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Short Communication

Commentary on Efficacy and Safety of Trabectedin in Metastatic Uterine Leiomyosarcoma: A Retrospective Multicenter Study of the Spanish Ovarian Cancer Research Group (GEICO)

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ABSTRACT

Uterine Leiomyosarcoma (uLMS) is a very rare and aggressive carcinoma which, at advanced or recurrent stage, has a median overall survival of below 12 months. The Spanish ovarian cancer research group (GEICO), carried out a retrospective, observational, multicenter study involving 36 adult patients with unrespectable advanced or metastatic uLMS who received trabectedin after an anthracycline-containing regimen. The efficacy and safety observations found with trabectedin in this study were in line with previously shown in clinical trials.

Trabectedin provides long-term carcinoma stabilization and adequate tolerability, thus it represents an appropriate option for the treatment of advanced uLMS. Beneficial effects are optimized when administered as second-line, after the failure of the anthracycline-containing regimen, which allows achieving longer clinical benefit and disease control. Furthermore, it is recommended to maintain the treatment with trabectedin until disease progression due to its better efficacy outcomes as well as its safety profile, allowing the long-term administration with no cumulative toxicities. Trabectedin has also demonstrated activity in diverse soft tissue sarcoma subtypes.

Keywords: Uterine leiomyosarcoma; Trabectedin; Efficacy; Safety; GEICO

INTRODUCTION

Uterine Leiomyosarcoma (uLMS) is a very rare and aggressive carcinoma whose incidence is 0.36-0.64 per 100,000 women per year [1]. The 5-year survival varies from 16% to 57%, depending the stage of the disease when diagnosed [2]. At advanced or recurrent stage, the median overall survival (OS) is below 12 months [3]. Surgical resection represents the only treatment option with the chance for cure so far, and probably a longer response than medical management [4]. Besides this, the recurrence risk within 2 and 5 years from the surgery is 40%-70% [5].

Doxorubicin, ifosfamide, or gemcitabine in monotherapy are some of the therapeutic armamentarium used for the treatment of uLMS, achieving objective response rates (ORR) of 13%–25%, 17%, and 21%, respectively [6,7]. The combination of gemcitabine plus docetaxel has also been shown a response rate varying from 27% to 53% [8,9]. Trabectedin is indicated for patients with advanced soft tissue sarcoma (STS) after failure of a previous treatment with anthracycline and ifosfamide, or when the patients unsuited [10]. Trabectedin received approval in 2007 by the European Medicines Agency, and in 2015 by the U.S. Food and Drug Administration, based on the efficacy and manageable safety profile demonstrated in diverse clinical trials [11,12]. Besides randomized, controlled clinical trials are the basis for the medical evidence, their applicability and generalizability require validation in non-interventional, real-world studies [13].

STUDY OBSERVATIONS

The Spanish ovarian cancer research group (GEICO), carried out a retrospective, observational, multicenter study involving 36 adult patients with unresectable advanced or metastatic uLMS who received trabectedin after an anthracycline-containing regimen [14]. The objective of the study was to determine efficacy and safety of trabectedin in routine clinical practice. The primary endpoint included its efficacy in terms of progression-free survival (PFS), whereas secondary endpoints encompassed

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OS, tumor response to trabectedin and the safety profile. The median number of trabectedin cycles was 6 (3-25 cycles). Since starting treatment with trabectedin, median PFS and OS were 5.4 and 18.5 months, respectively. The survival results of trabectedin treatment are shown in Table 1. The ORR was 27.8%, with median response duration of 11 months.

Mean months (95% confidence interval)	Progression-free survival	Overall survival
Total patients; n=36	5.4 (3.5–7.3)	18.5 (11.5-25.6)
Regarding previous lines		
First/second-lines; n=15	5.4 (0.0-11.1)	25.3 (0.0-66.7)*
Third line/beyond; n=21	5.7 (3.8-7.7)	15.1 (10.9-19.2)
ECOG at trabectedin initiation		
0-1; n=28	5.4 (3.7–7.0)	19.8 (12.9–26.7)
2-3; n=4	3.1 (1.7–4.5)	6.0 (2.4–9.6) **

Overall survival statistically different between: * first/second-lines versus third line/beyond (p=0.028); ** ECOG 0-1 versus 2-3 (p=0.013)

Table 1: Survival results with trabectedin treatment.

Patients receiving trabectedin as first or second line (after neoadjuvant or first-line anthracycline-containing regimen), showed a significantly higher median OS (25.3 months; 95% confidence interval, 95%CI: 0.0–66.7) than those in third-line or beyond (15.1 months; 95%CI: 10.9–19.2; p=0.028). Moreover, the number of patients achieving a complete or partial response was higher when receiving trabectedin in first-line after an anthracycline-containing regimen (16.7% and 50.0%, respectively) than those in second-line or beyond (0.0% and 20.0%).

At trabectedin initiation, patients with Eastern Cooperative Oncology Group performance status (ECOG) ≤ 1 also had a significantly higher median OS (19.8 months) than those with 2–3 (6.0 months; p=0.013). Regarding safety, most frequent adverse events were neutropenia (30.5% of patients), anemia (25.0%), fatigue (25.0%), nausea (13.9%), and vomiting (11.1%). No cumulative toxicity was reported.

CONCLUSION

Efficacy and safety observations found with trabectedin in this study were in line with those previously shown in clinical trials [13]. Trabectedin provides long-term carcinoma stabilization and adequate tolerability, thus it represents an appropriate option for the treatment of advanced uLMS [14]. Beneficial effects are optimized when administered as second-line, after the failure of anthracycline-containing regimen, which allows achieving longer clinical benefit and disease control [13].

Furthermore, it is recommended to maintain the treatment with trabectedin until disease progression due to its better efficacy outcomes as well as its safety profile, allowing the long-term administration with no cumulative toxicities [13-15]. Trabectedin has also demonstrated activity in diverse STS subtypes, including non-uterine leiomyosarcoma and liposarcoma, as well as rare subtypes, such as synovial sarcoma, myxofibrosarcoma, malignant peripheral nerve sheath tumors, rhabdomyosarcoma, or endometrial stromal sarcoma [16].

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