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Hyperthermic Intraperitoneal Chemotherapy with Mitomycin C versus Oxaliplatin after Cytoreductive Surgery for the Treatment of Peritoneal Metastases of Colorectal Cancer Origin

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Abbreviations:
HIPEC: hyperthermic intraperitoneal chemotherapy;
PM: peritoneal metastases;
CRC: colorectal cancer;
CRS: cytoreductive surgery;
MMC: mitomycin C.

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Rezumat

Chimioterapia intraperitoneală hipertermică cu mitomicină C vs oxaliplatină după intervenția chirurgicală citoreductivă pentru tratamentul metastazelor peritoneale ale cancerului colorectal

Context: Mitomicina C şi oxaliplatina sunt considerate principalii agenți chimioterapici utilizați în cadrul chimioterapiei hipertermice intraperitoneale (HIPEC) după efectuarea intervenției chirurgicale de citoreducție pentru metastazele peritoneale ale cancerului colorectal. Cu toate acestea, nu există un consens general acceptat cu privire la alegerea agentului chimioterapic de primă intenție. Acest studiu îşi propune să rezume într-o manieră cuprinzătoare datele disponibile, având în vedere că schemele individualizate de terapie țintită sunt în curs de dezvoltare.
Metode: Acest articol este un review narativ, comprehensiv, ce include toate studiile publicate până în martie 2022 care au raportat rezultatele perioperatorii şi/sau oncologice după utilizarea mitomicinei C şi/sau oxaliplatinei ca agenți principali în chimioterapia hipertermică după intervenția chirurgicală citoreductivă pentru metastazele peritoneale ale cancerului colorectal.
Rezultate: Acest review include datele dintr-un total de 23 de studii ce analizează un singur agent şi 13 studii ce compară utilizarea celor 2 subtanțe. În ciuda profilului de siguranță demonstrat al ambelor chimioterapice, eterogenitatea studiilor incluse, natura lor retrospectivă şi absența unor studii randomizate relevante împiedică stabilirea unor concluzii sigure cu privire la superioritatea unuia dintre cei doi agenți. Cu toate acestea, se pare că morbiditatea perioperatorie este mai redusă în cazul HIPEC pe

bază de oxalplatină, în timp ce mitomicina C apare ca o opțiune mai rentabilă.
Concluzii: Alegerea agentului optim pentru chimioterapia intraperitoneală pentru metastazele peritoneale ale cancerului colorectal după finalizarea intervenției chirurgicale de citoreducție este încă o chestiune în dezbatere, cu variații instituționale semnificative. Sunt necesare studii clinice randomizate suplimentare care să evalueze diferențele dintre cele două substanțe cel mai frecvent utilizante în HIPEC, în ceea ce privește rezultatele perioperatorii şi oncologice, costurile asociate îngrijirii medicale şi calitatea vieții pacienților.

Cuvinte cheie: mitomicina, oxaliplatina, hipertermie, chimioterapie, citoreducție

Abstract
Background: Mitomycin C and oxaliplatin are considered the main chemotherapeutic agents used in the context of hyperthermic intraperitoneal chemotherapy (HIPEC) after the performance of cytoreductive surgery for peritoneal metastases of colorectal cancer origin. However, there is lack of a generally accepted consensus regarding the optimal choice between them as upfront chemo-therapetic agent. Our paper aims to summarize in a comprehensive manner the available evidence, while individualised schemes with targeted therapies are under development.
Methods: We conducted a comprehensive, narrative review of the literature including all previous studies until 03/2022, which reported perioperative and/ or oncological outcomes after the use of mitomycin C and/ or oxaliplatin as main hyperthermic chemotherapy agents after cytoreductive surgery for colorectal peritoneal metastatic disease.
Results: Data from a total of 23 single-agent and 13 comparative studies were included in our review. Despite the demonstrated safety profile of both chemotherapeutics, the heterogeneity of the included studies, their retrospective nature and the absence of relevant randomized trials prohibits the drawing of safe conclusions regarding the superiority of one of the two agents. However, it seems that perioperative morbidity is less with oxaliplatin-based HIPEC, while mitomycin C appears as a more cost-effective option.
Conclusions: Selection of the optimal intraperitoneal chemotherapy agent for peritoneal metastases of colorectal cancer origin after the completion of cytoreductive surgery is still a matter of debate, with significant institutional variation. Further randomized clinical trials between the two commonest HIPEC agents are required, assessing the differences in perioperative outcomes, oncological outcomes, healthcare-associated costs and patients' quality of life.

