© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (4), 722-734, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1869_12.4.722

Review

Systematic review on the efficacy and safety of ixabepilone-based chemotherapy regimen in triple-negative breast cancer

[Revisión sistemática sobre la eficacia y seguridad del régimen de quimioterapia basado en ixabepilona en el cáncer de mama triple negativo]

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Abstract

Context: Triple-negative breast cancer (TNBC) has poor prognosis, high mortality, and recurrence rates. Ixabepilone or ixempra could be a promising agent for TNBC, especially in the taxane- and/or anthracycline-resistant population.

Aims: To evaluate the efficacy and safety of ixabepilone-based chemotherapy compared to ixabepilone-free chemotherapy in TNBC patients.

Methods: This review followed the preferred reporting items for systematic reviews and meta-analysis guidelines. The eligibility criteria included randomized control trials (RCTs) in 2013-2023 comparing ixabepilone-based with ixabepilone-free chemotherapy regimen in TNBC.

Results: This study identified four eligible RCTs. One study showed that patients treated with ixabepilone had a significant improvement in disease-free survival, had a better response, and a lower risk of disease recurrence compared to those treated with taxane-based regimen. However, two studies showed no differences in terms of overall survival (OS), disease-free survival, and pathological complete responses rates in both treatment arms. Ixabepilone addition to capecitabine significantly prolonged progression-free survival and objective response rate in TNBC patients, but did not significantly improve OS (n = 1).

Conclusions: The effectiveness and safety of ixabepilone-based chemotherapy versus ixabepilone-free treatment for triple-negative breast cancer (TNBC) patients vary among studies. More research is needed to better understand the effectiveness and safety of ixabepilone-based chemotherapy versus ixabepilone-free treatment in TNBC patients.

Keywords: effectivity; ixempra; toxicity; triple-negative breast cancer.

Resumen

Contexto: El cáncer de mama triple negativo (CMTN) tiene mal pronóstico, alta mortalidad y tasas de recurrencia. La ixabepilona o ixempra podría ser un agente prometedor para el CMTN, especialmente en la población resistente a taxanos y/o antraciclinas.

Objetivos: Evaluar la eficacia y seguridad de la quimioterapia basada en ixabepilona en comparación con la quimioterapia sin ixabepilona en pacientes con TNBC.

Métodos: Esta revisión siguió los ítems de informe preferidos para revisiones sistemáticas y guías de metaanálisis. Los criterios de elegibilidad incluyeron ensayos controlados aleatorios (ECA) en 2013-2023 que compararon el régimen de quimioterapia basado en ixabepilona con el régimen de quimioterapia libre de ixabepilona en TNBC.

Resultados: Este estudio identificó cuatro ECA elegibles. Un estudio mostró que los pacientes tratados con ixabepilona tuvieron una mejora significativa en la supervivencia libre de enfermedad, tuvieron una mejor respuesta y un menor riesgo de recurrencia de la enfermedad en comparación con los tratados con régimen basado en taxanos. Sin embargo, dos estudios no mostraron diferencias en términos de supervivencia global (SG), supervivencia libre de enfermedad y tasas de respuestas patológicas completas en ambos brazos de tratamiento. La adición de ixabepilona a la capecitabina prolongó significativamente la supervivencia libre de progresión y la tasa de respuesta objetiva en pacientes con CMTN, pero no mejoró significativamente la SG (n = 1).

Conclusiones: La eficacia y la seguridad de la quimioterapia basada en ixabepilona frente al tratamiento sin ixabepilona en pacientes con cáncer de mama triple negativo (CMTN) varían según los estudios. Se necesitan más investigaciones para comprender mejor la eficacia y la seguridad de la quimioterapia basada en ixabepilona frente al tratamiento sin ixabepilona en pacientes con CMTN.

Palabras Clave: cáncer de mama triple negativo; eficacia; ixempra; toxicidad.

ARTICLE INFO
Received: November 5, 2023.
Accepted: March 8, 2024.
Available Online: March 24, 2024.

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INTRODUCTION

Breast cancer is a type of tumor originating from the ductal or lobular epithelium of mammary tissue. Breast cancer is a preventable disease at an early stage (Gautama, 2022). Despite remarkable advancements in early detection and therapeutic approaches to breast cancer, it remains the most prevalent tumour reported globally. One out of all eight women worldwide suffered from breast cancer, and up to 15-20% of all breast cancer incidence was the most aggressive subtype, namely triple-negative breast cancer (TNBC) (Arnold et al., 2022; Yin et al., 2020).

Triple-negative breast cancer lacks expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 receptor (HER2) (Wolff et al., 2018). Triple-negative breast cancer has the worst prognosis compared to the other subtypes (Adiputra and Sudarsa, 2021). The mortality rate of TNBC is up to 40% in the first five years after diagnosis. The recurrence rate after TNBC surgery is reaching 25%. Patients suffering from TNBC experienced relapse in a shorter amount of time (19–40 months) than non-TNBC patients (35–67 months) on average. The overall mortality rate of TNBC patients three months after recurrence is significant, approaching 75% (Yin et al., 2020).

Given the lack of ER, PR, and HER2 expression, TNBC is insensitive to either endocrine therapy or molecular therapy. The combination of radiation and chemotherapy is the main therapeutic strategy to combat TNBC (Yin et al., 2020). Guidelines for advanced metastatic TNBC recommend sequential chemotherapy with or without targeted therapy whenever indicated for as long as there is a patient benefit (Ibrahim, 2021). Anthracycline/taxane-based regimens are generally accepted as the standard of therapy (Ge et al., 2022). However, increasing exposure to chemotherapy puts tumor cells under evolutionary pressure to develop genetic and non-genetic abilities to avoid drug reactions, resulting in resistance to certain drugs, including taxane and anthracycline (Ibrahim, 2021).

Ixabepilone, an epothilone agent (Fig. 1) (PubChem, 2023) straightly binds to β-tubulin subunits, suppresses dynamic instability, blocks the mitotic phase of the cell division cycle, and induces cell death (Ibrahim, 2021). Ixabepilone is a Food and Drug Administration (FDA)-approved treatment option for breast cancer patients, especially those with metastatic conditions and persistent disease progression after taxane and anthracycline therapy. This effect is due to the fact that ixabepilone is not a P-glycoprotein (P-gp) substrate and has a greater affinity for β-tubulin than taxanes (Ibrahim, 2021). In addition, ixabepilone is also active in β-III tubulin overexpression cells, which is associated with resistance to taxane and vinca alkaloids (Li et al., 2017).

