. No evidence was found that any group specified by age, stage, performance status, residual tumour bulk, extent of operation, histology or grade would do any better or worse when treated with either cP or P. The equality in results between cP and P is somewhat surprising since P is regarded to be superior to cP in testicular cancer and also in head-and-neck cancer and bladder cancer (90). However the results were very consistent both between trials and in the subgroup analysis.

The role of anthracyclines

Another meta-analysis was performed and published by the Ovarian Cancer Meta-Analysis Project (91). The background for the project was that five published randomised clinical trials (60, 70, 92–94) comparing CP vs CAP all showed a small but insignificant survival benefit for CAP.

In addition to the five studies mentioned above, one unpublished study was identified. The four largest studies (60, 71, 92, 93) had randomised 1187 patients. Individual patient data and updated observation times could be retrieved for patients included in these studies. No important imbalances regarding prognostic factors were found. The two other trials were smaller, with 96 and 32 randomised patients, respectively. The principal investigators could not verify data from these studies and therefore the analysis was mainly based on the four larger studies (60, 71, 92, 93). However, when the available data from the two smaller studies were included in the analyses, results were very similar. As in the original reports, a non-significant survival benefit for CAP was registered in all four studies. When the data from the four studies were pooled there was a statistically significant survival benefit for CAP ($p = 0.02$). The benefit was 5–7% between years two to six. The HR to die was 0.85 (CI 0.75–0.98) for the patients receiving CAP relative to those receiving CP. The survival benefit of CAP over CP was largest in patients with no residual disease (HR 0.73) and smallest in patients with bulky disease (HR 0.91). An update has been made (95) after a median follow-up period of more than 10 years. The reduction in the risk of death was still 16% ($p = 0.009$).

A'Hern and Gore (96) used the same material as in the meta-analyses by the The Advanced Ovarian Cancer Trialists Group (45) and the Ovarian Cancer Meta-Analysis Project (91) in another meta-analysis with a new question, namely the impact of the addition of anthracycline to regimens in general, when removing the confounding influence of other drugs. Data for addition of anthracycline were available from nine published (41, 55, 58, 60, 71, 75, 76, 92, 93) and one unpublished trial. Totally the analysis involved 1 702 patients. Six studies (55, 60, 71, 75, 92, 93) compared platinum-based chemotherapy with the addition of anthracycline and six published studies and one unpublished (41, 46, 54, 58, 75, 76) compared the addition of anthracycline to non-platinum regimens. The overall HR was 0.85 (CI 0.76–0.95; $p = 0.003$) for the addition of an anthracycline. This effect is of the same magnitude as that

found in the AOGCT-study for the addition of platinum, i.e. an improvement of the five-year OS rate by approximately 5%. The authors concluded that their data refuted the conclusions of the AOCTG overview that there was no evidence that non-platinum-containing combination therapy confers a survival advantage over single-agent non-platinum therapy. The A'Hearn and Gore analysis suggests that a regimen that contains anthracycline would be expected to be superior to a non-anthracycline, non-platinum single-agent regimen. They stated that the reason for the apparent discrepancy between the studies was caused by AOCTG not doing a separate analysis of the trials including anthracycline.

In spite of the relatively large number of patients in these three meta-analyses it is difficult to draw any firm conclusions, although the AOCTG-study (97) points to an advantage for immediate platinum-based combination chemotherapy. There is some uncertainty if the treatment effect found in the Ovarian Cancer Meta-Analysis Project study (91) was caused by greater dose-intensity or the addition of an anthracycline to a regimen. However, Fanning et al. and West et al. (98, 99) made two meta-analyses including the same five published studies that were used in the Ovarian Cancer Meta-Analysis Project and in addition several studies where all patients received CAP or CP. The two latter meta-analyses were based on published data only. Their analyses suggest that it is the addition of anthracycline, not the increased dose intensity that exerts the effect on survival.

Meta-analyses have been criticised. After a systematic survey of randomised chemotherapy studies in advanced ovarian cancer published in 1975–1988, Marsoni et al. (14) concluded that '… the internal coherence and development of randomised clinical trials in advanced ovarian cancer and their methodologic soundness are quite poor. In this situation, meta-analysis cannot go beyond a systematic attempt to answer the very general 'treatment effectiveness' question…'. Some of the problems Marsoni identified have been corrected in the meta-analyses by updated follow-up of individual patients and by applying a strict intention-to-treat principle and by re-including patients excluded after randomisation. Marsoni also points out that the randomisation procedure was not described in 76% of the studies and was not acceptable in 34%. In the overview (45) it was stated that the studies were included if '... believed to have been randomised in a manner that precluded prior knowledge of the next treatment assignment...'.