Key words: mitomycin, oxaliplatin, hyperthermia, chemotherapy, cytoreduction

Introduction

The development of peritoneal metastases (PM) from colorectal cancer (CRC) was until recently regarded as a terminal condition, with the patients being eligible only for palliative treatment (1). The advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been a revolutionary approach in the treatment of peritoneal dissemination of colorectal cancer and is now considered a standard of care in appropriately selected cases (2-5). This combined procedure aims to remove all the visible cancerous lesions in the abdomen and pelvis with the performance of the necessary surgical resections (cytoreduction). Sequentially, the intraperitoneal chemotherapy, usually in the form of a hyperthermic solution (HIPEC), is administered in

order to eliminate the residual non-visible metastatic deposits. With respect to peritoneal metastases of colorectal cancer origin, Verwaal et al (6) demonstrated in their landmark clinical trial the oncological superiority of CRS & HIPEC compared to the conventional palliative treatment. Moreover, there is mounting evidence that apart from a reliable and safe treatment modality for peritoneal metastases, HIPEC can have an important role as a means of prevention of peritoneal spread in high-risk patients with locally advanced colorectal cancer (7-9).

Given the magnitude of this complex procedure, the optimization of its technical aspects is of critical importance (10,11). In this framework, it is understood that since the performance of optimal cytoreduction lies mainly on the technical expertise of the surgical team and the appropriate patient selection, the optimization of HIPEC constitutes a field with notable clinical and translational research perspectives. Key features of HIPEC, such as the selection of the appropriate chemotherapeutic agent(s), the duration of chemoperfusion, the concentration and temperature of the perfusate represent technical parameters which could be further optimized, aiming to achieve a balance between the avoidance of systemic toxicity and maximal penetration to the residual disease after the completion of cytoreduction (12-14). When referring to HIPEC after CRS for colorectal peritoneal metastases, mitomycin C (MMC) and oxaliplatin are the most widely used principal chemotherapeutic agents in the peritoneal surface malignancy centers (15). From this perspective, it is of paramount importance that further improvement of the technique lies on the thorough knowledge of the pharmacokinetics of the chemotherapeutic agents, the mechanisms through which they exhibit their biological actions, as well as the expected adverse effects, at both local and systemic level. Combining the above-mentioned with the results of the various clinical studies using MMC-based or oxaliplatin-based HIPEC would enable the acquisition of a well-rounded approach towards the critical issue of chemo-therapeutic agent selection for the performance of HIPEC in the treatment of colorectal peritoneal metastases. Herein, we attempt to present in a comprehensive way the relevant clinical data, aiming to identify the similarities and differences between the profiles of MMC and oxaliplatin-based HIPEC for peritoneal metastatic disease arising from (non-appendiceal) colorectal cancer, providing a critical insight into the topic and highlighting the emerging opportunities and necessity for further clinical research in the field.

Methods

We performed a comprehensive review of the published studies assessing the use of MMC or oxaliplatin in intraperitoneal chemotherapy after cytoreductive surgery for peritoneal metastases of colorectal cancer origin, that were published until March 2022 in PubMed search engine, using the following combination of key words: "intraperitoneal chemotherapy", "HIPEC", "mitomycin", "oxaliplatin", "cancer", "metastases" and "colorectal". The relevant references of the retrieved manuscripts were manually scanned to further identify possible relevant studies. Case reports and case series were excluded, as were studies published in languages other than English.

