Cytoreductive surgery with intraperitoneal chemotherapy in the management of peritoneal surface malignancy: a pharmacist's perspective

Priya Mistry,¹ Faheez Mohamed,² Sanjeev Dayal,² Tom D Cecil,² Brendan J Moran²

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/ejpharm-2016-000877>).

¹Pharmacy Department, Basingstoke & North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Basingstoke, Hampshire, UK

²Peritoneal Malignancy Institute, Basingstoke & North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Basingstoke, Hampshire, UK

Correspondence to

Priya Mistry, Pharmacy Department, Basingstoke & North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Aldermaston Road, Basingstoke, Hampshire RG24 9NA, UK; priya.mistry5@nhs.net

Received 5 January 2016

Revised 4 March 2016

Accepted 14 March 2016

Published Online First

5 April 2016

ABSTRACT

Objectives To explore the use of intraperitoneal chemotherapy in conjunction with cytoreductive surgery for the treatment of peritoneal surface malignancy and highlight the challenges this provides for the hospital pharmacist.

Methods A literature search for relevant articles was performed using MEDLINE, PubMed and Cochrane databases. The following keywords and phrases were used: 'hyperthermic intraperitoneal chemotherapy', 'early postoperative intraperitoneal chemotherapy', 'carrier solutions' and 'cytoreductive surgery'. Local experience was also shared, referencing national guidelines and published literature.

Results The rationale behind intraperitoneal chemotherapy is to directly administer drugs into the peritoneal cavity and achieve exposure of higher concentrations of cytotoxic agents to tumour nodules within the abdomen and on peritoneal surfaces for a prolonged period of time, without significant systemic toxicity. This has been widely demonstrated in intraoperative and early postoperative settings. Hydrophilic chemotherapy drugs with high molecular weights and permeable to the peritoneum, but slow plasma clearance create high concentrations of the drug in the peritoneal cavity, with lower systemic circulation. Commonly used drugs include *mitomycin C*, *oxaliplatin*, *cisplatin*, *doxorubicin* and *5-fluorouracil*. Newer drugs such as the taxanes and *bevacizumab* have also shown promise. Heat increases drug penetration into body tissues and destroys tumour cells directly by causing damage to cells that have inherently faulty heat regulation pathways and also increases the cytotoxic effect of selected chemotherapeutic agents. Optimal temperature for hyperthermic intraperitoneal drug administration is between 41 and 43°C in a carrier solution that is compatible with the drug chosen. For early postoperative intraperitoneal chemotherapy high molecular weight starch carrier solutions prolong intraperitoneal dwell time and exposure of drug to tumour cells. Drugs are administered intraoperatively with the abdomen open or closed for between 30 and 120 min depending on the drug chosen and local protocols. Drug doses are traditionally calculated using body surface area. Toxicity such as neutropenia is encountered far less than with systemic chemotherapy.

Conclusions This paper discusses the rationale for intraperitoneal drug administration following cytoreductive surgery and describes appropriate drug selection, methods of drug delivery and potential challenges in the use of the intraperitoneal route. It provides evidence and practical guidance for hospital pharmacists who may be involved in the surgical management of peritoneal malignancy particularly in

dose calculation, preparation and administration of intraperitoneal chemotherapy.

INTRODUCTION

Peritoneal malignancy is the dissemination of tumour nodules to the peritoneal surfaces, either from a primary peritoneal tumour such as peritoneal mesothelioma or more commonly secondary to gastrointestinal and gynaecological malignancies. In the past it was associated with a bleak outlook; poor prognosis with the lack of definitive treatment options and limited survival. Traditional methods of treatment involved surgical resection with adjuvant systemic chemotherapy and/or radiotherapy. However, where the peritoneal surface had been involved there was limited improvement in long-term survival, due to inadequate penetration of chemotherapy into the peritoneal cavity.¹ The concept of direct application of chemotherapeutic agents into the peritoneal cavity seemed a logical approach and a step forward in the management of this disease. Intraperitoneal (IP) chemotherapy is being used increasingly in conjunction with cytoreductive surgery (CRS) for the treatment of peritoneal surface malignancy. Traditionally categorised as an unlicensed route of drug administration in the pharmaceutical world, it is now established in the form of hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC is administered intraoperatively after CRS. In the immediate postoperative period it may also be used as normothermic early postoperative intraperitoneal chemotherapy (EPIC) via drains that have been left in the abdomen at time of surgery.

