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REVIEW

LOCOREGIONAL ADVERSE EFFECTS OF CANCER THERAPY IN WOMEN WITH ADVANCED BREAST CANCER: AN INTEGRATIVE REVIEW

EFEITOS ADVERSOS LOCORREGIONAIS DA TERAPÊUTICA ONCOLÓGICA EM MULHERES COM CÂNCER DE MAMA AVANÇADO: REVISÃO INTEGRATIVA

EFECTOS ADVERSOS LOCORREGIONALES DE LA TERAPIA ONCOLÓGICA EN MUJERES CON CÁNCER DE MAMA AVANZADO: UNA REVISIÓN INTEGRADORA

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ABSTRACT

Objective: to identify the locoregional adverse effects of administering intravenous oncologic therapy in women with advanced breast cancer. Method: this was an integrative literature review using the PubMed/MEDLINE, CINAHL, LILACS, and EMBASE databases, without a time cut, in addition to a reverse search of the selected articles updated until May 2022. The population included women with advanced breast cancer undergoing intervention with intravenous oncologic therapy with chemotherapy, hormone therapy, or monoclonal antibody, and the outcome assessed locoregional adverse effects. Results: 2,789 studies were identified, and the final sample consisted of 8 clinical trials and 1 retrospective observational study, all of which were international studies published from 1986 to 2018. Predominantly, patients with stage IV breast cancer, were aged 50 years or older, and had multiple metastases. Locoregional adverse effects were phlebitis, ulceration and/or necrosis, pain, erythema, and unspecified injection site reaction. The studies did not detail the type of venous catheter, the osmolarity of the drugs, and preventive care to reduce these adverse effects. Conclusion: the evidence from these articles showed that locoregional adverse effects are present in efficacy research of oncologic drugs in women with advanced breast cancer. Nonetheless, the safety of administering cancer drugs is not elucidated in this review, indicating the need for follow-up studies of adverse effects.

Keywords: Breast Neoplasms; Drug-Related Side Effects and Adverse Reactions; Antineoplastic Agents; Evidence-Based Practice; Nursing.

RESUMO

Objetivo: identificar os efeitos adversos locorregionais da administração da terapêutica oncológica endovenosa em mulheres com câncer de mama avançado. Método: revisão integrativa da literatura, que utilizou as bases de dados PubMed/MEDLINE, CINAHL, LILACS e EMBASE, sem recorte temporal, além de busca reversa dos artigos selecionados, atualizada até maio de 2022. A população contemplou mulheres com câncer de mama avançado submetidas à intervenção com terapêutica oncológica endovenosa com quimioterapia ou hormonioterapia ou anticorpo monoclonal, e o desfecho avaliou efeitos adversos locorregionais. Resultados: identificaram-se 2.789 estudos, e a amostra final foi composta por 8 ensaios clínicos e 1 estudo observacional retrospectivo, sendo todos estudos internacionais e publicados no período de 1986 a 2018. Predominantemente, as pacientes tinham câncer de mama em estádio IV, idade de 50 anos ou mais e múltiplas metástases. Os efeitos adversos locorregionais foram: flebite, ulceração e/ou necrose, dor, eritema e reação no local da injeção não especificada. Os estudos não trazem detalhamento do tipo de cateter venoso, osmolaridade dos fármacos e cuidados preventivos para diminuição desses efeitos adversos. Conclusão: as evidências desses artigos mostraram que os efeitos adversos locorregionais estão presentes em estudos de eficácia dos fármacos oncológicos em mulheres com câncer de mama avançado. No entanto, destaca-se que a segurança da administração dos fármacos oncológicos não se apresenta elucidada nessa revisão, indicando necessidade de estudos de acompanhamento dos efeitos adversos.

Palavras-chave: Neoplasias da Mama; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Antineoplásicos; Prática Clínica Baseada em Evidências; Enfermagem.

RESUMEN

Objetivo: identificación de los efectos adversos locorregionales de la administración de la terapia oncológica intravenosa en mujeres con cáncer de mama avanzado. Método: revisión bibliográfica integradora, que utilizó las bases de datos PubMed/MEDLINE, CINAHL, LILACS y EMBASE, sin corte de tiempo, además de una búsqueda inversa de los artículos seleccionados, actualizada hasta mayo de 2022 La población incluyó mujeres con cáncer de mama avanzado, sometidas a intervención con terapia oncológica endovenosa con quimioterapia u hormonoterapia o anticuerpo monoclonal y el resultado evaluó los efectos adversos locorregionales Resultados: se identificaron 2.789 estudios y la muestra final se compuso de ocho ensayos clínicos, un estudio observacional retrospectivo, todos estudios internacionales, publicados desde 1986 hasta 2018. Predominantemente, las pacientes tenían cáncer de mama en estadio IV, edad de 50 años o más y metástasis múltiples. Los efectos adversos locorregionales fueron flebitis, ulceración y/o necrosis, dolor, eritema y reacción en el lugar de la inyección no especificada. Los estudios no detallan el tipo de catéter venoso, la osmolaridad de los fármacos y los cuidados preventivos para reducir estos efectos adversos. Conclusión: las pruebas de estos artículos mostraron que los efectos adversos locorregionales están presentes en

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los estudios de eficacia de los fármacos oncológicos en mujeres con cáncer de mama avanzado. Sin embargo, cabe destacar que la seguridad de la administración de los fármacos contra el cáncer no se dilucida en esta revisión, lo que indica la necesidad de realizar estudios de seguimiento sobre los efectos adversos.

Palabras clave: Neoplasias de la Mama; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Antineoplásicos; Práctica Clínica Basada en la Evidencia; Enfermería.

INTRODUCTION

Female breast cancer is among the most prevalent malignant neoplasms, with 2.1 million cases corresponding to 11.6% of all cancers.[1] In Brazil, the annual incidence of breast cancer is 66,280 thousand cases.[2] From 2005 to 2014, a drop in national survival estimates was observed, from 76.9 to 75.2%.[3–4] This drop is justified by late access to diagnosis and treatment, culminating in an unfavorable prognosis due to advanced stages.[3,4]

Advanced breast cancer comprises stages III and IV,[5] in which the primary tumors are larger than 5 cm and may extend to the chest wall, skin, lymph nodes, and distant organs.[6] Tumors are classified by histological type, degree of differentiation, antigen expressions, and hormone receptors.[7] Clinically, the tumor masses are visible or palpable and accompanied by hyperemia, skin retractions, nipple inversion, and other changes that impair women's quality of life.[7]

Advanced breast cancer is present in late diagnosis and women with recurrence.[8,9] Advanced breast cancer treatment depends on where the disease started and its spread, which must begin soon after diagnosis.[9] Furthermore, factors related to age, comorbidities, histological type, and surgical procedures can guide the type of treatment.[8,9]

There are two types of treatment: locoregional therapy, which can be surgical or radiotherapeutic, and systemic, carried out using oncologic drugs that comprise antineoplastic chemotherapy, hormone therapy, and monoclonal antibodies.[8,9] Drugs are currently effective treatments for solid tumors, including advanced stage, and the most common routes of administration are oral and intravenous.[9,10] Despite their efficacy and safety, drugs can trigger systemic and locoregional adverse effects, making it necessary for nurses to establish specific Nursing care to maintain women's quality of life regarding preventing or minimizing the adverse effects.[8–10]

The exposure of women with advanced cancer to cancer drugs is higher than patients in earlier stages of the disease.[9] Furthermore, many women with advanced disease undergo surgery for lymph node axillary dissection;[9,10] these conditions require Nursing care to prevent or minimize adverse effects.[11]

Locoregional adverse effects include mechanical and chemical phlebitis caused by inflammation of the venous endothelium, which is characterized by pain, edema, erythema, and purulent discharge.[11] There may also be infiltration and extravasation of vesicant or irritant solutions, causing skin pallor, decreased temperature at the site, burning, and altered sensitivity, which may lead to severe tissue damage, including necrosis and limb impairment.[12] These adverse effects range from mild discomfort to irreversible damage and treatment discontinuation, leading to possible disease progression.[11–13]

The peripheral venous catheter (PVC) is widely used in oncology clinical practice, although oncological treatment is performed in long cycles, requiring the use of central venous catheters (CVC).[12] It is important to note that Nursing interventions directed at women with advanced breast cancer must be based on the best evidence. Among the interventions, oncologic drugs and establishing preventive measures that minimize adverse effects stand out.[12–14]

The intravenous administration of oncologic drugs is the exclusive right of nurses in Brazil; it must be performed by qualified and skilled professionals with interventions that prevent locoregional adverse effects.[15] Safely administering the drugs includes verifying the treatment protocol, preparing the drug, calculating the dosages, and correctly identifying the patient and their clinical conditions, including the venous network.[14,16] It is essential to create strategies that reduce failures in administering oncologic drugs and minimize the adverse effects caused by the treatment.[14,16]

It is noteworthy that the adverse effects of advanced cancer treatment cause physical and emotional harm to women.[11] It is believed that the scientific evidence shown in this study can support the professional practice of nurses regarding the prevention and early recognition of adverse locoregional effects related to administering chemotherapy in women with advanced breast cancer.

Given the above, this study sought to identify the locoregional adverse effects of intravenous cancer therapy in women with advanced breast cancer.

