Hyperthermic intraperitoneal chemotherapic perfusion in colorectal cancer

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Introduction

The term peritoneal carcinomatosis (PC) includes all tumoral dissemination, either local or massive, to the peritoneal serosa and neighbouring anatomical structures. The term PC was first used by Simpson in 1931 to describe the peritoneal dissemination of an advanced ovaric cancer (1).

Traditionally, the PC is considered a stage IV tumour indistinguishable from other metastatic sites (2).

The PC may manifest very differently, since few millimetric implants adjacent to the primary tumour to the occupation of the entire abdomen and pelvis of bulky tumour masses. Most patients with PC progress to intestinal obstruction, ascites formation, tumour cachexia or combination of them all. The term PC is associated with very advanced tumours without therapeutic possibilities. Patients often suffer a significant deterioration in their quality of life before death (3-5).

The incidence of PC is difficult to establish with certainty due to the diagnostic limitations of image-based media and current biological measurement. The ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are sensitive to diagnose visceral recurrences, retroperitoneal, and some indirect signs of PC, but miss infracentimétric peritoneal disease (6).

Laparoscopy seems to be an effective method for diagnosis, establishing the location extension of peritoneal disease and to determine tumour histology, but has technical limitations, and involves a risk of peritoneal extent of spread (7).

Over 400,000 new patients/year are diagnosed of colorectal cancer in Europe, wherein PC is detected to coincide with the diagnosis of primary tumour in 10% of the patients (8). Recurrence is only at peritoneum in 10-35% of the patients who relapse after treatment of the colorectal tumour (3-5,9,10).

The usual treatment of the PC is palliative and therefore with limited survival. A prospective, multicenter study included patients with PC from colorectal cancer showed a survival of only 5.2 months (11). In other reports published before 2002, including large series of patients with PC of colorectal origin, the mean survivals were referred from 5 to 9 months (12). Current chemotherapy protocols that include new systemic drugs such as oxaliplatin or irinotecan alone or in combination with biologic agents get to prolong survival of these patients from 21.5 to 24 months. These studies have been conducted in patients with colorectal cancer who had any kind of metastatic disease (13-19). It is known that the natural history and response to systemic chemotherapy of the peritoneal disease are significantly worse than in other metastatic sites, such as liver or lung (13). To date, there are no published studies that have evaluated the response of patients with peritoneal metastatic disease exclusive to these new lines of chemotherapy. Surgery as sole treatment in the PC is associated, to a new peritoneal recurrence (14,20,21). It is rare that a patient diagnosed with PC treated with any type of palliative treatment, remains alive at 5 years.

In recent years, interest in the peritoneal dissemination of tumours has increased due to better clinical outcomes achieved with multimodal treatments and recent knowledge on the development and peritoneal tumour growth, which allowed considering the PC as a locorregional disease (22).

PC may benefit from intensificated regional therapy as successfully as metastatic liver disease.

In late 1980, Sugarbaker laid the foundations of a multidisciplinary approach that combines the PC radical surgery and immediate administration of intraperitoneal chemotherapy with or without hyperthermia, designed to eradicate microscopic residual tumour. This treatment has been quite favourable in the treatment of low-grade tumours, especially in the peritoneal pseudomyxomas from appendiceal origin and in some peritoneal mesotheliomas. In recent years, several working groups specialised in many centres in America and Europe are applying multidisciplinary treatment in the PC, and indications have been extended to other types of malignant tumours of the peritoneum, due to the good results published.

Controlled prospective studies are conditioned by the difficulties in recruiting patients with rare tumours with highly variable clinical presentations, the complexity of homogenisation of each of the elements of a complex treatment, especially surgery, and the patients agreement to be assigned to a palliative treatment arm versus the possibility of potentially curative treatment (23).

Pathophysiology of peritoneal carcinomatosis

The peritoneum is an organ that covers the three-dimensional structures contained in the abdominopelvic cavity. It cvomprises a single layer of mesothelial cells on a basal membrane and five layers of tissue with a total thickness of 90 microns. The layers of tissue includes interstitial cells and a matrix of collagen, hyaluronic acid and proteoglycans (24). The known functions of the peritoneum are the production of a lubricating substance to facilitate contact between the elements of the abdominal cavity to act as an important organ of defense against intra-abdominal infections. It is now recognised another function of the peritoneum in the development of neoplasms, acting as a first line of defense against the introduction and tumour development (25). Any injury or wound the peritoneum acts as a facilitator of tumour cell implantation into the abdominal cavity and is involved, along with other elements in tumour proliferation (26).

Neoplasms of the digestive, gynaecological and other sources often use the coelomic route for the tumour spreading.

Tumour cells can be released into the abdominal cavity from the serosal surface of the organ infiltrated by the tumour (27). Surgery can contribute very significantly to the exfoliation of tumour cells into the abdomen. It has been shown that during the extensive removal of primary tumours and/or lymph node involvement, a significant number of tumour cells are released into the abdominal cavity (28-30).