This review paper explores the role of IP chemotherapy with CRS for the surgical management of peritoneal surface malignancies. It explores commonly used chemotherapeutic agents and other significant variables such as heat, carrier solution and techniques used for administration. It is aimed at hospital pharmacists as a guide to provide background therapeutic knowledge around IP chemotherapy, a summary of published literature and a practical guide based on first-hand experience.

Cytoreductive surgery and IP chemotherapy

The combined approach of CRS with peritonectomy procedures to remove macroscopic disease, followed by HIPEC to treat residual microscopic disease has been described and developed by Sugarbaker over the last three decades.² Pharmacological research and development of radical surgical techniques has improved the

CrossMark

To cite: Mistry P, Mohamed F, Dayal S, et al. *Eur J Hosp Pharm* 2016;**23**:233–238.

treatment options now available. The success of managing peritoneal dissemination from low-grade appendiceal malignancies such as pseudomyxoma peritonei and primary peritoneal tumours such as multicystic peritoneal mesothelioma has led to the extension of this approach to colorectal peritoneal metastases and selected cases of ovarian cancer.³ A whole new standard of care has now been internationally recognised by surgeons and oncologists for the management of resectable peritoneal malignancy.⁴ In 2004, the National Institute for Health and Care Excellence in the UK approved Sugarbaker's technique for the management of pseudomyxoma peritonei.⁵ Work by Moran and his team led to the development of the first UK peritoneal malignancy treatment centre in Basingstoke, Hampshire in 2000.⁶ Sixteen years on two UK hospitals have been designated as specialist centres by the NHS Commissioning Board in assessment and treatment of pseudomyxoma peritonei.⁷

The peritoneum and rationale for IP chemotherapy

The peritoneum is a complex three-dimensional organ that forms the lining within the abdominal cavity, covering the organs within the abdomen and pelvis (visceral peritoneum), together with the abdominal wall (parietal peritoneum). It is a single layer of mesothelial cells overlying several layers of connective tissue. The peritoneal cavity is a potential space between the parietal peritoneum and visceral peritoneum which is filled with a small amount of serous-like fluid, produced by the mesothelial cells.⁸ The rationale behind IP chemotherapy is to directly administer drugs into the peritoneal cavity and achieve exposure of higher concentrations of cytotoxic agents to tumour nodules within the abdomen and on peritoneal surfaces for a prolonged period of time, without significant systemic toxicity. The retention of high concentrations of chemotherapy in the peritoneal cavity is facilitated by the peritoneal-plasma barrier which slows peritoneal clearance and provides dose-intensive therapy.⁹ Much research has gone into the properties of the peritoneum and potential hypotheses around rate of drug clearance and tissue penetration.¹⁰

METHODS

A review of the literature was performed by searching MEDLINE, PubMed and Cochrane databases for relevant articles. The following keywords and phrases were used: 'hyperthermic intraperitoneal chemotherapy', 'early postoperative intraperitoneal chemotherapy', 'carrier solutions' and 'cytoreductive surgery'. Local experience was shared, referencing national guidelines and published articles. Original research and review articles were selected based on relevance, literature published by globally recognised authors and well-established institutes.

RESULTS

From the articles selected details of commonly used drug protocols for peritoneal malignancies were identified including appropriate drug selection, delivery and toxicity. Practical guidance for hospital pharmacists was also established based on the literature and institutional experience.

Selection of drug

The key behind IP drug administration is the dose-intense therapy created by the retention of chemotherapy in the peritoneal cavity. There are several factors around the drug molecule and how it is delivered that make it more or less suitable for IP administration. Hydrophilic chemotherapy drugs with high molecular weights and permeable to the peritoneum, but slow plasma clearance create high concentrations of the drug in the

peritoneal cavity, with lower systemic circulation. Sugarbaker compared properties of common chemotherapy drugs using the area under the curve (AUC) ratio of IP versus plasma exposure.¹¹ A high AUC IP/intravenous ratio results in high peritoneal tissue concentration of the chemotherapeutic agent, and high penetration into the cancer nodule, which is governed by the slow diffusion of the drug molecule through the capillary endothelial wall. Once the drug has reached systemic circulation, its rapid metabolism and excretion minimises any systemic toxicity.

