European Journal of Cancer (2014) **50**, 722–730

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Intraperitoneal vascular endothelial growth factor burden in peritoneal surface malignancies treated with curative intent: The first step before intraperitoneal anti-vascular endothelial growth factor treatment?

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Available online 29 November 2013

KEYWORDS
Intraperitoneal VEGF
Peritoneal carcinomatosis
Cytoreductive surgery

Abstract ***Introduction:*** Vascular endothelial growth factor (VEGF) is one of the most important angiogenic factors in solid tumours and plays an important role in ascites development in peritoneal surface malignancies (PSM). The main goal of this study was to determine the evolution and factors influencing intraperitoneal (IP) VEGF burden during cytoreductive surgery (CRS) with curative intent.

Patients and methods: Ninety-seven consecutive patients with PSM were treated with CRS at a single centre with curative intent. Patient data were collected prospectively between February 2012 and October 2012. An enzyme-linked immunosorbent assay technique was used to assess VEGF levels in intravenous (IV) systemic blood samples before incision and after abdominal closure, and in IP samples during abdominal cavity exploration, after completion of CRS, after hyperthermic IP chemotherapy, and at 1 and 24 h after abdominal closure.

Results: The IP VEGF burden increased significantly after CRS, and then decreased progressively ($p < 0.005$). In multivariate analysis, neoadjuvant IV bevacizumab significantly decreased the preoperative IP VEGF burden, tumour load according to Peritoneal Cancer Index value increased significantly the preoperative IP VEGF burden and a low preoperative

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0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.11.005

IP VEGF burden was associated with significantly increased postoperative complications. Neoadjuvant IV bevacizumab is the only factor that influences the preoperative IV VEGF concentration.

Conclusion: For patients with PSM who were treated with curative intent, the IP VEGF burden increased after CRS, and was reduced prior to surgery by the administration of neoadjuvant IV bevacizumab.

1. Introduction

Vascular endothelial growth factor (VEGF) has been described as one of the most important angiogenic factors in solid tumours [1]. It plays an important role in ascites development from ovarian cancer [2]. Moreover, high VEGF in mucinous adenocarcinoma of the appendix or colon has been correlated with worse prognosis [3]. Before surgery, VEGF level in ovarian peritoneal carcinomatosis (PC) is a predictive factor for resectability [4].

Peritoneal surface malignancies (PSM) are fatal without treatment regardless of their origin. Systemic chemotherapy alone has a limited impact on survival [5,6], except in ovarian carcinomatosis [7,8]. The only curative treatment is complete cytoreductive surgery (CRS) combined with perioperative systemic chemotherapy and perioperative intraperitoneal (IP) chemotherapy according to origin. Targeted therapies have improved survival rates for metastatic disease. Bevacizumab is a recombinant humanised monoclonal antibody, specifically anti-VEGF. Systemic administration of bevacizumab combined with conventional chemotherapy significantly increases response rate and the overall survival in the treatment of metastatic colorectal and ovarian cancer [9–13]. Bevacizumab has been administered intraperitoneally for the palliative treatment of PC of ovarian origin with efficacy [14], but never with curative intent in combination with CRS or hyperthermic intraperitoneal chemotherapy (HIPEC). We aim to associate IP bevacizumab with CRS and HIPEC for the curative treatment of PSM. To assess the possibility of such an association, we need more information about the evolution of IP VEGF during CRS and HIPEC. No studies exist about the evolution of IP VEGF burden during a curative procedure combining CRS and/or HIPEC in patients with PSM. The main goal of this study was to determine this evolution, as well as the factors that influence IP VEGF burden during CRS.

2. Materials and methods

Between February 2012 and October 2012, all consecutive patients treated for PSM with curative intent at a single institution were included in the study. Data were collected prospectively. PSM diagnosis was pathologically confirmed before surgery. After a complete morphological workup combining body computed tomography, abdominal magnetic resonance imaging, and positron emission tomography, a treatment strategy was defined for all patients in a multidisciplinary meeting according to international guidelines before curative surgery. For patients treated with bevacizumab preoperatively, the treatment was discontinued at least 5 weeks before surgery. No patient received preoperative IP treatment.

2.1. Surgical management

Under general anaesthesia, all patients underwent a median laparotomy. The extent of peritoneal carcinomatosis was assess according to the Peritoneal Cancer Index (PCI) [15]. This PCI divides the abdomen and pelvis into nine regions and the small bowel into four regions. The lesion size of the largest implant is scored: 0, no implants; 1, visible lesion $\leqslant$5 mm; 2, lesion 5–50 mm; 3, lesion >50 mm. Thus, for PSM the score ranges from 1 (limited PSM) to 39 (PSM spread throughout the entire abdominal cavity). After a comprehensive exploration of the abdominal cavity, cytoreductive surgery was performed according to lesion origin and PCI. The goal of the surgical procedure was a complete resection of disease considered CC 0 (Completness Cytoreduction no residual node) or CC 1 (residual nodes <2 mm) [15], combining peritonectomy and organ resection as described by Sugarbaker [16]. According to PSM origin and ongoing clinical trials in the department, the HIPEC procedure was performed after complete cytoreductive surgery with the closed abdomen technique. An inflow drain (30F Silicone William Harvey drain; Bard-Cardiopulmonary Division, Boston, MA) was placed under each diaphragm and an outflow drain (32F) was placed in the pelvic flexure. All drains were connected to a closed system (Cavitherm; EFS Electronique, Millery, France). Oxaliplatin was administered at 360 mg/m^2 for 30 min for colorectal PC. For PCs of other origins, the cytotoxic agent depended on preoperative decisions in the multidisciplinary meeting, depending on each patient's response to neoadjuvant chemotherapy and PSM origin. The other cytotoxic agents used were doxorubicin, mitomycin, and cisplatin, alone or in combination. Two silicone drains were left after CRS and/or HIPEC: