Intraperitoneal Chemohyperthermia Versus Intraperitoneal Chemotherapy in Treatment of patients with Malignant Ascites

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Abstract

Background and study aim: There is a theoretical potential to increase exposure of tumor cells to antineoplastic agents by delivering it intraperitoneally. Hyperthermia has been used to augment cancer treatment for decades. Hypothetically, combining both methods together should maximize the toxic effects of chemotherapy. In this study intraperitoneal chemotherapy was compared to intraperitoneal Chemohyperthermia regarding the effect on viability of malignant cells in ascitic fluid cytology. Body weight and abdominal girth were used as clinical parameters for ascites regression. Patients and methods: 40 Patients with malignant ascites were recruited. Patients were alphabetically randomized into 2 groups, group 1 included 20 patients who were treated using intraperitoneal chemotherapy. Group 2 included 20 patients who were treated with intraperitoneal Chemohyperthermia. Results:Viable malignant cells were significantly lower in group 2 than in group 1in the first, second, third and fourth week of follow up of the two groups. Degenerative and necrotic cells were significantly higher in group 2 than in group 1 during the same follow up period. Body weight and abdominal girth in group 2 and in group 1 four weeks after the procedure were significantly decreased. Self limiting adverse effects as abdominal pain, anorexia, vomiting, constipation and low grade fever were observed in cases of Chemohyperthermia which were relieved by third day. Impairment in kidney functions as shown by increased creatinine occurred in some patients in group 1. Conclusion: Intraperitoneal Chemohyperthermia can affect the viability of malignant cells in patients with malignant ascites with minimal self limiting side effects than intraperitoneal chemotherapy alone. It also improves patient's quality of life due to regression of ascites.

Introduction:

Malignant ascites represents a tough challenge for doctors and a challenging threat for patients. Because patients with malignant ascites have poor prognosis, it is imperative to continue exploring for novel therapies. Intraperitoneal therapy gives us a new dimension for longevity and better life quality. Intraperitoneal administration of chemotherapy has the benefit of higher concentrations of cytotoxic drug delivered locally to the site of the tumor while minimizing systemic toxic effect[1]. It has been proven by experiment that tumor tissue is more sensitive to heat than normal tissue [2]. Hyperthermia has been used to augment other forms of cancer treatment for many years. There is evidence that the combination of chemotherapeutic agents and hyperthermia produces additive and synergistic killing effects on tumor cells. Hyperthermia also produces changes in blood flow and oxygen levels in tumor that may have beneficial clinical effects especially in combination with other agents [3].

Patients and methods:

Forty patients were recruited in this study. All patients had malignant ascites and were referred to Tropical medicine and Oncology departments in Kasr Elaini hospital, Cairo University. After explaining the procedure, the hazards and the expected outcome, a written consent was taken from all patients. Study period was from April 2004-Sep 2005.

Inclusion criteria:

Age range of the patients was between 43-70 years. All patients had a histopathologically confirmed diagnosis for their malignant ascites condition. It was either primary or secondary malignant ascites. Laboratory evaluation of these patients for prothrombin time bleeding time, activated partial thromboplastin time, thrombin time and creatinine were all normal. No previous therapy with cytotoxic chemotherapy or radiation therapy. Their life expectancy was 3 months or more according to stage of illness.

Exclusion criteria:

Any patient with history of cardiovascular diseases, allergic reaction, anaphylaxis or angioedema, bleeding disorder, impaired renal function tests or with history of previous trial of chemotherapy or radiotherapy was excluded.

Methods:

History and physical examination for all forty patients were done. All patients had laboratory evaluation which included: urine and stool analysis, complete blood count, liver function tests (bilirubin total, direct) AST,ALT, Alkaline phosphatase, total proteins, albumin, prothrombin time, prothrombin concentration. Serum tumor markers (alpha feto protein, CA19-9, CA 125). Abdominal ultrasonography was done to all patients using Hitachi EUB200 machine and 3.5 MHz linear transducer. Ascitic fluid aspiration was done and subjected to cytological examination. Ascitic sample was aspirated each session before and after treatment. Patients were alphabetically randomized into two groups: first group: included twenty patients who underwent intraperitoneal chemotherapy. Second group:

included twenty patients who underwent intraperitoneal Chemohyperthermia.

