Editorial Commentary

Bidirectional chemotherapy long-term as a treatment strategy for peritoneal metastases

Paul H. Sugarbaker^

Program in Peritoneal Surface Malignancy, Department of Surgery, Washington Cancer Institute, Washington, DC, USA

Correspondence to: Paul H. Sugarbaker, MD. Program in Peritoneal Surface Malignancy, Department of Surgery, Washington Cancer Institute, 110 Irving St NW, Washington, DC 20010, USA. Email: Paul.Sugarbaker@outlook.com.

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Introduction

A strategic plan for treatment of peritoneal metastases

The original plan for improved management of peritoneal metastases from gastrointestinal and gynecologic malignancy was clearly stated in early publications. First, a surgical procedure to completely clear all visible evidence of disease from the abdomen and pelvis was required. This has been referred to as complete cytoreductive surgery (CRS). In order to achieve this goal, a series of five peritonectomy procedures and between 0 and 4 visceral resections were required (1). This complete CRS is an extensive procedure in some patients requiring 10 to 14 hours to complete. Currently, a 3% mortality and a 20% class 4 adverse events are associated with the complete CRS (2,3). Over the course of several decades the procedure, once regarded as an overly aggressive surgery in patients obviously dying of cancer, has now evolved into an accepted surgical procedure that can be performed effectively but also safely at qualified institutions.

This complete CRS was to be followed by a perioperative intraperitoneal chemotherapy (IP) (4). The purpose of this chemotherapy instilled directly into the abdomen and pelvis was to preserve the "surgical complete response". The IP was introduced in a large volume of aqueous solution in an attempt to uniformly treat all of the abdominal and pelvic surfaces. It was thought that all surfaces were at risk for implantation and then progression of cancer cells present in peritoneal fluid or traumatically disrupted into the preperitoneal space by the surgical procedure. In order to minimize the effects of wound healing (adhesions) to interfere with a uniform distribution of the chemotherapy solution, the treatment was to be initiated in the immediate perioperative period.

Many of the chemotherapy agents that were available at the time these treatments were being tested were augmented in their cytotoxicity by heat. Consequently, moderate hyperthermia was suggested as a routine part of the perioperative chemotherapy treatments (5). This immediate intraoperative lavage of the peritoneal space became known as hyperthermic intraperitoneal chemotherapy (HIPEC). The chemotherapy agents most frequently used were mitomycin C and cisplatin.

There were of course, many drugs that did not require heat for maximal cytotoxicity and yet were pharmacologically candidates for intraperitoneal administration. These drugs were instilled for 1–5 days through a series of catheters into the abdominal and pelvic space. This treatment became known as early postoperative intraperitoneal chemotherapy (EPIC) (6). Ideally drugs used for EPIC had a slow clearance from the peritoneal space. The drugs used for EPIC are paclitaxel, docetaxel, gemcitabine and pemetrexed.

^ ORCID: 0000-0002-2431-7366.

Success with CRS plus HIPEC or CRS plus HIPEC and EPIC

In order to be accepted globally as a treatment for peritoneal metastases, it was estimated that the control of disease progression within the abdomen and pelvis following CRS and HIPEC should be high—near 50%. It was soon recognized that the progression of disease outside of the abdomen and pelvis was often the cause of a terminal condition. However, it was also clear that complete control of peritoneal metastases may result in a prolongation of life and would improve quality of life. This occurred in many patients despite the progression of disease at systemic sites (7).

Although CRS with perioperative chemotherapy has been used for multiple abdominal and pelvic neoplasms that cause peritoneal metastases, only 2 stand out as a true success of the original strategy. The initial successful treatments of peritoneal metastases were with the low-grade appendiceal mucinous neoplasms (LAMN). Also, the mucinous appendiceal cancers of intermediate type called MACA-Int could be cytoreduced completely and then treated with HIPEC mitomycin C with an 80% 20-year survival (8).