Ixabepilone has received approval for its use as a standalone treatment for metastatic or locally advanced breast cancer in individuals who have not responded to anthracycline, a taxane, and capecitabine. Its unique properties make it effective in bypassing typical resistance mechanisms, making it a preferred option for patients facing recurrent disease. Ixabepilone possesses a thoroughly characterized safety profile, featuring mild-to-moderate peripheral neuropathy that can be alleviated through dose adjustments (Ibrahim, 2021). Nevertheless, there is a lack of studies evaluating ixabepilone-based regimen for TNBC patients. In this study, ixabepilone-based chemotherapy is expected to demonstrate comparable or improved clinical efficacy and safety for TNBC patients when compared to ixabepilone-free regimens. This systematic review of randomized controlled trials (RCTs) attempts to better understand the efficacy and safety of ixabepilone-based chemotherapy compared to ixabepilone-free chemotherapy in TNBC patients.

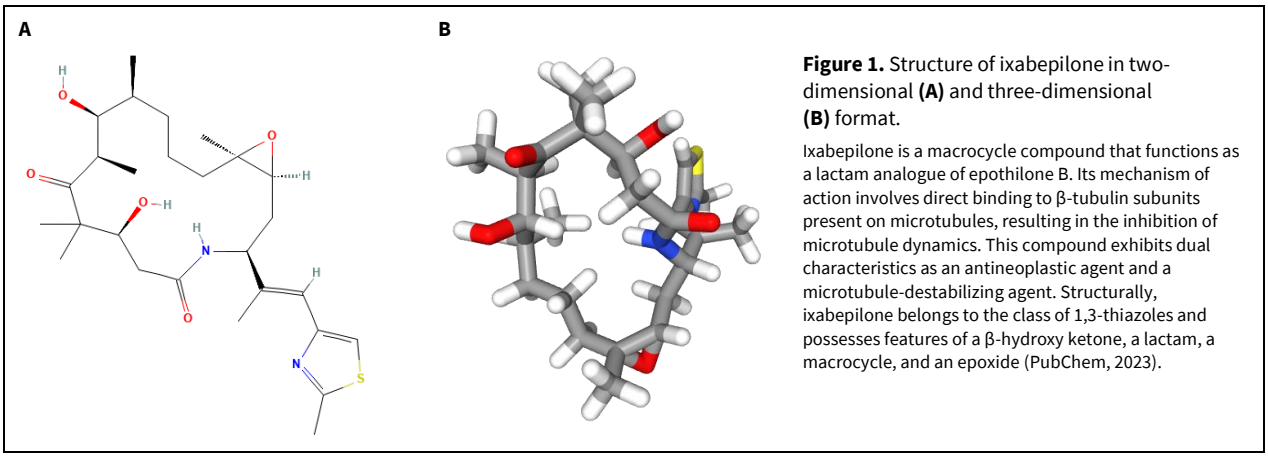

Figure 1. Structure of ixabepilone in two-dimensional **(A)** and three-dimensional **(B)** format.

Ixabepilone is a macrocycle compound that functions as a lactam analogue of epothilone B. Its mechanism of action involves direct binding to β-tubulin subunits present on microtubules, resulting in the inhibition of microtubule dynamics. This compound exhibits dual characteristics as an antineoplastic agent and a microtubule-destabilizing agent. Structurally, ixabepilone belongs to the class of 1,3-thiazoles and possesses features of a β-hydroxy ketone, a lactam, a macrocycle, and an epoxide (PubChem, 2023).

Table 1. PICO criteria for this review.

Population	Patients with TNBC (early-stage TNBC without metastasis, grade II/III, anthracycline-resistant and/or taxane-resistant, invasive TNBC stage T2-3, N0-3, and M0)
Intervention	Ixabepilone treatment that is either given following or prior to other chemotherapy medications (ixabepilone-based neoadjuvant chemotherapy)
Comparison	Other chemotherapy/ ixabepilone-free neoadjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel, standard FEC followed by docetaxel, or capecitabine monotherapy)
Outcome	Several pairs of parameters are used to evaluate effectiveness, including as disease-free survival (DFS), overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), objective response rate (ORR), and pathological complete response (pCR). Safety is determined by monitoring adverse effects.

MATERIAL AND METHODS

Eligibility criteria

To be further analyzed in this review, eligible studies had to meet all the following inclusion criteria: (i) phase II or III RCTs; (ii) RCTs including TNBC patients who received ixabepilone-based neoadjuvant chemotherapy in the experimental arm and ixabepilone-free neoadjuvant chemotherapy in the control arm (for RCTs involving patients with other than TNBC subtypes, only those with available results in the TNBC cohort were included); (iii) studies with available information on efficacy measured either by, but not limited to, disease-free survival (DFS), overall survival (OS), distant metastasis-free survival (DMFS), progression-free survival (PFS), objective response rate (ORR), or pathological complete response (pCR) in the experimental and control arms to estimate the odds ratio (OR) and 95% confidence intervals (CI). Exclusion criteria were: (i) non-RCTs conducted to evaluate the role of ixabepilone-based neoadjuvant chemotherapy in TNBC patients; (ii) RCTs investigating ixabepilone-based neoadjuvant chemotherapy in patients with other TNBC subtypes; (iii) ongoing studies with results not presented or published at the time of the literature search; (iv) study exploring ixabepilone-based neoadjuvant chemotherapy in both arms. Table 1 shows the PICO criteria for this review.

Information sources

Systematic searches were conducted on databases including EBSCO, Nature, Cochrane, and Wiley. The study involved a systematic review of existing randomized controlled trials (RCTs) that assessed the activity, efficacy, and safety of neoadjuvant chemotherapy with ixabepilone (experimental arm) versus ixabepilone-free regimens (control arm) in patients with triple-negative breast cancer (TNBC).

Search strategy

Eligible studies were identified by a systematic literature search of the EBSCO, Nature, Cochrane, and Wiley databases, with language restricted in English, and published from 2013 until 2023. Keywords used in this searching strategy were ("triple negative breast cancer" OR "TNBC") AND ("treatment*" OR "management*" OR "therap*") AND ("ixabepilone" OR "ixempra" OR "ixa"). Specific keywords and free text terms were combined with Boolean operators. Relevant articles were cross-referenced to confirm that all possible pertinent records were identified.

Selection process

A systematic literature review was made according to the preferred reporting items for systematic reviews and a meta-analysis (PRISMA) checklist and flow diagram to ensure the quality of this study. The systematic literature search was carried out independently by two authors (HAH and MRA), and any discrepancies were solved by discussion with all authors. This systematic review was conducted according to the PRISMA guidelines (Moher et al., 2009). The selection process comprises four primary stages: identification, screening, eligibility, and inclusion. Initially, duplicate studies were eliminated during the identification phase, followed by screening based on title and abstract. Subsequently, the eligibility of each study was evaluated, and its full text was reviewed to determine whether it met the inclusion criteria. Studies meeting these criteria were included for further synthesis.