The machine used for hyperthermia was SLH-100 microprocessor controlled machine for perfusional hyperthermia.(picture 1) 2 wide bore cannulas were fixed to the sides of the patient, 5% glucose (500cc) were infused into peritoneal cavity. A disposable set was connected to both cannulas and the pump was switched on as soon as the adjusted temperature was reached. The infused peritoneal fluid was 45º-48º to keep the temperature of peritoneal fluid 42º-43º. Cisplatin 200mg was infused in the arterial end to circulate in the peritoneal fluid during the time of session. The session duration was at least 60 minutes. Steady flow 150-300 cc per minute with total cycled fluid 12-16 liters. Paracentesis of 2 liters was done before the session and another 3 liters at the end of the session.

The chemotherapeutic agent used was Cisplatin. It was infused intraperitoneally in a dose of 200 mg in group 1 and at the beginning of the hyperthermia session in group2. Follow up was done by patient's weight and abdominal girth and by cytological examination of ascitic fluid at the end of first, second, third and fourth weeks after the session.

The machine used for hyperthermia: SLH – 100

This is a microprocessor-controlled machine for perfusional hyperthermia. It is both flexible in operator programming as well as safe in use for both patient and operator.

Results:

The age range of patients in group 1 was 48-68 years old (mean 54.9+/-6.0)while in group 2 the range was 43-66 years old (mean 54+/-6.3). all patients in group 1 were females. Group 2 included 12 females and 8 males. All patients suffered from weight loss, abdominal pains, fatigue and vomiting. Physical examination demonstrated: pallor, cachexia, hepatomegaly, peritoneal nodules, lymphadenopathy and ascites.

The pretreatment laboratory evaluation is shown in table (1).

Ultrasonographic examination showed the following data: Peritoneal nodules were detected in 16 patients (80%) in group1 and in 13 patients (65%) in group 2. Ovarian masses were detected in 5 patients of group 1 (25%) and 4 patients in group 2 (20%). No statistical difference were found between the studied groups (P-value >0.05)

Table 2 shows the aetiology of malignant ascites in the studied patients: Ovarian cancer had the upper hand in prevalence in both group, it was found in13 patients(65%) and12 patients(60%) in group 1 and 2 consequently. Pseudomyxoma peritonii represented 15% of cases (3 patients) in group 1 and 20% (4 patients) in group 2.There was no statistical significance regarding the type of tumors between the two groups (P -value > 0.05).

Table (2): Type of Tumors found in the studied patients

Variable	Group I		Group II	
	No.	%	No.	%
Gastric cancer	2	10 %	1	5 %
Gall bladder cancer	1	5 %	1	5 %
Ovarian cancer	13	65 %	12	60 %
Breast cancer	1	5 %	2	10 %
Pseudomyxoma peritoneii	3	15 %	4	20 %
Total	20	100%	20	100%

Laboratory characteristics of ascitic fluid did not show any statistically significant difference between the studied groups (P-value >0.05)

Table (1): Laboratory assessment of the studied patients with malignant ascites

Variable		Group I			Group II			P-value
		Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.	
CBC	RBCs	3.6 ± 0.6	2.2	4.7	3.3 ± 0.9	2.1	4.9	NS
	TLC	5225 ± 2403.5	2500	11000	5937.5 ± 3121	3000	13000	NS
	PLT	222350 ± 76662.1	67000	370000	228600 ± 64482.1	91000	340000	NS
LFTs	Alb (N = 3.5-5.5gm/dl)	3.8 ± 0.3•	3.2	4.4	3.4 ± 0.6•	2.5	4.6	0.013
	AST	109.7 ± 71.9	27	247	92.9 ± 80	25	316	NS
	T.Bil	1.2 ± 1	0.66	5.5	1.1 ± 0.9	0.48	3.5	NS
	D.Bil	0.6 ± 0.9	0.17	4.3	0.5 ± 0.7	0.11	2.7	NS
KFTs	Urea	21.6 ± 2.5	16	25	22.5 ± 1.5	19	24	NS
	Creatinine(N = 0.4 – 1.5mg/dl)	0.8 ± 0.28	0.3	1.4	0.9 ± 0.3	0.5	1.5	NS
Tumour markers	AFP (N = 0-9ng/ml)	8.3 ± 7.8	0.67	34	8.0 ± 7.2	0.7	27	NS
	CA19-9 (N = 0-37 u/ml)	19.5 ± 1	4	34	22.2 ± 14.0	5	54	NS
	CA125 (N = 0-35 u/ml)	130.5 ± 138.8	7	453	86.9 ± 97.2	7	312	NS

