Peritoneal Mesothelioma

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Opinion statement

Peritoneal mesothelioma is usually a rapidly fatal primary peritoneal surface malignancy with a median survival time of less than 1 year, mainly because of lack of effective treatment. The incidence is approximately one per 1,000,000; approximately one fifth to one third of all mesotheliomas are peritoneal. Because of its unusual nature, the disease has not been clearly defined in terms of its natural history, diagnosis, or management. Treatment options with intravenous chemotherapy are far from satisfactory. However, because malignant peritoneal mesothelioma usually remains confined to the peritoneal cavity for most of its natural history, regional chemotherapy is an attractive option. From a theoretic perspective, the treatments are most likely to succeed in selected patients with small-volume residual disease after cytoreductive surgery. Advantages of intraperitoneal chemotherapy include greatly enhanced drug concentrations in the peritoneal cavity and decreased systemic toxicity. In designing an intraperitoneal treatment strategy for the management of peritoneal mesothelioma, the limited number of active cytotoxic drugs and the timing of drug delivery pose problems. Prognosis as determined by clinical presentation, the completeness of cytoreduction, and gender (female patients survive longer than male patients) appears to be improved by the use of intraperitoneal chemotherapy. Over the past decade, the management of these patients has evolved similarly to ovarian cancer treatment and now involves cytoreductive surgery, heated intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin, and early postoperative intraperitoneal paclitaxel. These perioperative treatments are followed by adjuvant intraperitoneal paclitaxel and second-look cytoreduction. Prolonged disease-free survival and reduced adverse symptoms with the current management strategy are documented by a high complete response rate as assessed by a negative second look. This multimodality treatment approach with debulking surgery and intraperitoneal chemotherapy has resulted in a median survival of 50 to 60 months. Peritoneal mesothelioma is an orphan disease that is treatable, with expectations for "potential" cure in a small number of patients diagnosed and treated early with definitive local/regional treatments. A prolonged high quality of life is possible in the majority of patients.

Introduction

Peritoneal mesothelioma has evolved over almost 100 years from a clinical oddity to an established rare disease of increasing importance. In the United States, the incidence is estimated to be approximately 200 to 400 cases annually. A 1997 Surveillance, Epidemiology, and End Results report indicated that the incidence of pleural and peritoneal mesothelioma should have peaked by the year 2000 [1]. Peritoneal mesothelioma represents approximately one third of all forms of mesothelioma [2–4]. Although peritoneal mesothelioma is rare, there has been progress in its management. Survival has been extended, and selection factors by which patients may be allocated to aggressive management strategies have been defined.

Definitive diagnosis of malignant peritoneal mesothelioma can be difficult because of the rarity of

Table 1. Combination of symptoms and signs in 51 patients with peritoneal mesothelioma before definitive diagnosis

Symptom/sign	Total, *n* (%)	Men, *n* (%)	Women, *n* (%)
Increased abdominal girth	25 (49)	19 (56)	6 (35)
Pain	22 (43)	14 (41)	8 (47)
Weight loss	11 (22)	11 (32)	0
New onset hernia	6 (12)	5 (15)	1 (6)
Increased abdominal girth and pain	7 (14)	4 (12)	3 (18)
Incidental finding	4 (8)	0	4 (24)
Shortness of breath	4 (8)	4 (12)	0
Fever	4 (8)	3 (9)	1 (6)
Night sweats*	3 (6)	3 (9)	0
Abdominal mass	3 (6)	2 (6)	1 (6)
Diarrhea	3 (6)	1 (3)	2 (12)

*Two of which were night sweats related to fever.

this disease and because the distinction between malignant peritoneal mesothelioma and metastatic adenocarcinoma to the peritoneum is often unclear. Pathologically, a positive immunostain for calretinin has markedly increased the accuracy of diagnosis. In addition, the clinical presentation is nonspecific. A definitive diagnosis may require a multimodal approach involving clinicians, radiologists, and pathologists using immunohistochemical staining and occasionally electron microscopy [5].

