Safety and Potential Benefit of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Peritoneal Carcinomatosis From Primary or Recurrent Ovarian Cancer

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Objectives: To analyze the outcomes of cytoreductive surgery and HIPEC in patients with peritoneal carcinomatosis from ovarian cancer.
Methods: Fifty-three patients with peritoneal carcinomatosis from primary (45 cases) and recurrent (8 cases) ovarian cancer were previously treated by systemic chemotherapy with platinum and taxanes and then submitted to surgical cytoreduction and HIPEC (cisplatin and mitomycin-C) with a closed abdomen technique. The median follow-up period was 27 months (range: 3–107).
Results: At the end of operation a complete cytoreduction (CCR-0) was obtained in 37 patients (70%). Major morbidity occurred in 12 patients (23%); reoperation was necessary in 2 patients (4%), and no postoperative mortality was observed. Overall 5-year survival probability was 55%; it was 71% in CCR-0, 44% in CCR-1, and none in patients with CCR-2 or CCR-3 residual tumor (log-rank test: $P = 0.017$). The cumulative risk of recurrence in 37 CCR-0 cases was 54% at 5 years from operation.
Conclusions: The results of our study indicate the feasibility and the potential benefit of a protocol including systemic chemotherapy, surgical cytoreduction and HIPEC in patients with peritoneal carcinomatosis from ovarian cancer. A phase III trial to compare this approach with conventional treatment is needed.
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KEY WORDS: primary ovarian cancer; cytoreductive surgery; HIPEC; intraperitoneal chemotherapy; neoadjuvant chemotherapy

INTRODUCTION

Ovarian cancer is the sixth most common neoplasm in women, and age-standardized incidence and mortality rates reach the highest values in Northern-Western Europe and Northern America [1]. Due to the lack of specific symptoms and early tendency to peritoneal dissemination, in most cases diagnosis is made in advanced stages; this accounts for the poor prognosis recently reported by EUROCARE Working Group, with 5-year survival probabilities ranging between 30% and 40% [2].

The standard treatment of primary ovarian cancer with peritoneal dissemination involves optimal surgical cytoreduction followed by platinum/taxane based chemotherapy [3,4]. However, despite the notable chemosensitivity of this neoplasm, tumor recurrence occurs in most cases, particularly when extra-pelvic peritoneal dissemination is present, resulting in very low long-term survival probability [5–8]. In order to improve these results, perioperative normothermic intraperitoneal chemotherapy (IP) has been proposed, with the aim to increase the intraperitoneal concentration of chemotherapy agents and improve the contact with cancer cells. Phase III studies demonstrated a survival benefit of IP compared with systemic therapy [9,10]. However, these trials considered only patients submitted to optimal cytoreduction, and several complaints mainly related to the management of the cathether for IP and patient compliance were reported, so that less than half of patients finally complete the treatment [11].

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a locoregional treatment which involves the washing of peritoneal cavity with heated solution and high drug concentrations [12–15]. The rationale for HIPEC is based on direct cytotoxicity of hyperthermia against malignant cells, combined with heat-related enhanced cytotoxic effects and pharmacokinetic advantages of the intraperitoneal route of anticancer drugs. Intraperitoneal administration is associated with a significantly greater drug concentration in the abdominal cavity compared with systemic concentration. The "peritoneal plasma barrier" mechanism provides locally dose-intensive therapy, in addition to the synergistic effect of hyperthermia. Moreover, hyperthermia provides a greater depth of tissue penetration of antiblastic agents with respect to normothermic administration. In the treatment of peritoneal carcinomatosis, HIPEC is generally associated with surgical debulking and peritonectomy, with the aim to remove macroscopic tumor [16]. This advanced multimodality treatment is indicated in patients with pseudomyxoma peritonei, peritoneal mesothelioma and peritoneal carcinomatosis of colorectal origin, with significant

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; ICU, intensive care unit; IP, intraperitoneal chemotherapy; NAC, neoadjuvant chemotherapy; PCI, peritoneal cancer index; SD, standard deviation; SE, standard error.

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