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Review article

Rationale for perioperative chemotherapy treatment in peritoneal carcinomatosis

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A B S T R A C T

Peritoneal carcinomatosis, without special treatment, is a fatal sign of gastrointestinal and gynaecological malignancy. Cytoreductive surgery to remove gross disease is combined with perioperative intraperitoneal and intravenous chemotherapy to eradicate the residual microscopic disease. Knowledge of the effect of the peritoneal barrier on the pharmacokinetics of the chemotherapy agents, and the factors that affect this, enables a good combination of drugs, dosage and solution volume to be selected, in order to predict peritoneal and systemic exposure to the treatment and its toxicity. Timing of the chemotherapy as a planned part of the surgical procedure to maximise exposure of all peritoneal surfaces is crucial to success. In this article we update the pharmacokinetic basis for perioperative chemotherapy treatment of peritoneal carcinomatosis of gastrointestinal or gynaecological origin.

Bases farmacológicas de la quimioterapia perioperatoria en la carcinomatosis peritoneal

Palabras clave:
Quimioterapia intraperitoneal
Barrera peritoneoplasmática
Cáncer de apéndice
Cáncer colorrectal
Mesotelioma peritoneal
Cáncer de ovario

R E S U M E N

En los tumores digestivos y ginecológicos, la carcinomatosis peritoneal, sin tratamientos especiales, es una manifestación fatal de estas enfermedades. La cirugía citorreductora, que extirpa la enfermedad microscópica, se combina con quimioterapia perioperatoria intraperitoneal e intravenosa para eliminar la enfermedad microscópica residual. Entender bien el efecto de la membrana peritoneal en la farmacocinética de los quimioterápicos y los factores que la modifican permite elegir la combinación de fármacos, calcular su dosis y el volumen de disolución, lo que facilita predecir la exposición peritoneal y sistémica al tratamiento y su toxicidad. Coordinar la quimioterapia como una parte programada del

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tratamiento quirúrgico para obtener la máxima exposición en toda la superficie peritoneal es crucial para el éxito del tratamiento. En este artículo actualizamos las bases farmacocinéticas de la quimioterapia perioperatoria de la carcinomatosis peritoneal.

Introduction

Peritoneal carcinomatosis (PC) is a progressive intra-abdominal cancer condition that is seen in up to 7.7% of patients (with non-gynaecological cancer) at the moment of initial surgery.[1] In fact, Brodsky et al[2] confirmed that between 25% and 35% of patients with colorectal cancer had peritoneal involvement.

Left untreated, it is ultimately fatal, with a median survival time 8.5 months if the primary cancer is colorectal, 2.4 months in pancreatic cancer and 2.2 months in gastric cancer.[3] However, the result was not much better with the introduction of 5-florouracil (5-FU), with a median survival of 6.9 months in patients with colorectal cancer, 2.9 months for patients with pancreatic cancer, and 6.5 months for those with gastric cancer.[4]

The latest chemotherapy, based on oxaliplatin, irinotecan, and biological agents, has improved survival in patients with metastatic colon cancer by up to 16-20 months.[5-7] Unluckily, none of these studies shows data about the results in patients with PC, and it is just considered another kind of disseminated disease. Nevertheless, the classification of PC as a locoregional condition has opened up the possibility of new and promising approaches.

In 1980, Spratt et al[8] had already published the use of thiotepa in a patient with peritoneal pseudomyxoma and Speyer et al used 5-FU and methotrexate in 16 patients with PC. Shortly thereafter, Koga et al[10] reported the use of intraperitoneal chemotherapy with hyperthermia in 23 patients with PC of gastric origin.

Many phase II studies have explored the intraperitoneal route of drug administration and show promising results in patients with PC. In colorectal cancer with PC, they have achieved median survivals of 16 to 35.9 months, with overall 5-year survival rates between 25% and 47%.[11-16] Verwaal et al[17] in a phase III study, randomised patients with PC of colorectal origin for palliative surgery and systemic chemotherapy with fluorouracil-leucovorin or for maximum cytoreduction plus intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C and subsequent systemic chemotherapy. This study demonstrated a significant benefit in survival in the HIPEC arm, with a median survival of 22.2 months versus 12.6 months in the control group.

