Review Article on Gastric Cancer

Intraperitoneal chemotherapy in the treatment of gastric cancer peritoneal metastases: an overview of common therapeutic regimens

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Abstract: Peritoneal metastasis (PM) have an incidence of 10–20% in patients with gastric cancer (GC), and even up to 40% in patients with UICC Stage III GC. Due to the aggressive characteristic of adenocarcinoma of the stomach, GC is the third leading cause of cancer deaths worldwide. For GC with PM, the treatment of choice is according to national and international guidelines systemic chemotherapy, combined with biologic therapy against specific receptor antigen in with overexpression, such as HER-2. Multimodal treatment regimens including intraperitoneal application of chemotherapy and cytoreductive surgery (CRS) have been investigated and established all over the world. Driven by pharmacological studies and thoughts considering the increased benefits of cytotoxic agents used in the abdominal cavity, several drugs and drug combinations are widely used. In order to standardize treatment protocols, it is crucial to differentiate between normothermic and hyperthermic intraperitoneal chemotherapy (NIPEC, HIPEC). The requirements of an ideal cytotoxic drug different obviously dependent on its application method. Because of their high molecular weight and lipophilic structure, taxanes, such as paclitaxel or docetaxel have a long intraperitoneal retention time and are commonly used in NIPEC, while platin derivates, such as carboplatin or oxaliplatin are known for their synergistic effect to heat and are chosen in HIPEC. This review aims to explore and summarize different intraperitoneal treatment regimens strictly evaluated by supporting evidence in an effort to consolidate many regimens to a few evidence-based treatment protocols that deserve further investigation and distribution. This analysis included all studies focusing on intraperitoneal chemotherapy: Phase II, Phase III trials and non-randomized retrospective trials of larger cohorts of patients with GC and established PM or risk of PM. Interestingly, the protocols for NIPEC are quite uniform, with less variation between the therapeutic components in contrast to the different HIPEC protocols. This difference might be explained by the divergent evolution of NIPEC and HIPEC, as the former exclusively originated in Japan, while HIPEC experienced a more multicentric evolution and distribution in the United States, Asia, Europe, and worldwide utilization today.

Keywords: Intraperitoneal chemotherapy; hyperthermic intraperitoneal chemotherapy (HIPEC); peritoneal metastasis (PM); gastric cancer (GC); treatment protocol

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Introduction

Gastric cancer (GC) is the third leading cause of cancer deaths worldwide, following only lung and colorectal cancer in overall mortality, as reported by GLOBOCAN 2018 data. GC has the fifth highest incidence among cancers, with 5.7% of all new cases attributable to this disease. Approximately, one out of twelve oncological deaths are attributable to GC: more than one million new cases of GC are diagnosed, worldwide, each year (1). Among these patients, approximately 10–20% present with synchronous peritoneal metastasis (PM) at time of primary surgery, and up to 40% in patients with extended disease, such as stage III GC (2). Patients with peritoneal metastasized GC have a poor prognosis, reaching a median overall survival of only 3 to 7 months (3).

The therapeutic options for these patients are limited and include palliative systemic chemotherapy and/or best supportive care, according to the recommendations of the NCCN guidelines (4). During the last two decades, multimodal treatment approaches including intraperitoneal chemotherapy with or without cytoreductive surgery (CRS) have been developed to improve overall survival in selected patients with GC. Unfortunately, due to its aggressive tumor biology compared to other peritoneal malignancies, such as ovarian cancer or appendiceal neoplasm, only a small subset of patients with GC benefit from CRS. Therefore, patient selection is of major importance for a beneficial treatment. In very selected patients (5–8%), who present with good prognostic factors, (only localized PM or positive peritoneal cytology) and optimal treatment including systemic and IP chemotherapy with complete cytoreduction, long-term survival of more than ten years can be achieved (5,6).

Treatment protocols, the choice of chemotherapeutic drugs, as well as the application method (intravenous versus intraperitoneal) varying all over the world, and lack standardization in many regions. In the Western World, in which hyperthermic intraperitoneal chemotherapy (HIPEC) including a combination of platin derivates with or without mitomycin C (MMC) are commonly used as the core component of the treatment of peritoneal surface malignancies (PSM). In contrast, Asian countries are using either repeated doses of normothermic intraperitoneal (IP) chemotherapy via IP port systems or a combination of both HIPEC and normothermic IP chemotherapy.

During the last ten years a novel method of IP chemotherapy application called Pressurized Intraperitoneal aerosol chemotherapy (PIPAC) has emerged with promising results and high pathologic regression rates in patients with peritoneal metastasized GC, and has spread all over the world (7). For the purpose of clarity, PIPAC was not subject of this review.

