Int J Clin Exp Med 2018;11(6):5409-5417
www.ijcem.com /ISSN:1940-5901/IJCEM0067031

Review Article

Hematologic adverse events (HAEs) of Eribulin used in treating metastatic breast cancer (MBC): a meta-analysis of randomized controlled trials

Chongxiang Chen[1], Jiaojiao Wang[2], Qingyu Zhao[1]

[1]Department of Intensive Care Unit, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong Province, China; [2]Department of Tuberculosis, Pulmonary Hospital of Fuzhou of Fujian Province, Fuzhou, Fujian Province, China

Received October 11, 2017; Accepted February 6, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: Objective: The objective was to conduct a systematic review and meta-analysis of MBC focusing on HAEs comparing eribulin monotherapy with other therapeutic regimens. Methods: PubMed and The Web of Science were searched for RCTs comparing eribulin monotherapy with other regimens for the treatment of metastatic breast cancer. Meta-analyses were used to estimate the odds ratios (OR) of adverse events (AEs), severe adverse events (SAEs), discontinuation of therapy due to adverse events (DAEs), and HAEs, such as neutropenia, anemia, leucopenia, respectively. Results: We included in 3 RCTs of a total of 1968 patients with MBC and divided them into eribulin and comparator groups with 1114 patients and 854 patients, respectively. For AEs, the result comparing eribulin versus comparator (OR 4.09, 95% CI 3.33-5.01, I^2=89%) was significantly different with high heterogeneity. For either SAEs (OR 0.86, 0.68-1.08, I^2=0%) or DAEs (OR 0.79, 0.58-1.06, I^2=0%), the comparison was similar. For HAEs, overall neutropenia (OR 4.09, 3.33-5.01, I^2=89%), grade 3 neutropenia (OR 3.34 95% CI 2.50-4.46, I^2=92), grade 4 neutropenia (OR 7.92, 95% CI 5.25-11.94, I^2=90%), using MGF (OR 3.43, 95% CI 2.38-4.93, I^2=54%), and febrile neutropenia (OR 2.58, 95% CI 1.21-5.48, I^2=0%) showed significant differences. Whereas for overall anemia (OR 0.99, 95% CI 0.78-1.24, I^2=19%), grade 3 anemia (OR 1.06, 95% CI 0.78-1.24, I^2=49%), grade 4 anemia (OR 0.41, 95% CI 0.05-3.27, I^2=0%), overall leukopenia (OR 3.26, 95% CI 2.50-4.25, I^2=70%), grade 3 leukopenia (OR 4.76, 95% CI 3.01-7.52, I^2=83%), and grade 4 leukopenia (OR 4.49, 95% CI 1.35-14.97, I^2=0%), the results were similar in all groups. Conclusions: When treating patients with MBC that have previously been treated with more than two chemotherapy regimens, eribulin exerts more HAEs than others, and should be taken into consideration to treat with myeloid growth factor (MGF) support in all cycles if risk factors of febrile neutropenia are present.

Keywords: Eribulin, metastatic breast cancer, MBC

Introduction

Treatments based on anthracyclines or taxanes are widely used in first-line of MBC [1], and (neo) adjuvant stage. However, treatment decisions in subsequent lines are difficult [2].

Eribulin, a non-taxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs, is a structurally modified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai. Eribulin is different from other tubulin-targeting agents [3-7] in action through inhibiting the microtubule growth phase without affecting the shortening phase, and causing tubulin sequestration into non-productive aggregates.

In animal studies, eribulin induced less neuropathy than did paclitaxel and retained activity in cell lines that were resistant to paclitaxel [8] through B-tubulin mutations [9]. Therefore, Eribulin could be effective in patients who are resistant to other tubulin-targeting agents, and has been written in the NCCN guidelines version 2.2017 of breast cancer as a monotherapy for MBC that has previously been treated with more than two regimens and pooled healthy patients accompanied with no preventive AEs [10].