The meaning of free tumour cells in the abdominal cavity is still unknown. The number of tumour cells that are required to effectively implant in the peritoneum is much lower than those necessary for the development of other types of metastasizing tumour. This phenomenon is known as "metastatic inefficiency" and was corroborated by animal studies that demonstrated the greatest tumour tropism of some strains by peritoneum (31,32).

Free tumour cells in the abdominal cavity have to evade the immune system and develop a network of vascular substitution to meet their metabolic needs in order to survive. Due to the complexity of these processes, many tumour cells cannot become metastatic tumour deposits.

Tumour cells that remain viable are moved into the abdominal cavity by hydrodynamic movements associated with breathing and following predictable routes, which would explain the predominance of tumour implants on the surface of the right hemidiaphragm. The presence of ascites and resorption areas with high phagocytic capacity, as the omentum and epiploic appendices, justify the very large tumour accumulations, known as omental cake. Intestinal peristalsis, together with the effect of gravity, facilitate the distribution of the tumor in most areas slopes, such as Douglas sac, the parietocolic gutters, retrohepatic fossa and those fixed anatomical structures such as the ileocecal region and the first jejunal portion (33).

In women, tumour cells very often affect the ovaries, especially at points of follicular rupture. Tumour cells have high affinity for the intercellular matrix of the injured peritoneum or bloody areas caused by the surgery. The tumoral entrapment process is especially fast and can occur in minutes facilitated by the effect of integrins, cell adhesion molecules, and production of growth factors such as growth factor for fibroblasts (fibroblast growth factor, FGF), epidermal growth factor (epidermal growth factor, EGF) and transforming growth factor beta (transforming growth factor beta, TGF-) (34). All these molecules appear during the physiological mechanisms of inflammation and tissue healing. The binding of tumour cells with the intercellular matrix of tissues is also very strong and impossible to avoid using washing/stripping solutions commonly used during conventional surgery. After surgery, the implantation of tumour cells in the intercellular matrix is usually immediate and once they are coated with fibrin and other products in

the processes of tissue repair, they become "sanctuaries" where cells can proliferate protected from the external environment. Tissue adhesions formed early after surgery avoids the cytotoxic effect of intraperitoneal chemotherapy and the absence of a neovascular network prevents the access of systemic chemotherapy.

Multimodality treatment - Therapeutic basis

The approach and development of multidisciplinary treatment of the PC (radical surgery plus intraperitoneal chemotherapy +/- hyperthermia), also known as regional treatment of malignant diseases of the peritoneal surface or Sugarbaker's technique, is related to the current understanding of the pathophysiology of the peritoneum and the mechanisms for implementation and growth of tumours in the abdominal cavity.

In 1989, Sugarbaker defined PC as a locoregional manifestation of neoplastic nature. He proposed a treatment of "regional therapeutic enhancement" for the PC, based on a radical surgery, designed to remove the entire macroscopic tumour of the abdominal cavity, followed by immediate administration of intraperitoneal chemotherapy, with or without the use of hyperthermia (35,36).

The more widespread use of multidisciplinary treatment has advanced the definition and practice of the radical surgery, the type and timing of intraperitoneal chemotherapy, the adaptation of the techniques of hyperthermia, the protocols of care and postoperative controls and, particularly, in the appropriate selection of patients. Biannually since 1998, meetings of experts from the Peritoneal Surface Oncology Group International (PSOGI) are being held, and experiences are addressed and discussed on the treatment of these diseases. The 5th Workshop Meeting, held in Milan, was particularly relevant, since it addressed controversial issues of each part of the therapy and established consensus on issues as important as the methodology of the radical surgery, intraperitoneal chemotherapy and hyperthermia, the role of the various specialties involved in the management of these patients and, especially, the criteria for patient selection and multidisciplinary treatment indications. The most important conclusions of this meeting in Milan were published in a special issue of the Journal of Clinical Oncology (37).

Radical surgery

The prognosis of patients with PC undergoing multidisciplinary treatment is directly related to the extension of the disease and surgical radicality (38). The aim of radical surgery is to remove the abdominal tumour without leaving any visible macroscopic residual disease. The extent and distribution of the PC must be fully established before starting the process. The highest concentration of tumour is usually located in the retrovesical space, the pouch of Douglas, the parietocolic gutters, the right subhepatic space and more posterior subdiaphragmatic areas. Very often, the omental transcavity, the retrogastric compartment, the splenic hilum and the mesentery of intestinal segments, more fixed and less mobile (duodenojejunal angle, distal ileum and sigmoid colon) are affected. The postsurgical adhesions and structures with low venous return (hernia sacs) present special predisposition to tumor development. All anatomical regions of the abdomen and pelvis may be affected by tumour seeding and should be explored carefully. An important step of this operation corresponds to the identification of all tumour foci present in the abdominal cavity. The correct characterization and quantification of PC allows determining the technical and clinical benefits of the radical surgery. Sugarbaker described the peritonectomy procedures which are a key therapeutic element in the multidisciplinary treatment of PC (39). Peritonectomy procedures can eliminate the gross tumour present in the peritoneal serous as well as the removal of the viscera and surrounding structures deeply infiltrated by the tumour.

