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Phase II Trial of Weekly Locoregional Hyperthermia and Cisplatin in Patients with a Previously Irradiated Recurrent Carcinoma of the Uterine Cervix

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BACKGROUND. The biologic rationale for combining cisplatin with locoregional hyperthermia (HT) relates to the potentiating effect of HT on cisplatin cytotoxicity.
METHODS. Patients with recurrent cervical carcinoma, who had a pelvic recurrence after radiotherapy, were treated with weekly cycles of locoregional HT (using the 70-megahertz, 4 antenna-phased array system for 1 hour and cisplatin, 50 mg/m² intravenously [i.v.], for a maximum of 12 cycles.)
RESULTS. Twenty-three patients were entered in this study. A total of 169 cycles were given. Responses were observed in 12 of 23 patients, a response rate of 52% (95% confidence interval, 31–73%). Salvage surgery became possible in 3 of 12 responding patients, whose tumors were previously considered unresectable. The median duration of response was 9.5⁺ months, the median overall survival was 8⁺ months, and the 1-year survival was 42%. No correlation was found between treatment outcome and clinical parameters such as age, weight, performance status, and histology. Thermal parameters such as T20, T50, and T90 were higher in responding patients, but were not significantly different from nonresponding patients. Overall toxicity was moderate. Subcutaneous fatty necrosis due to HT occurred in 10% of the cycles, whereas 2 patients developed skin burns. Squamous cell carcinoma antigen proved to be a valuable tool for the evaluation of response and detection of progression.
CONCLUSIONS. Weekly locoregional HT and cisplatin, 50 mg/m² i.v., for a maximum of 12 cycles was effective treatment in patients with a previously irradiated recurrent carcinoma of the uterine cervix. *Cancer* **1997**;79:935–43.
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KEYWORDS: cisplatin, hyperthermia-induced, cervical carcinoma, toxicity, squamous cell carcinoma antigen.

Recurrences of carcinoma of the uterine cervix develop in almost half of the patients treated for primary invasive cervical carcinoma. The majority of these recurrences occur in the pelvis without

distant metastases. In this situation, radiotherapeutic or surgical treatment is seldom an option, because most patients have already received radiotherapy and very few are suitable for exenterative surgery. In this situation, systemic chemotherapy is a remaining treatment option. Standard chemotherapy, still represented by cisplatin as monotherapy, results in an overall response rate of 20–30%.[1–3] In patients who have previously been treated with pelvic irradiation the response rate in the pelvis is lower than in the extrapelvic sites, with an upper limit in almost all studies of only 15%.[1,4–8] The median duration of response is short (4–6 months), with a median survival of only 7 months.[1,3–6,8,9]

A possible way of improving the cytotoxicity of cisplatin is by combination with hyperthermia (HT). Cytotoxicity of cisplatin in vitro and in vivo is potentiated by heat and increases almost linear with increasing temperature. Thermal enhancement is maximal when HT and cisplatin are given simultaneously.[10–15] Furthermore, there is substantial evidence that cisplatin resistance can be circumvented by giving HT concurrently.[11,16–18] The biologic rationale for using HT and cisplatin is therefore strong and formed the basis of this clinical study. Recently, the authors showed that weekly locoregional HT in combination with cisplatin, 50 mg/m^2/week for a maximum of 12 cycles, was feasible with an acceptable toxicity.[19] The definitive results and toxicity of this weekly combination treatment schedule in 23 patients with a recurrence of a cervical carcinoma in a previously irradiated area are described in this article.

MATERIALS AND METHODS
Patient Selection
Patients were eligible if they had a cytologically or histologically confirmed recurrent cervical carcinoma, for which neither surgery nor radiotherapy were considered to be a realistic treatment option. A lesion measurable in one or two dimensions, located within the area intended to be heated, was required. In addition, an Eastern Cooperative Oncology Group performance status[20] of ≤2, an adequate bone marrow (leukocyte count ≥ 3.5 × 10^3/μL and platelet count > 100 × 10^3/μL) and adequate renal function (glomerular filtration rate [GFR] ≥ 60 mL/min) as calculated by the Cockroft formula[21] was mandatory.

