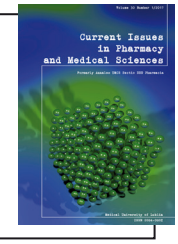
DOI: 10.1515/cipms-2017-0035 Curr. Issues Pharm. Med. Sci., Vol. 30, No. 4, Pages 187-189

DE GRUYTER OPEN

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/



Does additional HIPEC help after CRS in peritoneal disseminated gastric cancer?

Beate Rau*, Eva Pachmayr, Dusan Klos, Peter Thuss-Patience, Andreas Brandl

Chirurgische Klinik, Charité - Universitätsmedizin Berlin, Charité Campus Mitte Charité Platz 1, 10117 Berlin, Germany

ARTICLE INFO

Received 29 September 2017
Accepted 29 December 2017

Keywords:
gastric adenocarcinoma, hyperthermic intraperitoneal chemotherapy (HIPEC), peritoneal metastasis, peritoneal carcinomatosis, GASTRIPEC trial.

ABSTRACT

The incidence of synchronous or metachronous peritoneal metastases (PM) in patients with locally advanced gastric cancer is high, and associated with a poor prognosis. The recommended therapeutic option for these patients is systemic chemotherapy and leads to a median of 7-8 months. However, new approaches like cytoreductive surgery and hyperthermic intraperitoneal chemotherapy might help to improve the median survival in selected patients.

Indications, patient selection and the choice of the chemotherapeutic agent are described in this manuscript, as well as an overview of the most recent literature about this topic.

INTRODUCTION

Nearly one million new gastric cancer (GC) cases (6.8% of all cancers) have been diagnosed in 2012 [1]. Currently, stomach cancer is the fifth most common cancer worldwide, shifting from its spot as the most common malignancy in the last 40 years. In spite of this change, this neoplasm is the third leading cause of cancer-associated death (723 000 deaths) [2].

The NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer provide evidence- and consensus-based recommendations for a multidisciplinary approach for the management of patients with gastric cancer. For patients with resectable locoregional cancer, the guidelines recommend gastrectomy with a lymph node dissection [3]. In the case of additional distant metastasis, only systemic palliative chemotherapy is recommended.

GC metastases can be categorized by how they spread in the body: via the lymphatic system to the lymph nodes, via the haematogenic system to distant organs, and via dissemination to the peritoneal cavity – known as peritoneal metastasis (PM). Stomach cancer has the highest rate of peritoneal recurrence of all gastrointestinal cancers. Indeed, PM is a more common way of GC dissemination than distant metastasis, as PM is observed in other malignancies. Of note, Okines *et al*. have shown that GC PM associated deaths are seen 53-60% of the time, which is markedly higher than that in cases of distant metastases, for example, 40% for hepatic metastases [4].

* **Corresponding author**
e-mail: beate.rau@charite.de

Some pathological factors are associated with synchronous peritoneal metastasis: T3 and T4 tumors, lymph node invasion, signet ring cell pathology, diffuse infiltrative growth pattern and primary scirrhous-type tumor reaction. The impact of systemic chemotherapy in PM of GC origin is often limited [5,6]. In cases with distant metastases, the short duration response rate is about 43%, and the response for PM cases is less than 14% [7]. The reason for this is a barrier between blood and peritoneum that prevents high concentrations of intravenous drugs from accumulating within the peritoneal layer [7]. PM during an abdominal examination is observed in 10-20% of all patients who are scheduled for surgery, and up to 40% of all in stage III GC [8].

Therefore, new approaches for treatment regimen where developed to treat PM with locoregional chemotherapy directly into the abdominal cavity after complete extirpation of detectable tumor nodules.

INTRAPERITONEAL CHEMOTHERAPY

Signs of the effectiveness and safety of adjuvant intraperitoneal chemotherapy for patients with locally advanced resectable gastric cancer was seen in the work of Yan *et al*. This, when compared to the survival of patients without intraperitoneal chemotherapy, indicated that intraperitoneal locoregional chemotherapy may improve overall survival. Yan *et al*. included trials in which patients with gastric cancer were randomly assigned to receive surgery combined with intraperitoneal chemotherapy or surgery without intraperitoneal chemotherapy [9]. However, he found an increased risk of intra-abdominal abscess and neutropenia.

