Indian Journal of Surgical Oncology (March 2023) 14 (Suppl 1):S39–S59
https://doi.org/10.1007/s13193-023-01728-6

REVIEW ARTICLE

Peritoneal Mesothelioma: Systematic Review of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Protocol Outcomes

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Received: 1 February 2023 / Accepted: 25 February 2023 / Published online: 4 March 2023
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Abstract

Diffuse malignant peritoneal mesothelioma (DMPM) prognosis was improved by the locoregional treatment combining cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC is a multiparametric treatment with multiple protocols proposed and reviewed in this work. A systematic review of medical literature was performed according to PRISMA guidelines. The search strategy used "malignant peritoneal mesothelioma" and "HIPEC" as keywords in three databases. Studies were included if reporting precisely the HIPEC regimen and the related outcomes, if comparing regimen, or if reporting national/international guidelines. The GRADE methodology was used to rate the level of evidence. Twenty-eight studies were included in this review: 1 was a meta-analysis, 18 reported cohort outcomes, 4 retrospectively compared HIPEC regimens, and 5 were guidelines. Six HIPEC regimens were found, 4 with one drug (cisplatin, mitomycine-C, carboplatin, oxaliplatin), 2 using two drugs (cisplatin-doxorubicin or cisplatin-mitomycine-C). Cisplatin, up to 250 mg/m^2 over 90 min, appeared as the key HIPEC drug with a toxicity profile well controlled by the concomitant intravenous perfusion of sodium thiosulfate. Comparative studies tended to show that a bi-drug regimen led to better long-term oncologic outcomes, with cisplatin 50 mg/m^2 plus doxorubicin 15 mg/m^2 being safe and more efficient. This late protocol was the most widely used and recommended in 3 out of 4 international guidelines. Cisplatin was the preferred drug for HIPEC in DMPM patients. Most of the time, it was combined with doxorubicin for 90 min. A harmonization of protocols and further comparative studies are needed to optimize HIPEC regimen choice.

Keywords Peritoneal mesothelioma · Hyperthermic intraperitoneal chemotherapy · Protocol

Introduction

Peritoneal mesothelioma is a rare primary peritoneal disease characterized by multiple metastatic nodules spreading over the parietal and visceral peritoneal lining [1, 2]. Its incidence is around 2 cases/million/year, with sometimes an association with asbestos exposure and/or genetic abnormalities [3]. Vast majority of peritoneal mesothelioma presents as diffuse malignant peritoneal mesothelioma (DMPM), while two particular histologic forms also exist: multicystic peritoneal mesothelioma (MCPM) and well-differentiated papillary peritoneal mesothelioma (WDPPM)[4–6]. MCPM and WDPPM are described as borderline forms with mainly a risk of locoregional recurrence [5, 6].

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Although extra-peritoneal metastases remain rare, the natural history is made of locoregional progression leading to death in a median of 6 months [7]. Systemic treatments, including target therapies and immunotherapy, hardly improve patients' survival up to 15 months, making this disease chemoresistant [8–11]. The best oncological outcomes are obtained when disease distribution and the patients general condition allow a cytoreductive surgery (CRS) combining peritonectomies and organ(s) resection(s)[12–15]. Main prognosis factors are tumor characteristics (histologic subtype and Ki-67 expression), completeness of cytoreduction score (CC-score), and nodal status [12, 16–18].

As the peritoneal space contains all the DMPM metastases in most of the cases, multiple loco-regional treatment modalities have been developed [19–23]. A pharmacokinetic advantage for intraperitoneal (IP) chemotherapy is determined by the barrier effect of the peritoneal lining [19, 24]. This plasma-peritoneal barrier allows in situ delivery of high drug concentrations, prone to overcome chemoresistance of hypovascularized metastatic nodules, while limiting systemic toxicity [19, 25, 26]. The most used modality is hyperthermic intraperitoneal chemotherapy (HIPEC), consisting of a continuous circulation of a heated bath, usually between 41 and 43 °C, containing one or two antineoplastic drugs, during 60 to 120 min [27, 28]. HIPEC is a one-shot administration performed at the end of a complete CRS when all the peritoneal surfaces are exposed, aiming at eradicating the residual microscopic disease. Since its first description for DMPM patients in 1997, multiple HIPEC protocols have been proposed, based usually on cisplatin, mitomycine C (MMC), doxorubicin, and carboplatin, either alone or in combination [29, 30].

DMPM patients treated with CRS-HIPEC could reach a median overall survival of 50 months. The proper effect of HIPEC addition to complete CRS in these patients has never been evaluated through a randomized control trial for different reasons. Basically, the disease rarity would render the recruitment period too long to include enough patients to get the required statistic power. But, overall, international expert centers for peritoneal surface malignancies (PSM) considered CRS-HIPEC to be the recommended treatment option for operable and resectable patients based on consistent retrospective analysis [31–35]. The most recent guidelines were elaborated through a consistent and approved methodology: the GRADE assessment of the level of evidence available and the Delphi voting process [36–38]. As so such a trial would be judged as not ethical for the majority of PSM experts. However, the drawback of such a process is the heterogeneity of HIPEC protocols, precluding clear comparison and selection of the most adapted regimen, for DMPM patients as for other histologies [39, 40].

In the objective to propose a uniform treatment strategy, which will help in the future evaluation, the Peritoneal Surface Oncology Group International (PSOGI) constituted a steering committee to produce international guidelines focused on HIPEC in different histologies, using the methodology defined by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group [38, 41, 42]. We present here the results of a systematic review of HIPEC protocols used for peritoneal mesothelioma patients.

Methods

This systematic review was conducted to provide a comprehensive synthesis of available data to international experts implicated in the Delphi process organized by the PSOGI aiming at proposing a standardized protocol for DMPM patients. So, the aim was to answer the question: what is the impact of different HIPEC regimen on postoperative and long-term outcomes of DMPM patients? A search strategy was elaborated to retrieve any published peer-reviewed medical articles mentioning data related to HIPEC for peritoneal mesothelioma patients. The study has been registered on PROSPERO with the number CRD42021240382.

Search Strategy

A study protocol was prepared before conducting the review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, using the PRISMA assessment checklist [43, 44].

The electronic search was conducted on the 24th of January 2021 in the MEDLINE, Embase, and Cochrane Database. The search algorithm combined synonyms and related MeSH terms for DMPM and HIPEC and could be summarized as follows: ("Peritoneal mesothelioma" OR "DMPM" OR "Malignant peritoneal mesothelioma") AND ("HIPEC" OR "Hyperthermic intraperitoneal chemotherapy" OR "Continuous hyperthermic peritoneal perfusion" OR "CHPP"). The abstract published along the following conferences were also searched from 2015 to 2020: ASCO, ESMO, Society of Surgical Oncology, Peritoneal Surface Oncology Group International, and International Mesothelioma Interest Group. The gray literature was also explored to fulfil the research. No date or language limitations were imposed on the searches. References of all retrieved articles were reviewed for other potentially relevant studies; notably, review articles were all extensively explored. The full-text review was accomplished using dual-reviewer (VK and MD) screening for assessment of acceptance in light of inclusion/exclusion criteria.

