Should we continue intra-peritoneal chemotherapy in advanced ovarian cancer patients?

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Abstract

Ovarian cancer has the highest mortality of all gynecologic malignancies in the United States. Ovarian cancer is often diagnosed at advanced stage. Optimal cytoreduction, followed by intravenous chemotherapy consisting of platinum taxol containing agents represents the mainstay of ovarian cancer therapy. The introduction of intraperitoneal chemotherapy utilized a novel route of administration showing promise in treating ovarian cancer both in vitro studies and clinical trials. Currently, in gynecologic oncology practice, the efficacy and toxicity of intraperitoneal chemotherapy is not yet widely agreed upon. The major clinical trials and future therapies utilizing intraperitoneal chemotherapy will be review here.

Introduction and background

Ovarian cancer is the number one cause of death from gynecologic malignancies in the United States, and is typically diagnosed at an advanced stage with an exceedingly low five-year survival [1,2]. The low survival rate of ovarian cancer has stimulated many studies to identify new, improved chemotherapy dosing regimens, routes of administration and chemotherapy agents. The current standard of care are platinum agents combined with taxane agents administered through the intravenous route. These therapies are typically administered every three weeks for six cycles. In 1996, the GOG 104 study evaluated a new route of administration. The trial was conducted given that survival outcomes remained poor in advanced stage ovarian cancer despite aggressive surgical and intravenous chemotherapeutic management. The GOG 104 was based on a number of diverse studies which all supported the use of intraperitoneal (IP) chemotherapy [3]. Some of the studies were theoretical, using pharmacokinetic modeling, while other studies utilized successful in-vivo mouse and rat models which led to additional pilot clinical studies 4–6. In these early clinical pilot studies, radioisotopes were given intraperitoneally and showed an advantage for early stage ovarian cancer. In its infancy IP chemotherapy was frequently restricted to patients who needed palliative treatment of their advanced malignant ascites [4,5]. Eventually the technique and chemotherapy improved leading to a phase III trial from the GOG. This initial phase III study displayed a survival advantage in the IP arm for the treatment of advanced ovarian cancer. Since that initial randomized controlled trial there have been a number of similar trials, the four most influential being, GOG 104, GOG 114, GOG 172 and now GOG 252. These trials have been completed to help determine the efficacy, toxicity and plausibility of intraperitoneal chemotherapy. There have been a number of meta- and post hoc analyses to determine the safety, efficacy and tolerability of IP chemotherapy [7-9]. In gynecologic oncology, the debate over IP chemotherapy has been ongoing since its inception. The debate continues as these studies are largely heterogeneous with relation to chemotherapy dosing, toxicities, study design and delivery methods. These issues and variable results have led to slow uptake of IP chemotherapy in the clinical setting. The three clinical trials will be reviewed here, as will the biochemical and pharmacokinetic rationale to use intraperitoneal chemotherapy, the toxicities associated with intraperitoneal chemotherapy, the possibility of improving the IP delivery system and the future of intraperitoneal chemotherapy. This is an important discussion in the gynecologic oncology field as the current questions regarding the future of IP chemotherapy [10].

Biochemical and pharmacokinetic reasonings for intraperitoneal chemotherapy

Ovarian cancer at advanced stages will metastasizes to many different areas in the peritoneal cavity and thus portend a poor survival. The single most important prognostic factor in prolonging survival is achieving complete cytoreductive surgery to no visible residual disease. Unfortunately, it is not feasible to remove all microscopic residual tumor cells from the peritoneal cavity. Additionally, it may not be feasible to remove innumerable small tumors less than 1 cm from all peritoneal surfaces. Due to the difficulty, at times, of achieving complete cytoreduction, the idea of intraperitoneal (IP) chemotherapy was born. IP chemotherapy is thought to achieve higher concentrations of chemotherapy at and within the residual tumor surface.

As stated above, the theory with IP chemotherapy is to administer high doses of chemotherapy to the peritoneal cavity. Once in the peritoneal cavity, the therapy can directly act on both the individual microscopic tumor cells, and the surfaces of residual sub-centimeter tumoral implants.

The concept of placing medical therapy into the peritoneal cavity is not new, in fact, peritoneal dialysis was first used with patients who had renal insufficiency in 1923 [6,11]. With this technique in mind, theoretical models were developed to determine the distribution and elimination of chemotherapy when applied through an IP route [6,12].
Consistently, in-vivo studies nicely complimented and supported the theoretical models [12,13]. With encouraging results in-vivo, other areas of medicine began to apply this technique. One example was found in central nervous system (CNS) tumors. The subarachnoid space is known for being relatively difficult to be penetrated by chemotherapy. When neuro-oncologists found that IV treatment with methotrexate was ineffective for CNS leukemia, it was suggested that the therapy be placed directly into the subarachnoid space. In 1957 methotrexate was used intrathecally where they achieved a high concentration and altered the course of CNS leukemia [6,14]. Similarly, to the CSF, the peritoneal fluid has low concentrations of chemotherapeutics after intravenous administration. Conversely, IP infusion of chemotherapy achieved high levels of chemotherapeutics both systemically and intraperitoneally. Thus, the technique of bathing intraperitoneal tumors with IP chemotherapy was employed. In-vivo mouse models using IP administration of therapy revealed that the IP route not only maintained a high concentration intraperitoneally but also led to a maintained distribution systemically over a longer time interval [12,13]. The high systemic concentration can be explained by the fact that the chemotherapeutics are absorbed into the systemic circulation due to the large surface area of the peritoneal membrane and abundant blood supply [12,13]. Intraperitoneal injection also allows for a slow-release to the systemic circulation, allowing for similar sustainable systemic concentrations ast IV chemotherapy [12,13,15]. Thus, IP administration of chemotherapy should be efficient in targeting tumor cells directly in the intraperitoneal cavity as well as the tumor cells in the systemic circulation. Along these lines, in advanced ovarian carcinoma, higher concentrations of chemotherapy can be both directly delivered to the tumor’s surface and to the core of the tumor through systemic circulation leading to improved cytotoxic effects [12,13,16].