Data collection and synthesis process

The following variables were extracted from all the included RCTs, if available: name of the trial, year of publication, study design, number and characteristics of randomized patients, intervention protocol, number of patients with DFS, OS, DMFS, PFS, ORR, and pCR, and adverse events in the ixabepilone-based and ixabepilone-free neoadjuvant chemotherapy arms. Data extraction was done by two reviewers (HAH and MRA), and any discrepancies between reviewers

were discussed, and ATE, EN, SP, and EW were consulted. Information from the selected articles was manually gathered, organized into tables, and subjected to qualitative synthesis.

Data items

The extracted data items obtained from the reviews encompassed details such as study population and intervention characteristics, type of comparison, primary and secondary outcomes, study design, and the conclusions drawn by the authors. The primary objective of this systematic review was to compare the activity, efficacy, and safety of ixabepilone-based versus ixabepilone-free neoadjuvant chemotherapy in TNBC patients in terms of either DFS, OS, DMFS, PFS, ORR, or pCR, and adverse events.

Bias risk assessment

The study quality was evaluated by two reviewers (HAH and MRA), who evenly portioned the study using Cochrane risk of bias tools for the RCT study. Reviewer discrepancies were discussed, and ATE, EN, SP, and EW were consulted.

RESULTS

Study selection

This systematic literature review search identified 98 records from the searching process (Fig. 2). After the exclusion of duplicate records (n = 3), irrelevant articles (n = 86), and unavailable full text (n = 5), there were four eligible RCTs included in qualitative analysis. Several RCTs might appear to meet the inclusion criteria but then were excluded because they used chemotherapy other than ixabepilone (Tripathy et al., 2019), comparing ixabepilone-based therapy in both arms (Rodriguez et al., 2014), did not do subgroup analysis if they involved metastatic breast cancer patients (not only TNBC patients) (Jassem et al., 2012), or was a noncomparative study (Osborne et al., 2018).

Study characteristics

The overall characteristics of the four studies included in the analysis are summarized in Table 2. All but one RCT (Saura et al., 2013) was phase III clinical trials. Doxorubicin-cyclophosphamide (AC) chemotherapy (Saura et al., 2013; Yardley et al., 2017), fluorouracil-epirubicin-cyclophosphamide (FEC) chemotherapy (Campone et al., 2018) or capecitabine-based neoadjuvant chemotherapy (Rugo et al., 2018) were used in both arms. Three studies compared ixabepilone-based to taxane-based therapy (Campone et al., 2018; Saura et al., 2013; Yardley et al., 2017), while the remaining study compared regimen containing ixabepilone and capecitabine to capecitabine alone (Rugo et al., 2018). All patients participating in all but one RCT (Saura et al., 2013) were TNBC-confirmed patients with specific characteristics based on tumor stage (n = 2), chemoresistance (n = 1), and invasiveness (n = 1). A study exploring breast cancer patients should do subgroup analysis on TNBC patients to meet the inclusion criteria.

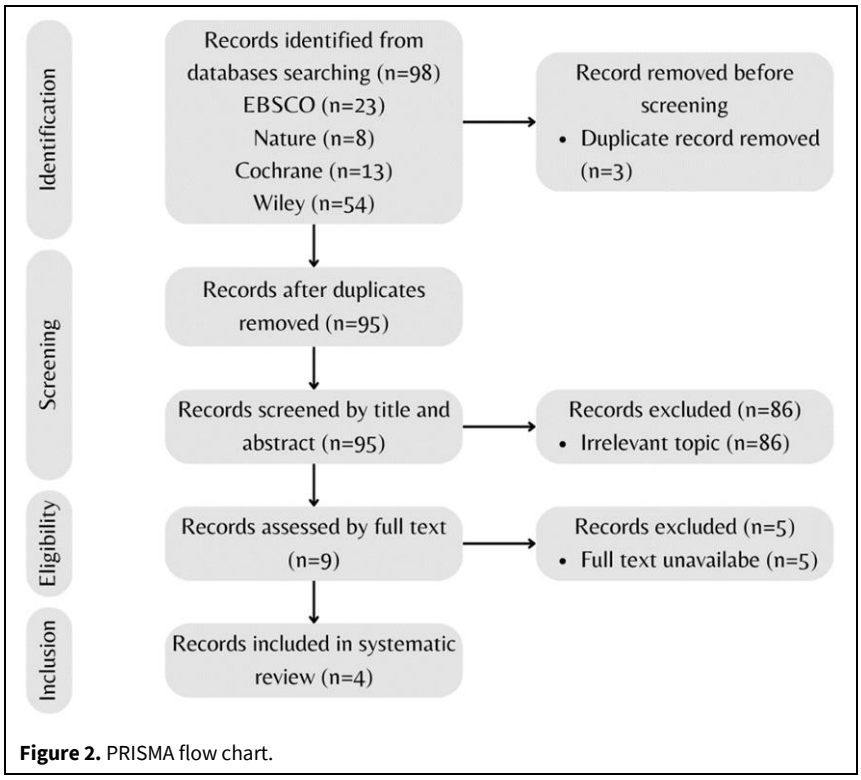

Figure 2. PRISMA flow chart.

Table 2. Characteristic of study.

Author (Year)	Design	Primary outcome	Secondary outcome	Treatment arms	Comparison arms	TNBC (N)	TNBC characteristic
Yardley et al. (2017)	Phase III	DFS at 3 years and 5 years	OS at 3 years and 5 years; Safety	Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 administered for 4 cycles of 21 days each, followed by ixabepilone at 40 mg/m^2 given for 4 cycles of 21 days each.	Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 administered for 4 cycles of 21 days each, followed by paclitaxel at 80 mg/m^2 weekly for 12 weeks	614	Early-stage TNBC without metastasis
Campone et al. (2018)	Phase III	DFS, OS	DMFS; Safety	Standard FEC (3 cycles) followed by 3 cycles of ixabepilone (40 mg/ m^2)	Standard FEC (3 cycles) followed by 3 cycles of docetaxel (100 mg/m^2)	762	Grade II/III node (-) TNBC
Rugo et al. (2018)	Phase III	OS (048) and PFS (046)	ORR, OS, safety (046); ORR, PFS, safety (048)	Ixabepilone 40 mg/m^2 (3-hour intravenous infusion, day 1), plus oral capecitabine 1000 mg/m^2 twice daily (days 1-14)	Capecitabine alone is 1250 mg/m^2 twice daily (days 1-14), every 3 weeks.	433	Anthracycline-resistant and/or taxane-resistant TNBC
Saura et al. (2013)	Phase II	pCR	ORR; Safety	Four cycles of doxorubicin (60 mg/m^2 intravenously) and cyclophosphamide (600 mg/m^2 intravenously) every 3 weeks (Q3W) to ixabepilone (40 mg/m^2, 3-hour infusion) Q3W for four cycles.	Four cycles of doxorubicin (60 mg/m^2 intravenously) and cyclophosphamide (600 mg/m^2 intravenously) every 3 weeks (Q3W) followed by paclitaxel (80 mg/m^2, 1-hour infusion) weekly for 12 weeks	144	Invasive TNBC stage T2-3, N0-3, and M0