Mitomycin C is probably the most widely used chemotherapeutic agent administered by the IP route in patients with peritoneal spread of appendiceal and colorectal tumours. Its relatively high molecular weight and AUC IP/intravenous ratio allow it to be confined to the abdominal cavity for a long time (table 1). Doses used vary from 10 to 35 mg/m², the lower doses being used when combined with EPIC.^{12–13} There have been no randomised controlled trials comparing the outcomes and toxicities of the varying doses. It is difficult to compare published outcomes of different centres due to the vast number of variables, such as the extent of surgical resection, completeness of the CRS, if EPIC was used, and if the patient received adjuvant/neoadjuvant systemic chemotherapy.

Oxaliplatin, a newer agent, has proven efficacy in appendiceal and colorectal malignancies.^{14–16} Its low AUC IP/intravenous ratio is compensated by rapid tissue absorption. Common chemotherapeutic agents such as *doxorubicin* and *cisplatin* have been used in combination for the treatment of peritoneal mesothelioma and ovarian cancer. They too have high molecular weights, however *doxorubicin*'s high AUC IP/intravenous ratio allows lower doses of 15 mg/m² to be used. *Doxorubicin* is also used with HIPEC for the treatment of appendiceal and colorectal peritoneal malignancies.¹⁷ Taxanes (eg, *paclitaxel*) and monoclonal antibodies such as *bevacizumab* have also shown some promise when administered intraperitoneally.^{18–20} Generally, the safe doses of most drugs instilled into the peritoneal cavity are identical to intravenous doses. An exception is *5-fluorouracil*, where a dose increase of 150% is possible due to its extensive hepatic metabolism. It is frequently used as an EPIC agent.

IP immunotherapy with novel agents such as *catumaxomab*, a non-humanised chimeric antibody is currently being studied for suppression of malignant ascites, but has not been widely tested at elevated temperatures.²¹ A protocol for the study of IP *catumaxomab* following surgery for peritoneal metastases from gastric cancer has been proposed.²² IP administration of small molecules, monoclonal antibodies and immunotherapy may hold promise for the future but current data do not support their routine use.

Penetration of tumour nodules plays an important part in the efficacy of IP drug delivery. Sugarbaker has again demonstrated variable tumour penetration for each drug and tumour type, however to be successful the drug must be able to penetrate the 1–2 mm of microscopic tumour deposits remaining after macroscopic removal during CRS.

Drug concentration at the tumour nodule is thought to be a more appropriate end point than AUC ratios.²³ If the tumour is known to be resistant to chemotherapy, as a result of previous systemic chemotherapy, an increase in concentration by administering it directly to the peritoneum may not produce the most optimal outcome. In such cases, based on individual institutional experience, an alternative suitable chemotherapeutic agent may be considered.

Drug delivery considerations

The science behind IP chemotherapy does not solely rely on the actual drug molecule and its mode of action on the cancer cell

Table 1 The properties of commonly used IP chemotherapeutic agents used with CRS and examples of treatment protocols

Chemotherapy drug	Molecular weight (daltons)	AUC ratio	Origin of peritoneal malignancy	Cited treatment protocols
Mitomycin C	334.3	23.5	Appendix Appendix Colorectal Peritoneal mesothelioma	HIPEC: 10 mg/m ² (Youssef 2011) ³ HIPEC: 12.5 mg/m ² (males) or 10 mg/m ² (females) (Glehen 2004) ¹⁶ HIPEC: 35 mg/m ² (Verwaal 2004) ¹² HIPEC: 40 mg per perfusate (Alexander 2013) ¹³
Oxaliplatin	397.3	16	Colorectal	HIPEC: 460 mg/m ² . Before HIPEC and during CRS patients received intravenous 5-fluorouracil 400 mg/m ² and folinic acid 20 mg/m ² (Elias 2009) ¹⁴ HIPEC: oxaliplatin 460 mg/m ² (Marcotte 2014) ¹⁵
Cisplatin	300.1	7.8	Appendix Peritoneal mesothelioma/ ovarian Peritoneal mesothelioma	HIPEC: 50 mg/m ² combined with doxorubicin 15 mg/m ² (Sugarbaker 2005) ¹¹ HIPEC: 250 mg/m ² (Alexander 2013) ¹³
Doxorubicin	579.99	230	Appendix/colorectal	HIPEC: 15 mg/m ² and mitomycin C 15 mg/m ² and systemic (intravenous) 5-fluorouracil 400 mg/m ² and folinic acid 20 mg/m ² (Sugarbaker 2013) ¹⁷
5-Fluorouracil	130.08	250	Appendix Appendix Appendix/colorectal	EPIC (post-HIPEC): 15 mg/kg days 1–4 post-CRS (Youssef 2011) ³ EPIC (post-HIPEC): 650 mg/m ² days 1–4 post-CRS (Glehen 2004) ¹⁶ EPIC (post-HIPEC): 600 mg/m ² (males) or 400 mg/m ² (females) days 1–4 post-CRS (Sugarbaker 2013) ¹⁷
Paclitaxel	853.9	1000	Ovarian Peritoneal mesothelioma	HIPEC: 175 mg/m ² with cisplatin 100 mg/m ² (Coccolini 2015) ¹⁹ EPIC: 20 mg/m ² days 1–4 post-CRS (Mohamed 2003) ¹⁸

