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Chapter 9

Management of Ovarian Cancer — Is There a Role for Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)?

Melissa Ching Ching Teo and Grace Hwei Ching Tan

Additional information is available at the end of the chapter

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Abstract

Ovarian cancer is one of the commonest malignancy in women worldwide, and is the most lethal of all the gynaecological malignancies. Ovarian cancer often presents at an advanced stage, with the involvement of the peritoneal surface either at the initial diagnosis or at recurrence. Despite the advances made in the surgical techniques and chemotherapeutic options regarding agents, schedule, and route of administration, majority of the patients recur and eventually succumb to their disease. The change in the surgical approach supporting more radical and extensive surgical procedures, in a bid to attain optimal cytoreduction with no gross residual disease, has seen improvement in the survival, as has the use of intraperitoneal chemotherapy in combination with i.v. agents. Although peritoneal carcinomatosis has always been a poor prognostic factor, it ceases to be a factor of much importance if complete cytoreduction can be achieved. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) provide the combined benefits of surgical eradication and effective chemotherapy, and can be performed with acceptable morbidity and mortality. Further trials are being undertaken to examine its role in the primary, as well as recurrent settings of advanced ovarian cancer and to determine the ideal drug combinations and dosages. We aim to discuss the role of CRS and HIPEC in the treatment of ovarian cancer.

Keywords: Ovarian Cancer, CRS, HIPEC

1. Introduction

Ovarian cancer one of the commonest malignancies in women worldwide, with an annual incidence of 239,000 [1, 2]. It is the most lethal of all the gynaecological malignancies, the fifth leading cause of cancer deaths, and claimed 151,917 lives in [1, 2]. Most patients with ovarian cancer present with ostensibly innocuous symptoms of abdominal bloatedness and discomfort, and hence are often diagnosed at an advanced stage, with 60–70% of patients having stage 3 or 4 disease at diagnosis [3]. The standard approach is optimal debulking and adjuvant chemotherapy with platinum-based and taxol-based chemotherapy. Even with optimal treatment, the median five-year survival is less than 50% [4] and in advanced ovarian cancer, this drops to less than 25% [4]. Up to 70% of all patients diagnosed with ovarian cancer relapse and ultimately succumb to their disease.

2. Optimal debulking

Surgery remains the foundation of the management of ovarian cancers, as it is often required initially to attain a diagnosis, to formally stage the patient, and is the mainstay of treatment in the majority of diagnosed cases [5]. The definition of optimal cytoreduction has evolved over the years, but was originally defined as residual disease less than 2 cm in size. This was further altered with evidence establishing the significantly superior survival of those with residual disease measuring less than 1 cm and subsequently 5 mm in size [6–8]. Even in those with traditionally defined optimal cytoreduction with residual disease measuring less than 1 cm, the risk of death increases considerably when compared with those with no residual disease [9]. Over the years, there has been a glut of data concluding that complete cytoreduction, with no gross residual disease, yields the best results in terms of survival [10]. Patients with no gross residual disease, 0.1–2 cm residual disease, and more than 2 cm residual disease had five-year survivals of 60,35, and less than 20%, respectively [11, 12].

3. What happens after debulking?

In the bulk of patients with ovarian cancer, adjuvant chemotherapy is required [13]. Initially, the chemotherapeutic agents of choice included a platinum-based chemotherapy and a classic alkylating agent, and common agents used were cisplatin and cyclophosphamide [14]. After the Gynaecological Oncology Group (GOG) 111 and OV10 trials, looking specifically at the combinations of cisplatin with either cyclophosphamide or paclitaxel, were performed, the standard of care following surgery for stage 3 and 4 ovarian cancer was a combination of a platinum-based agent and a taxane, with intravenous (i.v.) cisplatin and paclitaxel being the agents of choice. Subsequently, a combination of paclitaxel and carboplatin showed similar results for response and survival rates, but without the toxicity often related to cisplatin treatment, and with a better quality of life. The standard approach is six cycles of paclitaxel 175mg/m2 administered every three weeks, in combination with carboplatin area under the curve (AUC) 5–6 [15].