With the exception of one RCT [Saura et al., 2013], all the other trials conducted were phase III RCTs. In both treatment groups, either AC chemotherapy (Saura et al., 2013; Yardley et al., 2017), FEC chemotherapy (Campone et al., 2018), or capecitabine-based neoadjuvant chemotherapy (Rugo et al., 2018) were administered. Three studies compared ixabepilone-based therapy to taxane-based therapy (Campone et al., 2018; Saura et al., 2013; Yardley et al., 2017), while the remaining study compared a regimen containing ixabepilone and capecitabine to capecitabine alone (Rugo et al., 2018). All participants in the majority of the RCTs except one study (Saura et al., 2013) were confirmed TNBC patients with specific characteristics related to tumor stage (n = 2), chemoresistance (n = 1), and invasiveness (n = 1). Subgroup analysis of TNBC patients should be conducted in studies exploring breast cancer to fulfill the inclusion criteria. DFS: disease-free survival; DMFS: disease metastatic-free survival; FEC: fluorouracil-epirubicin-cyclophosphamide; ORR: objective response rate; OS: overall survival; pCR: pathological complete responses; PFS: progression-free survival, TNBC: triple-negative breast cancer; Q3W: every three weeks.

The outcomes were explained by four studies using parameters to measure the efficacy of the regimen differs among studies, such as DFS (n = 2), OS (n = 3), DMFS (n = 1), PFS (n = 1), ORR (n = 1), and pCR (n = 1). Disease-free survival was defined as the time elapsed between the date of randomization and the date of relapse (local, regional, or distant), invasive contralateral breast cancer, or death from any cause, whichever came first. Overall survival was defined as the period that elapsed between the randomization date and the date of death from whatever cause. Distant metastatic-free survival was designated as the gap between the date of randomization and the date of metastatic relapse. Progression-free survival was defined as the amount of time that a patient lives with cancer without the worsening disease during and after therapy. Objective response rate was stated as an assessment of tumor burden (TB) following a specific treatment in patients with solid tumors. The pCR rate referred to the percentage of patients with no histologic evidence of residual invasive carcinoma in the breast and axillary lymph nodes, regardless of the presence or absence of ductal carcinoma *in situ*.

Risk of bias in studies

Four eligible studies were evaluated for their quality and risk of bias. In this screening, the overall bias risk of each study was low. Therefore, these four studies were included in the review process. Details of risk assessment are mentioned in Table 3. While all the studies had a relatively low risk of bias, only one study reported a risk of bias due to missing results that can arise from reporting biases. In that study, there are mentions of missing data in certain variables such as lymphocytic infiltrate, CK5/6, CK14, and

Table 3. Risk of bias assessment using Cochrane risk of bias tools.

Author (year)	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participant and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Overall bias risk
Campone et al. (2018)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	Low risk	57% low risk
Rugo et al. (2018)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	Low risk	57% low risk
Yardley et al. (2017)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	Low risk	57% low risk
Saura et al. (2013)	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	42% low risk

Four eligible studies were undergoing assessment to determine their quality and potential for bias. During this evaluation, it was found that all four studies exhibited a low risk of bias (>40% low risk). As a result, these studies were deemed suitable for inclusion in the review process.

EGFR (Campone et al., 2018). Missing data can introduce bias if the missingness is not completely at random and is related to the outcome or other variables of interest. Nevertheless, it's not directly related to the studied variables, so it is still considered low risk.

Results of individual studies

In this study, qualitative synthesis was done to evaluate the efficacy of ixabepilone-based chemotherapy for TNBC patients. The results of individual studies are summarized in Table 4. A study done by Campone et al. (2018) exhibited significant DMFS improvement in ixabepilone-treated patients (HR for DMFS = 0.58; 95% CI = 0.37-0.90; p=0.014). There was also a better response in TNBC patients treated with ixabepilone-based treatment compared to taxane-based treatment using docetaxel, proven by a 23% reduction in the risk of disease recurrence in the intervention group, although it was not statistically significant (HR for DFS = 0.77; 95% CI = 0.53-1.11). Despite the satisfactory result in ixabepilone-arm, OS (HR = 0.88; 95% CI = 0.58-1.35; p=0.585) and DFS (p=0.168) rates were comparable in both arms (Campone et al., 2018). The study conducted by Yardley et al. (2017) stated that at a median follow-up of 48 months, the 3- and 5-year DFS rates for patients in the AC/ixabepilone arm were 88.6 and 87.1%, while for patients in the AC/paclitaxel arm were 88.8 and 84.7%, respectively (HR = 0.92, 95% CI; p=0.70). The 3- and 5-year OS rates were 92.4 and 89.7% for AC/ixabepilone and 93.8 and 89.6% for patients in the AC/paclitaxel arm, respectively (HR = 1.10, p=0.71). There was no significant difference in both arms regarding the DFS rate (HR = 0.92, p=0.70) and OS rate (HR = 1.10, p=0.71) (Yardley et al., 2017). These findings were in line with Saura et al. (2013), which found no significant difference in pCR (34.2% vs. 40.85%; 95% CI; p>0.05) and ORR (45.2% vs. 53.5%; 95% CI; p>0.05) between treatments in subgroups defined by ER, HER-2, or TNBC status (Saura et al., 2013).

Rugo et al. (2018) showed that the addition of ixabepilone to capecitabine significantly prolonged median PFS from 1.7 months (95% CI, 1.5-2.4 months) to 4.2 months (95% CI, 3.6-4.4 months) in pooled subset of TNBC patients corresponding to a 36% decrease in the projected likelihood of disease progression (HR, 0.64; 95% CI, 0.52-0.78; p<0.0001). Also, in the pooled study, the ORR and median OS was 31% (95% CI, 24.4-38.0%; 3% complete response) and 10.4 months, respectively, in the ixabepilone plus capecitabine group compared with 15% (95% CI, 10.4-20.5%; 1% complete response) and 9.0 months respectively in the capecitabine only group. However, the difference in OS between treatment arms was not statistically significant (HR = 0.88; 95% CI = 0.72-1.08; p=0.1802). Similar findings were found in the individual studies where the PFS (Study 046: 4.1 vs. 1.6 months; HR = 0.62; 95% CI = 0.46-0.83, and Study 048: 4.2 vs. 1.8 months; HR = 0.63; 95% CI = 0.48-0.84), ORR (Study 046: 35% vs. 11%, respectively; Study 048: 27% vs. 18%, respectively), and OS (Study 046: 9.3 vs. 7.3 months, respectively; HR = 0.83; 95% CI = 0.61-1.13; Study 048: 11.5 vs. 10.1 months, respectively; HR = 0.90; 95% CI = 0.69-1.19) were improved in ixabepilone-based versus ixabepilone-free arm (Rugo et al., 2018).

