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Efficacy of modern chemotherapy and prognostic factors in patients with ovarian metastases from gastric cancer: A retrospective AGEO multicentre study

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ABSTRACT

Background: Ovarian metastases from gastrointestinal tumours frequently lead to locoregional complications and undermine quality of life. The chemosensitivity of ovarian metastases from gastric cancer is unknown.
Aim: To evaluate the efficacy of modern chemotherapy regimens in first-line treatment for patients with ovarian metastases from gastric cancer.
Methods: All consecutive patients with ovarian metastases from gastric cancer who received at least one cycle of chemotherapy were included in this retrospective study.
Results: Thirty-five patients were included (median age, 50.5 years; synchronous ovarian metastases, 60%). Seventeen patients (48.6%) underwent oophorectomy. Patients were treated with first-line chemotherapy based on platinum ($n=14$), irinotecan ($n=8$), taxane plus platinum ($n=4$) or epirubicin plus platinum ($n=9$). The median PFS and OS were 6.8 and 18.8 months, respectively. The objective response rate (ORR) for extra-ovarian (13.6%) and ovarian (20.9%) metastatic sites was not significantly different ($p=0.55$). There was no significant difference in terms of ORR on ovarian metastatic site according to the first-line chemotherapy ($p=0.21$). In multivariate analysis, oophorectomy was an independent prognostic factor for OS ($p<0.01$).
Conclusions: This study suggests that ovarian metastases from gastric cancer are not more resistant than extra-ovarian metastases, and that oophorectomy is an independent prognostic factor significantly linked to OS. Prospective studies are needed to confirm these results.

1. Introduction

Gastric cancer is the fourth most common cancer and the second cause of cancer-related death, with more than 400,000 newly diagnosed cases each year worldwide [1,2]. Krukenberg's tumours are infrequent ovarian metastases from gastric cancer, initially

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described by Friedrich Ernst Krukenberg in 1896 [3]. Nowadays, Krukenberg's tumours are generally considered to be a metastatic lesion, usually from a primary gastrointestinal malignancy, of which gastric cancer is the most frequent [4–7]. Ovarian metastases from gastrointestinal cancer frequently cause loco-regional complications (mainly abdominal pain and bowel obstruction) and significantly impair health-related quality of life [8]. Median overall survival (OS) was estimated between 8 and 13 months for patients with ovarian metastases from gastric cancer [9–11].

Some studies have evaluated chemotherapy in patients with ovarian metastases from colorectal cancer (CRC), but none have specifically assessed modern drug combinations in patients with ovarian metastases from gastric cancer. Chemotherapy is the main treatment for advanced gastric adenocarcinoma, providing an improvement in quality of life and OS compared with best supportive care [12]. Several chemotherapeutic agents are effective in advanced gastric cancer but there is no standard international regimen. First-line drugs include fluoropyrimidine (5-fluorouracil (5-FU) or capecitabine), platinum salts (cisplatin or oxaliplatin), taxanes (docetaxel or taxol), epirubicin and irinotecan, alone or in combination [13–15]. The REAL-2 trial demonstrated non-inferiority between ECF (epirubicin, cisplatin, 5-FU), ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, 5-FU) and EOX (epirubicin, oxaliplatin, capecitabine) regimens [16]. Alternative first-line chemotherapy options are FOLFIRI [17] and taxane-based regimens, including DCF (docetaxel/5FU/cisplatin) [18] and TEF (docetaxel/5FU/oxaliplatin) [19,20].

These protocols of chemotherapy are considered efficient for advanced gastric cancer treatment in recent randomized trials, but the anti-tumour activity of these regimens in patients with Krukenberg syndrome is unknown. In this study, we therefore evaluated the efficacy of modern chemotherapy regimens on ovarian versus extra-ovarian metastases from patients with gastric cancer.

2. Patients and methods

2.1. Patients

This retrospective multicenter study was conducted in 7 French university hospitals. Patient files were retrieved from the tumour registries of pathology departments and the medical information systems of each hospital. All consecutive patients with ovarian metastases from histologically proven gastric cancer who received at least one cycle of chemotherapy between November 2001 and March 2014 were eligible for this study. The diagnosis of ovarian metastases was based on abdominal and pelvic computerized tomography (CT) or magnetic resonance imaging (MRI), and/or histological findings in patients who underwent oophorectomy. Patients with ovarian metastases from other primary cancers were excluded. This study was approved by the ethics committee of Pitié-Salpétrière Hospital (Paris, France).

2.2. Data collection

The patients' medical records were reviewed to collect relevant data on demographics, tumour characteristics, the number and location of metastatic sites, gastric and ovarian surgery, the chemotherapy regimen received and the number of cycles, the tumour response of ovarian and extra-ovarian sites, the date of disease progression and survival status at the end of follow-up.

Tumour responses were assessed in patients with measurable disease by means of CT and/or MRI, according to the RECIST criteria, version 1.0 [21].

2.3. Chemotherapy regimens and follow-up

The choice of chemotherapy regimen was left to clinician discretion for the treatment of patients with advanced gastric cancer. Routine imaging follow-up based on CT and/or MRI was performed every 2 months after the first day of treatment, or earlier in patients with suspected disease progression. Chemotherapy was continued until the patient declined further doses or until limiting toxicity or disease progression occurred. The cut-off date for the analysis was September 2015.

2.4. Statistical analysis

For the descriptive analysis, quantitative variables were presented as median and standard deviation, and qualitative variables as frequencies and percentages. Continuous variables were compared using Student test or Mann and Whitney test in case of normal distribution or not, respectively; and qualitative variables were compared using the χ^2 test or by the Fisher exact tests when the χ^2 test was not applicable. Progression-free survival (PFS) was defined as the time from the start of first-line chemotherapy until the date of progression. Living patients without disease progression were censored at the last follow-up date. Overall survival (OS) was defined as the time from the first day of first-line chemotherapy until death (all causes). Living patients were censored at the last follow-up date. Survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test. Median follow-up was calculated with the reverse Kaplan–Meier method.

Univariate and multivariate Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The following predefined variables were examined in univariate analyses for their prognostic value with respect to PFS and OS: age, histological grade (well/moderate versus poor), histological subtype (intestinal versus diffuse), albuminemia, gastrectomy, synchronous versus metachronous ovarian metastases, oophorectomy, number of metastatic sites, Eastern Cooperative Oncology Group (ECOG) performance status and first-line chemotherapy protocol. All variables potentially associated with PFS or OS (univariate p value <0.20) were included in multivariate analyses, and a maximum of 1 variable/10 events was applied. The most parsimonious and clinically relevant Cox models for OS and PFS were finally adopted. The prerequisite hypotheses for the Cox model were verified (log-linearity and proportionality of risks) and correlations were tested for eligible variables. To prevent co-linearity, when two variables were significantly correlated, one variable was retained for its clinical relevance or likelihood ratio. p values <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary NC) and R Version 2.15.3 software.

3. Results

3.1. Patient characteristics

Thirty-five patients were included in this study. The clinical characteristics are summarized in Table 1. Median age was 50.5 years (range, 16.5–83.7). Twenty-one patients (60.0%) had synchronous ovarian metastases and 31 patients (88.6%) had at least one extra-ovarian metastatic site. The peritoneum was the most frequent extra-ovarian metastatic site (85.7%). Seventeen patients (48.6%) underwent oophorectomy, including 8 before first-line chemotherapy. Median follow-up was 44.5 months (95% CI 25.5–59.0).