To further enhance the effectiveness of locoregional chemotherapy, but without side-effects, a combination of this with hyperthermia was then analyzed.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

Studies of the effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) usage in peritoneal metastases of GC have focused on the indications for the treatment of PM. In the Mi *et al*. study, only HIPEC trials were analyzed. Usage of HIPEC was not associated with a higher rate of anastomotic leakage, ileus, bowel perforation, myelosuppression, gastrointestinal reaction, but with a higher rate of abdominal pain [10]. In the meta-analysis by Sun *et al*. that was based on 10 RCTs, a significant improvement in the group which underwent HIPEC was shown [11]. Additionally, after HIPEC, a lower number of peritoneal recurrences were seen, and these were without higher rate of complications. These three studies analyzed prophylactic HIPEC in GC [12]. The latest meta-analysis shows that surgery with intraperitoneal chemotherapy (IPC) (no matter the type) improves 1-, 2- and 3-year mortality in patients who had regional lymph node metastases, and 1-, 2-year mortality in patients with serosal infiltration [13]. No difference in 5-year survival rate is seen. This meta-analysis includes mostly Asian studies of limited study population, so the authors of the meta-analysis have concluded that further evidence of the effectiveness of HIPEC is needed. Still, all studies so far have led to the inference that the HIPEC procedure in the case of GC PM is only possible in a small fraction of patients with limited PM and complete resectability of disease (CCR 0/1). Currently, no benefit is seen in the case of macroscopic tumor residue.

SELECTION OF CHEMOTHERAPY

The ideal drug for intraperitoneal administration should preferably have:

- proven activity,
- a pharmacokinetic profile,
- adequate tissue penetration,
- concentration- and exposure-related cytotoxicity,
- large molecular weight, preventing diffusion across the peritoneal barrier.

What is more, as the rationale for intraperitoneal chemotherapy, the drug should respect the peritoneal-plasma barrier, allowing high local concentrations of the agent in the peritoneal cavity, albeit without a concomitant increase in the plasma concentration, thus limiting systemic toxicity [14].

The most common drugs used for hyperthermic intraperitoneal chemotherapy are Mytomicin (MMC), Cisplatin (CDDP) and Etoposide (ETP), with temperatures ranging from 40-45°C during the 30 to 120 minutes of treatment session [15].

INDICATION FOR CRS AND HIPEC IN GASTRIC CANCER

Careful selection of patients is necessary. One of the important prognostic factors is the peritoneal carcinosis index (PCI) [16]. If the PCI is high, complete cytoreduction (CC0/1) is not achievable [17,18]. Moreover, in the case of extended peritoneal metastasis, the small bowel is usually involved and its mesentery is shrinking. In such situations, CC0 is not accessible. Hence, cytoreduction and gastrectomy in cases with a PCI > 12 are not recommended [17].

Currently, a randomized trial is assessing the beneficial effect of HIPEC (the GASTRIPEC Trial). Herein, patients with histologically-proven gastric cancer (including cancer of the esophagogastric junction (AEG)) and synchronous peritoneal carcinomatosis who fulfill the inclusion and criteria, can be recruited this study. There are two treatment groups (A and B). The chemotherapy applied intravenously is the same in both groups and is approved for the treatment of gastric cancer. Patients with negative or unknown HER-2 status will be administered Epirubicin, Oxaliplatin and Capecitabine (EOX). Patients with positive HER-2 status will be treated with Cisplatin, Capecitabine and Trastuzumab (CCT). The chemotherapy is followed by surgical cytoreduction in both groups. Patients randomized into group B will also be treated with an intraperitoneal hyperthermic chemoperfusion (HIPEC) with Mitomycin C and Cisplatin. Patients in both groups will then receive postoperative chemotherapy within 4-12 weeks after the surgical procedure and are followed up for 30 months. lf progress of the tumor is detected, the patient will no longer be treated according to the study therapy. Moreover, patients of group B may receivet a HlPEC intervention without surgical cytoreduction. This study has already recruited 88 patients and will stop after 180 patient enrollees [19].

MORTALITY AND MORBIDITY IN HIPEC

In a group of patients with locally advanced and metastatic gastric cancer, median survival is generally bad, therefore, morbidity due to treatment regimen should be avoided. Of note, aggressive treatment is usually combined with a higher rate of severe morbidity and mortality. Al-Batran recorded medical or surgical complications in 44 (40%) of 111 patients in the ECF/ECX group and 30 (25%) of 119 patients in the FLOT group who had at least one serious adverse event during preoperative chemotherapy [20]. Still, Costa *et al*. demonstrated that the association of perioperative systemic and intraperitoneal chemotherapy, plus radical surgery, is a feasible multimodality treatment, with acceptable complications of 20% with grade 3 morbidity [21].

Huang *et al*. investigated the safety and efficacy of intraperitoneal chemotherapy. Ten studies were judged to be of fair quality and entered into their meta-analysis. The perioperative mortality was 2.3% out of 8 studies with 643 patients and 15 events. Anastomotic leakage was 2.3% out

of 7 manuscripts with 516 patients and 12 events. Other severe complications included postoperative ileus in 4 of 242 patients (1.6%), bowel perforation in 5 of 219 patients (2.2%), pancreatic fistula in 5 of 138 patients (3.6%), bone marrow depression in 25 of 491 patients (5%), fever in 16 of 102 patients (15,6%) and intraabdominal abscess in 23 of 171 patients (13.4%) [22]. In comparison to a surgery only group without any intraperitoneal chemotherapy, intraperitoneal chemotherapy could significantly increase the incidence of marrow depression (OR = 5.74, P<0.01), fever (OR = 3.67, P = 0.02) and intra-abdominal abscess (OR = 3.57, P<0.01) after the treatment. Still, there were no significant differences between the two groups for perioperative mortality, anastomotic leakage, ileus, bowel perforation and pancreatic fistula [22].

