Review

Pros and Cons of Intraperitoneal Chemotherapy in the Treatment of Epithelial Ovarian Cancer*

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Abstract. *Development of the pros and cons of intraperitoneal (IP) chemotherapy in the treatment of epithelial ovarian cancer based on the most prominent data published on the evolution of IP chemotherapy and on experience with this therapeutic strategy in clinical routine. The literature published on IP chemotherapy in ovarian cancer between 1970 and 2008 was identified systematically by computer-based searches in MEDLINE and the Cochrane Library. Furthermore, a preliminary analysis of data recorded during an observational nationwide multicenter study of the Austrian AGO on IP-IV chemotherapy using the GOG-172 treatment regimen was performed. The literature review unequivocally revealed a significantly greater toxicity for IP than for intravenous (IV) cisplatin-based chemotherapy. However, according to a Cochrane meta-analysis, IP-IV administration of chemotherapy is associated with a 21.6% decrease in the risk for death. In agreement with earlier reports, the most frequently mentioned side-effects in the Austria-wide observational study were long-lasting neurotoxicity, abdominal pain, fatigue, gastrointestinal and metabolic toxicities, and catheter-related complications. Most of these toxicities were identified as mirroring the toxicity profile of high-dose IV cisplatin (≥100 mg/m^2). In some patients, the classic IP-IV regimen with cisplatin/paclitaxel was changed to an alternative schedule comprising carboplatin AUC 5 (d1) and weekly paclitaxel 60 mg/m^2 (d1, 8, 15) completely administered via the IP route. This treatment was better tolerated and quality of life was significantly less compromised. However, neutropenia and thrombocytopenia were the limiting side-effects of this IP regimen. In cases where optimal cytoreduction with residual disease ≤1 cm was achieved during primary surgery and disease was confined to the peritoneal cavity, IP chemotherapy should be given serious consideration, even at the expense of significantly increased, but manageable toxicity.*

Ovarian cancer is the second most common gynecological cancer, with an incidence of about 15 cases per 100,000 women in Western countries and approximately 205,000 new cases and 125,000 deaths worldwide, annually (1). Depending on the stage of the disease, the standard treatment consists of staging or maximal cytoreductive surgery followed by platinum-based chemotherapy. Although response rates to conventional first-line chemotherapy are high, five-year overall survival remains unacceptably low. Therefore, alternative therapeutic strategies including novel cytotoxics and so-called "small molecules" for targeted therapies, but also new treatment modalities such as changes in the route of drug administration are clearly warranted to improve survival of ovarian cancer.

As ovarian cancer generally remains confined to the abdominal cavity throughout its course and randomized trials have shown the superiority of partial intraperitoneal (IP) over conventional intravenous (IV) chemotherapy in

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optimally debulked patients (2-4), in the last three years the route of administration of cytotoxic agents became a subject of major debate in the treatment of ovarian cancer (5, 6).

Given the relevant number of open questions regarding IP chemotherapy in the treatment of ovarian cancer, a systematic review of the literature is warranted to provide information on evidence-based practice and to supplement these data with experience obtained in three years of daily clinical practice without the general restrictions of predefined inclusion and exclusion criteria of controlled clinical trials.

Arguments Supporting IP Chemotherapy in the Treatment of Ovarian Cancer

Pharmacokinetics. In more than 85% of ovarian cancer cases, dissemination of the disease remains confined to the peritoneal cavity. In these cases, locoregional delivery of cytotoxic agents in the proximity of the tumor may be an appealing approach for treating advanced ovarian cancer. This concept has the three-part advantage of achieving significantly higher drug concentrations for a more protracted period of time without a proportional increase in systemic toxicity. However, earlier ovarian cancer studies revealed that the efficacy of IP treatment is highly dependent on the diameter of the tumor nodules or plaques, with best responses in disease not exceeding 0.5 cm in diameter (2, 7). Limitations of drug penetration *ab externis* to the central part of the tumor have been understood to explain this phenomenon. Thus, at the International Consensus Meeting on IP Chemotherapy held in Innsbruck in February 2006, optimal surgical debulking resulting in residual disease ≤1 cm in diameter was stated to be a major prerequisite before IP chemotherapy is justifiable (8).