The most common clinical symptoms and signs are abdominal distension, weight loss, and new-onset hernia (Table 1) [4,6]. Occasionally, an abdominal mass, bowel obstruction, or perforation of the appendix may be present [4]. In our experience, peritoneal mesothelioma can be categorized as "pain-predominant" or "ascites-predominant" clinical type. Patients generally have one of these two clinical types, although 14% showed concomitant abdominal distension and abdominal pain. Patients with abdominal pain, usually localized, have a dominant tumor mass with little or no ascites. Those without abdominal pain have ascites and abdominal distension. The finding of ascites is a negative predictor for survival along with male gender, age older than 53 years, more extensive tumor volume, and weight loss.

Treatment

Diet and lifestyle

- Mesothelioma incidence is increasing and was expected to reach its peak around 2000 in industrialized nations, mainly because of high asbestos exposure after World War II [1]. Little is known about the etiology of this disease. Several carcinogenic agents have been identified since the first report of asbestos-related pleural mesothelioma by Wagner *et al.* [7] in 1960. The simian virus-40 has been hypothesized to play a role in the pathogenesis of mesothelioma and, together with asbestos, may be a co-carcinogen [8]. Other possible etiologies such as remote abdominal radiation and chronic peritonitis also have been reported [9,10]. Roushdy-Hammady *et al.* [11] recently reported a probable genetic susceptibility factor for malignant mesothelioma in the Cappadocian region of Turkey in which mesothelioma would segregate in autosomal-dominant fashion after exposure to erionite. However, the authors do not indicate what percentage was peritoneal. The incidence of the disease in other parts of the world is also high and clusters around shipyards, docks, asbestos mines, and asbestos-using factories.

Pharmacologic treatment

- The evaluation of chemotherapy regimens has been hampered by the rarity of the disease. Intravenous single-agent or combination chemotherapy has not achieved benefits (20% to 30% response rates) [4]. Doxorubicin is considered the most active drug. However, in a retrospective study of the Eastern Cooperative Oncology Group experience with mesothelioma, the single-agent activity of doxorubicin was only 14% [12].
- Preoperative (induction) intraperitoneal chemotherapy has been used to shrink and downstage advanced tumors and make them available to a more complete surgical resection [6].
- Postoperative intraperitoneal drug delivery after surgical debulking is thought to be a reasonable treatment option because these tumors remain confined to the abdominal cavity for most of their natural history [13].

Radiation therapy

- Total abdominal radiation therapy has been used in combination with intracavitary instillation of various agents [14] or in combination with chemotherapy. Although this therapy is useful in the palliation of pain, the effect is often brief [15]. Multimodality approaches commonly include radiation, usually as an adjuvant treatment after surgery, with or without chemotherapy.

Combined modality treatment using cytoreductive surgery and intraperitoneal chemotherapy

Rationale for aggressive local-regional treatments

- Peritoneal mesothelioma is a disease that produces symptoms and causes the patient's death as a result of disease progression confined to the surfaces of the abdomen and pelvis. Sometimes peritoneal mesothelioma will penetrate through the right or left diaphragm and involve the pleura, leading to respiratory symptoms. However, in most patients, metastasis to other sites does not occur. Death is usually caused by intestinal obstruction, fistula formation, and resulting starvation.
- The disease is thought to arise from a "field defect" of the peritoneal surface with multiple sites of simultaneous disease progression. In the pain-predominant clinical type of mesothelioma, multiple sites of cancer progression may be evident, although one clinically dominant mass may occur. Characteristically, patients in the earlier stages of the disease show a limited number of solid tumor masses simultaneously involving various peritoneal surfaces in the absence of large volumes of ascites [16••]. In the ascites-predominant clinical type, the copious intraperitoneal fluid has widely disseminated the cancer cells so that no peritoneal surfaces are free of implants.
- The disease is thought to have a multifocal origin from the mesothelial lining of the abdomen and pelvis. A single site for disease that spreads throughout the abdomen and pelvis, as in carcinomatosis, does not seem to occur. The diffuse nature of the disease within the abdomen and pelvis, its symptoms, and the disease progression causing obstruction of the gastrointestinal tract has led our group to pursue aggressive local-regional treatment strategies for selected patients with peritoneal mesothelioma. Over the course of a decade, an increasingly aggressive approach has evolved. Peritonectomy procedures are combined with intraoperative, early postoperative, and delayed cycles of intraperitoneal chemotherapy. In physically fit patients who are responding well to therapy, a second-look surgery is often recommended.

