Incidence and risk of eribulin mesylate related hematologic toxicity

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ABSTRACT

Eribulin mesylate, a microtubule dynamics inhibitor, has been approved for the treatment of several malignancies. Due to its novel mechanism of action, eribulin is often associated with a distinct profile of adverse events including hematologic toxicities. Here we searched PubMed and Embase database from reception to August 2017 for clinical trials with eribulin treatment. Eligible studies included trials with eribulin administered at a standard dose of 1.4 mg/m² intravenously on days 1 and 8 in a 21-day cycle, and adequate safety data profile reporting neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia. The overall incidence, relative risk (RR) and 95% confidence interval (CI) were calculated. A total of 39 studies with 6,092 subjects were included in this study. The incidences of eribulin related all-grade and high-grade hematologic toxicities were: neutropenia, 56% and 39%; leucopenia, 44% and 21%; anemia, 33% and 2%; febrile neutropenia, 5% and 5%; and thrombocytopenia, 12% and 12%. Compared with controls, eribulin was associated with a significant increased risk of all-grade (RR, 1.94; 95% CI, 1.37–2.74) and high-grade (RR, 2.58; 95% CI, 1.30–5.10) neutropenia, all-grade (RR, 1.81; 95% CI, 1.10–2.97) and high-grade (RR, 2.95; 95% CI, 1.36–6.39) leucopenia, but not with anemia and febrile neutropenia. Trial sequential analysis showed the results from neutropenia, leucopenia and anemia established sufficient and conclusive evidence. Our study suggested that eribulin therapy, compared with control, was associated with an increased risk of hematologic toxicities. Hence hematologic monitoring at regular intervals should be advised.

INTRODUCTION

Eribulin mesylate (hereafter referred as "eribulin"), a macrocyclic ketone analogue of Halichondrin B, is a completely synthetic, microtubule dynamics inhibitor [1, 2]. Unlike traditional tubulin-targeting agents which usually suppress growth and depolymerization of microtubules, eribulin inhibits microtubule polymerization through a special binding site on B-tubulin [3]. Preclinical evidence further reveals that eribulin suppresses the development of tumor by inhibiting mitotic spindle formation [3], reversing phenotype from epithelial-mesenchymal transition state to mesenchymal-epithelial transition state [4], and remodeling tumor vasculature [5]. Currently, eribulin has been approved by the US Food and Drug Administration (FDA) for the treatment of breast cancer (BC) [6], and recently, liposarcoma [7]. Additionally, it is reported that eribulin is being investigated in several malignancies such as non-small cell lung cancer, pancreatic cancer, head and neck cancer, prostate cancer, and ovarian cancer [8]. Accordingly the increase in the application of eribulin is expected in the future.

Due to its novel mechanism, eribulin treatment is often associated with a distinct profile of adverse events. Previous studies have showed that the common side effects of eribulin were myelosuppression, fatigue/asthenia, alopecia, and peripheral neuropathy [9–14]. Although hematologic toxicities associated with eribulin have been reported, there has been no systematic attempt to synthesize these data and the relative risk of hematologic toxicities induced by eribulin has yet to be evaluated. Therefore, here we conducted a meta-analysis of available clinical data to calculate the overall incidence and relative risk of developing hematologic toxicities, namely neutropenia, leucopenia, anemia, febrile neutropenia, and thrombocytopenia, in cancer patients treated with eribulin.

RESULTS

Search results

A total of 796 potentially relevant articles were found during the initial search, including 395 studies from PubMed and 401 trials from Embase. 361 articles were excluded because of duplications. After careful screening of titles and abstracts, 369 studies were removed since they did not meet the eligible criteria. Further reviewing the whole texts of the remaining 66 potentially eligible articles, 27 were not included because of different dose of eribulin (n = 19), insufficient data (n = 5) and duplication (n = 3). A total of 39 studies were enrolled for the final analysis. 33 were single arm trials [15–47], the other 6 were RCTs [9–14]. A flow chart was presented in Figure 1.

Population characteristics

6,092 patients were included in this meta-analysis (eribulin, 4,958; control, 1,134). 5,098 patients had breast cancer (eribulin, 4,227; control, 871) from 31 studies. 630 patients had soft tissue sarcoma (STS, eribulin, 406; control, 224) from 3 studies. 146 patients had non-small cell lung cancer (NSCLC, eribulin, 107; control, 39) from 2 studies. 105 patients had prostate cancer (PC; eribulin, 105; control, 0) from 1 study. 73 patients had ovarian cancer (OC; eribulin, 73; control, 0) from 1 study. 40 patients had head and neck cancer (HNC; eribulin, 40; control, 0) from 1 study. The dose and schedule of eribulin was 1.4 mg/m^2 in 2–5 minutes intravenously on days 1 and 8 on a 21-day schedule, the currently FDA-recommended dose until unacceptable toxicity, disease progression or patient refusal. In one study [14], pharmacokinetic and pharmacodynamical analysis revealed that 0.9 mg/m^2 is the optimal dose for NSCLC patients. The median treatment ranged from 1.5 months [34] to 7.7 months [23]. The basic clinicopathological characteristics of eligible trials were summarized in Table 1. The numbers of hematologic toxicities were presented in Table 2. It should be noted that not all studies consistently illustrated the five adverse event (AE) of our interest.

Overall incidence of hematological toxicity

A total of 4,958 patients from 39 non-randomized trials and treatment arms in RCTs were included. The overall incidences of all-grade neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia in patients treated with eribulin were 56% (95% CI, 46%–65%), 44% (95% CI, 30%–59%), 33% (95% CI, 25%–40%), 5% (95% CI, 3%–7%) and 12% (95% CI, 8%–15%), respectively (Table 3). Whereas the summary incidences of high-grade (grade III and grade IV) neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia were 39% (30%–48%), 21% (95% CI, 14%–28%), 2% (95% CI, 1%–3%), 5% (95% CI, 3%–6%), and 12% (95% CI, 6%–18%), respectively (Table 4). Significant heterogeneities were observed in the calculation of these hematological AEs. Therefore, the random-effects models were applied. Since most of these eligible trials were conducted in patients with breast cancer, the hematological toxicities of eribulin stratified by different cancer type were examined (Table 3 and Table 4). The incidences of all-grade (p = 0.76) and high-grade (p = 0.54) neutropenia were similar in BC patients and non-BC patients. Similarly, the incidences of all-grade (p = 0.69) and high-grade (p = 0.38) leucopenia did not show statistical difference between BC patients and non-BC patients. Meanwhile, the incidences of both all-grade (p = 0.004) and high-grade (p = 0.04) anemia in non-BC patients were statistically higher compared with BC patients. In contrast, the incidences of all-grade (p = 0.01) and high-grade (p = 0.02) thrombocytopenia in non-BC patients were lower compared with BC patients.