No previous chemotherapeutic treatment was allowed. Metastatic disease was not an exclusion criterium. Patients who had psychosis, central nervous system disease, or a cerebrovascular accident within the previous 6 months were excluded as were patients with cardiac disease (myocardial infarction within the previous 6 months, unstable angina pectoris, or congestive heart failure) or uncontrolled hypertension (di-

astolic pressure > 100 or systolic pressure > 180 mm Hg). Patients were also excluded in cases of an uncontrolled infection, or concomitant or previous second malignancy. Patients with extreme obesity and those with a pacemaker or metallic implants in the HT target area were excluded because of possible complications from HT. Patients in this study were treated between September 1992 and December 1995. Written informed consent was obtained from each patient after the treatment procedure was fully explained. The study was approved by the local Medical Ethical Committee.

Hyperthermia Treatment
Locoregional HT was administered with a 70-megahertz, 4 antenna-phased array system.[22] Hyperthermia was given at weekly intervals in combination with cisplatin. Heating started with a preheating phase with the goal of elevating the tumor temperature to 41 °C or higher. The effective heating period started when the maximum temperature in the tumor reached 41 °C and lasted 60 minutes. If after 30 minutes of heating the maximum temperature was still below 41 °C, this point was taken as the starting point of the effective heating period. The maximum temperature in the tumor tissue was not allowed to rise above 45 °C or to above 43 °C in normal tissue. If a patient developed third-degree burns, treatment was discontinued.

Thermometry
Thermometry was performed in all patients. Before each HT treatment thermometry catheters were placed in the bladder, rectum, and vagina. When possible, a catheter was positioned in the tumor. The catheters used were thin (1 mm) closed-end teflon catheters, Thermistor catheter, high flow 5-French, 40-cm long (Angiomed 0015-0040; Angiomed Nederland, Eemnes, The Netherlands); they were removed after each treatment. Just before the start of each treatment, multithermocouple probes (Ella CS; Hradec Králové, Czech Republic) were inserted in the catheters. Temperature sensors were located at fixed intervals of 0.5 or 1 cm and related to the position within the catheter, which was recorded by X-rays shortly before treatment. With the help of a computer program (Hyperthermia Treatment Control, Academic Medical Center, Amsterdam, The Netherlands) measured temperatures were collected in Hyperthermia Data Standard format according to Sapareto and Corry[23] and the specific temperature data were calculated with Hyperthermia Evaluation Software (HES— Academic Medical Center, Amsterdam, The Netherlands). In addition, E-field probes were positioned in the rectum and va-

gina for heat steering purposes according to the measured E-fields.

Thermal Parameters

All measurements of temperature at all intratumoral sites were utilized for analysis. For each HT treatment, time-averaged temperatures achieved in at least 20%, 50%, and 90% of all measured tumor temperature points were determined and expressed as T20, T50, and T90, respectively, in °C. In addition, the T50 above 41 °C was calculated and expressed in minutes; this reflected the average duration of a tumor temperature above 41 °C in at least 50% of the measured tumor temperature points.

Cisplatin Treatment

Patients were treated with cisplatin 50 mg/m² intravenously (i.v.) once a week in combination with HT. Cisplatin was given in 250 mL NaCl 3% in 90 minutes, ideally starting 30 minutes before the effective heating period began. In practice, cisplatin infusion was started 10 minutes before the start of heating. Prehydration consisted of 1 L NaCl 0.9% over 4 hours and posthydration of 2 L NaCl 0.9% (with 40 mMol KCl and 20 mMol MgSO₄) over 16 hours. If diuresis was <600 mL per 6 hours, patients received 100 mL of mannitol 20%. If this was ineffective, 5 mg furosemide was added. Platinum dose was adjusted to 50% in case of GFR < 60 mL/minute. Treatment was postponed in case of GFR < 45 mL/minute. If the leukocyte count was $<2 \times 10^3/\mu L$ and/or the platelet count was $<75 \times 10^3/\mu L$, treatment was postponed until recovery. When treatment had to be postponed for longer than 3 weeks the patient was removed from the study.