Study Selection

Considering that the outcomes relevant to the choice of an HIPEC regimen would be the specific toxicity, the rate and the nature of postoperative complications, and the long-term outcomes, studies' eligibility criteria were determined in accordance, using the acronym PICO:

Population: studies conducted in the population of malignant peritoneal mesothelioma patients with at least 5 cases and specifying if some had low-grade histologies were included. Studies focused on MCPM and WDPM were excluded, as the studies addressing global treatment of peritoneal carcinomatosis of various origins.

Intervention: studies evaluating CRS and HIPEC in this population were eligible for review as long as they reported details of the HIPEC regimen used (drug(s), doses, temperature, duration, and perfusate). The use of complementary intraperitoneal chemotherapy, such as early post-operative intraperitoneal chemotherapy (EPIC), was not an exclusion criterion.

Comparisons: the preferred studies to include were those comparing outcomes of the HIPEC regimen in DMPM patients. However, the absence of prospective comparative studies and the rarity of data led to include also phases I–II and consistent cohort studies issued from expert centers. The published clinical guidelines mentioning a choice of HIPEC regimen for these patients were also reviewed to feed the discussion. Case reports, letters or editorials, and studies published in other languages than English were excluded.

Outcomes: to analyze the three main mentioned outcomes (postoperative toxicities, postoperative complications, and long-term survival) were collected the completeness of the CRS score (CC-score), the peritoneal carcinomatosis index, the post-operative complications rate, the reoperation rate, the HIPEC-related toxicities, and the long-term oncologic outcomes (overall survival (OS) and progression-free survival (PFS)).

Data Extraction and Assessment of Study Quality

In instances, where multiple articles were published from the same group with enlarged cohorts and/or increased length of follow-up, the most recent article was used to calculate the number of patients treated with such regimen. However if more detailed data, notably regarding postoperative surgical complication, and/or toxicities were mentioned in the ancient publications, several articles from the same team could be selected.

With these data, tables were elaborated to summarize the main outcomes. Data extraction was conducted by one reviewer (VK) and audited by a second independent auditor (MD). The level of evidence brought by each selected article was rated according to the GRADE methodology [41, 42]. A meta-analysis was not feasible given the heterogeneity across trials.

Results

Article Selection

The study selection flowchart is exposed in Fig. 1. Of the 3 databases and gray literature, 713 citations were collected of which 238 remained after removing duplicates. After screening, 139 articles were eligible for a full-text analysis. The inclusion/exclusion criteria led to include 28 articles in the final analysis. No randomized control trial was available. Some patients were included in prospective phases I–II studies in the nineties, while the remaining were retrospective cohort analyses. Of the selected publications, 18 reported mono/multicentric cohorts results, which are presented in Table 1 and summarized in Table 2[45–62], 3 compared outcomes of HIPEC regimen and 1 compared HIPEC with one or two drugs [39], presented in Table 3[18, 63, 64], 1 was a systematic review with meta-analysis [13], and 5 were national/international guidelines summarized in Table 4.

Quality of Evidence

The quality of evidence assessment according to the GRADE system was synthetized in Table 5 regarding the three main outcomes considered (severe postoperative complications, postoperative toxicities, and long-term outcomes). The selected observational studies were judged of good methodological quality and consistency. Some uncertainty remained about directness as CRS-HIPEC is a multimodal treatment rendering difficult to link post-operative outcomes to each component with the scarce comparative data available. Moreover, in several studies, another intraperitoneal treatment was added in some patients. For each outcome, the overall quality was considered moderate, the importance critical, and the grade of evidence low (Table 5).

HIPEC Regimen for DMPM Patients

Schematically, 6 main HIPEC regimens were reported for DMPM patients as presented in Table 1. The most evaluated were cisplatin, MMC, and the combined protocols cisplatin-doxorubicin and cisplatin-MMC (Table 2). Apart from cisplatin dose escalation studies and for cisplatin-MMC regimen, protocols were homogenous. In the only meta-analysis available, chemotherapy agents used were, in 71% of patients, a combination of cisplatin, doxorubicin, and mitomycin [13]. In 9 studies (6 out of 10 reporting cisplatin-doxorubicin HIPEC outcomes), at least 2 patients had EPIC or other forms of IP chemotherapy in addition to HIPEC,

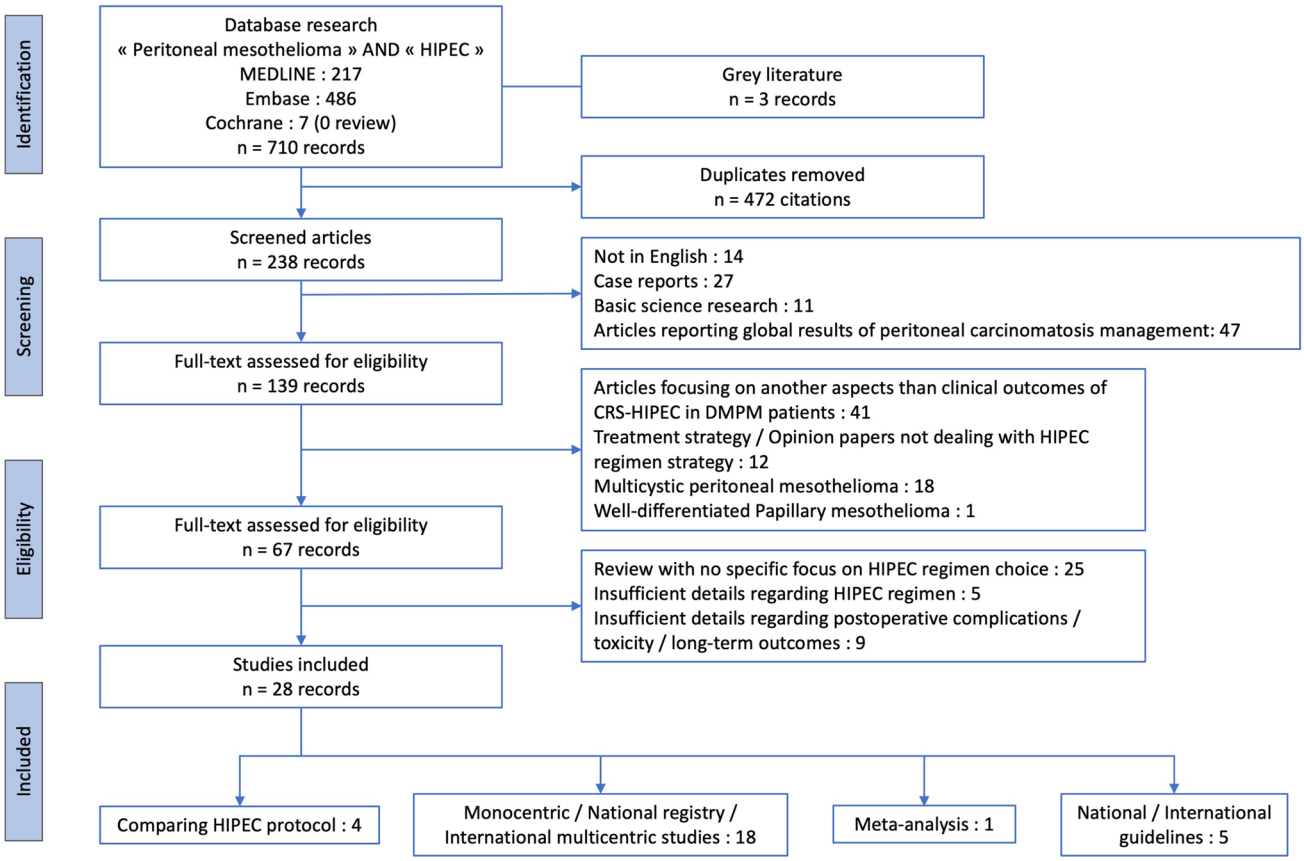

Fig. 1 PRISMA flowchart. HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; intraperitoneal chemotherapy; DMPM, diffuse malignant peritoneal mesothelioma

complexifying the analysis of the effects directly imputable to HIPEC (Table 1).

