Med Oncol (2013) 30:501
DOI 10.1007/s12032-013-0501-3

SHORT COMMUNICATION

Clinical benefit of trabectedin in uterine adenosarcoma

Brett A. Schroeder · Eve T. Rodler · Elizabeth T. Loggers · Seth M. Pollack · Robin L. Jones

Received: 28 January 2013 / Accepted: 6 February 2013 / Published online: 28 February 2013

Abstract Uterine adenosarcoma is an extremely rare uterine malignancy, and the utility of chemotherapy in this disease is not well defined. This study assessed the safety and efficacy of trabectedin in patients with recurrent/metastatic uterine adenosarcoma with sarcomatous overgrowth. A retrospective search of a prospectively maintained database was performed to identify patients with adenosarcoma treated with trabectedin between 2010 and 2012, within a compassionate use trial. Three patients with recurrent/metastatic uterine adenosarcoma treated with trabectedin were identified. All three patients tolerated the drug well. Two patients obtained prolonged clinical benefit from treatment, one having received 17 cycles and another 11 cycles of therapy. Trabectedin is well tolerated and has clinical activity in recurrent/metastatic uterine adenosarcoma.

Keywords Uterine adenosarcoma · Systemic therapy · Trabectedin · Clinical benefit

Background

Uterine adenosarcoma is a very rare malignancy originally described by Clement and Scully in 1974 [1]. This tumor typically affects postmenopausal women, with a median age of 57 years [1–3]. Total abdominal hysterectomy and bilateral salpingoophorectomy (TAH–BSO) is the mainstay of management of localized disease [1]. Uterine adenosarcoma is characterized by benign or occasionally atypical glands and a malignant (sarcomatous) stroma [1]. This disease is generally considered as being of low malignant potential, with local vaginal, pelvic or abdominal recurrences seen in approximately 25 % of cases [4]. However, some patients may have aggressive disease with poor outcome [3]. The role of systemic chemotherapy in patients with recurrent or metastatic disease is not well defined, with the literature limited to case reports [5–7].

Trabectedin is a synthetically produced alkaloid, originally derived from the Caribbean marine tunicate Ecteinascidia turbinate [8]. A number of potential mechanisms of action have been suggested for this drug, including binding to the DNA minor groove and consequently distorting DNA and inhibiting transcription, resulting in disruption of the cell cycle and inhibition of proliferation. Three Phase II trials showed that trabectedin has activity in soft tissue sarcoma patients resistant to anthracycline and ifosfamide, with a high proportion of patients achieving clinical benefit, with disease stabilization in up to 60 % of patients with leiomyosarcoma and synovial sarcoma [9–11]. A Phase II trial randomized liposarcoma and leiomyosarcoma patients to receive one of two trabectedin schedules: 1.5 mg/m^2 24 h infusion once every 3 weeks or 0.58 mg/m^2 over 3 h every week for 3 weeks of a 4 week cycle. The patients treated with the once every 3 week schedule had a significantly longer median time to progression (3.7 months) compared with the weekly arm (2.3 months), $p = 0.0302$ [12]. Fatigue, nausea, vomiting and elevated transaminases are the most common side effects of this drug, and it can rarely cause rhabdomyolysis [12]. Trabectedin seems to be particularly active in myxoid/round cell liposarcoma and has been approved in the European Union for the treatment of anthracycline and ifosfamide resistant soft tissue sarcoma. There is currently a Phase III trial randomizing

B. A. Schroeder · E. T. Rodler · E. T. Loggers · S. M. Pollack · R. L. Jones (✉)
Fred Hutchinson Cancer Research Center, University of Washington, 825 Eastlake Avenue East, Seattle, WA, USA
e-mail: rjones@seattlecca.org

patients with recurrent liposarcoma and leiomyosarcoma patients to receive either DTIC or trabectedin.

There is very little published data on the activity of systemic therapy in uterine adenosarcoma. The aim of this study was to report our experience of trabectedin in patients with recurrent/metastatic uterine adenosarcoma with sarcomatous overgrowth treated within a compassionate use program.

Methods

A retrospective search of the prospectively maintained University of Washington/Seattle Cancer Care Alliance Sarcoma database was performed to identify patients with metastatic uterine adenosarcoma treated with trabectedin between 2010 and 2012.