Table 2. Literature survey of survival for peritoneal mesothelioma

Study	*n*	Median survival, *mo*
Chailleux *et al.* [17]	11/167	10*
Antman *et al.* [3]	37/180	15*
Sridhar *et al.* [2]	13/50	9.5*
Markman and Kelsen [18]	19	9
Yates *et al.* [19]	14/272	14*
Neumann *et al.* [20]	74	12 (mean)
Eltabbakh *et al.* [21]	15†	12.5
Park *et al.* [22••]	18	26
Sugarbaker *et al.* [23••]	51	56

*Combined/pleural.
†All female patients.

- An aggressive combined approach of extensive cytoreductive surgery with peritonectomy procedures and intraperitoneal perioperative chemotherapy may be improving the quality of life and prolonging disease-free survival of these patients (Table 2).

Debulking peritoneal mesothelioma using peritonectomy procedures

- There are six different peritonectomy procedures that are used to resect cancer on visceral intra-abdominal surfaces or to strip cancer from parietal peritoneal surfaces. One or all six of these procedures may be required, depending on the distribution and volume of peritoneal disease.

Position and incision

The patient is in a supine position with the gluteal folds advanced to the break in the operating table to allow full access to the perineum during the surgical procedure. This modified lithotomy position is achieved with the legs extended in St. Mark's leg holders (AM-SCO, Erie, PA). Proper positioning is essential to avoid intraoperative pressure damage to the gastrocnemius muscle. Extra padding is placed beneath the sacrum. The weight of the legs must be directed to the bottom of the feet by positioning the footrests so that minimal weight is borne by the calf muscle. Myonecrosis within the posterior compartment of the leg may occur unless the legs are protected properly. All surfaces of the St. Mark's stirrups are protected by egg crate foam padding. The legs are surrounded by pneumatic compression devices (SCB Compression Boots; Kendall Co., Boston, MA). These should be operative before the induction of anesthesia for maximal protection against venothrombosis. A hyperthermia blanket is placed over the chest, arms, and head of the patient (Bair Hugger Upper Body Cover; Augustine Medical, Eden Prairie, MN) and beneath the torso (Cincinnati Sub-Zero Products, Cincinnati, OH).

Abdominal skin preparation is from mid-chest to mid-thigh. The external genitalia are prepared in men, and a vaginal preparation used in women. The Foley catheter is placed in position after the surgical preparation so that it can be accessed during the surgical procedure. A large bore silastic nasogastric tube is placed within the stomach (Argyle Salem Sump Tube; Sherwood Medical, St. Louis, MO).

Abdominal exposure

The abdomen is opened from xiphoid to pubis and the xiphoid excised. Generous abdominal exposure is achieved through the use of a Thompson self-retaining retractor (Thompson Surgical Instruments, Traverse City, MI). The standard tool used to dissect tumor on peritoneal surfaces from the normal tissues is a ball-tip electrosurgical handpiece (Valleylab, Boulder, CO). The ball-tipped instrument is

placed at the interface of the tumor and normal tissues. The focal point for further dissection is placed on strong traction. The 3-mm ball-tip electrode is used on pure cut at high voltage for dissecting. High voltage coagulation is used to transect small (< 2 mm in diameter) vessels.

Using ball-tip electrosurgery on pure cut creates a large volume of plume because of the electroevaporation of tissue. To maintain visualization of the operative field and to preserve a smoke-free atmosphere in the operating theater, a smoke filtration unit is used (Stackhouse, El Segunda, CA). The vacuum tip is maintained 2 to 3 inches from the field of dissection whenever electrosurgery is used.

