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Review

Advanced Cancer of the Ovary: Intraperitoneal Chemotherapy as a New Therapeutical Option

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Abstract. *Intraperitoneal (IP) chemotherapy has been used in patients presenting different stages of ovarian cancer. We performed a critical review of the available literature on IP as first-line treatment in advanced ovarian cancer to consider if this new option should be incorporated into the commonly applied guidelines for treatment of ovarian cancer. We concluded that without further data, it would not be ethically correct to administer chemotherapy intraperitoneally. Outside of planned clinical trials, patients should not be exposed to this treatment modality and its associated toxicity. The present international guidelines are still valid and recommended chemotherapy in advanced ovarian cancer remains treatment with paclitaxel and carboplatin. Further studies on this topic are, however, warranted.*

Important recent studies have shown significantly improved survival in women with epithelial ovarian cancer treated with intraperitoneal (IP) chemotherapy. This review is intended for all clinicians, including family physicians, general gynecologists and oncologists, caring for women with ovarian cancer. The subset of patients most likely to derive a survival benefit from IP chemotherapy should be selected because effective surgical debulking is critical to long-term survival for ovarian cancer. It is important that women known or suspected to have ovarian cancer should be referred to centers with the surgical expertise and resources necessary for aggressive tumor debulking and safe delivery of intraperitoneal chemotherapy.

The use of IP chemotherapy has been advocated in different settings for patients with ovarian cancer. The rationale for IP therapy in ovarian cancer derives from the pattern of growth with dissemination of tumor cells mainly into the abdominal cavity. The significance of IP chemotherapy in ovarian cancer has already been evaluated in several studies (1-12).

Four out of seven randomized phase III studies that compared IP to intravenous (IV) administration of platinum did not show any significant advantage. However, these trials were underpowered or terminated early due to slow recruitment and, therefore, cannot give clear results on this modality. In two larger phase III trials of the Gynecologic Oncology Group (GOG), protocols 104 and 172, a statistically significant survival advantage was shown for IP chemotherapy, while the third large trial, GOG 114, showed a significant advantage only for progression-free survival (PFS) and a nonsignificant trend for overall survival (OS) (l-7). Due to the recent publication of the GOG 172 study in the New England Journal of Medicine (1), IP chemotherapy as a treatment option in patients with ovarian cancer has once more moved to the focus of interest.

In patients with ovarian cancer FIGO stage III and residual tumor of <10 mm after radical surgery, the GOG 172 trial compared the combination chemotherapy with paclitaxel 135 mg/m^2 over 24 h, followed by cisplatin 75 mg/m^2 on day 2 intravenously every 3 weeks for six courses to paclitaxel 135 mg/m^2 over 24 h, followed by cisplatin 100 mg/m^2 administered IP on day 2 and paclitaxe160 mg/m^2 on day 8 every 3 weeks for six courses (1). After a median observation period of 4 years, median survival in the IP therapy arm was 65.6 months compared to 49.7 months in the IV therapy arm (p=0.03). PFS was also more favorable in the IP arm; the

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difference, however, did not reach significance. Adverse reactions differed significantly in both therapy groups. The frequency of both hematological and nonhematological grade 3/4 toxicities was significantly higher in patients of the IP arm, with quality of life being significantly poorer compared to the IV control group. Only 1 year after the end of treatment, patients treated with IP chemotherapy reached the level of quality of life of the control group, while the significantly higher neurotoxicity in the IP arm persisted even after 1 year.

Intraperitoneal and Systemic Chemotherapy

Cisplatin is the drug of choice because of its high response rate and minimal local toxicity. This treatment can be given to women with small residual disease after second look surgery, with surgically assessed complete response rates of approximately 30% , and with a prolonged survival in small subset of patients. However, the use of IP chemotherapy as consolidation treatment of pathologically complete responders after first-line systemic chemotherapy has not been definitively evaluated in a phase III trial.

The three larger GOG trials must be critically discussed. The GOG 104 trial was the only straightforward comparison, with administration route as the exclusive variable. It compared the following treatment regimens: 100 mg/m^2 cisplatin IP + 600 mg/m^2 cyclophosphamide IV every 3 weeks *versus* cisplatin 100 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks. Originally, the trial was designed for a smaller sample size, but after reaching the planned recruitment goal, it was extended because the investigators especially wanted to increase the patient group with minimal residual tumor who were believed to show the greatest benefit. After extension of recruitment, the trial obtained significant results, with an 8-month longer median survival in the IP arm. However, the results of the group with minimal residual tumor were not significant. In the meantime, a new standard within IV therapies had been developed, replacing cyclophosphamide with paclitaxel (GOG 111). Thus, results of the comparison of IP therapy with the old standard (cisplatin-cyclophosphamide) could not simply be transferred to the new standard (cisplatin-paclitaxel), especially because the gain from IP therapy was not any larger than the gain from the addition of paclitaxel (6 months for the IP-IV comparison, but 14 months for the paclitaxel *versus* the cyclophosphamide combination). Consequently, IP cisplatin therapy in combination with cyclophosphamide did not reach a high level of acceptance.