The diagnosis was confirmed in each case by an experienced soft tissue pathologist. The pathology was not re-reviewed for this study. Patients were treated with trabectedin at a dose of 1.5 mg/m^2, as a continuous infusion over 24 h, once every 3 weeks. Patients were treated within an expanded access trial of trabectedin for patients with soft tissue sarcoma. Re-staging CT scans were performed after every 2–3 cycles for the first 8 cycles.

Results

Three patients with metastatic uterine adenosarcoma treated with trabectedin were identified.

The first patient is a 65-year-old woman with early stage uterine adenosarcoma who underwent TAH–BSO in 2005 at an outside institution. She did not receive adjuvant radiation or chemotherapy. In April 2009, a recurrent 15 cm mass was detected on imaging. Surgical resection and left pelvic lymph node biopsy were performed, and pathology revealed adenosarcoma with 2 positive lymph nodes. In September 2009, a recurrent isolated 1.3-cm nodule in the left pelvis was detected and treated with CyberKnife therapy. Over the next 15 months, the patient had three further local pelvic recurrences which were all resected. On May 26, 2011, a postoperative scan showed a left abdominal wall recurrence. In view of the fact that the disease had recurred so quickly after surgery and radiation, a decision was made to treat her with systemic therapy. She declined anthracycline- and ifosfamide-based therapy due to potential toxicity. At this time, pazopanib was not approved by the FDA for recurrent soft tissue sarcoma. She was referred to our institution and commenced trabectedin in July 2011. She tolerated treatment well with only minimal fatigue. After cycle 6, a repeat CT showed a RECIST (Response Evaluation Criteria in Solid Tumors) partial response in the abdominal soft tissue mass (Fig. 1). The patient continued to tolerate trabectedin well and received 17 cycles until disease progression.

The second patient is a 71-year-old woman who was treated for early stage breast cancer in 2004, with surgery, radiation and adjuvant anthracycline-based chemotherapy. She subsequently developed metastatic breast cancer and was treated with capecitabine, navelbine, methotrexate and trastuzumab. The patient responded and continued on maintenance trastuzumab. In March 2009, she was diagnosed with stage 2 uterine adenosarcoma with sarcomatous overgrowth and underwent total abdominal hysterectomy. In January 2012, she underwent surgery for locally recurrent adenosarcoma. A repeat scan in March 2012 showed relapsed multifocal adenosarcoma. She was referred to our institution and commenced trabectedin in April 2012. Re-staging CT scans following 3 cycles showed stable disease by RECIST. A dose reduction to 1.2 mg/m^2 was performed due to Grade 3 fatigue. She has received 11 cycles of trabectedin and is well with no fatigue. The disease has remained stable.

The third patient was a 58-year-old woman who underwent TAH–BSO for uterine adenosarcoma with sarcomatous overgrowth in October 2008. In September 2009, she developed bulky lung, pelvic and bone metastases and underwent pelvic tumor debulking, followed by palliative radiation to bony metastases. She received 3 cycles of gemcitabine and docetaxel followed by disease progression and then doxorubicin and ifosfamide for 3 months followed again by disease progression. She was referred to our institution and commenced trabectedin in September 2010 and received two cycles. Unfortunately, her performance status deteriorated and she died in November 2010 of progressive disease.

Discussion

Uterine adenosarcomas are rare tumors and are usually of low malignant potential, with a proportion displaying clinically aggressive behavior [3]. The role of chemotherapy for patients with recurrent disease is not well defined. Individual case reports have described responses to several chemotherapeutic drugs [5–7]. As far as we are aware, there are no large published case series of systemic therapy in this subtype.

The clinical benefit derived by two of the three patients we treated with trabectedin is noteworthy and has not been previously reported in this rare malignancy. These patients have obtained prolonged clinical benefit on trabectedin, having progressed rapidly on previous therapy, consisting of surgery and radiation. In addition, trabectedin was well tolerated. One patient required dose reduction due to Grade 3 fatigue. Our findings suggest trabectedin is a potentially effective and well-tolerated agent in adenosarcoma with