Considering cohorts presented in Table 1 and after identifying duplicate patients and splitting where possible low and high-grade disease, a total of 833 mesothelioma patients treated with CRS and HIPEC were reported, of which 804 were DMPM. Four regimens were used in 94% of mesothelioma patients: cisplatin in 20%, MMC in 16%, cisplatin-MMC in 14%, and cisplatin-doxorubicin in 41%. Overall, cisplatin has been used as a HIPEC agent, alone or in combination, in 76% of mesothelioma patients treated with this technic. The summary of selected studies in Table 2 showed discrepancies in complete cytoreduction rates, a trend of a better 5-year OS after cisplatin-doxorubicin HIPEC with less severe complications.

Mono-drug Regimen

Cisplatin The Surgery Branch of the American National Cancer Institute led to phase I studies including peritoneal carcinomatosis patients treated with an escalating dose of cisplatin as a HIPEC agent. HIPEC parameters were 90-min duration, 42–43 °C as target temperature, closed-abdomen technic, flow rate of 1.5 L/min, and perfusion volume of 4–6 L according to the patient's size [65]. Because of the systemic passage of cisplatin, sodium thiosulfate was administered intravenously at the start of HIPEC with a loading dose of 7.5 g/m^2 diluted in 150 mL of saline over 20 min, followed by a total dose of 25.6 g/m^2 diluted in 1 L of saline infused over the subsequent 12 h [65–67]. The study was secondarily focused on DMPM patients as a clear oncological benefit was observed mainly for them [29, 59, 60, 68].

In the series presented by Ma et al., 10 mesothelioma patients (9 DMPM and 1 MCPM) were allowed to define the maximum tolerated dose (MTD) at 300 mg/m^2. One patient presented a grade 4 renal insufficiency as dose-limiting toxicity at 400 mg/m^2 justifying a de-escalation to 350 mg/m^2 where the same complication happened in 1 out of 5 patients [29]. The patient with grade 4 renal toxicity required dialysis for 1 month. Two patients had grade 3 thrombocytopenia, and one grade 3 leukopenia. Three patients had prolonged ileus [29]. As a result, 6 patients out of 10 had been treated above the MTD, 5 of which presented a grade 3 or 4 rise in creatinine [29]. The expansion of this cohort to 18 mesothelioma patients (17 DMPM—1 MCPM) with 5 patients having intraperitoneal and/or intravenous complementary

Table 1 Selected studies reporting outcomes of different HIPEC regimen in mesothelioma patients

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Cisplatin + Doxorubicin																		
Kyziridis 2019	29 (5 MCPM)	64% > 13	76%	Open	50 mg/m^2 15 mg/m^2	42.5–43	-	Ringer's lactate 2–3 L	+ IV Ifos (1300 mg/m^2) and 3 × Mesna (260 mg/m^2) 13 pat CC-1: + EPIC (5-FU)	-	med nr 5-y: 74% 8-y: 66%	-	CD	27%	21%	-	-	3%
Gilani 2018	37 (7 biph)	18 (3–39)°	49%	Open	50 mg/m^2 15 mg/m^2	42–43	60	-	X pat: MMC-HIPEC X pat: EPIC (doxo-cisp)	34 (6–152)*	mean 46 m (28–63) 3-y: 63% 5-y: 38%	mean 29 (15–42) 3-y: 35% 5-y: 35%	CD	-	7%	-	-	2.6%*
Stamou 2015	20 (3 low grade)	16 (3–39)°	80%	Open	50 mg/m^2 15 mg/m^2	42.5–43	90	Ringer's lactate 2–3 L	3 pat: no IP treatment 2 pat: HIPEC + EPIC (5-FU) 2 pat: EPIC	18	mean 47 (SE, 4)	-	-	-	20%	1 short gut syndrome 2 D: pulmonary embolism/ myocardial infarction	-	1%
Iheme-landu 2014	161 (14 sarc/biph)	18 (13)°	47%	Open	50 mg/m^2 15 mg/m^2	42	90	Peritoneal dialysis solution 3 L	19 pat: + Ifos in HIPEC + EPIC paclitaxel + IP Alimta 65 pat: + EPIC paclitaxel 29 pat: cisplatin alone or other drug or no HIPEC	28 (1–222)	med 77 m 3-y: 52% 5-y: 60%	-	CD	53%	17% (including G5)	-	-	3%
Robella 2014	42 (7 MCPM)	13 (4–34)°	90%	Open	100 mg/m^2 16 mg/m^2	41.5	60	Peritoneal dialysis solution adapted to BSA		-	med 65 m 3-y: 63% 5-y: 44%	-	CD	36%	24%	-	7%	7%
Baratti 2013	108 (15 sarc/biph)	17 (9)°	81%	Closed	45 mg/L 15 mg/L	42.5	90	4–6 L	6 pat: cisplatin (25 ml/m^2/L) + MMC (3.3 mg/m^2/L)	49 (37–61)	med 63 (30–97) 5-y: 52% 10-y: 45%	med 25 (5–45) 5-y: 38% 10-y: 36%	NCICTC v3.0	-	39%	14 anast leak/ perforation 10 respiratory morbidity 6 sepsis 7 hematological toxicity 10 renal toxicity	-	1.9%
Chua 2009	20 (3 sarc/ biph—1 MCPM)	17 (7)°	95%	Open	50 mg/m^2 15 mg/m^2	42	90	1.5% dextrose peritoneal dialysis—3 L		18 (0.5–87)	med 30 m 3-y: 46% 5-y: nr	med 7 (0.5–25)	-	65%	25%	2 pneumothorax 1 pleural effusion 1 bile leak with peritonitis	-	5%

Table 1 (continued)

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Yan 2006	100 (9 sarc/biph)	24 (11)°	69%	Open	50 mg/m^2 15 mg/m^2	42	90	Peritoneal dialysis solution 3 L	9 pat: induction IP + HIPEC + EPIC (cisp-dox) 56 pat: HIPEC + EPIC (paclitaxel)	48 (6–148)	med 52 (1–148) 3-y: 55% 5-y: 46%		-	51%	25%	8 anemia 18 sepsis 6 dehydration 5 pleural effusion 3 cardiac arrhythmia 5 postop-erative bleeding 3 anast leak 3 bile leak	11%	5%
Deraco 2006	40 +9 treated with cisplatin-MMC (6 biphas)	22 (2–39)	84%	Closed	25 mg/m^2/L 7 mg/m^2/L	42.5	60–90	Polysaline perfusate 4–6 L (3.5 L/m2)		20 (1–89)	5-y: 57%	med 39.7 (IC95, 26.8–52.6) 5-y 31%	WHO	-	18 G3 in 15% 9 GIII-IV tox in 12%	7 intestinal fistulas 1 gastric per-foration 12 sepsis 1 pulmonary embolism 1 pancreatic fistula 1 acute hypo-tension 2 G3 anemia 1 G3 leuko-penia 2 G3 gastro-intestinal tox 2 G3 acute renal failures 2 G4 chronic renal failures	-	0
Sebbag 2000	33 (3 low grade)	29°	52%	Open	50 mg/m^2 15 mg/m^2	41–41.5	-	1.5% dextrose peri-toneal dialysis 3 L	11 pat + neoadj IP (cisplat-doxo) 17 pat + EPIC (cisplat-doxo)	21.3 (1–79)	med 31 m 3-y: 56% 5-y: 47%	na	NCICTC v4.0	na	33%	1 bile leak 1 small bowel fistula 2intraab-dominal bleeding	7%	2%