Table 1. The baseline characteristics of included studies

	Age	Sum (E)	Sum (C)	Method (E)	Method (C)	OS (E)	OS (C)	PFS (E)	PFS (C)	Country
Cortes J 2011	≥18 2-5 prior chemo-therapy regimens.	508	254	Eribulin: 1.4 mg/m^2, iv2-5 min D1+D8 (21D cycle)	Treatment of physician's choice	13.1 (11.8-14.3)	10.6 (9.3-12.5)	3.7 (3.3-3.9)	2.2 (2.1-3.4)	USA
Kaufman PA 2015	≥18 Up to two prior chemotherapy regimens.	554	548	Eribulin: 1.4 mg/m^2, iv2-5 min D1+D8 (21D cycle)	Capecitabine (1.25 mg/m^2 bid D1-14)	15.9 (15.2-17.6)	14.5 (13.1-16.0)	4.1 (3.5-4.3)	4.2 (3.9-4.8)	USA
Vahdat LT 2013	≥18 At least one prior cytotoxic chemotherapy.	52	52	Eribulin: 1.4 mg/m^2, iv2-5 min D1+D8 (21D cycle)	Ixabepilone: starting 32-40 mg/m^2) D1 for each 21D cycle	/	/	3.47 (2.67-4.3)	3.17 (2.43-6.2)	USA
	Study		OR (E)	OR (C)	AE (E)	AE (C)	SAE (E)	SAE (C)	DAE (E)	DAE (C)
Cortes J 2011	E7389-G000-305		57/468	10/214	497/503	230/247	126/503	64/247	67/503	38/247
Kaufman PA 2015	E7389-G000-301		61/554	63/548	512/544	494/546	95/544	115/546	43/544	57/546
Vahdat LT 2013	E7389-G000-209		8/52	3/52	50/51	48/50	30/51	32/50	6/51	16/50

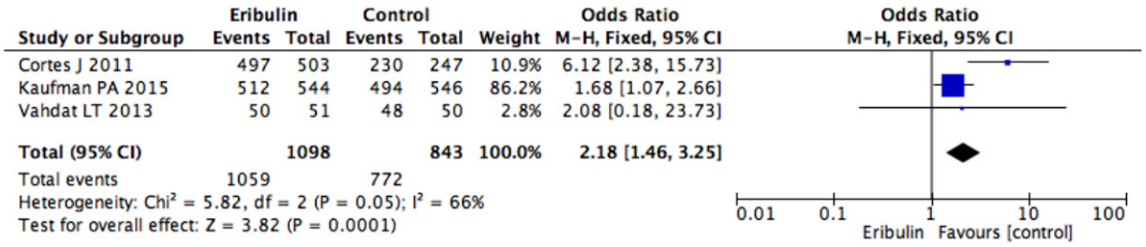

Figure 1. Comparison of AEs between eribulin and comparator.

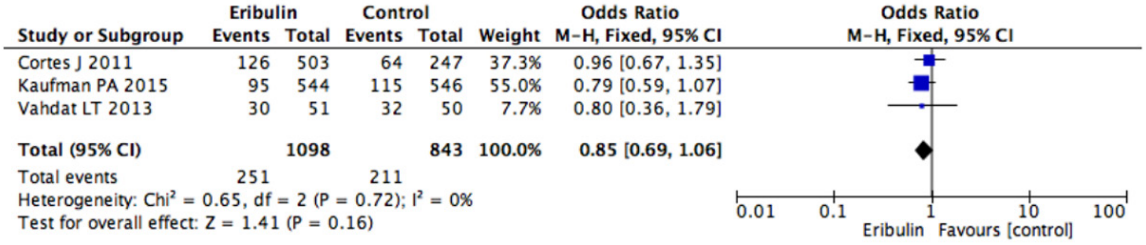

Figure 2. Comparison of SAEs between eribulin and comparator.

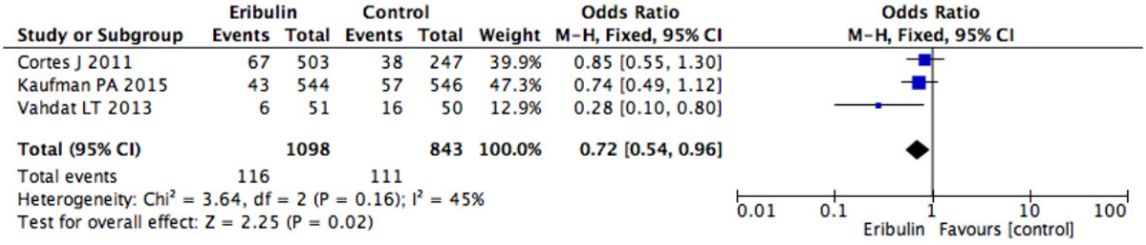

Figure 3. Comparison of DAEs between eribulin and comparator.

