ISSN: 2582-6751
Journal of Clinical Medical Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Locoregional Treatments in Peritoneal Metastasis from Gastric Cancer

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Citation: Spiliotis J, et al. Locoregional Treatments in Peritoneal Metastasis from Gastric Cancer. Jour Clin Med Res. 2024;5(2):1-5.

https://doi.org/10.46889/JCMR.2024.5210

Received Date: 02-08-2024

Accepted Date: 23-08-2024

Published Date: 30-08-2024

Abstract

Peritoneal Metastasis (PM) is a common site of dissemination of gastric cancer. PM remains a major cause of mortality and is associated with poor prognosis. For this reason the last 30 years the treatment of peritoneal disease is an important target for improving survival.

The therapeutic approaches of locoregional therapy for GCPM include different types of surgery and different types of intraperitoneal chemotherapy.

This review presents an overview of these modalities and summarizes the evolution of management the last years. It highlights in controversial options which existing in literature and focuses in the ongoing clinical trials that will help establish the role of locoregional treatments in GCPM.

Keywords: Peritoneal Metastasis; Gastric Cancer; Immunotherapy; Cytoreductive Surgery

Introduction

Gastric Cancer (GC) is estimated to have 26,500 new cases and 11.300 deaths in USA during last year. It remains a cancer with poor prognosis with only a third of patients surviving 5 years from diagnosis.

The delayed diagnosis means a large proportion of these patients (40%) presented with distant metastasis at the time of initial diagnosis with the 5-year relative survival dropping with a less than 7% of year survival [1,2].

The last two decades, the management of localized or diffuse metastatic disease from GC has been evolving due to the advancements in systemic chemotherapy, targeted therapies or immunotherapy [3].

Despite these advances there are controversial results concerning the treatment of gastric cancer peritoneal metastasis GCPM, which considered as stage IV even with macro or microscopically disease the NCCN guidelines recommend systemic chemotherapy alone and sometimes in selected ''responders'' patients offer a palliative gastrectomy [4]. The gastric cancer is aggressive malignancy and can give a wide variety of metastases, whereby up to 40% of GC patients have synchronous and 46% metachronous peritoneal metastases after curative surgery [5].

It is well establish that peritoneal dissemination, even positive cytology only without evidence of gross peritoneal metastasis is associated with poor prognosis, with an average survival of barely 3-6 months if treated with conventional systemic therapy and depending on response to systemic chemotherapy or histological subtype [6,7]. To improve survival are proposed different approaches of locoregional therapies and this review summarize and provide an overview of the major studies for each treatment modality.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Locoregional Treatments
On the reasons for poor outcome in GCPM is that exists the peritoneal plasma which limits the exposure of seeded cancer cells to systemic chemotherapy [8]. Thus locoregional treatment becomes an important tool in the management of PM.

Surgical resection can involve either a palliative gastrectomy or a Cytoreductive Surgery (CRS) with removal all the visible disease and decreases the intraperitoneal tumor volume.

Intraperitoneal chemotherapy can involve administration chemotherapy given Early Postoperative Intraperitoneal Chemo (EPIC) or Normothermic Intraperitoneal chemotherapy Long term (NIPEC-LT) or Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) or finally Heated Intraperitoneal Chemotherapy (HIPEC) usually at the time of cytoreductive surgery [9]. Most of all methods utilize a combination of surgical resection usually CRS to make use the main theoretical synergism.

Surgery
There is no base-evidence in western countries to recommended palliative resection in patients with GCPM including those with only positive cytology disease.

There is a lack of survival benefit with surgical resection in large studies from 1990 to 2013. However, more recent studies have demonstrated conflict results when newer systemic options are used, which significantly prolongs survival in a subset of patients [10,11].

On the other hand, the small size or retrospective studies have limited the results to clarify the positive role of surgical resection in GCPM. Most recently a Japanese multi-institutional randomized phase III trial (Regatta trial) compared gastrectomy plus systemic chemotherapy versus systemic chemotherapy alone in patients with GC with limited metastatic disease and found no significant differences in overall survival or progression free survival [12].

Another Chinese single arm phase II (GCOG0301trial) evaluating D2 gastrectomy followed by adjuvant S1 in patients with positive cytology in 47 patients and achieved a 2-year survival rate of 46% than that of historical controls of 13.3% [13].

