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Review Article

Eribulin Effectiveness and Safety in Metastatic Triple-Negative Breast Cancer: A Narrative Review

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Abstract

Triple-negative breast cancer is an aggressive and poor prognosis subtype of breast cancer. Eribulin has shown promise in the treatment of metastatic triple-negative breast cancer (mTNBC). This review aimed to provide a specific description, evidence, and discussion of the efficacy and safety of eribulin both as monotherapy and in combination with another agent in patients with mTNBC. The search was conducted in five databases (PubMed, ScienceDirect, PLoS One, Wiley Online Library, and Cochrane Library) towards published articles during the 2013-2023 period. A total of 237 articles were identified. After removing 69 duplicates, 168 articles underwent the screening process and 10 articles met the research criteria. Eribulin monotherapy effectiveness profile includes: overall survival (10.8-17.6 months), progression-free survival (2.8-3.2 months), partial response (21.0%-58.7%), progressive disease (15.5% -47.0%), and stable disease (28.8%-32%). However, there were no cases of complete response. Combination of eribulin with other agents' effectiveness profiles includes: overall survival (8.3-14.5 months), PFS (2.6-8.1 months), partial response (31.8-76.0%), complete response (2.4-8%), progressive disease (8.0-28%), and stable disease (8.0-52.3%). Eribulin monotherapy's safety profile is similar to that of combination therapy. No grade 5 adverse event was reported during monotherapy or in combination with other agents. The grade 4 adverse events reported are neutropenia, leukopenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, vomiting, dyspnea, back pain, arthralgia, febrile neutropenia, dyspnea, constipation, general physical health deterioration, alopecia. The all-grade adverse events with a percentage above 50% are neutropenia, leukopenia, thrombocytopenia, asthenia, alopecia, elevated AST, elevated ALT, hand-foot syndrome, fatigue, anemia, peripheral neuropathy, oral mucositis, and nausea.

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INTRODUCTION

Triple-negative breast cancer (TNBC), representing approximately 24% of all breast cancer diagnoses, is a highly aggressive subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression[1,2]. This unique receptor profile contributes to TNBC's poor prognosis, marked by a high mortality rate, frequent early recurrence, and significant metastatic potential[1,3,4]. Specifically, TNBC is associated with a less than 5-year overall survival rate and a disease-free survival rate below 18%. Furthermore, over one-third of TNBC patients develop distant metastases, often to visceral organs and the brain, within three years of diagnosis. The median overall

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survival for metastatic TNBC is typically limited to 12-18 months[4]. These clinical challenges underscore the urgent need for novel therapeutic strategies to improve outcomes for patients with TNBC.

Triple-negative breast cancer presents a significant clinical challenge due to its aggressive nature and high propensity for recurrence and metastasis. Consequently, chemotherapy remains a cornerstone of TNBC management, serving as the primary systemic treatment. Standard regimens typically incorporate anthracyclines, taxanes, and platinum-based compounds, which have demonstrated efficacy in improving overall survival and delaying disease progression. While targeted therapies are currently limited for TNBC, chemotherapy effectively induces tumor shrinkage and prolongs survival[5]. However, the inherent heterogeneity of TNBC poses a substantial challenge, as individual patient responses to chemotherapy can vary significantly, necessitating the exploration of personalized treatment strategies[6].

Metastatic triple-negative breast cancer (mTNBC) presents a significant clinical challenge due to its aggressive nature and limited therapeutic options. Chemotherapy remains a cornerstone of treatment, aiming to inhibit tumor growth and proliferation. However, mTNBC's characteristic low expression of ER, PR, and HER-2 renders it unresponsive to endocrine and HER-2 targeted therapies, thereby narrowing the range of effective chemotherapeutic agents. Standard first-line chemotherapy typically involves taxanes and anthracyclines. Unfortunately, the inherent phenotypic heterogeneity, diverse gene expression profiles, and propensity for chemoresistance in mTNBC often contribute to suboptimal treatment responses. The paucity of alternative chemotherapy options, particularly for patients exhibiting resistance or intolerance to taxanes and anthracyclines, underscores the urgent need for improved treatment strategies[4,7]. Consequently, current research efforts are focused on identifying predictive biomarkers and developing novel therapeutic approaches to enhance the efficacy and precision of chemotherapy in mTNBC management, ultimately aiming to improve patient outcomes[8,9].

Eribulin, a synthetic analog of halichondrin B isolated from marine sponges, serves as an antineoplastic agent in the treatment of metastatic breast cancer. Its primary mechanism of action involves the disruption of microtubule dynamics, a process critical for cell division, ultimately leading to apoptosis in cancer cells. Clinical trials have established that eribulin confers a survival benefit in patients with heavily pretreated metastatic breast cancer, particularly those who have progressed following anthracycline and taxane therapies[10,11]. Notably, eribulin exhibits a manageable safety profile, with the most frequently reported adverse events including neutropenia, fatigue, and peripheral neuropathy. The integration of eribulin into treatment protocols underscores the continuous evolution of therapeutic strategies aimed at enhancing outcomes for patients with advanced breast cancer[12-14].