The Food and Drug Administration (FDA) has authorized ixabepilone as a treatment choice for breast cancer patients who experience disease progression after anthracycline and taxane therapy (Li et al., 2017). However, it is essential to take into consideration a few adverse effects of ixabepilone usage. All patients experienced at least one side effect (Campone et al., 2018; Yardley et al., 2017). The side effects observed in all clinical trials evaluated in this review can be categorized based on the type of side effect (Table 5).

The most common treatment-related adverse events linked to ixabepilone included sensory neuropathy, fatigue, and neutropenia (Ibrahim, 2021). Peripheral neuropathy (PN) was a typical side effect of microtubule-stabilizing drugs, and its effect could be quite significant in treatment, leading to the most frequent reasons for dose reduction and premature treatment discontinuations (Saura et al., 2013; Yardley et al., 2017). Fortunately, PN symptoms could be alleviated through dose reductions of ixabepilone, and after such adjustments, the resolution of PN symptoms typically begins (Ibrahim, 2021; Rugo et al., 2018).

Table 4. Efficacy of ixabepilone-based chemotherapy and ixabepilone-free chemotherapy.

Author (year)	Ixabepilone arm	Comparison arm
Yardley et al. (2017)	DFS rate - 3-years DFS rate 88.6% (95% CI = 84.3-91.8) at 48 months - 5-years DFS rate 87.1% (95% CI = 82.6-90.5) at 48 months OS rate - 3-years OS rate 92.4% (95% CI = 86.9-93.7) at 48 months - 5-years OS rate 89.7% (95% CI = 85.5-92.7) at 48 months	DFS rate - 3-years DFS rate 88.8% (95% CI = 84.6-91.9) at 48 months - 5-years DFS rate 84.7% (95% CI = 79.7-88.6) at 48 months OS rate - 3-years OS rate 93.8% (95% CI = 90.2-96.1) at 48 months - 5-years OS rate 89.6% (95% CI = 85.0-92.9) at 48 months
Campone et al. (2018)	HR for DMFS = 0.58; 95% CI = 0.37-0.90; p=0.014 HR for DFS = 0.77; 95% CI = 0.53-1.11; p=0.168 HR for OS = 0.88; 95% CI = 0.58-1.35; p=0.585	-
Rugo et al. (2018)	OS - Pooled analysis: Median OS 10.4 months (95% CI = 9.1-11.8; *P*<0.0001) - Individual analysis : - Study 046: 9.3 months; HR = 0.83; 95% CI = 0.61–1.13 - Study 048: 11.5 months; HR = 0.90; 95% CI = 0.69–1.19 PFS - Pooled analysis: Median PFS 4.2 months (95% CI = 3.6-4.4; p<0.0001) - Individual analysis: - Study 046: 4.1 months; HR = 0.62; 95% CI = 0.46–0.83 - Study 048: 4.2 months; HR = 0.63; 95% CI 0.48-0.84 ORR - Pooled analysis: 31% (95% CI, 24.4%-38.0%; 3% complete response) - Individual analysis: - Study 046: 35% - Study 048: 27%	OS - Pooled analysis: Median OS 9.0 months (95% CI = 6.7-10.6; p<0.0001) - Individual analysis: - Study 046: 7.3 months; HR = 0.83; 95% CI = 0.61–1.13 - Study 048: 10.1 months; HR = 0.90; 95% CI = 0.69–1.19 PFS - Pooled analysis: Median PFS 1.7 months (95% CI = 1.5-2.4; p<0.0001) - Individual analysis: - Study 046: 1.6 months; HR = 0.62; 95% CI = 0.46 – 0.83 - Study 048: 1.8 months; HR = 0.63; 95% CI = 0.48-0.84 ORR - Pooled analysis: 15% (95% CI, 10.4%-20.5%; 1% complete response) - Individual analysis: - Study 046: 11% - Study 048: 18%
Saura et al. (2013)	ORR: 45.2% (n = 73; 95% CI; p>0.05) pCR: 34.2% (n = 73; 95% CI; p>0.05)	ORR: 53.5% (n = 71; 95% CI; p>0.05) pCR: 40.8% (n = 71; 95% CI; p>0.05)

Ixabepilone-based therapy showed favorable outcomes in terms of DMFS and PFS, but no significant differences were observed in OS and DFS rates between treatment arms in these studies. CI: confidence interval; DFS: disease-free survival; DMFS: distant metastatic free survival; FEC: fluorouracil-epirubicin-cyclophosphamide; HR: hazard ratio; ORR: objective response rate; OS: overall survival; pCR: pathological complete responses; PFS: progression-free survival; TNBC: triple-negative breast cancer; Q3W: every three weeks.

Table 5. Safety profile of ixabepilone-based chemotherapy and ixabepilone-free therapy.