Glehen et al[18] collected retrospective information on 506 patients with PC from 28 institutions who were treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy. The median overall survival was 19.2 months. Patients who underwent complete cytoreduction achieved a median overall survival of 32.4 months versus 8.4 months in the patients with incomplete cytoreduction.

There is no doubt that the clinical evidence that backs up combined treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy is increasing in the literature.[19-23] These studies confirm the crucial role of maximum cytoreduction, which must remove all tumour deposits larger than 1-2 mm.[24] In univariate and multivariate studies, cytoreduction with minimal residual (tumour deposits ≤2.5 mm) is the main prognostic factor.[14-18]

However, it is necessary to clearly understand the pharmacology and the pharmacokinetics of the perioperative use of chemotherapy in the treatment of peritoneal carcinomatosis. Analysis of the pharmacological data can achieve greater safety and achieve significant therapeutic innovations.

The Peritoneal-Plasma Barrier

The peritoneum is a complex 3-dimensional organ that covers the abdominal-pelvic organs and the abdominal wall and contains a large virtual space. Baron[25] studies gave us the most detailed description of the human peritoneum ultrastructure back in 1941.

It is composed of a simple layer of mesothelial cells over a basal membrane and five layers of connective tissue that have a total thickness of 90 µm. The layers of connective tissue include interstitial cells (primarily pericytes, parenchymal cells, and capillaries) and a matrix of collagen, hyaluronic acid, and proteoglycans.

There are 2 known functions of the peritoneum. First, reducing friction between intra-abdominal organs and the abdominal wall by producing a glycosaminoglycan and phospholipid-based lubricating substance.[26] The other essential function, together with the lymphocyte aggregates disseminated by the parietal peritoneum, is to defend the host against intra-abdominal infections. Another possible function of the peritoneum has also been proposed in neoplasms, where it acts as a first line of defence against peritoneal carcinomatosis.[27] Any rupture stimulates the adhesion-invasion cascade of tumour cells, which facilitates the development of tumour nodes in the abdominal-pelvic surface.[28]

"Pharmacokinetic Effect" of the Peritoneum

Intraperitoneal administration of chemotherapy allows for very high-dose treatment. In studies on peritoneal dialysis, Dedrick et al[29] observed that the peritoneal permeability to various hydrophilic antineoplastic drugs was considerably less than their plasma clearance which leads to a proportionally higher concentration in the peritoneal cavity. This permits exposure to residual tumour cells after cytoreduction at high drug doses, without increasing its

concentration and systemic toxicity. This advantage is reflected in the area under the curve (AUC) of intraperitoneal exposure versus plasma exposure. Table shows the molecular weight and IP/IV AUC rates of drugs used clinically or experimentally in patients with PC.[30]

Figure 1 shows the increased exposure of peritoneal surface to a paclitaxel solution that, given its high molecular weight (853.9 Da) and a hydrophilic component, crosses the peritoneal-plasma barrier very slowly. The AUC rate is approximately 1000.

Flessner[31] showed this membrane effect of the peritoneum with a mathematical model for diffusion that considers plasma to be a single component separated by an effective membrane with its own unique behaviour, the peritoneal cavity (Figure 2). The following equation is derived from this:

Rate of mass transfer = AP (C_P–C_B)

where AP is the area of permeability (mass transfer coefficient × fluid contact surface), C_p is the concentration in the peritoneal cavity, and C_B is the concentration in blood.

This formula provides a conceptual transport model and establishes the importance of the area of effective exposure. However, it requires an empirical calculation of the PA for each drug and does not give a true sense of the real penetration at the level of the peritoneal membrane. It also does not predict the penetration of the chemotherapy in tumour nodules, which is one of the most important factors in determining the response to pharmacological treatment.[32]

The ideal drug for intraperitoneal chemotherapy has a high concentration in peritoneal tissue, given its direct intraperitoneal administration, and a high penetration in the cancerous nodule. But it also requires slow diffusion into the endothelial capillary and deep penetration to the subperitoneal space. If the drug is also rapidly metabolised and excreted by the organism, it maintains a low systemic concentration, which leads to less toxicity.