Table 1 (continued)

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Cisplatin + mitomycin c																		
Huang 2015	44 (8 sarc/biph and 3 MCPM)	21 (10)	98%	Open	100 mg/m^2 12.5 mg/m^2	42–42.5	90	Dianeal 2 L + Saline 2 L	4 pat (9%): + EPIC	-	med 44.0 m (95%CI, 12.0–76.0)	-	CD	-	53%	4 renal impairment (7%) 24 collection (41%) 21 pleural effusion (36%) 16 infections (28%) 7 fistula (12%) 7 pneumonia (12%) 6 pneumothorax (10%) 5 ileus (9%) 4 pancreatic leaks (7%) 4 periop bleeding (7%) 4 small bowel obst (7%) mean 7 transfusion units	-	5.2%
Magge 2014	65 (8 sarc/biph and 4 low grade)	med Simplified PCI 12 (8–16)	86%	Closed	50 mg/m^2/L 30 + 10 (T60) mg	42	100	-		37 (12–53)	Med 46.2 m 2-y: 57% 5-y: 39%	Med 13.9 m disease-failure probability: 2-y: 68% 5-y: 83%	CD	72%	35%	4 enteric leak 1 intra-abdominal abscess 7 other 25 pulmonary 15 cardiac 16 wound complications	18%	6.2%
Brigand 2006	15 (2 biph and 1 MCPM)	-	73%	Closed	0.7 mg/kg 0.5 mg/kg	42–42.5	90	Isotonic dialysis fluid 4–6 L		47 (1–190)	CC-0/1 med 38 m 5-y: 44%	-	-	40%	na	1 extravasation with wound necrosis 1 acute renal failure	0%	0%

Table 1 (continued)

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Cisplatin																		
Schaub 2013	104 (14 sarc/biph)	15 (3–36)°	63%	Closed	240 to 450 mg/ m^2	40–42	90	-	69 pat (66%): + EPIC (Taxol + 5-FU) Use of sodium thiosulfate not mentioned	49.4 (1–195)	med 52 m (1–195) 3-y: 58% 5-y: 46%	med 21 m (1–81) 3-y: 26% 5-y: 13%	-	-	-	-	-	-
Blackham 2010	15 (1 biph)	-	73%	Closed	250 mg/m^2	40	60—120	Lactated Ringer's solution 3 L	+ sodium thiosulfate	1.9 y	med 10.8 m 3-y: 80%	med 10.6 m 3-y: 91% (complete CRS)	-	-	-	-	-	0
Park BJ 1999	18 (1 MCPM)	-	-	Closed	Escalating 100 to 400 mg/ m^2	41	90	4–6 L	+ sodium thiosulfate	19 (2–56)	med NR 2-y: 80%	med 26 m	NCICTC v2.0	24%	-	5 G3-4 renal impairment 3 G3 leukopenia 1 G3 thrombocytopenia 6 G3-4 transaminitis 9 G3-4 hyperbilirubinemia		
Feldman 2003	49 (4 sarc and 17 low grade)	-	47%	Closed	250 mg/m^2	41	90	4–6 L	+ sodium thiosulfate 35 pat: + EPIC	28 (1–106)	92 m	17 m	NCICTC v2.0	18 in 12 pat (25%)	-	1 fascial dehiscence 1 gastric perforation G3-4 toxicities: 13% neutropenia 4% thrombocytopenia 19% hepatic cytolysis 21% hyperbilirubinemia 15% rise in creatinine 4% anemia	4%	0

Table 1 (continued)

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Alexander 2013	105 (of 211 with 54 low grade and 44 unknown grade)	-	53%	Closed	250 mg/m^2	41	90	4–6 L	+ sodium thiosulfate	-	med 54.6 m 5-y: 47.5%	-	NCICTC	30%*	-	9.6%: fistula, perforation, dehiscence, or infection 5%: prolonged ileus, vomiting, or obstruction 4.4%: surgical site inf 12%: non-infectious cardiopulmonary events*	9.4%*	2.3%*
Mitomycin C																		
Blackham 2010	19 (3 biph)	-	58%	Closed	30 to 40 mg	40	60—120	Lactated Ringer's solution 3 L		6 y	med 40.8 m 3-y: 42%	med 8.3 m 3-y: 45% (complete CRS)	-	-	-	2 POD: neutropenic sepsis respiratory failure	-	10.5%
Shetty 2014	11 (1 biph)	-	64%	Closed	30 + 10 mg (T0–T60)	40.5–42	120	Lactated Ringer's solution 3 L		18 m	med 18 m 5-y: 27%	-	-	-	-	1 (9%) pancreatitis 2 (18%) prolonged ileus	-	0
Alexander 2013	106 (of 211 with 54 low grade and 44 unknown grade)	-		Closed	40 mg	41	90	4–6 L		-	med 27.1 m 5-y: 54.6%	-	NCICTC	30%*	-	9.6%: fistula, perforation, dehiscence, or infection 5%: prolonged ileus, vomiting, or obstruction 4.4%: isolated surgical site infection 12%: non-infectious cardiopulmonary events*	9.4%*	2.3%*

Table 1 (continued)

Ref (first author/ year)	Population characteristics			HIPEC characteristics						Long-term outcomes			Post-operative results					
	n	PCI	CC-0/1 (%)	Open/ closed	Dose	Temp (°C)	T (min)	Dialysate	Remark	Med FU (m/y)	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Loggie 2001	12	-	67%	Closed	30 + 10 mg (T0–T60)	40.5–42	120	Lactated Ringer's solution 3 L		45.2	med 34.2 m	-	NCICTC	-	-	1 bowel perforation 1 anastomotic leak 1 prolonged ileus	8.3%	8.3%
Oxaliplatin																		
Hubert J 2015	19 (4 MCPM)	19 (4–39)°	89%	Open	460 mg/m^2 + IV 5-FU (400 mg/m2) and LV (20 mg/m^2)	42–43	30	Peritoneal 5% dextrose solution 2 L/m^2		26.8 m (9–102)	med NR 3-y: 91% 5-y DMPM: 57% MCPM: 100%	med 19.7 m (DMPM 15.6 m—MCPM 39.2 m) 3-y: 50%	CD	-	57%	33% anastomotic leaks (4 leaks on 12 anastomoses) 11% hematomas 11% intra abdominal abscesses	-	-
Carboplatin																		
Shetty 2014	30 (2 biph and 1 WDPPM)	-	87%	Closed	600–800 mg/m^2	41.5	90	0.9% sodium chloride 3–4 L		22.5 m	med nr 5-y: 63%	-	-	-	-	1 neutropenia 6 (20%) pancreatic fistula	-	0