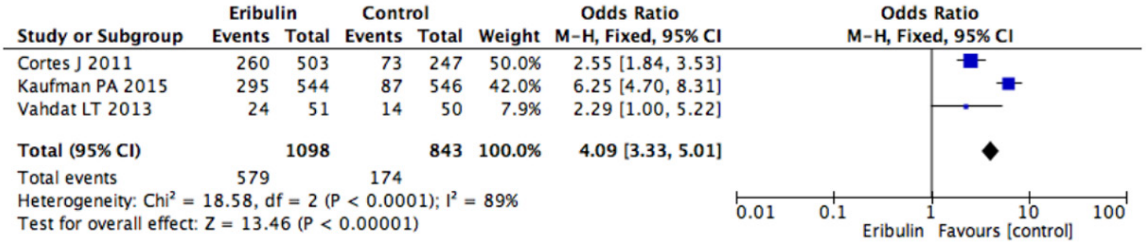

Figure 4. Comparison of neutropenia between eribulin and comparator.

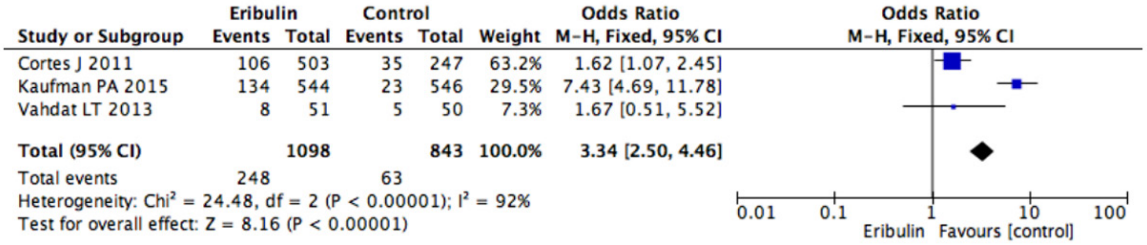

Figure 5. Comparison of grade 3 neutropenia between eribulin and comparator.

Methods

Search strategy

Two investigators independently reviewed the identified abstracts and selected articles for full review, Discrepancies were resolved by a third reviewer. The reference lists of eligible studies and relevant papers were also manually searched and reviewed. A total of 510 articles were found, and through reading the title and abstract 501 articles were excluded, leaving 3 articles [11-13] (**Table 1**).

Inclusion and exclusion

Inclusion: (1) Researched body, coincided with MBC. (2) Two groups and one of them included eribulin. (3) Outcome: including AEs, especially HAEs.

Exclusion: (1) Breast cancer in situ or first regimen in MBC. (2) Review or retrospective research. (3) insufficient data.

Data elected

Two authors extracted the data below: First author, country, sum of patients et al. and the baseline characteristics of these studies were included.

Statistical analysis

RevMan 5.3 was performed to analyze the clinical data for OR and with a 95% CI. Summary statistics for each study were expressed as OR with 95% CI for dichotomous outcomes (e.g. AEs, SAEs, DAEs, HAEs, using MGF, febrile neutropenia). Data were pooled and expressed with this as an OR with a 95% CI.

Results

Our study comparing eribulin and comparator groups demonstrated that eribulin, a new chemotherapy agent in metastatic breast cancer, exert more AEs than other monotherapeutic regimens (OR 4.09, 95% CI 3.33-5.01, I^2=89%), whereas either SAEs (OR 0.86, 95% CI 0.68-1.08, I^2=0%) or DAEs (OR 0.79, 95% CI 0.58-1.06, I^2=0%) were not different between the groups (**Figures 1**-**3**).

For HAEs, the results comparing groups were significantly different in neutropenia (OR 4.09, 3.33-5.01, I^2=89%), grade 3 neutropenia (OR 3.34, 95% CI 2.50-4.46, I^2=92), and grade 4 neutropenia (OR 7.92, 95% CI 5.25-11.94, I^2=90) with high heterogeneity (**Figures 4**-**6**).

For overall anemia (OR 0.99, 95% CI 0.78-1.24, I^2=19%), grade 3 anemia (OR 1.06, 95% CI 0.78-1.24, I^2=49%), and grade 4 anemia (OR 0.41 95% CI 0.05-3.27, I^2=0%), there was no significant difference in groups (**Figures 7**-**9**).

The results for leukopenia (OR 3.26, 95% CI 2.50-4.25, I^2=70%), grade 3 leukopenia (OR-4.76, 95% CI 3.01-7.52, I^2=83%), and grade 4 leukopenia (OR 4.49, 95% CI 1.35-14.97, I^2= 0%) showed a significant difference in groups (**Figures 10**-**12**).