Adverse events	Author (year)	Ixabepilone arm (affected/at risk; %)		Comparison arm (affected/at risk; %)	
		Grade 3/4 AE's	All Grade AE's	Grade 3/4 AE's	All Grade AE's
Blood and lymphatic system disorders					
Febrile neutropenia	Yardley et al. (2017)	3/305; 1%	3/305; 1%	1/304; 0.3%	1/304; 0.3%
	Campone et al. (2018)	39/353; 11%	40/353; 11%	68/404; 17%	69/404; 17%
	Rugo et al. (2018)	8/209; 3.8%	N/A	3/226; 1.3%	N/A
Neutropenia	Yardley et al (2017)	29/305; 9.6%	62/305; 20.3%	16/304; 5.2%	64/305; 21%
	Campone et al. (2018)	219/353; 62%	306/353; 86%	275/404; 69%	330/404; 83%
	Rugo et al. (2018)	38/209; 18.2%	N/A	2/226; 0.9%	N/A
	Saura et al. (2013)	59/145; 41.3%	110/145; 76.9%	12/144; 8.4%	77/144; 53.8%
Anemia	Yardley et al. (2017)	3/305; 1%	62/305; 20.3%	1/304; 0.3%	85/304; 27.9%
	Campone et al. (2018)	9/353; 3%	275/353; 79%	4/404; 1%	327/404; 82%
	Rugo et al. (2018)	7/209; 3.3%	N/A	3/226; 1.3%	N/A
	Saura et al. (2013)	2/145; 1.4%	130/145; 90.9%	7/144; 4.9%	135/144; 94.4%
Leukopenia	Yardley et al. (2017)	10/305; 3.3%	28/305; 9.2%	9/304; 2.9%	58/304; 19%
	Rugo et al. (2018)	17/209; 8.1%	N/A	1/226; 0.4%	N/A
	Saura et al. (2013)	52/145; 36.4%	111/145; 77.6%	7/144; 4.9%	111/144; 77.6%
Thrombocytopenia	Yardley et al. (2017)	7/305; 2.3%	18/305; 5.9%	-	6/304; 2%
	Campone et al. (2018)	8/353; 3%	75/353; 22%	2/404; <1%	74/404; 19%
	Rugo et al. (2018)	3/209; 1.4%	N/A	2/226; 0.9%	N/A
	Saura et al. (2013)	1/145; 0.7%	34/145; 23.8%	1/144; 0.7%	9/144; 6.3%
Cardiac disorders					
General cardiac disorders	Campone et al. (2018)	4/353; 1%	33/353; 9%	-	32/404; 8%
Congenital, familial, and genetic disorders					
Hand-foot syndrome	Rugo et al. (2018)	31/209; 14.8%	N/A	35/226; 15.5%	N/A
Gastrointestinal disorders					
Nausea/vomiting	Yardley et al. (2017)	3/305; 1%	53/305; 17.4%	-	43/304; 14.1%
	Saura et al. (2013)	1/145; 0.7%	25/145; 17.2%	-	17/144; 11.8%
	Campone et al. (2018)	20/353; 6%	283/353; 81%	15/404; 4%	327/404; 82%
Constipation	Yardley et al. (2017)	1/305; 0.3%	42/305; 13.7%	-	33/304; 10.9%
Diarrhea	Yardley et al. (2017)	5/305; 1.6%	44/305; 14.4%	2/304; 0.6%	40/304; 13.1%
	Rugo et al. (2018)	10/209; 4.8%	N/A	15/226; 6.6%	N/A
	Saura et al. (2013)	2/145; 1.4%	25/145; 17.2%	2/144; 1.4%	18/144; 12.5%
Stomatitis	Rugo et al. (2018)	4/209; 1.9%	N/A	1/226; 0.4%	N/A
General disorders					
Fatigue	Yardley et al. (2017)	11/305; 3.6%	90/305; 32.8%	12/304; 3.9%	113/304; 37.1%
	Rugo et al. (2018)	24/209; 11.5%	N/A	9/226; 4.0%	N/A
	Saura et al. (2013)	5/145; 3.4%	27/145; 18.6%	2/145; 1.4%	24/145; 16.7%
Fever	Campone et al. (2018)	1/353; <1%	85/353; 21%	-	59/404; 17%
Mucositis	Campone et al. (2018)	11/353; 3%	173/353; 49%	12/404; 3%	211/404;53%
Edema	Campone et al. (2018)	-	68/353; 17%	1/404; <1%	47/404; 13%

Table 5. Safety profile of ixabepilone-based chemotherapy and ixabepilone-free therapy (continued…)

Adverse events	Author (year)	Ixabepilone arm (affected/at risk; %)		Comparison arm (affected/at risk; %)	
		Grade 3/4 AE's	All Grade AE's	Grade 3/4 AE's	All Grade AE's
Hepatobiliary disorders					
Hepatic disorders	Campone et al. (2018)	-	14/353; 4%	2/404; <1%	31/404; 9%
Infections and infestations					
Infection	Campone et al. (2018)	12/353; 3%	111/353; 31%	11/404; 3%	121/404; 31%
Musculoskeletal and connective tissue disorders					
Bone pain	Yardley et al. (2017)	6/305; 2%	39/305; 12.8%	-	13/304; 4.3%
	Saura et al. (2013)	7/145; 4.8%	28/145; 19.3%	-	6/144; 4.2%
Musculoskeletal pain	Saura et al. (2013)	1/145; 0.7%	15/145; 10.3%	1/144; 0.7%	6/144; 4.2%
Arthralgia	Yardley et al. (2017)	9/305; 3%	77/305; 25.3%	3/304; 1%	48/304; 15.8%
	Rugo et al. (2018)	12/209; 5.7%	N/A	2/226; 0.9%	N/A
	Saura et al. (2013)	1/145; 0.7%	34/145; 23.4%	-	14/144; 9.7%
Myalgia	Yardley et al. (2017)	11/305; 3.6%	45/305; 14.7%	-	35/304; 11.5%
	Rugo et al. (2018)	16/209; 7.7%	N/A	3/226; 1.3%	N/A
	Saura et al. (2013)	4/145; 2.8%	41/145; 28.3%	1/144; 0.7%	19/144; 13.2%
Nervous system disorders					
Peripheral motor neuropathy	Campone et al. (2018)	5/353; 1%	47/353; 13%	1/404; <1%	34/404; 9%
	Rugo et al. (2018)	11/209; 5.3%	N/A	1/226; 0.4%	N/A
Peripheral sensory neuropathy	Campone et al. (2018)	12/353; 3%	152/353; 43%	-	100/404; 25%
	Rugo et al. (2018)	26/209; 12.4%	N/A	1/226; 0.4%	N/A
Neuropathy peripheral	Yardley et al. (2017)	25/305; 8.2%	154/305; 50.5%	19/304; 6.3%	190/305; 62.5%
	Rugo et al. (2018)	33/209; 15.8%	N/A	2/226; 0.9%	N/A
	Saura et al. (2013)	6/145; 4.1%	63/145; 43.4%	5/144; 3.5%	72/144; 50.0%
Dysgeusia	Yardley et al. (2017)	-	39/305; 12.8%	-	27/304; 8.9%
Skin and subcutaneous tissue disorders					
General cutaneous disorders	Campone et al. (2018)	7/353; 1%	101/353; 29%	10/404; 3%	159/404; 40%
Alopecia	Yardley et al. (2017)	-	31/305; 10.2%	-	32/304; 10.5%
Nail disorder/ ungueal	Yardley et al. (2017)	-	10/305; 3.3%	-	31/304; 10.2%
	Campone et al. (2018)	4/353; 1%	101/353; 25%	3/404; <1%	61/404; 17%

The primary causes for not getting the recommended dosages of therapy, according to Saura et al. (2013), were toxicity and worsening illness. The ixabepilone group had a greater rate of delayed treatment, dosage decrease, and discontinuation due to toxicity than the paclitaxel arm. Eighteen patients (12.9%) in the ixabepilone arm and 18 patients (12.6%) in the paclitaxel arm had one or more doses reduced mainly to adverse events and peripheral neuropathy (Saura et al., 2013).