Supportive Treatment

Prophylactic antiemetic treatment was comprised of ondansetron 2 times a day, 8 mg orally, and was started 1 hour before cisplatin treatment. In case oral treatment was not possible, ondansetron was given i.v. If treatment with ondansetron alone failed, dexamethasone, 20 mg i.v., was added. In these patients, ondansetron and dexamethasone were given together in the next cycles, 1 hour before cisplatin. In October 1993, after inclusion of seven patients, this policy was changed to the combination of ondansetron and dexamethasone i.v. starting in the first cycle. In case of failure in these patients, metoclopramide suppositories, 3×20 mg, were added and dexamethasone orally (when needed) on the following schedule: Days 2–3, 2×3 mg and Days 4–5, 2×1.5 mg.

Evaluation of Treatment

Pretreatment evaluation included a complete medical history, physical and gynecologic examination, com-

puterized tomography (CT) scan of the abdomen and pelvis, chest X-ray, bone scan, electrocardiogram, audiogram, squamous cell carcinoma antigen (SCC-Ag), and a complete blood chemistry survey. All patients were considered evaluable for response regardless of the number of received cycles of HT and cisplatin. Response was evaluated every four cycles with CT scan and gynecologic examination. In case of progressive disease after four cycles or no response after eight cycles, therapy was stopped. The maximum number of cycles given was 12.

Tumor response and duration of response were defined according to the World Health Organization (WHO) criteria.[24] Complete response (CR) was defined as disappearance of all known disease for a minimum of 1 month. Partial response (PR) was defined as a 50% or greater decrease in measurable disease in the treatment field for a least 1 month. In addition, no appearance of new lesions or progression of any existing lesion was allowed. Progressive disease (PD) was defined as a 25% or greater increase in the size of measurable disease in the treatment field or the appearance of new lesions. The remaining patients had stable disease (SD). In the case of measurable disease with both CT scan and gynecologic examination, the best response of both was taken into account.

Response duration was measured from the start of treatment in case of PR or, in the case of CR, from the date the CR was first recorded.

Overall survival was measured from the start of treatment. The duration of survival was calculated from this date until the date of analysis (December 1. 1995).

SCC-Ag response was defined as follows: CR was defined as normalization (< 1.9 ng/mL), PR as a decrease of ≥50% and PD as an increase of ≥25%. The remaining patients had SD. SCC-Ag was measured in the serum with a Microparticulate Enzyme Immunoassay (Abbott Laboratories, Abbott Park, IL).

All patients were considered evaluable for toxicity (WHO grading system[24]). Toxicity concerning hearing, fatigue, hypomagnesemia, and weight loss was scored according to the Common Toxicity Criteria of the National Cancer Institute of Canada (NCIC). Toxicity was monitored weekly during treatment. Ototoxicity was monitored with audiometry at the end of treatment or earlier when clinically indicated.

Patients were seen regularly at 1, 2, 3, 5, 7, 9, and 11 months after treatment and every 3 months thereafter.

Statistical Analysis

Thermal parameters for responders and nonresponders were compared with the help of SPSS (SPSS Inc.,

TABLE 1
Patients and Tumor Characteristics (n = 23)

Original FIGO stage	
IA	1
IB	5
IIA	2
IIB	6
IIIB	9
Recurrence site	
Central pelvis	1
Central pelvis and pelvic wall	16
Other[a]	6
Histology	
Squamous cell carcinoma	18
Adenocarcinoma	3
Mixed	2
Previous radiotherapy	23
Previous surgery	11
Metastases outside pelvis	5
ECOG performance	
1	16
2	7

FIGO: International Federation of Gynecology and Obstetrics; ECOG: Eastern Cooperative Oncology Group.

