Research Article

Adjuvant Bidirectional Chemotherapy Using an Intraperitoneal Port

Paul H. Sugarbaker and Lana Bijelic

Program in Peritoneal Surface Malignancy, Washington Cancer Institute, Washington, DC 20010, USA

Correspondence should be addressed to Paul H. Sugarbaker, paul.sugarbaker@medstar.net

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Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been established as treatment options for patients with peritoneal metastases or peritoneal mesothelioma. However, this novel treatment strategy remains associated with a large percentage of local-regional treatment failures. These treatment failures are attributed to the inadequacy of HIPEC to maintain a surgical complete response. Management strategies to supplement CRS and HIPEC are indicated. A simplified approach to the intraoperative placement of an intraperitoneal port for adjuvant bidirectional chemotherapy (ABC) was devised. Four different chemotherapy treatment plans were utilized depending upon the primary site of the malignancy. Thirty-one consecutive patients with an intraoperative placement of the intraperitoneal port were available for study. The incidence of adverse events that caused an early discontinuation of the bidirectional chemotherapy occurred in 75% of the 8 patients who had an incomplete cytoreduction and in 0% of patients who had a complete cytoreduction. All of the patients who had complete cytoreduction completed at least 5 of the scheduled 6 bidirectional chemotherapy treatments. Adjuvant bidirectional chemotherapy is possible following a major cytoreductive surgical procedure using a simplified method of intraoperative intraperitoneal port placement.

1. Introduction

Cancer chemotherapy can be given through a number of different routes of administration. Although intravenous delivery is most common, intraperitoneal, intrapleural, and intrathecal chemotherapy infusions have been utilized with good results. Also, intra-arterial perfusion of chemotherapy has been reported as successful by several groups. The low incidence of complications with simple intravenous drug delivery most likely accounts for its more common utilization. However, in some specific situations, intraperitoneal drug delivery, or intraperitoneal drug delivery combined with intravenous drug delivery have been definitely shown to improve outcome. In patients with ovarian cancer, three prospective and randomized studies with combined intraperitoneal and intravenous chemotherapy compared to only intravenous chemotherapy have consistently shown an improvement in long-term survival with the local-regional approach [1–3]. In patients with ovarian cancer that was resected so that all tumor masses greater than 2 cm were removed, survival was significantly longer in 546 randomized patients in those who received intraperitoneal cisplatin as compared to intravenous cisplatin ($P = 0.02$). Also, moderate to severe nervous system toxicity was reduced with the intraperitoneal cisplatin [1].

Many oncologists acknowledge that disease control may be significantly improved when chemotherapy is administered through the intraperitoneal route [4]. However, they are aware that the complications of intraperitoneal chemotherapy administration are frequent and occasionally life endangering [5]. There are, of course, adverse events with the use of intravenous ports that are used in a large proportion of patients receiving systemic cancer chemotherapy. Nevertheless they are used as standard of care. In contrast, the difficulties that may occur with placement of an intraperitoneal port, the patient discomfort that frequently accompanies chemotherapy administration, and the serious life endangering complications sometimes requiring reoperation discourage its routine use [6].
Successful randomized trials testing combinations of intraperitoneal and intravenous chemotherapy for gastrointestinal peritoneal metastases and for peritoneal mesothelioma have not been performed to date. However, the rationale for such an approach is strong. In this paper, we describe a new and simplified method for placement of an intraperitoneal port following cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. Our clinical experience with 31 consecutive patients having adjuvant bidirectional chemotherapy for peritoneal mesothelioma or gastrointestinal carcinomatosis from a variety of primary sites is reported.

2. Materials and Methods

All patients in this retrospective paper had peritoneal metastases documented within the abdomen and pelvis. They underwent cytoreductive surgery with an attempt to clear all of the malignancy from the abdomen. Following this, they were treated with a perioperative chemotherapy treatment using heated intraperitoneal or a combination of heated intraperitoneal and intravenous chemotherapy.