Molecular Weight and Rates of Area Under the Curve of Peritoneal/Systemic Exposure of Drugs Used for Treating Peritoneal Carcinomatosis

Drug	Molecular Weight, Da	Rate of Area Under the Curve
5-Flourouracil	130.08	250
Carboplatin	371.25	10
Cisplatin	300.1	7.8
Docetaxel	861.9	552
Doxorubicin	579.99	230
Etoposide	588.58	65
Floxuridine	246.2	75
Gemcitabine	299.5	500
Irinotecan	677.19	N/A
Melphalan	305.2	93
Mitomycin C	334.3	23.5
Mitoxantrone	517.41	115-255
Oxaliplatin	397.3	16
Paclitaxel	853.9	1000

The simplified 2-compartment model described above does not provide a good theoretical model of the penetration of intraoperative intraperitoneal chemotherapy in the space between the peritoneal membrane and the tumour nodules. Dedrick et al[31] proposed the mathematical model in Figure 3, which shows the tissue penetration of the low molecular weight molecules. The drug diffuses from its C_P to its C_B with an exponential concentration over the

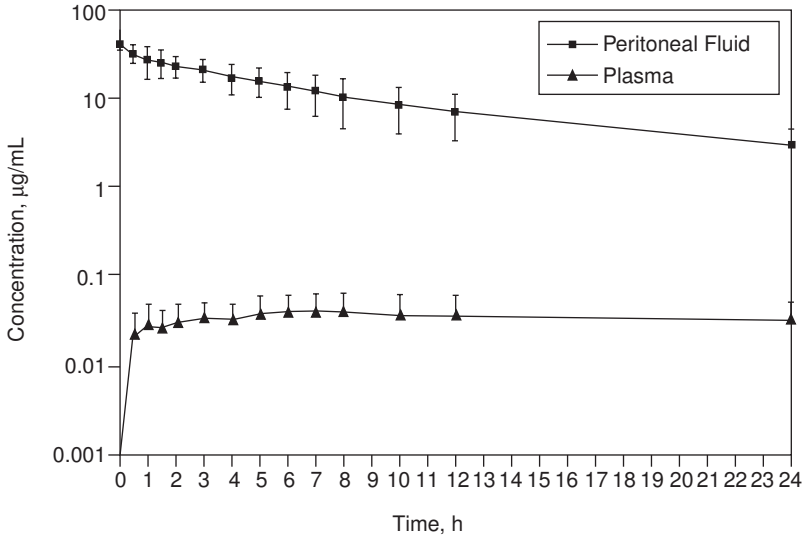

Figure 1 – Pharmacokinetic study of concentration versus time for intraperitoneal paclitaxel. Paclitaxel concentration in peritoneal fluid and plasma for 24 hours after being instilled as fast as possible in a dilution of 30 mg/m^2 of drug in a 1.5% dextrose peritoneal dialysis solution.

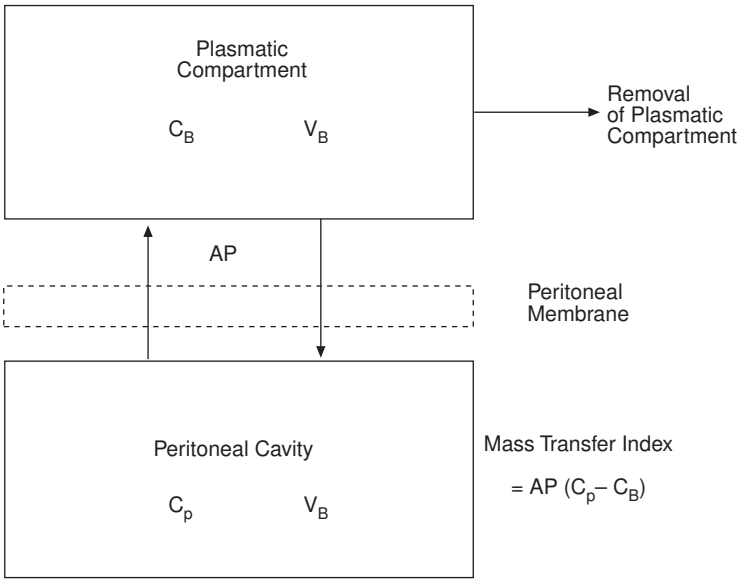

Figure 2 – Traditional bi-compartmental model of transperitoneal transport. The permeability area product controls this transfer and can be calculated by measuring the rate of disappearance of the drug from the cavity and dividing it by the total difference in concentration between the peritoneal cavity and the blood (or plasma). C_B indicates free drug concentration in blood (or plasma); C_P, free drug concentration in the peritoneal cavity; V_B, distribution volume in the body; V_P, peritoneal cavity volume.

peritoneum and the preperitoneal tissues. The extracellular concentration (C_e) can then be calculated according to the following formula:

$$C_e=C_B+(C_p–C_B)\exp[-(k/D)^{1/2}x]$$

where k (min^{-1}) is the elimination constant of the active drug from the tissue, D is the diffusibility (cm^2/min) and x is the distance from the serosal surface (cm). Dedrick et al postulated that the penetration distance is equal to the square root of the quotient between the tissue diffusibility and the elimination constant of the drug from the tissue $(D/k)^{1/2}$.