[a] Left buttock, abdominal wall, vagina/perineum, lymph nodes in the psoas region (twice) and a parailiac lymph node (once).

Chicago, IL) statistical software using the two-tailed, unpaired Student's *t* test. Correlation of clinical parameters (such as age, performance status, weight, and histology) with response was analyzed with the Mann–Whitney nonparametric test and the chi-square test. The survival proportion was estimated using the Kaplan–Meier method.

RESULTS
Patient and Tumor Characteristics
The characteristics of the 23 patients treated are presented in Table 1. There were no additional patients who started therapy but did not complete it. The mean age was 45 years (range, 27–71 years). The median interval between the first diagnosis of the primary tumor and recurrence was 15 months (range, 3–189 months). Five patients had distant metastases: bone metastases (two patients), with the major recurrence site in the central pelvis and pelvic sidewall or a parailiac lymph node, distant lymph node metastases (two patients), with the major recurrence site both times in the central pelvis and pelvic sidewall, and a lymphangitis carcinomatosa on the skin (also located in the HT treatment area) (one patient) with the abdominal wall as the major recurrence site. In all five patients the main tumor burden was located in the area intended to be treated with HT and cisplatin.

Treatment Characteristics
Overall, 169 cycles of HT and cisplatin were given, with a median of 8 cycles (range, 1–12 cycles) per patient. The received dose intensity (total cumulative dose/total weeks of treatment) was 37.9 mg/m^2/week, which was 88% of the projected dose intensity of 42.8 mg/m^2/week. The projected dose intensity was 42.8 mg/m^2/week rather than 50 mg/m^2/week because of the necessary response evaluations after every 4th cycle, which caused a delay of 1 week each time. The median total dose given was 350 mg/m^2 (range, 50–600 mg/m^2). Dose reduction to 25 mg/m^2, due to a GFR $<$ 60 mL/minute, was necessary in 32 cycles (19%) in 11 of the 23 patients, whereas therapy had to be postponed 10 times (6%). The reasons for postponement of therapy were GFR $<$ 45 mL/minute (5 times), leukocyte count $< 2 \times 10^3/\mu L$ (2 times), urinary tract infection (one time), subcutaneous fatty necrosis (1 time), and flu (1 time).

The number of cycles was given as planned in 14 patients; 6 patients received the maximal number of 12 cycles, 7 patients had to stop because of PD, and 1 patient stopped because of no response after 8 cycles. In 9 patients toxicity was the main reason therapy was stopped prematurely: GFR $<$ 45 mL/min (2 patients), subjective toxicity such as fatigue and malaise (5 patients), hearing loss (1 patient), and skin burn (1 patient).

Thermometry and Thermal Parameters
Tumor thermometry could be performed in 21 of the 23 patients. It was not possible to measure temperature in the tumor of two patients. The mean number of tumor probes was 1 (range, 1–3 probes), with a median number of 9 measuring points (range, 2–21 measuring points). The mean time needed to reach a temperature $>$ 41 °C was 13 minutes (standard deviation [SD] 7.6). After reaching this temperature, treatment was continued for a mean of 60 minutes (SD 4.1) The thermal parameters are presented in Table 2, as the mean of the measured temperature in every patient. There were no differences in tumor thermometry data, when these were expressed either as the mean of all treatments (n = 156) or as the mean of the measured temperature in every patient (n = 21). Mean oral temperature at the end of treatment was 37.6 °C (SD 0.3), with an upper range to 38.2 °C.

Hyperthermia-Related Toxicity
Subcutaneous fatty necrosis occurred in 9 patients (10% of the cycles), with pain as its most important manifestation. However, none of these patients had to stop treatment. Two patients developed skin burns. One sustained a first-degree burn on the vulva, which

TABLE 2
Thermal Parameters Expressed as Mean Temperature in °C and T50 > 41 °C Expressed in Minutes with Standard Deviation

	Responders (n = 11)	Nonresponders (n = 10)	All (n = 21)	P value[a]
T20[b]	42.3 (0.8)	41.6 (1.0)	41.9 (0.9)	0.12
T50[b]	41.5 (0.6)	41.1 (0.9)	41.3 (0.8)	0.21
T90[b]	40.6 (0.6)	40.3 (0.8)	40.5 (0.7)	0.36
T50 > 41 °C[c]	43 (15)	33 (19)	38 (17)	0.22

[a] Comparison responders and nonresponders (Student's *t* test).