*Results for the entire cohort; mean (range or standard deviation)

PCI, peritoneal carcinomatosis index; *CC-0/1*, completeness of cytoreduction score of 0 or 1 (complete cytoreduction rate); *Med FU*, median follow-up time in months (m) or years(y); *OS*, overall survival; *PFS*, progression-free survival; *T*, time in minutes (min); *C°*, complication rate; *GS*, grading system; *Sev*, severe; *R°*, reoperation rate; *D*, postoperative death; *CD*, Clavien-Dindo; *NCICTC*, national cancer institute common toxicology criteria; *pat*, patients; *sarc/biph*, sarcomatoïd or biphasic histologic sub-type; *SE*, standard error; *MCPM*, multicystic peritoneal mesothelioma; *WDPPM*, well-differentiated papillary peritoneal mesothelioma; *DMPM*, diffuse malignant peritoneal mesothelioma; *med*, median; *nr*, not reached; *L*, liter; *Ifos*, Ifosfamide; *tox*, toxicities; *anast*, anastomotic; *periop*, perioperative; *obst*, obstruction; *inf*, infection

Table 2 Summary of HIPEC protocols for mesothelioma patients

Regimen	N studies	CC-0/1	5-y OS	Severe C°	R°	D
Cisplatin + doxorubicin	10	47–95%	38–74%	7–39%	7–11%	0–7%
Cisplatin + mitomycin C	3	73–98%	39–44%	35–53%	0–18%	0–6.2%
Cisplatin	5	47–73%	46–47.5%	-	4–9.4%	0–2.3%
Mitomycin C	4	58–67%	27–54.6%	-	8.3–9.4%	0–10.5%
Oxaliplatin	1	89%	57%	57%	-	-
Carboplatin	1	87%	63%	-	-	0

CC-0/1, completeness of cytoreduction score of 0 or 1 (complete cytoreduction rate); *5-y OS*, 5-year overall survival; *Severe C°*, severe postoperative complication rate; *R°*, reoperation rate; *D*, postoperative death rate

chemotherapy in addition to cisplatin led to the same 6 patients treated above the MTD but no additional renal toxicity in the 13 other patients [59]. The median total cisplatin dose was 530 mg (range, 187–816), and no patients had grade 4 hematologic toxicity [59].

In parallel, Bartlett et al. explored the toxicity of HIPEC with cisplatin combined with TNFα in 27 patients with various histologies, including 5 DMPM patients [68]. Eighteen patients were treated with 250 mg/m^2 or more of cisplatin, of which 9 had also TNFα. A grade 4 renal toxicity was encountered in 2 of 2 patients who received the combined dose of 250 mg/m^2 cisplatin plus 0.3 mg/L TNFα. One of these patients required permanent dialysis. The MTD was therefore defined as 250 mg/m^2 of cisplatin plus 0.1 mg/L of TNFα [68]. No anastomotic complications happened upon 12 anastomosis and no evident association was seen between the dose of cisplatin and the postoperative time to regular diet [68]. Of note in this series, only 7 out of 29 patients had a complete CRS which could have influenced pharmacokinetic parameters and consequently the toxicity. Interestingly, the AUC measurements gave the impression of stagnation after 200 mg/m^2 while the tissular platinum uptake seemed to reach a plate from 250 mg/m^2[68].

Later on, Feldman et al. presented the results of 49 mesothelioma patients including those of the previously mentioned studies [60]. Overall, 35 out of 49 patients (72%) received also one administration of intraperitoneal 5-FU and paclitaxel, between the 7th and 10th postoperative days. The median dose of cisplatin was 250 mg/m^2 (mean 450 mg per patient (330–816)). Less than half of patients had a (sub-) complete CRS. Twelve patients (25%) presented 18 complications related to the operative procedure (2 patients required reoperation for fascial dehiscence or gastric perforation). The mean time between surgery and resumption of a regular diet was 8.5 days (range, 3 to 38 days)[60]. Regarding the toxicity, the EPIC treatment rendered difficult the interpretation of postoperative chemotherapy-linked side effects; however, the 15% of patients who presented Grades 3–4 creatinine increase could probably be imputed to the cisplatin-HIPEC (Table 1) [60]. Thirteen percent of patients had grade 3 or greater neutropenia in a time course consistent with an effect of paclitaxel and FU. Hyperamylasemia was observed in four patients (8%) but was not associated with symptoms of pancreatitis. Similarly, the hepatic biology perturbances were transient and not of clinical consequence [60]. At a median follow-up of 28.3 months (range, 1 to 106 months), the median actuarial PFS and OS were 17 and 92 months, respectively. Authors reported 36% of patients with low-grade histology, precluding an unbiased interpretation of the excellent survival results of this small cohort [60].

Finally, Schaub et al. reported the outcomes of 104 DMPM patients treated with cisplatin-HIPEC, from 250 to 400 mg/m^2, with 66% receiving also EPIC [58]. The median PFS and OS were 21 months (1–81) and 52 months (1–195) with 5-year PFS and OS of 13% and 46%, respectively [58].

Mitomycin C For mesothelioma patients, Loggie et al. reported a first series of 12 patients treated as part of a non-randomized phase II study evaluating 2 h HIPEC with MMC delivered as 2 fixed doses of 30 mg at T0 and 10 mg at T60 [61, 69, 70]. One patient died on the 60th postoperative day following a small bowel perforation with re-exploration [61]. Of note, this patient had 2 prior surgeries and multiagent systemic chemotherapy. One rectal anastomotic leak was efficiently treated conservatively while another patient presented a transient renal insufficiency [61]. All patients with ascites exhibited a resumption following the treatment. After a median follow-up of 45.2 months, the median OS was 34.2 months [61].

Further studies reporting outcomes of MMC-HIPEC for DMPM patients compared this protocol with cisplatine-HIPEC and are presented thereafter [18, 63, 64].

Oxaliplatin Oxaliplatin-HIPEC has been rarely used for mesothelioma patients. Hubert et al. reported a monocentric series of 15 epithelioid and 4 MCPM patients treated with complete CRS in 89% of cases [62]. Oxaliplatin was used at 460 mg/m^2 for 30 min with 2L/m^2 of peritoneal 5% dextrose solution heated to 42–43 °C, 1 h after the IV perfusion of 5-FU (400 mg/m^2) and leucovorin (20 mg/m^2) according to