Tumor effects

The action of chemotherapy in the intraperitoneal space can be broken into two categories, action of the chemotherapy on residual single tumor cells and the action of chemotherapy on sub-centimeter tumor tissue. Understanding how chemotherapy acts on both of these two tumor entities is important. The action chemotherapy has on residual single tumor cells is dependent on the chemotherapeutics’ ability to permeate the cell membrane. Consistently, systemic circulation may not easily access these individual tumor cells as these cells use the microenvironment to obtain nutrients from the host’s peritoneal fluid. Intraperitoneal chemotherapy may be a better approach for accessing the residual cells if the chemotherapy being used is hydrophobic (paclitaxel) and has the ability to pass through a cell’s phospholipid bilayer [17]. The second category of tumor cells to be targeted are the sub centimeter nodules. The current data on distribution of chemotherapy throughout this type of tumor tissue is limited [18]. Data from in-vitro models reported that chemotherapy cannot penetrate greater than 1 mm of cell layer thickness. The chemotherapy is highest at the periphery of a tumor and decreases as it moves toward the center, in this case, medication effectiveness will decrease at the center as the tumor diameter increases [6]. The nodules in a peritoneal cavity which are greater than 1 mm have cells affected by chemotherapy cells on the surface, while the core of the tumor can be accessed by the systemically absorbed chemotherapy [18]. Therefore, the IP route theoretically applies higher amounts of chemotherapy to nodules on the surface while also delivering therapy to the core of the tumor nodule through the systemic vascular supply. By this mechanism chemotheraphy has been found to be 10-15 times more concentrated in the tumor nodule from the IP route when compared to IV route, thus leading clinicians to study this route in advanced stage ovarian cancer [19,20].

Evolution of intraperitoneal chemotherapy

The following trials have been instrumental in helping to transition intraperitoneal chemotherapy to the clinical setting. The completed GOG trials along with pending results from GOG 252 will likely inform the future of IP chemotherapy. GOG 104, 114 and 172 will be compared and reviewed in detail here. The GOG 252 trial will be discussed in brief, but a much more detailed examination will be needed once the data has been published in manuscript form.

GOG 104: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer

The first phase III randomized controlled trial by Alberts et al. (GOG 104) comparing intraperitoneal to intravenous chemotherapy was conducted from June 1986 to July 1992 [21]. This trial was limited to patients with stage III disease (histologic diagnosis of epithelial-type ovarian cancer) and included 654 women who underwent an exploratory laparotomy with at least a bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and debulking of all tumor to a size of 2 cm or less. An exploratory laparotomy was completed within four weeks prior to enrollment in the study. The patients received either, arm I consisting of Intravenous cyclophosphamide 600 mg/m² and cisplatin 100 mg/m² both given on day one, or arm II consisting of intravenous (IV) cyclophosphamide 600mg/m² and intraperitoneal cisplatin 100 mg/m² diluted in 2 liters of normal saline. The IP mixture in arm II was instilled into the peritoneal cavity “as rapidly as possible”. Both IV cyclophosphamide and IP cisplatin were given on day 1. Both arms I and II had cyclophosphamide and cisplatin given every three

### Table 1. Cumulative Chemotherapy Dosages in GOG Trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Arms</th>
<th>Dosage Total After 6 Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104</td>
<td>Arm I</td>
<td>Cyclophosphamide: 3600 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin: 600 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Arm II</td>
<td>Cyclophosphamide: 3600 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin: 600 mg/m²</td>
</tr>
<tr>
<td>GOG 114</td>
<td>Arm I</td>
<td>Paclitaxel: 810 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Arm II</td>
<td>Paclitaxel: 810 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin: AUC 18*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel: 810 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin: 600 mg/m²/4</td>
</tr>
<tr>
<td>GOG 172</td>
<td>Arm I</td>
<td>Paclitaxel: 810 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Arm II</td>
<td>Paclitaxel: 1170 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin: 600 mg/m²</td>
</tr>
<tr>
<td>GOG 252†</td>
<td>Arm I</td>
<td>Carboplatin: AUC 36</td>
</tr>
<tr>
<td></td>
<td>Arm II</td>
<td>Carboplatin: AUC 36</td>
</tr>
<tr>
<td></td>
<td>Arm III</td>
<td>Carboplatin: AUC 36</td>
</tr>
</tbody>
</table>

mg/milligram, m²: meter squared, GOG: Gynecologic Oncology Group, AUC: Area Under the Curve

Findings from this trial were reported with a median survival of 41 months in the intravenous group and 49 months in the intraperitoneal (IP) group (Table 2). No treatment related deaths occurred in the intraperitoneal group. More patients in the intravenous group were found to have statistically significant difference between grade 3 or higher leukopenia and granulocytopenia when compared to the intraperitoneal arm. Additionally, hearing loss, moderate-to-severe tinnitus and grade 2 or 3 neuromuscular toxicity were found to be higher in the intravenous cisplatin group (Table 2). Expectedly, the IP group did have higher abdominal pain of grade 2 or more when compared to the IV group (statistically significant), notably the pain dissipated within 24 hours and was easily controlled. Dyspnea also resulted from decrease in lung volume after IP infusion and was transient but higher in the IP group (3 percent, vs. 0.4 percent in the IV group; P=0.002). The study shows 40 (40/279, 14%) patients in the IV group had cisplatin discontinued because of toxic effects versus 22 (22/267, 8.2%) patients in the IP group. The IV and IP group both had the same percentage of eligible patients receiving all 6 cycles of chemotherapy (58%).

Overall, this study showed a better median survival and lower toxicity for the intraperitoneal group when compared to the intravenous group (Table 2). There was no notation on catheter success or failure and there was no notation of how many patients were able to complete the intraperitoneal or intravenous arms of the study. The main advantage of this study is the use of similar dosages of chemotherapy in both arms, it is the only GOG study to date, not including GOG 252, that has utilized this control (Table 1). We are able to directly understand which regimen has more toxicity and feel comfortable attributing the toxicities to the route of administration. This fact also applies to the reliability of the improved median survival finding in the IP arm. The patients who received IP cisplatin did have dyspnea and abdominal pain, this was associated with infusion of volume “as fast as possible” and not a long term complication. The abdominal pain was noted to have resolved within 24 hours. Additionally, the transient dyspnea is not a clinically significant difference given that it was short term and only 2.6 percent higher than in the IV group. There was a similar percentage of patients in both the IP and IV arm that completed the 6 cycle treatment (58% percent did complete the IP arm, and IV 58%). This may indicate that both regimens were similarly toxic and had poor adherence, unfortunately we do not have the data to expand on this finding.