Results

Despite the various differences regarding the performance of HIPEC across the peritoneal surface malignancy centers (36), it is undisputed that MMC and oxaliplatin are the two most widely used and well-studied chemotherapeutic agents during HIPEC after cytoreductive surgery for peritoneal metastases of colorectal cancer origin, with their impact on oncological outcome being extensively investigated in various clinical studies (15), which are herein presented in a descriptive way (*Tables 1, 2)* for oxaliplatin-based HIPEC & *Tables 3-5* for Mitomycin C-based HIPEC

Table 1. Clinical studies evaluating the role of oxaliplatin-based HIPEC after cytoreductive surgery for colorectal peritoneal metastases (cont)

Authors/Date	Study Sample	HIPEC	EPIC	Intra-operative systemic chemotherapy	Temperature/ duration of perfusion	Study key-features / Outcomes
Nikolic et al, 2014 [37]	n=61	oxaliplatin (410 mg/m^2)	no	no	41 ° C for 30-60 min	• Median follow-up post-op 22 months (1-83 months) • Median OS 51 months (95% confidence interval/CI 22+) • Median DFS for patients without residual disease (57/61, 93.44%) was 23 months (95% CI 16+). • 1-,2- and 6-year OS (DFS) were 78.6% (68.3%), 58.7% (46.7%) and 50.5% (38.1%) respectively • Patients with PCI <13 (vs PCI≥13) had significantly longer OS and DFS [also confirmed for PCI subcategories (PCI <7 vs 7≥ PCI <13 vs PCI≥13)]
Elias et al, 2013 [38]	n=114	oxaliplatin alone (460 mg/m^2) n=25 or oxaliplatin (300 mg/m^2) + irinotecan (200mg/m^2) n=92	no	i.v. leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	mean 43 ° C for 30 min	• mean follow-up 4.5 years, median follow-up 3.9 years • post-op mortality 3.5% (4/114 patients) • at time of follow-up, 26% of patients alive without recurrence, 32% alive with recurrence and 41% deceased • increased risk of death was significantly associated with a rectal primary and a PCI> 10 / PCI > 10 remained a significant risk factor for recurrence • visible cardiophrenic angle lymph nodes not associated with decrease OS and DFS
Gervais et al, 2013 [39]	n=25	oxaliplatin (460 mg/m^2)	no	i.v. leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	mean 43 ° C for 30 min	• 20% grade 3-5 complications / post-operative mortality 4% (1/25) • 3- and 5-year OS rates were, respectively 61% and 36% for patients who received CRS+HIPEC with a 3-year DFS rate of 22% • PCI and lymph node status independent predictors of DFS
Hompes et al, 2012 [40]	n=48	oxaliplatin (460 mg/m^2)	no	i.v. folinic acid 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	41-42 ° C for 30 min	• 0% 30-day postoperative mortality / 52.1% overall morbidity (any grade) [2.1% haematologic toxicity] • At median follow-up of 22.7 (range 3.2–55.7) months, OS was 97.9% 95% confidence interval (CI) 86.1–99.7] at 1 year and 88.7% [(95% CI 73.6–95.4) at 2 years • DFS at 1 year was 65.8% (95% CI 52.3–76.2) and 45.5% (95% CI 34.3–55.9)

for colorectal cancer peritoneal metastases – trials with significant percentage of patients with appendiceal origin PM or unclear discrimination of the outcome aspects between patients with the colorectal vs appendiceal origin were not included as possible).

Through our literature search, which yealded a total of 36 studies, as demonstrated, the post-operative mortality and morbidity rates, as well as the oncological outcomes in MMC and oxaliplatin-based HIPEC are comparable; however, the methodological and technical differences, as well as the different patient selection criteria and tumor histo-logical variances across the existing studies prohibit the extraction of solid conclusions regarding the superiority or non-inferiority of these two chemotherapeutic agents.

With respect to the data from the performed comparative studies between mitomycin C vs oxaliplatin-based HIPEC for colorectal peritoneal metastases, there has been a significant increase of the relevant research output over the last two decades. More specifically, in one of the first comparative studies, Hompes et al (63), using two separate patient cohorts that underwent cytoreductive surgery and HIPEC for colorectal cancer peritoneal metastases with oxaliplatin (n=39

Table 2. Clinical studies evaluating the role of oxaliplatin-based HIPEC after cytoreductive surgery for colorectal peritoneal metastases

