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Prophylactic hyperthermic intraperitoneal chemotherapy in gastric cancer management: short- and long-term outcomes of a prospective randomized study

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ABSTRACT

Introduction. Assessment of toxicity and long-term results of hyperthermic intraperitoneal chemotherapy (HIPEC) treatment administered to patients with resectable serosa-invasive gastric cancers.

Material and methods. The study was carried out in 2008–2016 and is based on the results of the treatment of 154 gastric cancer patients (stage IIB–IIIC, III–IV Borrmann type) who were randomly assigned to two groups. 76 patients underwent HIPEC combined with radical gastrectomy (HIPEC group) and 78 patients underwent radical gastrectomy without HIPEC (control group). HIPEC was administered after alimentary tract reconstruction and wound closure and comprised 5–6 L of Ringer's solution (cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2) infused at an inflow temperature of 42°C for 1 hour.

Results. Although the total number of complications was higher in the HIPEC group than in the control group the difference was statistically insignificant — 20 (26.3%) and 12 (15.3%), respectively (p = 0.141). Surgery-related complications in the HIPEC and control groups were observed in 9 and 5 cases, respectively (p = 0.372). Non-surgical complications were recorded in 11 and 7 cases, respectively (p = 0.435). Overall, the proposed HIPEC regimen administered in combination with radical surgery demonstrated satisfactory patient tolerability. The frequency of grade III toxic reactions according to CTCAE *version* 5.0 was 9.2%, no grade IV–V toxicities were registered at that. These satisfactory short-term results were followed up with fairly good long-term treatment outcomes. There was an increase in 5-year progression-free survival (42.1 ± 6.3% *vs.* 16.3 ± 5.5%, p < 0.001) and in dissemination-free survival (45.2 ± 6.3% *vs.* 19.4 ± 5.9%, p = 0.001) in the HIPEC group *vs.* the control group with a trend toward improving cancer-specific survival (CSS) in the HIPEC-treated patients [45.1.0 ± 6.4% *vs.* 27.0 ± 6.7% (p = 0.050)].

Conclusions. While substantially improving long-term GC therapeutic effect, the proposed HIPEC regimen using cisplatin 50 mg/m^2 in combination with doxorubicin 50 mg/m^2 made it possible to minimize complications (frequency of 26.3%) and toxic reactions [the frequency of grade III toxic reactions was 9.2% (CTCAE, *version* 5.0)].

Key words: serosa-invasive gastric cancer, hyperthermic intraperitoneal chemotherapy, toxicity, randomized trial

Introduction

The present report focuses on analyzing and systemizing short- and longer-term outcomes of managing radical surgery/hyperthermic intraperitoneal chemotherapy (HIPEC) treated patients in the context of observed post-HIPEC toxicity in patients. Being a follow-up to our previous publications [1, 2] that dealt with long-term

preventive efficacy assessment of HIPEC with regard to the peritoneal recurrence of gastric carcinoma in patients, this report is likewise based on the outcomes of our randomized study undertaken at the National Cancer Center of Belarus in 2008–2016. The present report incorporates the study's underlying assumptions, principles and methodology and includes its main statistical data and descriptive information for the sake of ensuring coherence in the presentation of research results.

The trial was approved by the Ethics Committee of the N.N. Alexandrov National Center, and a written informed consent was obtained from all the patients.

Material and methods

Patients

As we reported previously [2], the study involved patients with histologically confirmed gastric cancer, aged 18–70, T4a-bN0-3M0, stage IIB–IIIC, with preoperative ECOG status of 0–I, without esophagus involvement, who underwent a potentially curative operation (i.e. R0 resection). Resectable serosa-invasive gastric cancer patients were included in the study only after intraoperatively obtaining morphological confirmation of serosal invasion (pT4) by employing a frozen section procedure. Borrmann type III–IV was used as an inclusion criterion. Resectability was established according to the results of a pre-operative CT and ultrasonographic examination.

Surgical treatment consisted of total or partial (distal subtotal resection) gastrectomy with free margins (R0 resection) and D2 lymph node dissection, in case of necessity supplemented by liver, distal pancreatic or transverse colon resections.

