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Improving outcome in the first-line management of advanced ovarian cancer

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ABSTRACT

Carboplatin plus paclitaxel is the standard first-line chemotherapy for ovarian carcinoma. Primary debulking surgery is likely to remain the standard of care for advanced disease until results from the EORTC trial on neoadjuvant chemotherapy are available. A number of methods of improving chemotherapy treatment have been investigated. However, few trials have been conducted and insufficient data collated to date to support intraperitoneal (IP) delivery as standard first-line chemotherapy, in part due to concerns over potential toxicity. There is an unmet need for an appropriate IP trial (preferentially with carboplatin) for comparison with intravenous carboplatin and paclitaxel. Triplet or sequential doublet combinations have similarly not yet shown any advantage over standard doublet therapy. There is also insufficient evidence to date that maintenance therapy following standard chemotherapy improves overall survival. However, it is hoped that current trials examining tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors and other multi-targeted biological agents will yield promising options for concomitant use with first-line chemotherapy or as maintenance therapy.

1. Introduction

More women die from ovarian cancer in the developed world than any other gynaecological cancer [1]. The current recommended standard for treating advanced ovarian cancer is debulking surgery to remove all macroscopic tumour tissue, followed by chemotherapy using six courses of carboplatin area-under-the-curve (AUC) 5–7.5 combined with paclitaxel 175 mg/m^2, for 3 hours every 21 days. This consensus standard was agreed between thirteen cooperative groups at the *Third International Ovarian Cancer Consensus Conference of the Gynecologic Cancer Inter Group* (GCIG) in 2004 [2]. However, data from the International Collaborative Group for Ovarian Neoplasia (ICON)-3 trial indicated that carboplatin can be used alone under some conditions, having a similar efficacy but lower toxicity than when combined with paclitaxel [3]. The management of ovarian cancer may also be improved by using other regimens and schedules, and these will be reviewed.

2. What is the role of neoadjuvant chemotherapy?

At present, the standard treatment of primary debulking surgery followed by chemotherapy still stands. In future,

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there may be a role for neoadjuvant chemotherapy, which is currently being assessed in the European Organization for Research and Treatment of Cancer (EORTC) trial. The study, which compares primary debulking surgery with neoadjuvant chemotherapy followed by interval debulking and platinum-based chemotherapy, is almost ready to close (as of late 2006) having enrolled 704 of 720 patients.

3. Triplets and sequential doublets

Does a triplet or sequential doublet combination incur any therapeutic advantage over standard doublet therapy? Three trials have looked at adding an anthracycline to the carboplatin (AUC 5–6) plus paclitaxel (175 mg/m^2) standard. In the Arbeitsgemeinschaft Gynäkologische Onkologie–Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (AGO-GINECO) trial, epirubicin 60 mg/m^2 was added to the standard regimen [4], while in the Nordic Society of Gynecologic Oncology–EORTC–National Cancer Institute of Canada (NSGO-EORTC-NCIC) study epirubicin was added at a dose of 75 mg/m^2 [5]. Both triplet studies proved negative for overall survival (OS) advantage. Pegylated liposomal doxorubicin 30 mg/m^2 has also been added every other course to standard therapy as a triplet in the Gynecologic Oncology Group (GOG)-182-ICON trial [6]. In this trial the progression-free survival and OS were not improved compared with carboplatin plus paclitaxel. The other three arms of the GOG182-ICON study were standard chemotherapy plus gemcitabine and two sequential arms. The first sequential treatment consisted of four cycles of carboplatin AUC 5 (day 3) plus topotecan 1.25 mg/m^2 (days 1–3), and the second sequential treatment of four cycles of carboplatin AUC 6 (day 8) plus gemcitabine 1000 mg/m^2 (days 1, 8). Both sequential treatments were followed by four cycles of standard chemotherapy. The trial closed in 2004 with 4312 patients enrolled. Preliminary OS data did not show any survival advantage in the experimental arms. Median progression-free survival (PFS) was 15.4–17.5 months (hazard ratios [HRs]: 0.94–1.07 months); 81% completed therapy, 4% progressed and 9% discontinued treatment due to toxicity. The expected haematological toxicity was related to the dose intensity of the regimen, and there were at least 42 treatment-related deaths (<1%) [6].

Meanwhile, another study has been conducted based on results of a phase II study that assessed sequential doublets of cisplatin plus topotecan followed by paclitaxel plus cisplatin [7]. The NCIC–EORTC–Grupo Español de Investigación en Cáncer de Ovario trial, which has recruited more than 800 patients, is investigating a schedule randomising patients either to eight 21-day cycles of standard regimen, or to treatment incorporating the topoisomerase inhibitor topotecan. In the latter arm, patients are administered four 21-day cycles of cisplatin 50 mg/m^2 (day 1) plus topotecan 0.75 mg/m^2 (days 1–5), followed by the standard carboplatin plus paclitaxel regimen for four 21-day cycles. This study has closed and results are due in 2007.

