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TRABECTEDIN-RELATED MUSCULAR AND OTHER ADVERSE EFFECTS; DATA FROM PUBLIC VERSION OF THE FDA ADVERSE EVENT REPORTING SYSTEM

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ABSTRACT

Objective: To describe the pattern and frequency of adverse events (AE) reported with use of trabectedin.

Research Methodology: Retrospective review of adverse event reports (AERs) submitted in the US-FDA Adverse Event Reporting System (AERS) database from 2007 to September 2011 was done. Any patient who reported an AE with the use of marine derived anticancer product trabectedin captured in the AERS was documented. After excluding arbitrary drug names and duplicated submissions, AERs were analyzed. Descriptive statistics were used.

Results: Based on 1,888,123 AERs submitted to AERS during study period, 193 reports were related to trabectedin out of which 171 (88.6%) were expedited, 19 (9.8%) periodic and 3 (1.5%) were direct. 93% reports were submitted by health care providers and 69% were submitted in 2010-11. Two-third reports were from males with average all patients age being 58.4 years. Predominant indication of use was sarcoma (76.2%). 58 (30%) reports were detected for trabectedin related muscular adverse events and rhabdomyolysis contributed to 39 (20%) AERs.

Conclusion: Data from FDA's AE reporting system, AERs, is useful for examining trabectedin-associated muscular adverse events. Trabectedin has only short history of use. The entire safety profile is yet to be explored. The data strongly suggests the necessity of well conducted clinical studies with respect to trabectedin associated muscular adverse events.

Keywords: Adverse events, Data mining, Trabectedin.

INTRODUCTION

Trabectedin (ecteinascidin 743, ET-743, Yondelis) is a marine derived anticancer agent from the Caribbean sea squirt *Ecteinascidia turbinate.* It was approved as a single agent for the treatment of soft tissue sarcoma (STS) in 2007 by European Union after failure of standard-of-care chemotherapy (doxorubicin and/or ifosfamide) or for patients unsuited to receive these agents, [1] Regulatory approval was also obtained (2009) for the treatment of relapsed, platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (PLD; Caelyx). [2] Its main mode of action is as alkylating agent against deoxyribonucleic acid. Pancytopenia, acute renal failure, increased blood creatinine, increased blood creatinine phosphokinase, dehydration have been reported as the most common adverse reactions with trabectedin. Rhabdomyolysis though serious, has been reported as an uncommon adverse reaction. [3-6]

In 2012, comprehensive safety analysis of trabectedin [7] determined the incidence of serious rhabdomyolysis events reported during trabectedin

treatment since the first phase I clinical trial in April 1996 up to September 2010. This analysis reported the global incidence of rhabdomyolysis as 0.7%. Majority of the cases occurred in cycle 2 of treatment and the incidence of fatal cases was 0.3%.

OBJECTIVES

The purpose of this study was to further explore adverse event profile with trabectedin. We used published evidence to define, a priori, specific adverse events of concern with trabectedin. Our analysis is focused mainly on muscular adverse effects of trabectedin. The muscular adverse effects such as rhabdomyolysis, though uncommon, can result in life-threatening renal and multi-organ failure with hypovolemia, hyperkalemia, metabolic acidosis, disseminated intravascular coagulation, and compartment syndrome, secondary arrhythmias, or cardiac arrest. [7-9] Although, other studies have documented adverse events with trabectedin, [10] our analysis is an important contribution because it uses the most recently available FDA adverse event reporting system (AERS) database that relies on reports of spontaneous adverse events generated by health professionals, consumers, and manufacturers. In this study, about 2 million AERs submitted to the AERS from 2007 to third quarter of 2011 were reviewed to assess the muscular adverse events induced by the administration of trabectedin.

RESEARCH METHODOLOGY

Data sources

Input data for this study was taken from the public release of the FDA's AERS database, which covers the period from the first quarter of 2007 to the third quarter of 2011.[11] The terms 'yondelis' and 'trabectedin' were considered as search terms for isolating all trabectedin related ADRs.[10] The data structure of AERS is in compliance with international safety reporting guidance, ICH E2B. Prior to analysis, all drug names were (including dosage descriptions, generic names, names outside the United States, misspellings, etc., as originally entered in the AERS database) were consolidated into one common name.[12] The total number of co-occurrences, i.e., drug-adverse event pairs, was 9,225,975. Rhabdomyolysis (asthenia, myalgia, muscle spasms and an increase in creatine phosphokinase level) were focused on as muscular adverse events.

RESULTS

Overview of adverse drug reaction reports

From January 2007 to September 2011 the AERS received 1,888,123 adverse event reports, including 193 reports for trabectedin. The trend of reporting for trabectedin is presented in Figure 1, which depicts an increased trend in reporting from 2009 onwards as its usage has expanded due to the additional approval for its use in ovarian cancer. The majority of the adverse event reports of trabectedin were in males (75.6%) with average age patients being 58.4 years. The predominant indication of trabectedin use was sarcoma (76.2%). The details regarding the indications are listed in table 1.