Relative risk of hematologic adverse events

The RRs and their 95% CIs of hematologic toxicities were calculated with 6 RCTs (3 phase III studies and 3 phase II studies including 2,546 patients) [9–14]. The relative risks of all-grade neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia were 1.94 (95% CI, 1.37–2.74; p = 0.01), 1.81 (95% CI, 1.10–2.97; p = 0.02), 0.95 (95% CI, 0.82–1.11, p = 0.53), 2.15 (95% CI, 0.79–5.82; p = 0.12), and 0.21 (95% CI, 0.12–0.36; p < 0.001) respectively (Figure 2). The relative risk of high-grade neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia in patients treated with eribulin were 2.58 (95% CI, 1.30–5.10; p = 0.02), 2.95 (95% CI, 1.36–6.39; p = 0.01), 0.77 (95% CI, 0.52–1.14; p = 0.19), 2.15 (95% CI, 0.79–5.82; p = 0.12), and 0.03 (95% CI, 0.00–0.21; p < 0.001) respectively (Figure 3). The fixed-effects models were applied in the analysis of both all-grade and high-grade anemia, febrile neutropenia, and thrombocytopenia because there was no evidence of

heterogeneity for these outcomes. Additional analyses using the random-effects models yielded similar results. Substantial heterogeneities were observed in RR calculation of all-grade and high-grade neutropenia and leucopenia. Sensitivity analyses were then carried out to identify potential sources of heterogeneities and to examine the impact of different exclusion criteria on the overall relative risk. Exclusion of one study [11] in which eribulin was compared with capecitabine did not changed the trend of overall risk estimate, but no significant heterogeneities were observed among the remaining trials (as shown in Table 5).

Trial sequential analysis (TSA) showed that the cumulative *z* curve crossed both the conventional boundary and the trial sequential monitoring boundary in neutropenia and leucopenia analysis, crossed the futility boundary and entered the futility area in anemia analysis (Figure 4). Both these cases established sufficient and conclusive evidence. Accordingly, further trials were not request and were unlikely change our conclusion. Because of the limited available data for febrile neutropenia and thrombocytopenia analysis, TSA was not conducted.

Publication bias

Egger's test and Begg's funnel plot were conducted to evaluate the publication bias for RR of both all-grade and high-grade neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia. The shapes of the funnel plots did not show any evidence of obvious asymmetry in all analysis.

DISCUSSION

To our knowledge, this is the first meta-analysis focused on hematologic toxicities associated with eribulin mesylate. Our data revealed that the overall incidences of eribulin related all-grade and high-grade hematologic toxicities were: neutropenia, 56% and 39%; leucopenia, 44% and 21%; anemia, 33% and 2%, febrile neutropenia, 5% and 5%; and thrombocytopenia, 12% and 12%. In addition, our analysis on RCTs revealed that the relative risk of all-grade neutropenia and leucopenia were approximately two-fold (three-fold for high-grade) in patients with eribulin treatment compared with those in the control arms. In contrast, no significantly increased risks were identified in terms of anemia and febrile neutropenia.

Accumulating evidence reveals that eribulin has many characteristics that makes it distinct from other microtubule-targeting agents [48]. Although still not completely clear, the specific biological effects of eribulin might underlie its unique impact on hematologic toxicities. Preclinical studies showed that

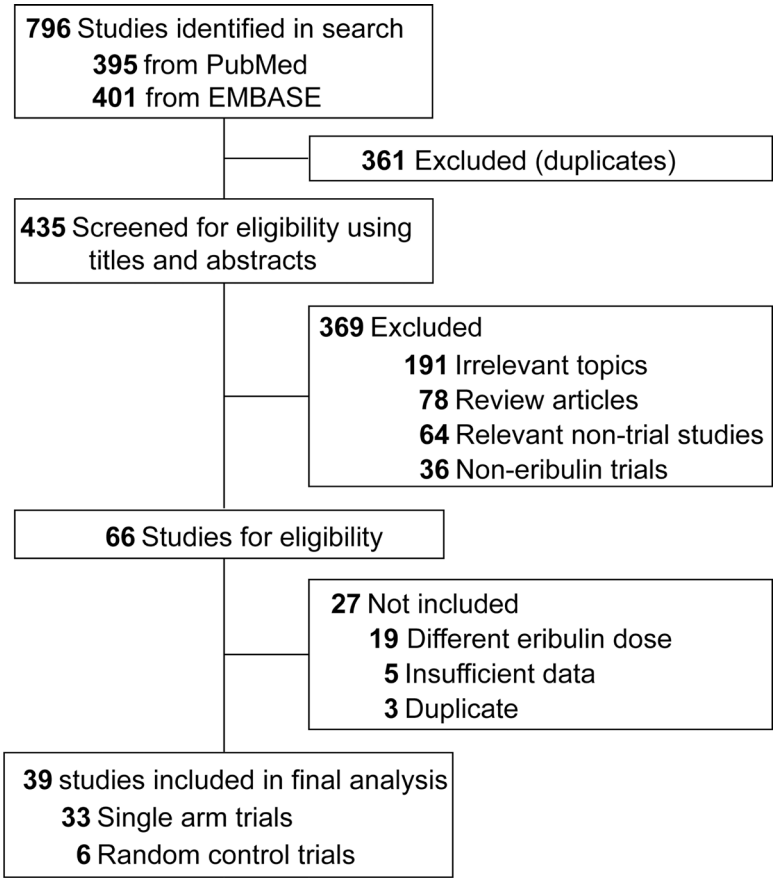

Figure 1: Flow-chart diagram of selected trials included in this meta-analysis.