Another triplet was assessed in the phase III AGO-OVAR-9-GINECO-NSGO study. Here, gemcitabine 800 mg/m^2 (days 1, 8) was administered in combination with the standard carboplatin plus paclitaxel regimen and randomised against the standard regimen itself. The trial closed in 2004 with 1720 patients enrolled and results will be available in 2007 [8].

A further ongoing phase III trial is comparing gemcitabine 1000 mg/m^2 (days 1, 8) plus carboplatin AUC 5 (day 1) with the standard carboplatin plus paclitaxel regimen, both every 21 days, for six cycles. The target accrual for this trial is 1208 patients and approximately 800 patients have been enrolled to date.

4. Incorporation of docetaxel into front-line therapy

Briefly, it is known from the Scottish Randomised Trial in Ovarian Cancer (SCOTROC), which involved approximately 1100 patients, that there was no clinically relevant difference in PFS or OS between docetaxel plus carboplatin and paclitaxel plus carboplatin regimens. The docetaxel plus carboplatin combination led to a higher rate of neutropenic fever (11%), but showed less neurotoxicity than observed with the carboplatin plus paclitaxel combination [9].

5. Assessment of intraperitoneal chemotherapy studies

The rationale for using intraperitoneal (IP) rather than intravenous (IV) administration in treating ovarian cancer is that the peritoneum, the predominant site of the tumour, can receive sustained exposure to high concentrations of anti-tumour treatment while normal tissues, such as the bone marrow, are relatively spared [10]. Three studies have compared IP and IV administration of chemotherapeutic combinations (Table 1).

5.1. The Alberts study

The study by Alberts et al. [11] compared cisplatin (IV) plus cyclophosphamide (IV) with cisplatin (IP) plus cyclophosphamide (IV), and demonstrated a statistically significant survival advantage among patients treated with IP chemotherapy: HR for OS was 0.72 (0.61–0.96); P = 0.02. However, there was a higher rate of abdominal complications in the IP than the IV regimen, and only 58% of patients received the planned six courses of IP cisplatin. Moreover, in the group where the greatest impact was expected, i.e., those with minimal residual

Table 1 – Trial schedules of regimens comparing IP and IV modes of administration [a]

Study	Design	No. of patients	Hazard ratio	OS
SWOG/GOG-104 (Alberts et al. [11])	Cisplatin 100 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV vs. Cisplatin 100 mg/m^2 IP + Cyclophosphamide 600 mg/m^2 IV	546	0.72 (0.61–0.96)	P = 0.02
GOG-114/SWOG (Markman et al. [12])	Cisplatin 75 mg/m^2 IV + Paclitaxel 135 mg/m^2 (24 hr) IV vs. Carboplatin AUC 9 IV q 28 d × 2 + Cisplatin 100 mg/m^2 IP + Paclitaxel 135 mg/m^2 (24 hr) IV	462	0.81 (0.65–1.0)	P = 0.05
GOG-172 (Armstrong et al. [10])	Cisplatin 75 mg/m^2 IV + Paclitaxel 135 mg/m^2 (24 hr) IV vs. Paclitaxel 135 mg/m^2 (24 hr) IV + Cisplatin 100 mg/m^2 IP + Paclitaxel 60 mg/m^2 IP on day 8	415	0.71 (0.58–0.97)	P = 0.03

[a] Abbreviations: OS, overall survival; IV, intravenous; IP, intraperitoneal; AUC, area-under-the-curve.

disease (<0.5 cm), there was no significant observed difference (P = 0.10).

5.2. *The Markman study*

In another medium-sized study, by Markman et al. [12], carboplatin (IV) was administered in the experimental arm followed by cisplatin (IP) and paclitaxel (IV) and compared with IV cisplatin and paclitaxel. There was a significant difference in PFS, and a borderline significant difference in OS: HR = 0.81 (0.65–1.00); P = 0.05. This study was difficult to assess because the cisplatin dosage differed between treatment arms (100 mg/m^2 in the IP group compared with 75 mg/m^2 in the IV group, both every 3 weeks for six cycles). The IP-chemotherapy group was also treated to two cycles of intensive-dose IV carboplatin (AUC 9), which meant that the number of cycles and platin exposure was different, and probably made the IP chemotherapy regimen difficult to administer due to toxicity. The authors concluded that this schedule should not be recommended as a standard of care because of its toxicity and borderline benefit in OS.

