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Intraperitoneal hyperthermic perfusion chemotherapy of patients with chemotherapy-resistant peritoneal disseminated ovarian cancer

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The purpose of this article is to evaluate in a prospective, open-label clinical trial the feasibility and efficacy of intraperitoneal hyperthermic perfusion chemotherapy (IPHC) on the survival and quality of life of patients with advanced, peritoneal disseminated ovarian cancer.

Thirty-six patients with ovarian cancer were accrued for the study, their selection being based on their progression following different systemic therapies with anti-neoplastic (multiple chemotherapy-resistant or -refractory) agents. The average number of chemotherapy cycles given before the first IPHC was 12.5. The patients' average Karnofsky-performance status was 60% and 17 out of 36 patients had ascites before IPHC. The input temperature of the solution for abdominal lavage was 48–49°C: the intraperitoneal temperature was 42–43°C. The flow-rate of the solution for heat exchange was 190–220 ml/min with treatment lasting 1 h at temperatures greater than or equal to 42°C.

Median overall survival time (MOS) from first diagnosis of disease (1stDx) was 49 ± 8 months and from the first IPHC-treatment 19 ± 4 months. The observed 1-year overall survival rate (OSR) of all patients from the start of the first IPHC was 65 ± 8% and the 5-year OSR was 16 ± 7%. Malignant ascites vanished within less than 3–5 IPHCs. Quality of life could be improved. The adverse effects were mild especially compared to systemic chemotherapy. In 3 out of 162 treatments, peritoneal disturbances with symptoms of subileus were observed.

We conclude that IPHC is technically feasible, safe, and associated with a marked prolongation of survival and improvement in quality of life. Even heavily pretreated patients could be treated safely. Some patients did respond to IPHC even after 25 IPHC treatments. From these results, it can be concluded that IPHC may also improve the treatment outcome of patients with ovarian cancer as salvage therapy, in second-line treatment or even as consolidation or maintenance therapy following induction chemotherapy to patients with suboptimal stage III and IV disease. This should be demonstrated in randomized controlled studies.

KEYWORDS: chemotherapy-resistance, hyperthermia, intraperitoneal hyper-

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thermic perfusion chemotherapy, ovarian cancer, peritoneal carcinomatosis, peritoneal sarcomatosis.

Ovarian cancer is most frequently diagnosed at an advanced stage. Only a minority of patients will have surgically curable localized diseases. A combination of paclitaxel plus platinum (TC) is the standard therapy with an average median survival time of 38 months (GOG-111) and 35.6 months (OV10)[1,2]. Single-agent sequential therapy may have long-term outcomes equivalent to the standard therapy but with less toxicity (GOG-132[3], ICON2[4], ICON3[5]) whereas triple drug combination regimens are likely to be slightly more effective but with greater toxicity[4,6]. Thus, single-agent carboplatin at an AUC of 6 remains an acceptable alternative for the initial treatment of patients with suboptimal stage III-IV ovarian cancer. Despite the high overall response rate of ovarian cancer to chemotherapy of 70% to 80%, up to 80% of patients with advanced disease will ultimately relapse from clinical remission.

In second-line chemotherapy, response rates between 25% and 60% are achieved. In this case, the median time to progression is 7–8 months and the median survival time less than 11 months. If the cancer relapses again, third-line systemic treatments have low remission rates of between 10% and 25% and short durations of remission. In platinum and paclitaxel-resistant or refractory diseases, several drugs, such as gemcitabine, anthracyclines, topotecan, ifosfamide, camptothecin, and PEG-liposomal doxorubicin, are at least partially effective.

The expected 1-year survival rate of patients with multiple chemotherapy-resistant/refractory peritoneal disseminated cancer of the ovary following second-line therapy is very poor. Palliative (debulking) surgery, full abdominal irradiation, irradiation with intraperitoneal radioisotopes (^{32}P), and intraperitoneal chemotherapy are palliative treatment options that have little influence on the survival. Less toxic palliative therapy options may also be possible with low-dose oral agents, such as cyclophosphamide, trofosfamide, etoposide, and capecitabine. In chemotherapy-refractory patients with peritoneal carcinosis, the median survival time is 3–5 months and the expected 1-year survival rate below 2%.