The two issues with this trial were as follows, the first, deals with the trial’s use of cyclophosphamide. GOG 111 had recently resulted after the completion of this trial and paclitaxel was gaining widespread use in the clinical setting only after the completion of the study. Given that both arms utilized cyclophosphamide the study still is able to give an unbiased comparison of IV versus IP cisplatin. It is possible that the cyclophosphamide contributed to the low percentage of patients completing all 6 cycles of chemotherapy. Unfortunately, because of cyclophosphamide use, the study findings are difficult to generalize to the current treatment population. The second issue was the cytoreductive surgery to less than or equal to 2 cm of disease. The current standard of care is cytoreductive surgery to no visible residual disease thus, it may be difficult to extrapolate the results from this trial and state that IP therapy will have the same effect on a patient who has no visible residual disease. The group did note the effect of treatment (either IP or IV) was not confounded by the extent of the residual disease, but based on theoretical models outlined previously it would reason that success of IP therapy would be influenced by the extent of residual disease. Until the completion of GOG 252 will gynecologic oncologist be able to better understand how residual disease versus no visible residual disease will alter the effect of IP chemotherapy.

GOG 114: Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the gynecologic oncology group, southwestern oncology group, and eastern cooperative oncology group

In GOG 114, the objective was to evaluate the advantage of combining systemic chemotherapy with IP cisplatin in patients also receiving intravenous paclitaxel. This trial was carried out as collaboration between the Gynecologic Oncology Group (GOG), Southwest Oncology Group, and the Eastern Cooperative Oncology Group (ECOG). It was a randomized, controlled phase III clinical trial of standard-dose IV cisplatin/ paclitaxel for six cycles, compared

Table 2. Toxicities and Outcomes in GOG Trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Arms</th>
<th>Thrombocytopenia (% of patients)</th>
<th>Neutropenia (% of patients)</th>
<th>Gastrointestinal (% of patients)</th>
<th>Metabolic (% of patients)</th>
<th>Neurologic (% of patients)</th>
<th>Catheter Complications (% of patients)</th>
<th>PFS (months) median</th>
<th>OS (months) median</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104</td>
<td>Arm I</td>
<td>9%</td>
<td>69%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>25%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Arm II</td>
<td>8%</td>
<td>56%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>16%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>41*</td>
</tr>
<tr>
<td>GOG 114</td>
<td>Arm I</td>
<td>2/1</td>
<td>49/13</td>
<td>9/8</td>
<td>1/8</td>
<td>8/1</td>
<td>N/A</td>
<td>N/A</td>
<td>49*</td>
</tr>
<tr>
<td>Arm II</td>
<td>25/24</td>
<td>49/28</td>
<td>17/20</td>
<td>7/3</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>GOG 172</td>
<td>Arm I</td>
<td>4%</td>
<td>64%</td>
<td>24%</td>
<td>7%</td>
<td>9%</td>
<td>N/A</td>
<td>18.3*</td>
<td>49.7*</td>
</tr>
<tr>
<td>Arm II</td>
<td>12%</td>
<td>76%</td>
<td>46%</td>
<td>27%</td>
<td>19%</td>
<td>19.5</td>
<td>23.8*</td>
<td>65.6*</td>
<td></td>
</tr>
<tr>
<td>GOG 252</td>
<td>Arm I</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>24.9</td>
<td>Pending</td>
</tr>
<tr>
<td>Arm II</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>27.3</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>Arm III</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>26</td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

mg: milligram, m²: meter squared, GOG: Gynecologic Oncology Group, AUC: Area Under the Curve, PFS: Progression Free Survival, OS: Overall Survival
* Statistical significance reached with P< 0.05, or 95 % confidence interval excluding zero per trial report
≡ Toxicity evenly distributed among treatment arms
5 Written as Grade 3/Grade 4 (% of patients)
6 Written as Grade 3 or greater (% of patients)
8 ARM I, II and III also had bevacizumab on cycles 2 to 22
with two cycles of single-agent carboplatin, followed by six cycles of IP cisplatin and IV paclitaxel. The Intraperitoneal Port (IP) cisplatin was delivered in 2 L of normal saline through a peritoneal dialysis catheter (ie, Tenckhoff catheter) connected to an indwelling port. The regimens were as follows, intravenous arm with paclitaxel 135 mg/m² by continuous IV infusion for 24 hours on day 1 followed by cisplatin 75 mg/m² IV on day 2, every 21 days for six cycles and the intraperitoneal arm consisted of carboplatin (AUC 9) IV for two cycles every 28 days, followed 4 weeks later by paclitaxel 135 mg/m² by continuous IV infusion over 24 hours on day 1, followed by cisplatin 100 mg/m² IP on day 2, every 21 days for six cycles. If cisplatin could not be given by the IP route because of catheter malfunction, cisplatin was administered IV at a reduced dose of 75 mg/m² to complete the six treatment cycles (Table 1).

From August 1992 until April 1995, a total of 523 patients were entered to the two arms. Of the 462 eligible patients, the treatment groups were similar in age, performance status, histologic subtype of ovarian cancer, residual disease status, race, and tumor grade. The majority of patients were Caucasian (91%), greater than 50 years old (67%), and of high grade serious pathology (63%). In the experimental arm, 6.8% of the patients did not receive IP therapy and 18.3% received two cycles or less of IP drug delivery. This was hypothesized to be because of IV cisplatin related bone marrow toxicity. There was more grade 4 neutropenia and grade 3-4 thrombocytopenia in the IV/IP arm and more Grade 3-4 gastrointestinal and metabolic toxicity. Two patients in each arm died from grade 4 hematologic toxicity, likely related to the high dose platinum in the IV/IP cohort and from cisplatin in the control group (Table 2).

In the control group, 86% of patients were able to complete 6 cycles of chemotherapy whereas in the IV/IP arm, 96% of patients were able to complete the IV carboplatin and 71% of patients were able to complete the additional 6 cycles of IP Cisplatin and IV Paclitaxel. This discrepancy could be related to the grade 3 and 4 toxicities mentioned earlier, as eight total cycles of chemo (IV/IP arm) is substantially more toxic than the six standard cycles administered in the conventional chemotherapy arm. Additionally, the IV/IP arm received a very high dose (AUC 9) of carboplatin which may have contributed to the previously mentioned toxicities (Table 1).

Progression free survival was longer in the experimental arm, with a median time to recurrence of 27.9 months compared with 22.2 months in the standard cisplatin/paclitaxel arm (p=0.01). Furthermore, there was an improvement in overall survival for the experimental arm with a median time to death of 63.2 months compared with 52.2 months in the standard cisplatin/paclitaxel arm (p=0.05) (Table 2).