5.3. *The Armstrong study*

Finally, a recently published phase III study by Armstrong et al. [10] compared IV cisplatin and paclitaxel with a regimen of IV paclitaxel followed by IP cisplatin and IP paclitaxel in patients with stage III ovarian cancer. This study showed a significant difference in OS between the treatment arms, with an HR for OS of 0.71 (0.58–0.97); P = 0.03. However, there were a number of problems with the trial design. A more complete analysis of the results, such as an intention-to-treat analysis, is needed and may show the outcome to be non-significant. Results show that the survival curves of the two treatment arms separate only after 15 months of therapy, indicating that the difference in OS measurements may well be explained by other factors (Figure 1).

The IP treatment group received far less IP cisplatin and paclitaxel than planned, but also a substantial number of patients received non-study therapy. For instance, 84 of 170 patients in the IP arm who received six cycles of treatment also actually received IV therapy. Of these, 44% received carboplatin plus paclitaxel instead of the more toxic paclitaxel and cisplatin regimen, which might have influenced the second-line therapy.

Toxicity

The IP regimen was also highly toxic. Of patients in the IP arm, 58% could not receive all six planned cycles, 8% did not receive any IP chemotherapy and 34% received only one or two IP regimens. There was significantly more grade III and IV toxicity for leucopenia, neuropathy, gastrointestinal infection, fatigue and pain ($P \leqslant 0.001$). Patients receiving the IP regimen had a worse quality of life during the first year than those receiving the IV regimen, which, in turn, was more toxic than the standard carboplatin plus paclitaxel regimen.

Inadequate trial design

Perhaps it could also be said that the design of the trial could have been improved. The study failed to ascertain whether IP was superior to IV chemotherapy because both the drug doses and schedules differed between treatment arms. The dose density of paclitaxel has been shown to be an important factor for efficacy in other tumour types such as breast cancer [13], and the same could be expected for ovarian cancer. IP cisplatin results in prolonged exposure. Therefore, less toxic regimens, including analogue drugs or continuous platinum infusions, could be studied instead of IP chemotherapy for a better outcome.

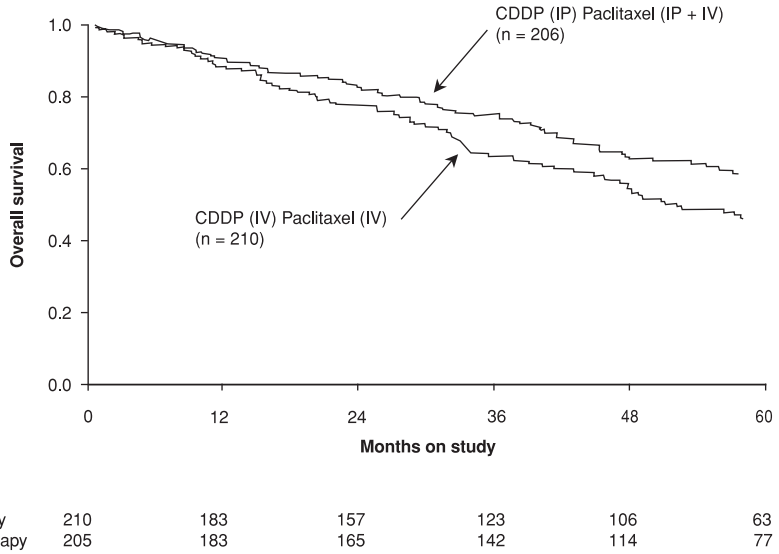

Fig. 1 – Overall survival between IP and IV regimens [10]. CDDP, cis-diamminedichloroplatinum; IP, intraperitoneal; IV, intravenous. Copyright © 2006 Massachusetts Medical Society. All rights reserved.

Based on the described evidence, women with ovarian cancer should not be subjected to IP chemotherapy outside the context of a properly designed clinical trial. In the meantime, there is an unmet need for an appropriate IP regimen and for guidelines on how IP chemotherapy could be integrated with targeted therapy in future trials [14].

6. Maintenance chemotherapy in ovarian cancer

There are several trials that use maintenance or consolidation therapy after standard chemotherapy. The AGO-GINECO group randomised patients to receive six cycles of paclitaxel and carboplatin followed by either four cycles of topotecan or surveillance [15]. The study concluded that the sequential addition of topotecan did not result in superior overall response, PFS or OS. Similarly, the MITO group randomised patients to receive standard therapy versus standard therapy plus four cycles of topotecan (1.5 mg/m^2 [days 1–5], every 21 days) and found no benefit for PFS [16]. An EORTC trial studied patients who had achieved complete remission after platinum-based intravenous chemotherapy. Patients were randomised to the treatment arm (four cycles of IP-administered cisplatin 90 mg/m^2) or received no further treatment. The study had to be closed prematurely because of poor accrual and the authors concluded that there was no difference in disease progression between the two groups [17]. Finally, a trial by Bolis et al. comparing four cycles of epidoxorubicin 120 mg/m^2 after standard chemotherapy versus observation also proved negative for complete response [18].

