Abstract

Complete cytoreductive surgery (CRS) and adjuvant chemotherapy is and has been the backbone of treatment for advanced ovarian epithelial and primary peritoneal carcinomatosis for many years. Studies have shown that adjuvant intraperitoneal chemotherapy has significant survival advantages over standard intravenous chemotherapy but has been incompletely adopted due to side effects.

Hyperthermia is known to be selectively lethal to malignant cells and also to increase the cytotoxic efficacy of a number of chemotherapeutic drugs. Phase 3 studies in gastrointestinal carcinomatosis using CRS and hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC) have shown significant survival advantages. However, this treatment technique has only been explored in a small number of gynaecological oncology services worldwide. There is non-randomised evidence that suggests that CRS and HIPEC may well be as efficacious in advanced epithelial ovarian and peritoneal cancers as in the case in gastrointestinal cancers. If this proves to be the case then CRS and HIPEC may be the way of the future. The results of a number of phase 3 studies around the world are eagerly awaited.

INTRODUCTION

Over the last 35 years the approach to and range of skills involved in surgical oncology has changed significantly. Thirty-five years ago the presence of disseminated disease was generally approached by abandoning treatment aimed at attacking the malignancy and moving to palliative care. This progress has gone from the simple surgical removal of primary tumours to the aggressive surgical treatment of metastatic disease. Some malignancies, particularly ovarian epithelial cancers, primary peritoneal cancers and some gastrointestinal (GIT) tumours frequently spread throughout the peritoneal cavity and often remain confined to that region for a considerable part of their natural history. Most of this work has initially been advanced through the treatment of metastatic GIT cancers, especially appendiceal carcinomas [1].

INTRAPERITONEAL CHEMOTHERAPY

The use of intraperitoneal (IP) chemotherapy is not new [2,3] however its implementation and acceptance have taken a long time and even today it is not generally accepted even in treatment areas where there is phase 3 evidence (see below). Early studies showed that more optimal cytotoxic concentrations were achieved in the peritoneal cavity with IP cytotoxic drug administration [4,5]. Furthermore, suggestions of improved outcome with IP chemotherapy from small initial studies were encouraging [6,7] and warranted further investigation. IP chemotherapy offered potential therapeutic advantages over systemic chemotherapy by producing high regional cytotoxic concentrations while at the same time being associated with reduced systemic distribution and therefore reduced systemic toxicities.

HYPERTHERMIA

It is known that malignant cells are selectively killed by hyperthermia in the temperature range of 41-43°C and the basis for these effects have been well elucidated [8]. Apart from the direct cytotoxic effects of hyperthermia it is also known that hyperthermia enhances the cytotoxic efficacy of a number of chemotherapy agents especially alkylating agents and to lesser extent also platinum compounds [8]. Hyperthermia initiates a number of advantages when combined with chemotherapy. It leads to increased chemotherapy uptake by malignant cells, improved drug pharmacokinetics, increased drug tissue...
penetration and inhibition of cellular repair mechanisms [8]. It therefore would seem reasonable that the addition of hyperthermia to IP chemotherapy may enhance the efficacy of this modality of cytotoxic delivery and this has certainly been shown for some gastro-intestinal cancers. Recent studies using a phase 3 trial with extensive long-term follow up, have shown cytoreductive surgery followed by HIPEC to have a statistically significant survival advantage over traditional systemic chemotherapy for peritoneal carcinomatosis of colorectal origin [9,10].

However despite the potential promise of this modality of treatment the take up of HIPEC following optimal cytoreductive surgery in gynaecological oncology has been desperately slow. Exploration into the reasons for this slow uptake is beyond the scope of this paper.

Of the various female genital tract cancers, the use of HIPEC only applies to those that tend to spread and for a good part of their natural history, remain confined to the peritoneal cavity. To a large extent this only applies to epithelial ovarian, tubal and primary peritoneal carcinomas. On occasions endometrial cancers may spread via a trans-coelomic route however this is the exception rather than the rule. Other female genital tract cancers, such as cervical, vaginal and vulval cancers primarily metastasise via the lymphatic system and are not likely to be amenable to IP chemotherapy treatment, hyperthermic or otherwise. The only exception to this, which will be addressed later, is the place of HIPEC in the management of intractable accumulation of ascites.