A second disease where an 75% local-regional success was achieved is malignant peritoneal mesothelioma (MPM) of the epithelial histologic subtype. The MPM was treated with CRS plus HIPEC and the survival rate at 5 years increased to approximately 50%. This was found to be true at numerous treatment centers (9). However, Sugarbaker *et al.* added to this regimen 5 cycles of bidirectional chemotherapy long-term (BCLT) as an adjuvant. The chemotherapy was bidirectional in that the pemetrexed was given intraperitoneal followed on the same day by cisplatin given intravenously. In a propensity matched study, this BCLT (CRS plus HIPEC plus long-term bidirectional chemotherapy) was superior to CRS plus HIPEC alone with an estimated 10-year survival of 75% (10).

More aggressive peritoneal metastases treated by CRS and HIPEC

The higher-grade abdominopelvic malignancies which frequently result in peritoneal metastases have shown marginal benefit after complete CRS with HIPEC. The cancers that have been treated are colorectal cancer, gastric cancer, and ovarian cancer. Traditional HIPEC with mitomycin C or with cisplatin does provide some benefit. To date, this success has not been robust enough to stimulate a global change in practice. In summary, data show that CRS and a single cycle of perioperative chemotherapy is effective for a large proportion of patients with peritoneal metastases from appendiceal mucinous neoplasms. In contrast, peritoneal metastases from high-grade abdominal or pelvic cancer have resulted in borderline benefit.

BCLT as a third requirement for effective treatment of peritoneal metastases

The peritoneum can be viewed as a porous surface penetrated by innumerable lymphatic stomata. These defects in the peritoneum allow cancer cells that have invasive potential to enter and then proliferate in subperitoneal lymphatic channels. These subperitoneal cancer cells are not accessed by traditional HIPEC. Visible nodules on the parietal and visceral peritoneum can be removed by CRS. Extensive parietal peritonectomy does not remove visceral peritoneum. The subperitoneal cancer is not eliminated by CRS or by traditional HIPEC. This results in a high failure rate especially on visceral peritoneal surfaces even if the CRS is visibly complete for the invasive cancers. This lack of success of a single perioperative treatment to sustain a "surgical complete response" achieved with CRS is the rationale to develop BCLT. Multiple cycles of chemotherapy are required to achieve the results desired.

For IP to be effective the administration must be optimized

Effective IP with durable beneficial effects must be administered properly. First, full doses of the drug given intraperitoneal must be used. In most instances this dose is the same or very near the same as a maximal systemic dose. This is because chemotherapy that is instilled first treats the abdominal and pelvic surfaces. However, it is eventually absorbed into the systemic circulation. Toxicity can be severe with an overdose of drug given intraperitoneal. There is a single drug that can be administered in larger doses intraperitoneally than systemically if liver function is normal. 5-fluorouracil is this drug. The decreased systemic toxicity is caused by the rapid metabolism of the fluorouracil leaving the peritoneal space through the portal blood and being metabolized within the liver. Gianola *et al.* showed that the maximal dose of intraperitoneal 5-fluorouracil given 5 days in a row was approximately 1 gm per day. The maximal dose of intravenous 5-fluorouracil was approximately 600 mg/m^2 given 5 days in a row (11).

A second requirement for effective IP is repeated chemotherapy administration over months, sometimes as long as 6 months following the CRS. Single doses of IP are ineffective. A Japanese adjuvant gastric cancer trial testing only a few doses of early postoperative intraperitoneal paclitaxel was unsuccessful (12). Also, when EPIC paclitaxel was added to the treatment of MPM the benefits were minimal, approximately 5% and not statistically significant (10). In contrast, repeated administration of a drug into the peritoneal space has been associated with benefit. Cashin and colleagues compared long-term intraperitoneal 5-fluorouracil to systemic treatment with FOLFOX in patients having had CRS for colorectal peritoneal metastases. Intraperitoneal 5-fluorouracil used long-term in a randomized controlled trial showed superior survival (13). Also, Scheithauer *et al.* showed that a combined intraperitoneal and intravenous 5-fluorouracil as an adjuvant to resected colon cancer was superior to systemic 5-fluorouracil only (14).