METHOD

This is an integrative literature review, which allows one to analyze, synthesize and update relevant studies on a topic. Through this research method, it is possible to gather scientific evidence to answer a research problem and indicate existing gaps for future studies. This review

followed six steps: 1) identifying the topic and research question; 2) establishing criteria for including and excluding studies/sampling and literature search; 3) defining the information to be extracted from the selected publications/its categorization; 4) evaluating the articles included in the integrative review; 5) interpreting the results; 6) synthesizing knowledge.[17]

In order to guide the formulation of the research question, the components of the acronym 'PIO' were followed, in which each letter represents a component of the question: P (patient) — a woman with advanced/metastatic/palliative breast cancer; I (intervention) — administration of intravenous oncological treatment with chemotherapy, hormone therapy, or monoclonal antibodies, and O (outcome) — locoregional adverse effects.[18]

The question constructed to guide this study was: What are the locoregional adverse effects of administering intravenous cancer therapy with chemotherapy, hormone therapy, monoclonal antibodies in women with advanced breast cancer? The following inclusion criteria were adopted: randomized clinical trials (RCT) and observational studies in Portuguese, English, or Spanish that included female patients with advanced breast cancer (stages III and IV), aged 18 years or older, undergoing intravenous chemotherapy, hormone therapy, or monoclonal antibodies with no cut-off time, and reporting locoregional adverse effects. Literature review studies, case studies, cross-sectional studies, qualitative studies, and those that had only systemic effects caused by chemotherapy, hormone therapy, and monoclonal antibody as an outcome or that did not differentiate systemic effects from locoregional effects were excluded.

The survey of indexed publications was conducted in November 2020 and updated through May 2022. The databases used to search for potentially eligible studies were the Cumulative Index to Nursing and Allied (CINAHL), Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed); Latin American Literature in Health Sciences (LILACS), and Excerpta Medica database (EMBASE). The search strategies can be seen in Figure 1.

Figure 1 - Search strategy in databases. Belo Horizonte, MG, November 2021

Database	Search strategy
PUBMED	(Antineoplastic Agents / adverse effects* OR Drug-Related Side Effects and Adverse Reactions OR Antineoplastic Combined Chemotherapy Protocols / adverse effects* OR Phlebitis OR Cellulitis OR Necrosis OR Exanthema OR Pain OR Pain Management OR Cancer Pain OR Breast Cancer Lymphedema OR Disease Progression OR Vascular System Injuries) AND (Breast Neoplasms) AND (Palliative Care OR Palliative Medicine OR Hospice and Palliative Care Nursing OR Neoplasm Metastasis)
EMBASE	((('breast tumor' OR 'inflammatory breast cancer'/exp OR 'triple negative breast cancer'/exp) AND 'chemotherapy'/exp OR ' palliative therapy'/exp) AND 'adverse drug reaction'/exp AND 'breast tumor'/exp AND ([cochrane review]/lim OR [systematic review]/lim OR meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND # (('breast tumor' OR 'inflammatory breast cancer'/exp OR 'triple negative breast cancer'/exp) AND chemotherapy'/exp OR 'palliative therapy'/exp) AND 'adverse drug reaction'/exp AND 'breast tumor'/exp AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)
CINAHL	(Breast Neoplasms AND Drug Therapy OR Drug Therapy, Combination OR Chemotherapy, Cancer OR Antineoplastic Agents) AND (Palliative Care OR Hospice and Palliative Nursing OR Neoplasm Metastasis) AND (Medication Side Effects (Saba CCC) OR Phlebitis OR Cellulitis OR Necrosis OR Exanthema OR Pain OR Disease Exacerbation)
LILACS	"breast cancer" [words] AND "chemotherapy" [words] AND (((("adverse injection site effect" OR "adverse injection site effect/" OR "adverse injection site effect/co" OR "adverse injection site effect/ve") OR "reaction") OR "extravasation") OR "phlebitis") OR "edema") OR "Nursing care" [words]

Source: prepared by the authors.

The studies were independently selected and included by two reviewers. Duplicate articles in the different databases were identified using Microsoft Excel. The studies were then read in two phases (phase 1: title/abstract and phase 2: full article). A third reviewer evaluated disagreements to meet the objective. A reverse search was performed on the selected articles. The acquisition of the full articles was made at the Capes Portal, Bibliographic Commutation between Libraries (COMUT) service (http://comut.ibict.br), and direct request to the authors via ResearchGate (https://www.researchgate.net) and e-mail. Notably, some studies were not found, despite the efforts mentioned.

Two researchers performed data extraction independently, and inconsistencies were reassessed by a third researcher. We formulated a survey containing the

following information: 1) characterization of the studies in terms of authorship, methodological design, language, the scope of the study, sample size, drugs used, route of administration, level of evidence, and degree of recommendation; 2) characterization of the study participants in terms of age, stage, functional capacity, treatments, presence of metastasis and the instrument used to assess adverse effects; 3) primary outcomes: pain, phlebitis, cellulitis, desquamation, necrosis, exanthema, lymphedema, or other sign and symptom arising from the administration of cancer therapy.