NS = nonsignificant P-value > 0.05

Significant P-value < 0.0

Table (3) shows the primary tumor pathology and cytological features of ascitic fluid in the studied groups: the primary tumor pathology was cystadenocarcinoma in 13 patients (65%) in group 1 and 12 patients (60%) in group 2. Adenocarcinoma in 3 patients (15%) in group 1 and 2 patients (10%) in group 2, mucinous adenocarcinoma in 3 patients (15%)in group 1 and 4 patients (20%) in group 2 and mammary duct carcinoma in a single patient (5%) in group 1 and 2 patients (10%) in group 2. There was no statistically significant difference (P-value >0.05) between the two groups.

Table (3): Primary tumor pathology and cytological features of ascitic fluid in the studied patients

Variable		Group I		Group II		P-value
		No.	%	No.	%	
Primary Pathology	Adenocarcinoma	3	15	2	10	NS
	Cystadenocarcinoma	13	65	12	60	NS
	Mammary duct carcinoma	1	5	2	10	NS
	Mucinous Adenocarcinoma	3	15	4	20	NS
Malignant cells	Sheets of malignant epithelial cells	13	65	11	55	NS
	Mucin secreting cells	7	35	9	45	NS
Mesothelial cells	Reactive	20	100	20	100	NS
	Non reactive	0	0	0	0	NS
Lymphocytes	Positive	20	100	20	100	NS
	Negative	0	0	0	0	NS
Total		20	100	20	100	

Cytological examination of ascitic fluid:

Sheets of malignant epithelial cells were detected in ascitic fluid of 13 patients (65%) of group I and 11 patients (55%) of group II while mucin secreting cells were detected in 7 patients (35%) of group I and 9 patients (45%) of group II with no statistical significant difference (P-value > 0.05). There were reactive mesothelial cells in ascitic fluid cytology of all patients of the two groups (100%). Excess Lymphocytes in ascitic fluid cytology of all patients of the two groups (100%) was detected.

Assessment of patients in the follow up schedule showed the following: Table (4) demonstrates the percent change in laboratory profile after the procedure, though serum creatinine in group 1 (35.2± 42.9) was significantly higher than group 2 (11.3± 23.6), other data did not show any statistically significant difference between the studied groups.

Table (4): Percent change in laboratory profile before and after the procedures

Variable		Group I	Group II	P-value
		Mean ± SD	Mean ± SD	
Percent change	RBCs (Before vs. After)	-0.3 ± 11.3	1.3 ± 13.0	0.673
	TLC (Before vs. After)	-8.1 ± 12.0	-5.8 ± 11.1	0.535
	Platelets (Before vs. After)	-1.8 ± 7.3	-2.1 ± 8.5	0.908
	AST (Before vs. After)	15.3 ± 28.1	2.5 ± 14.4	0.078
	ALT (Before vs. After)	3.0 ± 19.7	-0.4 ± 11.1	0.494
	Urea (Before vs. After)	89.2 ± 164.4	24.7 ± 79.0	0.122
	Creatinine (Before vs. After)	35.2 ± 42.9	11.3 ± 23.6	0.035

Adverse effects after the procedures were recorded and are shown in figure (1). Abdominal pain in 12 patients (60%) of group I and 6 patients (30%) of group II, anorexia in 6 patients (30%) of group I and 4 patients (20%) of group II, vomiting in 5 patients (25%) of group I and 4 patients (20%) of group II, fever reaching 38° C in 5 patients (25%) of group II only. When comparing group I with group II, there was a significant statistical difference regarding the presence of fever (p-value < 0.05) yet other data did not show any statistically significant difference (p-value > 0.05).

Figure-1 Adverse effects after the procedure.

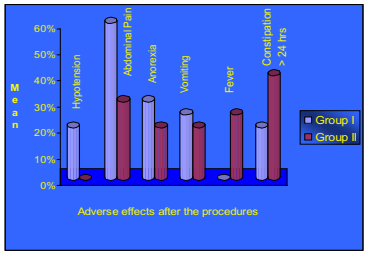

Figure 2 shows the clinical parameters used to evaluate the studied patients before and after the procedures. Body weight and abdominal girth were found to decrease after the procedures and in the next weeks but with no statistically significant difference between the two groups.