[b] T20, T50, and T90 are time-averaged temperatures achieved in 20%, 50%, and 90%, respectively, of all measured tumor sites.

[c] Time in minutes, in which 50% of the measured tumor sites were above 41 °C.

healed in 2 weeks, and the other sustained a third-degree burn on the buttock, which healed spontaneously in 2 months. No further treatment was given in this last patient.

Mild pain during HT was observed in 18% of the cycles. This pain was power-related, with a short duration (seconds-minutes) and reacted well to adjustments in heat steering. In none of these patients was the treatment stopped. Thermometry-catheter-related complications were scarce. In one patient the catheter dislocated into the abdominal wall and had to be removed surgically under local anesthesia.

Toxicity

All patients were evaluable for toxicity. Table 3 shows the overall toxicity. Grade 3 toxicity (mainly nausea/vomiting) occurred in 8 of 23 patients, but in only 12 of 169 cycles (7%). Two patients refused further therapy. In the remaining patients with Grade 3 nausea/vomiting, toxicity could be reduced to Grade 2 or less by changing the antiemetic policy as described earlier. This resulted in Grade 1 nausea/vomiting in two patients and Grade 2 toxicity in four patients.

After the change in the standard antiemetic prophylaxis as described earlier, Grade 3 toxicity occurred only in 7 of 131 cycles (5.3%). The two patients who stopped therapy were both treated before the change in antiemetic prophylaxis. Reversible hematologic toxicity (Grade 3) was observed in four patients without concurrent febrile neutropenia or bleeding complications. In five patients severe hypomagnesemia was observed; clinical signs or symptoms of hypomagnesemia were not encountered. The lowest mean value observed was a magnesium of 0.56 mMol/L (SD 0.19). Thirteen patients had mild (Grade 1) renal toxicity. Grade 2 renal toxicity (in one patient) completely resolved after a treatment delay. In two patients therapy was stopped due to a decrease in renal function (GFR < 45 mL/minute) that did not resolve in 3 weeks. In

the other patients GFR remained > 45 mL/minute. The overall GFR decreased to 66% of the calculated GFR at the beginning of therapy, with a range of 33–108%. During follow-up after therapy the GFR improved to a value of 77% of the starting value. The mean calculated GFR at the beginning of therapy was 91 mL/minute (SD 34).

Tinnitus (Grade 2), developed in six patients. However, in only one patient did symptomatic hearing loss occur after four cycles, which led to treatment discontinuation. In ten other patients asymptomatic high frequency hearing loss was recorded in the audiograms. Mild peripheral neurotoxicity, mainly paresthesia, was observed in six patients and Grade 2 toxicity in one patient. Significant weight loss occurred in 14 patients, with a mean weight loss of 4.8% (range, 0–11%). Infectious complications occurring outside periods of neutropenia were observed in five patients, lower urinary tract infection in two patients, pyelonephritis in two patients, and a superficial skin infection with *Staphylococcus aureus* in one patient. No alopecia was observed.