2.1. Preparation for Intraperitoneal Port Placement. Following completion of the cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, the abdomen and pelvis were again widely exposed. All intestinal reconstruction was completed. The abdomen was irrigated with 4 liters of a warm saline (37°C) solution. The irrigation solution contained the antibiotics neomycin and polymyxin B (XGen Pharmaceuticals, Big Flats, NY). The abdominal skin was again cleansed with a povidone iodine solution.

2.2. Technique for Intraperitoneal Port Placement. An 8 cm incision was made at the lateral aspect of the left rectus muscle. This transverse incision was in line with the lowest aspect of the ribcage. It was continued through the subcutaneous tissue to the anterior rectus sheath. At the lateral aspect of the rectus muscle, the external oblique aponeurosis was incised.

From this incision, subcutaneous tunnel and pocket for an intraperitoneal port system were constructed (Port-A-Cath, Smiths Medical MD, Inc., St. Paul, MN, USA). The port was located superior to and directly over the superior portion of the left rectus muscle. Care should be taken not to enter the abdominal incision with the tunnel or port pocket (Figure 1).

Through the incision in the external oblique fascia, a tonsil clamp is positioned, moving from the peritoneal cavity to the subcutaneous space with the stab incision. The clamp guides the catheter tip into the midabdomen. The tip is directed toward the jejunal loops of the small bowel. The Dacron cuff is secured with a resorbable purse string suture to the external oblique aponeurosis.

The catheter is cut to an appropriate length and secured to the port. The port is advanced through the tunnel into its pocket. The port is secured manually in its proper position and accessed with a noncoring right angle needle (Port-A-Cath, Gripper Plus, Deltec, Inc., St. Paul, MN, USA). The port and tubing are flushed with saline solution by irrigating the noncoring needle. Following this, the needle is capped off with a male adapter. The plastic base of the right angle noncoring needle is secured at its four corners with a 2–0 nylon suture (Figure 2).

The tunnel and incision are copiously irrigated with the antibiotic solution and hemostasis checked. Scarpa’s fascia is closed over the Dacron cuff with a resorbable suture and the skin closed with interrupted nonabsorbable sutures. The noncoring needle is covered by an occlusive gauze dressing.

Liberal placement of Seprafilm (Genzyme Biosurgery, Framingham, MA) on abdominal and pelvic surfaces devoid of parietal peritoneum and between the loops of small bowel is recommended.

At this point, the abdominal incision is closed. The port access with the Huber needle is retained for 10 days to ensure proper position of the port for easy access for the adjuvant bidirectional chemotherapy (ABC) treatments.

2.3. Chemotherapy Regimens Utilized. Four different combined intraperitoneal and intravenous chemotherapy regimens were utilized for different diseases treated by the ABC method. For peritoneal mesothelioma, a combination of intraperitoneal pemetrexed with intravenous cisplatin was used. For appendiceal or colorectal malignancy, a combination of intraperitoneal 5-fluorouracil and systemic oxaliplatin was used. For ovarian cancer, a combination of intraperitoneal paclitaxel and systemic cisplatin was used. Finally, for the pancreas cancer patients, intraperitoneal gemcitabine was used. No intravenous chemotherapy was combined with the intraperitoneal gemcitabine (see Table 1).

The selection criteria for intraoperative placement of the intraperitoneal port was variable depending on the patient’s diagnosis. All pancreas cancer patients during the study period had an intraperitoneal port placed if the R0 pancreaticoduodenectomy operation could be completed.
All peritoneal mesothelioma patients had port placement if a complete or near complete cytoreduction was possible. The same was true with the three papillary serous malignancy patients. In patients with appendiceal adenocarcinoma, intraoperative port placement was utilized if systemic treatment options had been exhausted. The same was true with rectal cancer patients.

3. Results

There were 31 patients treated using an intraperitoneal port placed following the completion of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Five patients had a diagnosis of appendiceal adenocarcinoma, 19 had peritoneal mesothelioma, 3 had pancreas cancer, 1 had rectal cancer, and 3 had papillary serous cancer. The median age on these patients was 49 with a range from 32 to 74. Twenty-three patients had complete or near complete (adequate) cytoreductive surgery prior to port placement. Eight patients had an incomplete cytoreduction.