Greater omentectomy and splenectomy

Standard procedure To free the mid-abdomen of a large volume of tumor, a complete greater omentectomy is performed. The greater omentum is elevated and then separated from the transverse colon using ball-tip electrosurgery. This dissection continues beneath the peritoneum that covers the transverse mesocolon so as to expose the pancreas. The gastro-omental (gastroepiploic) vessels on the greater curvature of the stomach are clamped, ligated, and divided. In addition, the short gastric vessels are transected. The mound of tumor that covers the spleen is identified. The peritoneum on the anterior surface of the pancreas may need to be elevated from the gland. Working from the anterior and posterior aspect, the splenic artery and vein at the tail of the pancreas are exposed. These vessels are ligated in continuity and proximally suture-ligated. This allows the greater curvature of the stomach to be reflected anteriorly from pylorus to gastroesophageal junction. Greater omentectomy is usually combined with splenectomy to achieve a complete cytoreduction. If the spleen is free of tumor, it is left in situ.

Peritoneal stripping from beneath the left hemidiaphragm

Standard procedure To begin exposure of the left upper quadrant, the peritoneum beneath the epigastric fat pad that constitutes the edge of the abdominal incision is stripped off the posterior rectus sheath. Traction is to be achieved on the tumor specimen throughout the left upper quadrant. The left upper quadrant peritonectomy involves a stripping of all tissue from beneath the left hemidiaphragm to expose diaphragmatic muscle, left adrenal gland, and the cephalad half of the perirenal fat. To achieve a full exposure of the left upper quadrant, the splenic flexure of the colon is released from the left paracolic sulcus and moved medially by dividing tissue along Toldt's line. The dissection beneath the left hemidiaphragm is performed with ball-tip electrosurgery and not by blunt dissection. Numerous blood vessels between the diaphragm muscle and its peritoneal surface must be electrocoagulated before their transection, or unnecessary bleeding will occur. Generally, tissue is transected using ball-tip electrosurgery on pure cut, but all blood vessels are electrocoagulated before their division.

Peritoneal stripping from beneath the right hemidiaphragm

Standard procedure The peritoneum and epigastric fat pad are stripped away from the right posterior rectus sheath to begin the peritonectomy in the right upper quadrant of the abdomen. Strong traction on the specimen is used to elevate the hemidiaphragm into the operative field. Ball-tip electrosurgery on pure cut is used to dissect at the interface of mesothelioma infiltrating the peritoneum and the muscle of the right hemidiaphragm. Coagulation current is used to divide the blood vessels as they are encountered to minimize the problems with postoperative hemorrhage.

Dissection beneath the tumor through Glisson's capsule

Standard procedure The stripping of the tumor from the muscular surface of the diaphragm continues until the bare area of the liver is encountered. At this point, tumor on the anterior surface of the liver is electroevaporated from the liver surface. With blunt and ball-tip electrosurgical dissection, the tumor is lifted off the dome of the liver by moving through or beneath Glisson's capsule. Hemostasis is achieved as the

dissection proceeds, using coagulation electrosurgery on the liver surface. Isolated patches of tumor on the liver surface are electroevaporated with the distal 2 cm of the ball-tip bent and stripped of insulation (hockey stick configuration). Ball-tip electrosurgery is also used to extirpate the tumor from and around the falciform ligament, round ligament, and umbilical fissure of the liver.

Removal of tumor from beneath the right hemidiaphragm, from the right subhepatic space, and from the surface of the liver

Standard procedure Tumor from beneath the right hemidiaphragm, from the right subhepatic space, and from the surface of the liver forms an envelope as it is removed en bloc. The dissection is simplified greatly if the tumor specimen can be maintained intact. The dissection continues laterally on the right to encounter the fat covering the right kidney. In addition, the right adrenal gland is visualized as the tumor is stripped from Morrison's pouch (right subhepatic space). Care is taken not to traumatize the vena cava or to disrupt caudate lobe veins that pass between the vena cava and segment 1 of the liver.