The shortcomings of this trial make it difficult to make sound conclusions. First, a significant number of patients (18.3%) received two or less of IP therapy. There is no discussion of the distribution of reasons the therapy was unable to be completed. There was also no discussion regarding whether or not it could have been related to Quality of Life or issues related to the catheter. Along those lines, other than commenting that if IP chemo could not be delivered, that IV Cisplatin would be used instead, there was no presentation, discussion, or details provided about how many of these patients there were. Their data was likely included in the overall analysis making it less valid. The chemotherapy regimens that these patients received needs to be considered when trying to make conclusions (Table 1). It would have been more helpful to compare IV Cisplatin to IV Paclitaxel plus IP Cisplatin head-to-head. The results are complicated not only by the addition of IV Carboplatin but also by the fact that the addition of these two cycles makes the comparison 6 cycles of conventional chemotherapy versus 8 cycles in the experimental arm (Table 1). Finally, it should be noted that the IV Carboplatin in the experimental arm was given at a very high dose (AUC 9). This makes it difficult to conclude if the toxicities are related to the IP chemotherapy, the two additional cycles of chemotherapy, or the added effect of a high dose of Carboplatin. Overall survival and PFS are difficult to attribute to the route of IP therapy alone, again for the reasons that the toxicity may have been higher in the IP group.

**GOG 172: Intraperitoneal cisplatin and paclitaxel in ovarian cancer**

The third phase III randomized controlled trial by Armstrong et al. (GOG 172) evaluated the efficacy and toxicity of intraperitoneal chemotherapy in 429 patients from March 1998 to January 2001 [1]. In this study patients with Stage IIIC epithelial ovarian or primary peritoneal carcinoma underwent cytoreductive surgery to residual less than or equal to 1.0 cm. These patients were required to enroll within six weeks of their staging surgery. The patients were then either randomized to arm 1, which consisted of 135 mg/m² of intravenous paclitaxel (over 24 hours) on day 1 and 75 mg/m² of intravenous cisplatin on day 2, or arm II which consisted of 135 mg/m² of intravenous paclitaxel (over 24 hours) on day 1 and 100 mg/m² of intraperitoneal cisplatin on day 2 with an additional 60 mg/m² of intraperitoneal paclitaxel on day 8 (Table 1). The treatments were infused every three weeks for a total of 6 cycles. A statistically significant difference was seen in the intraperitoneal arm with grade 3 and 4 pain, fatigue, hematologic, gastrointestinal, metabolic and neurologic toxic effects (Table 2). Forty -two percent (86/205) completed the planned six cycles of intraperitoneal therapy and eighty-three percent (174/210) received all six cycles of the planned intravenous therapy. The median interval between staging surgery and the first cycle of IP chemotherapy was 25 days, this was unknown for the IV arm. The improvement in progression-free survival and overall survival in intraperitoneal arm was statistically significant. The median duration of progression-free survival in the intraperitoneal group was 23.8 compared to the intravenous group at 18.3 months (5.5 months). The median duration of overall survival in the intraperitoneal group compared to the intravenous group was 65.6 and 49.7 months (15.9 months) respectively (Table 2). Quality of life was significantly worse in the intraperitoneal-therapy and remained at three to six weeks post treatment, at one year follow up the patients did not have a difference in the quality of life measure between the IP and IV group. Interestingly, the quality-of-life (QOL) assessment was completed with the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) before randomization of the patients into the intraperitoneal or intravenous arm. Incidentally, during randomization, the majority of patients with lower FACT-O scores were randomized into the intraperitoneal group compared to the intravenous group which was 65.6 and 49.7 months (15.9 months) respectively (Table 2).
patients with an infected catheter there is no notation if they had concomitant bowel resections and no description if there was delayed catheter placement for history of bowel resection. Eighteen out of 49 patients (37%) had their catheters placed during surgery and were able to complete six cycles, while 55 out of 133 (41%) of the patients had delayed catheter placement and were able to complete six cycles of IP chemotherapy. The study concludes there was no association between timing of catheter insertion and the inability to complete 6 cycles of IP chemotherapy. The issue with this conclusion is that 23 patients had a catheter placed at an undisclosed time during or after the surgery. Of the patients who never started IP therapy 68.8% (11/16) had bowel resections. Bowel resections occurred in 32.2% (66/205) of the patients allocated to the IP arm. There is no notation on the number of bowel resections in the IV arm.

The patients who did not undergo bowel resections were able to complete more IP chemotherapy cycles than those who did receive bowel resection. Forty-four percent (69/155) of the patients who had no left colonic resection were able to complete 6 cycles of IP chemotherapy compared to 34% (17/50) of patients who had a left colonic resection that were able to complete 6 cycles of IP chemotherapy.

In conclusion, the IP chemotherapy arm appears to have benefits in overall survival and PFS. Unfortunately, this result along with the toxicity results is difficult to interpret due to the heterogeneity of treatment between the two groups. There are many questions that remain unanswered, particularly, the true toxicity and efficacy of IP chemotherapy. The uncertainty comes from many areas in the study, the first and most important is that more chemotherapy was used in the intraperitoneal arm. There was 44% more paclitaxel and 25% more cisplatin used in the intraperitoneal group when compared to the IV group (Table 1). It is known that cisplatin has about 10 times higher concentration at the tumor surface when given intraperitoneal, additionally paclitaxel has about 1000 times higher concentration at the tumor due to its hydrophobic and bulky properties [16]. One can presume that the amount of chemotherapy directly given to the intraperitoneal organs are similarly high and thus increase toxicity to the intraperitoneal space. Furthermore, the aggressiveness of the surgeries in the IV arm were not disclosed, there was no report on the number of bowel resections or extent of surgery. Interestingly, the study group concludes that the survival advantage of the regimen may not be maintained if IP paclitaxel was removed, but there was a clear advantage in GOG 104 when cyclophosphamide was used IV and the only intraperitoneal chemotherapy was cisplatin. It is suspected that if the additional paclitaxel was not used in the IP arm there may not have been such high toxicities. We do not know the median interval time between surgery and the first cycle of IV chemotherapy, this could be delayed when compared to the time between surgery and chemotherapy in the IP arm. This delay in time would allow for better recovery in the IV arm and thus better reserve for the patient and possibly better adherence to the IV treatment. Lastly, there was not a standardization for the type of catheter used (could have been a Tenckhoff or implanted port with fenestrated catheter), and this could have been a factor leading to catheter failure.

To reduce toxicity and improve adherence to the IP arm it would be reasonable to have the experimental arm’s (IP) chemotherapy dosages and types equal the control arm (IV), additionally if we could improve and standardize catheters we may be able to increase the number of people completing the IP therapy by 19.5%. To do this we can focus on improving both blockage and infection rates. These rates could be optimized by placing catheters in patients without bowel resections, or by delaying placement in these patients.