Another requirement for successful IP is moderately uniform distribution of the chemotherapy solution within the abdomen and pelvis. This can be demonstrated by scintigraphy or preferably by computed tomography (CT) with intraperitoneal contrast. If the chemotherapy instillation is sequestered in one portion of the abdomen and pelvis, it cannot be expected to provide benefit for disease that is closed off by adhesions to direct contact by chemotherapy. Monitoring the distribution of chemotherapy solution and the expertise to maintain a uniform distribution remains as a challenging problem for long-term IP administration.

An essential requirement for optimal BCLT is simultaneous delivery of a systemic chemotherapy agent (15). Somehow physicians involved with the delivery of HIPEC forget that the peritoneal surfaces have two sides. There is the surface immediately adjacent to the abdominal contents. The other side is contiguous with the vascular and lymphatic supply of the body. Chemotherapy to systemic sites should have a different spectrum of toxicities than the intraperitoneal drug. It should also have a different mechanism of action as compared to the intraperitoneal drug. A drug augmentation or even drug synergy should be sought. Some drugs when given intravenously can be heat-targeted to a hyperthermic intraperitoneal surface. Drugs such as melphalan or ifosfamide should achieve many times the cytotoxicity at the peritoneal surface heated by a hyperthermic perfusion apparatus. This is known as heat-targeting of systemic chemotherapy (16).

Finally, optimal IP delivery will require repeated bidirectional instillation. This is not only over months, but may require daily instillation for over approximately 5 days for maximal effect. The drug, paclitaxel, can *in-vitro* produce a "peel the onion" effect if it is given over several days in a row (17). Realizing that the drugs are only effective over fractions of a millimeter in depth, this "peel the onion" concept is a very attractive one suggesting that daily administration of the intraperitoneal drug over approximately a week time period may be the optimal drug delivery technique.

Cytotoxicity as demonstrated by intravenous administration is not a requirement for benefit with repeated instillations of IP

Paclitaxel has not been identified as a drug with an acceptable response rate when given intravenously for gastric cancer. However, repeated intraperitoneal instillations of paclitaxel can, in a majority of patients with gastric cancer and peritoneal seeding, bring about a response within the peritoneal space (18). By cytology, free intraperitoneal cancer cells are eliminated. By laparoscopic examination small peritoneal nodules disappear after repeated doses of intraperitoneal paclitaxel.

Paclitaxel has not been demonstrated as a drug with acceptable cytotoxicity for MPM. Nevertheless, 6 patients treated long-term with this drug showed remarkable long-term survival when multiple cycles of adjuvant paclitaxel were used after CRS plus HIPEC for this disease (19). It seems that the high concentration of drug within the peritoneal space can bring about the destruction of cancer cells and cancer nodules that the lower systemic concentration of chemotherapy cannot provide. The high local-regional dose of intraperitoneal paclitaxel is essential for the response of peritoneal metastases to repeated doses of this drug. The work of Ito and colleagues is of special interest in that paclitaxel was effective in appendiceal adenocarcinomas. No literature would support the cytotoxicity of paclitaxel in appendiceal malignancy. Nevertheless, in this xenograft model the efficacy of paclitaxel given by intraperitoneal administration was well established. In addition, intraperitoneal delivery of paclitaxel was associated with reduced systemic side effects in this experimental model (20).

Safe and effective intraperitoneal access is a requirement for global acceptance of IP

A monumental study with IP was carried out by Armstrong

and colleagues (21). They demonstrated that a combined intraperitoneal and systemic delivery of cisplatin and paclitaxel gave approximately a 25% survival advantage over intravenous drug administration. However, this marked benefit with bidirectional chemotherapy never was accepted globally by the oncologic community. Why was this major improvement in survival not readily accepted? Walker *et al*. accumulated the list of adverse events that accompanied the intraperitoneal drug administration (22). By the completion of 5 cycles of chemotherapy, over 50% of the patients had an adverse event. Very often these adverse events required the cessation of intraperitoneal drug administration. Patients were then converted to intravenous drugs only. The morbidity of intraperitoneal access through an intraperitoneal port that was used in this study was too great to be accepted by the practicing oncologist. It also was extremely inconvenient for the physician managing the patient with ovarian cancer on the bidirectional chemotherapy protocol. Catheter malfunction meant numerous returns to the operating room for catheter revision. Patients developed pain with instillation. The technology for intraperitoneal access has in the past not been acceptable to the practicing physician.