The aim of this review is to explore and summarize different IP protocols of liquid chemotherapy and application methods and compare them regarding their level of evidence. Ideally, this manuscript will consolidate many proposals into only a few treatment regimens.

Pharmacological rationale of intraperitoneal chemotherapy

One of the main benefits of IP chemotherapy is the reduced systemic uptake of anticancer drugs applied to the peritoneal cavity, which leads to a higher regional concentration with a prolonged direct exposure time to PM and free cancer cells. Due to the peritoneal-plasma barrier a much slower peritoneal drug clearance compared to the plasma clearance results. Hence, one of the important aspects of the ideal intraperitoneal cytotoxic agent is the molecular characteristics of the drug. Small molecular hydrophilic drugs such as MMC and cisplatin are rather quickly absorbed compared to large molecular lipophilic drugs as paclitaxel and docetaxel, which are slowly absorbed (8). Another important aspect for the right choice for HIPEC is the augmentation by hyperthermia.

In the 1970s, early experiments in the application of intraperitoneal chemotherapy were performed by the group of Robert Dedrick. Despite its various pharmacokinetic advantages, he recognized one potential disadvantage of this method, which was the limited penetration depth of the chemotherapeutic agents (9,10). A few studies focused on this issue and found for example, paclitaxel, a penetration depth of 100-200 μm from the surface of the tumor (11,12).

In 1980, the first clinical application of HIPEC in a young patient with pseudomyxoma peritonei was published by Spratt *et al.* (13). The combination of hyperthermia and chemotherapy seems to be beneficial because of three reasons: (I) Hyperthermia itself has a selective cytotoxic effect on cancer cells (14); (II) hyperthermia enhances tissue perfusion and oxygenation and might therefore increase cytotoxic drug penetration (15); (III) several chemotherapeutic compounds, especially the platinum derivates (carboplatin, oxaliplatin) develop enhanced cytotoxicity through hyperthermia (16).

Table 1 Treatment and outcome of studies focusing on patients with gastric cancer with positive cytology or peritoneal metastasis treated with intraperitoneal chemotherapeutic

Author	Year	Trial	Inclusion criteria	Total number of patients	Comparative study	Response rate (%)	Treatment plan	Median overall survival	P value
Ishigami	2010	Phase II	Cyto pos/PM	40	Phase II	56–62	Chemo	22.6	
Fujiwara	2012	Phase II	Cyto pos/PM	18	Phase II	62.5–78	Chemo–Surgery–Chemo	24.6	
Imano	2012	Phase II	PM	15	Phase II	n.a.	Chemo	15.8	
Fushida	2013	Phase II	PM	27	Phase II	22–51.9	Chemo–Surgery–Chemo	16.2	
Yamaguchi	2013	Phase II	PM	35	Phase II	68–97	Chemo–Surgery–Chemo	17.6	
Ishigami	2017	Phase II	Cyto pos/PM	100	Phase II	64	Chemo–Surgery–Chemo	30.5 months (23.6–37.7)	
Ishigami	2018	Phase III	PM	164	IP + IV + S1	76	Chemo	17.7	0.08
					IV + S1		Chemo	15.2	
Yonemura	2020	NRCT	Cyto pos/PM	419	no	64.1	Chemo–Surgery–Chemo	CC-0: 20.5 CC-1: 12.0	<0.001

Cyto pos, positive cytology; PM, peritoneal metastasis; NRCT, non-randomized controlled trial; IP, intraperitoneally; IV, intravenously; S1, tegafur/gimeracil/oteracil; n.a., not available.

Clinical rationale of intraperitoneal chemotherapy

It is important to define different methodologies for IP chemotherapy applications, as one of the main differences is the utilization of heat. HIPEC is most commonly performed directly after extensive CRS in order to eliminate non-visible disease, such as free cancer cells. In the early postoperative phase, it was used less frequently months after the operation, and only most recently as a component of neo-adjuvant treatments. In nearly every case, HIPEC is applied through a heated circulatory machine in the operation room or on the intensive care unit.

A second possibility to treat with IP chemotherapy is through an IP port system as normothermic intraperitoneal chemotherapy (NIPEC). The peritoneal port system is usually introduced into the abdominal cavity under local anesthesia with its tip on the cul-de-sac of Douglas pouch. The port can be easily accessed to remove ascites (also for cytologic analysis) and for the application of cytotoxic drugs (17). This methodology can be used in an outpatient setting, as hospital admission is not necessary. Initially, one part of patients may receive treatment preoperatively. Treatment may continue after surgery as a combined bidirectional (systemic + IP) adjuvant regimen.