However, major complications were noted to be directly related to the magnitude of the procedure, including the extent of resections and peritonectomy, the number of anastomoses, the duration of surgery, and the doses of cytotoxic chemotherapeutic drugs used in HIPEC [23].

CONCLUSIONS

Hyperthermic intraperitoneal chemotherapy (HIPEC) after complete cytoreduction in gastric cancer with peritoneal metastasis is a promising treatment option. This is because, currently, 30% of all locally advanced gastric cancers develop peritoneal metastasis no matter the treatment regime. The chemotherapeutic regime, as well as the duration of HIPEC, dosage, patient characteristics, temperature, carrier solution, intraperitoneal pressure, and the use of open or closed technique warrants more experimental and clinical studies so as to determine the influence of each individual variable on toxicity profile and treatment outcome.

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al.: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
2. Ferlay J, Soerjomataram I, Dikshit R, et al.: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-E386.
3. Ajani JA, Bentrem DJ, Besh S, et al.: Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2013;11:531-46.
4. Okines A, Verheij M, Allum W, et al.: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v50-4. doi: 10.1093/annonc/mdq164.:v50-v54.
5. Chang JS, Kim KH, Keum KC, et al.: Recursive partition analysis of peritoneal and systemic recurrence in patients with gastric cancer who underwent D2 gastrectomy: Implications for neoadjuvant therapy consideration. J Surg Oncol. 2016;114:859-64.
6. Seyfried F, von Rahden BH, Miras AD, et al.: Incidence, time course and independent risk factors for metachronous peritoneal carcinomatosis of gastric origin--a longitudinal experience from a prospectively collected database of 1108 patients. BMC Cancer 2015;15:73. doi: 10.1186/s12885-015-1081-8.:73-1081, 2015
7. Yonemura Y, Endou Y, Sasaki T, et al.: Surgical treatment for peritoneal carcinomatosis from gastric cancer. Eur J Surg Oncol. 2010;36:1131-8.
8. Roviello F, Caruso S, Neri A, et al.: Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: overview and rationale. Eur J Surg Oncol. 2013;39:1309-16.
9. Yan TD, Black D, Sugarbaker PH, et al.: A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007;14:2702-13.
10. Mi DH, Li Z, Yang KH, et al.: Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. Int J Hyperthermia 2013;29:156-67.
11. Sun J, Song Y, Wang Z, et al.: Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer 2013;13:577. doi: 10.1186/1471-2407-13-577.:577-13.
12. Yan TD, Edwards G, Alderman R, et al.: Morbidity and mortality assessment of cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma--a prospective study of 70 consecutive cases. Ann Surg Oncol. 2007;14:515-25.
13. Coccolini F, Cotte E, Glehen O, et al.: Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol. 2014;40:12-26.
14. Van Der Speeten K, Stuart OA, Sugarbaker PH: Pharmacology of perioperative intraperitoneal and intravenous chemotherapy in patients with peritoneal surface malignancy. Surg Oncol Clin N Am. 22012;21:577-97.
15. Braam HJ, Schellens JH, Boot H, et al.: Selection of chemotherapy for hyperthermic intraperitoneal use in gastric cancer. Crit Rev Oncol Hematol. 2015;95:282-96.
16. Jacquet P, Sugarbaker PH: Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359-74.
17. Glehen O, Gilly FN, Arvieux C, et al.: Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:2370-7.
18. Gill RS, Al-Adra DP, Nagendran J, et al.: Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. J Surg Oncol. 2011;104:692-8.
19. Rau B, Löffler M, Rau HG, et al.: Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: A randomized phase III study (GASTRIPEC). J Clin Oncol. 2015;33, (abstr).
20. Al-Batran SE, Hofheinz RD, Pauligk C, et al.: Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-708.
21. Costa WL, Jr., Coimbra FJ, Ribeiro HS, et al.: Safety and preliminary results of perioperative chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) for high-risk gastric cancer patients. World J Surg Oncol. 2012;10:195. doi: 10.1186/1477-7819-10-195.:195-10, 2012
22. Huang JY, Xu YY, Sun Z, et al.: Comparison different methods of intraoperative and intraperitoneal chemotherapy for patients with gastric cancer: a meta-analysis. Asian Pac J Cancer Prev. 2012;13:4379-85.
23. Yang XJ, Huang CQ, Suo T, et al.: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol. 2011;18:1575-81.