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Bevacizumab plus microtubule targeting agents in heavily pre-treated ovarian cancer patients: a retrospective study

Irène Asmane[1], Jean-Emmanuel Kurtz[1], Agathe Bajard[8], Jean-Paul Guastalla[2], Pierre Meeus[3], Olivier Tredan[2], Intidhar Labidi Galy[2], Isabelle Moullet[4], Philippe Ardisson[4], Lionel Vincent[5], David Coeffic[6], Armelle Dufresne[7], Jean-Pierre Bergerat[1], Isabelle Ray-Coquard[2]

[1] CHU Hautepierre, Department of Oncology & Hematology, 1, avenue Molière, 67000 Strasbourg, France <irene.asmane@wanadoo.fr>
[2] Centre Léon-Bérard, Department of Oncology, 69008 Lyon, France
[3] Centre Léon-Bérard, Department of Surgical Oncology, 69008 Lyon, France
[4] Clinique de la Sauvegarde, Department of Oncology, 69009 Lyon, France
[5] Centre hospitalier régional de Roannes, Medical Oncology Unit, 42300 Roannes, France
[6] Institut Daniel-Hollard, groupe hospitalier mutualiste Grenoble, Medical Oncology Unit, 38000 Grenoble, France
[7] Centre hospitalier régional de Chambéry, Department of Oncology & Hematology, 73000 Chambéry, France
[8] Centre Léon-Bérard, Department of Statistics, 69008 Lyon, France

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Abstract. **Objectives.** As vascular endothelial growth factor (VEGF) is expressed in ovarian cancer, we assessed the efficacy and safety of bevacizumab (a monoclonal antibody targeting VEGF) plus microtubule targeting agents for heavily pre-treated ovarian carcinoma patients. **Methods.** We retrospectively reviewed 43 patients with recurrent epithelial ovarian carcinoma. Combined treatment included bevacizumab with paclitaxel in 32 (74%), docetaxel in 10 (23%), and vinorelbine in one (2.3%) patients, respectively. **Results.** The median number of combined treatment was six cycles (range 1-29). On RECIST criteria, the objective response rate (ORR) was 40% (16% CR and 24% PR). Clinical benefit (complete response [CR] plus partial response [PR] and stable disease [SD] lasting ≥ 3 months) was 74% (CI95%: 46.7-77%). Median duration of treatment and overall survival were 3.9 months (range 0.2-14.4 months) and 20.1 months (CI95%: 13.8-20.1) respectively. No toxic death was reported. Grade 3-4 toxicity occurred in 30% of patients. Gastrointestinal perforations and fistula occurred in 3 (7%) and 6 (14%) patients, respectively. **Conclusions.** Although being active in terms of ORR, bevacizumab plus microtubule targeting agents – mainly taxanes – leads to a high rate of gastro-intestinal perforations and fistula in heavily pre-treated ovarian carcinoma patients. ▲

Key words: , bevacizumab, microtubule targeting agents, ovarian cancer, gastro-intestinal perforations

Introduction

Despite the development of more effective drugs and the refinement of surgical techniques, ovarian cancer remains the leading cause of death from gynecological cancer in the Western World [1]. Around 75% of patients with ovarian cancer are diagnosed with advanced disease, for whom the combination of carboplatin and paclitaxel is currently the gold standard. Nethertheless, many patients experience disease recurrence [2, 3]. Salvage chemotherapy for recurrent ovarian cancer varies according to platinum sensitivity. Platinum sensitive patients may be re-challenged with platinum-containing regimen [4-7], and therapy for refractory or resistant platinum patients [8] typically involves non-platinum single agent, including liposomal doxorubicin, topotecan, gemcitabine, and weekly paclitaxel [9-13]. All of these palliative alternatives have modest activity, showing response rates ranging from 5 to 20% [14]. Response-wise, these compounds are generally viewed as equivalent and moderately active, with objective response rates (ORR) ranging from 6.5 to 25% with topotecan and weekly paclitaxel, respectively [9, 13]. Survival is also dismal, with equivalent progression-free survival (PFS) in phase III

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trial, ranging from 9.1 and 12 weeks with irinotecan or liposomal doxorubicin, respectively [9].