An enormous amount of work has been put into both the original randomised clinical studies and the meta-studies but we still do not have any conclusive evidence regarding the questions that have been prevailing since the early eighties. Is combination chemotherapy better than adequate single-drug treatment with a platinum compound? Which is the best platinum-based combination chemotherapy in advanced ovarian cancer?

As a consequence of the overview, a large randomised study ICON2 (100) was started. Patients with epithelial ovarian cancer FIGO stages I–IV that the oncologist felt needed chemotherapy were randomised to CAP vs cP administered according to renal function using Calvert's formula (101) (area under the curve, AUC = 5). The CAP regimen was C 500 mg/m^2, A 50 mg/m^2, and P 50 mg/m^2. The goal for the study was to randomise 2000 patients but the study was closed after inclusion of 1526 patients from 132 centres. When the data were analysed, seven hundred and twenty-eight patients had progressed or died, 368/766 allocated to CAP vs 360/760 allocated to carboplatin. The HR was 1.00 (CI 0.86–1.16; $p = 0.98$). There was no evidence of a difference in effectiveness between the two treatments within various subgroups. The study has caused confusion because it challenges the dogma of the superiority of combination chemotherapy. It has been criticised in various ways, and concern has especially been expressed regarding the multitude of centres randomising very few patients each. However, we are now into a new era with T combination chemotherapy. It is regrettable that a golden standard for platinum-based chemotherapy has not been established, which causes problems since it is uncertain whether the new T-based combinations were compared with the best available non-T chemotherapy.

Randomised studies with paclitaxel (T) combinations as first-line therapy

The first randomised phase-III study, which compared T (135 mg/m^2, 24 hour infusion) and P (75 mg/m^2) vs standard combination chemotherapy with C (750 mg/m^2) and P (75 mg/m^2) in non-optimally cytoreduced ovarian cancer FIGO stage III–IV (GOG-111) was published in 1996 (102). A significant advantage was shown for patients treated with PT with a relative death risk of 0.6. The median OS time was 38 months for patients treated with PT compared with 24 months for patients treated with standard chemotherapy ($p < 0.001$). In this study, few patients got T as salvage therapy. This is probably the only study that can evaluate the true difference in OS between T and non-T chemotherapy since in subsequent studies crossover to T as salvage therapy might diminish the difference in OS between the treatment arms. In a recent update made during the autumn of 1999 (103) the five-year OS was 16% (CI 11–21%) vs 28% (CI 20–33%; $p = 0.016$) with a HR of 0.71 (CI 0.58–0.89) with multivariate adjustment for prognostic factors. In large parts of the Western world, T combination chemotherapy became standard treatment in advanced ovarian cancer after this study was first reported. However, in order to give the therapy as an outpatient procedure, many started using cP instead of P and/or gave T as a three-hour infusion instead of the 24-hour infusion that was used in the study. None of these modifications had at that time been tested in randomised trials as first-line treatment in advanced ovarian cancer.

A confirmatory study (OV10) including 680 patients was performed by the Nordic Society for Gynecologic Oncology (NSGO), the EORTC, the Scottish Ovarian Cancer Study Group, and the National Cancer Institute of Canada (NCIC) (104). In this study, T was given at a higher dose (175 mg/m^2 with dose escalation to 200 mg/m^2 if minor toxicity compared to 135 mg/m^2 in GOG-111) and with a shorter infusion time (three hour instead of 24-hour infusion). Patients with optimally cytoreduced tumours were also included. The study recruited the predetermined number of patients in a very short time. With a median follow-up of 38.5 months 74% of the patients had progressed and 59% had died. The median PFS times were 15.5 months for patients randomised to PT vs 11.5 months for those randomised to CP ($p = 0.0005$). The median OS times were 36.5 and 28.5 months favouring patients randomised to PT. The HR was 0.74 (CI 0.63–0.88) for PFS and 0.73 (CI 0.60–0.89) for OS in favour of the PT-arm. Adjustment for prognostic factors in a Cox model did not change the HRs appreciably. A total of 34 patients, 14 in the CP group and 20 in the PT group received second-line therapy before disease progression was documented. Roughly half of the patients in the CP-arm received paclitaxel at first progression of disease. The high dose of paclitaxel per cycle (175–200 mg/m^2), the shorter infusion time, or the greater cumulative dose of paclitaxel compared with the GOG-111 resulted in an unacceptably high rate of neurotoxicity; 24% grade three to four compared with 4% in GOG-111.