Lesser omentectomy and cholecystectomy

Standard procedure The gallbladder is removed in a routine fashion from its fundus toward the cystic artery and cystic duct. These structures are ligated and divided. The plate of tissue that covers the structures that constitute the porta hepatis is usually infiltrated heavily by tumor. Using strong traction, the cancerous tissue that covers the structures is stripped from the base of the gallbladder bed toward the duodenum. To continue resection of the lesser omentum, one proceeds along the gastrohepatic fissure that divides liver segments 2, 3, and 4 from segment 1.

Special points The gallbladder can be preserved if it is not involved by the tumor. To avoid excessive blood loss, care must be taken not to traumatize the caudate process. The segmental blood supply to the caudate lobe is located on the anterior surface of this segment of the liver, and hemorrhage may occur with only superficial trauma. The left hepatic artery may arise from the left gastric artery and cross to the hepatogastric fissure. If this occurs, it is ligated and divided as it enters the liver and as it arises from the left gastric artery.

Stripping of the omental bursa

Standard procedure As one clears the left part of the caudate liver segment of tumor, the vena cava is visualized directly beneath. To strip the floor of the omental bursa, strong traction is maintained on the tumor. Ball-tip electrosurgery is used to divide the peritoneum joining the caudate lobe of the liver to the vena cava. Division of the phrenoesophageal ligament allows the crus of the right hemidiaphragm to be stripped of peritoneum. The common hepatic artery and the left gastric artery are skeletonized and avoided. Dissection of lesser omental fat using pressure between the thumb and index finger will help identify major branches of the right and left gastric artery. The multiple branches of the vagus nerve to the antrum of the stomach are divided, but the trunk of the anterior vagus nerve is preserved. Finally, dissection around the celiac lymph nodes allows the specimen to be released.

Special points The loss of a substantial number of branches of the left gastric artery may necessitate subtotal gastrectomy. Ligation of the coronary vein may cause gastric portal hypertension when all other venous drainage of the stomach is removed by dissection around this organ. The left hepatic vein or left inferior subphrenic vein are thin-walled and may be damaged inadvertently by sudden and unpredictable diaphragmatic contractions stimulated by electrosurgical dissection.

Pelvic peritonectomy

Standard procedure To begin, the peritoneum is stripped from the posterior surface of the lower abdominal incision, exposing the rectus muscle. The muscular surface of the bladder is seen as ball-tip electrosurgery strips tumor-bearing peritoneum and preperitoneal fat from this structure. The urachus must be divided and is placed on

upward traction as the leading point for dissection of the visceral surface of the bladder. Round ligaments are divided as they enter the internal inguinal ring on both the right and left in the female patient.

The peritoneal incision around the pelvis is completed by dividing peritoneum along the pelvic brim. Right and left ureters are identified and preserved. In women, the right and left ovarian veins are ligated and divided at the level of the lower portion of the kidney. A linear stapler is used to divide the colon at the junction of sigmoid and descending colon. The vascular supply of the distal portion of the bowel is traced back to its origin on the aorta. The inferior mesenteric artery is ligated and divided. This allows one to pack all of the viscera, including the proximal descending colon in the upper abdomen.

Ball-tip electrosurgery is used to dissect beneath the mesorectum. One works in a centripetal fashion to free the entire pelvis. An extraperitoneal suture ligation of the uterine arteries occurs just above the ureter and close to the base of the bladder. In women, the bladder is moved gently off the cervix, and the vagina is entered. The vaginal cuff anterior and posterior to the cervix is divided using ball-tip electrosurgery, and the perirectal fat inferior to the posterior vaginal wall is encountered. Electrosurgery is used to divide the perirectal fat beneath the peritoneal reflection. This ensures that all of the tumor that occupies the cul-de-sac is removed intact with the specimen. The mid-portion of the rectal musculature is skeletonized and a roticulator stapler (Autosuture, Norwalk, CT) is used to staple the rectal stump closed.