Table 3 Studies comparing HIPEC regimen in mesothelioma patients

Reference	Design	HIPEC regimen	n	CC-0/1 (%)	Open / closed	Temp (°C)	T (min)	Dialysate	Med FU	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Blackham et al. 2010	Comparative retrospective study	Cisplatin 250 mg/m^2 + sodium thiosulfate	15 (1 biph)	73%	closed	40	60—120	Lactated Ringer's solution 3 L	1.9 y	med 10.8 m 1-y: 80% 3-y: 80%	med 10.6 m 3-y: 91% (complete CRS)	-	-	-	-	-	0
		MMC 30 to 40 mg	19 (3 biph)	58%					6 y	med 40.8 m 1-y: 47% 3-y: 42%	med 8.3 m 3-y: 45% (complete CRS)				2 POD: neutropenic sepsis respiratory failure		10.5%
				$p=0.82$					$p<0.001$	med: $p=0.22$ 1-y: $p=0.05$	$p=0.36$						
Alexander et al. 2013	Comparative retrospective study	Cisplatin 250 mg/m^2 + sodium thiosulfate	105	53%	closed	41	90	4–6 L	-	med 54.6 m 5-y: 47.5%	-	NCICTC	30%	-	9.6%: fistula, perforation, dehiscence, or infection 5%: prolonged ileus, vomiting, or obstruction 4.4%: surgical site inf 12%: non-infectious cardiopulmonary events*	9.4%*	2.3%*
		MMC 40 mg	106 (54 low grade and 44 unknown)						-	med 27.1 m 5-y: 54.6%	-						
										HR 2.58, 95%CI 1.49–4.47, p < 0.01	-		-	-		-	-
Shetty et al. 2014	Comparative retrospective study	MMC 30 + 10 mg (T0-T60)	11 (1 biph)	64%	closed	40.5—42	120	Lactated Ringer's solution 3 L	18 m	med 18 m 5-y: 27%	-	-	-	-	1 (9%) pancreatitis 2 (18%) prolonged ileus	-	0
		Carboplatin 600—800 mg/m^2	30 (2 biph and 1 WDPPM)	87%		41.5	90	0.9% sodium chloride 3—4 L	22.5 m	med nr 5-y: 63%	-	-	-	-	1 neutropenia 6 (20%) pancreatic fistula	-	0
			NS	NS		-	-	-		$p=0.014$	-		-	-	-	-	-

Table 3 (continued)

Reference	Design	HIPEC regimen	n	CC-0/1 (%)	Open / closed	Temp (°C)	T (min)	Dialysate	Med FU	OS	PFS	C° GS	C° rate	Sev C°	Type	R° (%)	D (%)
Malgras et al. 2018	Comparative retrospective study	One drug	88	57%	closed 12%	42–43	30–90	-	2 y	Better with 2 drugs HR 0.54, 95%CI 0.31–0.95, p = 0.03 Better in CC-0 and epith and 2 drugs HR 0.25, 95%CI 0.09–0.72, p = 0.009 No stat diff between 2 drugs regimen		CD	-	30%		12.5%	-
		Two drugs	161	97%	closed 84%									40%		15.5%	-
				p = 0.48	< 0.001									p = 0.16	-	p = 0.82	-

Lines with gray background correspond to the comparison between groups

CRS, cytoreductive surgery; *HIPEC*, hyperthermic intraperitoneal chemotherapy; *MMC*, mitomycin C; *PCI*, peritoneal carcinomatosis index; *CC-0/1*, completeness of cytoreduction score of 0 or 1 (complete cytoreduction rate); *Temp*, temperature; *T*, time in minutes; *5-y OS*, 5-year overall survival; *C°*, complication grading system; *Severe C°*, severe postoperative complication rate; *R°*, reoperation rate; *D*, postoperative death rate; *POD*, postoperative death, *CD*, Clavien Dindo; *NCICTC*, national cancer institute common toxicology criteria

the Elias protocol [71]. There was no chemotherapy-associated toxicity reported in the postoperative period while major complications occurred in 57% of cases (anastomotic leaks (33%) with 4 leaks on 12 anastomoses, hematomas (11%), and intra-abdominal abscesses (11%)) [62]. After a median follow-up of 26.8 months (9–102.3), the estimated 3-year DFS and OS rates were respectively 50% and 91% with an expected significant survival advantage for MCPM patients [62].

Carboplatin Carboplatin-HIPEC has been mainly used for ovarian carcinomatosis and rarely in DMPM patients [72, 73]. A regimen of 600–800 mg/m^2 was compared to MMC-HIPEC to treat mesothelioma patients and will be presented above [64].

Bi-drug Regimen

In the largest multicentric retrospective analysis of DMPM patients treated with CRS-HIPEC, a bi-drug regimen was used in 87% of patients [12]. It was the case for 75% of the studies included in the meta-analysis of Helm et al. [13].

Cisplatin and Mitomycin C The combination of cisplatin and MMC has been proven to be synergistically enhanced by hyperthermia in vitro on the colorectal cancer cell [74]. Brigand et al. specifically reported results prospectively recorded of 15 DMPM patients treated with CRS-HIPEC performed with Mitomycin C (0.5 mg/kg) and cisplatin (0.7 mg/kg) for 90 min [57]. Six postoperative complications (40%) were recorded with no need for reintervention. Two of these complications were specifically related to the HIPEC procedure: one patient developed a superficial wound necrosis due to chemotherapy extravasation and one developed a transient acute renal failure. [57]

Cisplatin and Doxorubicin The combination of cisplatin and doxorubicin as the HIPEC agent was the most referenced in the selected cohorts (Table 1). It was first introduced in an Italian phase I study including 31 patients of which 6 had DMPM [75]. The MTD was established at 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin. The mean AUC ratio was 20 (+/−6) and 162 (+/−113) for cisplatin and doxorubicin, respectively. The limiting toxicity was a persistent ileus requiring reoperation and adhesiolysis in one patient treated with 19 mg L/1 of doxorubicin and 43 mg L/1 of cisplatin [75]. The team from the National Cancer Institute of Milan reported its early experience in CRS-HIPEC for DMPM patients using two bi-drug cisplatin-based protocols along a phase II study: cisplatin combined with MMC, then cisplatin with doxorubicin [53, 76]. The modification proceeded because of a

Table 4 Summary of guidelines regarding HIPEC protocol indication for DMPM patients

Scope	Reference	Methodology	Indication	Regimen
International—PSOGI	Kusamura S et al. 2020	GRADE—Delphi	Complete CRS Incomplete CRS Recurrence	Cisplatin + doxorubicin
American—Chicago Consensu Working Group	Turaga K et al. 2020	Modified Delphi	Complete CRS Incomplete CRS	No regimen advised
Latin America Registry of Peritoneal Disease (LARPD)	Quadros CA et al. 2018	Online survey	Complete CRS with no pleural attempt	Cisplatin 50 mg/m^2 + doxorubicin 10–15 mg/m^2 60 min
Brazilian Society of Surgical Oncology (BSSO)	Batista TP et al. 2017	Non-systematic review by the BSSO Committee on Peritoneal Surface Malignancies and HIPEC	Epithelioid DMPM with Ki-67 < 25% or Ki-67 < 10% when PCI > 17–20	Cisplatin 100 mg/m^2 + doxorubicin 15 mg/m^2—60 min Or Carboplatin 800 mg/m^2—60 min MMC unavailable at this period in Brazil 30% reduction if age > 60 years, previous multiple lines of systemic chemotherapy, need for GM-CSF for febrile neutropenia, radiation therapy to bone-marrow bearing regions, and extensive CRS (high PCI) Dose limitation: 1000 mg/m^2 (or 200 mg/m^2/L of perf) for carboplatin 240 mg (or 45 mg/L of perf) for cisplatin 15 mg/L of perfusate for doxorubicin
China Anti-Cancer Association	Li Y et al	Expert consensus	Not specified	Not specified

better pharmacological profile, following a phase I study [76]. Protocols were cisplatin 25 mg/m^2/L + MMC 3.3 mg/m^2/L and cisplatin 43 mg/L + doxorubicin 15.25 mg/L of perfusate. The volume of perfusate was approximately 3.5 L/m^2 of body surface area in most cases [53]. In the report of their 49 first DMPM patients treated with CRS-HIPEC, the HIPEC protocol was not independently associated with neither OS nor PFS [53]. Five-year PFS and OS were 31% and 57%, respectively. Eighteen severe postoperative complications occurred in 8 cases (15%) and 9 severe toxicities in 6 cases (12%), notably two chronic renal failures (grade 4) [53]. These results were confirmed with an expended cohort of 108 DMPM patients from the same center (including 6 patients treated with cisplatin-MMC HIPEC), with 81% of complete CRS, revealing a 10-year PFS and OS of 36% and 45%, respectively, with 25% of severe complications, mostly made of surgical complications 11% of patients submitted to reoperation (Table1) [50].