The only maintenance therapy study to yield a positive result was the phase III randomised trial by Markman et al. [19]. This trial investigated three versus twelve cycles of maintenance therapy with paclitaxel after complete response was achieved with platinum and paclitaxel-based chemotherapy. However, the trial lacked a non-treatment control arm and was prematurely closed because of a difference in progression-free survival. With the exception of peripheral neuropathy, there were no major differences in toxicity between the regimens. The median PFS was 21 and 28 months in the three- and twelve-cycle paclitaxel arms, respectively, and at study closure there was no difference in OS between treatment arms [19,20]. However, the authors questioned whether 7 months' improvement in PFS was sufficient to justify nine additional months of therapy and related toxicity without an improvement in OS [19]. Interestingly, an exploratory analysis strongly suggested an improvement in survival for patients who received twelve cycles of paclitaxel if the baseline CA-125 level was $\leqslant$10 units/ml, i.e., those individuals likely to have the smallest volume of clinically undetectable residual ovarian cancer when single-agent maintenance paclitaxel was initiated [20]. A follow-up trial, GOG-212, will provide further elucidation by including an observation arm, which will be compared with paclitaxel 175 mg/m^2 for 3 hours, every 28 days, for twelve cycles, or pegylated paclitaxel 175 mg/m^2 for 15 mins, every 28 days, for twelve cycles as the third arm.

7. Future directions for treating ovarian cancer

What does the future hold? Certainly, in the past 5 years many new drugs and biological agents have become available. These include chemotherapeutic agents such as the epothilones that stabilise microtubules, the antifolate drug pemetrexed and TLK286, a novel prodrug that is preferentially activated by glutathione S-transferase P1-1. Other agents include antibodies

directed against the epithelial cell adhesion molecule EpCAM and the monoclonal anti-idiotypic antibody ACA-125, which imitates the tumour-associated antigen CA-125; epidermal growth factor receptor inhibitors such as gefitinib, erlotinib and cetuximab; and vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab. Further agents include those of the c-erb family, e.g., trastuzumab, pertuzumab, lapatinib; farnesyl transferase inhibitors, e.g., lonafarnib; Raf-1 and MEK agents, and multiple-targeting agents such as enzastaurin, among many others.

Looking at trials of some of these agents for first-line therapy, erlotinib 150 mg/day is being investigated in a randomised GCIG EORTC-led study comparing 2-year maintenance following treatment with a platinum-based regimen versus observation. Target accrual is due in 2007.

Bevacizumab has resulted in interesting outcomes in colorectal, non-small-cell lung, breast and renal cell cancers, and in phase II trials in recurrent ovarian cancer [21]. However, in ovarian cancer, concerns have been raised due to the high frequency of bowel perforations observed during bevacizumab treatment. In the study by Cannistra et al., gastrointestinal perforations and bowel obstruction were both observed in 11% of patients [22]. This makes the use of this drug difficult when used in combination with primary and interval debulking surgery and in advanced recurrent ovarian cancer. Bevacizumab will be assessed in a phase III GCIG–Medical Research Council-led trial at a dose of 7.5 mg/m^2 together with paclitaxel 175 mg/m^2 and carboplatin AUC 6, every 21 days, for six cycles, followed by twelve cycles of maintenance treatment with bevacizumab every 3 weeks, and compared against the same regimen without bevacizumab.

Further studies, such as the three-armed GOG-218 trial, are under way. In this study, the bevacizumab dose is double that of the MRC-lead trial at 15 mg/m^2, and is administered concomitantly with cycles two to six of standard chemotherapy, and in a third arm additionally also as maintenance therapy for 14 months. This study began in 2005 and aims to accrue 2000 patients [23].

Another interesting drug, enzastaurin, selectively inhibits protein kinase C (PKC)-beta. PKC is involved in the regulation of key cellular processes such as cell survival and motility. It is an important mediator of the angiogenic action of VEGF. Furthermore, enzastaurin suppresses the PI3K/AKT pathway. The result is diminished tumour growth through multiple mechanisms: direct induction of tumour cell apoptosis, inhibition of tumour cell proliferation and inhibition of tumour-induced angiogenesis [24]. A randomised phase II trial following debulking surgery is due to start, in which enzastaurin combined with carboplatin and paclitaxel will be assessed against placebo plus paclitaxel and carboplatin.

8. Conclusion

Primary debulking surgery and carboplatin plus paclitaxel IV chemotherapy will remain the standard of care until the results of the EORTC trial on neoadjuvant chemotherapy are known. Although trials have investigated IP regimens, the risks associated with their use may overshadow any benefits for standard first-line chemotherapy. Similarly, maintenance therapy has shown no proven effect on OS to date but it is hoped that future multicentre phase III trials including tyrosine kinase inhibitors, VEGF inhibitors and anti-angiogenic agents, among others, may yield a promising future.

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