The results using MGF (OR 3.43, 95% CI 2.38-4.93, I^2=54%), and febrile neutropenia (OR 2.58, 95% CI 1.21-5.48, I^2=0%) showed a significant difference in comparisons (**Figures 13**, **14**).

Discussion

Treatments based on anthracyclines or taxanes are widely used as first-line therapy for MBC [1], and (neo) adjuvant stages. However, decisions of treatment in subsequent lines are hardly to decide [2].

Eribulin, a nontaxane microbiotubule dynamics inhibitor, belongs to the halichondrin class of anticancer agents [14, 15]. It is different from other tubulin-targeted agents in anticancer through binding predominantly to a small number of high-affinity sites on the growing plus ends of microtubules [16, 17]. This highly focused end binding may likely decrease the effects of eribulin on physiologic microtubule functions in nonmalignant cells [18, 19]. The ability of eribulin to block mitosis is irreversible contrasting to other tubulin-targeted agents, and intermittent drug exposure could result in long-periods of loss of cell feasibility [20].

Eribulin has been approved as monotherapy for patients with advanced breast cancer or MBC who have previously received two or more chemotherapeutic regimens. The results of the EMBRACE trial comparing eribulin and treatment of physician's choice groups (TPC) showed a significant benefit in overall survival (OS) for patients treated with eribulin (Median OS were 13.1 months versus 10.6 months). Median progressive-free survival (PFS) was 3.7 months

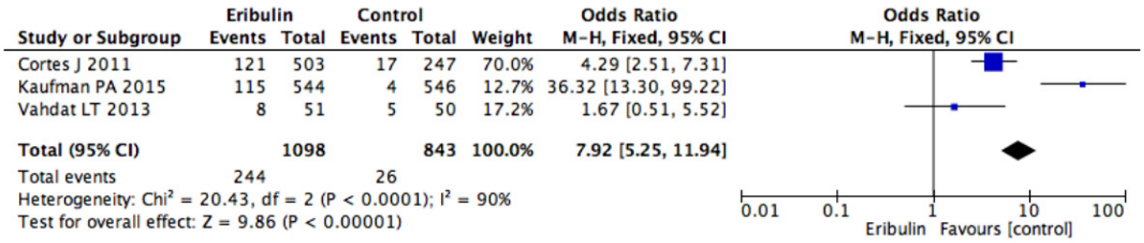

Figure 6. Comparison of grade 4 neutropenia between eribulin and comparator.

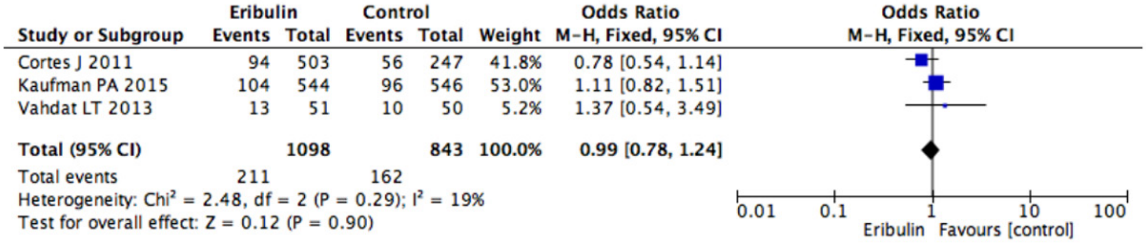

Figure 7. Comparison of anemia between eribulin and comparator.

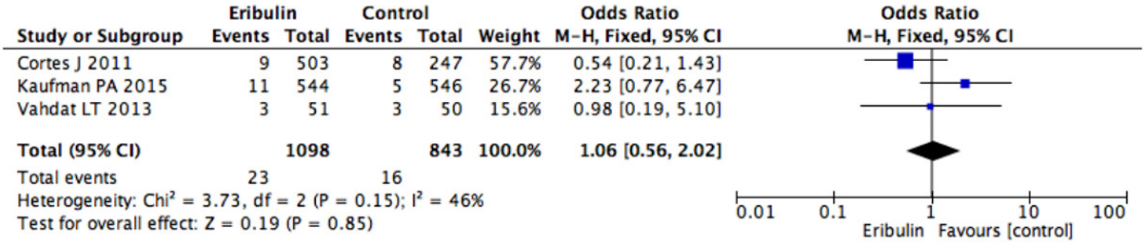

Figure 8. Comparison of grade 3 anemia between eribulin and comparator.

