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ORIGINAL ARTICLE

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Hyperthermia modifies pharmacokinetics and tissue distribution of intraperitoneal melphalan in a rat model

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Abstract *Background and objectives*: Peritoneal surface malignancy is a common manifestation of failure of treatment for abdominal cancers. Best results of treatment have been achieved with complete cytoreduction followed by heated intraoperative chemotherapy. Melphalan is a chemotherapeutic agent that shows increased pharmacological activity with heat. But the combination of intraperitoneal administration and heat have never been tested for this drug. The purpose of this study was to evaluate the effect of hyperthermia on the pharmacokinetics and tissue distribution of intraperitoneal melphalan in a rodent model. *Methods*: Melphalan was given by the intraperitoneal route to 20 Sprague-Dawley rats at a dose of 12 mg/kg over 90 min. Rats were randomized into two groups according to the temperature of the peritoneal perfusate: group NT received normothermic (33.5°C) melphalan; group HT received hyperthermic (42°C) melphalan. During the course of intraperitoneal chemotherapy, peritoneal fluid and blood were sampled at 5, 15, 30, 60 and 90 min. At the end of procedure, the rats were killed and tissues samples (heart, liver, ileum, jejunum, colon, omentum, and abdominal wall) were collected. Concentrations of melphalan were determined in peritoneal fluid, plasma, and tissues by high-performance liquid chromatography. *Results*: The area under the curve (AUC) of peritoneal fluid melphalan was significantly lower in the HT group than in the NT group ($P = 0.001$), whereas no significant difference in plasma AUC was found. AUC ratios (AUC peritoneal fluid/AUC plasma) were 12.1 for the NT group and 12.3 for the HT group. The mean time to reach the plasma peak was shorter in the HT group than in the NT group ($P = 0.004$). The HT group exhibited increased melphalan concentrations in all intraabdominal tissues. These differences were significant for the ileum ($P = 0.03$) and jejunum ($P = 0.04$). *Conclusion*: Hyperthermia affected the pharmacokinetics of intraperitoneal melphalan by decreasing the AUC of peritoneal fluid melphalan without increasing the plasma AUC. It increased intraabdominal tissue concentrations.

Keywords Hyperthermia · Melphalan · Intraperitoneal chemotherapy · Pharmacokinetics

Introduction

Melphalan (L-phenylalanine mustard) is an effective and well-known antineoplastic alkylating agent. It has been used to treat cancer patients for over 50 years [22]. Intravenous administration of cytotoxic agents usually does not penetrate into cancerous tissues at a high enough concentration to eliminate such diseases effectively. For gastrointestinal cancers that may disseminate to peritoneal surfaces, the therapeutic index of melphalan may be improved by changing the route of administration. The major advantage of intraperitoneal chemotherapy is associated with the high drug level that can be achieved at the peritoneal surface with low systemic exposure. After the surgical removal of a gastrointestinal cancer with peritoneal carcinomatosis, melphalan may be able to eliminate microscopic residual disease or small foci of persistent cancer at the margins of resection.

Further benefits may be obtained by combining regional hyperthermia with intraperitoneal melphalan. Hyperthermia has been shown to increase the beneficial effects of some anticancer agents, such as oxaliplatin, mitomycin C or cisplatin, by augmenting cytotoxicity and/or increasing the penetration of the drugs into tissue

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[1, 19, 20]. Melphalan has markedly increased pharmacological activity with heat, both in vitro and in vivo [17, 26, 27].

Clinically, melphalan remains the most effective single drug used in heated limb perfusion to treat intransit metastases from melanomas and advanced primary or recurrent extremity soft tissue sarcomas [15, 16]. Phase I and phase II pharmacokinetic studies performed by Howell et al. with intraperitoneal melphalan have shown that it is tolerated up to a dose of 70 mg/m^2 with no local toxicity [11]. The drug concentration in the peritoneal cavity averaged 63-fold more than in the plasma, with a peak of 93-fold [11]. No pharmacokinetic studies of heated intraperitoneal melphalan exist. Gutman et al. have shown that intraperitoneal melphalan alone or combined with tumor necrosis factor is an effective treatment in mice after subcutaneous injection of colon carcinoma cells [9].

