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# Role of bevacizumab in uterine leiomyosarcoma

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ABSTRACT

In the recent years, angiogenetic inhibitors have emerged for the treatment of several malignancies. In particular, bevacizumab has proved to be effective in many types of cancers (including sarcoma), but the limitations of antiangiogenic therapy have been shown in practice. Here, we sought to review the current evidence on the role and efficacy of bevacizumab in patients affected by uterine leiomyosarcoma. On April 2017, Literature was searched in order to identify studies reporting outcomes of patients affected either by early stage or advanced/recurred uterine leiomyosarcoma undergoing treatment with bevacizumab, alone or in combination with other chemotherapeutic regimens. Searching the literature data of 69 patients affected by metastatic, unresectable uterine leiomyosarcoma were retrieved; on the contrary, no data regarding the use of bevacizumab in patients with early-stage uterine leiomyosarcoma was published. Current evidence suggested that the addiction of bevacizumab to standard treatment modality does not increase grade 3 or worse toxicity (assessed by CTCAE). Pooled data regarding response rate suggested that 35%, 28%, 26% and 11% of patients experienced objective cure (complete + partial response), stable disease, progressive disease and unknown response, respectively. Data from the only one randomized controlled trial suggested that objective cure rate does not differ from standard chemotherapy treatment, thus limiting the indication to add bevacizumab in patients affected by metastatic, unresectable uterine leiomyosarcoma. The current evidence does not justify the use of bevacizumab into clinical practice. Further randomized studies testing the role of bevacizumab are warranted.

## 1. Introduction

Uterine leiomyosarcoma (ULMS) represents a rare uterine cancer, accounting for about 1% of all uterine malignancies with an estimated incidence of 0.55 per 100.000 women per year (Toro et al., 2006).

In the early stage of disease, standard treatment modality included surgery (hysterectomy with or without bilateral salpingo-oophorectomy), while data on the efficacy of adjuvant chemo and radiotherapy remains unclear (EESNW, 2012; D'Angelo and Prat, 2010; Koh et al., 2015). On the other hand, in case of advanced or recurrent unresectable disease, chemotherapy (including gembcitabine and docetaxel) represents the standard of care (EESNW, 2012; D'Angelo and Prat, 2010; Koh et al., 2015; Hensley et al., 2008).

Irrespective of treatment, ULMS are characterized by poor prognosis, and adverse outcomes are particularly pronounced in case of advanced or recurrent disease (Hensley et al., 2008, 2002). The 5-year relative survival rate in patients with localized disease is 63% (Hensley et al., 2008, 2002; Anon and., 2016). Approximately 50–70% of patients with early stage disease will experience loco-regional or distant recurrence within the first 2 years from diagnosis (Reed et al., 2008). Five-year survival rate is only 14% in patients with distant metastasis; in particular, owing to the low response rate to chemotherapy (about 35%) (Hensley et al., 2008, 2002; Anon., 2016).

A recent meta-analysis published by our group underlines that, even if the role of chemotherapy in early stage ULMS (after complete surgical resection) is still not completely clear, systemic treatment might have a major role in prevention of haematogenous dissemination in cancers with infiltrative pattern in the myometrial tissue (Bogani et al., 2016). In fact, literature data suggested that patients undergoing adjuvant chemotherapy experience a trend towards a lower risk (OR: 0.49 (95%CI: 0.24, 1.03)) of developing distant recurrences in comparison to radiotherapy (Bogani et al., 2016).

Over the last decade, the widespread development of innovative target therapies modified the treatment strategy in several solid gynecologic tumors (Leone Roberti Maggiore et al., 2013a,b,c, Leone Roberti Maggiore et al., 2013a,b,c; Leone Roberti Maggiore et al., 2013a,b,c; Bizzarri et al., 2016). In particular, the introduction of the humanized monoclonal antibody bevacizumab significantly improved the long-

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term outcomes different gynecological cancers (Leone Roberti Maggiore et al., 2013a,b,c, Leone Roberti Maggiore et al., 2013a,b,c; Leone Roberti Maggiore et al., 2013a,b,c; Bizzarri et al., 2016; Musella et al., 2016; Marchetti et al., 2016). The success of bevacizumab is due to its ability to interfere the neovascularization (Leone Roberti Maggiore et al., 2013a,b,c). Indeed, beyond microscopic size, tumors need to develop their own vasculature in order to receive oxygen and nutrients (Bizzarri et al., 2016). Bevacizumab binds all major isoforms of the vascular endothelial growth factor (VEGF) family, thereby preventing the activation of the VEGF-receptors and inhibiting endothelial cell proliferation and vessel formation (Leone Roberti Maggiore et al., 2013a,b,c; Bizzarri et al., 2016; Musella et al., 2016).