Gog 252: A phase III trial of bevacizumab with IV versus IP chemotherapy for ovarian, fallopian tube and peritoneal carcinoma: An NRG oncology study

The fourth and most recent phase III randomized controlled trial includes 1,560 participants and is currently ongoing (NCT00951496). Interval results on PFS were presented in March 2016 at the Society of Gynecologic Oncology Annual Meeting. This randomized trial studies the difference between IV chemotherapy and IP chemotherapy on patients who are also treated with bevacizumab. The participants in this study include patients with stage II-III fallopian tube, epithelial ovarian and primary peritoneal carcinoma. The primary outcome of the study is PFS, secondary outcomes are frequency and severity of adverse events defined by NCI CTCAE version 3.0, overall survival and quality of life scores [22]. There are currently three treatment arms: arm I consists of intravenous therapy of weekly paclitaxel (80 mg/m²) over 1 hour on days 1,8 and 15 along with carboplatin AUC 6 over 30 minutes on day 1 (Table 1), arm II applies IP carboplatin with AUC 6, on day 1 with weekly paclitaxel (80 mg/m²) over 1 hour on days 1, 8 and 15 (Table 1), finally arm III applies IV paclitaxel at 135 mg/m² on day 1 along with IP cisplatin 75 mg/m² and IP paclitaxel (60 mg/m²) on day 2 (Table 1). All three arms of this study also received bevacizumab 15 mg/kg IV on cycles 2-22. Eighty-four percent (1310/1560) of the patients had stage III disease and 57% (889/1560) of the patients were cytoreduced to no visible residual disease. Complications were similar in all three arms when looking at fistulas, GI perforations, leakage. Grade 2 peripheral neuropathy was reported in 30% of patients throughout all three arms. Hypertension induced by treatment was seen in 20.5% of the patients and grade 3/4 nausea/vomiting affected 11.2% of the patients. These two complications were seen more frequently in the IP cisplatin, arm III (Table 2). There was no significant PFS advantage when comparing the three arms in patients with stage II/III who were cytoreduced to 1 cm or less. In these patients the PFS for IP carboplatin compared to IV carboplatin was 2.4 months longer. The PFS for IP cisplatin compared to IV carboplatin was 1.1 months longer (Table 2). There was no difference in PFS between the three arms when comparing patients with stage III disease and cytoreductive surgery to no visible residual disease. Completion rates of 6 cycles were 84-91% between all three arms for platinum agents and 87-88% for taxane agents. The cross over to IV-only therapy was seen in 16% of the patients randomized to IP carboplatin and 28% of the patients randomized to IP cisplatin arm. Overall survival data was not mature at the time of the abstract publication [23].

This GOG study will help answer many questions from the IP debate in terms of toxicity, efficacy and tolerability. At this time the data may be too immature for use in clinical decisions. This study, as with the initial phase III randomized controlled trial (GOG 104), has equal dosages of chemotherapy between arms I and II allowing the investigators to truly test for the efficacy of the administration route, although the anti-angiogenic agent applied to all three arms may prove to be a confounding agent. Arm III will be somewhat more difficult to interpret given that cisplatin is given IP and paclitaxel is given in a 3-week manner both in the IV and IP route. Interestingly the study group decided to reduce the IP cisplatin dose below that of GOG 104, 114 and 172, likely to account for the high concentration achieved within the peritoneal cavity and thus at the surface of the tumor. The reduction of cisplatin may have also been done to help limit the toxicity of cisplatin. This dose of cisplatin is, in theory, closer to the amount...
that would be needed when completing IP chemotherapy given that the typical IV dose is 80 mg/m².

Many interesting points are raised by this study, the first point, IP is unnecessary in a patient with stage III disease who is cytoreduced to no residual visible disease. Certainly from the data presented it appears PFS showed no difference between the three arms, thus there is no role for IP chemotherapy in stage III patients with no visible residual disease after cytoreduction. This is intuitive from a theoretical standpoint, if there is no disease in the peritoneal cavity after cytoreductive surgery, there is no advantage for application of high concentration chemotherapy to the peritoneal cavity. The dose achieved in the intraperitoneal cavity through the intravenous route is likely adequate to stifle residual microscopic disease and thus, in this subset of patients IP chemotherapy is unnecessary.

This study is very well designed. There are many ongoing questions about IP chemotherapy that will certainly be addressed. To answer these questions fully though, more data will be needed. For instance, it is important to know the breakdown of stages in each arm. Overall the abstract reported there were 16 percent of the patients with stage IIA or IIB. These stages each will have different biologic impacts, in the case of stage IIA, all tumor cells would be removed with surgical staging leaving no benefit for IP. In this case, it is necessary to understand how many stage IIA or IIB reside in each arm of the study. Additionally, it may be helpful to complete subgroup analysis separating stage II patients from stage III and determining the PFS and OS between the three study arms. It will also be helpful to know the distribution of patients with cytoreduction to no visible residual disease in each arm of the study. The study reports a 2.4 month longer PFS and a 1.1 month longer PFS for IP carboplatin and cisplatin respectively, one reason there may have been minimal difference between the IP and IV groups is that 16-28% of the patients crossed over from IP to IV therapy, additionally it may be interesting to see a subgroup analysis where the 58% of the patients who were cytoreduced to no visible residual disease are separated from the group of patients with residual disease and determine if difference exists in PFS and OS. Further reasoning as to the minor difference in PFS between arms I and II may be due to the addition of a confounder as it may limit the amount of chemotherapy accessing the core of the nodule.

Certainly overall survival has not yet been determined and will be helpful in informing clinical decisions. One disadvantage of all the regimens in this study is the high neuropathy rate, 30% in each arm. The high rate could be due to paclitaxel dosing, all three arms have doses that range, during one cycle, from 210 mg/m² for Arm III and 240 mg/m² in Arm I and II (Table 1). Interestingly, the same sensory neuropathy result was seen in GOG 262 when dose-dense paclitaxel was given. The dose-dense group displayed higher rates of grade 2 to 4 sensory neuropathy (26% vs. 18%) compared to the every-3-week paclitaxel. The total dosage of paclitaxel in the dose-dense arm was 240 mg/m² for one cycle compared to the every-3-week dosing where a patient received 175 mg/m² of paclitaxel over the same time frame.

Intraperitoneal complications

There are two types of complications seen in women undergoing IP therapy; those related to the drugs themselves and those related to the catheter.