New approaches are focusing on the use of agents with molecular targets, such as receptors (EGFR, HER-2), signaling pathways (tyrosine kinases, ras), and angiogenesis. These "non-cytotoxics", a new class of anticancer drugs that target subcellular and extracellular molecular processes, are currently being investigated. Some of these trials are complete and have shown, to date, no significant trends towards superior survival (BAY 12–9566, marimastat).

Epithelial and stromal ovarian cancer spread primarily by direct extension of exfoliating cells into the peritoneal cavity where they can implant into the parietal and visceral peritoneum. All intraperitoneal surfaces are at risk. Most of the patients with ovarian cancer already present with peritoneal carcinomatosis on first diagnosis of the disease and most of the patients suffering relapse develop peritoneal metastasis. Cancer cells also disseminate by lymphatic spreading from the ovary, particularly to the pelvic sidewall lymph nodes and along the gonadal vessels.

Direct intraperitoneal installation of anticancer agents to treat peritoneal carcinomatosis or sarcomatosis has pharmacologic advantages compared to intravenous therapy in terms of local drug concentrations (Table 1). The peritoneal space/plasma barrier provides dose-intensive therapy. The ratio of antineoplastic agent in the dialysate compared to the levels in the blood, depending on the drug, is 18–1000 times greater. The increase of local concentrations of cytotoxic drugs leads to improved response rates (RRs) and significant increased recurrence-free survival but only moderately prolongs survival[7].

In addition, direct cytotoxic hyperthermia effects and synergistic antineoplastic effects between hyperthermia and some anticancer agents through the induction of apoptosis are clinically and experimentally observed (Table 2). The penetration of chemotherapy into tissues is improved by thermal effects and drug resistance can be reduced by heat. Immunologic effects on cellular effector cells and the secretion of cytokines, induced by heat, may also contribute to synergism. Increased response rates and survival may

Table 1. Rationale for intraperitoneal chemotherapy of patients with advanced ovarian cancer

1. Spread of epithelial and stromal type of ovarian cancer occurs most frequently into the peritoneal cavity.
2. Higher concentrations of cytotoxic drugs within the peritoneal cavity following i.p. drug administration compared to i.v. application (i.p./plasma concentrations 18–1000 fold).
3. Increased exposure time to antineoplastic agents due to the peritoneal space/plasma barrier.
4. Reduced toxicity following i.p. application owing to lower systemic concentrations of cytotoxic agents.

Table 2. Rationale for intraperitoneal hyperthermic perfusion

1. Hyperthermia induces apoptosis of cancer cells (direct heat-related cytotoxic effects)
2. Synergistic interactions of heat with selected antineoplastic agents
3. Reduced drug resistance (tissue penetration, membrane permeability & metabolism increased)
4. Immunologic effects on cellular effector cells (emigration, migration, chemotaxis & activation)
5. Induction of cytokines (IL-1, -2, -6, -12, TNF-α, NO, CSFs) and chemokines
3. Modulation of cell adhesion molecules

Table 3. Patient characteristics

Total number of patients accrued	36
Follow-up rate	94%
Age, years	
Median	55
Range	22–72
Performance status (WHO-index)	
1:	36%
2:	53%
3:	11%
Sites of disseminated metastases	pts. No. [%]
Peritoneal carcinosis	36 [100]
Ascites	17 [47]
Lymph nodes	8 [22]
Liver	5 [14]
Abdominal wall	3 [8]
Pleura	2 [6]
Spleen	1 [3]
Histology	n [%]
Adenocarcinoma[a]	29 [8]
Granulosa-stromal cell tumor	2 [6]
Undifferentiated carcinoma	2 [6]
Unclassified	3 [8]
Grading	n [%]
G1	2 [6]
G2	11 [30]
G3	15 [42]
G4	2 [6]
Unknown	6 [6]

[a]serous, mucinous, endometrioid

therefore be expected from intraperitoneal hyperthermic perfusion chemotherapy (IPHC).