Authors/Date	Study Sample	HIPEC	EPIC	Perioperative systemic chemotherapy	Temperature/ duration of perfusion	Study key-features / Outcomes
Elias et al, 2009 [41]	n=48 (plus n=48 controls -palliative)	oxaliplatin (460 mg/m^2)	no	i.v. leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	mean 43 °C for 30 min	• mean follow-up 63 months for the HIPEC group & 95.7 months for the standard group • 2-year and 5-year overall survival rates were 81% and 51% for the HIPEC group, respectively [65% and 13% for the standard group, respectively] • Median survival 23.9 months in the standard group versus 62.7 months in the HIPEC group
Ceelen et al, 2008 [42]	n=33 with CRC PM (total 52 patients with PM)	oxaliplatin (460 mg/m^2)	no	i.v. folinic acid 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	41-42 °C for 30 min	• 0% 30-day mortality, overall survival is 80% at 1 year post–operatively in the CRC patients • 0% clinically important bone marrow depletion • 24% post-op major morbidity (entire cohort of 52 patients)
Elias, et al 2006 [43]	n=30	oxaliplatin (460 mg/m^2)	no	i.v. leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	42-44 °C for 30 min	• Mean follow-up 55 months (range: 24-80) • Post-operative mortality 0%; 40% grade 2/3 post-operative morbidity • 2/24 patients experienced post-op bone marrow suppression • At 3 and 5 years, OS rates were 53% and 48.5% respectively • At 3 and 5 years, DFS rates were 41.5% and 34% respectively • Median survival 60.1 months
Elias et al, 2004 [44]	n=24 (only patients with a minimal follow-up of 18 months)	oxaliplatin (460 mg/m^2)	no	i.v. leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 over 1 hour	42-44 °C for 30 min	• 41.6% morbidity - Grade 2 or 3 complications, with 2/24 patients experienced • Mean follow-up 27.4 months (range 18.3–49.6) • Overall survival rates at 1, 2 and 3 years were, respectively, 83%, 74% and 65%, and disease-free survival rates were, respectively, 61%, 50% and 50% • Incidence of peritoneal recurrence at 1, 2 and 3 years was 11%, 32% and 32% for the 22 surviving patients. • PCI>24 had prognostic impact on recurrence, but the presence of associated visceral metastases did not

patients) and MMC (n=56 patients) from two different HIPEC-centers, performed a comparative analysis of the HIPEC-related toxicity and survival outcomes. Regarding the technical aspect of HIPEC, after the completion of cytoreduction, MMC was administered at a dose of 35 mg/m^2 for 90 min, while the oxaliplatin dose was 460 mg/m^2 for a period of 30 min. After statistical correction for the extent of PC, the researchers demonstrated that the overall postoperative complication rate was significantly higher in MMC - patients (OR=2.68 (95% CI: 1.04–6.91), P=0.04), with a comparable intra-abdominal complication rate (OR=0.78 (95% CI: 0.30–2.03), P=0.61) and a tendency towards more extra-abdominal complications in the MMC group (OR=2.23 (95% CI: 0.91–5.43), P=0.079). It should be noted that hematologic toxicity occurred only in the MMC group in 26.8% of patients, manifested as neutropenia or leucopenia; in both groups the post-operative mortality rates were 0%. Regarding the survival outcomes, with the median follow-up being significantly shorter for oxaliplatin-patients (2.8 years) than for MMC-patients (5.1 years), it was demonstrated that the median RFS was 12.2 months (IQR: 7.2-undefined) in the oxaliplatin group and 13.8 months (IQR: 7.0–25.8) in the MMC-group (P=0.87). Moreover, the median OS was 37.1 months (IQR: 22.4–52.8) for oxaliplatin-patients and 26.5 months (IQR:

Table 3. Clinical studies evaluating the role of MMC-based HIPEC after cytoreductive surgery for colorectal peritoneal metastases