Eribulin has emerged as a potential therapeutic agent in breast cancer, particularly in the challenging subtype of mTNBC. This subtype, characterized by the absence of estrogen and progesterone receptors and HER2 expression, presents significant treatment hurdles. While eribulin's efficacy and safety have been established in broader breast cancer populations, specific data regarding its application in mTNBC remain relatively sparse. Nonetheless, existing evidence suggests that eribulin may offer improvements in overall survival and maintain a tolerable safety profile in mTNBC patients, a significant finding given the limited therapeutic options available[5]. Eribulin's antimitotic mechanism, involving the disruption of microtubule dynamics and subsequent induction of apoptosis, is particularly relevant in targeting the rapid proliferation characteristic of TNBC. Further research is imperative to fully elucidate the potential benefits and optimize the utilization of eribulin in this context, thereby refining treatment strategies for mTNBC. To this end, this review aims to provide a comprehensive analysis of the efficacy and safety of eribulin, both as a monotherapy and in combination with other agents, specifically in patients with mTNBC.

MATERIALS AND METHODS

Materials

This review employed a systematic literature strategy to minimize bias and enhance the rigor of the analysis[15]. A comprehensive search was conducted across five databases: PubMed, ScienceDirect, PLoS ONE, Wiley Online Library, and the Cochrane Library. The search was limited to articles published between 2013 and 2023. To ensure a thorough retrieval of relevant literature, a combination of keywords and Medical Subject Headings (MeSH) terms was utilized, incorporating Boolean operators, truncation, nesting, quotation marks, and field tags. Specifically, the search terms included variations of "Triple Negative Breast Neoplasms" OR "Triple Negative Breast Cancer" OR "TNBC" OR "Triple Negative Breast

Carcinoma" OR "Triple Negative Breast Tumor," combined with "Metastatic," "Eribulin," and terms related to efficacy ("efficacy" OR "effectiveness") and safety ("safety" OR "adverse drug reaction" OR "side effect" OR "adverse event").

Methods

This review employed a systematic approach to identify relevant original research articles. Inclusion criteria mandated that articles be fully accessible, published in English, and represent observational or experimental studies within 2013 to 2023. Studies were selected based on their focus on patients with mTNBC receiving eribulin chemotherapy regimens. To ensure comprehensive data collection, articles were required to report on at least one of the following therapeutic outcomes: overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). Furthermore, articles had to document safety parameters, specifically adverse effects or reactions associated with eribulin treatment, and possess a digital object identifier (DOI). Exclusion criteria encompassed case reports, doctoral dissertations, and case series, ensuring a focus on robust, research-based evidence.

Data analysis

Articles quality assessment

To ensure the rigor and reliability of the included studies, a comprehensive quality assessment was conducted using the Critical Appraisal Skills Programme (CASP) tools. This systematic evaluation focused on assessing each study's trustworthiness, relevance, and the validity of its reported results. Depending on the study design, either the CASP Randomised Controlled Trial (RCT) checklist or the CASP cohort study checklist was applied. Articles were subsequently categorized into quartiles based on the number of "yes" responses to the checklist questions. Specifically: Quartile 1 (Q1) represented studies with 9-11 "yes" answers; Quartile 2 (Q2), 6-8 "yes" answers; Quartile 3 (Q3), 3-5 "yes" answers; and Quartile 4 (Q4), 0-2 "yes" answers. Studies falling within Q1 to Q3 were considered to be of good quality, while those in Q4 were deemed to be of poor quality. This stratification allowed for a nuanced understanding of the methodological strength of the included research and facilitated a more robust synthesis of findings.

Eribulin effectiveness

The assessment of eribulin's therapeutic efficacy in metastatic breast cancer relies on a comprehensive evaluation of both survival and response parameters. Survival parameters, including OS and PFS, provide insights into the long-term benefits of the treatment. Overall survival is defined as the time from the initiation of eribulin therapy to death from any cause[14], while PFS represents the duration of time during which the disease remains stable without progression[16]. Conversely, response parameters, such as CR, PR, PD, and SD, directly reflect the tumor's dimensional response to eribulin. These response parameters are categorized according to the World Health Organization (WHO) standardized response classification and the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[17]. Specifically, CR signifies the complete disappearance of invasive cancer in the breast and the absence of axillary lymph node involvement. PR is defined as a reduction of at least 30% in the sum of diameters (SOD) of target lesions. PD is characterized by a 20% or greater increase in SOD, the appearance of new lesions, or the progression of non-target disease. SD is assigned when tumor size changes do not meet the criteria for either PR or PD[17,18]. These standardized criteria allow for a consistent and objective evaluation of eribulin's impact on tumor burden and patient outcomes.

Eribulin safety

The safety profile of eribulin was evaluated by analyzing adverse events reported in clinical trials, encompassing both eribulin monotherapy and combination regimens. Adverse event data were categorized and reported according to their severity, spanning all grades or specifically focusing on Grade 3 and 4 events. To standardize the evaluation of adverse events, the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was employed. This classification system delineates five grades of severity: Grade 1, representing mild and asymptomatic events; Grade 2, indicating moderate events requiring localized or non-invasive interventions; Grade 3, denoting severe events necessitating hospitalization or prolonged hospitalization, but not immediately life-threatening; Grade 4, signifying life-threatening events requiring urgent medical intervention; and Grade 5, representing events resulting in patient mortality. This standardized approach ensured a consistent and comprehensive assessment of eribulin-related adverse events across the analyzed studies[19,20].