Table 1: Baseline clinicopathological characteristics of the clinical trials included in this study

Author	Region	Year	Underlying malignancy	Phase	Median age (range), year	Gender (male/female)	ECOG PS (0/1/2+)	Treatment duration, median (range), month	Median OS (95% CI), month	Median PFS (95% CI), month	Founding Source	Quality assessment (NOS)
Cortes [9]	Globe	2011	BC	III	55 (28–85) 56 (27–81)	0/508 0/254	217/244/39 103/126/22	3.9 (0.7–16.3) 2.1 (0.0–21.2)	13.1 (11.8–14.3) 10.6 (9.3–12.5)	3.7 (3.3–3.9) 2.2 (2.1–3.4)	Industry	9
Abraham [10]	US	2015	BC	II	50 (28–70) 48 (34–67)	0/30 0/19	NR NR	NR NR	NR NR	NR NR	Industry	7
Kaufman [11]	Globe	2015	BC	III	54 (24–80) 53 (26–80)	0/554 0/548	250/293/11 230/301/17	4.1 (0.7–45.1) 3.9 (0.7–47.4)	15.9 (15.2–17.6) 14.5 (13.1–16.0)	4.1 (3.5–4.3) 4.2 (3.9–4.8)	Industry	9
Vahdat [12]	US	2013	BC	II	52 57	0/51 0/50	21/29/1 20/28/2	3.8 (0.8–23.0) 2.6 (0.8–12.3)	NR NR	3.5 (2.7–4.3) 3.2 (2.4–6.2)	Industry	6
Schoffski [13]	Globe	2016	STS	III	56 (28–83) 56 (24–83)	67/161 82/142	111/114/3 90/121/13	NR NR	13.5 (10.9–15.6) 11.5 (9.6–13.0)	2.6 (1.9–2.8) 2.6 (1.8–2.7)	Industry	9
Waller [14]*	Europe	2015	NSCLC	II	59 (38–80) 60 (46–77)	25/16 26/13	10/31/0 3/36/0	NR NR	14.8 14.3	5.4 (3.2–9.9) 5.9 (4.3–7.5)	Industry	7
Watanabe [15]	Japan	2017	BC	II	59 (26–88)	2/949	481/364/106	3.5 (0.8–14.8)	NR	NR	Industry	8
De Bono [16]	Globe	2012	PC	II	71 (47–91)	105/0	48/57/3	2.6 (0.8–35.2)	18.6 (1.0–32.4)	2.1 (0.1–32.2)	Industry	7
Aftimos [17]	Belgium	2016	BC	II	55 (34–81)	0/141	NR	3.0 (0.3–21.8)	11.3 (8.7–12.3)	3.2 (2.7–4.0)	Industry	7
Aogi [18]	Japan	2012	BC	II	54 (31–72)	0/80	58/21/1	2.8 (0.0–14.5)	11.1 (1.0–25.9)	3.7 (0.3–14.8)	Non-profit	8
Arnold [19]	US	2011	HNC	II	61 (44–87)	29/11	19/21/0	NR	7.0 (5.0–10.0)	2.6 (0.0–13.1)	Industry	6
Cortes [20]	Globe	2010	BC	II	56 (26–80)	0/291	108/165/17	3.0 (0.3–20.3)	10.4 (0.6–19.9)	2.6 (0.0–13.1)	Industry	8
Park [21]	Korea	2017	BC	IV	51 (25–79)	0/101	30/69/2	2.1 (0.0–23.8)	NR	NR	Industry	4
Araki [22]	Japan	2017	BC	II	58 (31–76)	0/40	10/18/2	6.0 (0.3–18.8)	NR	10.7 (5.0–13.0)	Industry	5
Puhalla [23]	US	2016	BC	II	59 (31–81)	0/52	NR	7.7	NR	11.9 (6.0–19.1)	Industry	6
Maeda [24]	Japan	2017	BC	II	54 (31–75)	0/47	34/13/0	5.8	17.4	4.9 (3.5–7.0)	None	5
Takashima [25]	Japan	2016	BC	II	64 (40–75)	0/35	28/7/0	6.0 (0.3–15.8)	35.9	5.8 (4.8–8.1)	Industry	5
Yardley [26]	US	2016	BC	II	56 (32–84)	0/65	NR	NR	11.5 (9.0–17.3)	4.1 (3.2–5.6)	Industry	7
Garrone [27]	Italy	2016	BC	II	62 (33–80)	0/113	NR	3.0 (0.3–20.3)	11.6 (0.6–33.3)	3.3 (0.6–26.7)	None	6
Dell'Ova [28]	France	2015	BC	II	50 (18–80)	0/258	73/133/52	3.8 (0.3–14.3)	4.0 (3.3–4.3)	11.2 (9.3–12.1)	None	5
Smith [29]	US	2016	BC	II	62 (28–80)	0/67	60/7/0	NR	NR	NR	Industry	7
Wilks [30]	US	2014	BC	II	60 (31–81)	0/52	37/14/1	7.5 (0.0–28.5)	NR	11.6 (9.1–13.9)	Industry	7
Gitlitz [31]	US	2012	NSCLC	II	63 (35–83)	31/35	NR	3.0 (0.3–17.3)	11.6 (8.2–13.7)	2.7 (1.3–3.9)	None	6
Dranitsaris [32]	US	2015	BC	II	58 (36–86)	0/90	NR	2.3 (0.0–14.0)	NR	NR	Industry	5
Fabi [33]	Italy	2015	BC	II	58 (45–71)	0/78	NR	3.8 (0.3–13.5)	10.1 (8.1–13.0)	4.8 (3.4–6.4)	Industry	6
Hensley [34]	US	2011	OC	II	60 (38–80)	0/73	NR	1.5 (0.3–7.5)	22	3	Non-profit	6
Ates [35]	Turkey	2016	BC	II	50 (28–67)	0/66	29/30/7	2.3 (0.3–6.0)	8.0 (6.0–9.9)	5.0 (4.1–5.8)	None	5
Kawai [36]	Japan	2017	STS	II	52 (28–73)	23/28	27/24/0	3.0 (0.8–36.8)	13.2 (9.5–18.3)	4.1 (2.6–5.6)	Industry	7
Kaklamani [37]	US	2015	BC	II	53 (35–78)	0/30	NR	NR	NR	NR	Industry	6
Kessler [38]	Sweden	2015	BC	II	56 (35–74)	0/48	36/7/5	5.3 (0.8–15.8)	8.9 (4.5–13.0)	4.7 (4.2–6.0)	Non-profit	5
Lorusso [39]	Italy	2017	BC	II	62 (33–85)	0/91	32/46/13	2.9 (0.2–24.4)	11.6 (8.7–16.7)	3.1 (2.8–3.5)	Industry	7
McIntyre [40]	US	2014	BC	II	57 (31–85)	0/56	32/21/3	4.5	NR	6.8 (4.4–7.6)	Industry	6
Gamucci [41]	Italy	2014	BC	II	62 (30–79)	0/133	NR	3.8 (0.8–11.3)	14.3 (11.7–16.8)	4.4 (3.7–5.0)	None	5
Moscetti [42]	Italy	2017	BC	II	64 (31–85)	0/50	NR	3.8 (0.8–12.8)	9.0 (5.0–13.0)	4.0 (3.0–5.0)	None	6
Prestifilippo [43]	Italy	2017	BC	II	55 (40–76)	0/31	3/16/12	NR	5.5 (1.0–16.0)	2.0 (0.0–7.8)	Industry	6
Quaquarini [44]	Italy	2017	BC	II	57 (39–74)	0/44	21/20/3	4.5 (0.8–11.3)	11.8 (1.0–77.3)	4.5 (1.0–16.6)	Industry	5
Inoue [45]	Japan	2016	BC	II	55 (34–74)	0/51	25/22/4	3.0 (0.3–31.5)	11.7 (9.2–14.2)	3.6 (2.6–4.6)	Non-profit	7
Schoffski [46]	Europe	2011	STS	II	57 (18–83)	62/65	NR	3.0 (0.8–32.3)	NR	2.6	Industry	8
Vahdat [47]	US	2009	BC	II	52 (32–81)	0/33	18/15/0	3	9.0 (0.5–27.5)	2.6 (0.0–15.1)	Industry	8