Authors/Date	Study Sample	HIPEC	EPIC	Intra-operative systemic chemotherapy	Temperature/ duration of perfusion	Study key-features / Outcomes
Kuijpers et al, 2013 [45]	n=660 patients with CRC PM (plus 300 with PMP)	MMC 35 mg/m^2 or oxaliplatin 460 mg/m^2 in re-do procedures	no	i.v. folinic acid 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 in the oxaliplatin-based HIPEC cases	41-42° C for 90 min	• 3% mortality and 34% morbidity (grade 3-4 complications) [entire cohort] • Median follow-up 41 months (95 % confidence interval (CI), 36–46 months) [entire cohort] • Median PFS was 15 months (95 % CI 13–17 months) for CRC group • Median OS 33 months (95 % CI 28–38 months) months for CRC group • 3- and 5-year survival rates 46 and 31 % respectively for CRC group
Hamilton, et al, 2011 [46]	n=31	MMC 12-15 mg/m^2	5-FU 1000 mg days 1-5	no	40-42° C for 90 min	• median DFS was 9 months and median OS was 27 months • 3-year and 5-year DFS was 34% and 26%, respectively • 3-year and 5-year OS was 38% and 34%, respectively • At a median follow-up of 25 months, 19% disease free, 16% alive with disease, and 65% dead of disease
Chua et al, 2010 [47]	n=56	MMC 10–20 mg/m^2	no	no	42° C for 90 min	• mean follow-up period 20 months (range 3–63 months)/ median OS was 38 months • 1-, 2-, and 3-year OS rates 85%, 66%, and 48% respectively
Varban et al, 2009 [48]	n=142 (with n=14 having concurrent liver mets)	MMC 30-40 mg	no	no	40.5-42.5° C for 60-120 min	• postoperative morbidity was 57.1% among patients with HM and 40.1% among patients without HM / postoperative mortality was 7.1% among patients with HM and 7.7% among patients without HM • median OS for patients with HM was 23.0 months / 2-year and 4-year survival rates were 43.3% and 14.4%, respectively • patients without HM had 2-year and 4-year survival rates of 36.8% and 17.4%, respectively • OS was not significantly different for patients with and without HM
Yan et al, 2008 [49]	n=50	MMC 10-12.5 mg/m^2	5-FU 650-800 mg/m^2 days 1-5	no	42° C for 90 min	• 0% post-operative mortality, 30% post-operative morbidity • median follow-up of 14 months (range 1–56 months) • median survival was 29 months (range 1–56 months) • 1-, 2- and 3-year OS of 79%, 67%, and 39%, respectively • Well/moderate tumor differentiation & completeness of cytoreduction independent prognostic factors of improved survival

16.9–64.8) for MMC-patients (P=0.45); however, after the performance of logistic regression analysis, corrected for the extent of PCI, the RFS (HR=1.24 (95% CI: 0.75–2.05), P=0.39) and OS (HR=1.37 (95% CI: 0.74–2.54), P=0.32) were not significantly different between the two groups.

In a similar study, Glockzin et al (64), compared the post-operative mortality and morbidity in a total of 80 patients who underwent CRS+HIPEC for colorectal cancer PM. Specifically, the MMC group consisted of 40 patients, 40 patients received MMC at a concentration of 20 mg/m^2 and doxorubicin at a concentration of 15 mg/m^2 as HIPEC over a 60 min perfusion time. On the other hand, the oxaliplatin-based HIPEC group constituted of another 40 case-matched patients, with 35 of the 40 patients being treated with combined oxaliplatin at a concentration of 300 mg/m^2 for 30 min with additional intravenous administration of 5-FU (400 mg/m^2) and folinic acid (20 mg/m^2) prior to the chemoperfusion and the remaining 5 patients receiving only oxaliplatin 300 mg/m^2. Although the patients' demographics were similar between the two groups, the oxaliplatin group included significantly

Table 4. Clinical studies evaluating the role of MMC-based HIPEC after cytoreductive surgery for colorectal peritoneal metastases