Two studies have complicated the picture (105, 106). In GOG 132 (106), 614 patients were randomised between three alternatives, PT (P 75 mg/m^2 and T 135 mg/m^2/24 hours), single-drug T (200 mg/m^2/24 hours), and single-drug P (100 mg/m^2). The study result was that single-drug T was inferior as regards RR compared with the P regimens (42 vs 67%; $p < 0.001$) and PFS (HR = 1.41; CI 1.15–1.73; $p < 0.001$), while the OS was comparable in the three study arms. There were no statistically significant differences between P and PT regarding RR or OS. The combination arm had the best toxicity profile. The interpretation of this study is difficult because of early and frequent cross-over between the study-arms even before progression had been verified. This study gives support to the hypothesis that sequential treatment (first P, then T) might be as effective as combination chemotherapy. A theoretical advantage for sequential treatment is that the respective drugs can be delivered in higher doses. ICON3, first presented at the American Society of Clinical Oncology (ASCO) 1999 (105) and updated in 2000 (107) randomised between cPT (cP AUC > 5 and T 175 mg/m^2) vs single-drug cP (AUC > 5) (n = 1421) or between cPT and CAP (C 500 mg/m^2, A 50 mg/m^2, and P 50 mg/m^2) (n = 653). With a median follow-up of 29 months and 1 270 registered events, the median PFS times were 16.2 for controls vs 16.8 for patients randomised to cPT with a HR of 0.96 (CI 0.86–1.08) resulting in an absolute difference of 1% at one year. The median OS times were 36 months for controls and 38.7 for patients in the cPT-arm with a HR of 0.93 (CI 0.81–1.06) with an absolute difference of 2% at one year. The results of these two studies have raised a suspicion that CT might not have been compared with an optimal control arm in GOG-111 and OV10. A hypothesis that has been forwarded is that C could exert a negative interaction with P (106). There is, however, no hard evidence to support this hypothesis.

In order to reduce the side-effects of the PT combination, mainly neurological, P has been replaced by cP. Three studies have compared PT with cPT (27, 44, 68). The GOG-158 study (108) compared T as a 24-hour infusion when combined with P and as a three-hour infusion in combination with cP in patients with minimal residual disease, while the European studies (109, 110) administered T as three-hour infusions in both randomisation groups without restrictions on residual tumour. All three studies have been presented as abstracts with rather short follow-up. They showed no differences in RRs but a more favourable toxicity profile in the cPT arm. The German study (109) has also registered QoL of life, which was significantly better in the cPT arm.

Ongoing main studies

The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) compares TEcP with cPT. Preliminary results were presented at the 7th meeting of the International Gynecologic Cancer Society (IGCS) in 1999 (111). Seven hundred and twenty-two patients had been randomised. The clinical complete response (CR) rate was 81 vs 37% favouring TEcP. Figures for OS are expected in late 2000. The Intergroup (NSGO, EORTC, and NCI-C) is testing the same combination with minor differences in doses. The Scottish Group together with an international collaboration (SCOTROC) have randomised docetaxel + cP against TcP.

For the moment, it can be concluded that PT has been shown to be better than CP. cPT equals PT as far as RR is concerned with a better toxicity profile and better QoL. A combination of T and a platinum drug is regarded as standard first-line treatment. cPT has lately been chosen as standard at most centres since a meta-analysis (84) could not demonstrate any differences in effects between cP and P, and cPT seems to be equivalent to PT as regards RR with less toxicity and better QoL.

The literature shows that:

- Paclitaxel in combination with cisplatinum provides a survival benefit over cyclophosphamid combined with cisplatinum in advanced ovarian cancer and is at present considered to be the standard treatment. However, paclitaxel/cisplatinum has largely been substituted by carboplatinum because of equivalent response rates,

more favourable toxicity profile, and better QoL. However, this substitution is not yet sufficiently supported by data from fully published clinical trials.

- The median OS time for patients randomised to the paclitaxel-containing arm in GOG-111, OV10, and ICON3 is 36.5–38.7 months. Compared with historical data this represents a six to seven times longer median survival time than after surgery only. The probability of long-term survival for patients treated with a paclitaxel-platinum combination is too early to define.
- Three randomised studies have compared carboplatin/paclitaxel with cisplatin/paclitaxel. All three are hitherto only published as abstracts with short follow-up precluding survival analysis. None of them show any difference in response rates. All three show less toxicity and one better QoL with carboplatin/paclitaxel.
- The results of ICON3 are still only available in abstract form. It compares TcP with cP-single drug or a three-drug platinum combination (CAP). There are no statistically significant differences in progression-free or overall survival. The control arm in GOG-111 and OV10 might not have been the optimal non-paclitaxel platinum-containing regimen.

Standard chemotherapy in advanced ovarian cancer

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
M	3/11 035	2/6 256	–	5/17 291
C	9/7 168	–	–	9/7 168
Total	12/18 203	2/6 256	–	14/24 459

*For abbreviations, see above.