The majority of the reports were sumitted from United Kingdom (18%). Physicians, including other health professionals, represented the main reporting entities for trabectedin-related reports, where 61.6% of reports were submitted by physicians. Reports submitted by the manufacturer to the FDA were expedited (88.6%), i.e., received within 15 days of an adverse drug reaction. These included unlabeled/ serious events and followed by periodic i.e., received quarterly representing 9.8% of the manufacturer-submitted reports. Trabectedin was administered intravenously with a dosing range of 1.1-3.15mg/m^2. Table 2 describes the reports for trabectedin received during the study period.

Adverse effects with a reporting frequency of $\geq$10 reports during the study period are listed by organ system class in Table 3.

Rhabdomyolysis and other muscular adverse events

Rhabdomyolysis is an injury of skeletal muscle that releases potentially toxic muscle cell components (e.g., myoglobin, other intracellular proteins, and electrolytes) into the extracellular fluid and blood stream, which may result in renal damage.[13,14] Biochemically, rhabdomyolysis is defined by marked blood CPK elevation [typically greater than 10 times the upper limit of normal (ULN)] with creatinine increase.[15,16] Creatinine phosphokinase (CPK) elevation is the most sensitive marker for skeletal muscle injury.[17] During the analyses period, trabectedin was associated with 39 (20%) reports of rhabdomyolysis that also includes CPK elevation. Reports for the signs and symptoms of rhabdomyolysis included pain (n=16), malaise (n=6), fatigue (n=7), lethargy (n=5), fever (n=15), nausea (n=17), and vomiting (n=15). The majority of the reported cases for rhabdomyolysis and CPK increase (20%) were associated with a daily trabectedin dose ranging from 1.2- 3.15mg/m^2. 3 reports of death, were attributed to rhabdomyolysis. Other muscular adverse events were asthenia (n=17), muscle spasms (n=16), myalgia (n=1). The total number of muscular adverse events contributed to about 30% of the total trabectedin-related adverse event reports in AERS database.

Other adverse reactions

Other trabectedin-related adverse events at a frequency of ≥15 reports in the AERS included dehydration, pyrexia, pancytopenia, acute renal failure, increased blood creatinine, increased alanine aminotransferase, increased hepatic enzymes, ascites, hypoalbuminemia, diarrhoea, nausea, vomiting, increased blood creatinine phosphokinase, asthenia, myalgia, rhabdomyolysis, CHF, dyspnoea. The role of trabectedin in all adverse drug reaction reports was 31.5% primary, 60% secondary, 6.8% as interacting drug and 1.7% concomitant with other drugs.

DISCUSSION

The FDA AERS database was utilized to conduct this retrospective pharmacovigilance study for the evaluation of post marketing safety profile of trabectedin, approved by the FDA in 2007. 193 adverse event reports were documented during the study period ascribed to trabectedin use. Trabectedin was associated with a large number of reports of pancytopenia, acute renal failure, increased blood creatinine, increased blood creatinine phosphokinase, dehydration. Rhabdomyolysis accounted to 20% of adverse events reported and could be associated with life threatening adverse effects. Rhabdomyolysis as a life-threatening adverse toxicity of trabectedin is not well quantified. In the initial phase I trial, one patient experienced grade 4 rhabdomyolysis, renal failure requiring dialysis, grade 4 neutropenia and grade 3 thrombocytopenia. Hepatic toxicity in this patient was not reported. [1] In a subsequent French phase II trial, two patients suffered with rhabdomyolysis; however, little information was provided in these two cases, and side effects from ET‑743 were described as "non-cumulative, reversible and manageable."[18] Two cases of rhabdomyolysis were also reported with ET‑743 in another European phase II study.[17] Both of these patients died on treatment. [10]

The specificity of adverse events reported in the AERS is not thoroughly established. Thus, the causality assessment between trabectedin and rhabdomyolysis cannot be certain. The major confounding variables can be incorrect posology, previous or concomitant liver disorders with potential effect on the drug metabolism, concomitant medications (CYP3A4inhibitors, etc) and other etiologies contributing rhabdomyolysis.

The AERS database covers several million case reports on adverse events, and is characterized by spontaneity. Despite some limitations inherent to spontaneous reporting, the AERS database is a rich resource and the data mining tools can provide a powerful means of identifying potential associations between drugs and adverse events.

Pharmacovigilance aims to search for previously un-known patterns and automatically detect important signals, i.e., drug-associated adverse events, from such a large database.

The AERS database is considered a valuable tool; however, some limitations inherent to spontaneous reporting have been pointed out. [7] Firstly, the data may occasionally contain misspelling although the structure of AERS is in compliance with the international safety reporting guidance. Secondly, the system was started more than 10 years ago, and reporting patterns have changed over time.

