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Combination or single-agent chemotherapy as adjuvant treatment of gastric cancer
A systematic review and meta-analysis of published trials

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ABSTRACT

Background: Chemotherapy is standard care in resected gastric cancer (GC). Despite the evidence that combination chemotherapy (CT) increases overall survival (OS) as compared to single agent therapy in metastatic disease, no study proved this benefit in the adjuvant setting. We performed a systematic review and meta-analysis based on trial data on the role of combination over single agent CT as adjuvant treatment of GC.

Methods: MEDLINE/PubMed and Cochrane Library were searched for randomized phase III trials that compared combination vs. single agent CT in patients treated with radical surgery for non-metastatic GC. Data extraction was conducted according to the PRISMA statement. Statistical analyses were conducted to calculate the summary hazard ratio (HR) for OS and disease free survival (DFS) and 95% Confidence Intervals (CIs) by using random-effects or fixed effects models based on the heterogeneity of included studies. A subgroup analysis was performed in patients treated with D2 lymphadenectomy.

Results: A total of 3572 patients were available for this analysis, 1857 received D2 lymphadenectomy, and fluoropyrimidine was given in 97% of patients of the control arm. In the overall population, the combined therapy decrease the risk of death by 13% (HR = 0.87; 95%CI, 0.79–0.95; $p = 0.004$) with fixed effect and by 19% (HR = 0.81; 95%CI, 0.68–0.97; $p = 0.02$) with random effect; significant heterogeneity was found. When analysis was limited to studies that required D2 lymphadenectomy a significant reduction of the risk of death was found in favor of combination CT (HR = 0.86; 95%CI, 0.76–0.98; $p = 0.02$). In the 3487 patients valuable for DFS, combination CT decreased the risk of relapse by 23% (HR = 0.77; 95%CI, 0.70–0.84; $p < 0.001$) with fixed effect and by 27% (HR = 0.73; 95%CI, 0.49–1.09; $p = 0.12$) with random effect; significant heterogeneity was found.

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Conclusions: This analysis reported that adjuvant combination CT decreases the risk of death over single agent therapy in patients with non-metastatic GC.

1. Introduction

Gastric cancer (GC) is the third leading cause of cancer death in both sexes worldwide (8.8% of the total), with the highest estimated mortality rates in Eastern Asia and the lowest in Northern America. High mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America (Globocan, 2012).

Systemic chemotherapy is the cornerstone treatment of GC both in locally-advanced and metastatic disease. In the metastatic setting, combination chemotherapy (CT) decreased the risk of death by 12% (HR = 0.88) and the risk of progression by 19% (HR = 0.81) when compared to monotherapy such as fluoropirimidines (Oba et al., 2013).

In patients with radically resected GC, adjuvant chemotherapy was associated with a statistically significant decrease of death risk and tumor relapse as compared to surgery alone, and was able to increase the five-year OS from 49.6% to 55.3% (Paoletti et al., 2010; Miceli et al., 2014). Unfortunately, this analysis was only able to compare the benefit of postoperative chemotherapy with surgery alone but was not able to compare the role of the combination CT over single agents (Paoletti et al., 2010). Recently, two randomized trials compared an intensive sequential treatment to monotherapy, without finding any difference in terms of DFS and OS (Tsuburaya et al., 2014; Bajetta et al., 2014).

Considering the lack of definitive data for combined therapy over single agent in adjuvant setting, the aim of this meta-analysis is to estimate the effect of combination CT over single agents as adjuvant treatment in patients who received radical surgery for GC.

2. Methods

2.1. Definition of the outcome

For each trial, the combination CT was considered as the experimental arm and the single agent therapy as the control one. The main endpoint of this analysis was to define the reduction of the risk of death in patients treated with combination CT as compared to single-agent therapy as adjuvant treatment of resected GC. A secondary endpoint was the reduction of the risk of relapse. Results were reported for the entire cohort and for studies in which a D2 lymphadenectomy was required as inclusion criteria.

2.2. Selection of the studies

We reviewed MEDLINE/PubMed and Cochrane Library for citations up to October 31st, 2014. The search criteria were limited to articles published in English language and phase III clinical trials. The entry terms for the search were “adjuvant” and “gastric cancer”. The search was restricted to randomized controlled trials in which chemotherapy agents were administered such as combined or single agent adjuvant treatment. If more than one publication was found for the same trial, the most recent was considered for analysis.

Study quality was assessed by using the Jadad seven-item scale that included randomization, double blinding and withdrawals; the final score was reported between 0 and 5 (Jadad et al., 1996).

2.3. Data extraction

Data’s extraction was conducted independently by two co-authors (R.I. and M.D.B.) according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement (Moher et al., 2009); any discrepancies were resolved by consensus between their own. The data obtained for each trial were: first author’s name, year of publication, the number of patients evaluable, the number of arms, drugs used in the experimental and in the control arm, presence of D2 lymphadenectomy as inclusion criteria, median overall survival (OS) and disease free survival with the relative HRs and 95% confidence intervals (CIs).

2.4. Statistical method

HRs for OS and DFS with the relative 95% CIs were extracted from each study whenever unavailable (Parmar et al., 1998). Summary HRs was calculated with random- or fixed-effect models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using the inverse variance method.

Statistical heterogeneity between trials included in the meta-analysis was assessed using Chi squared test, and inconsistency was quantified with the I^2 statistic ($100\% \times [Q - df)/Q]$) (Higgins et al., 2003). The assumption of homogeneity was considered invalid for p values less than 0.1. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian et al. method (DerSimonian and Laird, 1986), which considers both within- and between-study variations. A two-tailed p-value of less than 0.05 was considered statistically significant. All data were collected using Microsoft Office Excel 2007; statistical analyses were performed using RevMan software for meta-analysis (v. 5.2.7) (Review Manager, 2012).

3. Results

The electronic search revealed 227 citations, among these 202 were excluded because related to subject different from the main endpoints of this analysis. The remaining 25 studies were analyzed as full papers and 18 were eliminated for reasons reported in Fig. 1. At the end of the review process, only seven articles were included in the meta-analysis because of their adequate quality and availability of data (Tsuburaya et al., 2014; Bajetta et al., 2014; Ahn et al., 2013; Zhang et al., 2011; Cascinu et al., 2007; Chang et al., 2002; Grau et al., 1998), and the characteristics of each study are presented in Table 1.

3.1. Population

A total of 3572 patients were available for this trial-based meta-analysis, among these 1857 received D2 lymphadenectomy. A total of 1861 patients were treated in the experimental arm as polichemotherapy and 1711 were treated in the control arm as monotherapy, then fluoropyrimidine was given in 97% of patients. All studies except one included a fluoropyrimidine as control, while one study used mitomycin C (Grau et al., 1998). Sequential therapy

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