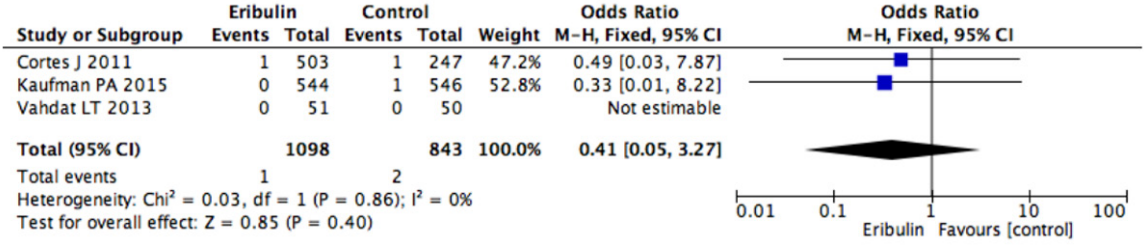

Figure 9. Comparison of grade 4 anemia between eribulin and comparator.

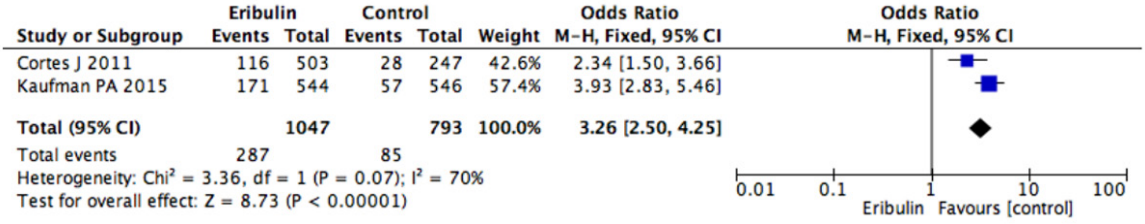

Figure 10. Comparison of leukopenia between eribulin and comparator.

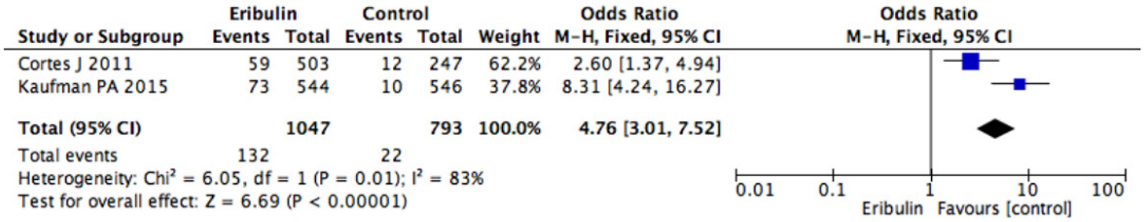

Figure 11. Comparison of grade 3 leukopenia between eribulin and comparator.

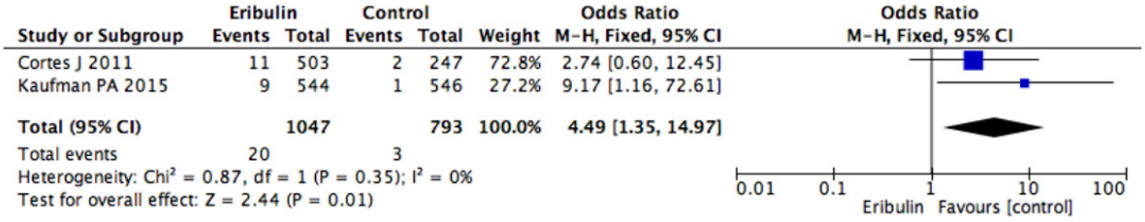

Figure 12. Comparison of grade 4 leukopenia between eribulin and comparator.

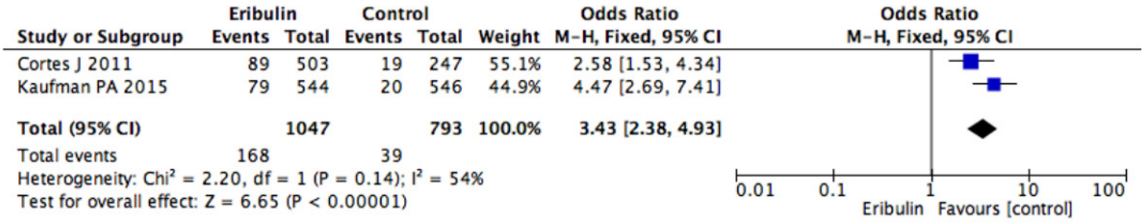

Figure 13. Comparison of using MGF between eribulin and comparator.