More than 20 year s ago, it has been observed in animal models that the leiomyosarcoma growth may be suppressed by the inhibition of the VEGF (Marchetti et al., 2016; Al-Husein et al., 2012; Folkman, 1971; Ferrara et al., 2004; Kim et al., 1993). However, clinical data on the use of antiangiogenic therapies in ULMS are scanty and often confusing. To date, only few studies investigated the efficacy of bevacizumab in ULMS (Wright et al., 2007; Takano et al., 2011; Dickson et al., 2015; D'Adamo et al., 2005; Hensley et al., 2015; Han et al., 2016). Here, we reviewed the current evidence on the role of bevacizumab in patients affected by ULMS, in order to assess possible beneficial effects and pitfalls on its use.

## 2. Methods

On April 2017, with the aim to evaluate the safety, tolerability and efficacy of bevacizumab in patients affected by ULMS, a systematical literature search was performed using the PubMed (MEDLINE), Web of Science, Google Scholar and SCOPUS databases. We identified all English language studies reporting data on bevacizumab in ULMS. For the process of evidence acquisition, literature was queried using the following terms "uterine leiomyosarcoma" OR "uterine sarcoma" AND "bevacizumab" OR "Avastin®". References of included studies were hand searched in order to identify potentially relevant adjunctive papers. For each study, in case of available data, we extracted the following information: number of patients, baseline characteristics, treatments data, disease-free and overall survival, and toxicity data.

In order to make comparable data from various studies, data on chemotherapy-related toxicity and response to treatment were assessed using Common Terminology Criteria for Adverse Events (CTCAE) and Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, respectively. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the processes of evidence acquisition and synthesis. Two independent reviewers (GB and CF) evaluated all studies in order to verify the inclusion criteria. Differences of opinions were resolved by agreement between the two reviewers. The quality and levels of recommendation of the investigations were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (Guyatt et al., 2008) and American College of Obstetricians and Gynecologists guidelines (ACOG) guidelines (Wright et al., 2011), respectively. Details of GRADE and ACOG guidelines are reported elsewhere (Bogani et al., 2016). Moreover, level of bias of the included studies was judged on the basis of the Cochrane Collaboration system (Gagnier, 2018). All data generated or analyzed during this study are included in this published article/as supplementary information files. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## 3. Results

Toward the process of evidence synthesis, six articles were available (Wright et al., 2007; Takano et al., 2011; Dickson et al., 2015; D'Adamo et al., 2005; Hensley et al., 2015; Han et al., 2016). Fig. 1 shows the flow diagram. Table 1 reports main characteristics of studies included, graded for their quality and levels of evidence.

Overall, the literature reports data on 69 patients affected by metastatic or unresectable ULMS treated with bevacizumab. Supplementary Table S1 displays details of chemotherapeutic regimens used within bevacizumab.

In 2007, Wright JD and colleagues, reported outcomes of 11 patients affected by recurrent uterine neoplasm who received

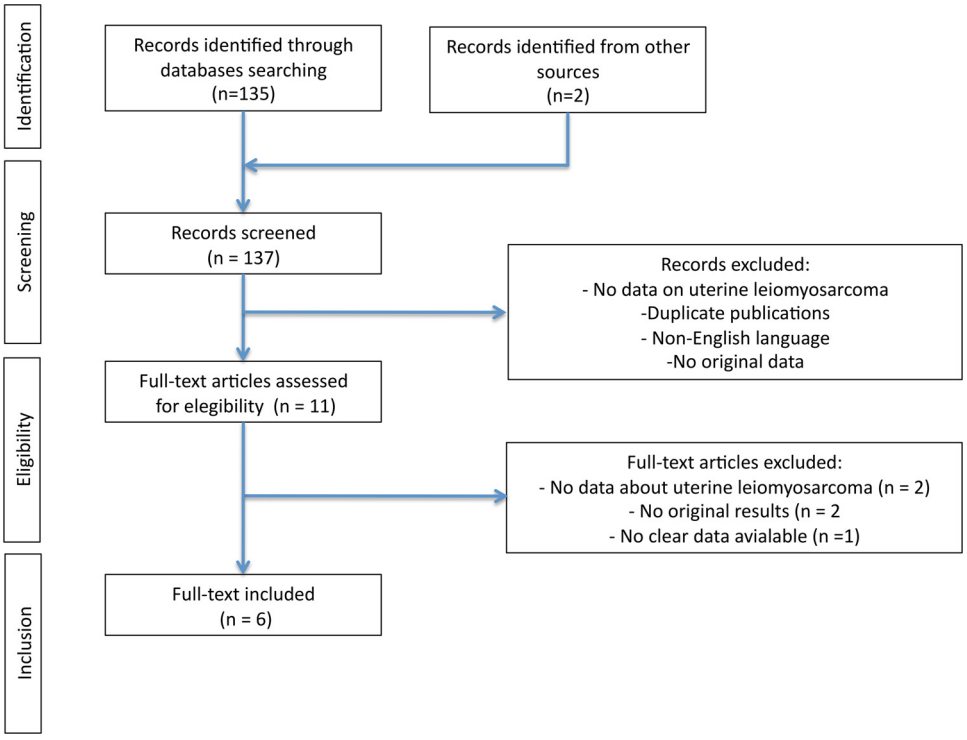


**Fig. 1.** Methods of literature review.