Authors/Date	Study Sample	HIPEC	EPIC	Intra-operative systemic chemotherapy	Temperature/ duration of perfusion	Study key-features / Outcomes
Verwaal et al, 2003/2008 [6,50]	n=54 (plus n=51 standard treatment arm)	MMC 17.5 mg/m^2, followed by 8.8 mg/m^2 every 30 min (70 mg max)	no	no	41-42° C for 90 min	• Disease-specific survival was 12.6 months in the standard arm and 22.3 months in the HIPEC arm • PFS was 7.7 months in the standard arm and 12.6 months in the HIPEC arm • median survival of 48 months / 5-year survival of 45% after complete cytoreduction
Piso et al 2007 [51]	n=32 (16/32 appendiceal)	MMC 20 mg/m^2 with doxorubicin 15 mg/m^2	5-FU 650 mg/m^2 days 1-3	no	41-42° C for 60 min	• 0% post-op mortality & 34% post-op morbidity [entire cohort] • median follow-up 12 months (range 3–28 months) [entire cohort] • 1-year OS 96% [entire cohort]
da Silva et al 2006 & Pestieau et al 2000 [52,53]	n=70 (complete CRS)	MMC 10-12.5 mg/m^2	5-FU 650 mg/m^2 days 1-5	no	41-42° C for 90 min	• post-operative morbidity 16% • mean follow up 46.5 months (range 6 to 241 months)/median survival of was 33 months • 1-, 3-, and 5-year OS 88%, 44%, and 32% respectively • PCI >20 and lymph node involvement at the time of the first procedure independent prognostic factors of survival
Zanon et al, 2006 [54]	n=25	MMC 15 mg/m^2	no	no	42° C for 60 min	• 4% post-operative mortality, 24% post-operative morbidity • Median OS was 30.3 months / PFS 17.3 months • 1- and 2-year OS 64% and 40% respectively
Verwaal et al, 2005 [55]	n=117	MMC 25-40 mg/m^2	no	no	41-42° C for 90 min	• 6% post-operative mortality / median survival was 21.8 months • 1-, 3-, and 5-year survival rates were 75%, 28%, and 19%, respectively • complete cytoreduction resulted in a median survival of 28 months, and an incomplete cytoreduction in a median of 10 month survival

higher number of patients with peritoneal carcinomatosis from appendiceal adenocarcinoma. The authors did not detect any significant differences regarding the intraoperative blood loss, operating time, peritoneal cancer index (PCI), number of performed anastomoses and completion of cytoreduction rates. Moreover, no statistically significant differences occurred in terms of overall length of hospitalization and ICU stay. The study demonstrated the presence of similar overall grade 3/4 complication rates, which were 42.5% in the oxaliplatin group and 37.5% in the MMC group, respectively (P=0.648), with no hematologic toxicity-related complications occurring in any of the two groups. In addition, the overall rate of revision surgery was 12.5% in the oxaliplatin group versus 15% in the MMC group (P=0.746). Finally, similar in-hospital mortality was noted (depending on the length of hospital stay), reaching 2.5% in the oxaliplatin group versus 0% in the MMC group; the 90-day mortality was 2.5% and 5%, in the oxaliplatin and MMC groups of patients, respectively.

The issue of possible existence of differences regarding the hematologic toxicity between MMC and oxaliplatin-based HIPEC after cytoreductive surgery has also been recently addressed by Votanopoulos et al in a retrospective review of a 187-patient cohort with peritoneal metastases arising from

Table 5. Clinical studies evaluating the role of MMC-based HIPEC after cytoreductive surgery for colorectal peritoneal metastases

Authors/Date	Study Sample	HIPEC	EPIC	Intra-operative systemic chemotherapy	Temperature/ duration of perfusion	Study key-features / Outcomes
Kecmanovic et al 2005 [56]	n=18	MMC 10-12.5 mg/m^2	5-FU 15 mg/kg days 1-5	no	42° C for 120 min	• 0% post-operative mortality / 44.4% post-operative morbidity (2 cases of bone marrow suppression) • Median follow-up was 21 months (range 1-56 months) • Median survival time 15 months (range 1-57 months)
Glehen et al 2004 [57]	n=53	MMC 40-60 mg (10 mg/mL)	no	no	46-48° C for 90 min	• 4% post-operative mortality / 23% post-operative morbidity • median follow-up was 59.5 (range 2–148) months / median OS 12.8 months • 1-, 2- and 5-year OS were 55%, 32% and 11% respectively • completeness of cytoreduction independent prognostic factor of survival
Shen et al, 2004 & Levine et al 2007, 2011 [58-60]	n=248 [entire cohort of 1000 patients]	MMC 30-40 mg [oxaliplatin 200mg/m^2 in selected cases]	no	no	40-43° C for 60-120 min	• 30-day postoperative morbidity and mortality were 42% and 3.8%, respectively for the entire cohort • median follow-up of 54.1 months, median OS was 29.4 months • 1-, 3-, 5-, 10-, and 15-year OS rates (± SE) were 72.3% (±1.5%), 44.6% (±1.7%), 31.5% (±1.8%), 18.1%, (±1.9%), and 10.7% (±2.7%), respectively for the entire cohort • median survival in CRC patients 16.4 months
Pilati et al 2003 [61]	n=34	MMC 3.3 mg/m^2/L and CDDP 25 mg/m^2/L	no	no	41.5° C for 90 min	• 0% post-operative mortality / 35% post-operative morbidity – no loco-regional or systemic toxicity • median follow-up was 14.5 months (range 6- 34 months) • 2-year overall survival 31%, and the median survival time and the median time to local disease progression were 18 and 13 months respectively
Witkamp et al 2001 [62]	n=29 (3/29 appendiceal origin)	MMC 15–40 mg/m^2	no	no	40-41° C for 90 min	• 3% treatment-related mortality & morbidity rate of 38% / grade III leucopenia in 9/29 patients • no long-term toxicity or morbidity related to HIPEC registered • Mean and median time to recurrence 12 and 11 months, respectively (range 3–29) • 1-(95% CI: 69–96%), 2- (95% CI: 27–63%) and 3-year (95% CI: 7–39%) survival rates 82%, 45% and 23%, respectively