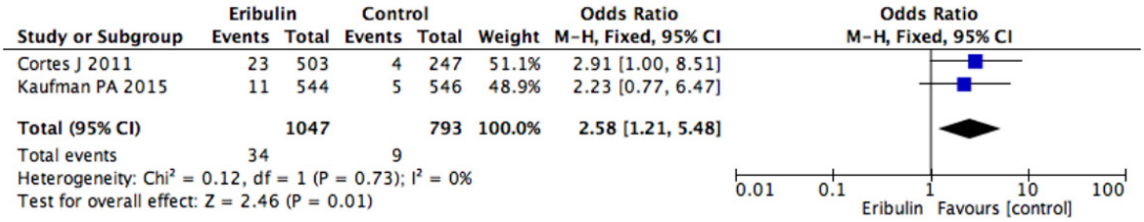

Figure 14. Comparison of febrile neutropenia between eribulin and comparator.

(95% CI 3.3-3.9) with eribulin and 2.2 months (2.1-3.4) with TPC [11]. The results of Study 301 comparing eribulin with capecitabine for advanced breast cancer or MBC demonstrated an increased trend in eribulin with 15.9 months (95% CI, 15.2-17.6) versus capecitabine with 14.5 months (95% CI, 13.1-16). As we can see, Capecitabine is commonly used in the first-, second-, and third-line settings for MBC and it has also been the control arm in several trials in MBC [21-24].

For the AEs, previously reported, manageable tolerability AEs, such as neutropenia, leukopenia, and peripheral neuropathy, have occurred in patients using eribulin. Neutropenia was managed with dose delays, reductions, and MGF according to practice. In the EMBRACE study 301 and study 209, the results of the occurrence of all grades neutropenia were 52%, 54.2%, and 47.1%, respectively; for grade 3 neutropenia were 21%, 24.6%, and 15.7%, respectively; for grade 4 neutropenia were 24%, 24.6%, 15.7%, respectively. Our analysis comparing eribulin versus comparator showed that overall neutropenia (OR 4.09, 3.33-5.01, I^2=89%), grade 3 neutropenia (OR 3.34 95% CI 2.50-4.46, I^2=92), or grade 4 neutropenia (OR

7.92, 95% CI 5.25-11.94, I^2=90) was significantly difference in comparisons [11-13].

The results with high heterogeneities in these analyses because Ixabepilone, which is like eribulin aiming at microtubule, is the comparator of the Study 209. In Study 209, the overall neutropenia (OR 2.29, 95% CI 1.00-5.22), grade 3 neutropenia (OR 1.67, 95% CI 0.51-5.52), or grade 4 neutropenia (OR 1.67, 95% CI 0.51-5.52) did not show significantly difference, but the results of the others (EMBRACE and study 301) showed a significant difference.

In our analysis, using MGF (OR 3.43, 95% CI 2.38-4.93, I^2=54%), and febrile neutropenia (OR 2.58, 95% CI 1.21-5.48, I^2=0%) showed significantly differences. In the EMBRACE study, the rate of using MGF was 18% versus 8% of eribulin and comparators, respectively, and in study 301, the rate was 14.6% versus 3.6%. The NCCN guideline version 2013 of MGF suggested preventive using MGF when the occurrence rate of febrile neutropenia is higher than 20%, and considering to preventive use when ranges from 10% to 20%. Although the occurrence rates of febrile neutropenia of eribulin group were relatively low in the EMBRACE and 301 study with rates of 5% and 2%, respectively [25].

One the one hand, according to the guidelines, other high-risk factors (e.g. older patient >65 years , radiation therapy or chemotherapy , neutropenia or one marrow involvement with tumor, neutropenia infection/open wounds, recent surgery, poor renal function or liver dysfunction) must be taken into consideration in febrile neutropenia. A low-risk regimen does not necessarily preclude the use of CSFs in a patient with high-risk factors [25].