The removal of the implants with diffuse and extensive distribution in the peritoneal surface requires the stripping of the entire peritoneum of the corresponding anatomical region. Few isolated implants of visceral or parietal peritoneum that infiltrate can be completely removed or electrovaporised by high voltage electric scalpel.

Bulky implants invading deeply into an organ or anatomical structure may obly to associate an excision of it. In the extensive or limited but high volume PC may require multivisceral resections and/or large bowel resections, sometimes multisegmental, followed by digestive anastomosis. Tumour involvement of a significant portion of the small intestine may limit or prevent any radical surgery. When the length of residual intestine does not ensure an adequate supply, surgery should be avoided. In addition to the extensive involvement and/or multisegmental bowel, other operative findings that impair or limit the complete cytoreduction in patients with CP, is the gross involvement of the hepatobiliary hilum, full retraction of the mesentery and/or massive retroperitoneal nodal involvement (40). The

use of electrocautery provides hemostasis while a bed of sterilized dissection plane of tumour cells

Intraperitoneal chemotherapy

Chemotherapy administered regionally aims to achieve high concentrations of a cytotoxic agent in tumours located at a particular point of the body. Administered intraperitoneally, enables a very intensive treatment of tumours located in the abdominal cavity in relation to the dose of drug used. Dedrick showed that in various chemotherapeutic drugs, hydrophilic peritoneal permeability was considerably less than its plasma clearance, resulting in proportionally much higher concentrations of intra-abdominal chemotherapy (41).

The primary objective of intraperitoneal chemotherapy is to achieve high concentrations of drug in the site of the tumour, minimizing the systemic side effects.

The first use of intraperitoneal chemotherapy correspond to Spratt, who used the intraperitoneal thiotepa in a patient with peritoneal pseudomyxoma, Speyer used 5-fluorouracil (5-FU) and methotrexate. Koga then associated intraperitoneal chemotherapy with hyperthermia in the treatment of gastric carcinomatosis (42).

The molecular weight of the drug, its lipid solubility and capillary permeability determines its passage into the systemic circulation. Other requirements that must be taken into account in the choice of intraperitoneal chemotherapy are the time of removal from the systemic circulation, the ability to pass the portal system and the empowerment of their effects by hyperthermia. Cell cycle-nonspecific drugs are a priority for the intraperitoneal use (43,44).

Several studies have established a maximum of 2-3 mm penetration of chemotherapeutic agents in tumour tissue. This ability to penetrate tissue explains that the ideal limit set of residual disease after radical surgery considered is equal to or less than 2.5 mm (45,46). Peritonectomy procedures do not affect the pharmacokinetics of intraperitoneal drugs (47,48). The molecules used are 5-FU, mitomycin C, oxaliplatin and irinotecan. Drugs can be administered alone or in combination (49).

The dose of chemotherapeutic agents administered in HIPEC is calculated from the body surface that correlates with drug metabolism and systemic toxicity. Nevertheless some authors propose to dosify based on drug concentration (mgr/L) (50).

The procedures for intraperitoneal administration of chemotherapy vary according to time and how to apply them in the abdominal cavity. The maximum benefit is achieved when used immediately after surgery, before the "entrapment" of tumour cells by fibrin and the partitioning of the abdominal cavity for surgical adhesions.

When chemotherapy is administered intraperitoneally from days 0 and 5 of immediate postoperative period is called early postoperative intraperitoneal chemotherapy (EPIC). The EPIC was initiated after tumour removal, allowing fibrin and microscopic cellular remnants removal from the abdominal cavity, which is then bathed with the chemotherapic solution. The solution is stored for 23 hours and removed daily through catheters (51). Several cycles of intraperitoneal chemotherapy are given to increase the chances of exposure of chemotherapy to tumour cells, but has the disadvantage that produces greater systemic adverse effects and allows the partitioning and sequestration of chemotherapeutic agents located favouring infection (52,53).

Hyperthermia

The association of heat to intraperitoneal chemotherapy enhances the therapeutic effect of some chemotherapic drugs and creates a "toxic shock" directly on tumour cells. At a meeting of the international medical community held in Madrid in 2004, it was agreed that this technique should be referred to as HIPEC (54).

