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Review

Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials

F. Coccolini [a,b,*], E. Cotte [b], O. Glehen [b], M. Lotti [a], E. Poiasina [a], F. Catena [c], Y. Yonemura [d], L. Ansaloni [a]

[a] General Surgery Dept., Papa Giovanni XXIII Hospital, Bergamo, Italy
[b] General Surgery Dept., Centre Hospitalier Lyon Sud, Hospices Civils de Lyon and EMR 3738, Université Lyon 1, France
[c] General Surgery Dept., Ospedale Maggiore, Parma, Italy
[d] General Surgery Dept., Kusatsu General Hospital, Yabase 1660, Japan

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Abstract

Introduction: An important component of treatment failure in gastric cancer (GC) is cancer dissemination within the peritoneal cavity and nodal metastasis. Intraperitoneal chemotherapy (IPC) is considered to give a fundamental contribute in treating advanced GC. The purpose of the study is to investigate the effects of IPC in patients with advanced GC.
Material and methods: A systematic review with meta-analysis of randomized controlled trials (RCTs) of IPC + surgery vs. control in patients with advanced GC was performed.
Results: Twenty prospective RCTs have been included (2145 patients: 1152 into surgery + IPC arm and 993 into control arm). Surgery + IPC improves: 1, 2 and 3-year mortality (OR = 0.31, 0.27, 0.29 respectively), 2 and 3-year mortality in patients with loco-regional nodal metastasis (OR = 0.28, 0.16 respectively), 1 and 2-year mortality rate in patients with serosal infiltration (OR = 0.33, 0.27 respectively). Morbidity rate was increased by surgery + IPC (OR = 1.82). The overall recurrence and the peritoneal recurrence rates were improved by surgery + IPC (OR = 0.46 and 0.47 respectively). There was no statistically significant difference in lymph-nodal recurrence rate. The rate of haematogenous metastasis was improved by surgery + IPC (OR = 0.63).
Conclusions: 1, 2 and 3-year overall survival is incremented by the IPC. No differences have been found at 5-year in overall survival rate. 2 and 3-year mortality rates in patients with nodal invasion and 1 and 2-year mortality rates in patients with serosal infiltration are improved by the use of IPC. IPC has positive effect on peritoneal recurrence and distant metastasis. Morbidity rate is incremented by IPC. Loco-regional lymph-nodes invasion in patients affected by advanced gastric cancer is not a contraindication to IPC.

Keywords: Gastric cancer; Intraperitoneal chemotherapy; HIPEC; Carcinosis; Nodal infiltration; Meta-analysis

Introduction

Gastric cancer (GC) is the second leading cause of cancer death and the fourth most common cancer in the world.[1,2] GC disseminates principally through the haematic torrent or through the peritoneal fluids. It has been demonstrated as peritoneal dissemination is more frequent than haematogenous metastases. The 40% of patients died for GC have hepatic metastases, while the 53–60% showed a disease progression and died with peritoneal carcinosis (PC). The two most important factors affecting prognosis in GC are the serosal invasion and the lymphatic spread.[3–5] When gastric serosa is infiltrated, PC could be considered practically unavoidable.[6] As a consequence, up to half of the patients with advanced GC will develop PC in spite even radical surgery.[8–11] PC is already present in 5–20% of patients explored for potentially curative resection also

* Corresponding author. General Surgery Dept., Papa Giovanni XXIII Hospital, Piazza OMS 1, 24127 Bergamo, Italy. Tel.: +39 (0) 352673486; fax: +39 (0)352674963.
E-mail addresses: federico.coccolini@gmail.com, fedecocco@iol.it (F. Coccolini).