Breast cancer is a neoplasm with chemotherapeutic sensitivity and a high survival rate. Patients with MBC, treated with eribulin and second-lines regimens, are almost always at an older age. In EMBRACE, median age of eribulin group is 55 years, ranging from 28-85 with a median age of the comparator group is 56 years, ranging from 27-81. In study 301, the median age of eribulin is 54 years, ranging from 24-80 with a median age of comparator group is 53 years, ranging from 26-80. MBC is often found when metastasizing to bone, destroying bone marrow, and influencing the function of hematopoiesis. Liver or kidney metastasis of MBC also carries a high risk of febrile neutropenia because of poor liver or kidney function. Above all, older age, destroying bone marrow, and poor liver/kidney function are often discovered as characteristic of patients with MBC who have treated with more than two lines regimens.

In the guideline, the regimens of breast cancer of which the occurrence rates of febrile neutropenia are more than 20% [e.g. Docetaxel + trastuzumab, Dose-dense AC (doxorubicin + cyclophosphamide) followed by T (Paclitaxel), TAC (docetaxel + doxorubicin + cyclophosphamide)] preventive treatment using MGF is required; other frequent regimens [(e.g. Docetaxel every 21 days, CMF (cyclophosphamide + methotrexate + fluorouracil), AC + sequential docetaxel, AC + sequential docetaxel + trastuzumab, FEC (fluorouracil + epirubicin + cyclophosphamide) + sequential docetaxel or Paclitaxel every 21 days)] are listed as 10-20% of the occurrence rate of febrile neutropenia, which also should consider preventive MGF treatment. According to the guidelines, almost all regimens treating patients with breast cancer are in the list of intermittent or high occurrence rates of febrile neutropenia. Patients with MBC that are treated with more than two regimens there are high risks of febrile neutropenia because of previous chemotherapy, preexisting neutropenia, and poor performance status, all of which are accounted for as risk factors of febrile neutropenia and are characteristic of the relevant treatments.

One the other hand, AC-T (cycling 3 weeks), which in the guideline is listed as an intermittent risk regimen, in some RCTs, of which the occurrence rate of febrile neutropenia is less than 5% in GEPARDUO study [26], and in a study conducted by Burnell M et al. [27] was 4.8%, but these two studies didn't use preventive MGF in AC-T (cycling 3 weeks) group. Another study conducted by Leone JP et al. [28] showed that in a total of 126 patients treated with FAC or CMF, only 2 patients had febrile neutropenia. In the guidelines, these regimens are all intermittent risk at 10-20%, so the data of Clinical trials should take this into consideration.

Because of the risk factors of pre-treatment and characteristics of patients, and high occur-

rence rate of neutropenia, clinicians should pay attention to select appropriate patients that are treated with eribulin to incorporate preventive MGF treatment.

Conclusion

During the clinical practice, doctor should take into consideration to assess status of the patients with MBC treated with eribulin of which have been pre-treated with more than two lines regimens. Because these patients, especially older than >65 years old, having history of neutropenia, and having metastasis to the liver or kidney, are more likely to develop a need for GCF for preventing neutropenia and febrile neutropenia.

Disclosure of conflict of interest

None.

Address correspondence to: Qingyu Zhao, Department of Intensive Care Unit, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng East Road, Guangzhou 510060, Guangdong Province, China. E-mail: zhaoqy163@163.com

References

[1] Andreopoulou E, Sparano JA. Chemotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer: an overview. Curr Breast Cancer Rep 2013; 5: 42-50.

[2] Moreno-Aspitia A, Perez EA. Treatment options for breast cancer resistant to anthracycline and taxane. Mayo Clin Proc 2009; 84: 533-545.

[3] Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, Welsh S, Zheng W, Seletsky BM, Palme MH, Habgood GJ, Singer LA, Dipietro LV, Wang Y, Chen JJ, Quincy DA, Davis A, Yoshimatsu K, Kishi Y, Yu MJ, Littlefield BA. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res 2001; 61: 1013-21.

[4] Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005; 4: 1086-95.

[5] Kuznetsov G, Towle MJ, Cheng H, Kawamura T, TenDyke K, Liu D, Kishi Y, Yu MJ, Littlefield BA. Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. Cancer Res 2004; 64: 5760-66.

[6] Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. Mol Cancer Ther 2008; 7: 2003-11.

[7] Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, Jordan MA. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. Biochemistry 2010; 49: 1331-37.

[8] Wozniak KM, Nomoto K, Lapidus RG, Wu Y, Carozzi V, Cavaletti G, Hayakawa K, Hosokawa S, Towle MJ, Littlefield BA, Slusher BS. Comparison of neuropathy-inducing effects of eribulin versus paclitaxel in mice. Cancer Res 2011; 71: 3952-62.