This model implies that there is an exponential reduction in the concentration of the drug from the abdominal-pelvic cavity, across the peritoneal membrane, to the plasma compartment. While the penetration is variable with each drug and each type of tumour, the penetration depth of each effective drug concentration is very small, some 1-2 mm.[34,35] Ozols et al[36] confirmed that adriamycin only penetrates 4-6 cell layers in a diaphragmatic tumour in a murine model.

Pharmacokinetic Basis of the Effect of Perioperative Chemotherapy in the Peritoneum

In order to understand the pharmacokinetics of concomitant intraperitoneal and intravenous chemotherapy, a new theoretical model is required, as is shown in Figure 4. In this case, the peritoneum does not behave as a simple barrier that is crossed by the molecules, but rather acts as a truly independent compartment that is capable of retaining part of the solution and, therefore, with an AP between the plasma and the peritoneal membrane and another AP between the peritoneal membrane and the peritoneal liquid.

According to typical experimental models (Figure 5), the movement of the drug molecules from the blood to the peritoneal liquid across the compartment made up of the peritoneum is rapid, while reverse movement is slower. Intravenous fluorouracil passes rapidly from the plasma compartment to the peritoneal cavity, which is then increased in size. It remains retained there in the artificial ascites created by HIPEC for a considerable amount of time, decreasing the rate of transfer towards the plasma. Given that plasma 5-FU is metabolised and eliminated by the body, the concentration in the liquid and the peritoneal membrane is maintained proportionally higher compared to the plasma. This diode and HIPEC reservoir liquid effect of the peritoneum provides a pharmacological advantage when eliminating residual tumour cells after cytoreduction.

Though the cause of this difference in flow in one direction or another is not known, it is believed that intracapillary pressure may be the cause of this effect. In fact, animal experiments[37,38] confirm the increase in intra-tumour accumulation and the anti-tumour effect of doxorubicin and cisplatin when the intra-abdominal

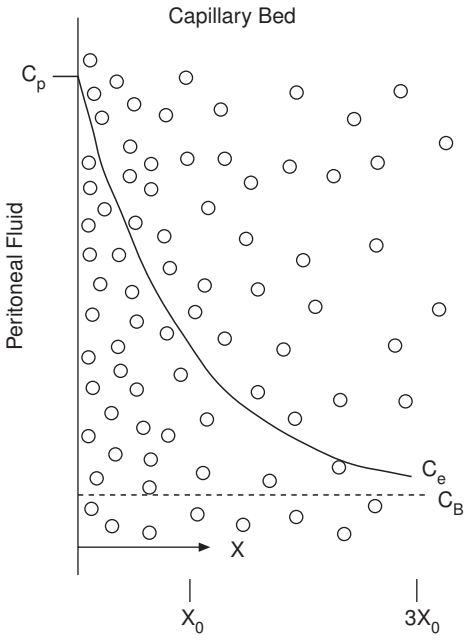

Figure 3 – Conceptual diagram of tissue adjacent to the peritoneal cavity. The continuous line shows the exponential decrease in the interstitial tissue concentration (C_e) as the drug is disseminated by the interstitial tissue and removed from the blood. The lower line shows the depth (X) and the points at which the difference in drug concentration between the interstitial tissue and the blood has dropped to 37% (X_0) and to 5% ($3X_0$) from their maximum value are shown. C_B indicates concentration of free drug in blood (or plasma); C_P, concentration of free drug in the peritoneal fluid. (Modified from: Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst. 1997;89:480-7.)