**OVARIAN EPITHELIAL AND PERITONEAL CARCINOMA**

Ovarian epithelial and primary peritoneal cancers are a major cause of mortality in developed countries [11]. With respect to gynaecological cancers, epithelial ovarian cancers and primary peritoneal cancers are a major cause of death. Ovarian epithelial cancer is often referred to by the lay public as “the silent killer” because of its poor prognosis and lack of symptomatology. The outcomes are generally poor, largely because of the frequent late presentation of patients. Some three out of four patients have advanced stage disease at the time of their diagnostic presentation. Unfortunately patients have little if any in the way of symptoms when they have early stage disease. However, when they do have symptoms, such as oesophageal reflux, bloating and weight gain, they are generally viewed as being non-specific and are frequently dismissed as insignificant in this group of generally postmenopausal women and often treated symptomatically. It is generally the case that investigation is not initiated unless the symptoms become intractable. Consequently three-quarters of patients have widely disseminated disease within their peritoneal cavity when they present.

Ovarian and peritoneal carcinomas tend to be a peritoneal surface disease for a considerable part of their natural history, with systemic metastatic disease usually being observed late in the natural history of the disease. These are also malignancies that are relatively sensitive to multiple chemotherapeutic agents. For decades the standard of care has been so called debulking surgery followed by adjuvant chemotherapy. However, with time there has been increasing evidence that simple debulking of the bulky tumour areas is insufficient and the importance of complete surgical cytoreduction has become more broadly appreciated. Most of the initial studies on debulking surgery and survival were small retrospective series that were not powered to answer such questions. Although no phase 3 randomised trials have been performed, a meta-analysis of 6,885 patients undergoing maximal cytoreductive surgery (CRS) has shown a distinct survival advantage [12] for those with maximal tumour removal and minimum residual disease.

Over the last 50-years considerable progress has been made in the treatment of these diseases with improvements in 5-year overall survival from 30 per cent in the 1960’s to 45-plus per cent in recent times [13]. It would seem that the major contributors to these improvements have been a far more aggressive surgical approach to tumour removal, resulting in significant improvements in CRS along with improvements in chemotherapy drugs and their delivery [14].

As ovarian and peritoneal cancers remain confined to the peritoneal cavity for much of their natural history, the prospects of providing adjuvant chemotherapy directly into the peritoneal cavity following surgical cytoreduction arose. As mentioned above while the use of IP chemotherapy in GIT malignancies dates back to the mid-1980’s, the use of IP chemotherapy for ovarian cancers pre-dates this by some three decades [15]. While interest in this mode of treatment waned for a long time, there has more recently been a re-awakening in interest in IP chemotherapy. Three large randomised studies of IP chemotherapy conducted by the Gynecologic Oncology Group (GOG) in the United States have demonstrated a significant improvement in survival for IP versus systemic chemotherapy [16-18].

Although the above GOG studies showed a considerable improvement in survival leading to the 2006 announcement from the National Cancer Institute recommending the incorporation of IP chemotherapy for patients who had had optimal CRS, the use of IP chemotherapy has only been partly embraced. A large part of the failure to widely adopt IP chemotherapy may be related to the morbidity associated with this treatment modality. This is evidenced by the fact that almost half of the patients allocated to the IP chemotherapy arm in GOG 172 [18], had opted out by the time they were half way through their adjuvant treatment, largely because of morbidity problems. Unfortunately, GOG 172 was only analysed on an ‘intention to treat’ basis. While this doesn’t really answer the original question: Is IP chemotherapy better than systemic chemotherapy? It does tell us that at least some IP component to a patient’s adjuvant cytotoxic treatment is beneficial. This would suggest that if anything it is the early cycle or cycles of IP chemotherapy that make a difference to patient survival.

Given the above benefits of hyperthermia it was only a matter of time before the question of combining hyperthermia with IP chemotherapy would arise and the use of hyperthermic intraperitoneal chemotherapy would be explored.

Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is a new approach only starting to creep into the management of gynaecological malignancies. It has however been used for some decades in the treatment of metastatic gastro-
intestinal tumours, that are limited to the peritoneal cavity with significantly improved survival results [8,9].

**Benefits of intraoperative chemotherapy**

The intra-operative provision of IP chemotherapy has certain advantages over postoperative IP chemotherapy as used in earlier studies [18]. It is at the end of the surgery that residual tumour volume will be at its smallest. As the chemotherapy is instilled into the peritoneal cavity towards the end of the surgery and therefore before any adhesion formation has occurred, there is a more uniform distribution of cytotoxics to all surfaces of the abdomen and pelvis. Further with the open or 'Coliseum' technique and the expander technique, the surgeon periodically manually manipulates the abdominal and pelvic viscera making certain that the chemotherapy reaches all surfaces. As the patient is anaesthetised, problems of abdominal pain and nausea/vomiting, so commonly encountered with adjuvant IP chemotherapy [18] are avoided.

**HIPEC METHODOLOGY**

There are a few different techniques for performing HIPEC, which we will look at briefly. However, while there may be some differences in administration, the principles are in effect the same:

- **Open 'Coliseum' technique**

  Following optimal CRS, the chemotherapy inflow and outflow catheters are put in place; usually there is a single inflow catheter and four outflow catheters. A plastic sheet is sutured to the edge of the skin incision and draped up and over the ring or arms of the self-retaining retractor. The sutures also go over the ring or arms of the self-retaining retractor. This has the effect of elevating the abdominal wall creating a 'Coliseum' configuration. A second plastic sheet is placed over the top of the self-retaining retractor and held in place with large clips. This allows for a gas extractor pipe to sit in the area between the two layers of plastic to evacuate any chemotherapy fumes. A longitudinal incision in made in the middle of the lower plastic sheet to allow access to the peritoneal cavity and its contents to allow for periodic manipulation, about every 20 minutes, to help evenly distribute the chemotherapy.

  The peritoneal cavity is filled with standard peritoneal dialysate fluid and the fluid circulated. When the peritoneal cavity volume is known and the system is in a steady state situation with respect to both peritoneal cavity fluid level and temperature the chemotherapy is added to the dialysate. After the required time, usually about 90 minutes, the perfusion fluid is removed, a surgical 'tidy-up' undertaken checking for any visceral damage or residual tumour nodules previously missed. The abdomen is then closed.

  **Closed technique**

  Following completion of optimal CRS, the chemotherapy catheters are placed as described above for the open technique. After temporary closure of the abdomen with a continuous suture the perfusate with chemotherapy is introduced. Periodically, while the chemotherapy is being cycled, about every 20 minutes, the abdominal wall is agitated in an attempt to increase uniform cytotoxic distribution. At the end of the perfusion time the chemotherapy fluid is evacuated, the abdomen is reopened and any remaining perfusate containing chemotherapy removed. Again a surgical 'tidy-up' is undertaken and the abdomen closed.

- **Expander technique**

  Again after optimal CRS a peritoneal cavity expander is inserted. This is an acrylic cylinder with the inflow and outflow catheters attached that is secured over the abdominal wound and into the peritoneal cavity. This allows the abdominal viscera to float freely in the perfusate during the HIPEC. Depending on the physical configuration of the expander manual manipulation of the abdominal and pelvic viscera may or may not be possible. At the end of the HIPEC the perfusate is drained, a surgical 'tidy-up' undertaken and the abdomen closed.

  Any required bowel anastomosis can be undertaken before or after the HIPEC at the surgeon’s preference. While there are published prospective randomised trials of HIPEC in GIT disease [19] there are no such studies with respect to ovarian epithelial or primary peritoneal cancer.

**HIPEC IN PRIMARY TREATMENT**

Of primary importance for the potential success of HIPEC is good patient selection. Apart from not having co-morbidities that would put the patient at undue risk, patients should be free of any demonstrable extra abdominal disease [20]. While there are no specific studies, as a general principle better success is likely to be obtained from patients who have either had, no previous cytotoxic exposure, a good response to neoadjuvant chemotherapy, or, in the case of recurrent disease, a long tumour free interval since previous treatment.