Improved clinical outcome. In a Cochrane meta-analysis performed by Jaaback and Johnson, 4 and 6 randomized studies comparing IP-IV *versus* IV chemotherapy in ovarian cancer were eligible for evaluation of disease-free and overall survival, respectively (9). Only one of these studies, the Taiwan Study with 118 patients enrolled, revealed a non-significant trend for inferior outcome in survival for patients treated with IP-IV chemotherapy (10). Overall, the meta-analysis revealed significantly improved disease-free and overall survival for patients treated *via* the IP-IV route, resulting in a 21.6% decrease in the risk for death (9). Survival benefit was most meaningful in the three largest phase III studies conducted in the United States, each enrolling more than 400 patients. The last of these three studies, the GOG-172 trial, was published in January 2006 and compared the standard arm of IV paclitaxel over 24 h followed by cisplatin on day 2 with IV paclitaxel over 24 h followed by IP cisplatin on day 2 and IP paclitaxel on day 8. Median progression-free survival was 23.8 months in the IP arm *versus* 18.3 months in the IV group, and median overall survival was 65.6 *versus* 49.7 months in the IP and IV arms, respectively (4). These GOG-172 results together with the consistent results of the two previous US studies led the NCI to issue a clinical alert in January 2006, recommending that women with stage III ovarian cancer who underwent optimal surgical cytoreduction (residual disease: ≤1 cm) should be considered for IP chemotherapy.

Arguments Against IP Chemotherapy in the Treatment of Ovarian Cancer

Data weaknesses. Some weaknesses in the data gave rise to scepticism in the community that study results were not mature for implementation of IP chemotherapy in clinical practice (6). Firstly, with the exception of the SWOG/GOG-104 study performed in 546 patients and published by Alberts *et al*., the trials were not purely tests of the IP administration route, but a number of other variables such as scheduling and doses per cycle were simultaneously changed and thus not identical for the control and the study arms (2-4). A further objection is surely that the control arms did not reflect the current standard of care. Although the control arms indeed represented the standard of care at the time each trial was designed, the standard of care in clinical practice changed during the course of the studies. The use of cisplatin instead of carboplatin plus paclitaxel could have inflated the benefit of the IP arm in the GOG-172 trial. Although no statistically significant differences between the two IV regimens (cisplatin-paclitaxel *versus* carboplatin-paclitaxel) were demonstrated in the GOG-158 or the German AGO trials, there was a clear trend for improved survival for the carboplatin-paclitaxel arm (11, 12). Overall, this tempted a considerable part of the community of gyneco-oncologists to speculate that the GOG-172 trial IP-IV arm would not have significantly outperformed the IV arm if the control arm had been carboplatin-paclitaxel.

Furthermore, some of the sceptics argued that it was not the route of drug administration but scheduling in terms of the additional paclitaxel given at 60 mg/m^2 *via* the IP route on day 8 that was decisive in explaining the large survival advantage seen for the IP-IV arm in the GOG-172 trial (6, 8). In accordance with this argument, at the 2008 ASCO meeting, the Japanese Gynecologic Oncology Group reported a phase III trial in first-line IV chemotherapy with in depth changes in paclitaxel scheduling in the experimental arm (13) that appears to reinforce the view that scheduling independently of the route of drug administration increases the efficacy of primary chemotherapy in ovarian cancer. This Japanese study randomly assigned 637 patients to receive carboplatin (AUC 6) with either paclitaxel at 180 mg/m^2 on day 1 or paclitaxel at 80 mg/m^2 on days 1, 8 and 15. Treatments were repeated every three weeks for six cycles.

After a median follow-up of 29 months, median duration of DFS in the standard three-weekly chemotherapy group and the experimental dose-dense group was 17.1 and 27.9 months, respectively (p=0.0014) and overall survival at two years was 77.7% and 83.6% , respectively (p=0.048) (13).

In addition, with regard to the GOG-172 trial, the question remains unanswered as to how the considerably higher benefit of 15.9 months in overall survival can be explained in light of the modest disease-free survival advantage of 5.5 months, which was of only borderline statistical significance (p=0.05). Should this be interpreted such that primary IP treatment has modest activity in avoiding the first recurrence in ovarian cancer but thanks to undefined long-term phenomena enables prolonged survival, or is there a certain bias (*e.g.* for second-line treatment) between the control and the experimental arms?