HIPEC regimen

HIPEC was performed after gastrectomy/alimentary tract reconstruction and wound closure. One inflow catheter (30F) was positioned beneath the left hemidiaphragm. Three outflow catheters (32F) were placed in both the true and false pelvises in the subhepatic area. Temperature probes were placed on the inflow and outflow catheter tips. HIPEC was administered for one hour with an automatic HIPEC device. Perfusate used was Ringer's solution (5–6 L) mixed with cisplatin 50 mg/m^2 + doxorubicin 5 0 mg/m^2 warmed to an inflow temperature of 42°C. Since the study was launched in 2008, i.e. prior to accepting perioperative chemotherapy as a standard requirement in GC management, none of the patients in the study was administered perioperative chemotherapy.

The severity of HIPEC-related side effects was measured using the CTCAE grading scale, v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_ quick_reference_5x7.pdf).

As was previously reported [2], progression-free survival (PFS) was the primary endpoint of the study. PFS was measured from the date of random assignment to the date of gastric cancer progression. Secondary endpoints included dissemination-free survival (DFS), measured from the date of random assignment to the date of gastric cancer progression with metachronous peritoneal metastases, cancer-specific survival (CSS), measured from the date of random assignment to the date of death from the same cancer, and overall survival (OS), measured from the date of random assignment to the date of death from any cause. All same cancer recurrences (metachronous peritoneal metastases, distant metastases) and deaths from the same cancer were accounted for as events.

Statistical analysis

Descriptive analysis variables were expressed as mean ± standard deviation (SD) or counts and percentages [n (%)], as appropriate. Also used for groups' comparison were t-test, Chi-square test, and Fisher's exact test, if assumptions of Chi-square test were violated. The survival rate was assessed applying the Kaplan-Meier estimator. Multivariate Cox model was used to determine PFS risk factors. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using an exponential transformation of the respective parameters of the models.

Statistical analysis of the data was performed using the R version 3.1.1 statistical software (GPL license) [3].

Results

Patient characteristics

As we mentioned previously [2], between 2008 and 2016 a total of 478 patients gave their consent to participate in the trial. However, as the trial progressed, 27 patients withdrew their consent to participate, 281 patients were excluded as not intraoperatively confirmed to have serosal invasion (pT2N0-3M0; pT3N0-3M0), and 16 patients were excluded due to the presence of co-morbidities that led to the reduction of the volume of lymph node dissection to D1. As a result, the trial included 154 patients with gastric cancer [stage IIB–IIIC (T4a-bN0-3M0), III–IV Borrmann type], without esophagus involvement, who underwent a potentially curative operation (i.e. R0 resection), and who were randomized after intraoperative

Table 1. Patient characteristics

Variable	HIPEC group, n = 68 (%)	Control group, n = 55 (%)	p
Gender (male/female)	44 (64.7)//24 (35.3)	34 (61.8)//21 (38.2)	0.74
Age [yrs], mean ± SD	56 ± 8	56 ± 9	0.75
pT			0.46
pT4a	55 (80.9)	48 (87.3)	
pT4b	13 (19.1)	7 (12.7)	
pN			0.76
pN0	23 (33.8)	14 (25.5)	
pN1	8 (11.8)	6 (10.9)	
pN2	15 (22.1)	14 (25.5)	
pN3	22 (32.4)	21 (38.2)	
G			0.14
GI	6 (8.8)	4 (7.3)	
GII	17 (25.0)	9 (16.4)	
GIII	39 (57.4)	29 (52.7)	
GIV	6 (8.8)	13 (23.6)	

SD — standard deviation

Table 2. Postoperative morbidity (surgical complications)