Intraperitoneal hyperthermic perfusion chemotherapy may be performed: a) perioperatively[8,9], prior to surgery (induction therapy) or during surgery, or b) postoperatively as a "closed" intraperitoneal perfusion therapy[10].

Patients and methods

Patient eligibility

Between December 1991 and July 1996, 36 women with histologically or cytologically confirmed peritoneal carcinosis from primary, suboptimal stage III or IV epithelial or stromal ovarian cancer who met the following eligibility criteria were included in the study: 18–75 years of age, measurable or nonmeasurable – but assessable (evaluable) – advanced multiple chemotherapy-resistant/refractory disseminated peritoneal carcinosis, and a life expectancy of at least 4 weeks (Table 3). The patients had to have received at least second-line chemotherapy before inclusion in this study or have stopped treatment because of severe toxic effects (Table 4). The exclusion criteria were: no prior platinum-and/or taxane-based regimen, concomitant systemic chemotherapy, extensive abdominal adhesions with a lavage fluid of less than 1.5 l, advanced symptoms of subileus, and bulky tumor masses in the abdomen (>2 cm in diameter) – except for patients with ascites (17 in total). In the latter case, the first goal was to eliminate the ascites. All patients provided signed, written, informed consent.

Methods

The abdomen was flooded with 3–4 l of normal saline at 40°C via a Veress needle. In the case of malignant ascites, the effusion was first completely drained and lavage of the abdomen performed before flooding with saline solution. A cytotoxic drug was then introduced. Subsequently, the Veress needle was exchanged for a semipermeable Periocart catheter. A single-needle system was preferred. The lavage was performed via the catheter with a heat exchange dialysate flow rate of 190–220 ml/min. The lavage solution was heated by an external heat exchanger comprising an aluminum plate heated to 48–52°C. The input temperature for the physiologic lavage solution containing antineoplastic agents was 48–49°C: the intraperitoneal temperature was between 42 and 43°C. The pump system used for intermittent lavage was manufactured by Bellco-Multimat, Sorin Biomedica Deutschland AG, Düsseldorf, Germany. The hyperthermia medical device used for the IPHC was designed and constructed by Theratherm, Vigevano, Italy.

Treatment plan

At an intraperitoneal temperature of about 40°C, 100 mg cisplatin or 450 mg carboplatin (and in one patient 30 mg mitoxantrone) was added to the dialysate. The intraperitoneal temperature of the solution was continuously increased up to 42–43°C. The duration of the treatment was 1 h at temperatures in excess of 42°C. At the end of the treatment, the dialysate was left in

Table 4. Prior chemotherapies and last treatment-free intervals

Prior chemotherapy i.v.	No. of pts. [%]	Av. No. of courses	
Platinum	34 [94]	5.7	
Cyclophosphamide	32 [89]	5.8	
Paclitaxel	18 [50]	4.2	
Others	18 [50]	6.0	
Average number of chemotherapy courses prior to 1st IPHC			No. = 12.5
Median time from 1st diagnosis of ovarian cancer to 1st IPHC			17.9 months
Last treatment-free interval, No. of patients [%]	<4 months		24 [67]
	4–12 months		7 [19]
	>12 months		5 [14]
Median treatment-free interval	97 days		

the abdomen and the catheter was removed. One cycle of IPHC consisted of two to three treatments at intervals of 5–7 days. Application of the optional third IPHC treatment depended on the patient's general condition. The next cycle of IPHC was performed after 4–6 weeks. The treatments were repeated as long as the space for IPHC was large enough for lavage (>1.5 l) and treatment was feasible and convenient for the patient.

Statistical analysis

The objectives of the study were a) to assess the feasibility of intraperitoneal hyperthermic perfusion chemotherapy, b) to determine the impact on median survival time and survival rate, c) influence on quality of life, d) maximum possible duration of therapy, and e) tolerability, safety, and adverse effects. The primary study endpoints were overall median survival time and overall survival rate and secondary endpoints were clinical benefit (quality of life) and tumor marker response (CA-125).