Figure-2 Follow up of viable malignant cells in ascitic fluid of the studied groups

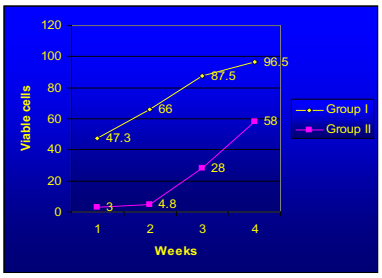

Figure (3) shows the mean value of viable malignant cells in ascitic fluid cytology after 1 week, 2 weeks, 3 weeks and 4 weeks of the procedure. Group2 was significantly lower than group 1 in viable malignant cell,

Figure-3 Follow up of degenerative cells in ascitic fluid in the studied groups

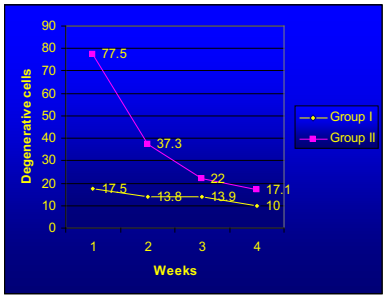

Figure (4) shows that the mean value of degenerative cells in ascitic fluid cytology after 1, 2, 3 and 4 weeks of the procedure in group 2 to be significantly higher than group 1

Figure-4 Follow up of necrotic cells in ascitic fluid in the studied groups

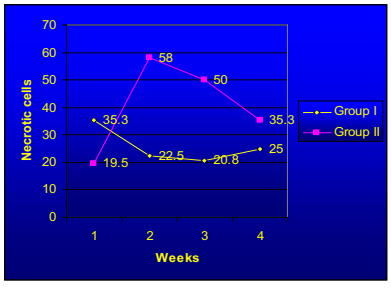

Figure (5) shows that the mean value of necrotic cells in ascitic fluid cytology after 1week of the procedure was significantly higher in group 1 than in group 2 (P-value <0.01).while in the second and third weeks of the procedure. Group 2 was significantly higher than group 1 (P-value <0.01).The mean value of necrotic malignant cells in ascitic fluid cytology after 4 week of the procedure was (25 ± 7.1) in group I and (35.3 ± 13.3) group II with no statistically significant difference (p-value > 0.05).

Table (5) shows the results of clinical parameters and cytology before the procedure versus 4 weeks after the procedures. All clinical parameters (body weight and abdominal girth) 4 weeks after the procedure were significantly lower in both groups than before the procedure. Regarding the cytology of ascitic fluid, in group 2, the mean value of viable malignant cells 4 weeks after the procedure was significantly lower than before the procedure (P- value <0.01). Also there was a significant change in degenerative and necrotic cells 4 weeks after the procedure (p-value <0.01). In group 1, the cytology of ascitic fluid did not show a significant change 4 weeks after the procedure.

Table (5): The results of clinical parameters and cytology before the procedures versus 4 weeks after the procedures

Variable	Group I	Group II			
		Mean ± SD	P-value	Mean ± SD	P-value
Body weight	Before	98.5 ± 14.8	0.00	103.1 ± 12.5	0.00
	After 4Ws	89.7 ± 14.3		90.6 ± 12.3	
Abdominal girth	Before	99.4 ± 19.5	0.00	98.0 ± 16.0	0.00
	After 4Ws	90.4 ± 18.1		85.8 ± 13.6	
Viable malignant cells	Before	100 ± 0.0	0.167	100 ± 0.0	0.00
	After 4Ws	96.5 ± 10.9		58 ± 26.3	
Degenerative malignant cells	After 1W	17.5 ± 8.7	1.00	77.5 ± 12.1	0.00
	After 4Ws	10 ± 0.0		17.1 ± 4.7	
Necrotic malignant cells	After 1W	35.3 ± 22.3	0.126	19.5 ± 10.5	0.00
	After 4Ws	25 ± 7.1		35.3 ± 13.3	

Significant (P-value < 0.05)

Cytomorphologic Criteria:

Cluster of cells with enlarged, variably-sized round or oval nuclei with prominent macronucleoli. Smear background is clean.

Discussion

Malignant ascites is a manifestation of advanced malignant disease that is associated with significant morbidity [4]. It is usually associated with a poor prognosis and a devastating effect on individuals' ability to function and on their quality of life. Elimination of cancer may be the only way to completely eliminate the fluid accumulation, yet it is not a realistic option. Treatment efforts therefore, focus on symptom control and supportive measures rather than definitive therapies[5]. The use of intraperitoneal drug delivery in treatment of malignant diseases confined to the peritoneal cavity is a definitive way to insure increased exposure of the tumor to antineoplastic agents leading to improved cytotoxicity [6] Literature reports that achieving an intraperitoneal temperature of at least 41ºC is desirable for optimizing drug diffusion into tissues and for maximizing the synergistic effect

with chemotherapy [2] , Gori et al [7] suggested that intraperitoneal hyperthermic perfusion chemotherapy is a feasible, well tolerated and promising alternative as consolidation therapy in patients with ovarian cancer.