Response and Survival

All patients were evaluated for response, including the two patients who received only one and two cycles, respectively. The median follow-up was 8+ months (range, 2–39+ months). Response was observed in 12 of 23 patients, resulting in a response rate of 52% (95% confidence interval [CI], 31–73%); 2 pathologic CR (duration 20+ and 35+ months, respectively), 1 CR (duration 33+ months), and 9 PR with a median duration of 7+ months (range, 4–26+ months). Salvage surgery became possible in 3 of 12 responding patients (2 pathologic CR and 1 PR), whose tumors were previously considered unresectable. In two patients no tumor cells were found in the resection specimen and in the other patient, with a tumor decrease of 80%, a complete resection could be performed. The median

TABLE 3
Toxicity[a] of Weekly Locoregional Hyperthermia and Cisplatin Expressed as Maximum Toxicity Observed in Every Patient (n = 23)

	0	1	2	3	4[a]
Anemia	3	7	9	4	—
Leukocytopenia	3	10	6	4	—
Thrombocytopenia	17	2	3	1	—
Nausea/vomiting	—	3	12	8	—
Renal	9	13	1	—	—
Peripheral neurotoxicity	16	6	1	—	—
Hearing[b]	7	10	6	—	—
Fatigue[b]	2	15	6	—	—
Infection	18	3	2	—	—
Hypomagnesemia[b]	6	2	10	5	—
Weight loss[b]	9	12	2	—	—
Alopecia	23	—	—	—	—

[a] World Health Organization toxicity grades.
[b] Common Toxicity Criteria of the National Cancer Institute of Canada (NCIC-CTC) grades.

duration of response in all patients was 9.5[+] months (range, 4–35[+] months). Response was observed after a median number of 8 cycles (range, 2–12 cycles). In 8 of 12 responders there was an additional decrease in tumor greatest dimension during further treatment. In 2 of 12 patients the tumor greatest dimension did not decrease any further and in 2 of 12 patients therapy was stopped at the moment of the observed response.

The overall median survival was 8[+] months (range, 2–39[+] months). In the responding patients median survival was 12[+] months (range, 6[+]–39[+] months) with 10 of 12 patients still alive at last follow-up, and in the nonresponding patients the median survival was 6 months (range, 2–12 months) with no patient still alive at last follow-up. The overall 1-year survival was 42% (standard error of the mean 11%).

In three of five patients with distant metastases, a difference in response was observed between the pelvic HT treatment area and the area of distant metastasis. One patient had a PR in the HT treatment area with SD in the bone. Two other patients had SD in the HT treatment area, but showed clear progression in distant lymph nodes. In two of five patients with distant metastases there was no difference between both sites. In one patient there was SD in both the HT treatment area and the bone. In the other patient with lymphangitis carcinomatosa of the skin both the deeply located tumor and the lymphangitis responded to therapy; however, the lymphangitis of the skin was also located in the HT treatment area. Therefore, in 2 of the 5 patients with distant metastases, a PR was observed with a duration of 4 and 8 months, respectively. The median survival was 9[+] months

(range, 2–13 months), with 1 of 5 patients alive at last follow-up.

Correlation of Treatment Factors with Response

Clinical parameters such as age, performance status, weight, and histology were not different in responders and nonresponders.

Although the thermal parameters such as T20, T50, T90, and T50 > 41 °C were higher in responders than nonresponders (Table 2), this difference did not reach statistical significance. There were also no significant differences between responders and nonresponders when these thermal parameters were calculated for Cycles 1–4 or for the best treatment given in every patient. Induction time to reach 41 °C in the tumor and steady state length at 41 °C were also not significantly different between responders and nonresponders.

Response Assessment Evaluation

Tumor response was assessed with the help of CT and/or gynecologic examination. In four patients tumor evaluation was only possible by CT scan and in two patients only by gynecologic examination.

In 17 of the 23 patients the results of response assessment by either CT scan or gynecologic examination could be compared. Gynecologic and CT scan assessment were independently performed by a gynecologist and radiologist, respectively. In 14 of 17 patients response assessment by both modalities was identical, resulting in an observed agreement of 82% (Kappa 0.62). In 2 of the 3 patients with a discongruent observation, a nonconfirmed 50% regression by CT scan was found with a clear confirmed regression at gynecologic examination.

