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Role of Intra-Peritoneal Chemotherapy in Advanced Ovarian Cancers - A Dilemma

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Abstract: *The Pharmacologic Basis for the delivery of anti-cancer drugs by the IP route was established in late 1970s & early 1980s.*
Epithelial Ovarian Cancers spreads prominently within the peritoneal cavity. IP drug administration in Ovarian Cancer conferred a pharmacologic advantage over IV administration, given the additional clinical benefit derived from achieving more efficient control of life threatening peritoneal disease.
The use of IP Cisplatin as part of initial approach in patients with stage III optimally debulked ovarian cancer is supported principally by the results of three randomized clinical trials (SWOG-8501, GOG-14 & GOG-172). These studies tested the role of IP drugs (IP Cisplatin in all three studies & IP Paclitaxel in the last study.) against the standard IV Regimen. In the three studies, superior progression free survival & Overall survival favouring the IP arm was documented.
The rate of completion of six cycles of treatment was less frequent in the IP arm i.e 42% vs IV arm of 83% because of toxic effects & catheter related problems.
We review the known data from various trials conducted on IP mode of Chemotherapy administration in Optimally Cytoreduced Stage III Ovarian Cancers & Explore its Practical Benefit in improving progression free survival & Overall survival with few modifications of IP regimen, so as to increase its Tolerability.

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I. INTRODUCTION

The most common route of spread of Ovarian Cancers is within Peritoneal Cavity. The Benefit of administering Chemotherapy directly into Peritoneal Cavity permits a several fold increase in Drug concentration to be achieved within the abdominal cavity [1].

There is now a growing body of evidence showing a survival advantage for IP Cisplatin as compared to IV administration of Platinum along with IV Taxane based Chemotherapy in woman with Optimally Cytoreduced (to<1.0cm)Stage III Epithelial Ovarian Cancers. However while the use of IP Chemotherapy is gaining acceptance, it is not universal, largely due to greater toxicity associated with this approach. The publication of results from the most recent of these trials, Gynecologic Oncology Group (GOG) trial 172 [2], led the US National Cancer Institute to issue a Clinical Alert in January of 2006, strongly encouraging the use of IP chemotherapy in this subset of patients [3].

RANDOMIZED CLINICAL TRIALS ON IP CHEMOTHERAPY:-

The use of IP Cisplatin as part of initial upfront approach in patients with stage III Optimally debulked Ovarian Cancer is supported principally by the results of three randomized clinical trials (SWOG-8501, GOG-14 & GOG-0172). [4-6]These studies tested the role of IP Drugs (IP Cisplatin in all three studies & IP Paclitaxel in the last study) against the standard IV regimen. In the three studies, superior progression free survival & Overall survival favouring the IP arm was documented. Specifically the most recent study GOG-0172 resulted in a median survival rate of 66 months for patients on IP arm versus 50 months for patients who received IV administration of Cisplatin & Paclitaxel (P=0.03). Toxic effects were greater in the IP arm, contributed to in large part by the Cisplatin dose per cycle (100mg/m2) & by sensory neuropathy from the additional IP as well as from IV administration of Paclitaxel. The rate of completion of six cycles of treatment was also less frequent in the IP arm (42% vs 83%) because of toxic effects & catheter related problems. [7]

In the first study, the GOG and Southwestern Oncology Group (SWOG) randomized patients between i.v. cisplatin plus cyclophosphamide and i.p. cisplatin combined with i.v. cyclophosphamide [9]. After the publication of that trial, i.p. chemotherapy was not accepted as standard of care because at that time cisplatin plus cyclophosphamide was no longer the standard because cyclophosphamide had been replaced by paclitaxel.

Furthermore, the morbidity was significantly greater in the i.p. group than in the i.v. group (e.g., only 58% of the patients in the i.p. arm received the planned six courses).

The second randomized GOG study was published by Markman et al. 1101. That study was criticized because the experimental arm differed in many ways from the standard arm. Indeed, in the experimental arm, the first two courses of carboplatin were administered at a high dose (AUC of 9), and the dosages of cisplatin were also different in the two arms. The toxicity was very high, and the authors concluded that i.p. chemotherapy as administered in their study could not be recommended as standard of care.