IP chemotherapy

In Asian countries, the placement of an IP port system for the repetitive usage of chemotherapeutic drugs is the most common practice. Usually, an intraperitoneal catheter and access port are implanted at the same time as staging laparoscopy, which is the gold standard diagnostic test to detect and document the size and distribution of PM in patients with GC. The catheter is placed in the small pelvis, and connected to a peritoneal access port, which is positioned in the subcutaneous fat tissue of the lower abdomen. The chemotherapeutic agent is dissolved in 500–1,000 mL of saline and is repeatedly infused through the IP port in the outpatient clinic. Peritoneal lavage cytology is available to monitor the efficacy of the treatment. The groups usually used a cis- or oxaliplatin containing intravenous chemotherapy combined with IP taxane, and oral Tegafur/gimeracil/oteracil (S-1). Taxanes, such as paclitaxel have a long retention time within the peritoneal cavity due to their relatively high molecular weight, while augmentation by heat is not necessary (18). Systematic reviews of randomized controlled trials demonstrated the benefit of adjuvant IP chemotherapy in patients with advanced GC with PM or with positive cytology and high risk (19,20).

Regarding the efficacy, Yonemura *et al.* could demonstrate a conversion rate from positive to negative cytology in patients with GC after neoadjuvant intraperitoneal-systemic chemotherapy (NIPS) of 69% in a total of 68 patients in 2012 (21). This treatment effect is associated with a low complication rate of 20.6% as reported by Emoto *et al.* in a series of 131 patients (22). The majority of the complications occurred either as an inflow obstruction or infection (7.6% and 6.9%) during a median period of IP

chemotherapy of 12.9 months (range, 0.8–61.5 months).

All RCT and non-randomized studies with more than 50 patients were included in our analysis. Treatment plan and oncologic outcome are illustrated in *Table 1*, details about the cytotoxic drug and regimen are shown in *Table 2*.

Therapeutic (positive cytology and/or PM)

In total, we could identify a total of 818 treated patients with PM or positive cytology of GC included in eight studies (5,23-29). Seven of eight groups used a singular IP drug (paclitaxel or docetaxel), while the group of Yonemura *et al.* used a combination of docetaxel and cisplatin. The most frequent dosage was for paclitaxel 20–80 mg/m^2, docetaxel 30–60 mg/m^2, and cisplatin 30 mg/m^2. The IP treatment was always accompanied by systemic chemotherapy. S-1 took a core part in the treatment of every group with a dosage of 80 mg/m^2 per day. Six of eight groups added chemotherapy intravenously to the therapeutic regimen, five of them applied paclitaxel 50 mg/m^2, while the group of Yonemura *et al.* utilized a combination of 30 mg/m^2 docetaxel with 30 mg/m^2 cisplatin. Three weeks was the common cycle length used by seven groups with IP and IV application of chemotherapy at Day 1 (n=7) and 8 (n=5), accompanied with oral S-1 from Day 1–14, and a break during the last week. Fushida *et al.* used a cycle of four weeks with IP chemotherapy at Day 1 and 15, accompanied with oral S-1 from Day 1–14, and two weeks of break (26).

The only Phase III trial, so called PHOENIX-GC trial so far was performed by Ishigami *et al.* and was published in 2018 (29). A total of 183 patients with PM of GC were randomized either to a combination of 20 mg/m^2 paclitaxel IP + 50 mg/m^2 paclitaxel IV + oral 80 mg/m^2/day S-1 or to systemic therapy only containing 50 mg/m^2 paclitaxel IV + oral 80 mg/m^2/day S-1. The primary endpoint was overall survival after two years after study enrollment. Important to mention was the inclusion of mainly patients with advanced peritoneal disease, who would not qualify for cytoreduction. Advanced PM was also reflected in the ratio of patients with localized peritoneal spread (P1) of only 3%. None of these patients were treated with surgery of the stomach nor of the PM. Impressively, the authors could demonstrate a median overall survival of patients in the IP arm of 17.7 months (95% CI, 14.7 to 21.5 months) compared to 15.2 months (95% CI, 12.8 to 21.8 months) in the systemic therapy arm (P=0.080). The study failed to reach the level of significance. As a potential explanation of the negative trial the authors discussed, that the results were affected by (I) baseline imbalance (PCI and amount of ascites), (II) crossover between arms (n=6), which were both in favor of the systemic chemotherapy group. Therefore, the clinical benefit of IP paclitaxel might be underestimated, which was strongly suggested by the explorative analysis performed by the authors.