RESULTS AND DISCUSSION

Based on the search process results across five databases, 237 articles covering the publication period from 2013 to 2023 were identified. After removing 69 duplicates, 168 articles underwent the screening process. Ten articles from this screened pool met the research criteria (**Figure 1**).

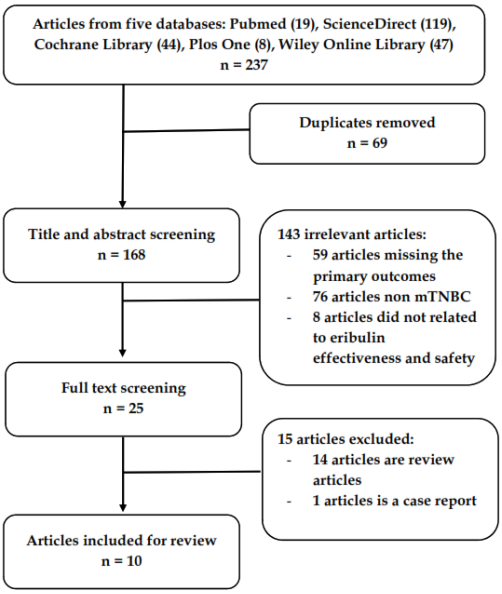

Figure 1. Article selection flowchart.

Out of the ten included articles, 8 were experimental studies, and 2 were observational studies. **Table I** presents the details of the study design and the quality assessment of each included article. Based on the CASP quality assessment, all the included articles were of good quality. Among the ten included articles, five reported on the effectiveness of eribulin as monotherapy[21-25], while the remaining five reported on its effectiveness and safety profile as a combination with other chemotherapy agents[26-30]. Eribulin as monotherapy in 5 articles using various doses; one article uses 2 mg/m^2, two articles 1.23 mg/m^2, and two articles 1.4 mg/m^2. All doses are given on day one and day eight every 21 days. From 5 articles that combine eribulin with other chemotherapy agents such as one article combines eribulin with camrelizumab and apatinib[26]; one article combines with gemcitabine[27]; one article combines with everolimus[28]; one article combines with doxorubicin and paclitaxel[29]; and one article combines with olaparib[21].

Table I. Articles quality assessment using CASP checklist.

Articles number	Design study	References	CASP Quality Assessment
1	Experimental study (phase I open-label study)	**21**	Q2
2	Experimental study (open-label, randomised study)	**22**	Q2
3	Experimental study (multicenter, single-arm study).	**23**	Q2
4	Experimental study (prospective single-arm, multicenter, phase II clinical trial)	**26**	Q2
5	Experimental study (open-label, multicenter phase II study)	**27**	Q2
6	Experimental study (single-center phase I trial study)	**28**	Q2
7	Experimental study (multicenter, prospective, non-randomized, open-label, single-arm, two-stage, phase II study)	**29**	Q2
8	Experimental study (open-label, multicenter, phase I/II trial study)	**30**	Q2
9	Observational study (retrospective study)	**24**	Q2
10	Observational study (retrospective study)	**25**	Q2

Overall survival remains the gold standard metric for evaluating breast cancer treatment efficacy. In mTNBC, OS with conventional chemotherapy regimens typically ranges from 8 to 13 months, reflecting the aggressive nature and poorer prognosis associated with this subtype[10,31]. The mTNBC is characterized by its high risk of early recurrence, high-grade malignancy, and a rapid relapse peak within three years of diagnosis[32]. Notably, eribulin monotherapy has demonstrated

an OS range of 10.8 to 17.6 months, as summarized in **Table II**. While PFS with eribulin monotherapy (2.8 to 3.2 months) aligns with that of other chemotherapeutic agents, the observed OS surpasses that of treatment of physician's choice (TPC)[14] and exceeds the OS reported in the EMBRACE study (8.3 to 13.1 months)[10,31,33,34].

Analysis of clinical trial data, as summarized in **Table II**, reveals that eribulin monotherapy demonstrates varying degrees of clinical benefit in mTNBC. Observed PR rates ranged from 21% to 58.7%, while PD was reported in 15.5% to 47% of patients. Stable disease was noted in 28.8% to 32% of cases. Notably, no CR were observed. While eribulin's efficacy surpasses that of TPC in certain contexts, the overall prognosis of mTNBC remains significantly influenced by the location of metastatic lesions. Specifically, patients with visceral metastases, such as those in the lung, liver, or brain, tend to experience shorter survival durations. Eribulin's mechanism of action, involving microtubule disruption, enables it to reach metastatic sites. In liver mTNBC, eribulin has been shown to modulate the hepatic microenvironment, inhibiting cancer cell growth and migration[35].