IVa. Chemotherapy related toxicities

The complications of IP chemotherapy are specific to the agents utilized. This primarily includes neurotoxicity with cisplatin and paclitaxel and cisplatin related nephrotoxicity for ovarian cancer patients. Consistently, in Gynecologic Oncology Group (GOG) 172, the incidence of serious (grade 3/4) renal toxicity was higher in patients receiving IP treatment compared with standard (IV) treatment [1]. Cisplatin via IP was shown by GOG 172 to cause increased renal toxicity, neurotoxicity was also a major complication for patients receiving IP therapy (Table 2). In GOG 172, IP treatment resulted in significantly worse neurotoxicity at three to six weeks after chemotherapy and one year later when compared with IV therapy [1]. This result to interpret because the dosages of paclitaxel and cisplatin were higher in IP versus IV therapy as outlined earlier. It may be reasonable, as has been done in GOG 252, to reduce cisplatin dose anywhere from 75 or 80 mg/m² given IP cisplatin has 10-15 times higher concentration at the tumor compared to IV therapy. The tolerability of the regimen may be substantially improved by reducing the IP cisplatin dose to 75 or 80 mg/m² [12,15,24].

Abdominal pain is more common and severe with IP therapy compared with IV administration of chemotherapy, this was highlighted best in GOG 104. The pain from IP chemotherapy is likely related to stretching and distention of adhesions throughout the abdomen, in particular between loops of bowel, or from irritation of the intercostal nerve. These two sources of pain are a product of the volume of chemotherapy fluid instilled [25]. In GOG 172, chemotherapy doses were reduced for patients reporting grade 2 abdominal pain. Discontinuation of IP treatment was required for those with grade 3 abdominal pain (5% of patients) or recurrent grade 2 abdominal pain despite dose reduction [4]. In GOG 172, abdominal pain scores were significantly worse prior to the fourth cycle of IP compared with IV treatment [1]. In all of the above outlined GOG studies the intraperitoneal fluid at a volume of 2 liters was infused “as fast as possible” additionally most of the abdominal pain resolved soon after the infusion was completed. Additionally, one year after completion of treatment, there was no difference in pain scores between the IV and IP arm. It might be beneficial to look toward the experiences of intraperitoneal dialysis when considering infusion rates given that most of the abdominal pain was secondary to volume of infusion and rate.

To reduce cisplatin induced neuro- and nephrotoxicity, there is an attempt, with GOG 252, to determine if carboplatin is a better alternative to cisplatin when delivered intraperitoneally. As outlined above GOG 252 has 1,560 trial participants randomized into three arms, arm I with IV carboplatin/IV paclitaxel, arm II with IV carboplatin/IV paclitaxel and arm III with IP cisplatin/IV and IP paclitaxel. Thirty percent of patients in each arm reported grade 2 peripheral neuropathy. Treatment induced hypertension (20.5%) and grade 3/4 nausea/vomiting (11.2%) were observed more often in the IP cisplatin arm, although there is no notation yet if this is statistically significant (Table 2). The confounder in this case is that paclitaxel is administered IV and IP. With IP administration there will be higher intraperitoneal concentrations and longer clearance time then when compared to IV, potentially leading to worsened neurotoxicity. In this case it will be difficult to draw conclusions on toxicity between cisplatin and carboplatin IP with this paclitaxel confounder. Importantly though,
GOG 252 has learned from GOG 172 and dose reduced cisplatin IP to 80 mg/m².

IVb. Catheter related complications

One of the acknowledged difficulties with IP chemotherapy is the inconsistent ability to complete six cycles of the chemotherapeutic agents after surgery. In GOG-104, GOG-114, GOG-172 and GOG-252, 58%, 71%, 42% and 84-91% of IP patients, respectively, received all six cycles of intended therapy via that route.

In the GOG 172, 119 women in the IP chemotherapy group did not complete the entire six courses of therapy, and catheter-related problems were the primary reason in 40 of these patients and a contributing cause in another 10 patients [7,26]. These problems included catheter-related infection (25 patients), a blocked catheter (10 patients), leakage around the port or into the subcutaneous tissues (five patients), access problems (eight patients), and vaginal leakage of infusion fluid (in two). Similar complication and completion rates were seen in other studies [7,26]. GOG-104 did not outline any catheter related complications but importantly, the same percentage of patients were unable to complete the IV therapy and may have not been related to catheter complications. In the new phase III (GOG 252) abstract 84-90% of patients completed 6 cycles of platinum and 87-88% completed 6 cycles of taxane. It will be interesting to see if the catheters contribute to these patient’s inability to complete 100% of the cycles.

To assess impact of outpatient intraperitoneal (IP) chemotherapy on quality of life (QOL), Gotimer et al., performed a cross sectional study of 71 patients with optimally cytoreduced stage III and IV ovarian cancer. These patients, after optimal cytoreduction, received IP chemotherapy at a single institution [27]. The investigators sent anonymous surveys looking at physical health (PH), mental health (MH), social health (SH) and patient subjective sense of worth (WO) of IP chemotherapy. In the PH portion, 50.0% reported that fatigue severely affected QOL. Other aspects were pain (39.6%), GI problems (37.5%) and “chemotherapy brain” (29.2%). In the MH portion, 25% reported significant stress and 20.8% experienced anxiety. In the SH portion, 27.5% reported therapy interfered with work. Interestingly, the majority (83.3%) reported that the effectiveness of IP chemotherapy made the side effects tolerable, 95.8% did not regret it, and 87.5% would recommend it [27]. This was the first study evaluating the patient’s sense of IP chemotherapy’s worth. Gotimer et al. concluded that while the side effects decrease QOL, the majority of patients reported that therapy is worth their cost, no regret is reported from the patient’s perspective.

V. Improving the delivery system

The first IP chemotherapy catheters were catheters originally developed for chronic peritoneal dialysis by Tenckhoff and Schechter [28,29]. This type of peritoneal access device had a higher risk of infection because the tip of the catheter was outside of the body. This prompted the development of intraperitoneal ports that were implanted below the level of the skin. Catheters now exist in multiple forms including single-lumen ports with a single opening at the intraperitoneal tip and also single lumen ports that are lined with fenestrations. Catheters come in multiple diameters and are made from a combination of materials including titanium, plastic, silicone, and polyurethane. One particular catheter that has been optimized for IV, and has been used in small IP chemotherapy studies, is the Power Port Implantable Ports [30]. These ports allow for slow infusion (up to 5 mL/s with 300 psi) of platinum and taxol agents. There is currently no standard port that is required to administer IP chemotherapy, leaving it up to the surgeon or oncologist to decide which ports to use creating heterogeneity throughout intraperitoneal chemotherapy.