The third GOG study, GOG 172, published by Armstrong et al. was the main reason given by the NCI for making their announcement. In the rest of this paper, we focus on the GOG 172 study. The main reasons why the experimental (i.p. chemotherapy) arm of the GOG 172 study cannot be regarded as standard of care are summarized as below:-

The main reasons why the experimental (i.p. chemo) arm of the GOG 172 study cannot be regarded as standard of care

1. The significance for overall survival was only borderline (p=0.03) and only a one-sided statistical lest performed.
2. The number of nonevaluable patients was higher than the absolute difference in survival.
3. For progression-free survival, the p-value (one-sided) was not significant.
4. The survival curves differ only after 15 months and this may be caused by second-line therapy.
5. The standard arm with paclitaxel and cisplatin has a substantially lower survival rate than the standard arms of other randomized trials in the same patient population.
6. More than half of the patients treated with i.p. chemotherapy were treated w ith i.v. chemotherapy (mostly paclitaxel plus carboplatin): paclitaxel plus carboplatin is less toxic than paclitaxel plus cisplatin (standard arm), and after paclitaxel plus carboplatin it is easier to administer second-line combination chemotherapy.
7. Only 42% of the patients could receive six cycles of i.p. chemotherapy.
8. i.p. chemotherapy resulted in significantly greater toxicity (bone marrow, gastrointestinal, neurological, etc)
9. Quality of life was worse during the first year after i.p. chemotherapy than after i.v. chemotherapy.
10.In the experimental i.p. arm, a higher dose of cisplatin was administered and paclitaxel was administered both on day 1 and day 8: these differences might have influenced the survival results.
11. The number of i.p. versus retroperitoneal relapses was not different in the i.p. arm compared with the i.v. Abbreviation: GOG. Gynecologic Oncology Group.

In spite of these problems, IP therapy for patients with optimally debulked Ovarian Cancer is receiving wider adoption & efforts are underway by the GOG to examine some modifications of the IP regimen used in GOG-0172 to improve its Tolerability (e.g. to reduce by >25% the total 3-h amount of cisplatin given, a shift from the less practical 24hrs IV administration of Paclitaxel to a 3-h administration. A Cochrane sponsored Meta analysis of all randomized IP vs IV trials shows a Hazard ratio of 0.79 for Disease free Survival & 0.79 for Overall survival , favouring the IP arm.[8] In another meta analysis of seven IP vs IV randomized trials that were conducted by cancer care of Ontario, the relative ratio of progression at 5 years based on the three trials that reported this endpoint was 0.91 (95% confidence Interval 0.85- 0.98) & the RR of Death at 5 years based on six trials was 0.88 (95% Cl 0.81-0.95).[7]

The three GOG trials are the most important trials on I.P. chemotherapy, and are summarized in Table below

	Study	Randomization	No. of Patients	Hazard ratio(Overall Survival)
1	SWOG/GOG 104 (9)	Cisplatin. 100 mg/ m^2 i.v.; cyclophosphamide, 600 mg/ Cisplatin, 100 mg/ m^2 i.p.; cyclophosphamide,600 mg/m2 ip	546	0.72 (0.61-0.96); p = .02
2	GOG 114 (10)	Cisplatin,75 mg/m2 i.v.; paclitaxel 135 mg/ m^2 24-hr i.v. Cisplatin, 100 mg/ m^2 i.p.; cyclophosphamide, 600 mg/ m^2 i.p	462	0.81 (0.65-1.0) P=0.05
3	GOG 172 (3)	Cisplatin, 75 mg/m^2 i.v.: paclitaxel. 135 mg/ m^2 24-hr i.v Paclitaxel, 135 mg/m^2 24-hr i.v.; cisplatin, 100 mg/m^2 i.p.; paclitaxel, 60 mg/ m2 i.p. on day 8	415	0.71 (0.58-0.97) P=0.03

DIFFICULTIES IN IP DRUG DELIVERY

IP Chemotherapy is more complex & time consuming than IV Chemotherapy. There is also a long learning curve in acquiring the proper techniques for surgically placing an IP Port & developing the clinical expertise in accessing the IP port for drug delivery. Other issues include , Type of catheter $_t$ single or multiple holes , site of catheter placement, patency of catheter , Distribution of drug in Peritoneal cavity , position of patient , Adhesions [9]etc. Multiple surgeries & certain Vesicant drugs increase catheter malfunction. Inflow obstruction causes backflow around the catheter & into the subcutaneous tissue. Outflow obstruction is common, it is probably related to a small amount of connective tissue within the rim of outflow orifice. The longer an IP catheter is left in place, more chances of outflow obstruction. If it is desirable to place catheter for long duration then it is better to maintain the patency of IP catheter by flushing the system with heparinized saline every 6 weeks.