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The response and survival rates vary between the different histological types, with the clear cell and endometrioid subtypes having the worst and best prognoses, respectively, and mucinous and serous subtypes having intermediate prognoses [16, 17]. High-grade features likewise affect the prognosis unfavourably and such diseases often take on a much more aggressive course [16, 17].

In an attempt to improve response rates to chemotherapy, and progression-free and overall survivals, dose intense and dose-dense chemotherapy were introduced. The former refers to the increase of dosages with each drug delivery, whereas the latter implies increasing the frequency of drug administration. It was thought that tumour growth escalated in the initial phase but slowed as the tumour volume increased; hence, delivering higher doses of chemotherapy from the start and at close intervals would increase tumour cell death. This theory was confirmed in a large meta-analysis studying the effects of dose-intense and dose-dense chemotherapy for ovarian cancer [18]. The encouraging results of the JGOG trial, with first-line dose-dense chemotherapy, depict an improvement of median progression-free survival from 17.5 to 28.2 months and an overall survival that was not reached [19].

4. The role of Intraperitoneal (IP) chemotherapy versus Intravenous (IV) chemotherapy

The route of administration of chemotherapy for ovarian cancer has traditionally been intravenous (i.v.). In the1960s, intraperitoneal (i.p.) chemotherapy was introduced with the aim of controlling malignant ascites. It was found that certain drugs such as cisplatin were cleared from the peritoneal cavity gradually, which meant that a high concentration of the drug could be delivered intraperitoneally without resulting in a systemic overdose of the drug.

Drugs that are particularly suited for i.p. delivery have high molecular weights and are water soluble, leading to a delayed peritoneal but high systemic clearance, and so having a pharmacological advantage for treating peritoneal disease.

Ovarian cancer is an ideal cancer for treatment via an i.p. route. The majority of diagnosed cases present with peritoneal disease in the absence of extra-peritoneal metastases [3]. Even in patients who have undergone seemingly curative surgery and adjuvant chemotherapy, up to 70% develop recurrent disease, the majority of which remains confined to the peritoneal cavity. The propensity for peritoneal recurrences as the only site of disease makes this cancer the model candidate for such loco-regional treatment. I.p. chemotherapy has also been used with significant success in mucinous tumours of the appendix and peritoneum [20], colon cancers [21], and has even been shown to provide improved survival in gastric cancers [22].

The underlying principle behind i.p. chemotherapy is the delivery of high concentrations of the appropriate drug to the site that is most likely to develop recurrences, at the opportune moment where tumour burden is at its minimum, i.e., after the performance of complete cytoreduction, with eradication of all macroscopic disease. It is critical that no gross residual disease is present, as penetration of i.p. chemotherapy is up to a depth of 2.5 mm [23–25]; hence,

there is an inherent risk that larger volumes of tumour deposits will not be sufficiently treated by the intraperitoneal chemotherapy.

There have been numerous studies examining the results of i.p. chemotherapy in the management of ovarian cancer. Amongst the first few randomized controlled trials (RCTs) was that conducted by the Southwest Oncology Group (SWOG) and GOG 104 trial, in which patients with then-defined optimal cytoreduction of less than 2 cm residual disease were administered i.v. cyclophosphamide and either i.v. or i.p. cisplatin. The patients who received the i.p. chemotherapy had significantly increased median overall survival [26]. The GOG 111 trial that combined i.v. paclitaxel with i.v. or i.p. cisplatin reached similar conclusions, in favour of the i.p. treatment. Other RCTs produced progression-free and overall survivals of 28 and 63–66 months, respectively. In the GOG 172 trial, the median overall survival was 65.6 and 49.7 months for the combination i.p./i.v. and cytoreductive surgery (CRS) and i.v. chemotherapy alone arms, respectively. There were criticisms of these trials as the i.p. arm in GOG 114 and GOG 172 received two cycles of carboplatin at AUC 9 and i.p. paclitaxel on day 8, respectively; hence, we await the results of additional RCTs that aim to study the effect of i.p. chemotherapy and determine the ideal algorithm for the management of ovarian cancer [27].