INTRAPERITONEAL CHEMOTHERAPY IN ADVANCED DISEASE

Intraperitoneal administration of cytostatics has been a controversial issue for decades. The proponents for this approach emphasise a so-called 'pharmacological advantage' i.e. the high concentration of the cytostatic agent in the peritoneal cavity compared with the plasma (112). This is, of course, indisputable for agents with slow transport from the peritoneal cavity to the general circulation. The crucial point is if this approach leads to a higher concentration of the cytostatic agents in the tumour cells. In animal models, the diffusion capacity in the tissues is limited (113). This is not unexpected since even very small tumours cannot rely on diffusion to get nutrition but must create a system of blood vessels. A slow clearance from the peritoneal cavity to the general circulation could result in prolonged exposure to the cytostatic agent via the intravenous route. This effect could also, in a more controlled way, be achieved by continuous intravenous infusion. The second main argument for intraperitoneal chemotherapy has been that ovarian cancer, even in advanced disease, often remains confined to the abdominal cavity. This may be true in many cases, but a substantial part of the patients, even with early ovarian cancer, have metastatic disease in retroperitoneal lymph nodes (114).

The vast majority of published studies on intraperitoneal chemotherapy in ovarian cancer are uncontrolled phase II studies. Lately, however, a few randomised studies have been published (115–117). An EORTC-study was forced to close because of very slow accrual. The first study (115) was an intergroup effort of three US groups, the Southwest Oncology Group (SWOG), the GOG, and the Eastern Cooperative Oncology Group (ECOG). Totally 654 (546 eligible) women were randomised between 1986 and 1992. The treatment alternatives were intraperitoneal P 100 mg/m^2 combined with intravenous C 600 mg/m^2 or the same drugs given intravenously every third week for six cycles. Only patients with optimal cytoreduction to a size of two cm or less were included. During the study a feeling emerged among gynaecological oncologists that the patients most likely to benefit from intraperitoneal therapy were those with a tumour mass no larger than 0.5 cm in the greatest dimension. Therefore, in 1991 accrual was extended for another year for patients with < 0.5 cm residual tumours. This was, according to the report, done without knowledge of interim results in subgroups. The aim was to be able to perform subgroup analyses. The HR for OS was 0.76 ($p = 0.02$) favouring intraperitoneal therapy. The subgroup with minimal residual disease (397 eligible patients) had a hazard ratio of 0.80 ($p = 0.10$). Thus, it could not be shown that intraperitoneal therapy was more efficient in this subgroup. There was less toxicity with intraperitoneal administration.

The second published study was performed by the Italian Gruppo Oncologico Nor-Ovest (GONO) (116). The study aimed at randomising 330 patients, but was closed with only 113 patients entered because of slow accrual. The study population was patients with less than two cm residual tumour after cytoreductive surgery randomised between P 50 mg/m^2 intraperitoneally plus intravenous E 60 mg/m^2 and C 600 mg/m^2 or the same drugs all intravenously every four weeks for six cycles. The median PFS time was 25 and 42 months and the median OS time 51 and 67 months, both favouring intraperitoneal therapy. The differences were not statistically significant.

Markman et al. reported the GOG-114 study (118) at ASCO 1998. Two cycles of cP (AUC 9) was followed by intraperitoneal P 100 mg/m^2 combined with intravenous T 135 mg/m^2 (24-hour infusion) or both drugs given intravenously in 523 (465 evaluable) patients cytoreduced to

< 1 cm residual tumour. Six courses were administered every third week. The initial intravenous cP in the experimental arm was given in order to further reduce tumours remaining after cytoreduction before the intraperitoneal treatment. The HR for PFS was 0.79 ($p = 0.020$, one-tailed) and for OS 0.79 ($p = 0.06$, one-tailed) favouring intraperitoneal therapy. The experimental regimen was associated with substantial toxicity, mainly in the form of myelosuppression.

A phase-II study (117) of intraperitoneal T in patients with minimal residual disease (< 0.5 cm) after a second-look operation has shown 61% surgically confirmed RR in patients cytoreduced to no macroscopic disease at second-look surgery, and 3% CR (1/33) in patients with any macroscopic disease (< 0.5 cm). The present GOG study (GOG-172) compares intravenous P 75 mg/m^2 and T 135 mg/m^2 (24-hour infusion) vs T 135 mg/m2 intravenously day 0 (24-hour infusion) and P 100 mg/m^2 intraperitoneally on day one, and T 60 mg/m^2 intraperitoneally on day eight.

The literature shows that:

- Intraperitoneal therapy with cisplatin resulted in better survival in one randomised study. This study has not yet been confirmed. Further studies have been inconclusive, but have shown an insignificant trend to better OS and PFS with intraperitoneal therapy. The accrual to studies has been poor reflecting that intraperitoneal therapy is a cumbersome and not easily accepted procedure.

Intraperitoneal chemotherapy in advanced ovarian cancer

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	1/465	1/546	1/113	3/1 124
Total	1/465	1/546	1/113	3/1 124

*For abbreviations, see above.