With increasing clinical interest in intraperitoneal hyperthermia, a better understanding of interactions between heat and cancer chemotherapy agents is required. Hyperthermia may cause changes in drug degradation, redistribution of blood flow to various intraabdominal organs, and alter drug metabolism. Using a rodent model, this experimental study was conducted to determine the effects of regional hyperthermia on the pharmacokinetics and tissue distribution of intraperitoneal melphalan administered with and without hyperthermia.

Materials and methods

Rats

Male Sprague Dawley rats (4 to 6 months old) weighing between 350 and 420 g were obtained from a single breeding colony (Harlan Sprague Dawley, Indianapolis, Ind.). Animals were individually housed and allowed free access to food and water.

Surgical procedure

All rats were anesthetized with an intraperitoneal injection of 0.5 to 0.7 ml/kg of a solution of 1.5 ml ketamine (100 mg/ml) with 1.5 ml xylazine (20 mg/ml) and 0.5 ml acetylpromazine (10 mg/ml) and underwent a standardized laparotomy. A multiperforated catheter (silicone tubing, 3.2 mm ID, 6.4 mm OD; Fisher Scientific, Norcross, Ga.) was placed in the pelvis through the abdominal incision. The catheter was coated with gauze in a standardized fashion to prevent occlusion by omentum or small bowel loops [12]. This catheter was used as an inflow drain and for peritoneal fluid sampling. It was secured within the abdominal incision with a running suture. Two additional multiperforated catheters were placed in each subphrenic space. These were extended through small incisions in the lateral walls of the abdomen and were secured with purse-string sutures. The catheters in the subphrenic spaces were used as outflow drains. The temperature was monitored by three thermic probes connected to a thermometer (digital dual channel thermometer; Fisher Scientific). One probe was placed in the inflow tube (inflow temperature), one in the abdominal cavity (intraperitoneal temperature), and one in the esophagus (body core temperature). In all rats, a catheter (polyethylene tubing, 0.58 mm ID, 0.965 mm OD; Becton Dickinson, Parsippany, N.J.) was inserted into the left femoral vein for blood sampling.

Experimental design

Twenty rats were randomized into two groups according to the intraperitoneal temperature. The normothermic (NT) group received intraperitoneal chemotherapy with intraperitoneal temperatures maintained between 32.5 and 34.5°C, and the hyperthermic (HT) group received intraperitoneal chemotherapy with intraperitoneal temperatures maintained between 41.5 and 42.5°C. The dose of melphalan was selected according to the clinical study performed by Howell et al. [11]. Melphalan at a dose of 12 mg/kg was diluted in 150 ml 0.9% NaCl solution immediately before administration. A closed perfusion system adapted from the description of Shiu and Fortner [24] was utilized. The perfusate was heated in a tube coil in a thermostatically regulated water bath and infused into the peritoneal cavity with a roller pump (Varistaltic pump; Cutin Matheson Scientific, Kennesaw, Ga.) at a rate of 80 ml/min for 90 min. Rhythmic massage of the abdomen was used to facilitate uniform heat distribution within the peritoneal cavity. When the proper temperature for the experiment was reached inside the peritoneal cavity, melphalan was added to the perfusate in the reservoir. For each animal, 0.5 ml peritoneal fluid and 0.5 ml blood were collected at 5, 15, 30, 60, and 90 min after the initiation of chemotherapy. The venous catheter was flushed with 0.2 ml of heparinized saline after each blood sampling. At the end of the procedure the rats were killed and tissues samples were taken.

Tissue harvest

A standardized methodology for the harvest of organs was followed. After harvest each tissue was touched to filter paper in order to remove excess surface fluid. The heart was harvested as an intact tissue and processed. Standardized portions of liver, stomach, colon, jejunum, ileum, omentum and abdominal wall were harvested.