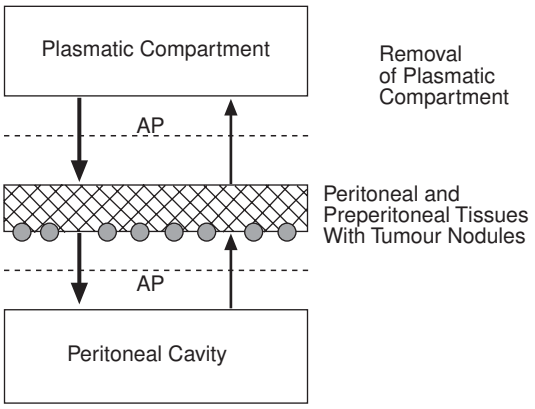

Figure 4 – Tri-compartmental model that treats the peritoneal membrane as an independent compartment with its own ability to accumulate the drug. In this case, it represents a higher rate of transfer to the peritoneal cavity than to the plasma.

Modifying Factors on the Pharmacokinetics of Perioperative Chemotherapy

The number of variations in treatment protocols with intraperitoneal chemotherapy is extensive. All of these variations reflect attempts to improve diffusibility D, permeability P, the effective membrane area, or to reduce the k constant. The pharmacokinetic effect of some of these factors is explained below.

Extent of the Peritonectomy

Contrary to intuition, elimination of the mesothelial covering, as is done during peritonectomy procedure, does not pressure is increased. Measurements of the local concentration of cisplatin over the length of the peritoneal tumour nodule radius demonstrated platinum penetration far beyond the 1 mm limit proposed by Los et al.[35] On the other hand, unpublished observations by Flessner et al[39] in a murine model demonstrated an unfolding of the extracellular space in the anterior wall of rats when the intra-abdominal pressure of the dialysis solution was increased from 0 to 4 cm H_2O. It is believed that intra-abdominal pressure creates a convective flow that forces the drug from the peritoneal cavity towards the subperitoneal tissue. Therefore, when there is no increase in intra-abdominal pressure, the intracapillary pressure would predominate, which would determine a greater flow from the plasma to the peritoneal liquid than in a reverse direction.

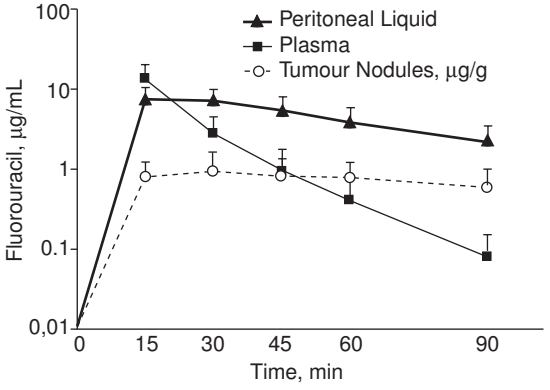

Figure 5 – Pharmacodynamics of 400 mg/m^2 of intravenous 5-fluorouracil during hyperthermic intraperitoneal chemotherapy (HIPEC) with 3 L of solution.

significantly alter the pharmacokinetic properties of the peritoneum. Flessner et al[39] demonstrated in a murine model that the elimination of the layer of retained fluid and the mesothelial covering does not influence the barrier's mass transfer coefficient (MTC). Indirect evidence of this hypothesis can be obtained in humans by the fact that increasing the peritonectomy in patients with PC barely alters the pharmacokinetics of intraperitoneal chemotherapy with mitomycin C or 5-FU.[40,41] Basic research shows that the wall of the capillaries and the surrounding interstitial matrix form a barrier for the transfer of molecules from the abdominal-pelvic space.[42]

Temperature

The addition of hyperthermia to the intraperitoneal chemotherapy may increase the tumour response to the drug through various mechanisms. First, the heat has an inherent direct anti-tumour effect. Hyperthermia above 41ºC induces selective cytotoxicity in malignant cells due to an unknown mechanism for which various theories have been proposed: alteration in DNA repair, protein denaturing and inhibition of oxidative metabolism in the microenvironment of malignant cells that leads to an increase in acidity, liposomal activation, and an increase in cell death.[43,44] However, it is also known that cells react to protein denaturing by stimulating heat shock proteins. This leads to the development of heat tolerance in tumour cells that may mean this first mechanism is of little clinical importance.[45] Second, the cytotoxic effects of some chemotherapeutic agents increases by applying moderate hyperthermia. This mechanism has been shown in doxorubicin,[46] the platinum complexes,[47,48] mitomycin C,[46] melphalan,[49] docetaxel, irinotecan, and gemcitabine.[50] And third, this increase in response may be the result of a change in the penetration depth of the chemotherapeutic agent.[51,52]