ROLE OF DOSE INTENSITY WITHOUT CYTOKINE OR BONE MARROW SUPPORT

The seminal article by Levin & Hryniuk (119) started the dose-intensity (delivered dose in mg/m^2/week) debate among oncologists. Levin & Hryniuk made a retrospective study on the relationship between outcome and planned dose intensity for first-line chemotherapy of advanced ovarian cancer. They analysed 65 groups of patients from 33 randomised trials and a few other studies. A positive correlation between the dose-intensity for combination and P chemotherapy and clinical response and median survival time was found. This relationship could not be verified for other drugs than P. In a later update with addition of 18 regimens from nine new randomised trials (120), the former results were confirmed and a borderline relationship also for A in multi-agent regimens was found. Multi-agent regimens containing A produced greater RRs than P alone for any fixed dose intensity for P. None of the multi-agent regimens incorporated A at a relative dose intensity for which the drug has been found to be effective as single agent. A dose-intensity relation was found both for A and for alkylating agents as single drugs but not in combinations. However, the variations in dose were small in the few studies with A as a single-drug and also in studies with alkylating agents.

It is important to realise, however, that the relative dose-intensities for P ranged from 0.4 to 1.7 with the standard dose at 15 mg/m2/week (corresponding to a relative dose intensity of 1.0). This means that these studies to a great extent compared under-dosing with adequate dosing. In vitro-studies suggest that a dose escalation in the range of 5 times is needed to overcome relative platinum resistance (121). The correlations were rather weak. The majority of patients were suboptimally debulked with stage III or IV disease. Dose intensity and total dose were not separately analysed. For many regimens a higher dose-intensity also meant higher total dose. The end point was RR and median survival time. RR is not necessarily predictive of survival (122) and median survival need not be correlated to long-term survival.

Repetto et al. (123) studied how the actually received dose intensity within two randomised trials (56, 93) affected RR and median OS and PFS. They found no statistically significant differences and concluded that modest dose modifications and brief treatment delays during first-line platinum-based chemotherapy do not affect RR, OS and PFS in patients with advanced ovarian cancer. The statistical power of these comparisons is low.

Randomised trials on platinum dose-intensity

The above-mentioned retrospective studies (119, 120) initiated several prospective randomised studies on dose-intensity in ovarian cancer (62, 124–128). The first prospective study showing a relationship between dose-intensity and OS came from the Hong-Kong Ovarian Carcinoma Study Group (128). It was a small study with a heterogeneous patient population also including some patients with progression after first-line treatment. An update was presented at the IGCS in 1999 (129). The OS at ten years were 48% for patients in the high-dose arm compared with 14% in the low-dose arm ($p = 0.008$). In a multivariate analysis, only residual disease after operation and dose were independently significant prognostic factors.

The next study was published by the Scottish Gynaecology Cancer Trials Group (126), which included 191 pa-

tients (159 eligible, see below) with stage IC–IV disease, optimally and non-optimally operated, randomised to C 750 mg/m^2 in combination with P 50 mg/m^2 vs C 750 mg/m^2 in combination with P 100 mg/m^{2}q for three weeks in six cycles. The overall RR was 34% in the low-dose group and 61% in the high-dose group. An update of OS with a median follow-up time of 57 months was published later (130). The OS was better in the high-dose arm, with marginally statistical significance. The HR for OS was 0.68 (CI 0.46–0.99; p = 0.043). For patients with bulky disease (> 2 cm) it was 0.57 (CI 0.36–0.92; p = 0.02) and 0.88 (CI 0.48–1.62; p = 0.69) for patients with minimal residual disease. A test for the interaction between the dose effect and the presence of bulky disease was, however, not significant. Toxicity (nausea and vomiting, alopecia, myelo-, and neurotoxicity) was worse in the high-dose group. Only 69% of the planned therapy was given in the high-dose group compared with 92% in the low-dose group. There were no episodes of neutropenic fever and no deaths due to toxicity. The long-term toxicity was significantly higher in the high-dose group and there was a difference in the frequency and degree of neuro- and ototoxicity throughout the follow-up period.

The GOG group (127) randomised 485 patients (458 eligible) with suboptimally cytoreduced (> 1 cm) stage III and any stage IV invasive epithelial ovarian malignancies to low-intensity C 500 mg/m^2 and P 50 mg/m^2 vs high-intensity C 1000 mg/m^2 and P 100 mg/m^2 every third week. The low-intensity regimen was given for eight cycles and the high-intensity regimen for four cycles, resulting in the same total dose. This study thus tested dose-intensity only. The ratio between the median dose intensities was 1.97. There were no significant differences between overall clinical RR (55 and 60%), or pathological CR rate (29 and 27%) for high-intensity and low-intensity regimens, respectively. The median PFS was 14 and 12 months and median OS 21 and 20 months. Both PFS and OS curves were superimposable up to four years. The toxicity was significantly greater with more intensive therapy (most commonly renal, haematological, and otic). For two patients in the high-dose arm and one in the low-dose arm treatment toxicity may have contributed to death.