Eribulin exerts its antineoplastic effects through a distinctive mechanism involving the disruption of microtubule dynamics, leading to cell cycle arrest at the G2-M phase and subsequent apoptosis. Specifically, eribulin inhibits microtubule polymerization by binding to β-tubulin at the plus ends of growing microtubules, effectively disrupting mitotic spindle formation and preventing the metaphase-anaphase transition. Beyond its direct mitotic effects, eribulin has demonstrated the capacity to reverse the epithelial-to-mesenchymal transition (EMT) and inhibit cancer cell migration, invasion, and metastasis. Notably, eribulin also enhances tumor perfusion through vascular remodeling, thereby alleviating hypoxia-driven tumor aggressiveness and potentially improving the efficacy of subsequent therapies[35-39]. A key distinction of eribulin from other antimicrotubule agents lies in its selective interference with microtubule polymerization without affecting the shortening phase[36] This characteristic renders rapidly proliferating cancer cells, which rely heavily on dynamic microtubule turnover, particularly susceptible to eribulin's effects. Furthermore, the irreversible nature of eribulin's antimitotic action positions it as a valuable treatment option for taxane-resistant mTNBC[40].

A primary strategy to augment the therapeutic efficacy of eribulin in mTNBC involves its combination with other antineoplastic agents. As detailed in **Table II**, eribulin has been investigated in conjunction with various drugs, including camrelizumab and apatinib (triple therapy)[26], gemcitabine[27], everolimus[28], doxorubicin and paclitaxel (triple therapy)[29], and olaparib[30]. These combination therapies have yielded OS rates ranging from 8.3 to 14.5 months and PFS rates between 2.6 and 8.1 months. While certain combinations resulted in a slightly lower OS compared to eribulin monotherapy, they demonstrated a notable improvement in PFS. Furthermore, combination regimens exhibited enhanced response parameters, with PR rates ranging from 31.8% to 76%, CR rates from 2.4% to 8%, PD rates from 8% to 28%, and SD rates from 8% to 52.3%. These findings collectively indicate that combining eribulin with other agents can significantly improve therapeutic outcomes in mTNBC[37].

The synergistic potential of combining eribulin with other therapeutic agents has demonstrated promising improvements in OS and PFS in mTNBC, primarily through the exploitation of distinct mechanisms of action[12,41]. Notably, the combination of eribulin with camrelizumab and apatinib has been shown to effectively prolong PFS to 8.1 months[26,42]. Furthermore, low-dose apatinib, when combined with other chemotherapeutic agents, has proven beneficial in mTNBC patients refractory to prior treatments[43,44]. Apatinib, an anti-angiogenic drug, functions by inhibiting the ATP binding site of vascular endothelial growth factor receptor 2 (VEGFR-2), thereby disrupting downstream signal transduction pathways. This inhibition of VEGFR-2 phosphorylation ultimately obstructs angiogenesis and induces tumor cell apoptosis[12,43,45]. Conversely, camrelizumab, an immune checkpoint inhibitor (ICI), operates by blocking the interaction between programmed cell death protein 1 (PD-1) and its ligand PD-L1, effectively reversing immune downregulation and facilitating tumor cell elimination[46-50].

Current clinical guidelines advocate for the integration of ICIs and anti-angiogenic agents into chemotherapy regimens to optimize the treatment of mTNBC. Specifically, the European Society for Medical Oncology (ESMO) Clinical Practice Guideline for the diagnosis, staging, and treatment of patients with metastatic breast cancer recommends the addition of bevacizumab as a first-line ICI in conjunction with chemotherapy[51]. Conversely, the National Comprehensive Cancer Network (NCCN) guideline suggests pembrolizumab as the preferred first-line ICI[52,53].

Gemcitabine, a nucleoside analog antimetabolite, exerts its cytotoxic effects by disrupting DNA replication through the inhibition of two key cell cycle checkpoints, leading to irreparable DNA damage and G1 cell cycle arrest[54]. Notably, the combination of eribulin with gemcitabine has demonstrated a synergistic effect on cell viability, particularly in solid tumors.

This combined regimen not only significantly reduces tumor cell viability but also induces DNA damage, as evidenced by increased levels of γ-H2AX and P21, ultimately resulting in enhanced apoptosis. This synergistic mechanism of action has been correlated with improved OS in patients with metastatic breast cancer, suggesting a promising therapeutic strategy for this challenging disease[55-57].

Table II. Eribulin effectiveness in mTNBC treatment.

No	Sample	Regiment therapy	Effectiveness						References
			Survival		Response				
			OS (months)	PFS (months)	PR (%)	CR (%)	PD (%)	SD (%)	
1	28 patients (median 59 (range 31-78) years)	Eribulin monotherapy (2mg/ m^2 every 21 days iv)	10.8	2.8	NA	NA	NA	28.6	**21**
2	1644 patients (mean 55±10.3 years)	Eribulin monotherapy (1.23 mg/ m^2 every 21 days iv)	12.4	NA	NA	NA	NA	NA	**22**
3	153 patients (median 55 (range 34-81) years)	Eribulin monotherapy (1.4 mg/ m^2 every 21 days iv)	NA	NA	21	0	47	32	**23**
4	46 patients (median 47 (range 30-65) years	Eribulin 1.4 mg/ m^2 combination with camrelizumab 200 mg (day 1) and apatinib 250 mg daily, on a 21-day cycle	NA	8.1	31.8	6.8	9.1	52.3	**26**
5	85 patients (56 (range 23-81) years)	Eribulin (0.88mg/m^2) combination with gemcitabine (1000 mg/m^2) on a 21-day cycle	14.5	5.1	34.9	2.4	NA	NA	**27**
6	27 patients (median 55 years)	Combination of eribulin and everolimus in three dosing levels: A1 (everolimus 5 mg daily; eribulin 1.4 mg/m^2), A2 (everolimus 7.5 mg daily; eribulin 1.4 mg/m^2), and B1 (everolimus 5 mg daily; eribulin 1.1 mg/m^2) on 21-day cycle	8.3	2.6	36	NA	28	36	**28**
7	13 patients (median 43 (range 35-75) years)	Doxorubicin 60 mg/m^2 and paclitaxel 200 mg/m^2 for four cycles, followed by Eribulin 1.4 mg/m^2 for four cycles.	NA	NA	76	8	8	8	**29**
8	24 patients (>18 years)	Olaparib was orally administered twice daily from level 1:25 mg twice daily to level 7:300 mg twice daily, with 1.4 mg/m^2 of eribulin on days 1 and 8	14.5	5.3	33.3	4.2	20.8	37.5	**30**
9	252 patients (mean 53 years)	Eribulin monotherapy (1.23 mg/ m^2 every 21 days iv)	17.6	NA	58.7	0.0	11.5	29.7	**24**
10	225 patients (median 54 (range 33-72) years)	Eribulin monotherapy (1.4 mg/ m^2 every 21 days iv) as fourth-line therapy	NA	3.2	NA	NA	NA	NA	**25**