Type of complications	n (%)	CTCAE v 5.0 grade
HIPEC group		
Postoperative pancreatitis	4 (44.4%)	II
Pancreatic fistula	1 (11.1%)	II
Volvulus of ileal loops, serosal peritonitis	1 (11.1%)	IV
Mesothrombosis	1 (11.1%)	V
Esophagojejunal anastomotic leak	2 (22.3%)	V
Total:	9 (100%)	
Control group		
Wound infection	2 (40.0%)	II
Postoperative pancreatitis	2 (40.0%)	II
Left liver lobe necrosis, paralytic intestinal obstruction	1 (20%)	IV
Total:	5 (100%)	

HIPEC — hyperthermic intraperitoneal chemotherapy

Table 3. Postoperative morbidity (non-surgical complications)

Type of complications	n (%)	CTCAE v 5.0 grade
HIPEC group		
Enterocolitis	1 (9.1%)	I
Fever of unclear genesis	2 (18.1%)	I
Pneumonia	5 (45.5%)	II
Pleural effusion	1 (9.1%)	II
Thrombophlebitis of subcutaneous veins	1 (9.1%)	II
Acute kidney failure	1 (9.1%)	II
Total:	11 (100%)	
Control group		
Pneumonia	4 (57.1%)	II
Myocardial infarction	1 (14.3%)	II
Acute ischemic stroke	1 (14.3%)	V
Acute gastroenteritis of allergic origin	1 (14.3%)	II
Total:	7 (100%)	

HIPEC — hyperthermic intraperitoneal chemotherapy

morphological confirmation of serosal invasion (pT4) based on frozen section procedure. The evaluation of toxicities and surgical complications was based on the results of treating the aforesaid 154 patients including 76 patients in the HIPEC group (male/female — 50/26) and 78 patients in the control group (male/female — 45/33). The assessment of long-term treatment results included 123 patients whose data were available for analysis. Excluded from this analysis as not meeting the study inclusion criteria were 8 patients from the HIPEC group (R1 resection — 2 patients, unconfirmed gastric cancer — 1 patient, Borrmann type I–II — 5 patients) and 23 patients from the control group (R1 resection — 2 patients, unconfirmed gastric cancer — 1 patient, Borrmann type I–II — 14 patients, refused to participate in the study — 3 patients, early withdrawal, no data available — 3 patients). The two groups were well balanced (Tab. 1).

Complications

Complications were observed in 13 patients in the HIPEC group and in 11 patients in the control group with 2 or more complications diagnosed in 5 patients in the HIPEC group and in 1 patient in the control group. Although the total number of complications in the HIPEC group was higher than in the control group it was statistically insignificant — 20 (26.3%) and 12 (15.3%), respectively (p = 0.141). Surgery-related complica-tions in the HIPEC and control groups were observed in 9 and 5 cases, respectively (p = 0.372) (Tab. 2), non-surgical complications — in 11 and 7 cases, respectively (p = 0.435) (Tab. 3).

Hematological toxicity was the most frequently registered side-effect reaction. However, no grade IV–V toxic reactions were observed, while grade III toxicities were basically of hematological origin and did not exceed

**Table 4. Toxicity profile of HIPEC-treated patients (CTCAE, v 5.0)**

Event	Degree of toxicity, n, %				
	I	II	III	IV	V
Gastrointestinal toxicity					
Nausea	18 (23.7%)	4 (5.3%)	–	–	–
Vomiting	4 (5.3%)	3 (3.9%)	–	–	–
Diarrhea	4 (5.3%)	2 (2.6%)	–	–	–
Hematological toxicity					
Anemia	20 (26.3%)	9 (11.8%)	1 (1.3%)	–	–
Lymphocyte count decreased	35 (46.1%)	19 (25%)	6 (7.9%)	–	–
Neutrophil count decreased	1 (1.3%)	–	–	–	–
Thrombocytopenia	–	–	–	–	–
Metabolic toxicity					
Aspartate aminotransferase	31 (40.8%)	3 (3.9%)	–	–	–
Alanine aminotransferase	24 (31.6%)	4 (5.3%)	–	–	–
Blood bilirubin increased	2 (2.6%)	3 (3.9%)	–	–	–
Creatinine increased	2 (2.6%)	3 (3.9%)	–	–	–
Constitutional symptoms	2 (2.6%)	2 (2.6%)	–	–	–

9.2% (7 patients). That puts our study at an advantage compared with earlier reported trials [7–10] (Tab. 4).