In summary, normothermic IP chemotherapy showed promising results in several Phase II and non-randomized retrospective studies with median overall survival of 12 and 30.5 months in patients with GC and PM or positive cytology. The response rates in the bidirectional neoadjuvant setting were between 22% and 97% and support the concept of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). The only Phase III trial by Ishigami *et al.* was negative, with a clear trend in favor of IP chemotherapy in patients with advanced PM of GC.

The therapeutic protocol was consistent between the different groups and contained a cycle of three weeks (in 7/8 studies). Also, IV application of paclitaxel 50 mg/m^2 on Day 1 and 8 combined with IP docetaxel or paclitaxel accompanied by oral S-1 80 mg/m^2/day on Day 1–14.

HIPEC

Patients with positive cytology without PM seem to be a favorable group that benefit from HIPEC. This has been reported in small RCTs and several retrospective cohort analyses (30,31). Additional evidence favoring HIPEC in the patients with localized PM was delivered by a recent large propensity score adjusted analysis (CYTO-CHIP), which evaluated CRS alone *vs.* CRS and HIPEC in a French retrospective multicenter study. The authors could demonstrate a significant improved 3-year recurrence-free survival rate and overall survival of 20.4% *vs.* 5.9% (P=0.001), and 18.8 *vs.* 12.1 months (P=0.005), respectively (32).

Today, there are several ongoing RCTs exploring the efficacy of HIPEC in patients with GC and PM in Germany (GASTRIPEC: NCT02158988), France (GASTRICHIP: NCT01882933), the Netherlands (PERISCOPE II: NCT03348150), and China (HIPEC-01: NCT02356276, N.N.: NCT02528110).

The inclusion criteria and the oncologic outcome of several randomized or non-randomized studies comparing surgical treatment ± HIPEC are illustrated in *Table 3*. Every RCT and non-randomized studies with a minimum of 50 included patients were selected to be included in this table. Details of the different treatment protocols of HIPEC application are depicted in *Tables 4*,*5*. Different doses of the cytotoxic drugs were utilized as described in

Table 2 Details of chemotherapeutic treatment protocols; Author names of studies with significant survival benefit of HIPEC are underlined

Author	Year	Trial	Inclusion Criteria	Number of patients	IP cytotoxic drug	Dosage (mg/m^2)	Volume (liters)	Systemic cytotoxic drug	Dosage	Cycle length (weeks)	Scheme
Ishigami	2010	Phase II	Cyto pos/PM	40	PTX	20	1	S-1 oral	80 mg/m^2/day	3	IP Day 1 & 8
								PTX i.v.	50 mg/m^2		IV Day 1 & 8
											S-1 Day 1–14
											Day 15–21 rest
Fujiwara	2012	Phase II	Cyto pos/PM	18	DOC	40–60	1	S-1 oral	80 mg/m^2/day	3	IP Day 1
											S-1 Day 1–14
											Day 15–21 rest
Imano	2012	Phase II	PM	15	PTX	80	1	S-1 oral	80 mg/m^2/day	3	IP Day 1 & 8
								PTX i.v.	50 mg/m^2		IV Day 1 & 8
											S-1 Day 1–14
											Day 15–21 rest
Fushida	2013	Phase II	PM	27	DOC	35–50	1	S-1 oral	80 mg/m^2/day	4	IP Day 1 & 15
											S-1 Day 1–14
											Day 15–28 rest
Yamaguchi	2013	Phase II	PM	35	PTX	20	1	S-1 oral	80 mg/m^2/day	3	IP Day 1 & 8
								PTX i.v.	50 mg/m^2		IV Day 1 & 8
											S-1 Day 1–14
											Day 15–21 rest
Ishigami	2017	Phase II	Cyto pos/PM	100	PTX	20	1	S-1 oral	80 mg/m^2/day	3	IP Day 1 & 8
								PTX i.v.	50 mg/m^2		IV Day 1 & 8
											S-1 Day 1–14
											Day 15–21 rest
Ishigami	2018	Phase III	PM	164	PTX	20	0.5	S-1 oral	80 mg/m^2/day	3	IP Day 1 & 8
								PTX i.v.	50 mg/m^2		IV Day 1 & 8
											S-1 Day 1–14
											Day 15–21 rest
Yonemura	2020	NRCT	Ctyo pos/PM	419	DOC	30	0.5	S-1 oral	60 mg/m^2/day	3	IP Day 1
					CIS	30		DOC i.v.	30 mg/m^2		IV Day 8
								CIS i.v.	30 mg/m^2		S-1 Day 1–14
											Day 15–21 rest

IP, intraperitoneally; NRCT, non-randomized controlled trial; Cyto pos, positive cytology; PM, peritoneal metastasis; i.v., intravenously; S1, tegafur/gimeracil/oteracil; PTX, paclitaxel; DOC, docetaxel; CIS, cisplatin.