ENTRY CRITERIA FOR IP DRUG THERAPY:-

At present one would prefer to consider the best candidate for IP therapy those who are previously untreated & Optimally Cyto Reduced Stage III Ovarian Cancer. IP Chemotherapy also plays important role as salvage IP therapy after initial IV Chemotherapy & Second look surgery with minimal residual disease.

PHARMACOLOGIC FEATURES:-

The rationale for i.p. chemotherapy is based on high drug concentration exposure in the peritoneal cavity leading to an increased cytotoxicity and avoiding a high level of systemic toxicity. [11-16]

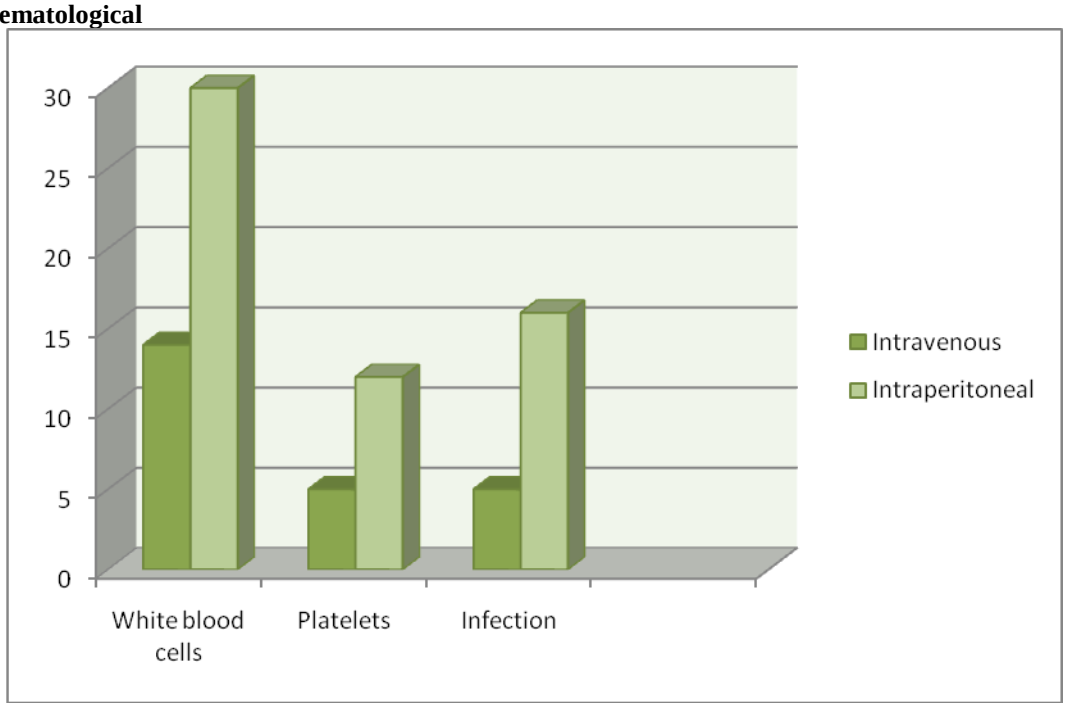
The Pharmacologic advantage of IP Therapy relates to high Intra-Peritoneal concentrations delivered to the tumour with less systemic toxicity compared with IV administration often expressed as the ratio between the AUC in the peritoneum & the AUC in the plasma. The efficacy of IP Therapy depends on the Peritoneal / Plasma concentration ratio (Pharmacokinetics) of the different drugs, their systemic absorption & the penetration into tumour tissue .Based on the phase III trials reviewed, the cytotoxic drugs widely used are Cisplatin, Carboplatin & Paclitaxel. Cisplatin is rapidly & well absorbed systemically following IP administration resulting in 50%-100% of systemic exposure compared with IV administration when comparable doses are given. It provides very high IP concentrations for Loco- Regional Disease. Dose limiting toxicity from IP administration is directly related to the systemic effects of Cisplatin (myelo- suppresion, neurotoxicity). Carboplatin is absorbed following IP administration 2-4 hrs after infusion. GOG158 trial demonstrated that IV combination of Carboplatin AUC 7.5mg/ml/min plus Paclitaxel 175mg/ m^2 in a 3-h infusion was not inferior to IV combination of Cisplatin 75mg/m^2 plus Paclitaxel 135mg/m^2 in a 24hrs continuous infusion in terms of Progression free survival & Overall survival because of these results IV Carboplatin replaced IV Cisplatin , but IP Carboplatin has not been compared against Cisplatin in IP setting. Paclitaxel has a high molecular weight & bulky structure, resulting in slow clearance from peritoneal compartment, thus increasing the exposure of tumour in peritoneal cavity. After IP Paclitaxel infusion the peak peritoneum / plasma concentration ratio is approximately 1000 & this is maintained for 24-48 hrs. Abdominal pain is dose limiting toxicity of IP Paclitaxel at doses of more than 125mg/m^2. Finally, it is important to note that the administered doses of cisplatin (75 mg/m^2 versus 100 mg/m^2) and paclitaxel (135 mg/m^2 on day 1 versus 135 mg/m^2 on day 1 and 60 mg/m^2 on day 8) are different. It has been shown that weekly paclitaxel is more efficient than 3- weekly paclitaxel in other diseases, such as breast cancer [10].