Abbreviations: BC, breast cancer; HNC, head and neck cancer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, prostate cancer, STS, soft tissue sarcoma; PFS, progress-free survival; OS, overall survival; ECOG PS, European cooperative oncology group performance status; NOS, Newcastle-Ottawa Scale; NR, not reported.*, eribulin mesylate at the dose of 0.9mg/m^2 on day 1 of every 21-day cycle.

eribulin decreased the expression of genes related with vascular endothelial growth factor (VEGF), Ephrin-EphR, Wnt, and Notch signaling pathways which were known to be critical in vascular functions [48]. *In vitro* evidence suggested that eribulin could down-regulate the expression of VEGF, CA9, Notch4, Dll4 and Efnb2 [5, 48]. In clinic, significantly decreased concentration of deoxyhemoglobin was observed in patients treated with eribulin [49]. Eribulin therapy could also decreased the plasma concentration of transforming growth factor beta

Table 2: Number of events reported in every trial included in this study

Author	Year	Underlying malignancy	No. of patients	Thrombocytopenia		Anemia		Neutropenia		Leucopenia		Febrile neutropenia		CTCAE
				All-grade	High-grade	All-grade	High-grade	All-grade	High-grade	All-grade	High-grade	All-grade	High-grade	
Cortes [9]	2011	BC	508	NR	NR	94	10	260	227	116	70	NR	NR	3.0
			254	NR	NR	56	9	73	52	28	14	NR	NR	
Abraham [10]	2015	BC	30	NR	NR	NR	NR	7	5	NR	NR	1	1	4.0
			19	NR	NR	NR	NR	2	0	NR	NR	0	0	
Kaufman [11]	2015	BC	554	NR	NR	104	11	295	249	171	82	11	11	3.0
			548	NR	NR	96	6	87	27	57	11	5	5	
Vahdat [12]	2013	BC	51	NR	NR	13	3	24	16	NR	NR	NR	NR	3.0
			50	NR	NR	10	3	14	10	NR	NR	NR	NR	
Schoffski [13]	2016	STS	228	13	1	67	16	99	80	36	23	NR	NR	4.02
			224	62	34	69	27	53	35	23	10	NR	NR	
Waller [14]	2015	NSCLC	41	NR	NR	8	4	12	7	3	1	NR	NR	NR
			39	NR	NR	15	4	11	7	7	2	NR	NR	
Watanabe [15]	2017	BC	951	33	17	63	35	633	569	593	480	73	73	3.0
De Bono [16]	2012	PC	105	8	2	30	2	45	33	29	13	4	4	3.0
Aftimos [17]	2016	BC	141	6	2	15	1	60	52	NR	NR	13	13	4.0
Aogi [18]	2012	BC	80	NR	NR	NR	NR	80	77	80	60	NR	NR	3.0
Arnold [19]	2011	HNC	40	NR	NR	20	1	13	4	12	5	NR	NR	3.0
Cortes [20]	2010	BC	291	NR	NR	82	6	174	157	64	41	16	16	3.0
Park [21]	2017	BC	101	NR	NR	12	3	92	90	11	6	NR	NR	4.03
Araki [22]	2017	BC	30	14	6	22	0	27	20	28	6	NR	NR	4.0
Puhalla [23]	2016	BC	52	NR	NR	13	1	31	20	9	3	4	4	4.0
Maeda [24]	2017	BC	47	10	0	23	4	47	25	38	16	4	4	3.0
Takashima [25]	2016	BC	35	18	0	18	0	34	22	31	9	2	2	4.0
Yardley [26]	2016	BC	65	NR	NR	16	3	29	24	8	7	NR	NR	4.0
Garrone [27]	2016	BC	113	8	1	32	3	41	22	19	5	1	1	4.0
Dell'Ova [28]	2015	BC	258	27	1	NR	4	99	54	NR	NR	NR	13	4.03
Smith [29]	2016	BC	67	NR	NR	NR	NR	5	5	NR	NR	1	1	NR
Wilks [30]	2014	BC	52	NR	NR	13	1	31	20	9	3	4	4	4.0
Gitlitz [31]	2012	NSCLC	66	7	1	43	0	41	36	41	19	NR	NR	3.0
Dranitsaris [32]	2015	BC	90	7	NR	28	NR	29	NR	NR	NR	8	NR	NR
Fabi [33]	2015	BC	78	NR	NR	NR	2	NR	17	NR	24	NR	NR	4.02
Hensley [34]	2011	OC	73	NR	NR	NR	1	35	NR	23	NR	1	NR	NR
Ates [35]	2016	BC	66	3	2	NR	NR	25	16	NR	NR	NR	NR	4.0
Kawai [36]	2017	STS	51	NR	NR	24	7	50	44	51	38	NR	NR	4.0
Kaklamani [37]	2015	BC	30	24	6	30	7	23	18	NR	NR	NR	NR	4.0
Kessler [38]	2015	BC	48	NR	NR	NR	NR	13	9	NR	NR	NR	NR	4.0
Lorusso [39]	2017	BC	91	4	0	15	2	27	11	NR	NR	NR	NR	NR
McIntyre [40]	2014	BC	56	NR	NR	20	2	40	28	19	12	NR	NR	4.0
Gamucci [41]	2014	BC	133	11	3	19	1	38	19	NR	NR	NR	NR	4.0
Moscetti [42]	2017	BC	50	NR	NR	16	0	33	2	NR	NR	NR	NR	4.0
Prestifilippo [43]	2017	BC	31	NR	NR	15	2	NR	NR	18	0	15	8	NR
Quaquarini [44]	2017	BC	44	3	2	19	2	23	5	22	4	1	1	4.02
Inoue [45]	2016	BC	51	2	0	15	3	29	18	30	12	4	4	4.0
Schoffski [46]	2011	STS	127	NR	NR	112	9	101	66	107	44	NR	NR	3.0
Vahdat [47]	2009	BC	33	1	0	5	0	23	20	5	5	1	1	3.0