The risk of bias assessment of the included studies was performed by three authors using the Joanna Briggs Institute critical appraisal tools for RCTs[19] and observational studies.[20] The RCT assessment includes 13 components;[19] the assessment for observational studies comprises a checklist with ten components.[20]

The risk of bias was determined as follows: a) low risk of bias, if the studies achieved more than 70% "yes" rating; b) moderate risk of bias if the "yes" scores were between 50 and 69%; and c) high risk of bias if the "yes" score was less than 49%.[21]

The evidence coming from the study and degree of recommendation was assessed using the Johns Hopkins University/School of Nursing guideline.[22]

RESULTS

In the electronic search, 2,789 articles were identified, of which 9 were selected[23–31] for the final sample. The complete flowchart, from the search to the final selection of studies, can be seen in Figure 2.

In the sample, we identified 8 RCTs[23–29,31] in different phases (88.9%%) and 1 observational study (11.1%)[30] published between 1986 and 2018, totaling 1,390 women with advanced breast cancer undergoing treatment with intravenous oncologic therapy in the nine studies of the final sample. For the most part, these studies were developed by medical authors and other health researchers, with the primary objective of evaluating the efficacy of the administered oncologic therapy on survival and disease progression-free time, as well as identifying the adverse effects of the treatment. No studies were found addressing Nursing care in drug administration. English was the language used, and Europe hosted most of the studies. The participants used several drugs, and the intravenous route was the most used. Notably, one study used the same drugs with different dose intervention arms. The detailed characteristics of the studies are listed in Figure 3.

Figure 4 lists the data regarding the characteristics of women in the study, with a predominance of women 50 years of age or older, low functional capacity, use of previous oncologic drugs and concomitant treatment, and all of them classified as stage IV, with various metastasis sites. The functional capacity of the women was assessed using the Zubrod[23,27,31] and ECOG[24,26,29,30] scales and the Karnofsky index.[25,28] The instruments used to measure adverse effects were the Common Terminology Criteria for Adverse Events (CTCAE)[28–31] and the Toxicity grading scale (TGS).[23,26]

The adverse effects in the included studies were unspecified injection site reaction, phlebitis, ulceration and/or necrosis, site pain, and erythema and were attributed to the various drugs and their associations.[23–31]

Unspecified injection site reactions were reported due to docetaxel, mitomycin + vinblastine, trastuzumab + paclitaxel with or without everolimus, vinflunine, cyclophosphamide, melphalan, mitomycin c, thiotepa, cisplatin, and carboplatin in a total of 75 women (4.4%).[25,29,31] Phlebitis was associated with bisantrene, docetaxel, mitomycin + vinblastine, vinorelbine + cisplatin, gemcitabine + cisplatin, and identified in 22 women (2.7%) of the total number of women.[23,27,30] Ulceration and/or necrosis were present in 16 women (1.2%)[25,26,29] and were related to the use of drugs such as docetaxel, mitomycin + vinblastine, doxorubicin + cyclophosphamide, epirubicin and cyclophosphamide, epirubicin, vinorelbine + epirubicin, doxorubicin, bortezomib, and pyridoxine. Injection site pain was seen when using the drugs fluorouracil + doxorubicin + cyclophosphamide + dexrazoxane and occurred in five women (0.9%).[24] Erythema was associated with liposomal doxorubicin, bortezomib, and pyridoxine, occurring in one woman (7.7%).[28]

The critical evaluation of the methodological quality of the selected studies showed that of the RCTs, most presented a moderate risk of bias,[23,24,26,27,31] two presented a low risk,[24,29] and one presented a high risk.[28] The methodological fragility presented itself mainly for the items of masking of participants, investigators, and evaluators of the results. The observational study was evaluated as having a low risk of bias,[30] and its methodological fragility is present in the items identifying confounding factors and strategies to reduce them, as well as in describing the combination of cases and controls. The details of the evaluation are listed in Figure 5.