Sample preparation and analysis

Blood samples were centrifuged and the plasma separated from the cells. Using a 15-ml polypropylene conical tube, a 300-µl sample of plasma was treated with 6 ml acetonitrile and mixed thoroughly on a vortex mixer. After centrifugation the acetonitrile extract was transferred to another polypropylene tube and evaporated at approximately 45°C under a gentle stream of nitrogen. The residue was resuspended in 150 µl mobile phase and filtered for injection into the HPLC system. Peritoneal fluid samples were diluted with mobile phase as required and filtered through 0.45-µm nylon syringe filters for injection into the HPLC system. Tissue samples (approximately 250 mg) were dried of surface moisture, accurately weighed, and homogenized in 5 ml acetonitrile. The homogenate was centrifuged and the acetonitrile extract was removed and evaporated as with the plasma samples. The residue was dissolved in 1 ml mobile phase and filtered for injection into the HPLC system.

Analytic assay

The melphalan concentrations were determined by HPLC. The instrument consisted of a Shimadzu LC7A equipped with an SPD-6AV detector, along with a C-R6A Chromopac data processor.

Control of the effect of hyperthermia on melphalan concentrations

The effect of hyperthermia on melphalan concentrations and melphalan hydrolysis over time was studied in the perfusate by using the same closed perfusion system at the same flow rate but without connection to the peritoneal cavity of a rat. Fluid samples were collected at 5, 15, 30, 60, and 90 min after the instillation of chemotherapy at 33.5°C and 42°C.

Statistical procedures

The area under the curve (AUC) of peritoneal fluid vs time, and plasma vs time were obtained using Prism for Windows, version 4.0 (GraphPad Software, San Diego, Calif.). All pharmacokinetic data and tissue concentrations were compared between the two groups using the Wilcoxon Rank Test using a commercially available program (Staview 4.5, Abacus, Berkeley, Calif.). For all statistical procedures, P values <0.05 were taken as significant. A nonparametric analysis was used because two groups with a low number of repeated measures were used and because these measures had no Gaussian distribution.

Results

Temperature measurements

The mean ± SD core temperatures over the 90-min procedure were 33.6 ± 1.1°C in group NT and 38.4 ± 0.8°C in group HT. The mean intraperitoneal temperature over the 90-min procedure was 33.5 ± 1.0°C in group NT and 42.2 ± 0.5°C in group HT (Fig. 1). Intraperitoneal temperatures were maintained at ± 1.0°C of the selected treatment temperature and temperature steady-state was achieved within the first 10 min of hyperthermic intraperitoneal infusion.

Effects of hyperthermia on intraperitoneal melphalan pharmacokinetics

The peritoneal fluid and plasma pharmacokinetics of melphalan are shown in Fig. 2. The mean peak peritoneal fluids levels were 30.3 ± 1.6 μg/ml in group NT and 31.4 ± 1.5 μg/ml in group HT (Table 1). The mean peak plasma levels were 2.43 ± 0.4 μg/ml in group NT and 2.11 ± 0.7 μg/ml in group HT. There was no significant difference between the peak ratios of group NT and group HT. In the plasma, the peaks were reached with a mean time of 50 ± 10.6 min in group NT and 36 ± 7.7 min in HT group. The difference between these two values was statistically significant ($P=0.004$).

The mean AUCs of melphalan in peritoneal fluid and plasma, and the peritoneal fluid/plasma ratios are shown in Table 1. The AUCs for peritoneal fluid melphalan were 2076.6 ± 278.5 μg/ml/min in group NT and 1848.6 ± 327.2 μg/ml/min in group HT. The difference between these two values was statistically significant ($P=0.001$). The AUCs for plasma melphalan were 174.6 ± 33.1 μg/ml/min in group NT and 145.4 ± 52.1 μg/ml/min in group HT. The mean AUC ratios were 12.1 ± 1.9 in group NT and 12.3 ± 3.6 in group HT. There were no significant differences in