Abbreviations: CTCAE, common terminology criteria for adverse events; BC, breast cancer; HNC, head and neck cancer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, prostate cancer, STS, soft tissue sarcoma; NR, not reported.

1 (TGF-β1), which linked to multiple gene that controlled the growth, proliferation, differentiation and apoptosis of blood cells [50]. Our results were consistent with pre-clinical discoveries and corroborated the theory that eribulin treatment increased the risk of myelosuppression in cancer.

Five types of hematologic toxicities were analyzed in the present study. Interestingly, high incidence rates and risks only occurred in two types of hematologic AEs, neutropenia and leucopenia. The incidence rates and risks of other two types of hematologic toxicities, anemia and febrile neutropenia, did not show significant

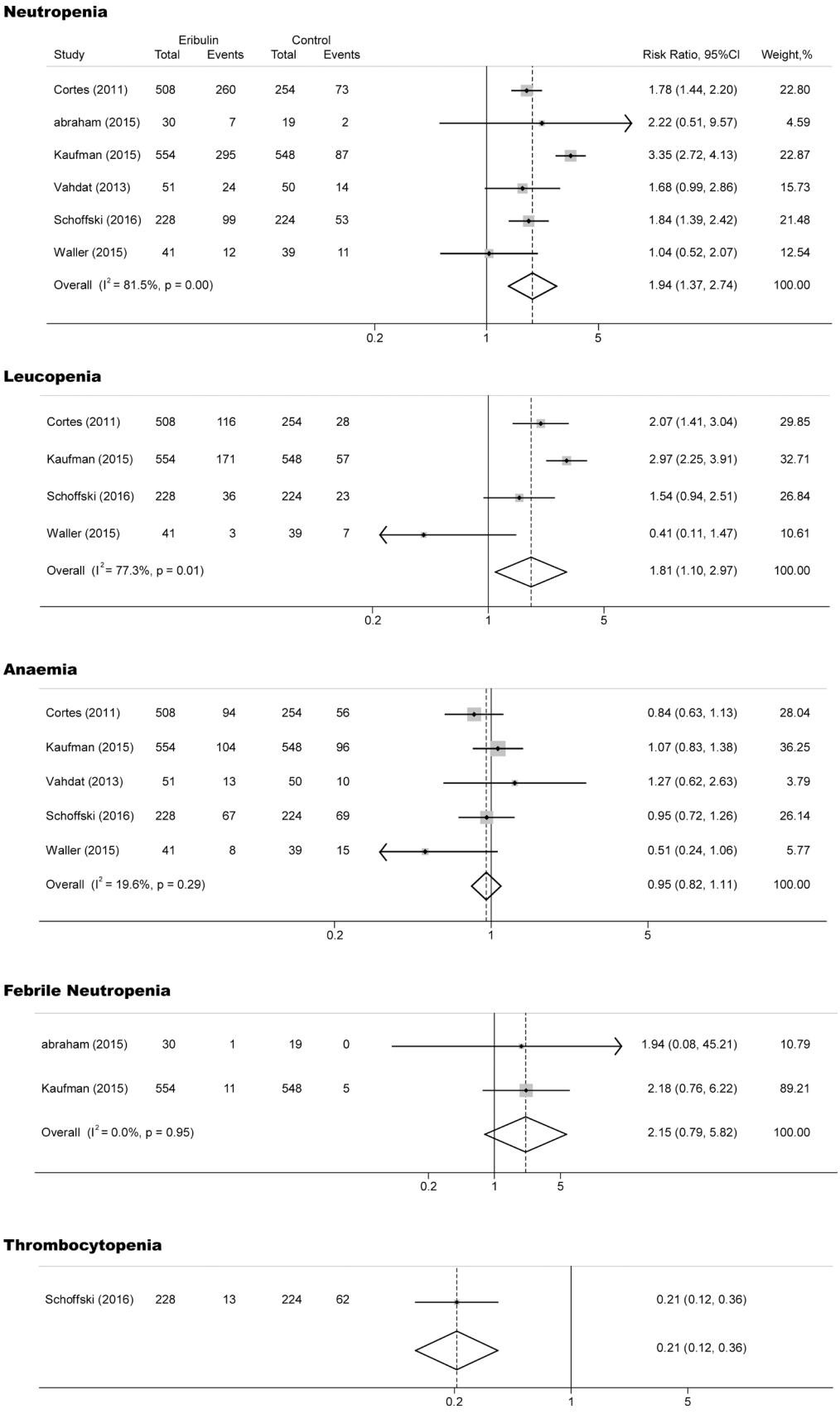

Figure 2: Forest plots of relative risk (RR) of all-grade hematologic toxicities associated with eribulin mesylate versus control in cancer patients.