Toxicity. Besides the significant improvement in survival, the clinical NCI announcement also mentions that IP chemotherapy is associated with increased toxicity, although this is short-term and manageable. Indeed, because of intolerance and toxicities in the three US studies mentioned, only 42% to 71% of the enrolled women completed the planned six cycles of IP-IV therapy. The most common reasons for discontinuation of IP treatment were catheter-related complications, abdominal pain, fatigue, gastrointestinal and metabolic toxicities (14). In the Austria-wide observational study that focused on the administration of IP-IV chemotherapy under daily routine conditions the aforementioned adverse events were also among the most frequently recorded acute side-effects, but did not necessarily prompt discontinuation of IP therapy. However, it seems worth reporting that in two of the 71 patients included in that study, a "leaky vaginal cuff" was the reason for discontinuation of treatment. Concerning catheter-related complications in terms of blockades and secondary infections, the reported frequency remarkably varies from study to study. This may be due to wrong choice of catheter and inadequate management of the port system during the whole period of IP therapy. A classical vascular-access silicon catheter is preferable for IP placement. Nonetheless, in this series complications in terms of obstructions and leakage in the port system were observed, especially at the beginning of the study, in 22% of the patients. Furthermore, it is felt that adequate management under sterile conditions before tapping the reservoir with a Gripper needle during the period of repeated IP administrations is the most important prophylaxis to avoid secondary infections of the catheter system and subsequent peritonitis. Catheter placement during primary surgery was avoided in cases in which large bowel resections were performed and instead delayed placement to three weeks later. Indeed, due to these rigorous measures, no catheter-related infections were recorded during an observation period of three years. The frequently registered symptom of abdominal pain and discomfort during and after IP drug administration can easily be improved or eliminated by adapting the IP-delivered fluid to the patient's physique, namely in asthenic patients, the volume of instilled fluid should be reduced from 2 to 1.5 litres. It is noteworthy that in the observational Austrian AGO study a steeply increasing learning curve was evident for proper catheter placement and the management of complications with IP administration.

In addition, it should be emphasized that myelotoxicity in IP-IV chemotherapy should not be underestimated, because neutropenia grade 3-4 was the most common side-effect registered in 80% of the patients and the most frequent cause of delay or omission of IP paclitaxel administration on day 8. A further important issue is the significantly higher degree of neurotoxicity associated with IP-IV chemotherapy. From the records obtained from the Austrian observational trial, which adopted the GOG-172 protocol, it was seen that the data reported by others (14) must be fully underscored and that the severity of neurological toxicity and the long-lasting character of this side-effect by far exceeded one year, deserving special emphasis. So far, observations on neurotoxicity stand in sharp contrast to the NCI clinical announcement, namely that the increased toxicity associated with IP-IV chemotherapy is short-term and manageable. Neurotoxicity is neither short-term, nor is it easily manageable. However, neurotoxicity, just as other relevant side-effects such as nausea, vomiting and metabolic toxicities reported for IP-IV chemotherapy, appears to mirror the toxicity profile of high-dosed (≥100 mg/m^2) IV cisplatin therapy and is not primarily a consequence of the route of drug administration. The higher incidence and greater severity of neurotoxicity reported for the IP-IV arm by some studies were obviously due to the lower doses of cisplatin administered in the respective IV control arm. The only large trial comparing cisplatin at an identical dose of 100 mg/m^2 in the experimental IP arm as well as the IV control arm was the SWOG/GOG-104 study, and indeed that trial revealed significantly more neurotoxicity in the IV than in the IP-IV arm (2).

In fact, in the Austria-wide observational study 47 (66%) of the 71 enrolled patients completed IP-IV treatment as planned. However, only ten (14%) of the study patients received complete IP-IV therapy without any grade 3-4 adverse event being recorded.

Cost effectiveness. A comparison of the various study arms of the GOG protocols 172 and 158 was performed to evaluate the cost effectiveness of IP-IV (GOG-172), IV carboplatin-paclitaxel (GOG-158) and IV cisplatin-paclitaxel (GOG-172 and GOG-158) for adjuvant treatment of optimally resected stage III ovarian cancer. For this purpose survival data from the respective study arms were used and costs for treatment regimens and for supportive care related to grade 3-4 adverse effects were estimated from Medicare

reimbursement rates and the Agency for Healthcare Research and Quality Database. This retrospective analysis revealed that IP-IV chemotherapy is associated with a modest extension in quality-adjusted survival time, but is by far more costly than IV treatment. At a seven-year time horizon, especially when compared to IV carboplatin-paclitaxel, IP-IV cisplatin-paclitaxel therapy is not cost effective. However, IP-IV treatment becomes more cost effective when a longer time horizon (11.5 years or lifetime) is modeled, provided the survival benefit can be assumed to persist longer than the currently available seven years. However, at any time horizon, IP-IV treatment remains more expensive than IV therapy (15, 16). First of all, these analyses suggest that efforts to reduce the costs of IP-IV chemotherapy, such as the development of regimens with equal therapeutic efficacy but feasible in outpatients with a better toxicity profile, are urgently needed to improve the overall value of this treatment strategy.