Note: OS = Overall survival; PFS = Progression free survival; PR = Partial response; CR= Complete response; PD = Progressive disease; SD = Stable disease; NA = Not available

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is frequently employed in combination with chemotherapy to enhance overall survival and treatment response in TNBC). The mTOR protein, a serine/threonine kinase, plays a crucial role in regulating mRNA translation through the activation of eukaryotic translational initiation factor 4E-binding protein (4E-BPI) and ribosomal protein S6 kinase[58]. Notably, the mTOR signaling pathway is a key component of the epidermal growth factor receptor (EGFR)-dependent signaling cascade. Given that approximately 70% of TNBC cases exhibit EGFR overexpression, the PI3K/AKT/mTOR pathway is frequently activated. This activation promotes tumorigenesis, cell cycle progression, drug resistance, increased cell motility, and metastasis[58-64]. Consequently, the strategic combination of everolimus, which inhibits mTOR, with other agents such as microtubule inhibitors like eribulin, has

demonstrated beneficial effects in mTNBC patients who have experienced disease progression following anthracycline or taxane therapies[40,65,66].

Analysis of **Table II** reveals that eribulin, when administered following doxorubicin and paclitaxel in a neoadjuvant setting, demonstrates the highest rate of CR across the reviewed studies. This suggests that sequential eribulin treatment within a neoadjuvant regimen significantly enhances pathological CR in patients with TNBC. Furthermore, evidence indicates that eribulin, when utilized after doxorubicin and paclitaxel, effectively reduces angiogenesis in mTNBC, contributing to improved tumor response and a decrease in tumor size[67,68].

The combination of eribulin and olaparib presents a promising therapeutic strategy for mTNBC, demonstrating comparable OS, PFS, and response rates to the eribulin-gemcitabine regimen. Olaparib, a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor, is particularly relevant for mTNBC patients with BRCA1/2 mutations. PARP, a crucial protein involved in single-stranded DNA break (SSB) repair, when inhibited, leads to the accumulation of SSBs, subsequently resulting in double-stranded DNA breaks (DSBs) and apoptosis. Importantly, olaparib exhibits a synergistic effect with eribulin by enhancing the sensitivity of cancer cells to microtubule inhibitors, specifically eribulin. This interaction optimizes the anti-microtubule impact of eribulin, particularly in mTNBC cells harboring BRCA1/2 mutations, thereby offering a potential avenue for improved therapeutic efficacy[69-71].

Analysis of the reviewed literature, as summarized in **Table III**, reveals that eribulin, both as monotherapy and in combination with other agents, exhibits a manageable safety profile with no reported Grade 5 adverse events (AEs). The safety profiles of eribulin monotherapy and combination therapy were found to be comparable. Grade 4 AEs were predominantly hematologic, with neutropenia being the most frequently observed[72]. This is consistent with the known myelosuppressive effects of many cancer chemotherapies, including eribulin, which suppresses bone marrow function. Eribulin-induced neutropenia is generally reversible and can be effectively managed through the use of granulocyte colony-stimulating factor (G-CSF) and dose modifications. However, eribulin is contraindicated in patients with an absolute neutrophil count (ANC) below 1,000/mm^3 or other Grade 2 hematologic AEs[20,73-76]. Elevated liver enzymes (AST/ALT) were also commonly reported across all grades, reflecting eribulin's primary hepatic elimination (82%) and partial renal elimination (9%). Even in patients with normal liver function, eribulin can lead to transient increases in hepatic enzyme levels, likely due to its metabolism by various cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1). While eribulin is a competitive inhibitor of CYP3A4, it is not an enzyme inducer, minimizing the risk of significant drug-drug interactions[72,76].

It is important to acknowledge several limitations inherent in this review. The included studies exhibited significant heterogeneity in study design, patient populations, eligibility criteria, treatment durations, prior therapies, and eribulin dosing, as well as the agents used in combination with eribulin. This variability makes direct comparisons between studies challenging[14]. Furthermore, some studies included patients with mixed metastatic breast cancer subtypes, potentially diluting the specific AEs associated with mTNBC[21,22,23]. The sample sizes across the included studies varied widely, ranging from 24 to 923 participants in the eribulin arm. Larger sample sizes are more likely to capture a broader spectrum of AEs[77].