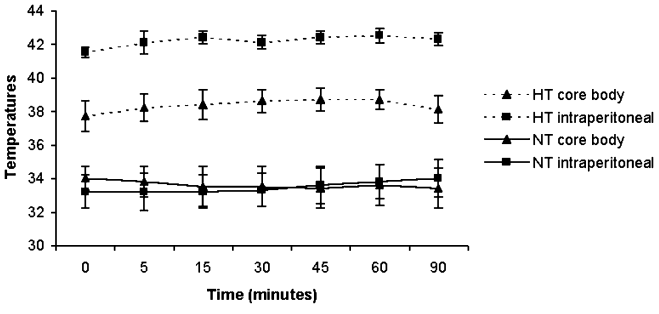

Fig. 1 Core body and intraperitoneal temperatures of rats treated with normothermic or hyperthermic intraperitoneal infusion of melphalan. Data points represent the means ± SD (*bars*) of ten measurements

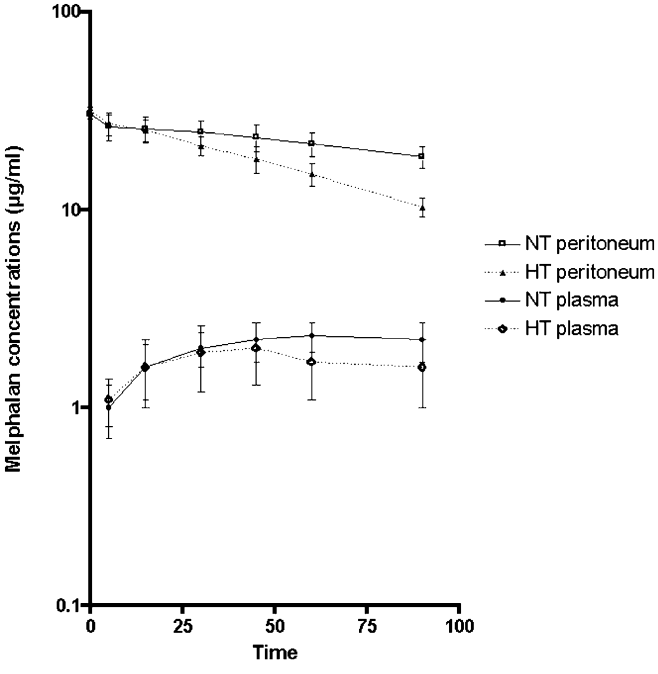

Fig. 2 Semilogarithmic plot of melphalan concentrations versus time in peritoneal fluid and plasma of rats treated with normothermic (*NT*) or hyperthermic (*HT*) intraperitoneal infusion of melphalan. Data points represent the means ± SD (*bars*) of ten measurements

Table 1 Effects of hyperthermia on melphalan pharmacokinetics. Values are means ± SD (P values <0.05 were considered significant)

Parameter	Normothermia	Hyperthermia	P value
Peritoneal fluid peak (μg/ml)	30.3 ± 1.6	31.4 ± 1.5	0.131
Plasma peak (μg/ml)	2.43 ± 0.4	2.11 ± 0.7	0.265
Time of plasma peak (min)	50 ± 10.6	36 ± 7.7	0.004
Peritoneal fluid/plasma peak ratio	12.8 ± 2.4	16.3 ± 5.1	0.08
Peritoneal fluid AUC (μg/ml/min)	2076.6 ± 278.5	1848.6 ± 327.2	0.001
Plasma AUC (μg/ml/min)	174.6 ± 33.1	145.4 ± 52.1	0.16
Peritoneal fluid/plasma AUC ratio	12.1 ± 1.9	12.3 ± 3.6	0.9

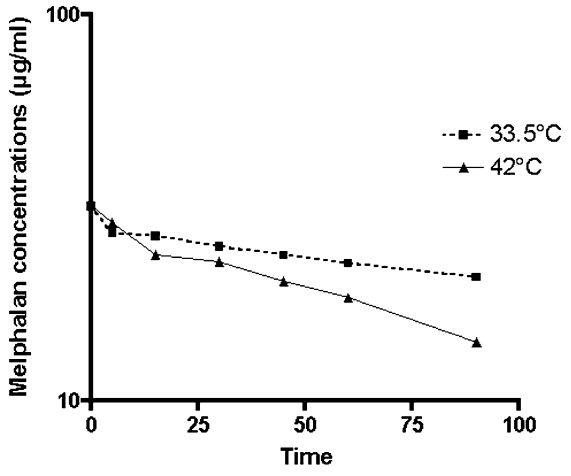

Fig. 3 Semilogarithmic plot of melphalan concentrations versus time in the closed perfusion system at 33.5°C and 42°C without connection to the peritoneal cavity. Data points represent the means of two measurements