The European AIO-FLOT3 phase II trial tested the efficacy of neoadjuvant FLOT chemo followed by surgery in 3 axis-resectable GC, limited metastatic GC and extensive metastatic GC [14].

The results demonstrated improved survival rate in patients with limited metastatic disease versus extensive metastatic disease (median O.S. 22.9 m vs 10.7 m $p<0.001$). All patients received complete macroscopic cytoreduction in group of limited GCPM.

Cytoreductive Surgery and HIPEC
Several retrospective studies have reported prolonged survival after CRS and HIPEC in GCPM. The largest retrospective study in Germany by Ran, et al., identified 215 patients with synchronous metastasis who received CRS plus HIPEC and divided in 3 groups depending on Peritoneal Cancer Index (PCI) in groups PCI (0-6, 7-15 and 16-39 respectively) [15].

The median overall survival differed between the three groups and were 18, 12 and 5 months respectively. The first randomized phase III trial investigating the efficacy of Hipec in GCPM was published by Yang, et al. [16]. Median overall survival was 6,5 months in the CRS group and 11 months in CRS+HIPEC group. The most important factors of better outcome identified HIPEC, complete cytoreduction, neo-adjuvant chemo, synchronous metastasis [17]. More recently a European randomized phase III trial GASTRIPEC comparing CRS alone vs CRS plus HIPEC in GCPM [18].

There was no difference of overall survival between the two groups, but Progression Free Survival (PFS) and distant Metastasis Free Survival (MFS) favored the addition of HIPEC to CRS.

Additional studies from Europe underlined two main factors, the importance of complete CRS and the benefit of low PCI. Single Spanish center trials by Caro, et al., demonstrate a survival benefit in GCPM with PCI≤6 [19].

The CYTO-CHIP study in France by Bonnot, et al., demonstrates 5-year OS in CCo of 24,8% versus 6,8% in those with CC1 resection [20]. Between the groups of CRS alone versus CRS+HIPEC. In the same trial the median OS was 18,8 m for HIPEC arm versus 12,1 for CRS alone ($p<0.05$).

Other studies from Netherland and USA non-randomized phase II trial demonstrate an improvement in survival in HIPEC groups [21-23].

Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Early Postoperative Intraperitoneal Chemotherapy involves per fusing on postoperative days 1 through 5. This procedure described by Sugarbaker in the early 90s, in an attempt to reduce recurrence by targeting the peritoneal and anatomic sites that are sealed by healing procedures [24].

The role of EPIC in GCPM is still uncertain and not very clears when we compare with peritoneal metastasis from colorectal and appendiceal cancer [25].

Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC)

Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC), a recently described new surgical procedure to administer chemotherapy directly to the peritoneum under pressure has added a new tool on the armamentarium of the oncologist to address the PM in those patients who are not suitable for CRS/HIPEC [26].

Most recently, Graversen, et al., reported a PIPAC trial from Denmark. The PIPAC-OPG2, in gastric cancer peritoneal metastasis patients who underwent 3 cycles of PIPAC at 4 to 6 weeks intervals and achieved a median OS of 14.1 months from diagnosis [27].

Most recently another study using PIPAC as neoadjuvant treatment in combination with neoadjuvant systemic chemotherapy in synchronous GCPM demonstrate better partial response rates as compared with non PIPAC group [28].

Future Directions

Our understating is increasingly evolving about heterogeneous behavior, tumor biology and therapeutic strategies of peritoneal surface malignancies. On the other hand, the regimens, applications and techniques of intraperitoneal chemotherapy have evolved over the last 25 years.

However, there are many questions than answers about the proper use, timing of cytoreductive surgery and HIPEC or PIPAC in GCPM. Proven evidence shows that complete CRS is a paramount importance for survival in gastric cancer after neo-adjuvant chemotherapy.

The propose from some investigators of prophylactic indication in high-risk gastric cancer to developed peritoneal metastasis remains controversial. The near future is waiting answers of currently ongoing trials which will shed more light on the indications for these locoregional treatment in well select patients with GCPM.

Conflict of Interests

The authors declare no conflict of interest regarding authorship roles or publication of article.

Acknowledgement
Not applicable

Financial Disclosure
No funding was not involved in the manuscript writing, editing, approval or decision to publish.

Authors Contribution
All the authors have equal contribution and all the authors have read and agreed to the published version of the manuscript.

Data Availability
Not applicable

Consent for Publication
Not applicable

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