In terms of drug selection there has been little consistency between the studies that have been undertaken and there is no agreement as to what may be the most effective individual drug or drug combination. While cisplatin has been used in most of the studies [21-25] there have been other drugs used either by themselves [26] or combined with cisplatin [23-26]. This of course makes comparison between studies effectively impossible. Certainly, a relatively recent review of all peer-reviewed studies up to 2009 showed that the overall morbidity ranged from zero to 40 per cent and mortality from zero to 10 per cent with overall median survival following HIPEC to range from 22 to 64 months [27]. The authors concluded that despite the heterogeneity associated with these studies complete CRS and HIPEC might well be a realistic and acceptably safe option for treatment compared with the current standards of care. As expected they raised the lack of prospective randomised trials, which are still missing. Likewise a more recent review published the following year reached similar conclusions [28].

**QUALITY OF LIFE CONSIDERATIONS**

The obvious issue that arises with respect to this ultra radical treatment (maximal CRS and HIPEC) is its possible impact on quality of life (QOL). There is also little on this topic in the literature, however a recently published study looking at this question [29] concluded at there was no significant adverse quality of life issues and that by 6-12 months the reduced QOL parameters had recovered. However, the two recent reviews
HIPEC IN RECURRENT DISEASE

If the treatment/relapse timeline is relatively short then secondary CRS is generally not offered, as the disease is deemed to be chemotherapeutically resistant. This is especially the case if the disease has progressed during primary adjuvant chemotherapy or within 6 months of completion of primary treatment.

Spiliotis et al. [31], looked prospectively at a group of 48 patients who had CRS and HIPEC for recurrent advanced ovarian cancer, stages III and IV. All patients had been initially treated with some degree of debulking surgery and systemic intravenous chemotherapy. In this non-randomised study of 48 patients, group A had 24 patients and were treated with CRS and HIPEC followed by systemic chemotherapy, while group B had 24 patients who were treated with CRS and systemic chemotherapy. The one-year survival was 85 per cent for group A compared with 35 per cent for group B (p <0.05) while the 3-year survival for groups A and B were 50 per cent and 18 per cent respectively. The median survival for groups A and B were 19.4 months and 11.2 months respectively. Two of the factors that heavily influenced survival in a negative way were a peritoneal cancer index (PCI) score of >15 and post surgical cytoreduction disease residuum.

A retrospective multi-institutional study involving 56 patients with recurrent ovarian cancer also showed promising results with the 5-year overall survival and progression free survival being 23 and 7 per cent respectively [32]. The largest but again retrospective study of 246 patients in a multicentre study [33] showed an overall median survival of 48.9 months suggesting that salvage with CRS and HIPEC may achieve long-term survival in highly selected patients with recurrent ovarian cancer. A systematic literature review in 2016 [34] identified 1,168 patients in 16 studies in which HIPEC seemed to confer survival benefits to patients with recurrent disease.

Spiliotis et al.[35], in a phase 3 prospective randomised study of recurrent epithelial ovarian cancer compared 60 patients who had CRS and HIPEC followed by systemic chemotherapy (Group A) with 60 patients who had CRS followed by systemic chemotherapy (Group B). The Mean survival for the two groups was 26.7 versus 13.4 months (p<0.006). Interestingly in the HIPEC group (group A) there was no difference between the platinum-resistant versus the platinum-sensitive group. Unlike the non-HIPEC group (group B) in which there was such a statistical difference (15.2 versus 10.2 months, p<0.002).

Finally a case controlled study of 37 cases of platinum sensitive recurrent ovarian cancer matched to 37 controls showed the duration of response to be 26 months in the cases and 15 months in the controls suggesting that CRS and HIPEC seems to improve survival rates [36].