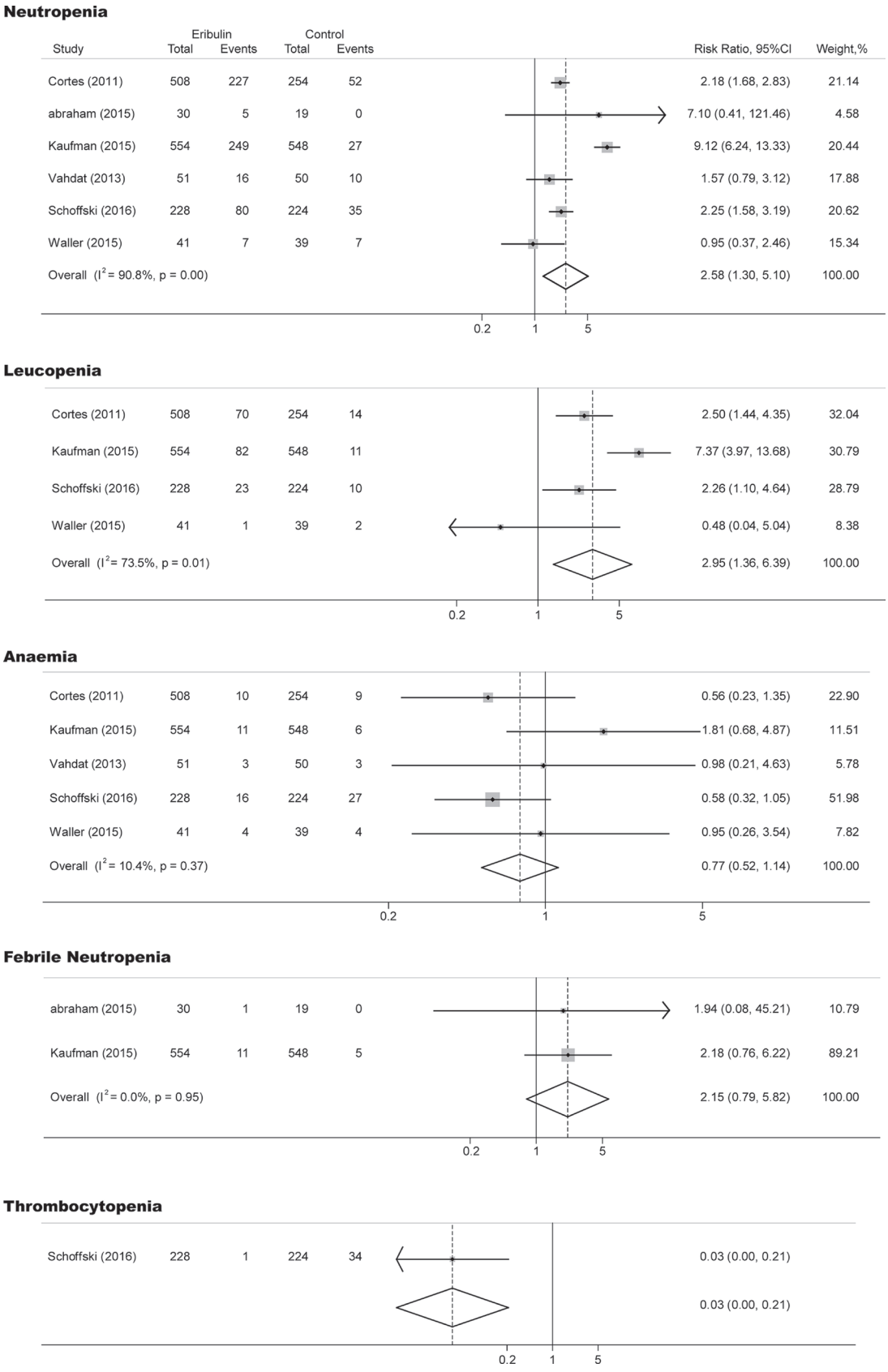

Figure 3: Forest plots of relative risk of high-grade hematologic toxicities associated with eribulin mesylate versus control in cancer patients.