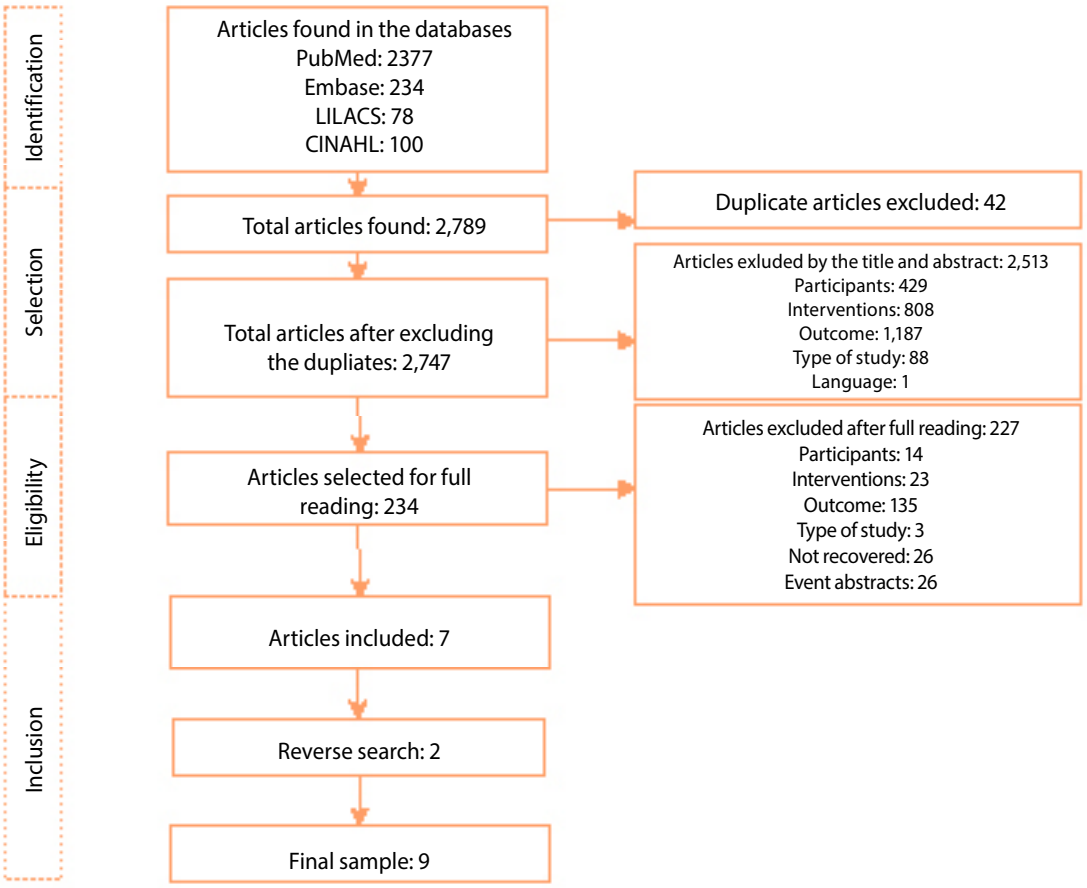

Figure 2 - Flowchart of the included studies. Belo Horizonte, MG, May 2022

DISCUSSION

This review allowed us to identify locoregional adverse effects in women with advanced breast cancer and the use of instruments to evaluate these effects, and we also observed the association of adverse effects with drugs used in oncologic therapy. The evaluation of the functional capacity of women was also a focus of study in the sampled articles. The articles included in this review were evaluated regarding methodological quality. We emphasize the unprecedented nature of this literature review focused on identifying locoregional adverse effects in women with advanced breast cancer.

Few review studies have provided data on locoregional adverse effects from administering chemotherapeutic agents in women with advanced breast cancer. One study that addressed the efficacy and toxicity of doxorubicin in women with advanced breast cancer[32] only cited the need for discontinuation of a patient's treatment due to reaction to the infusion and increased occurrence of extravasation due to the size of the doxorubicin liposomes. Another study analyzed two multicenter RCTs of 349 women with metastatic breast cancer and reported that pain at the injection site was one of the toxicities related to treatment, although no quantitative data was provided.[33,34]

In this review, all studies[23–31] contained chemotherapy protocols in multidrug therapy, depicting clinical practice. The protocols with multiple drugs aim to cause cell death of malignant neoplasms by different mechanisms of action and combat the disordered growth of cells.[8–10] In contrast, multidrug therapy also increases the diversity and intensity of adverse effects, including locoregional ones. Because of this, oncologic therapies are associated with improving treatment efficacy and meeting patient safety.[8–10]

The chemical composition of cancer drugs can be harmful to the venous network, especially to adjacent tissues, when the drugs are extravasated.[9,10,13] The damage can occur due to extravasation, in which vesicant drugs can cause ulcerative lesions and necrotizing, leading to physical disabilities.[9,10,13] Irritating drugs can cause erythema, pain, edema, and skin color changes. These conditions

Figure 3 - Characterization of the studies according to authorship, year of publication, methodological design, language, geographic origin, institutional coverage, sample, drugs studied, administration route, evidence level, and recommendation degree. Belo Horizonte, MG, November 2021