colorectal (including appendiceal) cancer (19). In this study, fifty-five patients (29.4%) had oxaliplatin-based HIPEC while 132 patients (70.6%) received MMC-based HIPEC. The authors demonstrated a 14.5% incidence of grade 3/4 neutrophil toxicity and a 10.9% incidence of grade 3/4 platelet toxicity among all patients treated with oxaliplatin-based HIPEC. More specifically, the patients of the oxaliplatin group had a significantly higher incidence of grade 3 and 4 platelet toxicity (7.3% vs 0.0% and 3.6% vs 3.0% respectively), compared to the MMC group (P =0.008). Moreover, a trend reaching statistical significance was noted regarding the occurrence of neutrophil toxicity, with oxaliplatin having a higher incidence of grade 2, 3, and 4 toxicity (P = 0.06). In order to enable a safer comparison of the hematologic toxicity, the authors examined the above-mentioned data according to the performance of splenectomy during the cytoreduction process. Comparing hematologic toxicities of

MMC and oxaliplatin among the cohort of patients who underwent splenectomy, those treated with oxaliplatin had a statistically significant higher incidence of grade 3/4 platelet and neutrophil toxicity. However, no statistically significant difference in hematologic toxicity was noted between the groups of patients who did not undergo splenectomy. Notably, the use of oxaliplatin as main chemotherapeutic agent in HIPEC was found to be independent prognostic factor for both platelet and neutrophil toxicity. The overall median survival for the 187 patients was 22.6±1.1 months following CRS-HIPEC. Finally, no difference in the survival was noted in the cohort of patients who underwent a splenectomy when compared to the cohort who had spleen preservation, (22.9 versus 21.8 months, P=0.92). Moreover, in the subset survival analysis comparing survival outcome between MMC and oxaliplatin in the cohort of patients who underwent a splenectomy, no significant difference was noted (23.8 vs 17.8 months, P=0.28).

The possibly greater risk of post-operative complications in oxaliplatin versus MCC-based HIPEC for colorectal PM was also the conclusion of another comparative retrospective study, performed by Rouers et al (65). The authors presented their relevant experience in a group of 21 patients with peritoneal metastases of colorectal origin who they treated in their Institution. The first 13 patients were treated with MMC alone (10 mg/m^2 for 90 min) and other 8 received 460 mg/m^2 of oxaliplatin for 30 min with intraoperative systemic chemotherapy of 5-FU (400 mg/m^2) and folic acid (20 mg/m^2) given one hour prior the hyperthermic chemoperfusion, with the two groups having similar extent of the peritoneal metastatic deposits. Regarding the oncological outcome, the overall and disease-free survival rates among the entire population were respectively 88.7% and 72.6% at 1 year, 72.9% and 37.1% at 2 years, 45.5% and 36.6% at 3 years, 36.6% both at 4 and 5 years. The median survival time was 34 months. After a median follow-up of 24.9 months (range 2-80 months), cancer recurrence was detected in 8 patients (38.0%). Although a comparison of the survival rates between the MMC and oxaliplatin groups was not feasible due to the incomplete follow-up of the oxaliplatin group patients, the authors demonstrated a significantly higher number of Grade 2/4 intra-abdominal complications in the oxaliplatin group; however, no extra-abdominal complications occurred in any of the patients included in the analysis. In a general overview, the morbidity and mortality rates were 23% & 7.6% in the MMC group versus 62.5% & 0% in the oxaliplatin group.