LIMITATIONS OF IP CHEMOTHERAPY:-

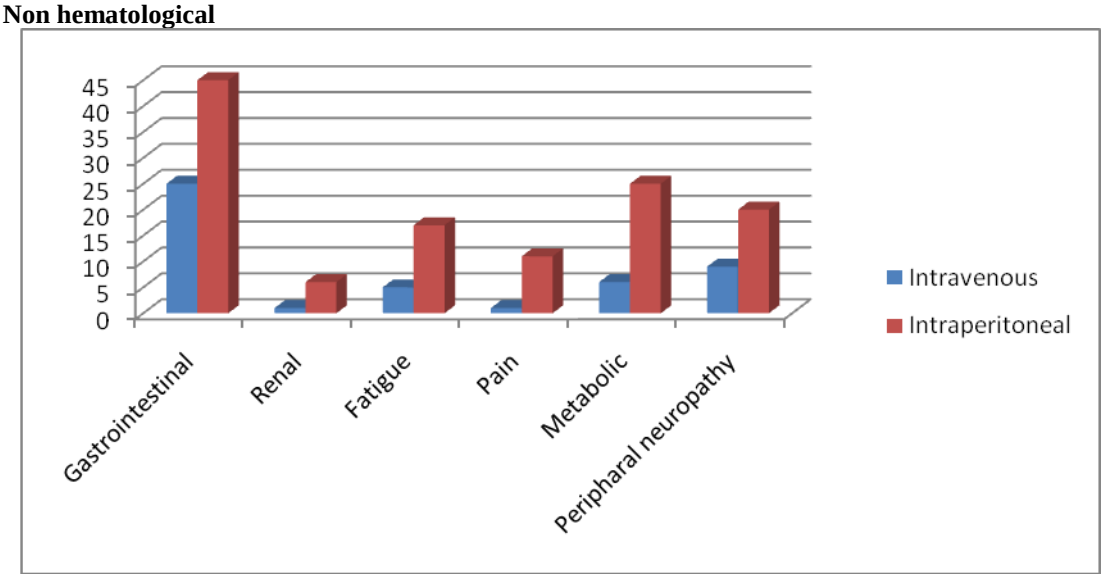
The benefit of IP Chemotherapy is uncertain in the setting of early stage disease, stage lV disease & in patients who have residual tumour greater than 1 cm in diameter. Tumour cells more than a few millimeters beneath the surface of tumour are not exposed to IP Chemotherapy (at least during the 1st cycle) since penetration of drug into tumour tissue is limited to a few surface layers.

The toxicity of the i.p. chemotherapy used in the GOG 172 trial was very high (Figs. 1 and 2).

A Hematological



B Non hematological



II. Conclusions

Intraperitoneal chemotherapy is associated with a higher toxicity rate than i.v. chemotherapy. For this reason, none of the regimens investigated in the three Gynecologic Oncology Group (GOG) studies can be used as standard treatment outside clinical protocols. The trials on i.p. chemotherapy have suggested a survival difference. However in the two most recent trials, i.p. chemotherapy or not was not the only research question because different schedules and dosages were used. In addition, the significance of the most recent GOG 172 study was only weak ($p = 0.03$), and the result was non -significant for progression-free survival. Intra peritoneal chemotherapy should be used only in the context of properly designed clinical trials. These trials must either assess i.p. therapy in comparison with the standard treatment or address the issue of route of administration for equivalent dosages and schedules of the same drugs, and not a mosaic of these questions. In addition, these trials should investigate i.p. regimens that are less toxic than the regimens used in the three GOG trials, and which can be combined with molecular targeted therapies.

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