AUC, area under the curve; CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal.

pathway. There are a number of other variables such as temperature, carrier solution, duration and technique of drug administration that affect the success of IP drug delivery.

Temperature

Heat increases drug penetration into body tissues and destroys tumour cells directly by causing damage to cells that have inherently faulty heat regulation pathways as a result of tumour angiogenesis. In addition, heat increases the cytotoxic effect of selected chemotherapeutic agents. Early studies by Teicher *et al.*²⁴ investigated the enhancement of cytotoxicity of mitomycin C towards hypoxic tumour cells by hyperthermia. They observed a 30%–50% increase in the alkylating activity of mitomycin C at elevated temperatures of 41–43°C, compared with 37°C. This suggested that the enhanced cytotoxicity of the drug with heat might be as a result of an increase in the activation of the drug.

In practice temperatures of 41–43°C are commonly used for HIPEC. There are many commercially available drug delivery systems which regulate the temperature and flow of the chemotherapy solution in the peritoneal cavity by use of heat exchangers, temperature probes and fixed-flow rate pumps. An example is shown in figure 1.

Carrier solution

A carrier solution is the vehicle in which a drug is administered into the peritoneal cavity.²⁵ The ideal solution should provide exposure of the peritoneal surface to high drug concentrations for as long as possible, a prolonged high IP volume, slow drug clearance from the peritoneal cavity and absence of adverse effects to the peritoneal membrane after prolonged exposure. This is especially important for EPIC where the maintenance of a high volume of chemotherapy solution in the peritoneal cavity over a prolonged time improves drug distribution due to prolonged exposure, and hence efficacy. EPIC is typically administered over the first 4 or 5 days following surgery when adhesion formation is minimal and drug distribution is likely to be maximised. As HIPEC tends to be carried out for between 30 and 90 min the choice of carrier solution is less important. In practice, isotonic salt solutions or dextrose-based peritoneal dialysis

solutions are most commonly used. Their low molecular weight, however, speeds up their clearance from the peritoneal cavity, which presents a particular problem to chemotherapeutic agents with a high molecular weight such as paclitaxel. Isotonic high molecular weight solutions such as hetastarch and icodextrin solutions have been used, both demonstrating increased exposure due to reduced peritoneal clearance. Similarly, studies using hypertonic saline solutions have also shown advantage over isotonic saline solutions by slowing down the clearance of IP fluid and hence maintaining a large distribution volume, although more work is required in this area.

Safety issues around the use of oxaliplatin in 5% glucose solution for HIPEC in the management of colorectal peritoneal metastases have caused concerns in practice with significant metabolic and electrolyte disturbances.²⁶ This led to Dutch centres looking at the analysis of degradation products of

Figure 1 Intraperitoneal chemotherapy being administered using a typical hyperthermic intraperitoneal chemotherapy machine.

oxaliplatin in vitro when diluted in various chloride-containing carrier solutions.²⁷ Chloride-containing carrier solutions may be a more effective alternative when HIPEC with oxaliplatin is used for 30 min.

Techniques: timing and duration

There are two recognised methods for the administration of HIPEC. The *open technique*, also described as the 'Coliseum technique', was first developed by Sugarbaker. After cancer resection is complete, the skin edges of the abdominal incision are elevated and sutured on a self-retaining retractor to create an open space in the abdominal cavity. A plastic sheet is incorporated into this suture to prevent chemotherapy spillage. During the chemotherapy perfusion duration, all anatomic structures within the peritoneal cavity are uniformly exposed to heat and chemotherapy (figure 2). This is further enhanced by the surgeon who continuously manipulates all viscera by hand to eliminate adherence of peritoneal surfaces. After the perfusion is complete, the abdomen is suctioned dry of fluid before surgery is completed.

