Intraperitoneal chemotherapy requires expertise and should be the standard of care for optimally surgically resected epithelial ovarian cancer patients

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Women presenting with epithelial ovarian cancer should be treated in centers with both aggressive surgical and chemotherapy teams prepared to confront the modifiable factors, which can optimize the patient’s outcome. This implies experience in extensive cytoreductive surgery, including the removal of the tumor from the upper abdomen. An intraperitoneal (IP) catheter should be left in place for the consideration of IP chemotherapy. The supportive care structures need to be in place with teams prepared to help women complete six cycles of intravenous and IP paclitaxel (Taxol) and IP cisplatin with the least toxicity. Survival figures of 128 months are to be expected when no residual disease is left behind and IP chemotherapy is administered successfully.

On 5 January 2006, the US National Cancer Institute (NCI) released a clinical announcement concerning recommended treatment for advanced ovarian cancer [1]. Based on the results of eight phase III clinical trials, the NCI encouraged the combination of intravenous (IV) and intraperitoneal (IP) chemotherapy. The combined approach, though more toxic, extends overall survival for women with advanced ovarian cancer by about a year compared with intravenous delivery alone. The best survival reported was achieved with the Gynecologic Oncology Group (GOG) 172 using paclitaxel (Taxol) 135 mg/m² IV with 24 h infusion day 1, cisplatin 100 mg/m² IP day 2 and paclitaxel 60 mg/m² IP day 8 delivered on a 21-day cycle for six cycles. Paclitaxel and Cisplatin provided by Oncology Supply in Dothan, Alabama. With the IP arm, the overall survival was 65.6 months versus 49.7 months for the IV arm (NCI 2006).

Epithelial ovarian cancer has been demonstrated to have improved overall survival based on younger age, excellent performance status, endometrioid histologic cell type, lower stage of disease, lower grade and lower co-morbidity scores [2, 3]. The above prognostic factors cannot be modified once the patient with ovarian cancer has been identified (Figure 1). There are only a few prognostic factors which can be modified based on the decisions of the patient, and their physicians with respect to surgical decision-making and chemotherapy administration choices. Achieving no residual disease at the completion of cytoreductive surgery (Figure 2) and completing six cycles of IP chemotherapy (Figures 3 and 4) are examples of modifiable decisions which improve survival and can only be achieved in enthusiastically committed institutions partnering with their surgeons. The intraoperative decision-making has been shown to influence patient survival. There should be willingness to carry out diaphragm resection, splenectomy, bowel resections,

This manuscript summarizes the importance of these decisions and the building of a team with the level of expertise needed. The effort required to achieve this improvement in survival and help the patient manage the side-effects is considerable and requires commitment and in this setting support can be found in using the American Society of Clinical Oncology guidelines for antiemetics [7]. Showing enthusiasm and trusting the final outcome help to give guidance to the uninformed patient and require referral to centers of excellence in ovarian cancer treatment. The United States is beginning a ‘pay for performance’ program where quality measures will influence reimbursement including surgical outcomes and the use of IP chemotherapy with the support of the Society of Gynecologic Oncology [8–11].

The first decision that needs to be made is to assess whether there is a candidate for upfront surgery or should be treated first with neoadjuvant chemotherapy (NACT). In fact, there are very few patients unlikely to benefit from primary surgery and they have a combination of poor co-morbidity scores, are aged over 74, or have stage IV disease [12, 13]. Another subset shown to benefit from NACT over primary surgery are those with metastatic implants >45 mm [14]. Aletti et al. [15] have demonstrated that tumor deposits >4 cm on the diaphragm or mesentry of the bowel are less likely to benefit from primary surgery. NACT has been shown to be beneficial to this small subset of patients with unresectable disease or those who have a high-mortality risk or complication risks [14]. Vergote et al. [16] reported that complete resection to no residual disease at interval debulking can also improve survival after NACT. A computed tomography (CT) scan or combined diffusion-weighted and gadolinium-enhanced magnetic resonance imaging can help the gynecologic oncologic surgeon, in consultation with the radiologist, to determine if the patient has unresectable disease [17, 18].