ID	Author/ year	Design	Language/ source	MC	N total	Drug comparison	Route	EL	RD
1[23]	F. A. Holmes et al. 1986	RCT Phase NR	English North America	NR	76	a) 300 mg/m2 Bisanthrene in 1000 mL D5W. b) 80 mg/m2 Bisanthrene in 500 mL D5W.	IV	1B	A
2[24]	S. M. Swain et al. 1997	RCT Phase NR	English North America	Yes	534	1. a) Fluorouracil, doxorubicin, and cyclophosphamide + Dexrazoxane b) Fluorouracil, doxorubicin, and cyclophosphamide + placebo 2. a) Fluorouracil, doxorubicin, and cyclophosphamide + Dexrazoxane b) Fluorouracil, doxorubicin, and cyclophosphamide + placebo	IV	1B	A
3[25]	J.M. Nabholtz et al. 1999	RCT Phase III	English Europe North America Africa	Yes	392	a) Docetaxel (n = 203) b) Mitomycin and vinblastine (n = 189)	IV	1B	A
4[26]	S. Chan et al. 2004	RCT Phase III	English/ Europe	Yes	160	a) Doxorubicin (Myocet) and cyclophosphamide (n = 80) b) epirubicin and cyclophosphamide (n = 80)	IV	1B	A
5[27]	B. Ejlertsen et al. 2004	RCT Phase III	English Europe	Yes	387	a) Epirubicin (n = 194) b) Vinorelbine and epirubicin (n = 193)	IV	1B	A
6[28]	W. J. Irvin en et al. 2010	RCT Phase II	English North America	No	13	a) Liposomal doxorubicin, bortezomib, and pyridoxine	IV E VO	2B	B
7[29]	S. A. Hurvitz et al. 2016	RCT Phase III	English Intercontinental*	Yes	719	a) Everolimus, trastuzumab and paclitaxel (n = 46) b) Placebo, trastuzumab, and paclitaxel n=27	a) VO e IV b) VO e IV	1B	A
8[30]	J. Wang et al. 2017	Observational	English Asia	No	48	a) Vinorelbine and cisplatin (n = 22) b) Gemcitabine and cisplatin (n = 26)	IV	1B	A
9[31]	J. Cortes et al. 2018	RCT Phase III	English Europe	Yes	594	a) Vinflunine (n = 298) b) Alkylating agent (oral or iv cyclophosphamide, oral or iv melphalan, mitomycin C, thiotepa, cisplatin, or carboplatin) (n = 296).	a) IV b) IV ou VO	1B	A

ID: study identification, RCT: randomized clinical trial, OCT: open clinical trial, MC: multicenter, n: sample size, NR: not reported, adm: administration; Route: administration route; IV: intravenous, EL: evidence level, D5W: glucose serum, OA: oral administration; RD: recommendation degree

*Africa, Asia, North America, South America, and Europe. Source: prepared by the authors.

Source: elaborated by the authors

can interfere with women's quality of life and even interrupt treatment.[9,10,13]

The instruments[35,36] used in the articles to assess locoregional effects of infusion were Common Terminology Criteria for Adverse Events (CTCAE)[25-27,29,31] and Toxicity grading scale (TGS),[23,27] both of which are suitable for the assessment of adverse effects. The CTCAE was developed by the US National Cancer Institute and revised various times; it is widely used in the literature for evaluating treatment-related adverse effects to all organ systems, including skin and adjacent tissues (it scores the effects from 1 to 5). The TGS was developed by the World Health Organization in 1979 to standardize oncology treatment-related reactions. The TGS classified adverse effects on skin tissue from scores of 0 (no skin changes occur at the site of chemotherapy infusion) to 4 (when tissue necrosis occurs).

In three RCTs,[25,29,31] the injection site reactions were unspecified as to their characteristics, only reported as local