The GOG 114 trial compared a new IP therapy regimen including paclitaxel to the new standard of cisplatin-paclitaxel. In contrast to GOG 104 in which the same drugs were tested in the same dosage but with different routes of administration, in the GOG 114 trial, the experimental arm started off with an additional high dose of carboplatin before IP therapy. Moreover, the dose of cisplatin in the IP arm was by one third higher, while eight cycles were planned compared to six cycles in the standard arm. Thus, not the route of administration, but the dose intensity and the total dose of platinum, the duration of treatment, and the combination of two platinum analog were introduced as additional variables, a design in which, in the end, the results could not be attributed to any variable. The results indicated a significant advantage for the experimental arm regarding PFS but only a nonsignificant trend in favour of the IP arm with respect to OS. The experimental therapy led to significantly more adverse events and toxicities, to the extent that 18% of patients received only a maximum of two cycles of IP therapy and only 71% completed therapy as planned. The authors concluded that the experimental therapy was not appropriate for routine clinical use. Consequently, the IP regimen was not accepted as standard therapy. However, the superior PFS and the favourable OS trend led to the initiation of further studies evaluating IP therapy.

The publication of GOG 172 was accompanied by a National Cancer Institute announcement (2). The publication of Armstrong *et al.* reports a *p*-value of 0.03 in the comparison of survival of patients treated with IP and IV therapy, which just reaches significance, however, the upper limit of the confidence interval was 0.97, slightly below 1. This is even more important given that the published analysis was not an intention-to-treat population. However, according to the criteria of evidence-based medicine, such an intention-to-treat analysis is essential in order to prevent potential influence (bias) of patient selection (8). Fourteen randomized patients were not included in the analysis, with more than half of them (nine *versus* five) being excluded from the IP arm. Although this is a relatively low number, it can be of importance regarding the rather small absolute numbers on which significance was based.

Moreover, when interpreting the data, it should be taken into consideration that more than twice as many patients in the IP arm were recorded as being lost to follow-up (11 *versus* 5). This is not a huge difference, but the number of observed deaths in both arms only differed by 26 (127 and 101 events) and even a shift of 3 deaths from one arm to the other would have led to a nonsignificant result. Especially if statistical differences are marginal, they must be accurately analyzed regarding exclusion of patients and those lost to follow-up in particular if they point in the same direction and cumulate in one study arm, and by means of intention-to-treat analysis, a potential influence of these differences on the results must be ruled out.

The rather small differences in the absolute number of patients might indicate that solely focusing on median survival figures might overestimate the effect. Further

uncertainty could be assumed considering the fact that the median observation period of this trial (48 months) did not even cover the median OS in the inferior arm. By the time of analysis, the absolute difference in patients who were still alive (15 patients) was smaller than the number of patients who were lost to follow-up (16 patients). Fifteen out of more than 400 recruited patients account for only a small part. Therefore, the question remained open as to whether such a small subgroup can justify the implementation of a therapy associated with significantly higher toxicity and poorer quality of life as standard therapy. Furthermore, the difference regarding the progression-free interval was even lower, and a further 11 patients in the IP arm had not relapsed (difference not significant). However, since all patients who relapse will ultimately die from their disease, the difference in survival can become even less over a longer observation period.

The significant difference between treatment arms can be traced back to the different courses of the disease observed after progression or relapse. The differences in PFS between IP and IV therapy were 2.4 months for completely debulked patients and 2.9 months for patients with macroscopic residual tumor. Surprisingly, the difference in median survival was 12.5 months in patients with macroscopic residual tumor and 15.9 months for the entire population. There are two explanations for this: a) either patients with recurrence after IP therapy lived longer because the IP therapy changed the tumor biology of the recurrence, or b) patients received more effective second-line treatment after IP therapy. Unfortunately, Armstrong *et al*. do not report any details of their patients' second-line treatment (1). Therefore, the question remains whether the observed survival advantage might be attributed to differences in second-line therapy. The fact that second-line therapy can influence survival has been shown by at least three positive randomized phase III studies (10) and Gordon *et al*. (11), supported by two smaller trials (12, 13). Due to this reason, at the third International Consensus Conference on Ovarian Cancer 2004, the Gynecologic Cancer Intergroup identified PFS as the preferable primary end point for the evaluation of efficacy of primary therapy (14, 15)

Compliance with assigned treatment was surprisingly low in the IP arm of GOG 172. Even in experienced study centers of the GOG, only 42% of patients received IP therapy as planned. Detailed analyses of data on therapy compliance show that in the experimental arm, 8% did not receive any IP therapy and a further 34% only one to two cycles. It appears that one to two cycles in one third of patients results in a significant difference. Such a huge effect stands in contrast to the rather minor difference as reported in other IP trials (GOG 104 and GOG 114) in which a greater proportion of patients actually received the planned treatment.