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lymphadenectomy and thorough peritoneal resections of all tumors, procedures which require experience and consistent level of effort and time commitment [8, 15]. The goal must not be ‘optimal surgical resection’, as previously defined by GOG of 1 or 2 cm of residual tumor nodules, which was previously required for enrollment into the GOG IP chemotherapy [19–21]. The standard surgical outcome must be ‘no gross residual disease’ as defined by Bristow et al. [4] and Chi et al. [5]. The next difficult management decision is the choice of chemotherapy. The high-volume ovarian cancer treatment center team would have already assumed that the patient will either be enrolled in a prospective clinical trial or be treated with IP chemotherapy to improve survival. The IP chemotherapy port would already be in place as an integral part of the primary debulking surgery to prevent delaying the initiation chemotherapy postoperatively. The port can be removed if the patient chooses an alternative treatment, or is randomly on a clinical trial (with no IP therapy), without delaying her treatment. Patients should be treated as soon as they resumed a normal diet, have normal bowel function and are ambulatory at home, as important evidence that the patient is without risk of surgical complications [22]. Chemotherapy should start within 21 days of primary surgery.

The chemotherapy treatment decisions involve three choices: IV carboplatin and paclitaxel given on a 3-week schedule, as in GOG#182 [23]; IV carboplatin every 3 weeks with dose-dense weekly intravenous paclitaxel, as in the JGOG study [24] or IV paclitaxel, and IP cisplatin and IP paclitaxel, as in GOG#172 [21]. The survival advantage of IP chemotherapy has not been directly compared with the standard carboplatin/paclitaxel regimens, so some assumptions are made when making comparisons. The easiest way to communicate with the patient is to describe the

Figure 1. An example of a prognostic factor which cannot be modified by the ovarian cancer treatment center. Endometrioid adenocarcinoma has a better survival than the serous type and the worst outcome is observed with clear cell carcinoma and mucinous adenocarcinoma which requires new personalized treatments using specific rare tumor studies or phase I programs. Landrum et al. [3].

Figure 2. The effect of residual disease on median survival of women treated with IP cisplatin chemotherapy using the data combined from GOG-114 and GOG-172. Landrum et al. [3].
treatment schedule and convenient factors. The side-effects should be clearly explained, and the patient must be willing to accept more nausea, neuropathy, abdominal pain and infections, with the IP administration schedule [6]. The Jaaback review in 2011 demonstrated a consistent finding of an overall survival benefit across all randomized, controlled trials with a HR = 0.81 (0.72–0.90). Survival in women with no residual disease after surgical resection of stage III ovarian cancer and treated with IP GOG#172 was reported by Landrum et al in 2013, showing a median survival of 128 months. This outcome compares favorably with the results of GOG#182 reported by Bookman et al. [23], where patients treated with IV carboplatin/paclitaxel showed a survival of 68 months. Unfortunately, the survival of women treated with dose-dense (weekly) paclitaxel with every 3-week carboplatin has not been reported with respect to patients with no residual disease after surgical cytoreduction.

A direct comparison of IP cisplatin and paclitaxel chemotherapy versus dose-dense paclitaxel and every 3-week carboplatin was made in GOG#252, a randomized trial in the US population, which will be available for PFS analysis of in 2014 [25] (Figure 4). The third arm was the IP administration of carboplatin with IV dose-dense paclitaxel. The comparison of IV versus IP carboplatin will be an important finding for future patient treatment decisions as well. At this time, we cannot consider IP carboplatin as a standard of care regimen.

GOG#252 also included bevacizumab in cycles 2–22 and this addition is not expected to affect the comparison between the cytotoxic treatment arms.

The optimal dose and schedule of cisplatin and paclitaxel have not been established as GOG#172 utilized 100 mg/m² of cisplatin in the peritoneal cavity on a 3-week cycle had considerable toxicity. The neuropathy, metabolic derangements,
renal insufficiency and failure to complete six cycles in 60% of patients, observed in GOG#172, make modification of the dose a consideration for future studies. Of note, ondansetron and aprepitant were not available at the time of conducting GOG#172, and this may have caused excessive GI toxicity, which may not occur today. Also alternative dose schedules have been proposed, such as cisplatin 50 mg/m² on days 1 and 8 in combination with IV paclitaxel showing acceptable single-institution results [26]. GOG#252 was modified to achieve an outpatient regimen and reduce toxicity with as yet unknown effects on efficacy (Figure 5). For example, paclitaxel at 135 mg/m² IV (over 24 h) was given on day 1, cisplatin 75 mg/m² IP on day 2 and paclitaxel 60 mg/m² IP on day 8 as a modification of the GOG#172 experimental arm. It is quite possible that with excellent hydration (2 l of normal saline, ondansetron, aprepitant, decadron, benedryl, cimetidine that 100 mg/m²2 would have been successful. A planned randomized, phase II study will hopefully shed some light on alternative regimens by comparing weekly IV paclitaxel 80 mg/m² days 1 and 8 and days 1 and 8 IP cisplatin at 50 mg/m² and day 15 IP paclitaxel 60 mg/m² versus weekly paclitaxel 80 mg/m² IV days 1 and 8 and IP cisplatin 100 mg/m² day 1 and IP paclitaxel 60 mg/m² day 15. Toxicity rates and completion of six cycles will be the outcome measures in a single-institution study before embarking into a larger multi-institutional phase III trial.