The development of targeted therapeutics might be of outstanding importance to improve survival in advanced epithelial ovarian cancer, as angiogenesis is a key feature governing disease pathogenesis and outcome. Indeed, vascular endothelial growth factor (VEGF) is an important mediator of angiogenesis and is expressed in a majority of ovarian cancer samples [15]. Preclinical studies have demonstrated VEGF over-expression and its association with tumor angiogenesis, ascites constitution, malignant progression and early recurrence [16-18]. Monk *et al*. described a persistent response in resistant ovarian carcinoma patient treated by bevacizumab alone [19]. Bevacizumab monotherapy was evaluated in phase II trials and revealed encouraging response rates [20, 21]. Moreover, combining bevacizumab with chemotherapy was described as efficient in preclinical and clinical models. Accordingly, bevacizumab in combination with paclitaxel reduced ovarian xenograft burden and ascites development [22-25]. Garcia *et al*. explored the combination of bevacizumab with low dose oral cyclophosphamide, with promising results in ovarian cancer [26]. In metastatic breast cancer O'Shaughnessy and Brufsky reported outstanding results from the synergistic combination of paclitaxel plus bevacizumab [27]. Given these data, we decided to evaluate, through a retrospective study, in a non-selected population of patients, bevacizumab combined with chemotherapy in recurrent ovarian cancer patients treated in routine practice.

Methods

Patients

We conducted a retrospective study from six oncology centers. Patients were selected through a pharmacologic electronic database, using the words "ovarian cancer" and "bevacizumab, chemotherapy". We identified 43 histologically proven recurrent epithelial ovarian cancer patients who were treated between July 2007 and October 2009. All patients received informations on benefits and risks of treatment and gave oral informed consent for the combination treatment. All data – including patients' characteristics – were recorded, as well as medical history and prior cancer-related treatment procedures (including surgery and previous chemotherapy lines) by the same person through the six medical centers.

Treatment

We assessed treatment characteristics in all patients, including bevacizumab dose and schedule, type of chemotherapy, dose and schedule. Blood pressure, proteinuria, and renal function were assessed prior to bevacizumab administration and during treatment. Dose adjustments or treatment schedule modifications were recorded as well. All patients were to receive appropriate supportive care, including anti-emetics.

Evaluation of efficacy and toxicity

Response rate was assessed through Response Evaluation Criteria in Solid Tumors (RECIST) V1.0 [28] and CA125 levels modified per Rustin criteria [29], every two cycles of bevacizumab combined regimen (1 cycle is D1-D28). In patients with measurable disease, clinical or radiological tumor assessment took priority over CA125 measurements, and progressive disease during treatment could not be declared on the basis of CA125 alone. Clinical benefit was defined as CR plus PR and SD lasting greater or equal to 3 months. General factors (age, performance status), factors related to ovarian cancer (pathological subtype, histological grade, extension of disease, number of prior lines), and specific factor related to bevacizumab activity (high blood pressure), that might be associated to response/failure to bevacizumab-based therapy [30] were analyzed. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) V2.0. Concerning gastro-intestinal toxicity, we attempted to identify if bowel involvement, macroscopic residue after last surgery, high number of prior surgical procedures, high number of prior lines, prior hyperthermic intraperitoneal chemotherapy (HIPEC), prior abdominal radiation, could be identified as factors of toxicity [30, 31].

Statistical analysis

Categorical variables were expressed as frequencies and percentages. The distribution of continuous variables was calculated as mean ± standard deviation. The association between response rate and potentially related factors was tested with Fisher exact or Chi^2 tests for categorical variables and with the non-parametric Wilcoxon signed-ranked test for continuous