Six major events occurred in eight patients (75%) who had incomplete cytoreduction. Four patients had disease progression, 1 patient had bowel perforation, and 1 patient had a port occlusion after 3 cycles which was not remedied and intraperitoneal treatments ceased. In these six patients, the adverse event resulted in a discontinuation of the ABC.

In the 23 patients who had complete or near complete cytoreduction, there were 6 events. One patient had systemic progression at cycle 3 and the combined intraperitoneal and intravenous chemotherapy was discontinued. One patient developed methicillin-resistant Staphylococcus aureus infection of the port postoperatively. In these two patients (9%) the adverse event resulted in discontinuation of the ABC.

Four patients had events which did not significantly impede or disrupt their chemotherapy treatments, 1 patient had port occlusion after 5 cycles so that the final cycle of ABC was given systemically. One patient had a port occlusion successfully treated by laparoscopic intervention and successfully completed the ABC. One patient had an infected port which was removed; one cycle of pemetrexed and cisplatin chemotherapy was given intravenously and then the port replaced and the bidirectional treatment completed. One patient required hospitalization after ABC treatments on 3 occasions. His final cycle of pemetrexed and cisplatin was then given systemically. One patient had port infection when on second line intraperitoneal chemotherapy and her adverse event (peritonitis) was not included in these statistics.

4. Discussion

4.1. Developmental Plan for Adjuvant Bidirectional Chemotherapy. The ABC regimens used on these patients were designed from pharmacologic data obtained in chemotherapy agents known to show a response in the primary disease to be treated. Also, morbidity and mortality testing showed that the doses and schedules of drugs used were safe [7]. The effectiveness of these combined intraperitoneal and intravenous treatments has not been tested in a randomized study against their intravenous counterparts. This second important step in the development of the ABC approach has yet to be initiated.

4.2. Need for Complete Cytoreduction. By these early data, patient selection for ABC treatment is shown to be necessary. The clinical correlate most impressive was the impact of

### Table 1: Clinical data on 31 consecutive patients given chemotherapy through a permanent intraperitoneal port placed prior to the closure of the abdomen.

| Gender |        |
|--------|--------|
| Male   | 16     |
| Female | 15     |

| Age  |        |
|------|--------|
| Median | 49    |
| Range  | 32–74 |

| Diagnosis                  |        |
|----------------------------|--------|
| Peritoneal mesothelioma    | 19     |
| Appendiceal adenocarcinoma | 5      |
| Papillary serous cancer    | 3      |
| Pancreas cancer            | 3      |
| Rectal cancer              | 1      |

| Cytoreduction               |        |
|----------------------------|--------|
| Complete or near complete (CC-0/CC-1) | 23     |
| Incomplete cytoreduction    | 8      |