Pressure

As was mentioned above, the increase in intra-abdominal pressure produces an increase in diffusibility and, therefore, the depth of penetration and the cytotoxic effect of intraperitoneal chemotherapy. Nevertheless, the clinical limitation of the use of increasing intra-abdominal pressure is dictated by respiratory and haemodynamic tolerance. In practice, clinical application of HIPEC with controlled intra-abdominal pressures has up to now been limited to palliation of debilitating malignant ascites using laparoscopic HIPEC at 10-15 mm Hg.[53,54]

Carrier Solutions

Different solutions have been evaluated in different treatment protocols, attempting to increase the residual peritoneal and tumour exposure to the chemotherapeutic agent. This is especially important within the context of early postoperative intraperitoneal chemotherapy (EPIC), where maintaining a high intra-abdominal fluid volume for a long period of time increases the distribution of the drug and the efficacy of treatment. A hetastarch or icodextrin-type high molecular weight solution, which maintains an artificial ascites, shows higher drug availability by increasing the volume of peritoneal fluid.[55-57]

Conversely, in HIPEC, with a relatively short intra-abdominal time, a hypotonic solution can be expected to increase tissue and tumour absorption. Nevertheless, Elias et al,[58] using 100 and 150 mOsm/L dextrose solutions, demonstrated that not only that the tumour penetration did not increase, but that a high incidence (50%) of postoperative peritoneal bleeding and severe thrombocytopenia is induced, which has led to the contraindication of the use of hypotonic solutions.

Vasoactive Agents

These agents may contribute to delay in peritoneal cavity clearing because the blood flow from the peritoneal and subperitoneal vascular network will, to a large degree, control the movement of molecules across the peritoneal and subperitoneal tissues. The results obtained from the effects of vasoactive agents are confusing and at times contraindicative due to the variety of experimental systems, complex interactions of locoregional and systemic effects of the vasopressor agents, and the large differences in neovascularisation of the tumour nodules and the normal capillaries.[32,59-63]

Intraperitoneal Chemotherapy Dosing

Rubin et al[64] demonstrated that there is no perfect correlation between the peritoneal surface, a determining factor in drug absorption, and the calculated body surface area. However, drug dosage calculation is preferably performed as a function of body surface area since it is a good predictor of drug metabolism and, therefore, useful in estimating systemic toxicity and so much more if the dissolution volume is also determined by body surface area.[65]

Intraperitoneal Chemotherapy Distribution

A wide variety of open and closed methods for administering intraperitoneal chemotherapy has been described.[66-70] The open method for distributing chemotherapy is done intraoperatively (such as HIPEC), since the surgeon distributes the solution in the abdomen by manually shaking the intestinal loops. Conversely, the closed method can be used such as HIPEC or EPIC, though in this case the distribution of the solution within the abdomen depends on postural changes. In both cases, the absence of adhesions is essential in order to obtain the maximum distribution of the drug.

Theoretically, the closed abdomen techniques have a lower loss of heat during perfusion and a lower environmental risk for the surgical team, while the open techniques provide better spatial distribution of the solution over the peritoneal surface and a more uniform heat distribution.[69] However, no study to date has been capable of detecting an occupational risk for healthcare personnel[71-73] nor has any difference between the 2 methods of distribution of the drug been demonstrated, given that only the extent of PC, the absence of extra-peritoneal

disease and performing a complete cytoreduction have shown a correlation with survival.

Chemotherapeutic Solution Volume

According to the equation described on peritoneal-plasma membrane mass transfer, increasing the solution's contact surface area increases mass transfer. Keshabiah et al[74] demonstrated an increase in mass transfer by increasing the volume of the dialysis solution. Elias et al[75] and Sugarbaker et al[65] confirmed that at the same total dose, a lower concentration of the drug in the chemotherapy solution led to less absorption, and with that lower systemic toxicity, though also to less penetration in the cancerous nodules. Because of this, they concluded that it is necessary to regulate both the dose of chemotherapy as well as the volume of the solution as a function of the patient's body surface area, and avoid administering variable volumes as a function of the volume of the abdominal cavity, which may have a variable surface area, which makes the total drug absorption and its toxicity unpredictable.[65]

Some institutions that use the closed HIPEC method calculate the drug dose per litre according to the body surface area and they dilute it in a large volume of carrier solution (up to 6 L), which is left in a reservoir.[76-79] With this method, the amount of chemotherapy solution that comes into contact with the peritoneal surface may vary as a function of different conditions (the level of abdominal cavity distension induced by the chemotherapy solution [2-6 L], the patient's gender, the amount of preoperative ascites or the extent of the visceral resection), which makes the absorption of the drug, and therefore its toxicity, less predictable.