Table 3 comparative studies of patients with gastric cancer ± peritoneal metastasis treated with surgery ± hyperthermic intraperitoneal chemotherapy (HIPEC)

Author	Year	Trial	Inclusion Criteria	Total Number of patients	Nr. of patientsHIPEC	Survival	Nr. of patients Control	Survival	P value
Gastric cancer without peritoneal metastasis									
Koga	1988	RCT	cT4	47	26	Median OS: 30 months: 83%	21	Median OS: 30 months: 67.3%	n.s.
Kaibara	1989	RCT	cT4	82	42	5-year: 71.5%	40	5-year: 59.7%	n.a.
Hamazoe	1994	RCT	cT4	82	42	5-year: 64.3%	40	5-year: 52.5%	n.s.
Ikeguchi	1995	RCT	cT3	174	78	Median DFS: 30 months	96	Median DFS: 23 months	n.a.
Fujimoto	1999	RCT	cT4	141	71	2-, 4-, 8-year: 88%, 76%, 62%	70	2-, 4-, 8-year: 77%, 58%, 49%	0.0362
Yonemura	2001	RCT	cT3–T4	95	48	5-year: 61%	47	5-year: 42%	n.a.; RR 0.69 [0.45, 1.06]
Cui	2014	RCT	cT4	192	96	1-, 3-year: 84.5%, 49.3%	96	1-, 3- year: 79%, 25%	0.002
Koga	1988	NRCT	cT4	93	38	3-year: 73.7%	55	3-year: 52.7%	<0.04
Yonemura	1995	NRCT	cT4	160	79	5-year: ≈ 48%	81	5-year: ≈ 35%	0.052
Hirose	1999	NRCT	cT4	55	15	Median OS: 33 [7–59] months	40	Median OS: 22 [18–26] months	0.0142
Kunisaki	2002	NRCT	cT4	124	45	5-year: 51%	79	5-year: 61%	n.s.
Zhu	2006	NRCT	cT3-T4	118	42	2-, 4-, 6-year: 83.0%, 70.5%, 67.9%	54	2-, 4-, 6- year: 63.7%, 52.1%, 37.7%	0.0143
Kang	2013	NRCT	cT4	112	29	5-year: 43.9%	83	5-year: 10.7%	0.029
Gastric cancer with peritoneal metastasis									
Yang	2011	RCT	PM	68	34	Median OS: 11.0 months	34	Median OS: 6.5 months	0.046
Rudloff	2014	RCT	PM	17	9	Median OS: 11.3 months	8	Median OS: 4.3 months	n.s.
Fujimoto	1997	NRCT	PM	66	48	1-, 3-, 5-, 8- year: 54.0%, 41.5%, 31.0%, 25.4%	18	Median OS: 8.1 months	0.00167
Kunisaki	2006	NRCT	PM	73	21	n.a.	52	n.a.	
Li	2010	NRCT	PM	54	10	Median OS: 11.8 months	44	Median OS: 6.0 months	<0.001
Zhibing	2013	NRCT	PM	101	52	Median OS: 7.5 months	49	Median OS: 6.7 months	n.s.
Bonnot	2019	NRCT	PM	277	180	Median OS: 18.6 months	97	Median OS: 11.4 months	0.002

RCT, randomized controlled trial; NRCT, non-randomized controlled trial; n.a., not available; n.s., not significant; OS, overall survival; DFS, disease free survival; PM, peritoneal metastasis.

Table 4 Therapeutic details focused on hyperthermic intraperitoneal chemotherapy (HIPEC) application