The rate of complications when using IP ports ranges from 7-40% [31]. These complications include infection, obstruction of the port, abdominal pain, peritonitis, retraction of the port from the peritoneal cavity, and access issues. The most common complications experienced are obstruction (37.6%) and infection (31.4%). As a result of these complications it has been shown that 15% of patients are unable to complete their scheduled courses of IP chemotherapy [31]. This, in turn, causes a change in therapies, potential delays in chemotherapy schedules and could alter patient’s clinical course. There have been some studies that evaluate the impact of timing IP port placement (primary versus secondary procedure) and how this changes the rate of complications. These studies are difficult to assess as they do not compare head-to-head delayed IP port placement versus immediate port placement in patients with bowel resections [32-34]. Along the same line, GOG 172 is unable to show a difference in delayed catheter placement versus immediate placement, although they were unable to account for the timing of catheter placement in 23 patients. Timing of catheter placement will continue to be an ongoing debate, but intuitively the more aggressive surgery, the more likely the patient is to have complications afterwards, this includes catheter complications. Therefore, it may be reasonable to delay placement of the catheter until the patient has recovered from an aggressive cytoreduction. Interestingly, it has been shown that when seasoned surgeons place ports, and when experienced nurses care for ports, there are lower rates of complications [31]. With this, more efficient/experienced surgeons, along with designated care teams and new techniques, gynecologic oncologists may be able to decrease the risk of IP port failure and other associated complications [30].

As the data about IP chemotherapy continues to mature, efforts have also been paid toward developing novel methods to deliver of IP chemotherapy. One such delivery method is Hyperthermic IntraPeritoneal Chemotherapy (HIPEC). HIPEC is the application of highly concentrated, heated (41-43 degrees Celsius) chemotherapy directly to the abdomen during surgery for 30 minutes to two hours. It is hypothesized that heating the chemotherapy and exposing patient’s abdomens early in the process, prior to formation of adhesions, may yield a therapeutic advantage. Many in-vivo mouse models show that heating of chemotherapy increases tumor cell uptake and cytotoxicity by increasing blood flow and obtaining improved penetration of the chemotherapy [35].

There are a variety of chemotherapies that can be used in this setting and evidence suggests that while up to 35% of patients may experience associated morbidity, it is generally safe in gynecologic oncology patients [36-38]. Furthermore, there have been case-control studies [39] as well as retrospective reviews [40-42] which have yielded promising results in terms of OS and PFS when compared with standard therapies. With this being said, we are currently awaiting the results of four RCTs to mature [37]. These, we hope, will provide us with evidence to support the use of a novel therapeutic modality we can offer our patients. As we wait for these results, we expect the development and implementation of additional IP chemotherapies such as targeted agents, the use of nanoparticles, and other novel agents to move toward evaluation in clinical trials.

Future of intraperitoneal chemotherapy

Despite NCI recommendations released in 2006, Wright et al.
reported an overall rate of IV/IP chemotherapy of 47% at six NCCN cancer centers [43]. We speculate that the uptake and application of IP chemotherapy for the treatment of advanced ovarian cancer can be improved as the delivery system evolves and as novel therapies are introduced. This will hopefully minimize the complications associated with catheters that were seen in GOG 172. Below are some examples of relatively novel concepts that may improve IP chemotherapy safety and efficacy in the treatment of this difficult disease.

Vla. Antibodies

Currently available to clinicians is an antibody toward VEGF, clinicians use this antibody in combination with the standard of care in advanced ovarian cancer. GOG 218 showed that this antibody (bevacizumab) improved OS by 3 months. Throughout the years since the approval of bevacizumab, clinicians have employed bevacizumab in the IP route in small case series when malignant ascites was present [44-46]. Since its use in the peritoneal cavity has been pioneered by these groups it is trusted that bevacizumab may be used intraperitoneally. In order to prognosticate which patients may benefit from IP bevacizumab Chia et al. correlated levels of IP VEGF with overall and disease-free survival [47]. Intravenous (IV) VEGF levels were taken before surgery, whereas IP VEGF levels were taken at various time points during and after surgery from 97 patients. These patients were treated for peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [47]. The authors reported a lower IP VEGF level prior to surgery, they state that this lower IP VEGF level was associated with improved survival. With this result they conclude that the use of preoperative intraperitoneal bevacizumab for patients with a larger tumor burden might be considered [47]. In advanced ovarian cancer, the utilization of IP bevacizumab has not been investigated fully. There is an ongoing clinical trial which is aimed at investigating the treatment of malignant ascites of ovarian cancer with IP bevacizumab combined with IP hyperthermic perfusion chemotherapy (NCT01838538). The concern regarding the impaired wound healing with using bevacizumab in the front-line setting is likely one of the main reasons large randomized controlled trials on this topic are limited.

Vlb. Nanoparticle delivery

Despite the advantages of IP therapy in PFS and OS compared to IV chemotherapy, IP chemotherapy has had low uptake in the clinical realm. IP chemotherapy may be better tolerated and utilized widely if there was improved drug delivery control. In order to improve this aspect of IP chemotherapy, Sun et al., developed an injectable crosslinkable hydrogel depot containing paclitaxel nanocrystals (PNC) [48]. In-vivo mouse models showed that the gel remained in the peritoneal cavity and maintained a high level of local paclitaxel concentration for 2 weeks. In cellular toxicity test and MTD assessment, PNC-gel provided better cell death and greater tumor cell toxicity than PPT-gel containing larger paclitaxel particles. Extended survival of mice with tumor was seen in a single IP administration of PNC-gel, this was significantly better than with standard paclitaxel injection. The in-vitro cell toxicity tests and in-vivo mouse model show the possible beneficial effect of particle size reduction of the paclitaxel nanocrystals which lead to a greater dissolution rate and cellular uptake of paclitaxel. This demonstrates the promise of a gel depot with nanocrystals as an IP drug delivery system [48].

Vlc. Immunotherapy

The effects of IP therapy, and chemotherapy in generally, likely have effects beyond direct cytotoxicity of the tumor cells. IP chemotherapy, in particular likely leads to perturbations in the peritoneal and omental stroma and microenvironment, chemotherapy additionally may enhance host immune response in the peritoneal cavity [49]. The investigation of the immune and microenvironment response to local and systemic effects of IP chemotherapy is being investigated by GOG-0271. In this trial there will be a focus on evaluating the immunomodulatory cytokines and tumor-associated alterations in the peritoneal fluid, washings, and blood. These results will help to elucidate how chemotherapy, in particular IP chemotherapy, may be altering the immune system in the peritoneal cavity.