Table III. Eribulin adverse event.

No	Drugs regiment and sample size	Adverse events (AEs; %)			References
		All Grade	Grade 3	Grade 4	
1	Eribulin monotherapy (2 mg/m^2 every 21 days iv) n = 28 TNBC patients	**Hematologic AE:** Neutropenia 78.6; Leucopenia 75; Thrombocytopenia 60.7; Anemia 28.6; Febrile neutropenia 25 **Non-hematologic AE:** AST increased: 82.1; ALT increased 78.6; Stomatitis 57.1; Alopecia 53.6; Malaise 42.9; Pyrexia 39.3; Decreased appetite 39.3; Dysgeusia 39.3; Nausea 39.3; Gamma GT increased 39.3; Peripheral sensory neuropathy 35.7; Rash 28.6; Hypertriglyceridaemia 21.4; Pruritus 21.4	**Hematologic AE:** Neutropenia 14.3; Leucopenia 25; Thrombocytopenia 25; Febrile neutropenia 25 **Non-hematologic AE:** AST increased: 14.3; ALT increased 17.9; Gamma GT increased 10.7; Stomatitis 10.7; Decreased appetite 3.6; Hypertriglyceridaemia 3.6	**Hematologic AE:** Neutropenia 53.6; Leucopenia 17.9; Thrombocytopenia 7.1 **Non-hematologic AE** -	21

No	Drugs regiment and sample size	Adverse events (AEs; %)			References
		All Grade	Grade 3	Grade 4	
2	Eribulin monotherapy (1.23 mg/m² every 21 days iv) n = 923 patients in the eribulin arm (total sample 1644)	**Hematologic AE:** Neutropenia 53.6; Leukopenia 27.4; Anemia 19 **Non-hematologic AE** Alopecia 38.7; Nausea 28.8; Peripheral neuropathy 28.5; Fatigue 23.7; Asthenia 21.8; Pyrexia 17.3; Diarrhea 17; Constipation 16.5; Headache 15.9; Vomiting 15.7; Dyspnea 13.8; Back pain 13.3; Weight loss 13.3; Cough 12.1; Arthralgia 11.4; Anorexia 10.8; Bone pain 10.4; Pain in extremity 10.1; Decreased appetite 7.8; LT increased 6.4; Febrile neutropenia 3.4; Palmar-plantar erythrodysesthesia syndrome 0.9	**Hematologic AE** Neutropenia 23.4; Leukopenia 12.1; Anemia 1.8 **Non-hematologic AE:** Nausea 0.8; Peripheral neuropathy 6.9; Fatigue 2.6; Asthenia 4.8; Pyrexia 0.3; Diarrhea 0.4; Constipation 0.3; Headache 0.5; Vomiting 0.5; Dyspnea 3.1; Back pain 1; Weight loss 0.3; Cough 0.4; Arthralgia 0.5; Anorexia 0.2; Bone pain 1.6; Pain in extremity 0.9; Decreased appetite 0.2; ALT increased 2.5; Febrile neutropenia 2.4; Palmar-plantar erythrodysesthesia syndrome 0.2	**Hematologic AE:** Neutropenia 22.3; Leukopenia 1.9; Anemia 0.1 **Non-hematologic AE** Peripheral neuropathy 0.4; Fatigue 0.3; Diarrhea 0.1; Vomiting 0.2; Dyspnea 0.4; Back pain 0.2; Arthralgia 0.1; Febrile neutropenia 3.4	22
3	Eribulin monotherapy (1.4 mg/m² every 21 days iv). n = 153 patients	**Hematologic AE** Neutropenia 42.6; Anemia 10.6; Thrombocytopenia 4.3; Febrile neutropenia 9.2 **Non-hematologic AE** Asthenia 73.8; Alopecia 54.6; Peripheral neuropathy 46.1; Infectious 27.7; Anorexia 22.7; Myalgia 21.3; Nausea 21.3; Diarrhea 17.7; Dyspnea 16.3; Stomatitis 14.2; Constipation 12.1; Pyrexia 9.9; Vomiting 8.5; Abdominal pain 7.8; Back pain 7.8; Cough 7.1; General physical health deterioration 7.1; Headache 7.1; Peripheral edema 6.4; Pain in extremity 4.3; Lacrimation increased 2.8; Liver function test abnormality 2.8; Pulmonary embolism 2.8; Bone pain 2.1; Dry skin 2.1; Hypokalemia 2.1; Muscle spasm 2.1; Rash 2.1; Weight loss 2.1	**Hematologic AE** Neutropenia 23.4; Anemia 0.7; Thrombocytopenia 1.4; Febrile neutropenia 5.7 **Non-hematologic AE** Asthenia 9.2; Peripheral neuropathy 7.1; Infectious 3.5; Anorexia 2.1; Myalgia 1.4; Nausea 0.7; Diarrhea 0.7; Dyspnea 5; Stomatitis 2.8; Pyrexia 1.4; Vomiting 0.7; Abdominal pain 2.8; Back pain 3.5; Cough 2.1; General physical health deterioration 2.8; Pain in extremity 1.4; Liver function test abnormality 1.4; Pulmonary embolism 2.8; Bone pain 1.4; Rash 0.7	**Hematologic AE** Neutropenia 13.5; Febrile neutropenia 3.5 **Non-hematologic AE** Dyspnea 0.7; Constipation 0.7; General physical health deterioration 0.7	23
4	Eribulin 1.4 mg/m² combination with camrelizumab 200 mg (day 1) and apatinib 250 mg daily, on a 21-day cycle n = 46 mTNBC patients	**Hematologic AE:** Leukopenia 65.2; Neutropenia 52.2; Thrombocytopenia 34.8; Hemoglobin reduction 10.9 **Non-hematologic AE:** Elevated AST 74; Elevated ALT 65.2; Hand-foot syndrome 54.3; Alopecia 41.3; Fatigue 39.1; Rash 34.8; Cancer sore 23.9; Anorexia 21.7; Gingivitis 17.4; Lose weight 17.4; Pneumonia 17.4; Voice hoarse 17.4; Diarrhea 15.2; Hypertension 15.2; Hypothyroidism 15.2; Proteinuria 15.2; Capillary hemangioma 15.2; Insomnia 13; Fever 13; Elevated bilirubin 13; Pain 13; Elevated CK-MB 10.9; Hypoalbuminemia 10.9; Constipation 8.7; Hemoglobinuria 8.7; Headache 8.7; Hydropericardium 6.5; Infusion reaction 6.5; Stomachache 6.5; Hyperthyroidism 4.3; Blurred vision 4.3	**Hematologic AE:** Leukopenia 8.7; Neutropenia 19.6; Thrombocytopenia 15.2; Hemoglobin reduction 4.3 **Non-hematologic AE:** Elevated AST 17.4; Elevated ALT 17.4; Hand-foot syndrome 6.5; Rash 4.3; Pneumonia 2.2; Hypothyroidism 2.2; Fever 2.2; Elevated bilirubin 6.5; Pain 2.2; Hydropericardium 2.2; Infusion reaction 6.5; Stomachache 6.5; Hyperthyroidism 4.3; Blurred vision 4.3	**Hematologic AE:** Leukopenia 4.3; Neutropenia 10.9; Thrombocytopenia 4.3	26