The last consideration is whether there are individual patient findings which should be factored into the decision of which regimen should be selected. Landrum et al. [3] looked into the effects of lymphadenectomy and nodal metastasis with regards to the benefits of IP chemotherapy utilizing the data abstracted from both the GOG#114 trial [20] and the GOG#172 trial [21]. Patients with metastatic tumors in lymph nodes survived a median of 63 months when treated with IP compared with 56 months when receiving IV chemotherapy. Therefore, the presence of retroperitoneal metastasis is not a contraindication to treatment with IP chemotherapy. Another fascinating finding was that patients who had not undergone lymphadenectomy had a worse survival than patients whose involved retroperitoneal lymph nodes were resected. Women without nodes lived 54 months after receiving IP arms, whereas those on IV chemotherapy only had a median survival of 40 months. Does this mean that resection is beneficial? Alternatively, the question could be raised whether the decision ‘not to perform lymphadenectomy’ was secondary to some poor prognostic factor perceived by the surgeon, or less commitment of the surgeon to the paradigm of ‘no residual disease’.

An important long-term quality-of-life finding by Landrum et al. is a decrease in recurrence in the abdominal cavity after chemotherapy is administered via the IP route. Sparing patients the suffering from ascites and inability to eat when they recur is a tremendous survivorship benefit.

The immunohistochemistry analysis using BRCA 1 antibodies on the tumors, and being part of the GOG#172 protocol, showed that patients with a low expression were those most likely to benefit from IP chemotherapy. Such patients yielded a survival of 84 months with IP chemotherapy compared with a survival of 47 months when treated with IV chemotherapy (\(P = 0.0002\)) [27]. These results led to the hypothesis that pretreatment IHC for BRCA 1, and in addition for BRCA 2, may help to triage women to IP chemotherapy. This study result is scheduled to be confirmed in GOG-252 in 2014. There would be a patient toxicity benefit if we knew which patients are most likely to benefit versus only suffer from toxicity of IP cisplatin. Women with normal BRCA expression may be best treated with IV dose-dense paclitaxel and carboplatin to optimize survival and avoid unnecessary toxicity. It may indeed be the case that women with abnormal somatic BRCA expression should receive IP chemotherapy and a PARP inhibitor, when available, to give them the chance of cure or a >10-year survival. A future consideration to study the best combination results from all the studied treatments to identify those that can be treated with curative intent by using weekly IV paclitaxel, IP cisplatin and paclitaxel, and a PARP inhibitor in women with abnormal genetic or somatic expression of BRCA.

Patients who choose to be treated with IP chemotherapy who do not already have peritoneal catheters can have devices implanted.

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**Figure 5.** Gynecologic Oncology Group Study GOG-252 Clinical Trial, which completed accrual of 1565 patients in July 2012. The progression-free survival report is expected in 2014 [25].
by interventional radiologists or surgeons familiar with laparoscopic techniques using the right upper quadrant entry techniques. Mini-laparotomy in the right lower quadrant is also generally successful if resection of the terminal ileum or right colon did not occur. A careful review of the cytoreduction operative report can improve outcomes with IP port and catheter placement and avoid complications, by avoiding likely adhesions of the bowel to the anterior abdominal wall. [22, 28]. Failures of IP catheter scan sometimes be corrected. However, infected catheters should be removed and not replaced. Blocked catheters can be replaced if the patient has free space in the IP area remaining between bowel loops and has not had peritonitis as a complication of surgery or chemotherapy. Access problems due to a rotated port can be easily corrected. Most patients, however, complete their chemotherapy with IV treatment once catheter complications occur.

In conclusion, setting up an ovarian cancer treatment center must include the training and maintenance of a committed multidisciplinary team to deal with the modifiable risk factors that affect survival, i.e. residual tumor volume after surgery and chemotherapy choices. Adequate information for the patient on these items is therefore essential. This team of gynecologic oncologists, radiologists, chemotherapy nursing, supportive care staff, genetic counselors and many others should be self-monitored for objective quality indicators, including the following outcomes: advanced directives discussed and completed, as well as appropriate hospice referral 30 days prior to death; genetic testing for Fanconi pathway, Lynch and BRCA 1 and 2 abnormalities; appropriate selection of poor prognosis patient for primary treatment with NACT; operative 30-day mortality; residual disease following surgical cytoreduction; enrollment on clinical trial; and completion six cycles of IP chemotherapy.

disclosure

The author has declared no conflicts of interest.

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