Tubes and drains required for intraoperative and early postoperative intraperitoneal chemotherapy

Closed suction drains are placed in the dependent portions of the abdomen. This includes the right subhepatic space, the left subdiaphragmatic space, and the pelvis. A Tenckhoff catheter (Quinton spiral peritoneal catheter; Quinton, Seattle, WA) is placed through the abdominal wall and positioned in the pelvis. All transabdominal drains and tubes are secured with purse-string sutures at the skin level. Right-angle thoracostomy tubes (Deknatel, Floral Park, NY) are inserted on the right and left to prevent fluid accumulation in the chest as a result of intraperitoneal chemotherapy. As soon as the abdomen is closed, irrigation of the abdomen with 1.5% dextrose dialysis solution (Dianeal; Abbott Laboratories, Chicago, IL) is started.

Heated intraoperative intraperitoneal chemotherapy by the coliseum technique

- After the cytoreductive surgery is complete and the Tenckhoff catheter and closed suction drains in place, a temperature probe is secured to the end of the Tenckhoff catheter. Using a running monofilament suture, the skin edges are secured to the Thompson self-retaining retractor, and a plastic sheet incorporated into these sutures to create an open space beneath (Thompson Surgical Instruments). A slit in the plastic is made to allow the surgeon's double-gloved hand access to the abdomen and pelvis. During the 90 minutes of perfusion, all the anatomic structures within the peritoneal cavity are uniformly exposed to heat and to chemotherapy. The surgeon vigorously manipulates all viscera to keep adherence of peritoneal surfaces to a minimum. A roller pump forces the chemotherapy solution into the abdomen through the Tenckhoff catheter and pulls it out through the drains. A heat exchanger keeps the fluid being infused at 44° C to 46° C so that the intraperitoneal fluid is maintained at 42° C to 43° C. The smoke evacuator is used to pull air from beneath the plastic cover, preventing any possible contamination of air in the operating room by chemotherapy aerosols. The standardized orders for heated intraoperative intraperitoneal chemotherapy for peritoneal mesothelioma are given in Table 3.

Table 3. Physician orders for heated intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin

1. For gastric and ovarian cancer, mesothelioma, and sarcoma: add cisplatin _____ mg to 2 L of 1.5% dextrose peritoneal dialysis solution. Dose of cisplatin 50 mg/m^2.
2. Add doxorubicin _____ mg to same 2 L of 1.5% dextrose peritoneal dialysis solution. Dose of doxorubicin 15 mg/m^2.
3. Use 33% dose reduction for heavy prior chemotherapy, marginal renal function, age > 60 years, extensive intraoperative trauma to small bowel surfaces, or prior radiotherapy.
4. Send 1 L of 1.5% dextrose peritoneal dialysis solution to test the perfusion circuit.
5. Send the above to operating room _____ at _____ o'clock.

Table 4. Instructions for early postoperative intraperitoneal chemotherapy

Operative day, immediate postoperative abdominal lavage (day of operation)

1. Run in 100 mL 1.5% dextrose peritoneal dialysis solution as rapidly as possible. Warm to body temperature before instillation. Clamp all abdominal drains during infusion.
2. No dwell time.
3. Drain as rapidly as possible through the Tenckhoff catheter and abdominal drains.
4. Repeat irrigations every 1 h for 4 h, then every 4 h until returns are clear; then every 8 h until chemotherapy begins.
5. Change dressing covering Tenckhoff catheter and abdominal drain sites using sterile technique once daily and as required.

Postoperative days 1 to 5, early postoperative intraperitoneal paclitaxel

1. Paclitaxel _____ mg (20 mg/m^2 x _____ m^2) (maximum dose: 40 mg) in _____cm^3 1.5% Dianeal* via intraperitoneal catheter on _____.
   Last dose _____.
2. Infuse as rapidly as possible via Tenckhoff catheter. Dwell for 23 h and drain for 1 h before next instillation.
3. Use 1 L 1.5% Dianeal for body surface 1 to 2 m^2, 1.5 L for body surface > 2.0 m^2.
4. Continue to drain abdominal cavity after last dose until Tenckhoff catheter is removed.
5. During initial 6 h after chemotherapy infusion, patient's bed should be kept flat. The patient should be on the right side during infusion. Turn at 30 min after infusion onto the left side and continue to change sides at 30-min intervals for 6 h.
6. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy.
7. Remove venous compression boots during first 6 h after chemotherapy administration to facilitate turning.

