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General Information

Key Personnel (in addition to PI):

First Name:
Last name:
Degree:
Primary Affiliation:
SCOPUS ID:

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_coi_2.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s):

1. [NCT01343277 - A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma or Leiomyosarcoma](#)
2. [NCT00060944 - A Randomized, Multicenter, Open-label Study of Yondelis \(ET-743 Ecteinascidin\) Administered by 2 Different Schedules \(Weekly for 3 of 4 Weeks vs. q3 Weeks\) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Follo](#)
3. [NCT00210665 - A Study to Provide Access to Trabectedin in Participants With Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Persistent or Recurrent Disease and Who Are Not Expected to Benefit From Currently Available Standard of Care Treatme](#)
4. [NCT00786838 - A Study to Assess the Potential Effects of a Single-Dose Administration of Trabectedin on the QT Intervals of the Electrocardiogram](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all

supporting documentation

Research Proposal

Project Title

Safety of re-administration of trabectedin in soft tissue sarcoma patients experiencing CK elevation

Narrative Summary:

Trabectedin is a chemotherapy used in sarcoma (a rare cancer). A unique toxicity of trabectedin is rhabdomyolysis (muscle break-down) which can be mild, but sometimes leads to kidney failure and death. Given the potential for severe consequences, physicians are often wary about re-administering trabectedin once a patient has had this toxicity. There may be instances, however, where trabectedin re-challenge can be safe. Identifying parameters for re-treatment with trabectedin after mild or moderate muscle break-down will help physicians make more informed treatment decisions and will help prevent premature discontinuation of this drug in patients who are benefiting.

Scientific Abstract:

Background: Trabectedin is an effective chemotherapy for refractory soft tissue sarcoma patients with a unique side effect of rhabdomyolysis. Certain patients experiencing this toxicity can be re-challenged uneventfully with this drug. Approximately 10-15% of patients exposed to trabectedin derive long-term benefit (at 3-4 years). Therefore, identifying which patients can be safely re-challenged with this agent is of significant importance to clinicians.

Objective: To identify patients re-challenged with trabectedin after CK elevation and circumstances and outcomes surrounding the treatment continuation.

Participants: Patients enrolled in NCT01343277, NCT00060944, NCT00210665 and NCT00786838

Main Outcome Measures: Trabectedin re-administration after CK elevation

Study Design and Statistical Analysis: This is a retrospective analysis of the data from four clinical trials of trabectedin to determine the incidence of re-challenge with trabectedin after a CK elevation. We will also aim to identify factors involved in re-challenge and patient outcomes after re-challenge. Data will be summarized graphically, using frequencies, percentages, means, medians, and standard deviations. Descriptive statistics will be used to analyze characteristics of those patients who were re-challenged with trabectedin after CK elevation.

Brief Project Background and Statement of Project Significance:

Soft tissue sarcomas (STS) are a rare, heterogeneous group of mesenchymal tumors. In 2018, there will be an estimated 13,040 cases of newly diagnosed soft tissue cancers associated with 5,150 deaths in the United States. STS are anatomically, histologically and biologically diverse making treatment complex. These tumors can occur anywhere in the body: commonly in the extremities, thorax and visceral sites such as the uterus. Median overall survival for patients with metastatic or refractory soft tissue sarcoma remains under two years (1).

Trabectedin is a marine derived alkaloid chemotherapy that was FDA approved in 2015 for refractory soft tissue sarcoma. A unique but uncommon toxicity of trabectedin is rhabdomyolysis for which the etiology is unclear.

Rhabdomyolysis is diagnosed in patients experiencing muscle cramping and an marked elevation in CK. The CK is typically at least five times the upper limit of normal; however, no strict cut-off has been defined. Other concomitant problems include renal injury and electrolyte abnormalities. A recent comprehensive analysis estimated the incidence of this toxicity at 0.7% with a 0.3% rate of fatal toxicity (2). Interestingly, this event generally occurs between the second and third cycle of chemotherapy – a time point when patients are often re-imaged for efficacy as well.