CONCLUSION

Rhabdomyolysis is a life‑threatening adverse toxicity of trabectedin. Serum creatinine phosphokinase should be regularly checked and monitored closely in patients receiving trabectedin treatment. Physicians need to be aware of this toxicity as this active drug will likely become part of standard therapy for soft tissue sarcomas and in the treatment of other advanced solid tumours as well. Given the voluntary nature of the AERS robust observational epidemiologic studies, including longitudinal designs, are recommended to establish causality and risk factors for adverse reactions. Furthermore, longer durations of post marketing data are needed to quantify the risks further and examine the safety of rhabdomyolysis related to trabectedin.

DECLARATION ON CONFLICT OF INTEREST: The authors declare no conflict of interest

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Table 1. Indications of trabectedin

Type	n
Ovarian cancer	56
Ovarian cancer metastatic	2
Ovarian cancer recurrent	8
Ovarian epithelial cancer	1
Sarcoma	10
Liposarcoma	9
Sarcoma uterus	8
Sarcoma metastatic	6
Uterine leiomyosarcoma	3
Leiomyosarcoma	1
Leiomyosarcoma metastatic	2
Product used for unknown indication	11
Pancreatic carcinoma	2
Chemotherapy	2
Metastases to lung	1

Table 2. Description of adverse event reports for trabectedin in the US Adverse Event Reporting System for 2007–2011

Characteristics	n (%)*
Patient age (years)*	
30–44	6 (8.1)
45-59	20 (27)
60-74	24 (32.4)
Age not mentioned	24 (32.4)
Patient gender*	
Female	15 (20.2)
Male	56 (75.6)
Not mentioned	3 (4)
Report types#	
Expedited	171 (88.6)
Periodic	19 (9.8)
Direct	3 (1.5)
Reporter profession#	
Physician	119 (61.6)
Other health care provider	60 (31)
Pharmacist	5 (2.5)
Consumer	4 (2)
Reporter country#	
United Kingdom	35 (18.1)
United States	26 (13.4)
Overseas	132 (68.3)

*N=74 patients

#N=193 ADR reports

Table 3. Distribution of adverse event reports for trabectedin by organ system

Body system	Adverse event	N
Body as whole	Dehydration	21
	Pyrexia	15
	Sepsis	10
	Generalised physical health deterioration	10
	Palmar-Plantar Erythrodysaesthesia Syndrome	9
	Fatigue	7
	Vasovagal syncope	7
	Malaise	6
	Phlebitis	6
	Lethargy	5
	Death	5
Hematology	Pancytopenia	38
	Neutropenia	13
	Neutropenic sepsis	13
	Anemia	12
	Thrombocytopenia	11
	Leucopenia	11
	Bone Marrow Failure	11
Genitourinary	Acute renal failure	25
	Increased blood creatinine	23
	Anuria	11
	Renal failure	8

	Urinary retention	6
	Urinary Tract Infection	6
Gastrointestinal	Increased Alanine aminotransferase	20
	Increased hepatic enzymes	13
	Ascitis	13
	Hypoalbuminemia	12
	Diarrhoea	13
	Nausea	17
	Vomiting	15
	Abdominal pain	14
	Oesophageal candidiasis	9
Musculoskeletal	Increased blood creatinine phosphokinase	23
	Asthenia	17
	Myalgia	16
	Rhabdomyolysis	16
	Hypocalcemia	6
	Muscle spasms	1
Cardiovascular	CHF	17
	Palpitation	9
	Chest pain	7
	Arterial Thrombosis	7
	Cardiac arrest	6
	Peripheral ischemia	5
Respiratory	Dyspnoea	18
	Respiratory failure	10
	Pleural effusion	8
	Hypoxia	8
	Cough	5
Neurological	Cognitive disorders	12
	Visual hallucination	5
Others	Drug interaction	35
	Ovarian cancer	9
	Stomatitis	5

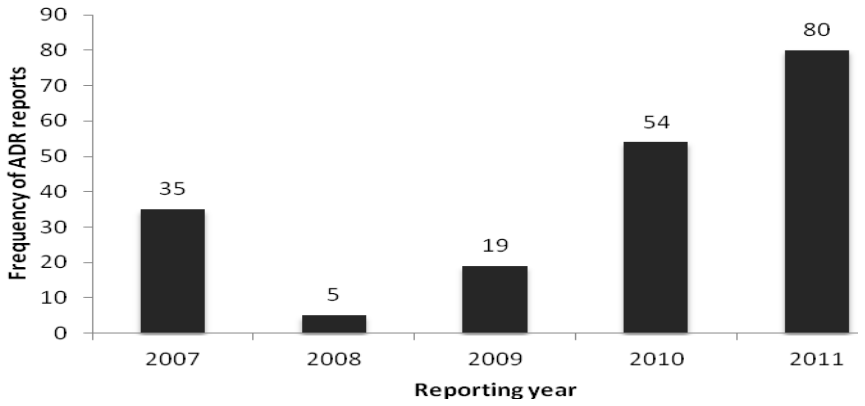

Figure 1: Trend of adverse event reports for trabectedin in the US Adverse Event Reporting System for 2007–2011.