For the *closed technique* the laparotomy skin edges are sutured watertight to create a closed circuit. The chemotherapy solution is similarly perfused and the abdominal wall is manually agitated in an attempt to promote uniform heat distribution. After the perfusion the abdomen is reopened and perfusate evacuated. Differences between the techniques have been discussed although never compared in a randomised controlled trial.²⁸

The main benefit of the open technique is adequate and uniform distribution of the chemotherapy solution throughout the abdominal cavity. Comparatively, the closed technique produces non-uniform chemotherapy distribution which can lead to pooling and accumulation of heat and chemotherapy, leaving certain areas undertreated.

Minimal heat loss allows the closed technique to rapidly achieve and maintain hyperthermia. There is also minimal

Figure 2 The open technique ('Coliseum') for intraperitoneal chemotherapy administration.

contact or aerosolised exposure of the heated chemotherapy to the surgeon and theatre staff.

A wide variety of HIPEC regimes have been used with varying perfusion times between 30 and 120 min. Generally speaking, it is accepted that with longer duration there is increased exposure to the chemotherapeutic agent. However, consideration needs to be made to the peritoneal clearance of the drug. Most regimes using *oxaliplatin* have a perfusion time of only 30 min as its low AUC IP/intravenous ratio suggests it is rapidly absorbed. Whereas *mitomycin* with a slightly higher AUC IP/intravenous ratio is administered over 60–90 min depending upon institutional preference.

Drug concentration and volume

Drug doses are generally derived from calculations based on body surface area (BSA) which are expressed as mg/m^2 . It has been proposed that sex differences exist, causing an imperfect correlation between the BSA and the peritoneal surface area with women having a 10% larger peritoneal surface in proportion to body size than men.

The final volume of the perfusate combined with the chemotherapy solution has to be sufficient to coat the entire surface of the abdominal and pelvic cavity and all its structures. This varies between 2 and 6 L for different centres. A larger volume of perfusate is generally needed to establish the circuit when the closed technique is used. Increasing the volume without changing the drug dose can reduce concentration and thus efficacy by lowering the diffusion gradient between the peritoneal space and the tissue.

Toxicity

Systemic side effects from the IP chemotherapy drug are usually minimal and are more likely related to the magnitude of the surgery. Careful fluid management and physiological monitoring are key in preventing metabolic and renal toxicities during HIPEC.²⁹ We have already discussed the metabolic complications related to the use of large volumes of glucose solutions as a carrier solution for HIPEC.

Local side effects from the chemotherapeutic agents are rare. Adverse effects on wound healing resulting in bowel perforation and anastomotic dehiscence have been linked to the use of *mitomycin C*. Neutropenia occurring approximately 10 days from HIPEC with *mitomycin C* has also been reported. Peritoneal sclerosis and abdominal pain have been described with the use of *doxorubicin*. HIPEC in combination with CRS can also contribute to a postoperative paralytic ileus and patients may require parenteral nutrition support.³⁰ HIPEC regimes continue to evolve to minimise side effects.

DISCUSSION

Role of the pharmacist

The hospital pharmacist plays a central role in the overall provision of IP chemotherapy in accordance with the needs of the surgical team. All units need to ensure they have robust chemotherapy administration protocols and standard operating procedures for HIPEC and EPIC, which have involved the pharmacist and been approved by the local chemotherapy group. All staff handling chemotherapy should be familiar with these protocols, what to do in case of spillage and how to deal with wastage.

IP chemotherapy dose calculations

Dose calculations may require adjustments for factors such as age, significant abdominal distension or body mass index as this may affect the body composition and hence drug distribution.

Recent prolonged treatment with systemic chemotherapy may increase risks of postoperative complications at anastomotic sites. At our centre we reduce the dose by a third in these cases. An example of our prescription chart can be seen in online supplementary figure.

Practicalities of chemotherapy preparation

The chemotherapy solutions will need to be prepared in a pharmacy compounding unit with diluent and concentration in mind to optimise stability without compromising efficacy. Understanding how the HIPEC machine delivers the chemotherapy will help determine volumes required and how to deliver the chemotherapy solution in a form to maintain a closed system at all times to minimise risk of contamination and spillage. The pharmacist should be aware of whether an open or closed HIPEC technique is used by the surgeon, infusion time and the number of ports available for infusion so that the drug and perfusate can be delivered in an appropriate volume.