The current study aimed to show the effect of intraperitoneal chemotherapy in comparison to intraperitoneal Chemohyperthermia as treatment modalities in patients with intraperitoneal malignancies. The efficacy of each treatment was assessed using viability of malignant cells in ascitic fluid cytology and effect on body weight and abdominal girth as clinical parameters for treatment success. Most of our patients had ovarian cancer, this goes in agreement with Sato et al [8] who reported that the most common malignancies to spread along the peritoneum are from the gastrointestinal tract and ovary.

In this work, Cisplatin was the chemotherapeutic agent of choice used intraperitoneally. Cisplatin is known to have 15 times higher concentration if given intraperitoneally than if given systemically as mentioned by Piso et al [9]. It is one of the antineoplastic agents most frequently used in intraperitoneal Chemohyperthermia (IPCHT). The rationale for its use depends on its potential to work at high temperatures and its ability to act at any stage of malignant cell replication [9]. Synergism between Cisplatin and hyperthermia has been shown in several clinical trials. In animal models this finding was considered to be a consequence of higher and selective uptake of the drug by the cancer cells [10].

Our results showed improvement in the quality of life in our patients after the procedures. This was shown by the significant decrease in body weight and abdominal girth after regression of ascites. Patients experienced some relief of pressure symptoms as shortness of breath, upper GIT symptoms, low back ache and fatigue. In both groups there was significant lowering of body weight and abdominal girth four weeks after the procedures. This goes in agreement with McQuellon et al, [11] who reported that IPCHT is effective in preventing recurrence of ascites.

In the current study, cytological analysis of ascitic fluid showed some encouraging results. The viable malignant cells after 1, 2, 3 and 4 weeks of the procedure were significantly lower in group2 than in group 1.

In group I there was no significant difference in percentage of viable, necrotic or degenerative malignant cells before versus 4 weeks after the procedure.

However, in those patients undergoing intraperitoneal chemohyperthermia (Group II) the effects were more pronounced. This was shown by the significant difference in the percentage of viable cells over the 4 weeks as well as the percentage of degenerative cells in ascitic fluid cytology.

At the end of the follow up period, no significant difference regarding viability of malignant cells was observed in patients undergoing intraperitoneal chemotherapy (group I) than before the procedure. However the difference was still significant in those undergoing intraperitoneal chemohyperthermia.

This could be explained by the fact that Intraperitoneal chemotherapy has an objective in the eradication of the microscopic residual disease and tiny tumor nodules that the surgeon cannot see or remove because of a diffuse involvement of small bowel peritoneum [12]

The effects of hyperthermia on malignant tissue seem to be mediated by direct cytotoxicity and the microcirculation peculiar to neoplasms. Moreover, hyperthermia synergistically enhances the chemosensitivity of tumor cells to chemotherapy. Mechanisms of action include increased cellular accumulation and activation [1].

In the current study the adverse effects noted within the first 48 hours after the procedures were abdominal pain, anorexia, vomiting and constipation. Slight elevation of body temperature to 38° C was a significant finding in those undergoing intraperitoneal chemohyperthermia. Most side effects were relieved by the third day after the procedures.

Deraco et al.[13]analyzed the morbidity of chemohyperthermic treatment. The most frequent complications were ileus, renal failure, pancreatitis, bone marrow toxicity, pelvic infection.

The significant adverse effect related to the combined approach of intraperitoneal perfusion hyperthermia with chemotherapy which is ileus was not observed in our work,

There was a significant impairment of renal function indicated by some elevation of serum creatinine in patients undergoing intraperitoneal chemotherapy. This effect was not pronounced in group II of our study.

No significant adverse effects were noted on blood picture or other blood chemistry profiles in this work.

In conclusion: intraperitoneal chemohyperthermia proved to be superior on intraperitoneal chemotherapy regarding viability and degenerative effects on malignant cells. Side effects were tolerable and better quality of life was attainable. It can be a promising alternative in treatment of malignant ascites.

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