Figure 4 - Sociodemographic and clinical data. Belo Horizonte, MG, November 2021

ID	Mean age	Stage	Functional capacity	Prior treatments	Concomitant treatment	Metastasis
1[23]	a) 50 b) 51	IV	Zubrod 0 to 3; life expectancy of 8 weeks;	- Chemotherapy - Hormone therapy - No surgery reported	NR	Yes. a) Visceral (n = 67), bone (n = 22) and soft tissue (n = 11). b) Visceral (n = 54), bone (n = 31) and soft tissue (n = 20)
2[24]	1. a)58 b) 56 2. a) 56 b) 59,5	IIIB ou IV	ECOG 0 a 2	- Hormone therapy - Radiotherapy - No surgery reported	NR	Yes. 1. a) Visceral (n = 126), bone (n = 31) and soft tissue (n = 10). b) Visceral (n = 138), bone (n = 28) and soft tissue (n = 15). 2. a) Visceral (n = 52), bone (n = 22) and soft tissue (n = 7). b) Visceral (n = 67), bone (n = 27) and soft tissue (n = 9)
3[25]	a) 51 b) 52	IV	Karnofsky index >_60	- Chemotherapy - Hormone therapy - No surgery reported	-dexamethasone, -antiemetic	Yes. a) Soft tissue (n = 17), bone (n = 116), viscera (n = 153), and liver (n = 102). b) Soft tissue (n = 18), bone (n = 122), viscera (n = 138), and liver (n = 88)
4[26]	a) 54 b) 54	IV	ECOG 0 to 2; life expectancy of >_3 months.	- Chemotherapy - Hormone therapy - Radiotherapy - No surgery reported	No	Yes, NR. a) NOI 1-2 (n = 58); >_3 (n =22). b) NOI 1-2 (n = 57); >_3 (n = 23)
8[27]	a) 55 b) 55	IV	ECOG 0 a 2	- Chemotherapy - Hormone therapy - Radiotherapy - No surgery reported	NR	Yes, NR. a) NOI 1 (n = 84); 2 (n = 72) >_3 (n =38). b) NOI 1 (n = 79); 2 (n = 68) >_3 (n = 46)
6[28]	13	IV	Karnofsky index >_60; Life expectancy ≥ 3 months	NR	- Hormonal contraceptive; - Ondansetron; - Ranitidine; -Dexamethasone; -Diphenhydramine; - Other antiemetics	Yes. Liver (n = 11); lung (n = 10); bone (n = 9); lymph nodes (n = 3); other (skin, peritoneum) (n = 2)
7[29]	a)54 b)52	IV	ECOG equals 0 or 1	- Hormone therapy	NR	Yes a) Visceral (n = 338), liver (n = 177), lung (n = 217), liver and lung (n = 72), and bone (n = 210). b) Visceral (n = 169), liver (n = 110), lung (n = 103), liver and lung (n = 51), and bone (n = 117)
8[30]	a) 48 b) 49	IV	ECOG: 0 to 2. Expected survival of more than 3 months	- Radical or modified mastectomy - Chemotherapy	- Zoledronic acid IV - Chemotherapy - 5-HT3 receptor antiemetic therapy antagonists	Yes. a) Lymph nodes or soft tissue (n = 8), chest wall (n = 3), lung (n = 12), liver (n = 5), bone (n = 8), and brain (n = 1). b) Lymph nodes or soft tissue (n = 10), chest wall (n = 4), lung (n = 13), liver (n = 7), and bone (n = 11)
9[31]	a) 58 b) 57	IV	ECOG: 0 a 2	- Radiotherapy -monoclonal antibody -chemotherapy - Hormone therapy	- Antiemetic; - Laxatives; - Colony-stimulating factors and erythropoietin	Yes. a) Visceral (n = 248), liver (n = 171), lung (n = 106), and bone (n = 208). b) Visceral (n = 244), liver (n = 169), lung (n = 121), and bone (n = 214)

ECOG: Eastern Cooperative Oncologic Group performance scale, RT: radiation therapy, 5-HT3: serotonin, IV: intravenous, LVEF: left ventricular ejection fraction at rest, NOI: number of organs involved, NR: none reported, WHO: World Health Organization. Source: prepared by the authors.

Figure 5 - Critical methodological assessment of the studies according to the Joanna Briggs Institute assessment. Belo Horizonte, MG, Brazil, 2022

Clinical trial									Observational study	
	ID									ID
Questions	1[23]	2[24]	3[25]	4[26]	5[27]	6[28]	7[29]	9[31]	Questions	8[30]
1. Real randomization?	NC	Yes	Yes	No	Yes	No	Yes	Yes	1. Comparable groups?	Yes
2. Hidden allocation?	No	Yes	No	No	No	No	Yes	No	2. Combined CaC?	NC
3. Similar groups at the base?	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	3. Similar criteria for identifying CaC?	Yes
4. Participant blinding?	NC	Yes	No	No	No	NC	Yes	No	4. Reliably measured exposure?	Yes
5. Interventionist researcher blinding?	NC	Yes	No	No	No	No	Yes	No	5. Similar measure for CaC?	Yes
6. Outcome evaluator blinding?	NC	Yes	No	No	No	No	No	No	6. Confounding factors identified?	No
7. Were the groups treated identically?	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	7. Strategies for confounding factors?	No
8. Was follow-up completed for both groups?	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	8. Reliably evaluated results?	Yes
9. Participants analyzed in the randomized groups? ITT?	No	NC	Yes	Yes	Yes	Yes	Yes	Yes	9. Is the exposure period adequate?	Yes
10. Are the measured results similar in both groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	-
11. Reliably measured results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	-
12. Appropriate statistical analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	-
13. Appropriate methodological design?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	-	-
Total yes (%)	53.8	92.0	69.2	61.5	69.2	25.0	92.0	69.2	-	70.0
Risk classification	M	L	M	M	M	H	L	M	-	H

Legend: NA: Not applicable, NC: Not clear; H: High Risk; M: Moderate Risk; L: Low Risk; CaC: Case and Control.

reactions. The association of these reactions occurred in protocols with irritant drugs belonging to the classes of alkylating agents, mechlorethamine derivatives, and vesicant drugs belonging to the pharmacological classes of vinca alkaloids and taxanes.[25,29,31] Also associated with the protocols are drugs classified as non-irritant and non-vesicant drugs belonging to the class of monoclonal antibodies.[25,29,31]

Phlebitis has been reported in studies with vesicant drugs belonging to the vinca alkaloids class, anthracyclines and antitumor antibiotics, and irritant drugs belonging to the alkaloids and alkylating pharmacological class.[23,27,30] Two studies[23,30] attributed phlebitis to PVC use without detailing the type of peripheral catheter, conditions of the venous network, osmolarity, and drug infusion speed. Phlebitis is characterized by inflammatory and painful processes of the venous network caused by microextravasations, drug osmolarity, and infusion speed.[37]