Despite the heterogeneity of these comparative studies and the presence of significant methodological limitations, it seems that o xaliplatin-based HIPEC appears to result in a more frequent occurrence of post-operative complications. Laboratory evidence also points towards this direction, suggesting a higher rate of metabolic and electrolyte disturbances, such as hyponatremia, hyperglycemia and hyperlactemia, in oxaliplatin-based HIPEC, in spite of the usually shorter duration of the hyperthermic chemoperfusion, fact which has been proposed to be attributed to the implementation of the dextrose solution in this technique instead of the more "balanced" carrier solutions in MMC-based HIPEC, which resemble the peritoneal fluid constitution to a greater extent (31). To similar conclusions came Rueth et al (30), who compared the post-HIPEC electrolyte disturbances between a group of 60 patients who underwent MMC-based HIPEC (dose range 12.5–50 mg/m^2) and another group of 20 patients receiving oxaliplatin-based HIPEC (dose range 300-400 mg/m^2). Compared with MMC, patients receiving oxaliplatin had significantly higher rates of 24-h postoperative hyponatremia, hyperglycemia and metabolic acidosis. In this study, the overall non-electrolyte complication rate was 56.2%. (MMC n=33, 55.0%; oxaliplatin n=12, 60%) with a 0% 30-day mortality rate in both groups. Interestingly, although oxaliplatin-based HIPEC resulted in a greater number of metabolic and electrolyte abnormalities post-operatively, these electrolyte disturbances were not associated per se with higher overall

complication rates.

The most recent meta-analysis of Zhang et al, published in 2020, including a total of 11 clinical studies with a sum of 2091 patients, demonstrated similar survival outcomes for the patients who received MMC-based versus oxaliplatin-based HIPEC (66). However, the authors reported, after synthesis of the data from the included studies, that oxaliplatin-based HIPEC was associated with a significantly higher rate of major of postoperative complications, leading them to suggest that MMC-first approach should be considered initially. After the publication date of the above-mentioned meta-analyses, two more comparative studies have been published. Benzaquen et al (67) concluded that MMC vs oxaliplatin-based HIPEC were equally safe, with similar toxicity profiles and oncological benefits, however MMC-based HIPEC was significantly less expensive, raising the issue of cost-effectiveness in the balance between the two agents. To the contrary of their results, a retrospective comparative study by Spiliotis et al (68), suggested that MMC-based HIPEC resulted in a significant increase of the overall survival (54 versus 26 months), compared to oxalipatin-based HIPEC.

Conclusions

Mitomycin C and oxaliplatin are the main chemotherapeutic agents used in HIPEC for the treatment of peritoneal metastatic disease of colorectal cancer origin, with their safety profile and impact on oncological outcomes having been extensively studied in numerous clinical studies. However, the distinct differences in terms of pharmacology, pharmacokinetic and pharmacodynamic behavior in the context of HIPEC reasonably pose the issue of superiority between these two agents, focusing mainly on the reduction of post-operative mortality and morbidity, as well as the survival outcomes. Combining the latter with the biological and molecular heterogeneity of colorectal cancer, aiming to proceed towards a patient-tailored therapeutic approach, the importance of chemotherapeutic selection emerges as an issue of cardinal importance for the optimization of HIPEC and its potential implementation as a preventive strategy in high-risk patients for developing peritoneal metastatic disease.

Until, though, the establishment of individualised HIPEC regimens, combining the data from the available clinical studies, it appears that mitomycin-based HIPEC as an adjunct to successful cytoreductive surgery for colorectal peritoneal metastases bears a lower toxicity profile and is overall more cost-effective compared to oxalipatin-based HIPEC. However, we strongly advocate that the choice of HIPEC regimen should be an issue to be decided on a multidisciplinary basis, in a joint manner between the surgical and medical oncologists, taking into account the individual patients' surgical history and the types of previously received systemic chemotherapy. Finally, we believe that systematic inpatient and outpatient follow-up of these patients should be performed through national specialist electronic registers, in order to facilitate the relevant clinical research and allow long-term clinical follow-up in a structured manner.

Conflict of Interest Statement

The authors have no competing interests to declare.

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