[9] Kuznetsov G, TenDyke K, Yu MJ, Littlefield BA. Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells in vitro. Proc Am Assoc Cancer Res 2007; 48: 275, abstr C58.

[10] National Comprehensive Cancer Network (2017). NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast cancer, version 2.

[11] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Diéras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377: 914-23.

[12] Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, Olivo MS, He Y, Dutcus CE, Cortes J. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015; 33: 594-601.

[13] Vahdat LT, Garcia AA, Vogel C, Pellegrino C, Lindquist DL, Iannotti N, Gopalakrishna P, Sparano JA. Eribulin mesylate versus ixabepilone in patients with metastatic breast cancer: a randomized Phase II study comparing the incidence of peripheral neuropathy. Breast Cancer Res Treat 2013; 140: 341-51.

[14] Kuznetsov G, Towle MJ, Cheng H, Kawamura T, TenDyke K, Liu D, Kishi Y, Yu MJ, Littlefield BA. Induction of morphological and biochemical

apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. Cancer Res 2004; 64: 5760-5766.

[15] Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, Welsh S, Zheng W, Seletsky BM, Palme MH, Habgood GJ, Singer LA, Dipietro LV, Wang Y, Chen JJ, Quincy DA, Davis A, Yoshimatsu K, Kishi Y, Yu MJ, Littlefield BA. In vitro and in vivo anticancer activities of synthetic macro-cyclic ketone analogues of halichondrin B. Cancer Res 2001; 61: 1013-1021.

[16] Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005; 4: 1086-1095.

[17] Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. Mol Cancer Ther 2008; 7: 2003-2011.

[18] Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, Jordan MA. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. Biochemistry 2010; 49: 1331-1337.

[19] Wozniak KM, Nomoto K, Lapidus RG, Wu Y, Carozzi V, Cavaletti G, Hayakawa K, Hosokawa S, Towle MJ, Littlefield BA, Slusher BS. Comparison of neuropathy-inducing effects of eribulin mesylate, paclitaxel, and ixabepilone in mice. Cancer Res 2011; 71: 3952-3962.

[20] Thadani-Mulero M, Nanus DM, Giannakakou P. Androgen receptor on the move: boarding the microtubule expressway to the nucleus. Cancer Res 2012; 72: 4611-4615.

[21] Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-2743.

[22] Hortobagyi GN, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, Jassem J, Lerzo GL, Pivot XB, Hurtado de Mendoza F, Xu B, Vahdat LT, Peck RA, Mukhopadhyay P, Roché HH. Analysis of overall survival from a phase III study of ixabepilone plus capecitabine versus capecitabine in patients with MBC resistant to anthracyclines and taxanes. Breast Cancer Res Treat 2010; 122: 409-418.

[23] Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23: 792-799.

[24] Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, Jassem J, Pivot XB, Klimovsky JV, de Mendoza FH, Xu B, Campone M, Lerzo GL, Peck RA, Mukhopadhyay P, Vahdat LT, Roché HH. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 2007; 25: 5210-5217.

[25] National Comprehensive Cancer Network (2013). NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Myeloid Growth Factors.

[26] von Minckwitz G, Raab G, Caputo A, Schütte M, Hilfrich J, Blohmer JU, Gerber B, Costa SD, Merkle E, Eidtmann H, Lampe D, Jackisch C, du Bois A, Kaufmann M. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 2005; 23: 2676-85.

[27] Burnell M, Levine MN, Chapman JA, Bramwell V, Gelmon K, Walley B, Vandenberg T, Chalchal H, Albain KS, Perez EA, Rugo H, Pritchard K, O'Brien P, Shepherd LE. Cyclophosphamide, epirubicin, and Fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by Paclitaxel versus Doxorubicin and cyclophosphamide followed by Paclitaxel in node-positive or high-risk node-negative breast cancer. J Clin Oncol 2010; 28: 77-82.

[28] Leone JP, Leone J, Vallejo CT, Pérez JE, Romero AO, Machiavelli MR, Romero Acuña L, Domínguez ME, Langui M, Fasce HM, Leone BA, Ortiz E, Iturbe J, Zwenger AO. Sixteen years follow-up results of a randomized phase II trial of neoadjuvant fluorouracil, doxorubicin, and cyclophosphamide (FAC) compared with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in stage III breast cancer: GOCS experience. Breast Cancer Res Treat 2014; 143: 313-23.