The majority of surgical lists for CRS will be planned. Pharmacists need to be included in circulation lists of operation dates and work with the surgical teams to obtain prescriptions in a timely manner, in order to manage their workload and facilitate the ordering of raw materials or final product, if they are outsourcing from an external compounding unit. Dose banding will improve pharmacy capacity and reduce wastage.

The issues discussed above will also affect EPIC administration, more so as it is likely to be done in a clinical ward setting rather than the confinement of the theatre, by nursing staff managing the care of several patients. Communication between the ward and pharmacy department is again vital to ensure timely delivery of chemotherapy once the go ahead has been given by the surgical team on a daily basis.

The shelf-life of chemotherapy and potential issues around drug degradation need to be communicated to the theatre/nursing team including how the drug should be stored if not used immediately, with consideration of microbial contamination, photosensitivity and temperature. Different brands and concentrations of the same drug (eg, *fluorouracil*) may have different storage recommendations. *Cisplatin* as a compound is photosensitive and carries the risk of precipitation at extreme temperatures. When given intraperitoneally in combination with *doxorubicin* it is provided in a more stable form as separate drugs, which can be infused simultaneously using a piggyback system to maintain a closed system, without compromising stability or safety.

CONCLUSION

IP chemotherapy has become an integral part of the surgical management of peritoneal malignancy. Many pharmacists will have limited experience of IP drug delivery, but use is likely to increase as evidence accumulates on the efficacy of CRS with HIPEC. Although there is no national guidance or licensing of drug regimes, pharmaceutical companies can provide stability/compatibility data and there is now a substantial amount of published research and literature available. First-hand experience is priceless and most established centres will have decades of experience in hundreds of patients, with a team comprising surgeons, oncologists, anaesthetists, nurses, theatre staff and pharmacists. It is vital to seek out these experts for advice and use their valuable knowledge when setting up new centres to ensure safe and effective IP chemotherapy administration.

Contributors PM was responsible for the conception and design of the work; acquisition, analysis and interpretation of data and drafting the article. FM