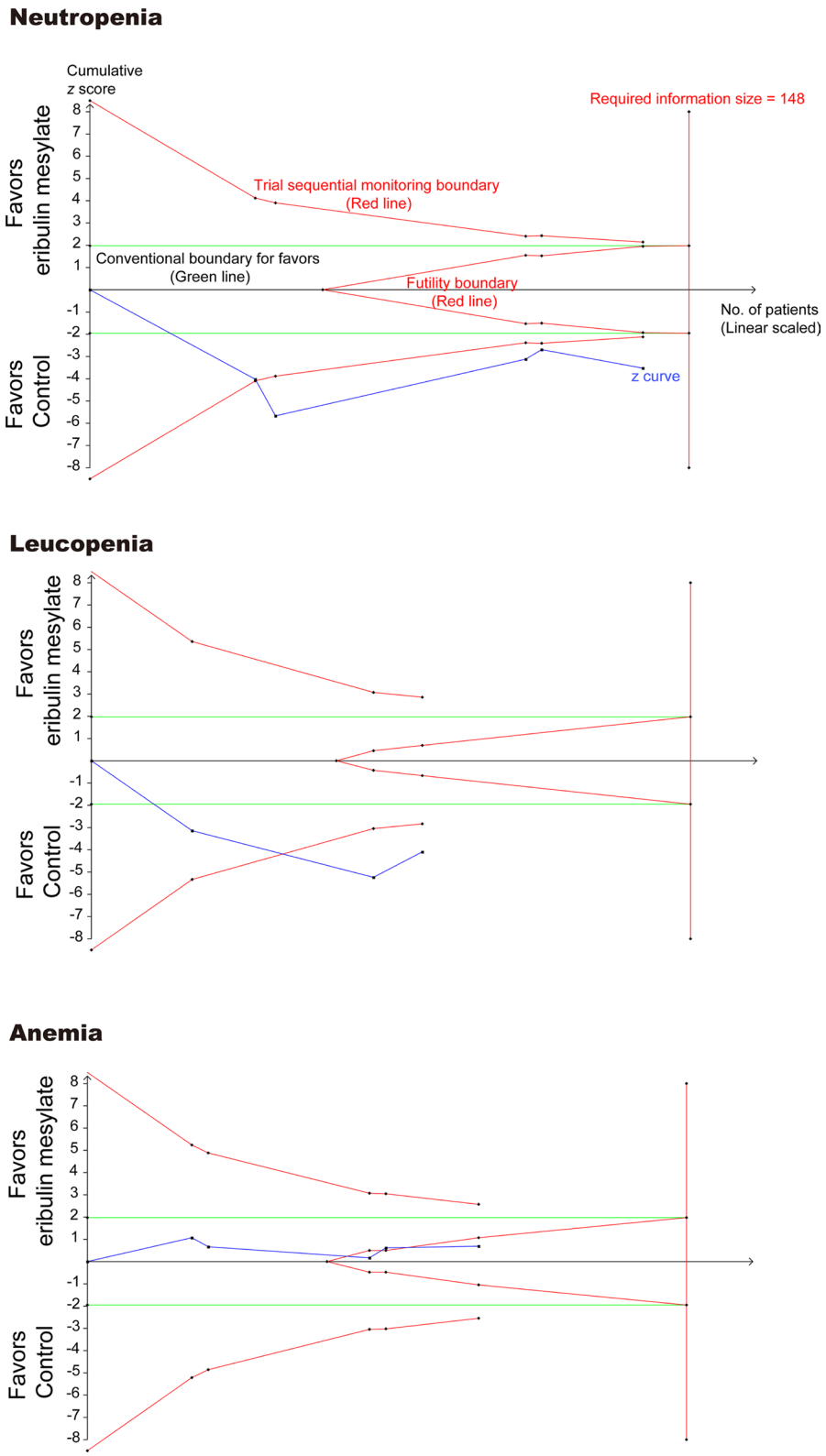

Figure 4: Trial sequential analysis (TSA) of eligible studies comparing eribulin therapy with control. The cumulative *z* curve crossed both the conventional boundary and the trial sequential monitoring boundary in neutropenia and leucopenia analysis, crossed the futility boundary and entered the futility area in anemia analysis; establishing sufficient and conclusive evidence and suggesting that further studies were not required. X axis, Number of patients randomized; Y axis, cumulative *z* score; horizontal green lines, conventional boundaries (upper line, *z* score = 1.96; lower line, *z* score = −1.96; two sided $p = 0.05$); sloping red lines with black filled square, trial sequential monitoring boundaries; blue line with black filled squares, *z* curve; vertical red line, required information size.

Table 3: Overall incidences of all-grade hematologic toxicities in patients treated with eribulin

Hematologic toxicities	No. of trials	No. of patients	Incidence (95% CI)	I^2 (%)	*p*
Neutropenia	37	4,849	56% (46%–65%)	98.7	0.00
BC	29	4,118	56% (45%–66%)	98.8	0.00
Non-BC	8	731	55% (34%–76%)	98.2	0.00
Leucopenia	26	3,825	44% (30%–59%)	99.4	0.00
BC	18	3,094	44% (26%–61%)	99.4	0.00
Non-BC	8	731	45% (13%–77%)	99.5	0.00
Anemia	31	4,258	33% (25%–40%)	97.3	0.00
BC	24	3,600	27% (22%–32%)	93.1	0.00
Non-BC	7	658	47% (24%–70%)	97.8	0.00
Febrile neutropenia	18	2,760	5% (3%–7%)	80.0	0.00
BC	16	2,582	6% (3%–8%)	81.8	0.00
Non-BC	2	178	2% (0%–5%)	10.3	0.29
Thrombocytopenia	18	2,512	12% (8%–15%)	90.9	0.00
BC	15	2,113	13% (9%–17%)	92.4	0.00
Non-BC	3	399	7% (4%–9%)	0.0	0.45

Table 4: Overall incidences of high-grade hematologic toxicities in patients treated with eribulin

Hematologic toxicities	No. of trials	No. of patients	Incidence (95% CI)	I^2 (%)	*p*
Neutropenia	36	4,764	39% (30%–48%)	98.2	0.00
BC	29	4,106	39% (29%–49%)	98.4	0.00
Non-BC	7	658	41% (23%–59%)	96.4	0.00
Leucopenia	26	3,830	21% (14%–28%)	97.2	0.00
BC	19	3,172	20% (12%–28%)	97.5	0.00
Non-BC	7	658	24% (14%–28%)	96.2	0.00
Anemia	33	4,577	2% (1%–3%)	41.7	0.01
BC	25	3,846	2% (2%–3%)	23.2	0.15
Non-BC	8	731	4% (2%–6%)	68.7	0.00
Febrile neutropenia	17	2,855	5% (3%–6%)	74.8	0.00
BC	16	2,750	5% (3%–7%)	76.4	0.00
Non-BC	1	105	4% (0%–7%)	NA	NA
Thrombocytopenia	17	2,422	12% (6%–18%)	37.0	0.06
BC	14	2,023	13% (6%–21%)	43.3	0.04
Non-BC	3	399	6% (0%–14%)	0.0	0.49

BC, breast cancer.

difference compared with control. The incidences and relative risk of eribulin related thrombocytopenia needed further investigation. These discrepancies might be due to the differences in the mechanisms of action among these hematologic toxicities [48]. Hematologic events were one of the most common adverse events that could lead to therapy adjustment and discontinuation in clinical trials. High-grade neutropenia and leucopenia were often clinically significant and needed careful medical intervention considering these AEs potentially led to hemorrhage and sepsis in patients. In fact, some large RCTs even reported that fatal adverse events occurred because of hematologic toxicities [9, 11, 13]. During eribulin treatment, patients who developed neutropenia and leucopenia were usually managed with dose reduction, treatment delays and granulocyte colony-stimulating factor (G-CSF). The application of G-CSF to manage eribulin related high-grade neutropenia was at the physician's choice in accordance with relevant clinical practice guidelines such as European Society for Medical

Table 5: Relative risk of neutropenia and leucopenia excluded one study [11]

	Hematologic toxicities	RR (95% CI)	I^2	*p*
All-grade	Neutropenia	1.75 (1.50–2.04)	0.0%	0.65
	Leucopenia	1.71 (1.28–2.29)	36.0%	0.05
High-grade	Neutropenia	2.10 (1.73–2.56)	6.7%	0.37
	Leucopenia	2.29 (1.49–3.51)	0.0%	0.40

Oncology (ESMO) [51] and European Organization for Research and Treatment of Cancer (EORTC) [52]. It should be noted that neutropenia was reported at a higher incidence in the Asian population than that in the Western patients partly because of the pharmacogenomics [18].