Another positive outcome of the proposed HIPEC regimen was survival rate improvements compared with surgery-only GC treatment. There was a statistically significant increase in 5-year progression-free (42.1 ± 6.3% *vs.* 16.3 ± 5.5%, p < 0.001) and dissemination-free (45.2 ± 6.3% *vs.* 19.4 ± 5.9%, p = 0.001) survivals in the HIPEC group with a trend toward improving cancer-specific survival (CSS) in the HIPEC-treated patients [45.1.0 ± 6.4% *vs.* 27.0 ± 6.7% (p = 0.050)] (Fig. 1–3).

The effect of the proposed combined HIPEC/surgery treatment on prognosticating GC progression risks was measured by means of a regression analysis based on the Cox proportional hazards model. Covariates used in the model included HIPEC proper, the state of regional lymph node (pN0, pN1-2, pN3), and performed surgical procedure. The model did not include universally known factors of adverse prognostication used as inclusion criteria in the present study (macroscopic growth form – stage III–IV in the Bormann classification, serosal invasion by tumor or tumor invasion of adjacent structures – pT4a–b, and D2 lymph node dissection) (Tab. 5).

As we reported earlier [2] our multivariate Cox model analysis showed an increased risk of disease progression in (a) cases of regional lymph node metastases; (b) cases requiring gastrectomy or combined gastrectomy; and (c) the control group. The analysis manifestly demonstrated a high risk of GC progression in the absence of HIPEC treatment and highlighted
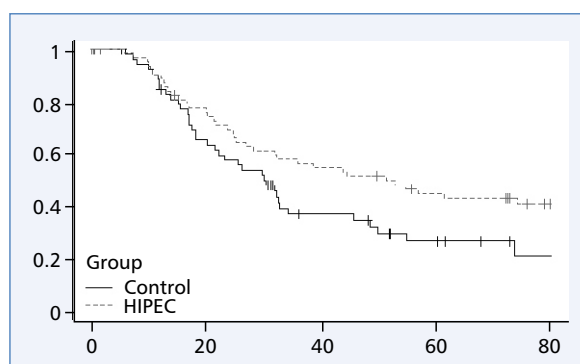
Figure 1. Cancer-specific survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy
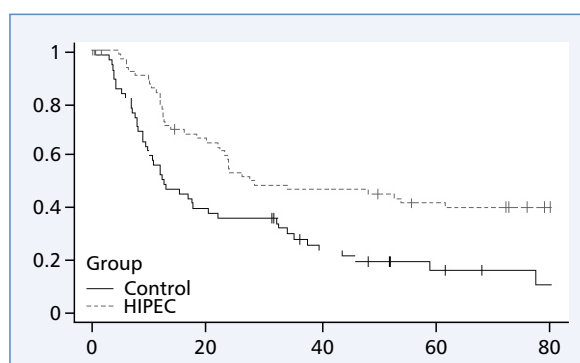
Figure 2. Progression-free survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy
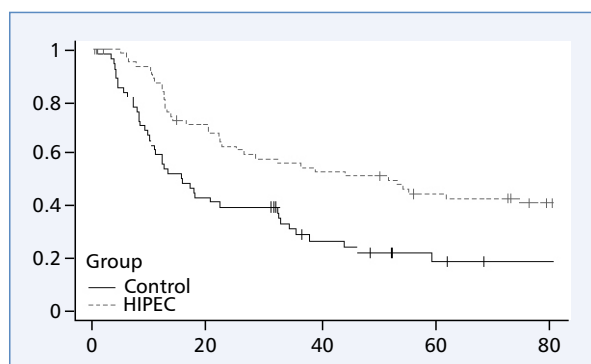
Figure 3. Dissemination-free survival in the HIPEC and control groups; HIPEC — hyperthermic intraperitoneal chemotherapy

Table 5. Factors associated with gastric cancer progression (Cox model)