Rugo et al. (2018) discovered that patients who got ixabepilone with capecitabine had a greater rate of dosage reduction owing to toxicity (43.1%) than those who received capecitabine alone (22.1%). Dose delays due to toxicity were also more prevalent in individuals who got ixabepilone + capecitabine (2.4%) compared to capecitabine alone (0.4%) (Rugo et al., 2018). On the other hand, the study by Yardley et al. (2017) reported that patients receiving paclitaxel (as a comparison arm) had greater peripheral neuropathy, dosage adjustments, and study termination due to toxicity than those receiving ixabepilone. During adjuvant therapy, 61 patients (20%) on the ixabepilone arm and 85 patients (28%) on the paclitaxel arm required at least one dosage decrease (Yardley et al., 2017).

Treatment was delayed in 249 patients (33%), according to Campone et al. (2018), with a slightly lower rate in the comparison arm (30%) compared to the ixabepilone arm (37%). Hematological toxicity (40%) and patient requests (14%) were the most common causes of treatment delays (Campone et al., 2018). One study indicated that ixabepilone may possess a better safety profile compared to comparison therapy, as evidenced by lower rates of dose reductions, delayed therapy, and discontinuation due to toxicity (Yardley et al., 2017). Conversely, Campone et al. (2018), Rugo et al. (2018), and Saura et al. (2013) found that the safety profile was better in the comparison arm than in the ixabepilone arm (Campone et al., 2018; Saura et al., 2013; Rugo et al., 2018).

DISCUSSION

This is the first systematic literature review assessing the efficacy and safety of ixabepilone-based chemotherapy as a neoadjuvant treatment in TNBC patients. This systematic review indicates that ixabepilone has comparable effectiveness to taxanes such as docetaxel or paclitaxel, particularly as an adjuvant treatment after AC and FEC therapy in patients with TNBC thus can be beneficial in the taxane-refractory population (Campone et al., 2018; Rugo et al., 2018; Saura et al., 2013; Yardley et al., 2017). In a previously randomized phase 2 trial, substituting weekly ixabepilone or nabpaclitaxel for paclitaxel did not improve efficacy and resulted in a slight increase in toxicity in metastatic breast cancer (Rugo et al., 2013). A randomized phase 2 neoadjuvant trial assessed the identical regimens utilized in the adjuvant study reported here and found no difference in pCR rate between AC/ixabepilone and AC/paclitaxel in early-stage breast cancer (Saura et al., 2013). The PACS-08 study compared three cycles of ixabepilone with docetaxel as adjuvant therapy in patients with TNBC, following four courses of regular FEC, and failed to provide evidence of DFS and OS improvement for the ixabepilone regimen (Campone et al., 2016). This finding aligns with the study of Yardley et al. (2017). Nonetheless, the PACS-08 study found that ixabepilone had a substantial benefit for DMFS (HR = 0.49; 95% CI 0.30-0.78, p=0.003) (Campone et al., 2016).

In the case of anthracycline- and taxane-resistant, capecitabine can also be one of the treatment options for TNBC. However, capecitabine and nucleobase/nucleoside analogs that interrupt DNA replication also gain more concern due to clinical resistance. It may reflect the number of cells in the S phase of the cell cycle within the tumor, creating a restricted treatment window. Higher doses of these medications or other measures to extend the therapeutic window, on the other hand, are frequently linked with unacceptable toxicity. Ixabepilone is beneficial in this situation since it also exhibited synergistic effects with capecitabine to prolong PFS and alleviate response in patients with anthracycline- and/or taxane-refractory advanced TNBC with manageable safety profile (Rugo et al., 2018).

The clinical trial therapy regimen was successfully delivered and generally well-tolerated, as evidenced by a completion rate of therapy above 80% (Campone et al., 2016; Saura et al., 2013; Yardley et al., 2017). The adverse effects that occur are also manageable with dosage reduction and delayed therapy (Rugo et al., 2018). Three of the four clinical trials participating in the study state that the comparison arm had a better safety profile than the ixabepilone arm based on the incidence of dose reductions, delayed treatment, and discontinuation due to toxicity (Campone et al., 2018; Rugo et al., 2018; Saura et al., 2013). Peripheral neuropathy (PN) was discovered and was the most prevalent adverse effect in three out of four investigations (Rugo et al., 2018; Saura et al., 2013; Yardley et al., 2017), where mild-to-moderate PN may be reversed using dosage adjustment approaches (Ibrahim, 2021).

Triple-negative breast cancer is an endocrine therapy-insensitive breast cancer, leaving chemotherapy as the current best treatment option (Furlanetto and Loibl, 2020). Standard chemotherapy currently used for TNBC patients are anthracycline- and/or taxane-based regimens with taxanes being the first-line therapeutic alternative for TNBC (Lim et al., 2014). However, recurrent exposure to chemotherapy results in evolutionary stress towards cancer cells and eventually acquires genetic and non-genetic features resisting drug action. P-glycoprotein, also recognized as multidrug resistance 1 (MDR1) and multidrug resistance protein (MRP), exhibited the ability to promote resistance to anthracyclines and taxanes in metastatic breast cancer as well as ovarian cancer. Taxane resistance is additionally correlated to β-tubulin mutations, the protein found at the growing end of the microtubule (Christie et al., 2019).

Ixabepilone is a potent epothilone anti-tubulin agent that stabilizes cell microtubules, resulting in cell cycle arrest and, eventually, apoptosis (Ixempra, 2015). Taxanes and epothilones are both microtubule stabilizers, although they are structurally distinct and have distinct β-tubulin binding mechanisms. Ixabepilone has shown efficacy in taxane-resistant cell lines in preclinical experiments despite the presence of ABC efflux drug pumps and β-tubulin mutations. Epothilones have a greater affinity for β-tubulin but not to P-gp substrates compared to taxane, thus allowing it to act against taxane- and/or anthracycline-resistant tumor cells via elevation of P-gp expression. In addition, ixabepilone is also considered more bene-

ficial for TNBC patients since this agent is more active in β-III-overexpressed cells such as TNBC and ER-negative breast cancer (Saura et al., 2013). Early research of anticancer efficacy in a variety of xenograft models has stimulated the investigation of ixabepilone in breast cancer, including TNBC (Fig. 3) (Ibrahim, 2021).

Despite initial satisfactory results of ixabepilone-based chemotherapy, either as an alternative to taxane or as an adjuvant, this study still has several limitations. Search engines used in this study are only four databases. There is also diversification regarding clinical endpoints used to evaluate the efficacy of such regimen; thus, a meta-analysis could not be established. One study reported unexpected discontinuation of participants, resulting in decreased power of the study. Additionally, recurrence rates in both regimens in this trial were lower than expected since two-thirds of participants were in the early disease stage rather than the late stage (Yardley et al., 2017). Therefore, more clinical trials are still needed to ensure the efficacy and safety of ixabepilone-based neoadjuvant chemotherapy.