Some animal studies show that chemohyperthermia offers a greater therapeutic benefit above that of hyperthermia or chemotherapy administered intraperitoneally alone (55). Hyperthermia destroys tumour cells when temperature reaches 43 ℃. Normal cells are heat resistant up to 45 ℃ (47). Cellular metabolism increases with temperature until a point at which irreversible damage occurs. The critical point of human cells is 43.5 ℃, while *in vitro* temperature of 42.5 ℃ produces a high cytotoxic effect by acting on the interstitial pressure in tumour tissue, favouring the penetration of drugs such as mitomycin C, cisplatin, oxaliplatin and irinotecan, or acting directly on the cell itself and its molecular composition. It has been described effects on the cytoskeleton, such as changes in the stability and fluidity of cell membrane alterations in cell shape, decreased intercellular transport mechanisms, alterations in membrane and induction of apoptosis. Also, alterations in protein synthesis, protein denaturation, aggregation of nuclear matrix proteins and induction of synthesis of heat shock proteins (HSP) have been demonstrated in the intracellular proteins. Heat has also shown effects on nucleic acids, decreased synthesis of RNA/DNA, inhibition DNA repair enzymes and alteration

of the latter. Hyperthermia influence cellular function by affecting the metabolism of several intracellular substrates expression of the genes and signal transduction. Other effects are related to the cellular immune response with the induction of those already mentioned HSP involved in antigen expression and tumoral immunity.

Hyperthermia has shown clinical efficacy in several randomized studies, either as direct mechanism or due to the enhancing effect on radiation therapy and chemotherapy. Clinically, the major tumoricidal effects of hyperthermia are achieved between 41 and 43 ℃ (56).

There are two ways to settle the perfusion. The technique described by Sugarbaker, called open technique or coliseum, is the most widespread. It involves the administration of HIPEC leaving the abdomen open.

The other mode, called the closed technique is applied with a temporarily closing of the abdomen for the administration of chemohyperthermia. This type of HIPEC is supposed to increase the drug penetration in the tumour by an increased abdominal pressure. There are no studies to demonstrate which mode provides greater clinical benefit to patients. The technical feasibility of HIPEC has been established in recent years by several authors (57,58).

The optimum temperature of the HIPEC is a very important parameter. Most chemotherapeutic agents used are chemically stable to 50 ℃. Studies *in vitro* and in cell culture show that the cytotoxicity is more effective at 45 ℃ than at 41 or 42 ℃, so it would be reasonable to use the maximum temperature within the limits of clinical tolerance checked, which, as we mentioned above, is marked by tolerance of the small intestine and corresponds to 43 ℃ (59,60).

Other parameters

The carrier solution used in intraperitoneal chemotherapy can modify the exposure time of chemotherapeutic agents in the abdomen. With the aim of increasing the exposure time, various types of solutions have been used. A high molecular weight creating ascitis maintains a higher availability of the drug. The selection of the solution is particularly relevant in the EPIC (61,62). In HIPEC, with a dwell time relatively short, one might expect that a hypotonic solution increases the uptake. But Elias demonstrated that dextrose solution of 100 and 150 mOsm/L, which not only does not increase tumour penetration, but also is associated with a high rate of serious complications (50%) and peritoneal bleeding and thrombocytopenia, so this author contraindicated hypotonic

solutions as transport solution for HIPEC (63).

The duration of HIPEC is an issue still debated. The safety of hyperthermia has only been demonstrated in established empirically based schemes: temperature of 41 ℃ for 90 minutes or 43 ℃ for 30-40 minutes. In clinical practice, the duration of administration of HIPEC is set between 30 and 90 minutes, and varies according to the pharmacokinetic characteristics, the total dose of chemotherapy and the protocols. The intra-abdominal pressure during HIPEC directly influences the diffusion and penetration into the tissues and, consequently, a greater cytotoxic effect of chemotherapy.

Multidisciplinary treatment indications

The multidisciplinary treatment is widely recommended for the PC secondary to colorrectal tumours (33,34,37). Current indications were recently updated in the Journée Nationale du Traitement par des Carcinoses Peritoneal Chirurgie et Chimiothérapie Intrapéritoneale (Paris, May 2008).

These Indications were previously discussed at the Fourth International Workshop on Peritoneal Surface Malignancy (Madrid, December 2004) and Peritoneal Surface Malignancy in the Workshop-Consensus Statement (Milan, November 2006). Data from the United States calculates an incidence of 130,000 new cases per year, in colorectal cancer, of which between 10-15% will start with peritoneal involvement.

In Europe, annual incidence data of the PC are even higher: 25,000 to 37,500 new cases annually of PC of colorectal origin. An analysis by the French groups dedicated to the treatment of PC, estimated that approximately 10% of patients with CP can benefit from a multidisciplinary treatment applied with curative criteria (64).

Patient slection

Preoperative assessment

The indication of the multidisciplinary treatment of PC has to be done from a strict selection of patients. The highest survival rates described with this treatment correspond to those patients who were able to perform a complete tumour debulking. The incomplete cytoreduction was associated with a mean survival about 6 months (65,66). The distribution and especially the extension of the PC are the main determinants to achieve complete cytoreduction, so it is essential to establish preoperatively the characteristics of

the PC to define the indications.

There are several techniques to help identify patients likely to undergo multidisciplinary treatment: CT, MRI, PET, laparoscopy and tumour markers.