The GONO (124) randomised 145 patients (139 eligible) with FIGO stage III and IV disease, suboptimally cytoreduced (> 2 cm postoperative residual tumour) to six cycles of E 60 mg/m^2 and C 600 mg/m^2 and P 50 mg/m^2 vs the same combination but with P 100 mg/m^2 every fourth week. The patients in the high-dose arm received twice the total dose at doubled dose rate. The study was prematurely closed because an interim analysis showed more episodes of severe myelo-, neuro-, and nephrotoxicity in the high-dose arm. The overall objective RR was 58% in the high-dose arm and 61% in the low-dose arm. Clinical CR was 45% and 42%. Sixty-three patients were eligible for a second-look. There were no significant differences in pathologically confirmed RR. The curves for OS and PFS were superimposable with 29 and 24 months median OS and 18 and 13 months median PFS for high-dose and low-dose, respectively.

The DACOVA Group (62) randomised 222 patients with stage II–IV disease to cP AUC = 4 vs AUC = 8 according to Calvert's formula (101) together with C 500 mg/m^2 every fourth week for 6 cycles. Both dose-intensity and total dose were varied. The frequency of pathologic CR was 15 and 16% with all included patients as denominator and 30 and 32% with performed second-look operations as denominator. The median OS was 19 months in both arms and the five-year OS was 24 and 27% for the high-dose group and low-dose group, respectively.

Colombo et al. (131) randomised 306 patients with stage III and IV disease to low-intensity P 75 mg/m^2 every third week for 6 cycles vs high-intensity 50 mg/m^2 weekly for 9 cycles. The total dose was similar with double dose-intensity in the high-intensity arm. About 45% of the patients were stage III with small postoperative residual volumes. More toxicity was registered in the high-dose arm. No significant differences could be found in pathologic CR rate (24% and 28%) or median PFS (21 and 18 months) or median OS (36 and 33 months) for high- and low-dose-intensity, respectively.

Cocconi et al. (132) randomised 101 patients between P 100 mg/m^2 every third week for 6 cycles and 100 mg/m^2 every week for two triplets of three cycles separated by a five-week interval. Additionally, patients in both arms received four cycles of AC. The clinical CR rates were 22% and 14% and PR rate 55% and 48% giving an overall RR of 77% and 62% for high-dose and low-dose respectively (not significant). With a median follow-up of 9.7 years, the survival curves were similar for the first two years but diverged thereafter, albeit not significantly, in favour of the high-dose arm (p = 0.07). The five-year OS was 12% and 30%, respectively. The study was fairly small and the differences, although pointing to an advantage for the high-dose arm, were not statistically significant.

Gore et al. (125) randomised 227 patients with stages II–IV or relapsed stage I ovarian cancer to cP AUC = 6 every fourth week for 6 cycles vs cP AUC = 12 every fourth week for 4 cycles. Both dose-intensity and total dose varied. The RRs were similar, 64% (CI 53–75%) and 55% (CI 43–67%) with clinical CR rate 32 vs 31%. There were no statistically significant differences in PFS or OS between the arms. Subgroup analysis of optimally vs non-optimally operated patients showed no evidence of improved survival for the high-dose group. In a multivariate analysis, treatment was not a significant factor and the HRs 1.11 (CI 0.79–1.57; n.s.) regarding PFS and 1.18 (CI 0.79–1.77; n.s.) for OS actually favoured the low-dose arm. The haematological toxicity was significantly increased in the high-dose arm. Seventy-five per cent of the patients in the high-dose arm required one or more platelet transfu-

sions vs 1% in the low-dose group. Significantly more blood was transfused to the high-dose patients. Grade 3–4 infections were registered in 10% vs 0% and median days spent in hospital were 19 vs 0. There was no non-haematological toxicity in the low-dose arm and few in the high-dose arm (< 3%).

Thus, there are three positive studies (126, 128, 132). These three studies have randomised 101, 159 and 50 eligible patients. One reason for the partly conflicting results could be that some studies vary only dose-intensity and thus give rather few cycles of chemotherapy in the dose-intensity arm. The positive Scottish study (126) varied both dose intensity and total dose. It has also been discussed if an effect is more likely in patients with optimal tumour reduction but this hypothesis was not supported by subgroup analyses in the Scottish study (130) and the study of Gore et al. (125). Most of the negative studies have comparatively low power, which means that although the results show no differences the studies cannot rule out that small differences between the treatment alternatives could exist.

The literature shows that:

- There is no convincing support for a survival benefit from dose-intensification (notably of cisplatin) within the 'standard' range in advanced ovarian cancer. Neither is there any subset of patients that seems to benefit.
- Retrospective data and one randomised trial (44) suggest that under-dosing is detrimental.