Duration

The duration of HIPEC will vary between 30 and 90 minutes as a function of the pharmacokinetic characteristics and the total dose of the drug employed.

Carrier Macromolecules

Modification of the pharmacokinetics of chemotherapeutic agents administered intraperitoneally by using carrier molecules is an alternative that is in the experimental phase. The results obtained so far do not permit making conclusions.[80,81]

Individual Sensitivity of Tumours to the Drug With or Without Hyperthermia

The selection of drugs used in perioperative chemotherapy has been based on research on the responses obtained with systemic administration, the pharmacodynamic and pharmacokinetic properties of the drug with intraperitoneal administration, the increase in cytotoxicity with hyperthermia and the synergy between the chemotherapeutic agents. However, the tumours are heterogeneous and have variable responses to chemotherapeutic agents,[82,83] even in the case of PC samples.[84] Though in the future one may be able to perform an individualised selection of drugs in patients with PC, there still are no prospective data that support an improvement in clinical results through the use of choosing the drug based on in vitro sensitivity tests.

Coordinating Chemotherapy With Surgery

When considering the moment when chemotherapy is applied in relation to surgery in patients with PC, this can be applied at four different times.

Intraperitoneal and/or Intravenous Induction Chemotherapy

Also known as neoadyuvant intraperitoneal and systemic chemotherapy (NIPS), it attempts to reduce the amount of tumour to be eliminated through cytoreductive surgery. Though clinical and radiological responses have been obtained,[85-87] there are some potential disadvantages: adhesions from previous surgical interventions may interfere with an adequate distribution of the drug, complete responses are very rare or subsequent surgical treatment may add to morbidity and mortality.[88] This is currently in the evaluation phase for cases where complete cytoreduction is not considered possible.

Intraoperative Intraperitoneal Chemotherapy

This has been the most widely used modality, with constant clinical improvements in phase II studies and one in phase III.[11-23] Whether using an open or closed technique, more and more authors choose a 2-directional intraoperative chemotherapy technique that combines intraoperative intravenous and hyperthermic intraperitoneal chemotherapy in order to create a bidirectional diffusion gradient that optimises the delivery of chemotherapy to the target peritoneal nodules.[60] Nevertheless, the most effective combination of administration (continuous perfusion versus bolus versus repetitive boli), dosing and drug combination in this bidirectional strategy has to be refined.

Early Postoperative Intraperitoneal Chemotherapy

Used in normothermic conditions and combined or not with HIPEC, it has some theoretical advantages: it is administered following cytoreductive surgery at a moment of minimal residual tumour disease, it is initiated before the wound heals which minimises the risk of altering the distribution of the drug due to adhesions, and it may eliminate cells trapped in postoperative fibrin deposits. The adequate selection of chemotherapeutic agents according to their pharmacological principles invites one to use drugs that are specific for the cycle, such as 5-FU or taxanes.

Long Term Combined Intraperitoneal and Systemic Chemotherapy

This strategy, adjuvant and non-perioperatively, has been shown to improve survival of patients with stage-III ovarian cancer with optimal cytoreductive procedures when compared to intravenous chemotherapy alone in phase III studies,[90-92] though

with significant complications that have limited its use. It can also be used as a "chemotherapy bridge" between incomplete initial surgery and the final cytoreduction.

Conclusions

The administration of perioperative chemotherapy in patients with peritoneal carcinomatosis must be governed by pharmacological principles. Studies of failures published on cytoreductive surgery plus perioperative chemotherapy conclude that the abdominal-pelvic cavity is the most frequent site of cancer recurrence.[93,94] Coordinating chemotherapy as a scheduled part of surgical treatment is crucial for successful treatment of patients with minimal residual disease following cytoreduction surgery.

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