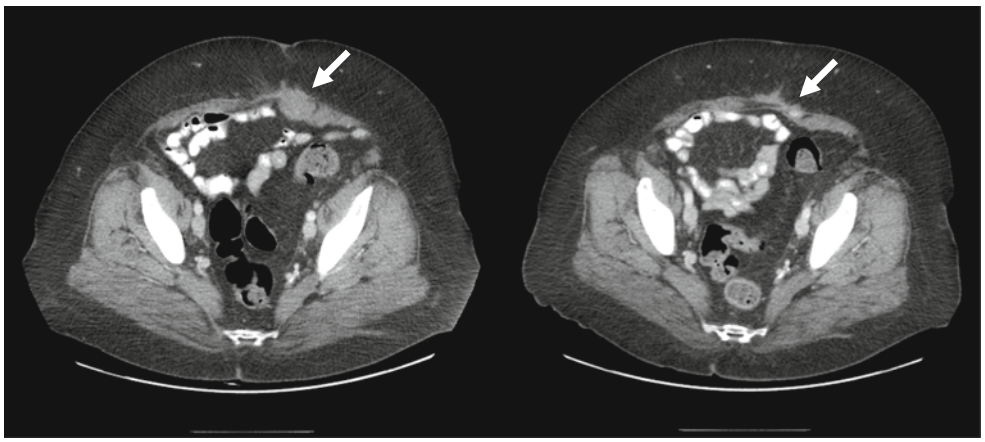

Fig. 1 CT scan images showing a response in a patient with recurrent adenosarcoma (baseline and post 6 cycles of trabectedin)

sarcomatous overgrowth, warranting further evaluation in this rare histological subtype.

In view of the rarity of uterine adenosarcoma, international collaboration will be required to investigate the underlying biology and other therapeutic options for patients with this disease.

Conflict of interest Dr Jones has conducted trials with trabectedin, sponsored by Johnson and Johnson. All other authors declare no conflict of interest.

References

1. Clement PB, Scully RE. Müllerian adenosarcoma of the uterus. A clinicopathologic analysis of ten cases of a distinctive type of mullerian mixed tumor. Cancer. 1974;34:1138–49.
2. Andrade LA, Derchain SF, Vial JS, Alvarenga M. Mullerian adenosarcoma of the uterus in adolescents. Int J Gynaecol Obstet. 1992;38(2):119–23.
3. Kaku T, Silverberg SG, Major FJ, Miller A, Fetter B, Brady MF. Adenosarcoma of the uterus: a gynecologic oncology group clinicopathologic study of 31 cases. Int Gynecol Pathol. 1992;11(2):75–88.
4. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol. 1990;21(4):363–81.
5. Huang GS, Arend RC, Sakaris A, Hebert TM, Goldberg GL. Extragenital adenosarcoma: a case report, review of the literature, and management discussion. Gynecol Oncol. 2009;115(3):472–5.
6. Carmen MG, Lovett D, Goodman A. A case of Müllerian adenosarcoma of the uterus treated with liposomal doxorubicin. Gynecol Oncol. 2002;88:456–8.
7. Roman LD, Mitchell MF, Tornos C, Glover A, Kavanagh JJ. Dedifferentiated extrauterine adenosarcoma responsive to chemotherapy. Gynecol Oncol. 1993;49:389–94.
8. Krikelis D, Judson I. Role of chemotherapy in the management of soft tissue sarcomas. Expert Rev Anticancer Ther. 2010;10(2):249–60.
9. Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, Taamma A, Jimeno J, Martin C, Salhi Y, Cvitkovic E, Misset JL. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol. 2004;22(5):890–9.
10. Le Cesne A, Blay JY, Judson I, Van Oosterom A, Verweij J, Radford J, Lorigan P, Rodenhuis S, Ray-Coquard I, Bonvalot S, Collin F, Jimeno J, Di Paola, Van Glabbeke M, Nielsen OS. Phase II study of ET-743 in advanced soft tissue sarcomas: a European organisation for the research and treatment of cancer soft tissue and bone sarcoma group trial. J Clin Oncol. 2005;23(3):576–84.
11. Garcia-Carbonero R, Supko JG, Manola J, Seiden MV, Harmon D, Ryan DP, Quigley MT, Merriam P, Canniff J, Goss G, Matulonis U, Maki RG, Lopez T, Puchalski TA, Sancho MA, Gomez J, Guzman C, Jimeno J, Demetri GD. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004;22(8):1480–90.
12. Grosso F, D'Incalci M, Cartoafa M, Nieto A, Fernandez-Teruel C, Alfaro V, Lardelli P, Roy E, Gomez J, Kahatt C, Soto-Matos, Judson I. A comprehensive safety analysis confirms rhabdomyolysis as an uncommon adverse reaction in patients treated with trabectedin. Cancer Chemother Pharmacol. 2012;69(6):1557–65.