There is consensus on the need to perform a colonoscopy in all patients. The CT has great value in the detection of primary lesions or recurrences affecting solid organs and retroperitoneum, but has limitations in identifying small peritoneal implants, particularly those located in the small intestine, and mesenteric leaves. When CT fails to detect this type of implants, the disease is usually advanced and we consider a limiting data to achieve a complete cytoreduction. The CT findings of small bowel obstruction in several segments or the presence of tumour greater than 5 cm located outside the terminal ileum are associated with 88% chance of incomplete surgical resection. Contrary, the absence of these two radiologic findings, achieves a 92% complete cytoreduction. Helical CT was compared with operative findings and the sensitivity obtained was 25% to 37% with a negative predictive value ranging from 47% to 51% (67).

MRI is an exploration that provides a sensitivity and specificity of intestinal tumour involvement in the PC of 73% and 77%, respectively (68). Other studies provide a sensitivity of 84-100% for detecting peritoneal metastases with this test (69). In patients undergoing surgery, chemotherapy or prior radiotherapy and/or associated inflammatory diseases, the specific diagnosis of peritoneal involvement is difficult to determine by MRI.

The PET scan has a low sensitivity in small tumours (<1 cm), poor specificity and limitation in low-grade tumours. It also presents difficulties in the interpretation of lesions in the diaphragm, lung bases and top of the liver due to breathing artephacts. Any of the current means of imaging has limitations to establish the extent and exact location of the peritoneal tumour disease. The use of CT, MRI, PET and/or laparoscopy should be individualised and considered as part of a diagnostic-therapeutic approach of patients with PC, which may depend on the availability, cost and experience of the radiologist. The result of the consensus of Milan was to consider CT as the imaging technique essential to investigate the indications of multidisciplinary treatment.

Some centres use laparoscopy to determine the possibilities of multidisciplinary treatment, as it has the advantage of providing direct visualisation, allows detection of small lesions and practice biopsies. The disadvantages of this technique are its relative invasiveness, technical difficulties due to adhesions, limitations on access to the retroperitoneal compartment, the risk of implantation at trocar sites and the increased cost to the overall therapeutic process. There is a study evaluating the role of exploratory laparoscopy in the selection of patients with PC candidates for complete cytoreduction. In this study laparoscopy could be performed in all patients with a mean operative time of 38 minutes (range, 23-75 minutes) was well tolerated in all patients, it achieved a very accurate set of the real characteristics of the peritoneal disease and adequately identified patients for complete cytoreduction (70).

Another study, involving 97 patients with PC undergoing laparoscopy for peritoneal staging, concluded that laparoscopy allowed establishing the extent of PC in 96 of the 97 patients and only two were classified in a lower stage. It shown a good correlation between the findings of laparoscopic exploration and open surgery. Laparoscopy showed no mortality in this group of patients and observed no tumour implantation at port sites. In patients with inadequate or contradictory information on the extent of the PC, laparoscopy is a useful technique to establish the extent and distribution of the PC, to visualise the small bowel involvement and determine the possibility of a complete debulking more accurately (71).

Intraoperative assessment

The importance of establishing with certainty the distribution and extent of peritoneal disease to determine the applicability of multidisciplinary treatment has forced to design intraoperative quantification of the extent of the PC.

Currently we have three staging systems to assess the intraoperative peritoneal spread of the disease, none of which has been shown to have prognostic value for all types of PC. Gilly et al. (72,73) described a system for intraoperative measurement of the PC and it has shown to correlate with the patient outcomes in certain types of PC. Zoetmulder et al. established a simplified system of Sugarbaker's classification (74). Simplified Peritoneal Cancer Index (SPCI) demonstrated the validity in peritoneal pseudomyxoma and PC of colorectal origin. This system is also a predictor of complications and acts as a guideline in selecting patients for multidisciplinary treatment. The most universally used system of quantification is the Peritoneal Carcinomatosis Index (PCI) described by Jacques and Sugarbaker (75). It describes 13 anatomical regions, dividing the abdomen into 9 regions and the small intestine in 4. It rates each region from 0 to 3 depending on the size of the tumour lesion: 0 point, no macroscopic lesion;

1 point, tumour exceeding 0.5 cm; 2 points, a tumour of 0.5 to 5 cm and 3 points, greater than 5 cm or tumour confluence, resulting in a maximum score of 39 points. The PCI ranks of the PC extension, determines the possibilities of radical surgery and helps to establish the prognosis of patients. It also has proven to be predictive in survival of patients with PC of colorectal origin being PCI 20 the cutting point (76). This system of intraoperative tumour quantification was considered in the consensus meeting of Peritoneal Surface International Workshop Malignancy, in Milan, as the most useful, reliable and reproducible in the multidisciplinary treatment of the PC (77).