The management of rhabdomyolysis including supportive care with fluids and dialysis when appropriate is well-known. However, the safety of re-challenge with trabectedin after recovery in patients with mild or moderate CK elevations is unclear. At our center we treated approximately 300 patients on the expanded access program with trabectedin for STS. In our clinical practice, we have re-challenged responding patients with both mild CK elevations as well as those with more severe presentations. In the latter situation by using a dose reduction. In one such instance a patient with CK elevation of 3000, neutropenia and thrombocytopenia was re-challenged at a lower dose upon recovery. This patient remains on trabectedin 4 years later with stable disease and without any major toxicity. Our center has extensive experience managing the toxicity of trabectedin. STS can be treated by a wide

group of practitioners: academic medical oncologists, community medical oncologists or gynecologic oncologists. Rhabdomyolysis is not a toxicity commonly seen in patients receiving chemotherapy. Therefore, developing recommendations on when trabectedin can safely be re-administered especially in responding patients would be invaluable to those not as familiar to the side effect profile of the drug.

Specific Aims of the Project:

1. Determine the incidence of patients re-challenged with trabectedin after a CK elevation in available datasets
2. Identify factors involved in the decision to re-challenge (severity of initial presentation, timing of recovery, concomitant comorbidities, dose reduction, and status of disease control)
3. Identify outcomes of those experiencing CK elevation who were then re-challenged with trabectedin
4. Develop practice guidelines for medical oncologists especially those in the community on the management of CK elevation/rhabdomyolysis in patients who receive trabectedin

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment safety

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Inclusion

1. Patients re-challenged with trabectedin after experiencing CK elevation on NCT01343277, NCT00060944, NCT00210665 or NCT00786838 clinical trials.

Exclusions

None

Main Outcome Measure and how it will be categorized/defined for your study:

- 1) Incidence of trabectedin re-administration in patients with A) CK increase with renal injury B) CK increase without concomitant renal injury

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Cases of trabectedin re-administration after CK elevation and degree of toxicity patient experienced

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Factors involved in the decision to re-challenge after trabectedin related CK increase including: severity of initial presentation, timing of recovery, concomitant comorbidities, dose reduction, and status of disease control
Outcomes of patients re-challenged with trabectedin after experiencing drug related CK elevation

Statistical Analysis Plan:

This is an exploratory analysis, so we do not provide power calculations. There will be no formal hypothesis testing for the primary aims of this study. Data will be summarized graphically, using frequencies, percentages, means, medians, and standard deviations. Cases of patients with CK elevation will be identified from the trial databases. Descriptive statistics will be used to analyze characteristics of those patients who were re-challenged with trabectedin after CK elevation. Outcomes of these patients will be characterized as complete response, partial response, stable disease or progressive disease per the trial databases.

Project Timeline:

Anticipated Project Start: May 2018

Analysis Completion Date: September 2018

Draft Manuscript and Results Reported to YODA Project: January 2019

Dissemination Plan:

We would expect to have an abstract submitted to the American Society of Clinical Oncology Conference 2019. In addition, we would consider submitting the manuscript to journals such as American Journal of Oncology, Oncologist, Sarcoma or Clinical Sarcoma Research all of which have had articles related to trabectedin in the past.

Bibliography:

1. Italiano A, Mathoulin-Pelissier S, Cesne AL, et al: Trends in survival for patients with metastatic soft-tissue sarcoma. *Cancer* 117:1049-54, 2011
2. Grosso F, D'Incalci M, Cartoafa M, Nieto A, Fernández-Teruel C, Alfaro V, Lardelli P, Roy E, Gómez J, Kahatt C, Soto-Matos A, Judson I. A comprehensive safety analysis confirms rhabdomyolysis as an uncommon adverse reaction in patients treated with trabectedin. *Cancer Chemother Pharmacol.* 2012 Jun;69(6):1557-65. doi: 10.1007/s00280-012-1864-4. Epub 2012 Apr 7.