The study was designed as a prospective open-label, single-arm phase II observational study. Thirty-six patients with symptomatic multiple chemotherapy-resistant/refractory peritoneal disseminated metastases from epithelial or stromal ovarian cancer were accrued and treated with "intraperitoneal hyperthermic perfusion chemotherapy" (IPHC) in combination with cytotoxic agents.

The median overall survival time and overall survival rates were calculated from first diagnosis of disease (1stDx) and from the first application of intraperitoneal hyperthermic perfusion chemotherapy (1stIPHC) until death. All analyses were performed on an intention-to-treat basis. The survival curves were estimated based on Kaplan-Meier life table analyses. Patients still alive at the time of assessment were censored at a date equivalent to the last patient visit or data being transferred from other physicians.

Objective response criteria of changes in CA-125 serum levels were used according to the definitions developed by the working group of the Gynecologic Cancer Intergroup[11]. According to this, a doubling from the nadir has been shown to predict progression with a false positive rate of<2%. The serum CA-125 levels were compared between the value on days before first IPHC to the nadir or maximum 4–8 weeks after the first IPHC course.

The safety analyses included all IPHC-treatments. Descriptive statistical methods were used without any formal statistical testing.

Results

Patient characteristics

Thirty-six patients were enrolled into this trial. The follow-up rate was 94%; the survival of the lost patients were calculated at the date of the last patient visit. Two patients developed during follow-up primary breast cancer. The total accrual time for the trial was from 12/1991 to 07/1996 with approximately 1 years' interruption due to technical reasons (certification of the specific hyperthermia medical equipment). The total accrual time was therefore 4.6 years and the real time 3.7 years. At the time when the data was evaluated (11/1999), the follow-up time was 3.3 years. Seven patients (19%) were still alive at the time of assessment.

The median age of the patients was 55 years (range 22–72 years). The patients' average Karnofsky performance status was 60% (range 30% to 80%) and 17 out of 36 patients had ascites on commencement of first IPHC. Most of the patients had been platinum-resistant/refractory. Half of the patients received paclitaxel as second-line therapy. The percentage of patients experiencing recurrent disease within 4 months after the last systemic chemotherapy was 67%. Nineteen percent of the patients relapsed within 4–12 months and five patients after 12 months. The median time of the treatment-free interval between the last systemic chemotherapy and IPHC was 97 days. On

Table 5. Survival rates of patients with advanced disseminated chemotherapy-resistant or refractory ovarian cancer treated with intraperitoenal hyperthermic perfusion chemotherapy

Date of determination	1-year (%)	2-year (%)	3-year (%)	4-year (%)	5-year (%)
1st Dx of AOC	97 ± 3	82 ± 6	60 ± 8	48 ± 8	35 ± 8
1st IPHC	65 ± 8	39 ± 8	30 ± 8	16 ± 7	16 ± 7

average, the patients had been treated with 12.5 chemotherapy cycles before their introduction into the IPHC trial.

The median overall survival time (MOS) from first diagnosis of stage III or IV disease (1stDx) was 49 ± 8 months. Dated from the first IPHC treatment, the MOS was 19 ± 4 months. For patients without ascites (19 in total), the MOS was 24 ± 2 months and for patients with ascites (17 in total), 15 ± 2 months. The observed 1-year overall survival rate (OSR) based on all the patients was 65 ± 8% from the start of the first IPHC (see Table 5). The 5-year OSR was 16 ± 7%. The respective Kaplan-Meier survival curves for patients with and without ascites at the time of the first IPHC are shown in Fig. 1.

Even after only the first IPHC, malignant ascites frequently had diminished and could be eliminated over an average of 1.4 IPHC cycles (between 3 and 5 IPHCs).

The tumor marker CA-125 decreased in 14% of the patients from increased serum levels to normal within 4–8 weeks (see Table 6) after the first IPHC cycle, and decreased by over 50% in 42% and between 25 and 50% in 14% of the patients. An increase of more than 25% but less than 100% was observed in 17% of the cases and a doubling in 8%.