Author	Year	Trial	Inclusion criteria	Total number of patients	cytotoxic drug	Dosage	Volume [liters]	Concentration [mg/L]	HIPEC duration [min]	HIPEC [°C]	HIPEC technique
Gastric cancer without peritoneal metastasis											
Koga	1988	RCT	cT4	47	MMC	64–100 mg	10–12	6.4–10.0	50–60	42	closed
Kaibara	1989	RCT	cT4	82	MMC	n.a.	n.a.	n.a.	n.a.	n.a.	closed
Hamazoe	1994	RCT	cT4	82	MMC	10 mg/L	n.a.	10	50–60	40–42	closed
Ikeguchi	1995	RCT	cT3	174	MMC	80–100 mg/m^2	8–10	12.8–20	n.a.	40–42	n.a.
Fujimoto[&]	1999	RCT	cT4	141	MMC	10 mg/L	3–4	10	120	43–44	closed
Yonemura	2001	RCT	cT3-T4	95	CIS	300mg	6–8	37.5–50 *	n.a.	42–43	open
					MMC	30mg		3.75–5.0 *			
Cui[&]	2014	RCT	cT4	192	CIS[#]	60 mg/m^2	3	32	90	41–43	closed
					5-FU	0.75 g	3	250			
Koga[&]	1988	NRCT	cT4	93	MMC	64–100 mg	10–12	6.4–10.0	50–60	42	
Yonemura	1995	NRCT	cT4	160	MMC	30 mg	8	3.75	60	41.5–43.5	open
					CIS	300 mg		37.5			
Hirose[&]	1999	NRCT	cT4	55	MMC	20 mg	4–5	4–5	50	41–44.5	open
					CIS	100 mg		20–25			
					Etoposide	100 mg		20–25			
Kunisaki	2002	NRCT	cT4	124	MMC	15 mg	5–6	2.5–3	40	42–43	open
					CIS	150 mg		25–30			
					Etoposide	150 mg		25–30			
Zhu[&]	2006	NRCT	cT3-T4	118	MMC	5 mg/L	5–6	5	60	43±1.0	open
					CIS	50 mg/L		50			
Kang[&]	2013	NRCT	cT4	112	MMC	10 mg/L	3–4	10	60	41–43	closed
					CIS	30 mg/L		30			
					Etoposide	20 mg/L		20			
Gastric cancer with peritoneal metastasis											
Yang[&]	2011	RCT	PM	68	MMC	5 mg/L	6	5	60–90	43±0.5	open
					CIS	20 mg/L		20			
Rudloff	2014	RCT	PM	17	Oxaliplatin	460 mg/m^2	n.a.	n.a.	30	41	closed
Fujimoto[&]	1997	NRCT	PM	66	MMC	10 mg/L	3–4	10	120	43–44	closed
Kunisaki	2006	NRCT	PM	73	MMC	30 mg	5–6	5–6	40	42–43	n.a.
					CIS	300 mg		50–60			
					Etoposide	300 mg		50–60			
Li[&]	2010	NRCT	PM	54	MMC	5 mg/L	5–6	5	60	43.0±1.0	open
					CIS	50 mg/L		50			

Table 4 *(continued)*

Table 4 *(continued)*

Author	Year	Trial	Inclusion criteria	Total number of patients	cytotoxic drug	Dosage	Volume [liters]	Concentration [mg/L]	HIPEC duration [min]	HIPEC [℃]	HIPEC technique
Zhibing	2013	NRCT	PM	101	CIS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bonnot[&]	2019	NRCT	PM	277	MMC[+]	30–50 mg/m^2	n.a.	n.a.	60–120	41–43	Open or closed
					Irinotecan[+]	200 mg/m^2			60–120	41–43	
					CIS[+]	50–100 mg/m^2			60–90	42–43	
					DOX[+]	15 mg/m^2			60–90	42–43	
					Oxaliplatin[+]	300–460 mg/m^2			30	43	

[&], studies with significant survival benefit of HIPEC; *, calculated; [+], several combinations; [#], on postoperative day 1 & 4. RCT, randomized controlled trial; NRCT, non-randomized controlled trial; CIS, cisplatin; PM, peritoneal metastasis; MMC, mitomycin C; n.a., not available; DOX, Doxorubicin;

Table 5 Therapeutic details of ongoing RCTs on hyperthermic intraperitoneal chemotherapy (HIPEC) application

Principle Investigator Indication	Acronym	Randomization	Inclusion criteria	Planned Nr of patients	cytotoxic drug	Dosage, mg/m^2	Volume [liters]	Concentration [mg/L]	HIPEC duration [min]	HIPEC [℃]	HIPEC technique
Ongoing RCTs											
Rau NCT02158988	GASTRIPEC	CRS ± HIPEC	PM	180	MMC	15	5	5.4	60	42–43	Open or closed
					CIS	75		27.2			
Glehen NCT01882933	GASTRICHIP	Surgery ± HIPEC	T4 or Cyto pos	367	Oxaliplatin	250	2 L/m^2	125	30	42–43	Open or closed
						50					
van Sandick NCT03348150	PERISCOPE II	CRS + HIPEC *vs.* systemic chemo	Cyto pos or PM (PCI<7)	106	Oxaliplatin	460	n.a.	n.a.	30	42	Open
					DOC	50			90	37	
Cui NCT02356276	HIPEC-01	Surgery ± HIPEC (2 times)	cT3-T4	584	PTX	1st 75	3–4	30–40	60	43	n.a.
						2nd		40–53.3			
NCT02528110	n.a.	Surgery ± HIPEC	cT3-T4	100	PTX	75	3–4	30–40	60	43	n.a.
					5-FU	15		6–8			