Intraoperative determination of the intensity of the radical surgery has the same importance as determining the extent of the PC. There is a direct relationship between the size of residual disease after surgery and the survival of patients undergoing multidisciplinary treatment. We have several systems that classify the size of residual disease after debulking. Most of these classifications belong to the R residual tumour classification and correspond to changes in the American Joint Committee on Cancer (78): Lyon (79) classification, Netherland's classification (80) and Winston-Salem's (81). The classification used is the Completeness of Cytoreduction Score (CC) (82), which rates residual disease after surgery in: CC-0 in the absence of gross residual disease, CC-1 if the residue tumour is equal to or less than 2.5 mm, CC-2 if the residue is 2.5 to 25 mm and CC-3 when the residue is above 25 mm or confluent persists after tumour surgery. This system does not provide the definition of microscopic residual disease in PC. The rationale for setting between 0 and 2.5 mm size limit of residual disease and appropriate to establish the concept of complete cytoreduction is due to the ability of a chemotherapeutic intraperitoneal to penetrate the tumour tissue.

But the definition of complete cytoreduction currently most accepted corresponds to the CC-0 and CC-1 cytoreduction and incomplete, CC-2 and CC-3. The CC has been associated with patient survival in carcinomatosis of colorectal origin (74,83-85).

In the future the use of more active chemotherapeutic agents can modulate the effort of the cytoreductive and the definition of radical surgery matches other criteria of residual tumour volume.

The type of previous surgery performed on the primary tumour has also been associated with chances of achieving a complete cytoreduction and the prognosis of patients who undergo multidisciplinary treatment. Sugarbaker introduced the Prior Surgical Score (PSS) (83). The PSS determines the number of regions dissected during surgery prior to the multidisciplinary treatment, and has been shown to correlate with survival.

Inclusion and exclusion of patients

The multidisciplinary approach provides a significantly higher survival rates than conventional palliative treatments, but is associated with significant morbidity and mortality. The identification of factors associated with the outcome of multidisciplinary treatment application and the patient selection is important to establish the treatment indications and maximise the clinical benefit (86).

Currently the parameters considered most useful are the following:

- Performance status (Eastern Cooperative Oncology Group): 2.

- Absence of extra-abdominal tumoral disease.

- Less than three hepatic lesions which are technically resectable.

- Absence of biliary obstruction.

- Absence of ureteral obstruction.

- Unique location intestinal obstruction.

- Absence of intense involvement of the small intestine disease.

- Little bulky disease in the gastrohepatic ligament.

ECOG patients with 2 to 3 have a median survival of 9.5 months, while patients classified from 0 to 1 is significantly higher, 21.7 months. Patients with bowel obstruction or malignant ascites and subsequent malnutrition have a worse survival than those without these complications, 6.3 and 23 months, respectively (87). Even so, in patients with malignant ascites multidisciplinary treatment prevented the recurrence of ascites in 75% of patients,being HIPEC recommended in these clinical circumstances (88). Regarding the extension of PC, Sugarbaker refers to the prognostic value of PCI in patients with PC of colorectal origin. A PCI below 10 was associated with 50% survival at 5 years, while survival was 0% in those cases with a PCI greater than 20 (P<0.0001). This author considers this treatment contraindicated in patients with PCI over 20, while others raise the PCI to values of 26. Verwaal used as a criterion for extension of PC the level of affectation of the different regions. Of the total of seven, more than five affected regions are associated with lower survival benefit and high morbidity rates (65). There is consensus among experts that the best long-term clinical benefits with the multidisciplinary treatment are achieved

in patients with limited extent of the peritoneal disease (89). In the evaluation of preoperative CT, patients with PC of colorectal origin class III presenting involvement of the small intestine or the mesentery (as classified by Yan), bulky retroperitoneal lymph node involvement and/or radiological PCI over 20 should be excluded for multidisciplinary treatment.

There are other useful recommendations on patient selection and indication of the multidisciplinary treatment of colorectal origin with PC that are based on primary tumour staging (90):

- T4 N0 M1 tumours (in the form of limited peritoneal disease): upfront multidisciplinary treatment.

- T4 N2 M1 (with limited peritoneal disease): treatment with chemotherapy for 3 months followed by multidisciplinary treatment and best systemic chemotherapy.

- Clinically asymptomatic patient with resectable extensive disease, ascites and small bowel involvement: multidisciplinary treatment followed by the best systemic chemotherapy.

- The multidisciplinary treatment should be scheduled at least 1 month after the last administration of systemic chemotherapy.

The type and degree of histological differentiation of the tumour causing the PC have also shown to impact on survival.

The most suitable application of multidisciplinary treatment corresponds to: "young" patients with good general condition, no previous treatments, localised PC caused by tumours of low mitotic activity and completely resectable. The short-term clinical outcomes (morbidity and mortality) and long-term (survival and quality of life) of the multidisciplinary treatment are closely related to the proper application of these criteria in the selection of patients.

Exclusion criteria accepted by most of the groups are:

- Patients who have a PC judged unresectable by clinical or paraclinical: mesenteric retraction evident on CT, infiltration/retraction bladder by endoscopy.

- Extrabdominal metastases or unresectable liver metastases or requiring major hepatectomy conditioning a limited hepatic reserve.

- The presence of other malignant disease.

- Multisegmental complete bowel obstruction.

- Active infection or other condition that prevents or incapacitate the patient to receive the proposed treatment per protocol.