The outcomes from other series evaluating the cisplatin-doxorubicin regimen were less easy to interpret as a notable proportion of patients were also treated with EPIC (Table 1). Of note, Robella et al. proposed an increased dose of cisplatin to 100 mg/m^2 combined with 16 mg/m^2 of doxorubicin in 42 patients with 24% of severe morbidity and 7% of postoperative mortality [49]. Authors demonstrated that this high rate of morbi-mortality was influenced by a learning-curve effect. The presence of 7 MCPM in this cohort precludes clear analysis of long-term outcomes which were 44% of 5-year OS [49].

Comparison Between HIPEC Regimen In 2014, Helm et al. produced a meta-analysis of 20 selected studies reporting CRS-HIPEC outcomes for malignant peritoneal mesothelioma [13]. By extrapolating the mortality rates, cisplatin alone and the drug combinations including doxorubicin, MMC, and cisplatin as HIPEC agents showed the best long-term outcomes with 49% and 45% of 5-year OS, respectively [13]. Multiple biases jeopardize the interpretation of these results. In the large retrospective cohorts evaluating the HIPEC regimen as prognosis factors on OS, results varied. The report from the Milan center presented before did not show a significant survival impact of the cisplatin or

Table 5 Qualityassessment of studies according to GRADE methodology

No of studies	Quality assessment					Overall quality	Importance	Grade of evidence
	Design	Quality	Consistency	Directness	Other modifying factors			
Severe post-operative complications								
Cisplatin + doxorubicin (10)	Observational	No serious limitations	No important inconsistency	Some uncertainty about directness	None	Moderate	Critical	Low
Cisplatin + mitomycin C (3)								
Cisplatin (5)								
Mitomycin C (4)								
Post-operative toxicities								
Cisplatin + doxorubicin (10)	Observational	No serious limitations	No important inconsistency	Some uncertainty about directness	Dose–response gradient for renal insufficiency	Moderate	Critical	Low
Cisplatin + mitomycin C (3)								
Cisplatin (5)								
Mitomycin C (4)					None			
Long-term outcomes: overall survival								
Cisplatin + doxorubicin (10)	Observational	No serious limitations	No important inconsistency	Some uncertainty about directness	Impact of the histologic sub-type	Moderate	Critical	Low
Cisplatin + mitomycin C (3)								
Cisplatin (5)								
Mitomycin C (4)								

The number between braquets indicates the number of studies included in the review evaluating the mentioned protocol

doxorubicin total doses, nor an advantage of cisplatin-doxorubicin on cisplatin-MMC; however, very few patients were treated with the second regimen [50]. Conversely, Ihemelandu et al. found a significant influence of the HIPEC regimen on survival, favoring a five-drug bidirectional protocol (cisplatin-doxorubicin HIPEC together with intravenous ifosfamide (1300 mg/m^2) followed by 5 days of paclitaxel-EPIC (20–40 mg/m^2; maximum dose 80 mg) and adjuvant bidirectional chemotherapy with intravenous cisplatin (75 mg/m^2) and intraperitoneal pemetrexed (500 mg/m^2) for 6 months) over cisplatin-doxorubicin (HR4.3, IC95%, 0.98–19.0, $p = 0.05$) and cisplatin alone (HR24.9, IC95%, 2.8–219, $p < 0.001$). Several biases shall weigh the extent of these results: the different time periods, the heterogeneity of the sub-groups regarding main DMPM prognosis factors, the variety of perioperative systemic chemotherapies, and some HIPEC performed in the recurrent setting [48].

Apart from that, the four studies focusing on the comparison between HIPEC regimens in mesothelioma patients are reported above (Table 2).

Platinum Salt vs Mitomycin C Blackham et al. retrospectively compared outcomes of 19 DMPM patients treated with MMC-HIPEC before 2004 to 15 cisplatin-HIPEC patients treated from 2004 [63]. The complications were not reported but 6 patients died within 90 postoperative days without knowing which protocol they had. Regarding oncologic outcomes, there was a trend in favor of cisplatin-based HIPEC with a median failure-free survival of 8.3 vs 10.6 months ($p = 0.26$) and a median OS of 10.8 versus 40.8 months ($p = 0.22$) for the MMC and cisplatin-HIPEC regimen, respectively [63]. These results should be balanced by the high rates of incomplete CRS (54% and 73%) and the proportion of biphasic variant (17% and 7%) in the MMC and cisplatin groups, respectively [63]. Three of the biphasic patients died within the 3 postoperative months. The small population, the non-comparability for main DMPM prognostic factors, and the learning-curve effect prevail over a definitive conclusion regarding this OS difference. However, one postoperative death in the MMC group was due to a neutropenic sepsis, a usual toxicity of intraperitoneal MMC [63].

Shetty et al. compared retrospectively carboplatin and MMC-based HIPEC with the same kind of limitations [64]. Eleven patients in the MMC group were compared to 30 patients treated with carboplatin-HIPEC including one WDPPM patient. The mean length of intensive care unit and hospital stays was significantly longer in the MMC group (12.5 vs 2.3 days and 18.9 vs 8.7 days, respectively), and so was the number of packed red blood cell units transfused (3.54 vs 0.83). One patient in the carboplatin group developed neutropenia. The 5-year OS was 27% and 63% in the MMC and carboplatin groups, respectively ($p=0.014$) [64].

Finally, in a retrospective analysis of 211 DMPM patients treated at 3 referral centers in the USA (106 MMC, 105 cisplatin), Alexander et al. reported that, in patients who had an optimal CRS, MMC was associated with a lower OS (HR2.58, IC95% 1.49–4.47, $p<0.01$) in multivariate analysis [18]. The median OS was 54.6 and 27.1 months and the 5-year OS was 47.5% and 31.4% ($p<0.01$) after cisplatin and MMC-based HIPEC, respectively [18].

One Drug vs Bi-drug HIPEC Protocols Malgras et al. explored HIPEC regimens applicated in 249 patients from the multicentric RENAPE database, of which 71 were of low grade [39]. Five drugs were used alone or in combination: cisplatin, doxorubicin, MMC, oxaliplatin, and irinotecan. The analysis was performed by comparing a one-drug group (cisplatin, MMC, or oxaliplatin, 88 patients) to a bi-drug group (cisplatin-doxorubicin, cisplatin-MMC, or oxaliplatin-irinotecan, 161 patients) [39]. These groups were comparable for main parameters except mean PCI, significantly higher in the one-drug group (19 (14–26) vs 15 (9–12), $p=0.006$), and the closed HIPEC technic performed more often in the bi-drug group (84% vs 12%, $p<0.001$) [39]. OS was better in the combined chemotherapy group (HR0.54, 95%CI 0.31–0.95; $p=0.03$); however, the mix of low-grade histologies and the different disease extent jeopardize the relevance of this result. Interestingly, when stratifying on epithelioid and CC-0 patients, OS remained better in the bi-drug group than in the one-drug group (HR0.25, 95%CI 0.09–0.72; $p=0.009$), while the improvement of PFS was just above the threshold of statistical significance (HR0.48, 95%CI 0.21–1.07; $p=0.07$) [39]. There was no statistical difference in OS between the different regimens of combined chemotherapy, although the oxaliplatin-irinotecan combination had the best prognostic impact [39]. Major morbidity was 30% and 40% ($p=0.16$) and the reoperation rate was 13% and 16% ($p=0.11$) in the one-drug and bi-drug groups, respectively [39].