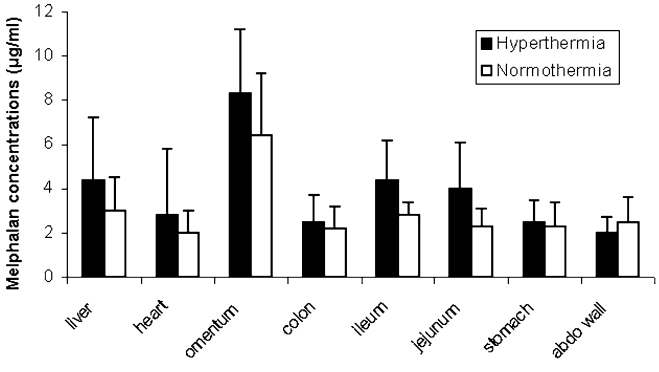

Fig. 4 Melphalan concentrations in tissues after 90 min of normothermic or hyperthermic intraperitoneal infusion

plasma AUC levels or in the AUC ratios between the treatment groups.

Effects of hyperthermia on melphalan concentrations in perfusate

The melphalan concentrations in perfusate over time were lower at 42°C than at 33.5°C (Fig. 3). The difference showed a trend toward significance ($P = 0.052$). There was a 35% total loss of melphalan over 90 min at 33.3°C and a 55% loss at 42°C.

Effects of hyperthermia on melphalan tissue concentrations

Melphalan concentrations in the different tissue samples after 90 min of intraperitoneal chemotherapy are shown in Fig. 4. For both groups, the highest melphalan concentrations were found in omentum (8.3 ± 2.9 µg/ml in the HT group and 6.4 ± 2.8 µg/ml in the NT group). Except for abdominal wall, rats of group HT exhibit higher tissue concentrations of melphalan. These increases in tissues concentration were significant for the ileum ($P = 0.03$) and jejunum ($P = 0.04$).

Discussion

Intraperitoneal administration of anticancer drugs has many pharmacokinetic advantages and gives high response rates within the abdomen because the "peritoneal plasma barrier" provides dose-intensive therapy. High concentrations of anticancer drugs may be in direct contact with tumor cells with reduced systemic concentrations and lower systemic toxicity [7]. Experimental studies have demonstrated that regional cytotoxicity of intraperitoneal chemotherapy may be improved by delivery of the drug by hyperthermic perfusion [10, 14]. Intraperitoneal chemohyperthermia is now used in different clinical settings as an adjuvant and palliative treatment of digestive and gynecological cancers [4, 6, 8, 23, 25]. Although mitomycin C and cisplatin have been the drugs most frequently tested in these clinical trials, melphalan may be an attractive candidate for such an approach, not only because of its known activity in ovarian carcinoma, but also because of its markedly increased pharmacological activity with heat [17, 26, 27]. Melphalan exerts its antineoplastic effect through the formation of interstrand DNA crosslinks. It is thought that the formation of these DNA crosslinks is facilitated at elevated temperatures leading to enhanced cell kill [26]. Clues to a potential clinical advantage of this chemotherapy technique can be obtained from pharmacokinetic investigations such as this study.

Dedrick et al. have shown that high molecular weight drugs are retained for prolonged periods in the peritoneal cavity after peritoneal administration [3]. With a molecular weight of 305.20, melphalan is considered to be of moderate molecular weight as compared to other chemotherapy agents used with peritoneal instillation such as taxanes. Other causes of the marked difference between high peritoneal concentrations and low plasma levels maintained over 90 min in both normothermic and hyperthermic experimental animals may exist. The high hydrophilicity of melphalan may contribute. Also, the presystemic metabolism may lower plasma concentrations as degradation occurs in the interstitial tissues. The AUC ratio for melphalan demonstrates excellent regional exposure of the drug and a potential for a favorable antitumor effect on minute peritoneal surface or resection site tumor deposits. The relatively large molecular weight of melphalan and its hydrophilic properties may be the mechanism by which the drug is retained in the peritoneal cavity after intraperitoneal administration.