supervised the conception of the work, and acquisition, analysis and interpretation of data. FM, TDC, SD and BJM were responsible for revising the paper critically for important intellectual content. All named authors were responsible for the final approval of the version published, and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Kerscher AG, Chua TC, Gasser M, *et al.* Impact of peritoneal carcinomatosis in the disease history of colorectal cancer management: a longitudinal experience of 2406 patients over two decades. *Br J Cancer* 2013;108:1432–9.
- 2 Sugarbaker PH. Peritonectomy procedures. *Surg Clin North Am* 2003;12:703–27.
- 3 Youssef H, Newman C, Chandrakumar K, *et al.* Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. *Dis Colon Rectum* 2011;54:293–9.
- 4 Mohamed F, Cecil T, Moran B, *et al.* A new standard of care for the management of peritoneal surface malignancy. *Curr Oncol* 2011;18:e84–96.
- 5 National Institute for Health and Clinical Excellence (NICE). Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique):IPG56. 2004. <https://www.nice.org.uk/guidance/ippg56> (accessed 12/09/2015).
- 6 Moran BJ. Establishment of a peritoneal malignancy treatment centre in the United Kingdom. *Eur J Surg Oncol* 2006;32:614–18.
- 7 NHS Commissioning Board. Clinical Commissioning Policy: Cytoreductive Surgery for Peritoneal Carcinomatosis:NHSCB/A8f. 2013. <http://www.england.nhs.uk/wp-content/uploads/2013/04/a08-p-a.pdf> (accessed 12/09/2015).
- 8 Flessner MF. The transport barrier in intraperitoneal therapy. *Am J Physiol* 2005;288:F433–42.
- 9 Dedrick RL, Flessner MF. Pharmacokinetic Problems in Peritoneal Drug Administration: Tissue Penetration and Surface Exposure. *J Natl Cancer Inst* 1997;89:480–7.
- 10 Sugarbaker PH, Van der Speeten K, Stuart OA. Pharmacological rationale for treatments of peritoneal surface malignancy from colorectal cancer. *World J Gastrointest Oncol* 2010;2:19–30.
- 11 Sugarbaker PH, Torres Mora J, Carmignani P, *et al.* Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. *Oncologist* 2005;10:112–22.
- 12 Verwaal VJ, Boot H, Aleman BMP, *et al.* Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome. *Ann Surg Oncol* 2004;11:375–9.
- 13 Alexander HR, Bartlett DL, Pingpank JF, *et al.* Treatment factors associated with long-term survival following cytoreductive surgery and regional chemotherapy for patients with malignant peritoneal mesothelioma. *Surgery* 2013;153:779–86.
- 14 Elias D, Lefevre JH, Chevalier J, *et al.* Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009;27: 681–5.
- 15 Marcotte E, Dubé P, Drolet P, *et al.* Hyperthermic intraperitoneal chemotherapy with oxaliplatin as treatment for peritoneal carcinomatosis arising from the appendix and pseudomyxoma peritonei: a survival analysis. *World J Surg Oncol* 2014;12:332.
- 16 Glehen O, Mohamed F, Sugarbaker PH. Incomplete cytoreduction in 174 patients with peritoneal carcinomatosis from appendiceal malignancy. *Ann Surg* 2004;240:278–85.
- 17 Sugarbaker PH. Cytoreductive surgery & perioperative chemotherapy for peritoneal surface malignancy. Chapter 1: an overview of peritonectomy, visceral resections, and perioperative chemotherapy for peritoneal surface malignancy. In: Paul Sugarbaker PH, ed. *Textbook and video atlas*. North Woodbury, CT: Cine-Med Publishing, Inc., 2013:24–6.
- 18 Mohamed F, Marchettini P, Stuart OA, *et al.* A comparison of hetastarch and peritoneal dialysis solution for intraperitoneal chemotherapy delivery. *Eur J Surg Oncol* 2003;29:261–5.
- 19 Coccini F, Campanati L, Catena F, *et al.* Hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer: a multicenter prospective observational study. *J Gynecol Oncol* 2015;26:54–61.
- 20 Passot G, Dupré A, Rivoire M, *et al.* Intraperitoneal bevacizumab combined with cytoreductive surgery: as pre-clinical study of tolerance and pharmacokinetics in an animal model. *Clin Transl Oncol* 2012;14:931–6.
- 21 Heiss MM, Murawa P, Koralewski P, *et al.* The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: Results of a prospective randomized phase II/III trial. *Int J Cancer* 2010;127:2209–21.
- 22 Goëré D, Gras-Chaput N, Aupérin A, *et al.* Treatment of gastric peritoneal carcinomatosis by combining complete surgical resection of lesions and intraperitoneal immunotherapy using catumaxomab. *BMC Cancer* 2014;14:148.

- 23 Van der Speeten K, Govaerts K, Stuart OA, *et al.* Pharmacokinetics of the Perioperative Use of Cancer Chemotherapy in Peritoneal Surface Malignancy Patients. *Gastroenterol Res Pract* 2012;2012:378064.
- 24 Teicher BA, Kowal CD, Kennedy KA, *et al.* Enhancement by hyperthermia of the in vitro cytotoxicity of mitomycin C toward hypoxic tumor cells. *Cancer Res* 1981;41:1096–9.
- 25 Mohamed F, Sugarbaker PH. Carrier solutions for intraperitoneal chemotherapy. *Surg Oncol Clin N Am* 2003;12:813–24.
- 26 Ceelen WP, Peeters M, Houtmeyers P, *et al.* Safety and efficacy of hyperthermic intraperitoneal chemoperfusion with high-dose oxaliplatin in patients with peritoneal carcinomatosis. *Ann Surg Oncol* 2008;15:535–41.
- 27 Mehta AM, Van den Hoven JM, Rosing H, *et al.* Stability of oxaliplatin in chloride-containing carrier solutions used in hyperthermic intraperitoneal chemotherapy. *Int J Pharm* 2015;479:23–7.
- 28 González-Moreno S, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: Rationale and technique. *World J Gastrointest Oncol* 2010;2:68–75.
- 29 Thanigaimani K, Mohamed F, Cecil T, *et al.* The use of cardiac output monitoring to guide the administration of intravenous fluid during hyperthermic intraperitoneal chemotherapy. *Colorectal Dis* 2013;15:1537–42.
- 30 Vashi PG, Gupta D, Lammersfeld CA, *et al.* The relationship between baseline nutritional status with subsequent parenteral nutrition and clinical outcomes in patients with cancer undergoing hyperthermic intraperitoneal chemotherapy. *Nutr J* 2013;12:118.