*Abbott Laboratories, Chicago, IL.

- The rationale for chemotherapy in the perioperative period is obvious. Although the debulking using peritonectomy has removed 95% to 99% of the cancer, visible disease remains. The largest volume is on the surfaces of the small bowel and its mesentery. A uniform treatment of the abdominal and pelvic cavity is required to prevent the widespread implantation of cells on new tissue surfaces.
- After the intraoperative perfusion is complete, the abdomen is suctioned dry of fluid and reopened. Then, reconstructive surgery is performed. It should be emphasized that no anastomoses are constructed until after the intraoperative chemotherapy perfusion is complete.

Immediate postoperative abdominal lavage in preparation for early postoperative intraperitoneal paclitaxel

- To keep the catheters for drug instillation and abdominal drainage clear of blood clots and tissue debris, an abdominal lavage is started in the operating room. This lavage uses the same tubes and drains positioned for the heated intraoperative intraperitoneal chemotherapy. We have used large volumes of fluid that are rapidly infused and then drained from the abdomen after a short dwell time. The standardized orders for immediate postoperative lavage are given in Table 4. All intra-abdominal catheters are withdrawn before the patient is discharged from the hospital.

Table 5. Long-term intraperitoneal paclitaxel for peritoneal mesothelioma

Cycle # _____, height _____, weight _____, m^2 _____.

1. CBC, platelets, profile A, and appropriate tumor marker before treatment; and CBC, platelets 10 days after initiation of treatments.
2. Paclitaxel _____ mg (20 to 40 mg/m^2) (maximum dose 80 mg daily) added to 1000 cm^3 1.5% dextrose dialysis solution every day for 5 days. Warm to body temperature. Infuse into Tenckhoff or temporary intraperitoneal catheter as rapidly as possible.
3. Infuse intraperitoneal paclitaxel for 5 consecutive days on _____ through _____.
4. Compazine* 25 mg per rectum every 4 hours as necessary for nausea.
   Outpatient only: May dose x 4 for use at home.
5. Percocet† 1 tablet by mouth every 3 h as necessary for pain.
   Outpatient only: May dose x 4 for use at home.
6. Routine vital signs.
7. Out of bed ad lib.
8. Diet is regular, as tolerated.
9. Daily dressing change as needed to intraperitoneal catheter or to Tenckhoff catheter skin exit site.
10. In patients with extensive ascites, completely drain ascites before infusion.

*GlaxoSmithKline, Philadelphia, PA.
†DuPont Pharmaceuticals, Wilmington, DE.
CBC—complete blood count.

Early postoperative intraperitoneal chemotherapy with paclitaxel

- Intraperitoneal chemotherapy with paclitaxel using a 23-hour dwell time is initiated on the first postoperative day. Before beginning the chemotherapy, the patient must be stable with minimal blood in the lavage fluid. The chemotherapy distribution within the abdomen and pelvis is facilitated by turning the patient from side to side. The clearance of paclitaxel from the peritoneal cavity is so slow that an antiemetic is seldom required (Table 4).

Long-term intraperitoneal chemotherapy with paclitaxel

- Except for a few patients with the pain-predominant type of peritoneal mesothelioma, visible disease remains after even the most meticulous cytoreduction. To continue the aggressive local regional treatment strategy, six additional cycles of intraperitoneal paclitaxel are initiated. These begin 6 to 8 weeks after discharge from the hospital.
- The preferred method for peritoneal access for long-term chemotherapy treatment is catheter placement by paracentesis. The adequacy of chemotherapy distribution is assessed radiologically. To maximize distribution, chemotherapy is administered through a temporary catheter that is placed under radiologic control by paracentesis (8.3-French all-purpose drain catheter; Meditech, Watertown, MA). We have used a CT scan with intraperitoneal contrast to demonstrate uniform distribution of fluid within the abdomen in some patients.
- In some patients, access to the peritoneal cavity can be maintained by using a subcutaneous infusion port and a curled Tenckhoff catheter. The intraperitoneal catheter is positioned surgically in the left upper quadrant with the tip of the catheter as close to the ligament of Treitz as is possible. The jejunum is a portion of the small bowel that is in the most active peristalsis and assists to prevent Tenckhoff catheter entrapment by intestinal fibrosis.
- Standardized orders for long-term intraperitoneal paclitaxel are shown in Table 5. The dose of paclitaxel is escalated from 20 to 40 mg/m^2 daily as tolerated by the patient.