Variables	β	HR (95% CI)	p
pN1–2 *vs.* pN0	0.88	2.4 (1.3–4.6)	0.008
pN3 *vs.* pN0	1.51	4.5 (2.4–8.6)	< 0.001
Gastrectomy + combined gastrectomy *vs.* subtotal gastric resection	0.63	1.9 (1.1–3.1)	0.013
Surgery *vs.* surgery + HIPEC	0.7	2.0 (1.3–3.0)	0.003

HR — hazard ratio; CI — confidence interval; HIPEC — hyperthermic intraperitoneal chemotherapy

the importance of this adjuvant treatment mode in the management of radically operated GC patients.

Discussion

The data presented above are consistent with the findings of some authors [4–6], who also observed no difference in the number of postoperative complications between the HIPEC/surgery group of patients and the surgery-only group of patients. For example, Kim and Bae (2001) [4] reported that the number of postoperative complications in the patients of the HIPEC and control groups was 36.5% and 33.3%, respectively. In our study these figures were 25.6% and 15.4%, respectively. Also, compared with similar published studies [7–10], a noteworthy outcome of the proposed HIPEC regimen was the absence of grade IV–V toxic reactions.

Chemo-tolerability in the overall evaluation of the efficacy of any chemotherapy regimen is a no less important factor ensuring adequate quality of life than improvements in long-term GC treatment outcomes [11].

Since the first trials of HIPEC prophylactic treatment of peritoneal recurrence after GC surgery were initiated in the late 1980s — the early 1990s [12–15],

researchers have been faced with a dual task of assessing and improving HIPEC prophylactic efficacy, and simultaneously, of striving to maintain toxicities at a tolerable level. Both of these tasks have been tackled with a varying degree of success by experimenting with the choice, dosage and delivery of chemotherapy drugs.

According to some researchers, most of the cases of HIPEC-related nephro- and hepatotoxicity were caused by cisplatin [8, 16, 17]. For example, Farma et al. (2005) [8] observed hematological toxicity in 27.8% of patients and impaired kidney function in 16.7% of patients at a cisplatin dosage of 150–300 mg/m^2. Kusamura et al. (2006) [17] showed that the administration of cisplatin at a dose of ≥ 240 mg/m^2 was associated with a high risk of grade III–IV complications according to the WHO criteria. Juan et al. (2018) [10] reported that the platinum-based HIPEC regimen was fraught with a heightened risk of kidney function impairment — RR 3.04 (95% CJ 1.71–5.39), p < 0.001. According to some reports, the use of cisplatin in combination with mitomycin C caused hematological toxicity in 2.5–5.3% of cases [7, 9]. In particular, it was reported that the use of only cisplatin at 1 mg/kg or of cisplatin at 0.5 mg/kg in combination with mitomycin C at 0.7 mg/kg resulted in grade III–IV hematological toxicity in 4.6% of cases and nephrotoxicity — in 1.3% of cases [7]. When using a combination of cisplatin at 25 mg/m^2/L + mitomycin C at 3.3. mg/m^2/L or cisplatin at 43 mg/L + doxorubicin 15.25 mg/L, Kusamura et al. (2007) [9] observed grade III–IV hematological toxicity in 5.3% of cases and nephrotoxicity in 5.7% of cases.

Proceeding from this information, we decreased the dosage of cisplatin to 50 mg/m^2. We also took note of the research data emphasizing the need for a combined application of cisplatin with other chemotherapy drugs to ensure long-term GC treatment improvements compared with treatment outcomes based on cisplatin-only intraperitoneal chemotherapy [5, 18–20]. Analyzing three cisplatin-only HIPEC efficacy trials [18–20], Feingold et al. noted in their meta-analysis (2017) [5] that the RR of the 5-year mortality was 0.79 (95% CI 0.60–1.04; p = 0.09) with 2 of these studies (including one conducted in Europe [18]) failing to produce any statistically significant reduction in 5-year mortality.