Results of multidisciplinary treatment

Morbidity

Complications can arise directly from surgery,

chemotherapy, hyperthermia or the sum of these. Radical surgery in the treatment of CP is usually the most important cause of complications and the main reason to alter the therapeutic process. Elias recently described a specific classification system for complications related to the multidisciplinary treatment of PC (91). This author considers 6 degrees of complications, defined as grade 0: no complications, grade 1: complications that do not require action or minor treatment as oral antibiotics, basic controls···, grade 2: complications requiring moderate actions, as intravenous medication, parenteral nutrition, prolonged nasogastric tube, pleural drainage, grade 3: complications requiring hospital readmission, reoperation or interventional radiology, grade 4: chronic complications, removal of organs or digestive derivations, and grade 5: complications leading to death of the patient. At the consensus meeting in Milan was agreed to use the new Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 as a system of classification of complications. This is an extensive guide which includes types of complications in 28 categories, based on the anatomy and pathophysiology (92). The complication rate grade III-IV is around 30 to 65%. Specific surgical morbidity is 30% and relates mainly to digestive sutures dehiscence, perforation, intestinal fistulas, collections, intra-abdominal abscesses and postoperative bleeding. Around 10% of patients require one or several surgical operations (93-95). A multivariate analysis fulfilled by the group from Washington Hospital Centre determined that the rate of postoperative complications is related to the extension of the PC (PCI), duration of surgery and the number of digestive anastomosis performed (96). Although the morbidity described in this complex treatment is not higher than that referenced in the gastrointestinal major surgery extreme care is required, especially in the immediate postoperative period. Systemic complications correspond to those of any major surgery but may be covert or increased by the effects of systemic toxicity, gastrointestinal or haematological of HIPEC. Patients undergoing peritonectomy have an altered inflammatory response caused by surgical removal of the peritoneum and the effect of intraperitoneal chemotherapy, which often affect an evident decrease in peritoneal-abdominal pain that hinders the clinician to early diagnose postoperative abdominal complications. The immediate follow-up of these patients should be performed in a unit of critically ill patients with specific clinical protocols and expert staff.

Mortality

The reported mortality in the multidisciplinary treatment of PC ranges from 0 to 14%. Mortality rate of 2-6% are the most frequent in most published studies. Mortality is related with the intensity of surgical invasiveness, reflected in the number of peritonectomy procedures performed, the PCI, the number of digestive anastomosis and volume of perioperative blood transfused (97).

The causes of mortality referenced in the literature are related to intestinal perforations, bone marrow suppression, respiratory failure, pulmonary embolism and infection by methicillin-resistant Staphylococcus aureus. There are several factors that predict mortality in the multidisciplinary treatment of PC, as the presence of abundant ascites, bad general status and bowel obstruction (87). Both the morbidity and mortality in the multidisciplinary treatment are directly related to the surgical team's experience and proven the importance of the learning curve in this treatment. The series providing 100 or more patients usually have a lower rate of complications, and these are less severe (98,99).

Quality of life

Studies addressing the quality of life of patients undergoing HIPEC conclude that it is a complex and invasive therapy but generally well tolerated (100,101). Usually patients can be with a similar activity pattern to its previous one at 3 months after surgery. Almost half of the survivors at 3 years return to work with the same intensity as before treatment. The groups of patients who benefit the most, according to the quality of life scales applied, were those with ascites before surgery. These results were similar to those published by the National Cancer Institute (Bethesda) about a group of patients assessed at 3, 6 and 9 months after surgery (102). The interpretation of the evidence of the published studies on quality of life in the multidisciplinary treatment is difficult to establish by several factors(103-107): the clinical heterogeneity given by the variation in the type of underlying disease, degree of surgical cytoreduction and the mode to administer intraperitoneal chemotherapy, the methodological heterogeneity between studies and variations in the scales used to measure the quality of life and the lack of a control group using the assessment of patients with the same condition subject to other treatments. The clinical significance of these variations is difficult to establish.

Failure of multidisciplinary treatment

Peritoneal recurrence occurs in 70% of patients (108-109).

Patterns of recurrence following multidisciplinary treatment can help to detect the cause of treatment failure and to modify it. A localized form of peritoneal recurrence could correspond to a failure of the surgery for "forgetting" a tumour foci between the adhesions and scar tissue where intraperitoneal chemotherapy is less effective against free tumour cells. Peritoneal recurrence detected in the intestinal wall may be due to a failure of the electrofulgeration, while the diffuse peritoneal recurrence may be due to failure of intraperitoneal chemotherapy to eradicate minimal residual tumour disease after surgery.

It is important to determine the characteristics of the multidisciplinary treatment failures in order to advance in its development and to establish which patients may benefit from a new therapeutic approach. Another type of multidisciplinary treatment failure, is the spread of peritoneal carcinomatosis in the pleural cavity or the lung parenchyma, which occurs mainly in low-grade mucinous tumours associated with peritoneal pseudomyxoma. Sugarbaker considered the most likely mechanisms for the extension of the disease to extra-abdominal compartment were: (I) presence of congenital diaphragmatic hiatus holes or, (II) laceration of diaphragm muscle fibres caused by surgery, (III) communication openness and surgical abdominal and pleural cavities, and (IV) pulmonary tumour emboli.