5. Recurrent ovarian cancer

Despite optimal treatment, up to 70% of all patients diagnosed with ovarian cancer suffer from relapse. In the past, early detection of persistent disease by second-look laparotomies was often performed, but as it was found to make no difference in GOG-0158 it is no longer practiced [28]. Currently, the practice of close follow-up of patients by serial CA-125 levels at intervals of one to three months is practiced. In patients who are in clinical complete remission, an increase in CA-125 from initial levels is the most common method to detect disease relapse. However, the MRC-OV05 trial [29], which examined the consequences of early treatment for recurrence versus treatment delayed until clinical symptoms appeared, showed that there was no benefit in the detection of the early presence of disease by CA-125, with only a 1.4 month benefit in survival for the early treatment group.

In patients with clinically evident relapse, treatment options include secondary cytoreduction with or without hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic chemotherapeutic regimes. Systemic treatment is dependent on the platinum sensitivity of the disease. In platinum-sensitive disease, re-treatment with a platinum or platinum-containing combination is advocated, and in platinum-resistance disease, clinical trials involving topotecan, docataxel, gemcitabine, paclitaxel, pemetrexed and bevacizumab should be considered.

6. The rationale for Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Hyperthermic intraperitoneal chemotherapy (HIPEC) was first introduced in the early 1980s for the treatment of peritoneal carcinomatosis. CRS and HIPEC were popularized for the

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management of peritoneal surface malignancies by Dr. Sugarbaker in the 1990s [21]. The addition of hyperthermia to the i.p. chemotherapy has been shown to boost penetration of the chemotherapy and improve its absorption into the tumour cells, increasing the intracellular accumulation of the drug [30]. The cytotoxic effect appears to be similarly potentiated, secondary to an impairment of the cells' ability to perform DNA repair, and thus has a greater deleterious effect [30, 31]. The drugs selected must be heat stable, with a high molecular weight and a low water solubility to be optimally used in the process of HIPEC. Cisplatin, mitomycin-C, and doxorubicin are the frequently employed drugs.

HIPEC is performed intraoperatively, while the patient is under general anaesthesia, via a pump that maintains the temperature and circulation of the drug solution. In addition to patient comfort, advantages include an ability to ensure that the entire peritoneal surface is bathed in the chemotherapeutic agent, before the formation of obstructing adhesions that may develop in the postoperative period. If HIPEC is administered in an opened-abdomen fashion, the surgeon would be able to manually swirl the chemotherapy to achieve this target. The most important prognostic factor remains the completeness of cytoreduction, with a 5.5% increase in the median overall survival for every 10% of patients undergoing optimal cytoreduction [5], leading to the inevitable conclusion that the changing surgical paradigm for ovarian cancer embracing radical CRS has resulted in meaningfully better survival results [32].

The combination of CRS and HIPEC has shown promising results, with median overall and progression-free survivals of up to 64 and 57 months, respectively [30, 33, 34]. Optimal cytoreduction yields five-year survivals of 12–66% [34]. These results are compatible with those of the author's institution [35]. A meta-analysis examining i.p. versus i.v. trials also conclusively showed the superiority of the i.p. over the i.v. arms, with hazard ratios of 0.79 for both disease-free and overall survivals [36]. Patients with platinum-sensitive disease have better response rates of 20–77% compared with up to 28% in those with platinum-resistant disease [37].

7. CRS and HIPEC: When to do it?

The time points at which CRS and HIPEC have been used in the management of advanced ovarian cancer include the primary setting, after neoadjuvant chemotherapy, at the point of recurrence, and as a second-line treatment [38]. In the Milan 2006 consensus statement, it was concluded that CRS and HIPEC could be feasible at all of these time points.

The morbidity and mortality for such a procedure range from 0 to 40 and 0 to 10%, respectively [34, 35], and include nausea and vomiting, gastrointestinal disturbances and ileus, anastomotic leaks, perioperative bleeding, pleural effusions and pneumothoraces, intra-abdominal collections/abscesses, and sepsis. The key is in patient selection, and it is imperative that patients with a good ECOG and an ability to tolerate such a radical procedure be chosen. The best candidates have long disease-free intervals and low volume disease that can be confidently optimally debulked. Many of the studies included in the review of CRS and HIPEC for advanced ovarian cancer show the usage of this modality of treatment in the recurrent setting. However, evidence supporting the use of i.p. chemotherapy in the initial setting of advanced ovarian