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in early gastric cancer.[6,7] Surgical resection associated to systemic chemotherapy is the mainstay of treatment. Systemic chemotherapy improves median survival in advanced and/or metastatic GC to not more than 12 months.[12–15] The same gain in term of survival has not been described with macroscopic PC[16–19] due to the inadequate diffusion of systemic chemotherapy into the abdominal cavity.[20]

As many patients present with advanced-stage-disease, the research for more effective treatments is mandatory. An important component of treatment failure is cancer dissemination within the peritoneal cavity and nodal metastasis. In contrast to lymphatic and haematogenous dissemination, peritoneal spread should be regarded as a loco-regional disease extension rather than systemic metastasis.[21] Taking the natural history of GC into account, the use of intraperitoneal chemotherapy (IPC) as a targeted adjuvant treatment after surgery may be considered a rational prophylactic/therapeutic approach. Actually IPC has been progressively more used in advanced GC due to the appealing theoretical rationales. Although many different regimens of IPC exist, they all could be considered as the different applications of the same treatment method. IPC allows to reach an high intraperitoneal drug concentration and allows the drugs to directly act on the free-tumour-cells and peritoneal nodules. Drugs absorbed through the peritoneum enter the portal vein, and also have a chemotherapeutic effect on the liver.[22] It remains controversial if the IPC has a positive effect on the lymph-node metastasis. The purpose of the present meta-analysis of randomized controlled trials (RCT) investigating the effects of IPC in patients with advanced GC.

Material and method

Literature search strategy

Electronic searches were performed using Medline, Embase (1988–December 2012), PubMed (January 1980–December 2012), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR) and CINAHL from (1966–2012). The search terms were: 'intraperitoneal chemotherapy', 'stomach', 'gastric cancer', 'carcinosis', 'randomized trial', 'meta-analysis' combined with AND/OR. Research included also all the MeshTerms. No search restrictions were imposed. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Review articles were also obtained to determine other possible studies. Duplicate published trials with accumulating numbers of patients or increased lengths of follow-up, were considered only in the last or at least in the more complete version.

Selection criteria

Studies which have been judged eligible for this systematic review and consequent meta-analysis are those in which patients with advanced GC (with or without PC) were randomly assigned to receive either surgery combined with IPC or surgery without IPC. All included patients must have histologically-proven gastric or gastro-oesophageal-junction adenocarcinoma and underwent potentially curative resection. Included studies consider both patients with locally advanced GC with macroscopic serosal invasion, and patients with peritoneal carcinomatosis but without distant metastasis. All forms of IPC in addition to surgery were included. No language restrictions have been applied. Eligibility for study inclusion into the meta-analysis and study quality assessment were performed independently by two authors (EC, FeCo). Study data were extracted onto standard forms independently by two authors (EC, FeCo). Discrepancies between the two investigators were resolved by discussion and evaluation of the question with a senior investigator. The final results were reviewed by three senior investigators (YY, LA, OG).

The primary outcome measures for the meta-analysis were the impact of IPC on 1, 2, 3 and 5-year mortality and the effect of IPC on the mortality of patients with loco-regional nodal metastasis. For this last outcome were included data from studies in which at least the 80% of patients had loco-regional nodal metastasis at the time of intervention. The same criteria has been adopted to evaluate the impact of IPC on survival in patients with serosal invasion (secondary outcome) (including studies with at least the 80% of patients with serosal infiltration at the time of diagnosis). To evaluate the mortality rates studies were divided into two sub-groups: studies that included patients with and without PC. Moreover the impact of IPC on recurrence (overall, peritoneal, lymph-nodal) and haematogenous metastasis and morbidity, has been evaluated.

Assessment of risk of bias

There is a potential risk of overestimating the beneficial treatment effects of RCT with a resultant risk of bias. The risk of bias was assessed comprehensively according to guidelines of the Cochrane Collaboration[23,24] and six items have been considered relevant (Table 1): 1) whether the method of allocation was truly random; 2) whether there was proper allocation concealment; 3) whether the groups were similar at baseline; 4) whether the eligibility criteria were documented; 5) whether loss to follow-up in each treatment arm was specified; 6) whether intention-to-treat analysis was conducted. Therefore the evaluation of the quality level of the study was conducted as follows: Positive answer to at least six questions was required for a trial to be rated as high quality. With a positive answer to five or four questions the study was considered of fair quality. With a positive answer to three or fewer questions the study was registered as low quality. When studies did not report adequate information to determine the above-mentioned assessment criteria, an attempt to obtain direct additional data from the investigators was made. Studies reported in