It is very important to avoid aperture, and if it occurred, should be left the peritoneal-pleural communication open during the HIPEC phase to allow removal of the tumour cells migrated to the thorax by chemohyperthermia.

Summary

As occurred in the past with metastatic liver disease from colorectal cancer, peritoneal dissemination in colorectal cancer is still considered a widespread condition and treated with palliative procedures. For years, the locoregional treatment of liver metastases by the combination of liver surgery and chemotherapy has modified previous therapeutic concepts and criteria and has provided significant benefits on the survival in these patients. Currently the PC of colorectal origin is also considered a locoregional tumour manifestation confined to the abdomen.

Evidence in the different studies regarding the efficacy of

HIPEC for the PC from colorectal origin show that the survival after treatment varies between 22 and 60.1 months, and that survival rates at 5 years are between 11% and 48.5%, with a disease free survival of 34% for the same time period (66).

The 2-year survival of these patients is higher than that observed with the treatment without surgical cytoreduction and intraperitoneal chemotherapy, as evidenced by a properly randomized study (65). Patients in which it was possible to achieve a complete cytoreduction had better results. The results of a phase III trial demonstrated the clinical benefits of the multidisciplinary treatment compared with systemic chemotherapy and palliative surgery, and was first published survival rates of 5 years in the treatment of colorectal PC (11).

Elias presented 5-year survivals of 48.5% of patients with 34% of patients free of disease in this same period and a median survival time of 60.1 months using the open technique and a bidirectional chemotherapy consisting of application, 1 hour before HIPEC, a dose of 5-FU + folinic acid systemically. The intraperitoneal chemotherapy used was oxaliplatin at a dose of 460 mg/m^2 administered over 30 minutes at 43 ℃. Patients followed adjuvant chemotherapy. The risk for this clinical benefit was a 27% chance of developing complications grade III or higher toxicity (91).

In the past 10 years a large number of specialized centres have incorporated this therapeutic modality in the treatment of malignant diseases of the peritoneum, with improvements in therapeutic procedures, criteria for patient selection in the adjuvant chemotherapy and subsequent monitoring for the detection of early peritoneal recurrence and radical rescue surgery. The standardization of the entire therapeutic process has been reflected in better survival rates at 3 and 5 years and declines in the figures relating to morbidity and mortality, particularly evident in those studies involving over 100 patients in their series. It is considered that 130 patients treated by the same team, are the appropriate number of patients to complete the learning curve with this type of treatment.

Most important groups consider appropriate selection of patients according to their general, the extension of the PC (five or least affected regions or ICP <25) and the absence of multiple interventions and/or lines of chemotherapy failed. The feasibility of a complete cytoreduction (CC0-CC1) is crucial as an inclusion criterion (110).

It has been shown that the survival of the patients with PC of colorectal origin undergoing multidisciplinary treatment depends basically on the extent of PC at the time of surgery and the completion of surgical debulking. Almost all studies agree on the impact of the debulking with no macroscopic residual tumour in terms of survival. The patients who achieved a complete cytoreduction had a survival rate nearly twice that those patients in whom it was not possible to perform (111).

The risks are that between 25-50% of major complications (surgical or medical), although they do not significantly differ from those referred for patients undergoing major digestive surgery.

The multidisciplinary treatment is associated with risk of death by 5-12%.

Although there are two randomized controlled trials, only one could conclude as planned, while the other had closed prematurely due to difficulties in recruiting patients (66). So most of this evidence is level 3 (case series, most of them retrospective), and part was summarized as intermediate quality in a systematic review of the literature (112).

It has been shown that the survival of colorectal origin of PC patients undergoing multidisciplinary treatment depends largely on the extent of the PC at the time of surgery (PCI) and the completion of the surgical cytoreduction (CC). Almost all studies agree on the important impact that involves debulking with no macroscopic residual tumour (CC0) on survival.

Most groups consider important the proper selection of patients according to their status, the PCI <26 (<10 according to Sugarbaker) and the absence of previous surgery and/or lines of chemotherapy failed and the chances of achieving full cytoreduction (CC0-CC1) are crucial to the outcome of these patients.

An ongoing Phase III trial (NCT00769405) addresses this question of how much of the survival benefit is derived from the cytoreduction and how much from hyperthermic intraperitoneal chemotherapy, as patients will be randomly assigned to hyperthermic intraperitoneal chemotherapy or no hyperthermic intraperitoneal chemotherapy after complete cytoreductive surgery.

It is important to conduct controlled clinical trials that redefine the role of HIPEC in the era of new biological molecules and the effect of the best selection of patients using the benefits of recent genomic studies on biopsy material, to establish predictive factors associated with this treatment.

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