Second-look surgery

- Approximately 6 weeks after the final treatment with long-term intraperitoneal paclitaxel, the patient is a candidate for second-look surgery. If there is evidence of persistent disease, a final treatment with heated intraoperative intraperitoneal chemotherapy is used.

Special points regarding debulking surgery using peritonectomy and intraperitoneal chemotherapy

- A key to these aggressive local-regional treatment strategies is the use of an intraperitoneal route of chemotherapy in the perioperative period after the surgeon has maximally cytoreduced the mesothelioma. Maximal contact and penetration of the chemotherapy into residual cancer should be possible at this time, because the absence of adhesions allows uniform distribution of chemotherapy to all of the peritoneal surfaces. The goal of treatment is to use surgery and regional chemotherapy maximally in every patient, to the limits of patient tolerance [24].
- We have previously reported our experience with 33 patients with mesothelioma [25••]. Between 1989 and 1999, 47 cytoreductive procedures were performed on 33 patients with peritoneal mesothelioma by the same surgeon at the Washington Cancer Institute, Washington, DC. Patients who had high comorbidity or unresectable peritoneal mesothelioma had a less extensive debulking procedure. When compared with patients with a more complete resection, a survival advantage approached statistical significance in favor of major cytoreduction ($P = 0.07$). Eleven patients had a scheduled second-look cytoreduction surgery 6 to 9 months after the first operation, combined with perioperative intraperitoneal chemotherapy in 10. Three patients had a third-look operation. Median survival was 35 months in the 11 patients who had a second-look surgery compared with 16 months in the other 22 patients; this was statistically significant ($P = 0.002$). The survival advantage in favor of second-look surgery may have resulted from selection factors inherent to that group of patients.
- Recent pharmacologic studies in humans with paclitaxel show that it is an ideal drug for intraperitoneal use [26•,27]. Consequently, early postoperative intraperitoneal paclitaxel (five times at 20 mg/m^2 daily) has been added to the perioperative treatments. In addition, intraperitoneal paclitaxel given by a permanent intraperitoneal port has been used as an adjuvant for 6 months postoperatively. Second-look surgery and a final cycle of heated intraoperative intraperitoneal chemotherapy completes the aggressive local-regional approach.
- Recent reports show a more systematic approach to peritoneal mesothelioma with debulking surgery and systemic chemotherapy, including paclitaxel, cisplatin, or doxorubicin [18,21,22••]. A phase I trial with 18 patients reported a similar approach to ours with promising results [22••].
- The prognosis is grim after diagnosis of peritoneal mesothelioma: survival of 7 to 13.5 months and only a few long-term survivors reported. The median survival in our patients was 56 months from diagnosis, with a projected 3-year survival of approximately 60%. These results need to be interpreted with caution due to short follow-up and small study population. However, the evolution of increasingly aggressive treatments with this disease and continued improvement of survival are similar to those seen with other successful multimodality and multiple-drug regimens.

Complications

- The morbidity and mortality rates have been reported of 200 consecutive patients who had cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for peritoneal carcinomatosis [28]. In these patients, there were three treatment-related deaths (1.8%). Peripancreatitis (7.1%) and fistula (4.7%) were the most common major complications. There were 25.3% of patients with grade 3 or 4 complications.
- After these treatments, the patient is maintained on parenteral feeding for 1 to 3 weeks. Approximately 10% of patients, especially those who have had extensive prior surgery or who have a short bowel, will need parenteral feeding for several weeks after they leave the hospital.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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