While there are to date no published phase III studies of HIPEC in patients with advanced ovarian cancer there are at present several phase III trials underway as follows:

1. Intraoperative Hyperthermic Intrapertitoneal Chemotherapy with Ovarian Cancer: NCT01091636
2. Phase 3 Trial Evaluating Hyperthermic Intrapertitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer: NCT01628380
3. Secondary Debulking Surgery +/- Hyperthermic Intrapertitoneal Chemotherapy in Stage III Ovarian Cancer: NCT00426257
4. Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer treatment: NCT01376752
5. Hyperthermic Intra-Peritoneal Chemotherapy in Ovarian Cancer Recurrence: NCT01539785
6. Hyperthermic Intrapertitoneal Chemotherapy with Paclitaxel in Advanced Ovarian Cancer: NCT02681432
7. Cytoreduction With or Without Intraoperative Intrapertitoneal Hyperthermic Chemotherapy (HIPEC) in Patients with Peritoneal Carcinomatosis from Ovarian Cancer, Fallopian Tube or Primary Peritoneal carcinoma: NCT 02328716.

INTRACTABLE ASCITES

This is one of the most difficult to treat and frequently unrewarding areas of management in patients with recurrent peritoneal carcinomatosis. Further it leads to a substantial deterioration in the patient's quality of life. In 2008 Facchiano et al. [37], published a small retrospective series of five patients whose malignant ascites, secondary to unresectable peritoneal carcinomatosis from gastric cancer were treated with laparoscopic HIPEC leading to complete resolution of the ascites and associated symptoms. The following year a small multi-institutional series of 52 patients showed again that Laparoscopic HIPEC was successful in managing intractable ascites in these patients with no treatment related mortality [38].

While laparoscopic HIPEC has only been used in a small number of patients, it would certain appear to be efficacious and further studies are warranted for this form of management to improve the quality of life of these palliative patients.

CONCLUSIONS

Despite the current lack of phase III trials data, accumulating evidence to date suggests that CRS followed by HIPEC has the potential to be of significant benefit to selected patients with both primary and recurrent ovarian and primary peritoneal cancers. Increasing evidence for its acceptable morbidity and mortality is also accumulating.

In 2015 Huo et al. [39], undertook a systematic review and meta-analysis of 9 comparative studies and 28 studies examining HIPEC + CRS for primary and/or recurrent epithelial ovarian cancer. Meta-analysis showed CRS + HIPEC + chemotherapy had significantly better 1-year survival compared either CRS + chemotherapy alone. Furthermore, these survival benefits were
maintained for 2-, 3-, 4-, 5- and 8-years. They concluded that the addition of HIPEC to CRS and chemotherapy improves overall survival for both primary and recurrent ovarian cancer.

Obviously phase III evidence is badly needed and should be forthcoming over the next several years. The results are eagerly awaited. At the present time, given the state of our knowledge and lack of phase III data, HIPEC should probably not be offered outside of a formal trials environment.

FUTURE PERSPECTIVE

While in the future molecular biology and more selective chemotherapy may well be the answer to long-term survival in ovarian cancer this is certainly not the case at present. Chemotherapy has been promising significant advances since the coming of Cisplatin in the late 1970’s. However, the reality is that the steps have been painfully small and horrendously expensive and pale almost into insignificance when compared with the efficacy of complete cytoreduction to no visible disease. HIPEC may well become the pinnacle of treatment for years until molecular biology produces the good.

EXECUTIVE SUMMARY

- Treatment primarily aimed at attacking the tumour has generally been abandoned in the presence of peritoneal carcinomatosis.
- Newer approaches have been aimed at removing all visible cancer prior to adjuvant chemotherapy.
- It has been shown in phase 3 studies that postoperative intraperitoneal (IP) chemotherapy is associated with a significant survival advantage but it has not been uniformly adopted because of ongoing side effects.
- Hyperthermia between 41 – 43 degrees Celsius is known to selectively kill malignant cells.
- Hyperthermia is also known to increase the cytotoxic efficacy of certain chemotherapy agents that can be used for treating ovarian and peritoneal cancer as well as increasing tumour penetration.
- The combination of hyperthermia and IP chemotherapy in the form of hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown in phase 3 studies to be efficacious in significantly prolonging the lives of patients with disseminated gastrointestinal carcinomas.
- HIPEC has only been explored by a small number of gynaecological cancer services worldwide.
- Non-randomised studies suggest that HIPEC may be the way of the future for the treatment of advanced ovarian and peritoneal cancer avoiding many of the ongoing side effects of current IP chemotherapy.

REFERENCES