cancer [39] suggests that there is sound rationale behind CRS and HIPEC, even in the primary setting. There are more than 40 studies that have reported on the role of HIPEC in the management of ovarian cancer, but many of these studies are small in number and heterogeneous in their design. Further trials such as the Italian HORSE study (available at http://clinicaltrials.gov/show/ NCT01539785) that randomizes patients with platinum-sensitive disease to CRS and HIPEC with cisplatin 75mg/m2 and CRS alone, and the French CHIPOR study (available at http://clinicaltrials.gov/show/NCT01376752) that randomizes patients with recurrent platinum-sensitive disease (relapse beyond six months) after they have received platinum-based chemotherapy and optimal cytoreduction (less than 2.5 mm residual disease) to HIPEC with i.p. cisplatin 75mg/m2 and no HIPEC [37] will provide answers about the role of HIPEC in patients with platinum-sensitive disease. There is a need for phase 3 randomized trials to elucidate which timing and cohort of patients would be most beneficial for CRS and HIPEC.

8. Future directions

8.1. CRS and HIPEC

It is evident that complete cytoreduction, with no residual disease, yields the best clinical outcome. However, in a significant proportion of patients recurrence in the peritoneal cavity occurs, and CRS and HIPEC are considered. Perhaps the role of CRS and HIPEC as an adjuvant treatment should be considered an upfront treatment option for primary ovarian cancers, especially with improved morbidity results for this treatment modality. A randomized trial examining the overall and disease-free survivals of patients managed with CRS and adjuvant i.v. chemotherapy and those who undergo CRS and HIPEC, with adjuvant i.v. chemotherapy, for ovarian cancer in the primary setting would enable this questions to be addressed.

8.2. Intraperitoneal bevacizumab

The role of vascular endothelial growth factor (VEGF) in ovarian cancer has received much attention because VEGF increases vascular permeability and enhances angiogenesis [40]. Overexpression of VEGF has been reported in ovarian cancer [41-43] and several studies have indicated that VEGF-regulated angiogenesis is an important component of ovarian cancer growth [44, 45]. Microvessel density and level of VEGF expression in ovarian cancer directly correlate with poor prognosis, suggesting that angiogenesis, possibly mediated at least in part by VEGF, influences disease progression [44, 45]. Currently, vascular endothelial growth factor receptor (VEGFR) antibody, bevacizumab, is given intravenously for select patients with ovarian cancer.

The role of intraperitoneal VEGF inhibition using bevacizumab has been explored for the treatment of malignant ascites [46]. In a mouse peritoneal model of human ovarian cancer, the author demonstrated that the administration of i.p. bevacizumab and rapamycin not only reduced ascites, but was also able to suppress the development of peritoneal carcinomatosis [47]. This is an indication that this therapy may potentially be useful for the treatment of peritoneal carcinomatosis and may also be a novel, efficient strategy for reducing recurrence of ovarian cancers.

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9. Conclusion

Ovarian cancer often presents at an advanced stage, with the involvement of the peritoneal surface either at initial diagnosis or at recurrence. Despite the advances made in surgical techniques and chemotherapeutic options regarding agents, schedule, and route of administration, the majority of the patients relapse and eventually succumb to their disease. A change in the surgical approach, supporting more radical and extensive surgical procedures in a bid to attain optimal cytoreduction with no gross residual disease, has seen an improvement in survival, as has the use of intraperitoneal chemotherapy in combination with i.v. agents. Although peritoneal carcinomatosis has always been a poor prognostic factor, it ceases to be a factor of much importance if complete CRS can be achieved [31, 48]. CRS and HIPEC provide the combined benefits of surgical eradication and effective chemotherapy, and can be performed with acceptable morbidity and mortality [49]. Further trials are being undertaken to examine its role in the primary as well as recurrent settings of advanced ovarian cancer, and to determine the ideal drug combinations and dosages [50–52].

Author details

Melissa Ching Ching Teo* and Grace Hwei Ching Tan

*Address all correspondence to: melissa.teo.c.c@nccs.com.sg

Department of Surgical Oncology, National Cancer Centre Singapore, Singapore

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