Vld. Radiotherapy

Recent research has focused on investigating the efficiency of immune therapy combined with chemotherapy and radiotherapy. Yan et al. investigated changes in T-lymphocyte subsets after hyperthermic intraperitoneal chemotherapy (HIPEC) or radiotherapy by utilizing flow cytometry in lung cancer patients [50]. A total of 957 patients (male: 555; female: 402; median age: 49.3 years) with lung cancer who received HIPEC or radiotherapy were enrolled in the study. No statistical difference was seen in patients between their pretreatment levels and after chemotherapy treatment levels in the CD3, CD4 and CD8 T-cells, but there was an elevation in the patient’s CD3+ T-cells three months after radiotherapy (78.71 ± 9.36 vs 68.15 ± 9.65, P < 0.05) [50]. In another study by Bian et al. IP chemotherapy was combined with radiation. The study reported on patients with locally recurrent colon cancer 8 months after radical cytoreductive surgery and 6 cycles of adjuvant chemotherapy [51]. The patient’s recurrent disease was treated with synchronous intensity modulation radiation therapy and intraperitoneal (IP) perfusion chemotherapy with irinotecan (100 mg/m²) which resulted in a complete response. The authors suggested that a combination of therapies, including radiotherapy, IP perfusion chemotherapy and surgery, may be beneficial and effective in patients with recurrent colon cancer [51]. Combining the conclusions from these two studies it may be reasonable to presume that radiation therapy will prime the immune system and IP chemotherapy will work in a synergistic way to cause tumor cell death. There currently have been attempts to evaluate this possible link, for instance, researchers from University of Utah had a protocol to study whole abdomen radiation in conjunction with IP chemotherapy for treatment of small volume recurrent ovarian carcinoma, unfortunately the study was withdrawn for inability to accrue adequate numbers of patients (NCT00942838). Given the interface of radiotherapy and the immune system along with the possibility of a synergistic effect of IP chemotherapy this remains an area of interest in the treatment of ovarian cancer patients.

Vle. Genomics to identify potential responders

Currently, to identify patients who are candidates for IP chemotherapy, clinicians use factors such as age, histology, degree of cytoreduction and extent of surgery (with or without bowel resection) [52]. Gynecologic oncologists may be able to add genomic alterations to the list of factors which may help determine which patients will benefit from IP chemotherapy. A recent analysis of BRCA1 mutations in 393 patients from the GOG-172 demonstrated an effect on overall survival [2]. In the analysis of the GOG-172 participants, loss of BRCA1 was seen in 48%. Among the BRCA1 mutated cohort, the median OS for intravenous vs. intraperitoneal therapy was 84 vs. 47 months (P = .0002), which led to a 33% reduction in the hazard for death. Among patients with normal expression of BRCA1, there was no difference between intraperitoneal and intravenous therapy [2]. Histology has
also proven to be important, as patients with serous cancer, seem to benefit from intraperitoneal therapy, it is likely that there are similar genomic mutations in these serous subtypes that are contributing to their sensitivity. This result needs to be taken cautiously given the unequal amounts of chemotherapy, both cisplatin and paclitaxel, given to the IP arm of the trial.

Biomarkers are another area which could prognosticate a response to IP chemotherapy in high grade serous ovarian cancer (HGS OvCa) patients. Seagle et al, utilized The Cancer Genome Atlas (TCGA) to assist in identification of expressed genes associated with DFS and OS after treatment with adjuvant IP or IV chemotherapy [53]. Statistically significant decreases in DFS and OS after IP chemotherapy were seen with increased expression of NCAM2 and TSHR and decreased expression of GCNT3. A non-significant DFS increase after compared to IV chemotherapy was associated with high tumor expression of FZD4, LMAN2, FZD5 and STT3A. Alternatively, low expression of APC2 and high expression of FUT9 was associated with OS of 5.5 and 7.2 months after IP to IV chemotherapy respectively (p \leq 0.007) [55]. This study highlights, that not only do the chemotherapy agents have differences among cancer with altered genetic expression, but that the rate of an agent may also be affected by the differential genetic expression of a tumor cell. In light of the morbidity of IP chemotherapy, it may help to search for biomarkers or mRNA expression to assist in triaging which patients may benefit IV or IP chemotherapy.

Conclusion

Intraperitoneal chemotherapy was initially developed based on pharmacokinetic models. The theory was then evaluated in-vivo with rat and mouse models leading to early clinical trials. Since 1996, there have been rigorous phase III trials evaluating the effectiveness of IP chemotherapy. With all of the available data and phase III trials, gynecologic oncologists are still reluctant to accept IP chemotherapy as a staple in advanced ovarian cancer treatment. This is likely due to the heterogeneity in dose and type of chemotherapeutics seen throughout each of these phase III trials. Some of the heterogeneity is found within studies, for example, there are significant differences between chemotherapy dosing in the experimental and control arms in GOG 172 and GOG 114 (Table 1). In some studies, there are limited details on how many patients had bowel resections in the IV versus IP groups, what types of catheters were used and incomplete data on timing of IP catheter placement. Confounding is present in other studies where immunologic anti-angiogenic agents are applied to all participants, such as in GOG 252 and therefore clouds comparison between IV and IP chemotherapy. Heterogeneity between studies has also made it difficult to combine trial results and develop an overall consensus regarding IP chemotherapy.

The question of the efficacy of IP chemotherapy needs to be answered with well-designed clinical trials. With these trials we hope to determine if toxicity is truly worse and if efficacy is truly improved among IP versus IV administration. Until this is determined, studies like “Utilization and Toxicity of Alternative Delivery Methods of Adjuvant Chemotherapy for Ovarian Cancer” (determined IP patients were more likely to be seen in the emergency room, admitted to the hospital and have higher per-patient cost of hospitalization), are difficult to interpret because of the heterogeneity of IP chemotherapy regimens and administration devices. Attempts to identify and quantify the effects of IP chemotherapy regimens on the health care system are important but we must also understand the degree of heterogeneity in the IP treatment regimens. Before compiling results from heterogeneous studies and abandoning a possibly effective therapy, we must conduct homogenous phase III trials and analyze the results closely. Homogeneity that is exemplified in the new GOG 252 study, where the IV and IP carboplatin arms (same dosages of chemotherapy) have been found to have no difference in toxicity and about the same rates of cycle completion.

While we are waiting for GOG 252 results it is important to continue advocating for standardized intra-peritoneal chemotherapy regimen in carefully selected patients. It may also be important to determine new ways to deliver IP treatment such as developing new catheter systems, advancing the surgical techniques for placement of IP catheters, standardizing protocols for maintaining catheters in the outpatient infusion center. In the near future we may also consider stratifying patients for IP therapy by using genetics, gene expression and surgical outcomes.

References

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