Toxicity Profile of Intraperitoneal Chemotherapy

The main difference between IP and IV therapy is the clearly higher toxicity of the former. For instance, one out of six patients develops serious abdominal pain from IP therapy that she would not suffer from conventional treatment. Other IP trials report even worse abdominal pain (6), with catheter complications added to this being the most common cause for treatment discontinuation in the GOG 172 trial. The highest complication rate was found in patients with bowel resection, which is why the GOG sees a limited indication for this collective, which accounts for approximately one third of patients. The significant difference regarding toxicity not only became apparent in compliance and frequent grade 3 and 4 adverse events, but also led to significantly poorer quality of life in the IP arm. This difference is of even greater importance when taking into consideration that the actual standard treatment is carboplatin-paclitaxel, rather than cisplatin-paclitaxel, since the former is significantly less toxic, resulting in significantly improved quality of life (18). If IP therapy had been compared to the current standard (carboplatin-paclitaxel), even greater differences regarding toxicity and quality of life could be expected. Unfortunately, the other IP trials did not include investigation of quality of life (16).

In conclusion, IP therapy as evaluated in GOG 172 (and also GOG 114) showed a high toxicity profile in the majority of patients resulting in low compliance. Only 58% of patients experiencing dose-limiting toxicity and not being able to tolerate any new regimen would commonly not pass a classical phase I/II design. If at all, such a toxic regimen can be considered only if it induced a maximum long-term survival benefit (and not only median survival), which was not the case in GOG 172 as the numbers of patients alive indicated.

The carboplatin-paclitaxel combination has shown superior toxicity and better quality of life compared to the older standard cisplatin-paclitaxel, GOG 158 and AGO-OVAR 3 (17, 18, 21). Furthermore, in the studies of Armstrong *et al*. and Markman *et al*., carboplatin-paclitaxel showed a non-significant trend for better outcome in optimally debulked patients. These favourable data led the Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference to state that any new regimen should be compared to the actual standard IV carboplatin-paclitaxe1 (14, 15). The control arm used in GOG172 was IV cisplatin-paclitaxel. If the patients in the control arm of GOG 172 had had a therapy outcome similar to that of one of the four mentioned trials, comparison to IP therapy would not even have been marginally significant. Cross-trial comparison clearly does not substitute for prospectively randomized comparison and on its own might not stand strongly. However, future trials should compare any new treatment regimen to the best actual standard regimen, and this is currently IV carboplatin-paclitaxel.

Conclusion

There is much debate in the literature both for and against the use of IP chemotherapy in the first-line treatment of optimally debulked ovarian cancer patients. The recent Cochrane meta-analyses of eight randomized trials enrolling 1,819 patients has shown that first-line IP chemotherapy improves PFS and OS of patients with minimal residual disease after initial surgery (22). However, the potential for catheter-related complications, abdominal pain with infusion, and toxicities needs to be taken into consideration for decision making in each individual woman.

Rectosigmoidal surgery can be associated with gross contamination of the operative field and, in this case, the catheter placement should not be performed during primary surgery but should be delayed to 3 weeks later. Patients should be provided with information on the survival and toxicity under both IP and systemic treatments, as well as practical information about the administration of each regimen, so that they may be involved in the decision-making process (23).

Armstrong *et al*. have contributed to the discussion of IP therapy and offered incentives for the initiation of further trials. IP therapy showed some survival benefit in all three large randomized trials and, therefore, might be a sensible alternative for a subgroup of patients with advanced ovarian cancer. However, before IP therapy becomes a clinical routine, it should be possible to identify those patient subgroups who might benefit and a tolerable regimen should be developed. Further trials on this issue are clearly warranted.

The international guidelines (22) are still valid and recommended chemotherapy in advanced ovarian cancer remains treatment with paclitaxel 175 mg/m^2 over 3 h IV and carboplatin AUC (area under the curve) 5 over 0.5-1 h IV, on day 1, respectively, every 3 weeks for six cycles. Without further data, it would be dangerous to administer other unevaluated combinations intraperitoneally (*e.g.* carboplatin-paclitaxel). Outside of thoroughly planned clinical trials, patients should not be exposed to this treatment modality and its associated excessive toxicity.

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