Squamous Cell Carcinoma Antigen

Twenty patients had either a squamous cell carcinoma (n = 18) or a mixed histology (n = 2). In 11 of these 20 patients (55%), the SCC-Ag level (normal level < 1.9 ng/mL) was increased before the start of therapy. The mean value was 41.8 ng/mL (range, 11–123 ng/mL). In 7 of 11 patients, SCC-Ag decreased > 50%, resulting in a response rate of 64%. Only one of these patients did not have a clinical response. In 5 of 11 patients (45%) there was even a complete normalization. The positive predictive value for detecting a clinical response in the case of a SCC-Ag response was 86% and the negative predictive value in the case of no SCC-Ag response was 100%. The sensitivity of a SCC-Ag response for detecting a clinical response was 100% and the specificity was 75%. Four of the six correctly identified SCC-Ag responders had developed clinical

PD at last follow-up; in all four patients SCC-Ag increased significantly.

DISCUSSION

In this article the authors present the results of weekly treatment with locoregional HT and cisplatin, 50 mg/m^2/week, in 23 patients with a recurrent cervical carcinoma who had a pelvic recurrence after radiotherapy. Response was observed in 12 of 23 patients, resulting in a response rate of 52% (95% CI, 31–73%). No relation was found between treatment outcome and clinical parameters such as age, weight, performance status, and histology. Salvage surgery became possible in 3 of 12 responding patients (2 pathologic CR and 1 PR), whose tumors were previously considered unresectable. In two patients no tumor cells were found in the resection specimen.

In patients with a pelvic recurrence after radiotherapy the response rate after treatment with cisplatin alone is low, with an upper limit of only 15% in most studies. These responses are short, with an overall median survival of only 7 months.[1,4–6,8,9] In a study by Lele et al.[4] with weekly cisplatin in a dose of 1 mg/kg for 6 cycles, but without HT, the response rate in patients with previously irradiated pelvic recurrences was <10%. In contrast, Daly et al.[3] claimed a 50% response rate (7 of 14) in patients with previously irradiated pelvic recurrences. They gave 4 weekly cycles of cisplatin, 50 mg/m^2, followed in responders by 4 more cycles every 2 weeks. However, in this study only 58% of the recurrences were histologically proven and in only 70% of the cases was response confirmed by CT scan or ultrasound. The overall median response duration was 6 months, the median survival was 8 months, and the 1-year survival was 28%.

The observed median duration of response of 9.5$^+$ months (range, 4–35$^+$ months), the median overall survival of 8$^+$ months (range, 2–39 months), and the 1-year survival of 42% with the combination of weekly locoregional HT and cisplatin appears promising in comparison to these historic data. The biologic rationale for the combination of HT and cisplatin is strong and the clinical results are compatible with the observed magnitude of thermal enhancement of cytotoxicity in vitro and in vivo.[11,12,15] Another observation, which was also in line with the thermal enhancement of cisplatin cytotoxicity, was the observed difference in response in three of five patients with tumor in both the HT treatment area and in a distant metastatic site.

A report by Planting et al.[25] showed that the maximal tolerable dose of cisplatin without HT, given once weekly for 6 cycles, was 85 mg/m^2/week; 50 mg/m^2/week did not cause serious toxicity. A few clinical studies in different tumors showed that it was feasible to use cisplatin and HT in a dose of 50 mg/m^2/week for a period of 6 weeks.[26–30] Because the authors believed that 6 weekly cycles might not be sufficient for induction of worthwhile responses, they chose to treat patients for a maximum of 12 cycles with a cisplatin dose of 50 mg/m^2/week. The dose intensity of this schedule is more than adequate in comparison with the standard dose intensity used in recurrent cervical carcinoma of 50–75 mg/m^2 every 3 weeks.[1,2,6] This combination of weekly HT and cisplatin proved to be feasible with acceptable toxicity.[19,31]

The received dose intensity was 37.9 mg/m^2/week, which represented 88% of the projected dose intensity. The median total dose given was 350 mg/m^2. Dose reductions were necessary in 19% of the cycles and postponement of therapy was necessary in 6%. In 9 of 23 patients therapy was stopped prematurely because of subjective or objective toxicity. Overall toxicity was moderate. The most common toxicity observed was Grade 3 nausea and vomiting in 8 of 23 patients, but only in 7% of the cycles. The frequency and severity of nausea and vomiting was equal to that observed in other weekly cisplatin-containing regimens without HT.[3,25,32,33] Other observed Grade 3 toxicity (hematologic and hypomagnesemia) did not result in complications or clinical sequela.