Taking into account the data on the ways of improving HIPEC efficacy available prior to the start of our trial we opted in favor of combining cisplatin with doxorubicin as one of the most effective cytostatic drugs in GC treatment, yet proven safe in intraperitoneal application as was reported by Sugarbaker et al. (2005) [21]. Our choice of cisplatin/doxorubicin combination was also prompted by their multidirectional cancer-killing potential thereby producing a synergic cancericidal effect. Proceeding from the published research data about the relatively low level of doxorubicin-related toxicities [21],

we raised its dosage to 50 mg/m^2 to add to the anti-cancer potential of cisplatin whose dosage was lowered in our study on account of its comparatively high toxicity.

Despite the increase in the doxorubicin dosage to 50 mg/m^2 exceeding that in similar studies, for example, a doxorubicin dose escalation study by Sugarbaker [22], no clinical manifestation of peritoneal adhesions was observed during the follow-up monitoring period. Nor were there any pronounced adhesion processes or intestinal fibrosis registered during second-look laparoscopy. This outcome could possibly be attributed to a larger than usual volume of perfusate used in our study (5–6 L).

Viewed overall, the above discussed dosage combination of cisplatin and doxorubicin proved to be effective both in terms of ensuring adequate patient tolerability and achieving good prophylactic efficacy outcomes of the proposed HIPEC regimen.

A serious downside of the present study was the absence of systemic chemotherapy in the management of radically operated GC patients that is accounted for by the fact that at the time of launching the trial in 2008 there was no universal standard of applying perioperative chemotherapy in the GC treatment.

As if to highlight this drawback, the results of our study amply showed a need for supplementing adjuvant HIPEC with systemic chemotherapy in view of an increased risk of distant metastases [$\beta = 0.2$; RR 7.5 (95% CI 2.2–25) p < 0.001] against the backdrop of a reduced risk of developing metachronous peritoneal metastases [$\beta = -1.60$; RR 0.2 (95% CI 0.11–0.37), p < 0.001] [2]. In our subsequent study combining HIPEC (cisplatin 50 mg/m^2 and doxorubicin 50 mg/m^2) and 8 cycles of systemic chemotherapy (capecitabine + oxaliplatin or tegafur + oxaliplatin) we managed to improve long-term treatment outcomes by reducing the frequency and cumulative incidence of both metachronous peritoneal and distant metastases while achieving an adequate patient tolerance to the combined application of HIPEC and adjuvant systemic chemotherapy [23, 24].

Furthermore, the low toxicity levels of the proposed HIPEC regimen (cisplatin 50 mg/m^2 and doxorubicin 50 mg/m^2) demonstrated in our study give grounds to hypothesize the possibility of combining this HIPEC regimen not only with postoperative chemotherapy but also with chemotherapy administered perioperatively. Such a treatment strategy seems to be especially promising for managing patients exposed to a high risk of developing peritoneal dissemination, for example, patients with grade pT4b cancer. Obviously, further studies are needed to explore this possibility.

Conclusions

While substantially improving long-term GC therapeutic effect, the proposed HIPEC regimen using cisplatin 50 mg/m^2 in combination with doxorubicin 50 mg/m^2 made it possible to achieve satisfactory patient tolerability results both in terms of complications (frequency of 26.3%) and toxicity (the frequency of grade I–III toxic reactions was 9.2% according to CTCAE, *version* 5.0).

However, it is obvious that despite a growing number of positive reports on using adjuvant HIPEC for the treatment of gastric cancer associated with a high risk of implantation metastasis it is in many cases a 'hit-or-miss' process which means that we are still a long way off from developing definitive evidence-based recommendations and guidelines on the most effective HIPEC procedural techniques and combinations of chemotherapy agents to offer to clinicians, and likewise, from proposing optimal systemic chemotherapy regimens to be used in combination with HIPEC, a goal that can only be attained by conducting further studies in this field of research.

Conflict of interest

The authors have declared no conflicts of interest.

Ethics approval

The trial was approved by the Ethics Committee of the N.N. Alexandrov National Cancer Center.

Consent to participate

Written informed consent was obtained from all patients before trial entry.

Consent to publish

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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