The patients' quality of life was improved. A biostatistical analysis of the influence of the IPHC on quality of life will be presented and discussed subsequently.

The adverse effects were mild, especially compared to systemic chemotherapy (see Table 7). The most severe side effects were nausea and vomiting, but this has to be considered on the background of this heavily pretreated population (on an average 12.5 chemotherapy courses). In three out of 168 treatments, peritoneal disturbances with symptoms of subileus were observed and in 5% peritoneal irritations. Local reactions with vaccination metastases were seen in two patients. No bowel obstruction nor catheter related infections or peritoneal fibroses induced by IPHC was observed.

IPHC was technically feasible, safe and well tolerated by the patients and was associated with a marked prolongation of survival and an improvement in quality of life. Even heavily pretreated patients could be treated safely. Some patients responded to IPHC even after 25 intraperitoneal treatments (see, for example, the tumor marker response of the case report shown in Fig. 2).

Discussion

Intraperitoneal hyperthermic perfusion chemotherapy is a safe and effective new treatment method for pa-

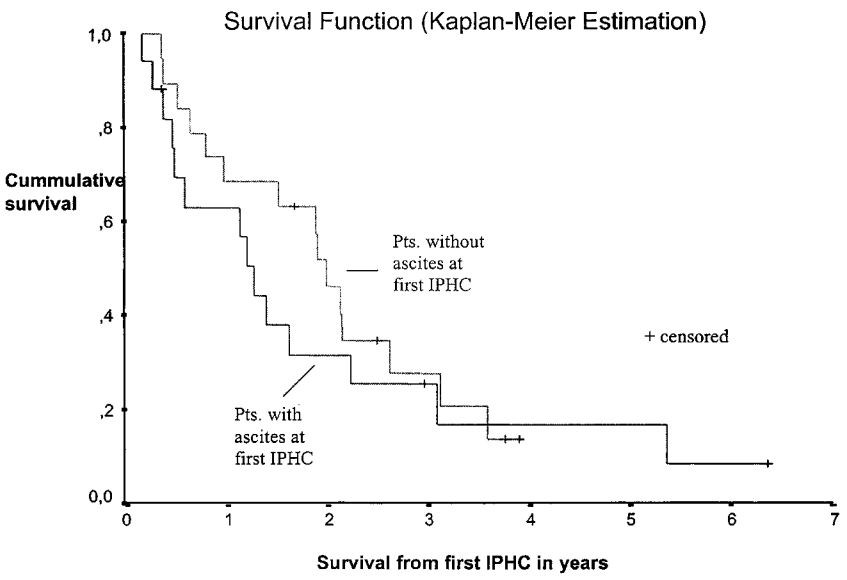

Fig. 1. Kaplan-Meier curve for survival estimation of patients with ascites compared to patients without ascites on commencement of intraperitoneal hyperthermic perfusion chemotherapy (7 patients censored)

Table 6. Tumor marker CA 125 response after 4–8 weeks after the first IPHC

CA-125	Response	Patients
Decrease	>50%	42%
Decrease	>25% <50%	14%
Increase	>25 <100%	17%
Increase	≥100%	8%
No change	+/−25%	19%

Table 7. Frequency of adverse effects of intraperitoneal hyperthermic perfusion chemotherapy as a percentage of total treatments (168 in total)

WHO grade	0	1	2	3	4
Gastrointestinal					
Nausea/Vomiting	30	29	27	14	—
Diarrhea	97	2	1	—	—
SGOT/SGPT	100	—	—	—	—
Blood					
Leucocytes	96	2	2	—	—
Platelets	99	—	—	—	1
Hemogobulin	92	5	3	—	—
Renal					
Creatinine	92	6	2	—	—
Fever					
Temperature >38.5°C	97	3	—	—	—

tients with advanced, peritoneal disseminated epithelial or stromal ovarian cancer. High response rates are obtained in patients with recurrent, chemotherapy-resistant/refractory, peritoneal disseminated ovarian cancer. Reversal of drug resistance is obviously possible in combination with heat, at temperatures above 42°C. The increase in overall survival is substantial and quality of life can be improved or sustained for a long period of time. Compared to the treatment options currently available, this treatment provides an option affording improvements in survival time, quality of life and toxicity levels. Under the stated conditions, adverse drug reactions are significantly less severe compared to systemic palliative chemotherapy or intraperitoneal chemotherapy without hyperthermia but with higher dosages of cytotoxics. Even patients with a poor performance status can be treated safely. The optimal dose and schedule has yet to be defined.