HIPEC, hyperthermic intraperitoneal chemotherapy; Cyto pos, positive cytology; PM, peritoneal metastasis; CIS, cisplatin; MMC, mitomycin C; n.a., not available; DOC, docetaxel; PTX, paclitaxel; 5-FU, Fluorouracil.

the manuscripts. For the purpose of a better comparison, doses were unified in concentrations [mg/L] using regional mean body surface areas as an assumption. Therefore, 1.81m^2 was selected according to a Dutch study of 1,868 participants representing the European and Northern American population, and 1.60 m^2 according to the results of a Chinese study about 3,951 participants representing patients from Asian trials (33,34).

The information of the study of Kaibara *et al.* (1989) was extracted from the abstract only, as the full manuscript was not online accessible (35).

Prophylactic (advanced GC and/or Cytology positive)

In total there are 17 studies; 13 of them were published, while four are ongoing RCTs focused on the efficacy of HIPEC in prophylactic indication for patients with advanced GC or positive cytology at any stage of treatment (35-48). The French GASTRICHIP trial is the only non-Asian study for this indication.

Eight groups used a singular IP cytotoxic agent (MMC or Oxaliplatin or Paclitaxel), six used two (a combination of Cisplatin, MMC, Paclitaxel and Fluorouracil), and three publications reported three cytotoxic agents (MMC + Cisplatin + Etoposide) used for HIPEC. The most common concentrations were: MMC 2.5–17.5 mg/L (n=11), Cisplatin 20–50 mg/L (n=7), Oxaliplatin 125 mg/L (n=1), Paclitaxel 30–53.3 mg/L (n=2), Fluorouracil 6–250 mg/L (n=2), and Etoposide 20–30 mg/L (n=3). The HIPEC duration was between 50 and 120 minutes, with the exception of Oxaliplatin, which was used for 30 minutes only. The HIPEC temperature was 40.0–44.5 ℃ with the usage of both open or closed circulation techniques.

Regarding the highest level of evidence, two RCTs showed an overall survival benefit in patients with advanced GC using either MMC 10 mg/L for 120 minutes with 43–44 ℃ or Cisplatin 35 mg/L in combination with Fluorouracil 250 mg/L for 90 minutes with 41–43 ℃ in a closed circulation system.

In total, four non-randomized controlled trials demonstrated an increased overall survival using either the triplet combination MMC 4–5 or 10 mg/L, Cisplatin 20–25 or 30 mg/L, Etoposide 20–25 mg/L or MMC 5 mg/L, Cisplatin 50 mg/L or MMC 6.4–10 mg/L monotherapy for 50–60 minutes with 41–44.5°C in an open or closed system.

Therapeutic (PM)

In total, nine studies were included in this analysis including two European ongoing RCT (GASTRIPEC, PERISCOPE II) (32,44,49-53). Three groups used a singular cytotoxic agent (MMC or Cisplatin or Oxaliplatin), four used two drugs (MMC + Cisplatin or Oxaliplatin + Docetaxel), and one group used a combination of MMC + Cisplatin + Etoposide. The drug concentrations ranged between: MMC 5–6 mg/L (n=5), Cisplatin 20–60 mg/L (n=4), Oxaliplatin 125 mg/L (n=1), Docetaxel 50 mg/m^2 (n=1), and Etoposide 50–60 mg/L (n=1). The duration of HIPEC was between 30 and 120 minutes using a temperature between 42–44 ℃ with both circulation techniques (open and closed).

The RCT from Yang *et al.*, demonstrated a survival benefit for patients treated with HIPEC using MMC 5 mg/L + Cisplatin 20 mg/L for 60–90 minutes with 43±0.5 ℃ (11.0 *vs.* 6.5 months, P=0.046) (49).

Three non-randomized comparative trials were able to show an increased overall survival using either MMC 10 mg/L as monotherapy for 120 minutes with 43–44 ℃ or the combination of MMC 5 mg/L + Cisplatin 50 mg/L for 60 minutes with 43.0±1.0 ℃ (51,52). The CYTOCHIP study from Bonnot *et al.* could not be analyzed regarding the HIPEC regimen, due to the variety of different HIPEC regimens, which have been included in this multicenter study (32).