No	Drugs regiment and sample size	Adverse events (AEs; %)			References
		All Grade	Grade 3	Grade 4	
5	Eeribulin (0.88 mg/m²) combination with gemcitabine (1000 mg/m²) on a 21-day cycle AE was reported only in 84 patients.	**Hematologic AE:** Neutropenia 59.5; Anemia 42.9; Thrombocytopenia 30.9 **Non-hematologic AE:** Fatigue 66.6; Elevated ALT/AST 58.3; Nausea 36.9; Alopecia 23.8; Diarrhea 19; Constipation 17.9; Peripheral neuropathy 14.3; Rash 14.3; Vomiting 11.9; Oral mucositis 10.7	**Hematologic AE:** Neutropenia 16.7; Anemia 1.2; Thrombocytopenia 2.4 **Non-hematologic AE:** Fatigue 5.9; Elevated ALT/AST 25; Nausea 1.2; Alopecia 2.4; Constipation 1.2; Peripheral neuropathy 1.2; Rash 2.4; Vomiting 1.2	**Hematologic AE:** Neutropenia 7.1 **Non-hematologic AE:** Alopecia 1.2	27
6	Combination of eribulin and everolimus in three dosing levels: A1 (everolimus 5 mg daily; eribulin 1.4 mg/m²), A2 (everolimus 7.5 mg daily; eribulin 1.4 mg/m²), and B1 (everolimus 5 mg daily; eribulin 1.1 mg/m²) on 21 day cycle n = 27	**Hematologic AE:** Neutropenia 74; Leukopenia 70.4; Lymphopenia 44.4; Anemia 44.4; Thrombocytopenia 11.1; Febrile neutropenia 3.7 **Non-hematologic AE:** Abdominal pain 11.1; Constipation 11.1; Diarrhea 7.4; Dysphagia 3.7; Mucositis oral 33.3; Nausea 14.8; Oral pain 7.4; Vomiting 7.4; Fatigue 48.2; Failure to thrive 3.7; Infection 11.1; Urinary tract infection 7.4; Weight loss 11.1; Anorexia 14.8; Dehydration 3.7; Hyperglycemia 11.1; Hypoalbuminemia 11.1; Hypokalemia 11.1; Hyponatremia 3.7; Hypophosphatemia 7.4; Generalized muscle weakness 7.4; Paresthesia 7.4; Peripheral sensory neuropathy 11.1; Cough 7.4; Dyspnea 11.1; Pneumonitis 7.4; Sore throat 7.4; Alopecia 14.8; Skin and subcutaneous disorder 3.7; Hypertension 11.1; Lymphedema 3.7	**Hematologic AE:** Neutropenia 14.8; Leukopenia 18.5; Lymphopenia 22.2; Anemia 7.4; Thrombocytopenia 3.7; Febrile neutropenia 3.7 **Non-hematologic AE:** Abdominal pain 7.4; Diarrhea 3.7; Dysphagia 3.7; Mucositis oral 11.1; Oral pain 3.7; Vomiting 3.7; Fatigue 29.6; Failure to thrive 3.7; Infection 7.4; Anorexia 3.7; Dehydration 3.7; Hyperglycemia 3.7; Hypoalbuminemia 3.7; Hypokalemia 3.7; Hyponatremia 3.7; Hypophosphatemia 3.7; Generalized muscle weakness 7.4; Paresthesia 3.7; Peripheral sensory neuropathy 3.7; Cough 3.7; Sore throat 3.7; Skin and subcutaneous disorder 3.7; Lymphedema 3.7	**Hematologic AE:** Neutropenia 22.2; Leukopenia 7.4 **Non-hematologic AE:** -	28
7	Doxorubicin 60 mg/m² and paclitaxel 200 mg/m² for four cycles, followed by Eribulin 1.4 mg/m² for four cycles. n = 13	**Hematologic AE:** Anemia 54; Neutropenia 54; Leucopenia 15 **Non-hematologic AE** Peripheral neuropathy 54; Elevated ALT 46; Elevated ASR 31; Nausea 31; Myalgia 31; Asthenia 23; Vomiting 54; Mucosal inflammation 23; Conjunctivitis 46	**Hematologic AE:** Neutropenia 15 **Non-hematologic AE** Vomiting 8	**Hematologic AE:** - **Non-hematologic AE:** -	29
8	Olaparib was orally administered twice daily from level 1: 25 mg twice daily to level 7: 300 mg twice daily, with 1.4 mg/m² of eribulin on days 1 and 8. n =24 (phase II)	**Hematologic AE:** Leucopenia 100; Neutropenia 100; Anemia 91.7; Febrile neutropenia 33.3 **Non-hematologic AE:** Low albumin 20.8; Elevated AST 8.3; Elevated ALT 4.2; Elevated creatinine 25; Hair loss 41.7; Headache 4.2; Insomnia 12.5; Fatigue 12.5; Malaise 29.2; Weight loss 16.7; Pain 12.5; Musculoskeletal disorder 4.2; Oral mucositis 54.2; Dysgeusia 25; Nausea 50; Vomiting 33.3; Abdominal pain 4.2; Diarrhea 16.7; Constipation 12,5; Edema 4.2; Maculopapular rash 16.7; Peripheral sensory 41.7; Cough 16.7; Infection 25; Fever 33.3	**Hematologic AE:** Leucopenia 83.3; Neutropenia 83.3; Anemia 41.7; Febrile neutropenia 33.3 **Non-hematologic AE:** Diarrhea 4.2	**NA**	30