The same rodent model has been used to study the effect of heat on pharmacokinetics of intraperitoneal oxaliplatin and doxorubicin [13, 20]. These studies have shown that hyperthermia ranging between 42 and 43°C does not affect significantly the pharmacokinetics of

these intraperitoneal drugs. The present study suggests that hyperthermia at the same level changed significantly the pharmacokinetics of intraperitoneal melphalan. Hyperthermia significantly decreased peritoneal AUC of intraperitoneal melphalan and significantly shortened the time to reach plasma peaks but did not affect the AUC ratio or mean peak levels in plasma which were approximately at the same levels with and without heat. This may be explained by the enhanced hydrolysis of drug with hyperthermia, already reported in experimental and clinical studies using heated melphalan in isolated limb perfusion for the treatment of malignant melanoma [18, 21]. The hydrolysis which occurred at 42°C as compared with 37°C was increased 1.5-fold in canine plasma and 1.9-fold in porcine plasma [21]. In the present study, the control experiment using the same closed perfusion system without connection to the peritoneal cavity of rats showed decreased concentrations of melphalan over time when hyperthermia at 42°C was utilized. This may be explained by the increased hydrolysis induced by heat.

A second factor may have contributed to the significantly lower peritoneal AUC of heated intraperitoneal melphalan. Rats treated with hyperthermia exhibited increased concentrations of melphalan in all intraperitoneal tissues. Noting that melphalan measurements were performed on dried tissues, these results suggest that the increment in tissue concentrations was a result of a direct increase in drug uptake by tissues rather than a simple edema. This increased uptake of melphalan was statistically significant only for ileum and jejunum. Dewhirst et al. have demonstrated that normal tissues consistently respond to hyperthermia with a marked increase in blood flow as long as tissue temperature levels do not exceed 45°C [5]. The physiological stress induced by high levels of hyperthermia may cause redistribution of blood flow to various intraabdominal organs. With moderate hyperthermia, because of its relatively high vascularization, small bowel may have been exposed to more melphalan delivered via both direct diffusion and the systemic circulation. This phenomenon of increased drug delivery to the gastrointestinal tract is supported by a report of bloody diarrhea in dogs treated by hyperthermic Adriamycin [2], and was previously observed with hyperthermic doxorubicin in the same experimental model [13].

In conclusion, this study demonstrated that abdominal hyperthermia affected the pharmacokinetics of intraperitoneal melphalan. Despite a significant decrease of peritoneal AUC with an increased hydrolysis of drug, hyperthermia increased melphalan concentrations in intraperitoneal tissues and especially in small bowel. These findings support the use of moderate hyperthermia with intraperitoneal melphalan in clinical studies. A phase I-II study of intraperitoneal heated melphalan is currently underway in patients with recurrent carcinomatosis or peritoneal carcinomatosis with poor prognostic factors.