At the end of therapy an overall GFR decrease to 66% of the initial value was observed. When cisplatin was given without HT for only 6 cycles at a dose of 50 mg/m^2, a GFR decrease to 80% of the initial value was observed.[25] Other studies with weekly cisplatin at different dose levels also resulted in nephrotoxicity, but comparison with the current results is inappropriate because of differences in dose intensity, total dose, and renal function at the start of therapy.[4,6,32]

Ototoxicity (mostly asymptomatic hearing loss) appeared to occur more frequently than previously described with cisplatin alone,[33,34] although some of these findings may be explained by the meticulous examination including standard audiometry. The observed neurotoxicity was in line with other observations.[3,33] Other relevant toxicity were a mean weight loss of almost 5% and–infrequent–infectious problems.

HT-related toxicity, such as reversible pain and subcutaneous fatty necrosis, was observed, but did not result in treatment discontinuation. Skin burns occurred in two patients, but healed spontaneously. The only thermometry-catheter-related complication was a catheter dislocation.

The target temperature (T > 41 °C) was not able to be reached in all tumor points. However, T20, T50, and T90 were adequate in comparison to other reports.[35,36] Theoretically, these temperatures should be

high enough to increase the cytotoxicity of cisplatin, because this is a linear process starting at 37 °C.[10,11] Although in general temperatures, expressed as T20, T50, and T90, were higher in responding patients than in nonresponding patients, this difference was not statistically significant. This may be caused by the relatively low number of patients with the implication of limited statistical power, because Issels et al.[35] were able to predict response on the basis of thermal parameters in a study of 65 patients.

Systemic temperature was most often below 38 °C. This might be the reason that nephrotoxicity was not enhanced to those levels observed in whole body hyperthermia studies in animals[37] and in humans.[38] However, one should be very cautious in extrapolating the results to other HT equipment, because greater systemic temperature elevation, as observed with the equipment used in the current study, might lead to an increase in renal side effects.

A comparison considering response evaluation was made between gynecologic examination and CT. The observed agreement of 82% was high. Response evaluation of pelvic recurrences of cervical carcinoma is difficult, with gynecologic examination in combination with CT as probably the most reliable method in cases in which endosonography is not available.[39]

The SCC-Ag proved valuable for the evaluation of response and for detection of progression after a period of response. The sensitivity of a SCC-Ag response for detecting a clinical response was 100% and the specificity was 75%. In all patients who showed clinical progression after a clinical and serologic response, SCC-Ag again increased significantly. Others have also reported that SCC-Ag levels reflected response to therapy in patients undergoing palliative chemotherapy for a recurrence.[40] The authors' recommendation for response evaluation in patients with pelvic recurrences is to perform a gynecologic examination, CT, and measurement of SCC-Ag in case baseline SCC-Ag is increased, because they believe that by combining these results one can best determine if there is a response or not.

In conclusion, weekly HT and cisplatin, 50 mg/m²/i.v., in patients with a previously irradiated recurrent carcinoma of the uterine cervix is an effective treatment. The fact that 25% of the responding patients were able to undergo salvage surgery is also encouraging. Overall toxicity was moderate.

Although the response rate of 52% is high, unequivocal evidence concerning improvement in survival and/or quality of life is needed before this new combination treatment can be implemented as a standard option. Therefore, a prospective randomized trial comparing weekly HT and cisplatin with cisplatin alone will be initiated in the Netherlands in cooperation with several European institutions. Because the most benefit (with a potential for salvage surgery) can be expected in patients with a local recurrence only without distant metastases, the trial will be limited to those patients.

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