Since we cannot access to any individual patient data, we did not correlate the risks of infection, bleeding and mortality with neutropenia and leucopenia. Although previous studies reported that poor performance status, advanced age, and low baseline blood cell counts were significant predictors for the severity of neutropenia [53], there were still no appropriate technique to determine which patients were at high risk of neutropenia and leucopenia. Accordingly, regular monitoring was essential for patients treated with eribulin.

Here we conducted a comprehensive review using the most up-to-date published data, which made our results more extensive. Moreover, with the accumulating evidence and enlarged sample size, we had enhanced the statistical power to provide more precise and reliable estimates. However, our study was restricted by some limitations. First, this was a meta-analysis conducted at the trial level and no clinicopathological variable at the patient level could be analyzed. Second, pooled incidence rates had significant heterogeneities, and this might be due to the different types of underlying malignancies, sample size, insufficient follow-up data among the included trials.

In conclusion, our meta-analysis revealed that eribulin mesylate was associated with an increased risk of hematological toxicities compared with controls. Clinical doctors should be acknowledged of these potential adverse events and hematologic monitoring at regular intervals may be advised.

MATERIALS AND METHODS

The present study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [54].

Literature search and study selection

A systematic search of Embase and PubMed database from January 1966 to August 2017 was conducted without any language restrictions. The only search keyword and Medical subject heading used was eribulin. Both inclusion and exclusion criteria were pre-specified. To be eligible, published studies had to meet the following criteria: (1) population: non-phase I trials in patients (n > 30) with solid tumor; (2) intervention: eribulin was administered at a standard dose of 1.4 mg/m^2 in 2–5 minutes intravenously on days 1 and 8 in a 21-day schedule, the currently FDA-recommended dose until unacceptable toxicity, disease progression or patient refusal; (3) clinical outcomes: events or events rates and sample size information for both all-grade and high-grade hematologic toxicities including neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia. Phase I trials were not included because of the small size of patients and various doses in these studies. Other publications on this topic, including review articles, conference abstract, pre-clinical papers, early versions of data later published, editorials, articles not dealing with eribulin were not included (Figure 1). Considering recent progress with eribulin had not been published, electronic searches were also carried out in two major international congresses' proceedings (American Society of Clinical Oncology Annual Meeting and European Society of Medical Oncology).When multiple publications of the same study occurred, only the most recent and/or most complete reporting study was included. Any discrepancies were settled by discussion and consensus. Two authors independently conducted the initial search, screened the titles and abstracts, and classified trials as excluded, included and uncertain. Any discrepancy was resolved by consensus.

Data extraction

Eligible abstracts were collected and full texts of relevant articles were checked for the trial design and reporting of hematologic toxicities. The following items were extracted: name of the first author, region, year of publication, underlying malignancy, number of patients enrolled, median age, gender, European cooperative oncology group performance status (ECOG PS), median treatment duration, median overall survival (OS), median progression-free survival (PFS) (Table 1), numbers of events of the following AEs (for both all-grade and high-grade): neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia (Table 2). The number of subjects evaluated for toxicity was used as the number analyzed for each study, unless it was indicated otherwise.

Quality assessment of the eligible studies

Newcastle-Ottawa Scale (NOS) was conducted to assess the methodological quality of all included studies [55]. This scale used a star system to evaluate any study in three sections: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest.

Statistical analysis

The primary analysis examined the overall incidence, relative risk and corresponding 95% CI of all-grade and high-grade hematologic toxicities in cancer patients treated by eribulin. To calculate the incidence, the number of patients receiving eribulin and the number of hematologic toxicities were extracted from the eligible single-arm and randomized controlled trials. The proportion of patients with neutropenia, leucopenia, anemia, febrile neutropenia and thrombocytopenia and 95% CIs were derived from each trial. We calculated RRs and their CIs with data extracted from RCTs only, comparing the incidence of each adverse event in patients assigned to eribulin arms with patients in placebo or control arms. Statistical heterogeneity between different trials or subgroups was evaluated by Cochrane's Q statistic. The I^2 statistic was calculated to assess the extent of inconsistency contributable to the heterogeneity across different studies [56]. The assumption of homogeneity was considered invalid for $I^2 > 25\%$ or $p < 0.05$. Summary RRs and incidences were calculated using fixed-effects or random-effects models depending on the heterogeneity of included trials. Potential publication bias was assessed by visual inspection of a funnel plot, and also evaluated using the tests of Egger et al. [57] and Begg et al. [58]. Two-sided $p < 0.05$ were considered statistically significant. All analysis was performed using Stata version 12.0 (StataCorp, USA).

Trial sequential analysis

Random errors increase the risk of type I error (false-positive results) in meta-analysis because of sparse data and/or repetitive examining [59, 60]. As a result, trial sequential monitoring boundaries, namely trial sequential analysis (TSA), were conducted [59, 61, 62]. It can determine whether the data in any meta-analysis is reliable and conclusive. When the cumulative z curve crosses the trial sequential monitoring boundary or enters the futility area, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed. If the z curve crosses none of the boundaries and the required information size has not been reached, there is insufficient evidence to reach a conclusion. Here, we estimated the required information size using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power of 80%). All analysis was conducted by TSA version 0.9.5.9 Beta (http://www.ctu.dk/tsa).

CONFLICTS OF INTEREST

None.

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