This study has implications for practice, policy, and future research. Positive findings from this study could influence clinical practice guidelines, potentially leading to the inclusion of ixabepilone-based chemotherapy as a recommended treatment option for TNBC patients. Clinicians may consider ixabepilone-based regimens as part of the treatment armamentarium for TNBC patients, particularly those who have failed other standard therapies or have specific clinical characteristics predictive of response to ixabepilone. An improved understanding of the efficacy and safety profile of ixabepilone-based chemotherapy may lead to better-informed treatment decisions and potentially improved outcomes for TNBC patients. On the other hand, positive results from the study may affect healthcare policies related to access and reimbursement for ixabepilone-based chemotherapy, ensuring that eligible TNBC patients have access to this treatment option. Healthcare systems may need to allocate resources for training, infrastructure, and drug procurement to support the implementation of ixabepilone-based chemotherapy in clinical practice. Further research is warranted to identify biomarkers predictive of response to ixabepilone-based chemotherapy, allowing for more personalized treatment approaches and improved patient outcomes. Future studies could explore the efficacy of ixabepilone in combination with other targeted therapies or immunotherapies, potentially enhancing treatment efficacy and overcoming resistance mechanisms in TNBC. Long-term follow-up studies are essential to assess the durability of treatment responses, evaluate late toxicities, and determine the impact of ixabepilone-based chemotherapy on overall survival and quality of life. Health economic analyses can evaluate the cost-effectiveness of ixabepilone-based chemotherapy compared to standard treatments, informing healthcare decision-makers about the value of integrating this therapy into clinical practice.

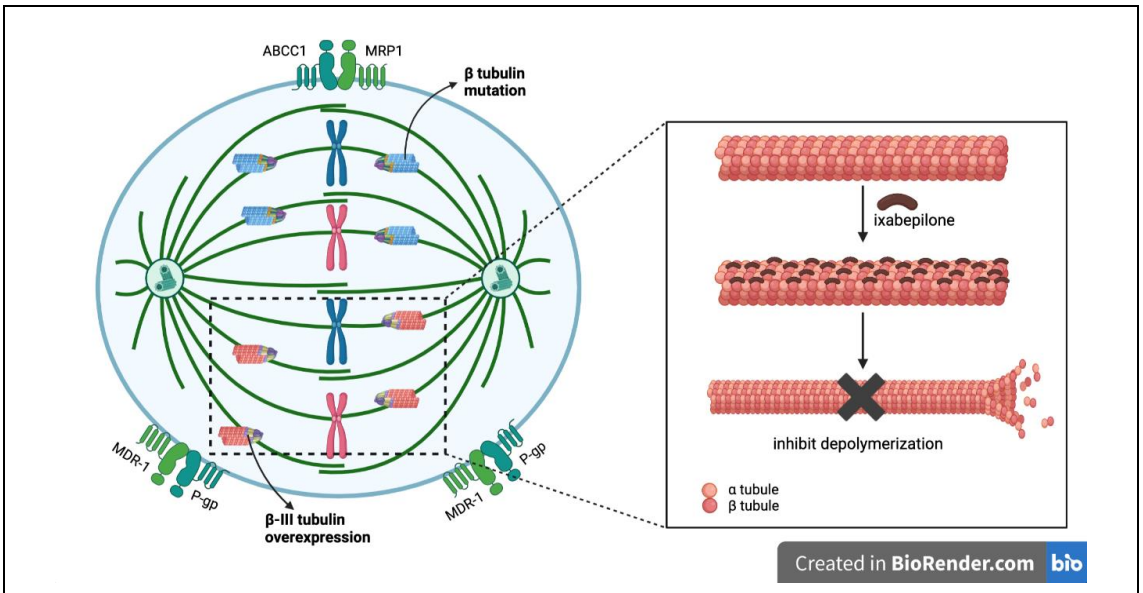

Figure 3. Common mechanism of taxane or chemotherapy resistances (left) and ixabepilone mechanism of action (right).

Recurrent exposure to chemotherapy induces evolutionary stress on cancer cells, leading to the acquisition of genetic and non-genetic characteristics that confer resistance to drug treatments. P-glycoprotein, known as multidrug resistance 1 (MDR1) and multidrug resistance protein (MRP), plays a significant role in promoting resistance to anthracyclines and taxanes in metastatic breast cancers. Resistance to taxanes is also associated with mutations in β-tubulin, a protein located at the growing end of microtubules. Despite the presence of ABC efflux drug pumps and β-tubulin mutations, preclinical experiments have demonstrated that ixabepilone exhibits effectiveness against taxane- and/or anthracycline-resistant cell lines by binding exclusively to β3-tubulin. This interaction results in depolymerization inhibition.

CONCLUSION

The efficacy and safety of ixabepilone-based chemotherapy compared to ixabepilone-free chemotherapy for triple-negative breast cancer patients appear to vary across studies. While some studies demonstrate improvements in disease-free survival, progression-free survival, and objective response rate with ixabepilone-based therapy, others report comparable outcomes between the two approaches. However, ixabepilone usage is consistently associated with significant adverse effects, notably peripheral neuropathy, which can lead to dose reductions and treatment discontinuations. Discrepancies in the safety profile further underscore the need for cautious consideration of both efficacy and safety when determining the most appropriate treatment regimen for triple-negative breast cancer patients. Additional research is necessary to clarify the efficacy and safety profiles of ixabepilone-based chemotherapy and ixabepilone-free chemotherapy in this patient population.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the Faculty of Medicine, Universitas Brawijaya, for the support provided. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Contribution	Azizah MR	Hanum HA	Norahmawati E	Fakurazi S	Kawamoto Y	Permana S	Widodo E	Endharti AT
Concepts or ideas	x	x						x
Design	x	x						
Definition of intellectual content	x	x	x	x	x	x	x	x
Literature search	x	x	x	x	x	x	x	x
Experimental studies			x	x	x			x
Data acquisition	x	x				x		
Data analysis							x	x
Statistical analysis								
Manuscript preparation	x	x						x
Manuscript editing	x	x						x
Manuscript review	x	x	x	x	x	x	x	x

Citation Format: Azizah MR, Hanum HA, Norahmawati E, Fakurazi S, Kawamoto Y, Permana S, Widodo E, Endharti AT (2024) Systematic review on the efficacy and safety of ixabepilone-based chemotherapy regimen in triple-negative breast cancer. J Pharm Pharmacogn Res 12(4): 722–734. https://doi.org/10.56499/jppres23.1869_12.4.722