The role of dose-intensity

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	6/1 511	2/151	–	8/1 662
Total	6/1 511	2/151	–	8/1 662

*For abbreviations, see above.

HIGH-DOSE CHEMOTHERAPY WITH BONE MARROW SUPPORT

High-dose chemotherapy with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell-support (PBSC) has only been evaluated in phase II studies, mostly in heavily pre-treated patients. Only in a few studies has the therapy been given in the first-line situation. The high-dose approach leads to high RR, but in the salvage situation there is unfortunately still short duration of response. Horowitz et al. (133) reported at ASCO 1997 that 421 patients were registered in the Autologous Blood and Marrow Transplant Registry-North America (ABMTR) as having received autotransplants for ovarian cancer from 1989–1996. ABMTR collects information from 40–50% of all transplant centres in North America. Median age was 48 years, which should be compared with between 60–70 for ovarian cancer patients in general (134). Sixty-seven per cent had chemosensitive disease pretransplant, 28% resistant, and 5% unknown. Half of the patients were in CR prior to transplant. One hundred-day mortality was 11% and two-year transplant-related mortality 14%. The overall RR was 63% with 42% CR. Two-year estimated OS was 37% (CI 30–44%) for the total patient material, and 51% (CI 37–65%) for patients with CR pretransplant, 29% (CI 10–48%) for those with SD, and 10% (CI 0–21%) for those with PD ($p < 0.0001$). Overall estimated PFS at two years was 15%. There was no difference between different high-dose regimens. Age, performance score, non-clear cell histology and platinum sensitivity were prognostic factors. Considering that this is a selected patient population, the figures do not suggest any dramatic difference between high-dose chemotherapy and conventional salvage therapy.

The present status of high-dose chemotherapy highlights the problem that when a technically advanced and expensive treatment, attractive to both doctors and patients, becomes available it will be used. If the medical society cannot provide data from clinical trials timely, the risk is that the therapy becomes established, without supporting evidence, and it will then be hard to recruit patients to controlled clinical trials.

A possible place for high-dose chemotherapy could be in the first-line situation with curative intent or as consolidation therapy in responders to induction chemotherapy with minimal residual disease. Several randomised studies of first-line therapy have started.

The literature shows that:

- Controlled data supporting survival benefit from high-dose chemotherapy with haematological stem cell support are lacking. High-dose chemotherapy with ABMT or PBSC should only be used within controlled clinical trials.

High dose chemotherapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
R	–	1/421	–	1/421
Total	–	1/421	–	1/421

*For abbreviations, see above.

SALVAGE CHEMOTHERAPY

A high proportion of patients (60–80%) with advanced ovarian epithelial cancer respond to first-line chemotherapy. Unfortunately, most of these patients (about 70%) will later have disease progression and thus be candidates for second-line chemotherapy. No study has compared rechallenge with chemotherapy with best supportive care; hence the impact of salvage chemotherapy on survival and QoL is largely unknown.

The probability of response to second-line therapy is heavily dependent on the response and temporal relation to previously given chemotherapy. The possibility of response gets progressively higher with longer progression-free interval (135, 136). These relations are best studied after platinum-based therapies but probably apply to chemotherapy of ovarian cancer in general. The following clinical definitions for predicting the susceptibility to chemotherapy are generally agreed on (137). Patients who progress or have stable disease during chemotherapy have drug-refractory disease (to the administered drugs), and those who, after response to previously given chemotherapy, have verified disease progression within less than six months after the completion of previous chemotherapy are considered to have drug-resistant disease. Patients with response to the most recently given drug regimen and disease progression more than six months after completing previous drug regimen, on the other hand, are considered to have potentially drug sensitive disease. The probability of response is also markedly dependent on the number of preceding chemotherapy regimens. Third- or fourth-line chemotherapy has very low RRs. However, unique patients responding to multiple rechallenges with even the same kind of chemotherapy are sometimes observed. A large study of predictors of response to salvage therapy in ovarian cancer (138) shows that tumour burden (as assessed by size of the largest lesion and number of disease sites) and histology (serious histology best) are independent predictors of response to salvage therapy. Time from last treatment had no independent predictive value and was highly correlated with tumour size. It is imperative that studies of salvage therapies define the patient characteristics in these respects.

The first sign of progression is usually heralded by a rise in the serum levels of the tumour marker CA-125 (139). This can give a lead-time before clinical detection of a relapse of typically two to four months, but occasionally, years. It has not, however, been shown that immediate chemotherapy at the time of a CA-125-rise in patients without objectively detectable disease leads to better results than chemotherapy initiated when objective verification of progression can be made. A prospective randomised study organised by the British MRC is aimed at studying the question whether to give immediate salvage therapy when CA-125 increases, or to wait and treat symptomatic disease. Tamoxifen has been proposed as a non-toxic alternative for patients with epithelial ovarian cancer with increased CA-125 as the only sign of disease (140, 141).