HIPEC Regimens Proposed in Guidelines Five articles reporting national/international guidelines were reviewed [31–35]. All recommended the addition of HIPEC to CRS in selected patients. Two guidelines did not specify the protocol [32, 35]. In the PSOGI guidelines, 93% of the voters were prone to a cisplatin-based regimen, and 85% judged the cisplatine-doxorubicin combination as the preferred regimen [31]. HIPEC after an incomplete cytoreduction down to residual disease > 2.5 mm could be considered in DMPM patients [31]. The Latin America Registry of Peritoneal Disease proposed also cisplatin 50 mg/m^2 with doxorubicin 10–15 mg/m^2 but for 60 min [33]. The Brazilian Society of Surgical Oncology recommended the same regimen or carboplatin 800 mg/m^2 as an alternative, considering that MMC was unavailable in Brazil [34]. Interestingly, authors specified several application criteria with dose limitations (Table 3).

Discussion

Regarding the question of which HIPEC regimen would be the most appropriate for mesothelioma patients, two facts seem to emerge from this analysis: cisplatin appeared as the central HIPEC drug with a manageable toxicity profile, and a combined drug regimen could lead to better long-term outcomes, favoring HIPEC with cisplatin-doxorubicin. This late protocol was the preferred one in the national/international guidelines for peritoneal mesothelioma patient management.

The comprehensive treatment combining exhaustive CRS followed by HIPEC in expert centers led to the best long-term outcomes in DMPM patients, profoundly modifying the prognosis of the eligible patients. No randomized control trial support the benefit of adding HIPEC to CRS because of that disease rarity and aggressivity, but also because the corpus of retrospective data obtained in international expert centers from prospectively maintained database led to confirm the indication in international guidelines. However, several pitfalls have accompanied the development of this technique, one of them being the heterogeneity of the HIPEC protocols, not only for mesothelioma patients. To harmonize clinical practice and reinforce the evaluation of HIPEC, the PSOGI initiated a consensus-building process supported by the GRADE and Delphi methodologies, justifying this systematic review. Determining the most appropriate HIPEC regimen for mesothelioma patients remains difficult after this work as data were scarce, mostly retrospective, rarely comparative, obtained over a large period of time, and, finally, of low level of evidence. Moreover, several parameters biased the analysis of the selected studies. The histologic diagnosis of peritoneal mesothelioma gained clarity and reproducibility this last decade thanks to collaborative works [4], but a majority of reports included low-grade mesothelioma with no independent analysis of their long-term outcomes, despite their intrinsic far better prognosis. Typically, the 35% of patients described as low-grade peritoneal mesothelioma in the Feldman et al. series would probably be more precisely characterized nowadays

thanks to immunohistochemistry and BAP1 expression [60, 77]. Biphasic and sarcomatoid peritoneal mesothelioma are of poorer diagnosis but these patients do not seem to respond differently than epithelioid forms to HIPEC treatment when CRS is complete [78], while mixing malignant and borderline mesothelioma patients preclude survival analysis in small cohorts. The second bias was the interference of perioperative treatments. In 60% of the selected studies reporting cisplatin-doxorubicin-HIPEC outcomes, some patients were also treated with EPIC, jeopardizing the interpretation of postoperative toxicities and complications. The variable rate of complete CRS, from 47 to 98% overall, could also hamper the HIPEC effects. CC-score is probably the strongest prognostic factor for mesothelioma patients treated with CRS-HIPEC and the extent of CRS has been reported to influence the systemic passage of the drug administered intraperitoneally, and so its toxicity [79].

Peritoneal mesothelioma, similar to the pleural form of the disease, presents high rates of homologous recombination deficiency correlated to a sensitivity to cisplatin [80, 81]. Consistently with the intravenous chemotherapy strategy, the preferred drug for HIPEC in this review was cisplatin [11, 82–84]. This is one of the most ancient drugs used for IP administration in normothermic or hyperthermic condition, namely because of an enhanced cytotoxicity with hyperthermia, a good AUC ratio profile, and a tissular penetration of 2.5 mm demonstrated in vivo [65, 66, 85–88]. The main toxicity induced by cisplatin-based HIPEC is renal insufficiency in a dose-dependent manner, potentially leading to chronic dialysis. This nephron toxicity has been proven to be efficiently prevented by concomitant intravenous perfusion of sodium thiosulfate. The phase I studies from the Surgical Branch of the NCI allowed to determine 250 mg/m^2 as the MTD for HIPEC as long as intravenous sodium thiosulfate was concomitantly used. Interestingly, none of the selected cisplatin-doxorubicin HIPEC studies reported the use of sodium thiosulfate and the dose proposed was, most of the time, 50 mg/m^2 in addition to doxorubicin 15 mg/m^2. Robella et al. proposed cisplatin 100 mg/m^2 and Baratti et al. 45 mg/L with 4 to 6 L used as HIPEC bath leading to a mean dose of 181 mg (41) [49, 50]. Postoperative complications were not detailed in the first cohort, while 10 renal toxicities were reported in the second, in 9% of patients without knowing the grade and the duration of the impairment. In the report of their early experience, the same team described two grade 3 acute renal failures and two grade 4 chronic renal failures on 40 mesothelioma patients [53]. A retrospective study comparing two periods of cisplatin-based HIPEC, one with and one without thiosulfate, showed a complete disappearance of post-operative renal failure with nephroprotection [89]. In parallel, the pharmacokinetic study together with the measurement of tissular platinum uptake by Bartlett et al. suggested that a benefit of increased dose of cisplatin could be expected up to 200 mg/m^2[68]. These reports analyzed together suggest that the cisplatin dose in the combined regimen could be the object of an escalating dose trial.

Conclusion

This systematic review of the literature regarding the choice of HIPEC regimen in addition to CRS for DMPM patients highlighted two main alternatives: cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2 over 90 min, and cisplatin 250 mg/m^2 with concomitant IV perfusion of sodium thiosulfate. A trend toward a survival advantage with bi-drug regimens suggests that cisplatin + doxorubicin protocol probably explains the reason why this protocol was recommended in international guidelines. Further clinical studies are needed, namely to evaluate a cisplatin dose escalation in combination with doxorubicin.

Author Contribution VK: conceptualization, data curation, formal analysis, writing original draft, review, and editing.
OS: conceptualization, formal analysis, draft review, and editing.
FM: conceptualization, formal analysis, draft review, and editing.
LV: conceptualization, formal analysis, draft review, and editing.
SK: conceptualization, data curation, formal analysis, draft review, and editing.
OG: conceptualization, formal analysis, draft review, and editing.
MD: conceptualization, data curation, formal analysis, draft review, and editing.

Data Availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of Interest The authors declare no competing interests.

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