Future Directions

As most of the side-effects mentioned, apart from those related to the catheter, appear to mirror the toxicity profile of cisplatin and are not primarily due to IP drug delivery, it is tempting to speculate that substitution of the better tolerated carboplatin for cisplatin in IP regimens could result in a more favourable therapeutic index for the IP treatment approach in ovarian cancer. In the IV setting of ovarian cancer treatment, three earlier large trials, namely the Dutch/Danish study, the German AGO study and the GOG-158 trial, documented similar efficacy for the use of carboplatin instead of cisplatin in combination with a taxane (11, 12, 17). However, the adoption of carboplatin for IP regimens has raised several pharmacokinetic concerns because of the inverse relationship between molecular weight and tumor penetration and the fact that the molecular weight of carboplatin is greater than that of cisplatin. Conversely, it must be remembered that a substantial fraction of carboplatin administered by the IP route will be systemically absorbed and reach the tumor *via* the blood stream. In fact, Fujiwara *et al*. reported excellent activity of IP carboplatin-based chemotherapy in the first-line treatment of ovarian carcinomas, provided that the given dose of carboplatin is higher than 400 mg/m^2 (18). Ongoing clinical phase III trials are currently investigating the better-tolerated carboplatin as a principal compound in the IP setting (19, 20).

At the Department of Obstetrics and Gynecology Innsbruck, eight patients, because of either intolerance or their own preference, were switched from the GOG-172 IP-IV protocol to carboplatin-paclitaxel given exclusively *via* the IP route, where IP paclitaxel was given weekly at a dose of 60 mg/m^2 to avoid the abdominal pain observed when IP paclitaxel is given at doses above 175 mg/m^2. This regimen was by far better tolerated and quality of life was considerably less compromised. Surprisingly, the profile of side-effects was different from that usually observed for the combination of both drugs given intravenously. First of all, no hair loss and no hypersensitivity to paclitaxel were noticed, and neurological toxicity was evidently reduced under this regimen. However, myelosuppression was seen to be the most relevant adverse effect and in particular severe thrombocytopenia was dose-limiting. This toxicity profile is probably due to the poor absorption of paclitaxel into the systemic circulation as demonstrated by Krasner *et al*., who showed on the one hand that in plasma the initial peak concentration following IP paclitaxel administration was ten times lower than the peak measured after IV administration, but found on the other hand that the duration of plasma concentrations greater than 0.05 μmol/l, a threshold that has been associated with pharmacological effects of the drug, was longer for IP than for IV administration (21). Nonetheless, it remains uncertain whether the systemic paclitaxel concentrations obtained after IP delivery are sufficient to therapeutically access central regions of the tumor that are segregated from direct drug penetration. Obviously, achieved plasma paclitaxel concentrations are not sufficiently high to induce hair loss or to protect against carboplatin-induced thrombocytopenia.

The introduction of other cytotoxic agents such as topotecan or gemcitabine into IP regimens is under investigation, and encouraging results were recently reported from phase I and II trials (22-24). Furthermore, only a small number of reports deal with IP chemotherapy as salvage treatment for patients with persistent disease after first-line systemic chemotherapy or patients with small surgically accessible recurrences. A recent review of the literature on this topic by Gadducci and Conte concluded that IP chemotherapy should only be given to patients with small-size residual disease after second-look laparotomy; this results in surgically assessed response rates of approximately 30% and is associated with prolonged survival in a small subset of patients. It is, however, worth noting that consolidation IP chemotherapy does not seem to improve clinical outcome in complete responders after systemic first-line therapy as compared to no further treatment (25).

Discussion and Conclusion

Even though the list of cons appears to be larger than that of pros, the most significant endpoint in oncological therapies is certainly overall survival, and this should be decisive in the choice of treatment modality, even at the expense of greater toxicity. The Austria-wide observational study on IP chemotherapy in clinical routine revealed a steeply increasing learning curve for proper catheter placement, for the management of complications with IP drug delivery and

for treatment-related toxicities. Indeed, in this series 66% of the patients completed IP-IV chemotherapy as planned, which is a higher rate than that reported for the GOG-172 trial. It must be emphasized that the drop-out rate was significantly higher during the first six months of the study than in the last six months of that ongoing observational trial. Thus, the observations unequivocally advocate that if IP chemotherapy is indicated, it should be administered at referral centers experienced in the management of typical side-effects and complications. Nonetheless, substantial concerns about quality of life, technical difficulties associated with IP administration and the clinical relevance of available data together with certain conflicts of interest raised by smaller oncological care units have limited the adoption of IP chemotherapy as a new standard treatment in ovarian cancer.

It is therefore thought that the introduction of carboplatin as a replacement for cisplatin in IP regimens will be an important step forward in the field of ovarian cancer treatment. Carboplatin-based IP regimens are much better tolerable, have proved to be feasible in outpatients and are by far more cost effective. However, substantial data from large randomized trials on carboplatin-based IP regimens demonstrating either non-inferiority in comparison to cisplatin-containing IP schedules or superiority over conventional IV carboplatin-taxane chemotherapy are still lacking. The results of these ongoing studies are urgently awaited (19, 20).

It is concluded that in cases where optimal cytoreduction with residual disease ≤1 cm was achieved during primary surgery and disease was confined to the peritoneal cavity, IP chemotherapy should be given serious consideration, even at the expense of increased but manageable toxicity.

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