In patients with initially platinum sensitive tumours and long treatment-free interval several chemotherapy agents show significant antitumour activity with notably high RRs also to the drugs that were included in first-line treatment. In patients with chemosensitive disease there is as yet no evidence that retreatment with the same drugs (e.g. platinum compounds, taxanes) that were used primarily is inferior to using drugs not given primarily. Thus, given the supposedly palliative effect from tumour regression, retreatment with a platinum compound alone or in combination with a taxane is often recommended. However, it should be observed that this recommendation is mainly based on non-comparative data. The median progression-free interval in responding patients is typically four to six months. The median OS time is around nine to ten months, and about 10% of the patients experience long-term survival (43). In patients with disease refractory/resistant to first-line therapy, the availability of non-cross-resistant drugs would be of importance. However, RRs generally tend to be low in this setting which points to the fact that true non-cross-resistant drugs have not yet been developed.

A number of uncontrolled phase II trials indicate RRs mostly in the range 10–30% in the salvage situation, e.g. for single agent altretamine (136, 142–146), topotecan (147–150), paclitaxel (43, 97, 151–166), docetaxel (167, 168), etoposide (169–173), liposomal doxorubicin (174), and gemcitabine (175, 176). Paclitaxel and topotecan have been licensed by the Swedish Medical Products Agency for second-line single drug treatment of advanced ovarian cancer. For paclitaxel the licensing was based on high RRs observed in phase II trials in patients treated after failure of cisplatin.

In a randomised multicentre comparative trial in patients progressing during or after a platinum-based regimen, topotecan was compared with T in 226 patients; topotecan was administered at 1.5 mg/m^2 daily for five days and T at 175 mg/m^2 for three h every three weeks (147). RRs tended to be better for topotecan than for T; 13 vs 7% ($p = 0.3$) in platinum-resistant and 29% vs 20% ($p = 0.2$) in platinum-sensitive patients and median time to progression was statistically significantly longer for topotecan; 23 vs 14 weeks ($p = 0.002$) whereas median OS did not differ significantly; 61 vs 43 weeks ($p = 0.52$).

Almost all data in the literature on the efficacy of salvage chemotherapy in ovarian cancer derive from, mostly small, uncontrolled phase II trials, often with patients being heterogeneous with respect to prognostic factors. The considerable ranges of tumour RRs observed will depend on baseline prognostic factors making it difficult to compare data across studies. There are no published randomised controlled trials supporting combinations over

single-drug chemotherapy in the relapse situation. From an evidence-based medicine perspective, the literature provides little guidance on second-line treatment of platinum resistant ovarian cancer, although the favourable outcome for topotecan over paclitaxel should be observed. Thus, inclusion of these patients into well-designed controlled trials is recommended.

The literature shows that:

- Controlled data supporting a survival benefit from salvage chemotherapy over supportive care alone are lacking.
- The RRs to salvage chemotherapy might be high in patients with a progression-free interval over six months since the end of first-line platinum-based chemotherapy and response to this therapy. Given the supposedly palliative benefit from tumour regression, therapy is recommended for the drug-sensitive patients. The first choice in patients who have received platinum and/or paclitaxel in first-line treatment and have chemosensitive disease is retreatment with platinum as single-drug or in a combination with paclitaxel. However, the scientific basis for this recommendation is limited.
- In patients with platinum-resistant disease, the expected response rates are low and the literature provides no convincing guidance for the choice of treatment. These patients should preferably be included in controlled clinical trials.

Salvage chemotherapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	1/226	–	–	1/226
P	33/3 264	–	–	33/3 490
Total	34/3 490	–	–	34/3 490

*For abbreviations, see above.

LITERATURE

The articles included in the reference list were classified and graded as follows:

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
M	3/11 035	2/6 256	–	5/17 291
C	24/10 755	7/1 323	2/262	33/12 340
P	35/3 525	1/68	–	36/3 593
R	–	1/421	–	1/421
Total	62/25 315	11/8 068	2/262	75/33 645

*For abbreviations, see above.

* Studies that provide background information
** Studies that were included in the meta-analyses by the Advanced Ovarian Cancer Trialists Group (refs 45 and 84) and A'Hearn & Gore (ref 96)
*** Studies that were included in the meta-analyses by the Ovarian Cancer Meta-Analysis Project (refs 74 and 150)

Most studies marked ** or *** in reference list were not evaluated and graded individually because they were included only as part of the meta-analyses. They were, however, considered as fulfilling the quality requirements of the meta-analyses. In the meta-analyses it was strictly not the original results that were used since follow-up has been updated, and methodological corrections made (e.g. re-inclusion of wrongly excluded patients after randomisation, analysis according to intention-to-treat principle etc). For completeness they were included in the reference list.

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