| % of patients completing 5 or more cycles of with adverse events requiring removal of intraperitoneal port |        |
|----------------------------------------------------------------------------------------------------------|--------|
| Complete or near complete cytoreduction                                                                | 9% (2/23) |
| Incomplete cytoreduction                                                                                | 75% (6/8) |
infections will occur in those patients who have had a bowel
function of the port. It is possible that more port or catheter
in a larger study, will be shown to influence the long-term
function on satisfactory port function was the completeness of
In these data, the only clinical feature that had an impact
4.7. Factors That May Impact on Satisfactory Port Function.
base for access with the non-coring needle. Making a long
tunnel to the ribscape is unnecessary. Also, this long tunnel
4.6. Position of Port in Left Subcostal Space. Our technique
is considerably different in terms of the anatomic placement
of the port than other techniques. The port is placed in
the subcostal space in the upper left portion of the abdomen.
The base of the port is stabilized by the anterior rectus sheath
and flexion of the rectus muscle by the patients gives a solid
base for access with the non-coring needle. Making a long
tunnel up to the ribscape is unnecessary. Also, this long tunnel
and port placement on the chest wall is uncomfortable for
patients.
4.7. Factors That May Impact on Satisfactory Port Function.
In these data, the only clinical feature that had an impact
on satisfactory port function was the completeness of
cytoreduction. Undoubtedly, there are other factors which,
in a larger study, will be shown to influence the long-term
function of the port. It is possible that more port or catheter
infections will occur in those patients who have had a bowel
anastomosis or some other potential contamination of the
peritoneal space by enteric organisms. It is possible that
the extent of peritoneectomy, and therefore the extent of
intra-abdominal adhesions, will be important in long-term
function. In the patients in this study, all had very extensive
cytoreduction and therefore data regarding the extent of
cytoreduction was not available. It is possible that the use of
adhesion-prevention agents may be important. For example,
the liberal use of Seprafilm to cover peritoneectomy sites
may be advisable. Also, Seprafilm can be used between the
loops of small bowel and its mesentery. Alternatively, the
use of early postoperative intraperitoneal 5-fluorouracil or
paclitaxel may reduce the extent of abdominal and pelvic
adhesions and thereby facilitate more adequate long-term
port function [8]. Finally, in this study we only gathered
data on those patients who had an intraoperative placement
of the intraperitoneal port. Whether this placement is best
performed in the operating room with the cytoreductive
intervention or later on following full recovery from surgery
has yet to be determined.
4.8. A Unique Phase II Study. In a survey of the literature
regarding the use of an intraperitoneal port, no prior data
regarding port placement after CRS and HIPEC was found.
This is the first phase II study that attempts to prospectively
gather clinical information on port insertion along with
the definitive cytoreductive intervention. ABC is feasible
using this methodology, and it was thought to be acceptable
to patients with a small inconvenience. Trials to test ABC
versus traditional systemic chemotherapy may now be
appropriate.
4.9. Advantages of Combined Intraperitoneal and Intravenous
(Bidirectional) Treatments. Theoretically, it would be possible
to administer all of the chemotherapy agents presented in
Table 2 by the intraperitoneal route as opposed a
bidirectional treatment as proposed in this review. We did
not mix drugs for simultaneous two-drug infusions for
several reasons. First of all, there are issues with drug incompatibility.
For example, 5-fluorouracil cannot be mixed with
other drugs because of problems with precipitation. Also,
the safety of two drugs simultaneously administered into the
peritoneal cavity has not been previously explored. Phase
1 protocols to test the safety of two drugs administered
simultaneously into the peritoneal cavity would be necessary.
Perhaps most importantly, pharmacologic data suggests that
drugs administered intravenously with an artificial ascites
will target the peritoneal surfaces [9]. Van der Speeten and
colleagues showed that patients who received intravenous 5-
FU along with a volume of intraperitoneal fluid maintained
a higher level of 5-FU in the peritoneal space as compared
to the intravenous drug levels over a prolonged time period.
The area under the curve ratio of peritoneal fluid to plasma
was 2.3. These data suggest that intravenous drugs can be
targeted to the peritoneal surface if administered simultane-
ously with a large volume of intraperitoneal chemotherapy
solution.
Table 2: Four different combined intraperitoneal and intravenous chemotherapy (bidirectional) treatment options.

| Disease                          | Combined intraperitoneal and intravenous chemotherapy treatment option                                                                 |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Peritoneal mesothelioma          | Pemetrexed (500 mg/m²) in 1000 mL 1.5% dextrose peritoneal dialysis solution as a 60-minute rapid infusion through the intraperitoneal port. Cisplatin (75 mg/m²) in 250 mg of normal saline is given over 120 minutes immediately following the pemetrexed infusion. |
| Adenocarcinoma                   | 5-fluorouracil (600 mg/m²) in 1000 mL 1.5% dextrose peritoneal dialysis solution through the intraperitoneal port with the administration as rapid as possible. After the intraperitoneal chemotherapy infusion is complete, oxaliplatin (130 mg/m²) in 250 mL of dextrose in water is given as a 2-hour intravenous infusion. |
| Pancreas cancer                  | Gemcitabine (1000 mg/m²) in 1000 mL 1.5% dextrose peritoneal dialysis solution through the intraperitoneal port as rapid as possible is given on days 1, 8, and 15 of a 4-week cycle. |
| Papillary serous and ovarian cancer | Paclitaxel (20 mg/m²) in 1000 mL 6% Hetastarch through the intraperitoneal port. Intravenous cisplatin (75 mg/m²) is given after the paclitaxel infusion is complete over 120 minutes. |

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