Translational research

There are only few reports about animal studies regarding PM of GC. The clinical application of IP chemotherapy as it is commonly used today in several expert centers, was developed with a relatively low complication rate and low morbidity. In combination with an aggressive disease in which the patients usually face a median overall survival of few months and the additionally lack of therapeutic alternatives, the clinical implementation of IP chemotherapy progressed without a broad fundament of preclinical models. This situation is similar to other diseases addressed by HIPEC, such as PM of colorectal cancer. The only preclinical studies were conducted in Japan, where the incidence of GC is very high, and innovative therapeutic options were eagerly explored.

Animal model and chemosensitivity

In 2003, Nakanishi *et al.* demonstrated an increased survival of nude mice, which have been intraperitoneally inoculated with a green fluorescence protein (GFP)-tagged human GC cell line (GCIY) and treated with oral S-1 at a dose of 20 mg/kg/day (54).

In 2005, Yonemura *et al.* examined *in vitro* chemosensitivity

Drug	Dose	Application	Day
S-1	80 mg/m^2 per day	Oral, twice daily	1–14
Paclitaxel	20 mg/m^2	Intraperitoneal	1 & 8
or			
Docetaxel	30–50 mg/m^2	intraperitoneal	1 & 8
Paclitaxel	50 mg/m^2	Intravenously	1 & 8

Figure 1 IP chemotherapy (NIPEC) regimen.

Suggestion I: Monotherapy

Drug	Dose	Duration	Temperature
Mitomycin C	10 mg/L	60 or 120 minutes	43 °C

Suggestion II: Combined Therapy

Drug	Dose	Duration	Temperature
Mitomycin C	5 mg/L	60 or 90 minutes	43 °C
Cisplatin	20–50 mg/L		

Suggestion III: Combined Therapy

Drug	Dose	Duration	Temperature
Cisplatin	32 mg/L	90 minutes	43 °C
Fluorouracil	250 mg/L		

Figure 2 Hyperthermic intraperitoneal chemotherapy (HIPEC) regimen.

using a collagen-gel method on 165 primary GCs, and the efficacy of intraperitoneal chemotherapeutic drugs in nude mice, which were intraperitoneally inoculated by 10^7 MKN-45-P cells (55). The authors could conclude, that the combination of oral S-1 with intraperitoneally cisplatin, fluorouracil, docetaxel or carboplatin improved overall survival in this animal model.

Patient-derived Xenograft (PDX) model

Today, there are no reports about orthotopic PDX models of PM of GC so far.

Conversion surgery (CS)

The term CS is defined as surgical treatment aimed at curative resection in patients with positive cytology or limited PM, that responded significantly to neoadjuvant chemotherapeutic regimens. The rate of patients with positive cytology, that transformed to negative after NIPS or NIPEC was reported between 69% and 78%, and even after systemic chemotherapy alone conversion rates in patients with positive cytology or PM of 66% or 15% were reported, respectively (21,29,56). CS has been proved to be safe, and seems to prolong overall survival compared to patients without CS, as a study of Ishigami *et al.* demonstrated (30.5 *vs.* 14.3 months) (28). The question whether the survival benefit is a result of the surgical intervention or solely the result of the selection of patients with a potentially better tumor biology, remains until the conduction of a randomized controlled trial unanswered. The data of the REGATTA trial showed, that surgical treatment of the primary without removal of metastasis prior chemotherapy and therefore irrespective of any response evaluation do not add a survival benefit to the patients (57).

Standardization of protocols

The standardization of treatment protocols is generally a challenging task. Especially due to the lack of translational studies, a simplification of treatment protocols can only be suggested. In order to define a standard of therapy, translational research including chemosensitivity testing, evaluation of HIPEC application, etc. have to be conducted using animal, PDX models, and clinical trials.

Obviously, the treatment protocols of HIPEC differed significantly. Three out of five trials favoring HIPEC in the prophylactic setting contained the monotherapy with MMC 10 mg/L, as represented in Suggestion I. Suggestion III originates from the largest positive RCT conducted by Cui *et al.* (41).

Nevertheless, our review explored the most commonly used IP protocols for the treatment of patients with PM of GC and summarizes the results as follows:

IP chemotherapy (NIPEC)

Indication: positive peritoneal cytology or peritoneal metastasis of gastric cancer.

Application: treatment: Day 1–14; Resting: Day 15–21 (*Figure 1*).

HIPEC

Indication: Positive peritoneal cytology or cT3–4 or peritoneal metastasis.

Suggestion I–III: *Figure 2*.

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Footnote

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