The tumor marker CA-125 plays an important role in the individual management of patients with ovarian cancer. It is an early indicator of treatment response and failure during therapy and follow-up. A reduction of the tumor marker of more than 25% within 4–8 weeks after the first IPHC cycle in 56% of patients with resistance to cytotoxic agents is promising. A doubling in CA-125, predicting progression, was observed only in three (8%) patients.

The trial was performed without a control group. But the patients in this study were at beginning of the IPHC at an advanced stage of disease with a long history of antineoplastic therapies and had not been offered any other options by oncologists or tumor centers because it was expected that they would not respond further to systemic chemotherapy. The patients gathered for this trial therefore only had palliative care options available to them. It could be expected that a comparable control group without IPHC would have had a very poor survival. Intraperitoneal irradiation with ^{32}P, intraperitoneal chemotherapy without hyperthermia or biologic agents (trastuzumab) would have been another experimental alternative. The results can be compared with corresponding historical groups.

Conclusions

From these results, it may be concluded that IPHC could be recommended as "palliative" therapy for the

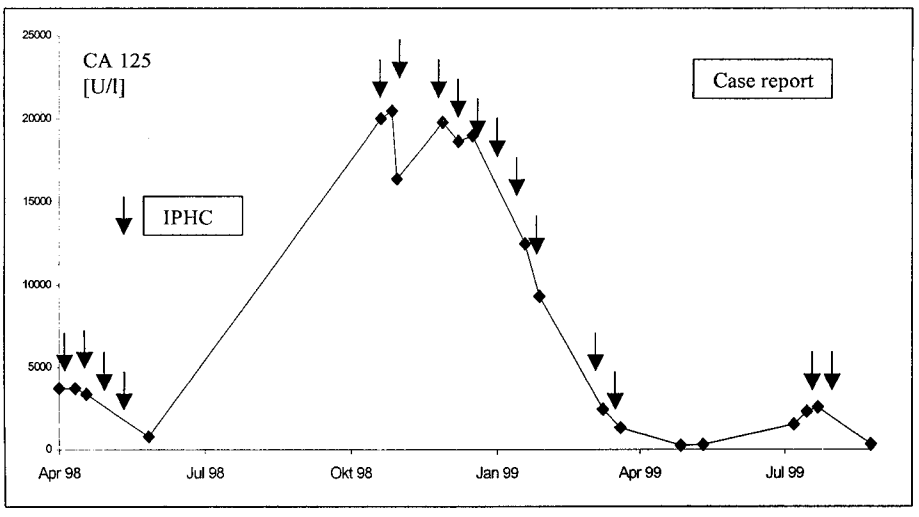

Fig. 2. Response of tumor marker CA 125 on repeated intraperitoneal hyperthermic perfusion chemotherapies of a patient with an initial hemorrhagic ascites (04/98) from chemotherapy-resistant peritoneal ovarian carcinomatosis (still alive in April 2001).

treatment of patients with chemotherapy-resistant/refractory peritoneal disseminated carcinomatosis or sarcomatosis resulting from ovarian cancer. IPHC could also be of advantage in a salvage therapy setting. IPHC may be considered for consolidation therapy of suboptimal stage III and IV patients with complete remissions or as maintenance therapy in cases of minor residual disease following induction therapy. Further phase II studies and randomized phase III studies are warranted.

Contraindications are extensive gastrointestinal adhesions, large tumor volumes, fistulae, subileus at an advanced stage, and peritonitis.

This technique could also be used for the treatment of patients with peritoneal disseminated stomach and colon cancer, malignant pleural effusion, and recurrent bladder cancer.

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