No	Drugs regiment and sample size	Adverse events (AEs; %)			References
		All Grade	Grade 3	Grade 4	
9	Eribulin monotherapy (1.23 mg/m² every 21 days iv). n = 252	**Hematologic AE:** Neutropenia 31; Leucopenia 27.4; Lymphopenia 6; Hemoglobinemia 20.6 **Non-hematologic AE:** Alopecia 30.6; Fatigue 65.1; Decrease appetite 32.5; Nausea and vomiting 23.4; Stomatitis 11.9; Taste abnormality 16.7; Elevated ALT/AST 8.3; Increased CK 0.4; Weakness 40.1; Fever 2.8; Peripheral neuropathy 31.3	**NA**	**NA**	24
10	Eribulin monotherapy (1.4 mg/m² every 21 days iv) is the fourth-line therapy. n = 47	**Hematologic AE:** Anemia 26.2; Neutropenia 31.2; Thrombocytopenia 6.4; Febrile neutropenia 2.1 **Non-hematologic AE:** Neuropathy 19.4; Emesis 10.6; Edema 7.1; Elevated liver enzymes 6.4; Stomatitis 6.3; Rash 2.1; Bleeding events 2.1	**NA**	**NA**	25

CONCLUSION

Eribulin monotherapy demonstrated a range of clinical efficacy in metastatic breast cancer, with overall survival reported between 10.8 and 17.6 months, progression-free survival between 2.8 and 3.2 months, and partial response rates from 21% to 58.7%. Notably, no complete responses were observed with monotherapy. In contrast, eribulin combination therapies exhibited a broader range of outcomes, including overall survival of 8.3 to 14.5 months, progression-free survival of 2.6 to 8.1 months, and partial response rates of 31.8% to 76%, with complete responses observed in 2.4% to 8% of patients. The safety profiles of eribulin monotherapy and combination therapies were generally comparable, with no reported Grade 5 adverse events in either group. Grade 4 adverse events included hematologic toxicities such as neutropenia, leukopenia, thrombocytopenia, and anemia, as well as non-hematologic toxicities such as peripheral neuropathy, fatigue, diarrhea, vomiting, dyspnea, back pain, arthralgia, febrile neutropenia, constipation, and general physical health deterioration. Common all-grade adverse events, occurring in over 50% of patients, comprised neutropenia, leukopenia, thrombocytopenia, asthenia, alopecia, elevated AST and ALT, hand-foot syndrome, fatigue, anemia, peripheral neuropathy, oral mucositis, and nausea. These findings highlight the clinical utility of eribulin, both as monotherapy and in combination, while underscoring the importance of careful monitoring for potential adverse events.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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