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References

1. Barlogie B, Corry PM, Drewinko B (1980) In vitro thermochemotherapy of human colon cancer cells with cis-dichlorodiammineplatinum(II) and mitomycin C. Cancer Res 40:1165
2. Daly JM, Wang YM, Kapelanski D, Frazier OH (1984) Systemic thermochemotherapy: toxicity and plasma pharmacokinetics of methotrexate and doxorubicin. J Surg Res 37:343
3. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr (1978) Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 62:1
4. Deraco M, Rossi CR, Pennacchioli E, Guadagni S, Somers DC, Santoro N, Raspagliesi F, Kusamura S, Vaglini M (2001) Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer: a phase II clinical study. Tumori 87:120
5. Dewhirst M, Gross JF, Sim D, Arnold P, Boyer D (1984) The effect of rate of heating or cooling prior to heating on tumor and normal tissue microcirculatory blood flow. Biorheology 21:539
6. Elias D, Pocard M (2003) Treatment and prevention of peritoneal carcinomatosis from colorectal cancer. Surg Clin North Am 12:543
7. Glehen O, Beaujard AC, Arvieux C, Huber O, Gilly FN (2002) Les carcinoses péritonéales. Traitement chirurgical, péritonectomies et chimiohyperthermie intrapéritonéale. Gastroenterol Clin Biol 26:210
8. Glehen O, Mithieux F, Osinsky D, Beaujard AC, Freyer G, Guertsch P, Francois Y, Peyrat P, Panteix G, Vignal J, Gilly FN (2003) Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. J Clin Oncol 21:799
9. Gutman M, Sofer D, Lev-Chelouche D, Merimsky O, Klausner JM (1997) Synergism of tumor necrosis factor-alpha and melphalan in systemic and regional administration: animal study. Invasion Metastasis 17:169
10. Hahn GM, Strande DP (1976) Cytotoxic effects of hyperthermia and adriamycin on Chinese hamster cells. J Natl Cancer Inst 57:1063
11. Howell SB, Pfeifle CE, Olshen RA (1984) Intraperitoneal chemotherapy with melphalan. Ann Intern Med 101:14
12. Jacquet P, Detroz B (1991) Intraperitoneal hyperthermia, a rat model. Acta Gastroenterol Belg 54:A84
13. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH (1998) Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol 41:147
14. Koga S, Hamazoe R, Maeta M, Shimizu N, Kanayama H, Osaki Y (1984) Treatment of implanted peritoneal cancer in rats by continuous hyperthermic peritoneal perfusion in combination with an anticancer drug. Cancer Res 44:1840
15. Koops HS, Vaglini M, Suciu S, Kroon BB, Thompson JF, Gohl J, Eggermont AM, Di Filippo F, Krementz ET, Ruiter D, Lejeune FJ (1998) Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. J Clin Oncol 16:2906
16. Lienard D, Eggermont AM, Kroon BB, Schraffordt Koops H, Lejeune FJ (1998) Isolated limb perfusion in primary and recurrent melanoma: indications and results. Semin Surg Oncol 14:202

17. Mohamed F, Marchettini P, Stuart OA, Urano M, Sugarbaker PH (2003) Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. Ann Surg Oncol 10:463
18. Norda A, Loos U, Sastry M, Goehl J, Hohenberger W (1999) Pharmacokinetics of melphalan in isolated limb perfusion. Cancer Chemother Pharmacol 43:35
19. Oleson JR, Calderwood SK, Coughlin CT, Dewhirst MW, Gerweck LE, Gibbs FA Jr, Kapp DS (1988) Biological and clinical aspects of hyperthermia in cancer therapy. Am J Clin Oncol 11:368
20. Pestieau SR, Belliveau JF, Griffin H, Stuart OA, Sugarbaker PH (2001) Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol 76:106
21. Riviere JE, Page RL, Aucoin DP, Rogers RA, Williams PL (1991) Effect of hyperthermia on the in vitro hydrolysis of melphalan. Int J Hyperthermia 7:527
22. Sarosy G, Leyland-Jones B, Soochan P, Cheson BD (1988) The systemic administration of intravenous melphalan. J Clin Oncol 6:1768
23. Shen P, Levine EA, Hall J, Case D, Russell G, Fleming R, McQuellon R, Geisinger KR, Loggie BW (2003) Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. Arch Surg 138:26
24. Shiu MH, Fortner JG (1980) Intraperitoneal hyperthermic treatment of implanted peritoneal cancer in rats. Cancer Res 40:4081
25. Sugarbaker PH (2001) Cytoreductive surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. Eur J Surg Oncol 27:239
26. Urano M, Ling CC (2002) Thermal enhancement of melphalan and oxaliplatin cytotoxicity in vitro. Int J Hyperthermia 18:307
27. Urano M, Kuroda M, Nishimura Y (1999) For the clinical application of thermochemotherapy given at mild temperatures. Int J Hyperthermia 15:79