Administration of intraperitoneal neoadjuvant chemotherapy is much better tolerated than IP adjuvant chemotherapy which would follow the CRS

After a CRS, the abdominal and pelvic spaces will be diffusely involved by peritoneal adhesions. The peritoneal space may be divided off into numerous subspaces that do not communicate. In contrast, if the IP is given prior to a surgical procedure the peritoneal access should be uniform and proceed without difficulty. This has been the experience reported by numerous investigators involved with neoadjuvant chemotherapy administration.

The neoadjuvant IP should involve pharmacologically well qualified drugs for intraperitoneal administration. These well qualified drugs are paclitaxel, docetaxel, gemcitabine, pemetrexed, and 5-fluorouracil. All 5 of these drugs have been given intraperitoneally over many months and are not associated with adverse effects from the peritoneum itself. Other drugs such as mitomycin C, cisplatin, doxorubicin and several others should not be instilled repeatedly into the peritoneal space because they will cause peritoneal sclerosis.

It may be suggested that all neoadjuvant chemotherapy given to patients with peritoneal metastases should have the drugs pharmacologically well qualified for intraperitoneal administration given by this route. In other words, when a patient is receiving neoadjuvant chemotherapy for gastric cancer with peritoneal metastases, the docetaxel in FLOT should be given intraperitoneal. In patients receiving neoadjuvant chemotherapy for ovarian cancer, the paclitaxel should be given intraperitoneal. In patients who are given FOLFOX in a neoadjuvant setting for peritoneal metastases from colon cancer, the 5-fluorouracil should be given intraperitoneally. One would expect to observe a more beneficial response local-regionally with neoadjuvant chemotherapy if drugs appropriate for intraperitoneal administration are administered intraperitoneal.

Administration of intraperitoneal adjuvant chemotherapy after CRS is possible but presents a more technical challenge

After a CRS or after any major abdominal or pelvic cancer resection, access of a peritoneal catheter will be made more difficult. Adhesions will develop that may make catheter placement challenging. Adhesions will continue to develop around a catheter and cause pain with instillation. Also, benign causes of cancer obstruction may be difficult or impossible to distinguish from cancer progression in and around a catheter causing its malfunction.

If intraperitoneal adjuvant chemotherapy is to be used antiadhesion treatments used with CRS should be considered. This includes EPIC 5-fluorouracil or intraperitoneal starch solutions given over the first postoperative week (23). Adhesions are not inevitable. Adhesions can be prevented with proper treatments. Research regarding the best methods for preventing adhesions after CRS need to be pursued and then acted upon.

Summary

The management of peritoneal metastases has, of necessity, become more complex as it improves. The starting point has always been and continues to be complete removal of the visible peritoneal implants by CRS. This would include peritonectomy procedures and visceral resections. In the immediate postoperative period, HIPEC with or without EPIC is administered in an attempt to remove single tumor cells suspended in peritoneal fluid or tumor cells that are loosely adherent to the recently traumatized abdominal pelvic surfaces. In this review, I show that

BCLT is an essential part of success with the treatment of peritoneal metastases from the high-grade malignancies. This includes gastric cancer, colorectal cancer, and ovarian malignancy. HIPEC shows little effect after CRS in these high-grade diseases except in patients who have a very low peritoneal cancer index. Greater success will be achieved when the chemotherapy is given by both intravenous and intraperitoneal administration and is continued for approximately 5 months postoperatively. Reliable peritoneal access devices are necessary for this third component of the peritoneal metastases treatments to be accepted as effective, safe, and involving minimal morbidity from the intraperitoneal access device.

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