The CVC is not recommended for continuous infusion of vesicant drugs because phlebitis, infiltrates, and extravasations are the main adverse effects related to the infusion of intravenous oncology drugs.[37,38] The Oncology Nursing Society (USA) and National Health Surveillance Agency recommend the CVC for administering vesicant drugs.[37,38] The handling of the CVC requires knowledge and constant monitoring by the Nursing team to avoid adverse effects.[37,38]

Pain at the injection site was only reported in one study, which employed the drugs of the class of antimetabolites, alkylating agents, and antitumor antibiotics with vesicant properties.[24] Erythema was also reported in only one study, which used the irritant drugs of the vinca alkaloid and proteasome inhibitor classes.[28]

Ulceration and necrosis have been reported in clinical trials with vesicant protocols[25,26,29] in drugs belonging to the classes of taxanes, antitumor antibiotics, alkylating agents,

proteasome inhibitors, and vinca alkaloid associated with irritating drugs of the alkylating agent class. Ulceration and necrosis are severe, impactful locoregional adverse effects that prevent immunosuppressive treatments from continuing until the lesion has healed; these lesions can cause pain, infection, bleeding, and disease progression.[11,37]

Pain and erythema were the adverse effects with the lowest frequencies in the studies.[24,28] There is a lack of similarity in evaluating adverse effects between the studies since phlebitis, ulceration, and necrosis are adverse effects accompanied clinically by pain and erythema in women.

Only two studies detailed that woman who presented unspecified injection site reaction[29,31] and ulceration and necrosis[29] were submitted to mastectomy and lymph node chain dissection. This surgery prevents the use of one or both upper limbs for the peripheral administration of cancer drugs, making the patient even more vulnerable to adverse effects due to the overload of the venous network.[4,6]

In order to analyze the functional capacity of the women, we used the ECOG scale (Zubrod) validated by the World Health Organization. The Karnofsky scale uses parameters comparable to the ECOG (Zubrod).[39] The women evaluated in five studies[24,26,27,30,31] had functional capacity assessed by the Zubrod performance scale, which ranged from 0 to 2. This same scale was used by one study[29] whose patient's performance ranged from 0 to 1, and by another study with scores ranging from 0 to 3.23 Women receiving Zubrod 0 showed no signs and symptoms related to the disease; Zubrod 1 indicated signs and symptoms but could perform preserved activities of daily living; Zubrod 2 was out of bed more than 50% of the time; and Zubrod 3 was in bed more than 50% of the time and required more intensive care. Functional capacity scales can be used from the time neoplasms are diagnosed. It is recognized that advanced disease highlights the need for palliative care in various scenarios of the patient's life, whether in the hospital, home, or office. Assessing the functional capacity assists the team in making clinical decisions. Two studies used the Karnofsky scale, and the patients had scores greater than or equal to 60%; at this level, the patients may need primary care but can perform the activities of daily living.

In all the studies analyzed,[23–31] the evaluations of functional capacity allowed us to visualize that the women had altered health status, with functional capacities that limited the activities of daily living and required constant help, with a life expectancy below eight months. Thus, it is evident that oncological therapies must promote interventions to improve the quality of life, including reducing locoregional adverse effects.[4,6] Nonetheless, the studies aimed to analyze survival and time free of disease progression.

Nurses consider that the adverse effects of women in palliative care at the end of life must be addressed since the symptoms arising from these effects cause pain and discomfort and negatively impact patients' quality of life.[23-31] Therefore, Nursing care must be planned from a palliative, preventive, and rehabilitative perspective to safely administer oncological drugs.[40]

Regarding nurses' clinical practice, this study highlighted the need to establish practices and conduct studies to prevent adverse effects related to safely administering cancer drugs. To this end, the importance of knowledge based on scientific evidence of the pharmacokinetic and pharmacodynamic properties of drugs is encouraged, and their effects to establish preventive measures in intravenous treatments.

It is important to point out that there is a lack of research carried out by nurses that seek to prevent locoregional adverse effects, thereby emphasizing the need for nurses to develop new studies addressing locoregional effects of cancer therapies in women with advanced breast cancer since most of the studies in the sample were conducted by other health professionals.[23–31]

The limitations in developing this study may have been the search for studies in only four databases, which may have compromised the eligibility of other studies. The databases were chosen for their access to the Capes Portal and the international and national scope of indexing studies in health and Nursing.

CONCLUSIONS

Locoregional adverse effects in women with advanced breast cancer, such as phlebitis, ulceration and necrosis, pain, erythema, and unspecified injection site reactions, have been identified in the literature in studies that sought to evaluate the comparative efficacy of therapeutic protocols focusing on survival and disease progression.

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