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Safe prescription of systemic antineoplastic treatment in oncology: integrative literature review

Prescrição segura do tratamento antineoplásico sistêmico em oncologia: revisão integrativa da literatura

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ABSTRACT

The objective of this study was to identify the available evidence on the parameters that should be considered to improve the quality and safety of the prescription of systemic antineoplastic treatment. This is an integrative review carried out in the EMBASE, LILACS, and PubMed databases, from 2015 to 2019. The methodological quality of the included studies was assessed by the tools of the Joanna Briggs Institute. Eight studies were included, of which 5 addressed adverse events related to systemic antineoplastic treatment, including 4,970 patients treated with immunotherapy, target therapy, and chemotherapy. One study assessed the safety of prescribing antineoplastic agents and 2 studies addressed pharmacovigilance and risk management by assessing treatment- related adverse effects. Chemotherapy, target therapy, and immunotherapy have different toxicity profiles. The evidence suggests that assessment of treatment toxicity as well as risk management should be considered to improve the quality and safety of prescribing systemic antineoplastic treatment.

Keywords: Antineoplastic agents; Immunotherapy; Drug-related side effects and adverse reactions; Patient safety.

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RESUMO

O objetivo deste estudo foi identificar as evidências disponíveis sobre os parâmetros que devem ser considerados para melhorar a qualidade e a segurança da prescrição do tratamento antineoplásico sistêmico. Trata-se de uma revisão integrativa realizada nas bases de dados EMBASE, LILACS e PubMed, no período de 2015 a 2019. A qualidade metodológica dos estudos incluídos foi avaliada pelas ferramentas do Instituto Joanna Briggs. Oito estudos foram incluídos, dos quais 5 abordaram eventos adversos relacionados ao tratamento antineoplásico sistêmico, incluindo 4.970 pacientes tratados com imunoterapia, terapia alvo e quimioterapia. Um estudo avaliou a segurança da prescrição de agentes antineoplásicos e 2 estudos abordaram a farmacovigilância e o gerenciamento de risco avaliando os efeitos adversos relacionados ao tratamento. Quimioterapia, terapia-alvo e imunoterapia têm perfis de toxicidade diferentes. As evidências sugerem que a avaliação da toxicidade do tratamento, bem como o gerenciamento de risco, devem ser considerados para melhorar a qualidade e a segurança da prescrição do tratamento antineoplásico sistêmico.

Descritores: Agentes antineoplásicos; Imunoterapia; Efeitos colaterais e reações adversas relacionados a medicamentos; Segurança do paciente.

INTRODUCTION

It is estimated that there will be 21.9 million new cases of cancer, with 11.4 million global deaths, by 2025. There is a wide diversity in the incidence of different primary sites among various regions worldwide due to socioeconomic and lifestyle differences.[1] In Brazil, in the year 2020, approximately 309,000 and 316,000 new cancer cases were estimated for men and women, respectively. If non-melanoma skin cancer cases are not considered, the more frequent in men were cancers of the prostate, intestine, lung, stomach and oral cavity, while in women they were breast, intestine, cervix, lung and thyroid. [2]

Systemic antineoplastic treatment, which involves the use of chemotherapy cytotoxic, hormone therapy and immunotherapy, is used in a wide variety of patients with cancer and can be administered for potentially curative or palliative purposes. [3] Although there is a recognized benefit of systemic antineoplastic treatment, adverse drug reactions in patients with cancer are still very common, leading to delays in subsequent prescribed cycles, non-adherence to treatment, and additional healthcare costs for toxicity management. [4]

Patients undergoing chemotherapy may have side effects that vary in severity and include nausea, vomiting, mucositis, diarrhea, fatigue, and bone marrow suppression. [3]

The use of immune checkpoint inhibitors (ICPis), another example of therapy systemic anticancer, is associated with a spectrum of adverse effects related to their mechanism of action that is quite different from other systemic therapies. The adverse effects are usually immune-mediated and can affect various organs or body systems such as the skin, gastrointestinal tract, lungs, thyroid, adrenal gland, pituitary gland, musculoskeletal system, kidneys, nervous system, hematological system, cardiovascular system, and eyes. [5]

ICPis therapy can usually be continued in the presence of immune-related adverse events (irAEs) with rigorous monitoring. However, moderate to severe irAEs may be associated with severe declines in organ function and quality of life, and fatal results have been reported; therefore, these toxicities require early detection and appropriate management. [5]

In addition to the high potential to cause morbidity, systemic antineoplastic treatment, in which the entire therapeutic advent is weighed, also poses a significant risk of mortality in patients when not properly planned. Thus, it is essential to review the quality and safety of systemic antineoplastic treatment prescription. [3]

Strategies to ensure safety in the prescription of antineoplastic treatment were addressed in a literature review, having defined 68 recommendations, among which the authors point out the toxicity of the treatment as an important parameter for prescribing antineoplastics. [6]

This integrative review aimed to synthesize knowledge about the systemic antineoplastic treatment toxicity profile to be adopted as a parameter for safe prescription. It is intended to obtain evidence that can improve the quality and safety of systemic antineoplastic treatment prescription, in order to provide information on treatment toxicity as well as risk management strategies in this context.

METHODS

This study was an integrative review conducted in six stages, namely establishment of the research hypothesis or question, sampling or literature search, categorization of studies, evaluation of studies included in the review, interpretation of results and synthesis of knowledge, and presentation of the review. [7] The *Preferred Reporting Items for Systematic Reviews and Meta-Analyzes* (PRISMA) flowchart was used as a guide to conduct the research and report the results. [8]

Guiding question

In this stage, the PICO (patient/problem, intervention, comparison, and outcome) strategy was used, based on the construction of a question to guide the search for evidence. [7] The question was as follows: what parameters related to systemic antineoplastic treatment toxicity profile should be considered to ensure patient safety during systemic antineoplastic treatment?

Thus, the PICO strategy was employed by conferring the following: P, cancer patients undergoing systemic antineoplastic treatment; I, parameters for safe antineoplastics prescription; C, no comparator; and O, patient safety.

Search strategy

The studies were identified using an individual search strategy for each of the following electronic databases: EMBASE (Excerpta Medica dataBASE), LILACS (Latin American and Caribbean Literature on Health Sciences), and PubMed (developed by the National Center for Biotechnology Information), in addition to searching the grey literature using Google Scholar. We used the following controlled descriptors indexed in databases such as Emtree, DECs, and MeSH as well as synonyms descriptors, with the Boolean operators AND and OR: ("antineoplastic agents" OR "anticancer agents" OR "antineoplastic drugs" OR "antineoplastics" OR "antitumor agents" OR "antitumor drugs" OR "cancer chemotherapy agents" OR "cancer chemotherapy drugs" OR "chemotherapeutic anticancer agents" OR "chemotherapeutic anticancer drug" OR "antineoplastic agents, immunological" OR "immune checkpoint" OR "checkpoint inhibitors" OR "checkpoint inhibitor" OR "antineoplastic agents, immunological" OR "immunological antineoplastic agents" OR "immune therapy" OR "immunotherapy" OR "checkpoint inhibitors" OR "immune-checkpoint" OR "immune checkpoint inhibitor" OR "immune checkpoint inhibitors" AND "drug-related side effects and adverse reactions" OR "adverse reactions" OR "drug toxicity" OR "drug related side" OR "effects and adverse reactions" OR "side effects of drugs" OR "drug side effects" OR "adverse drug reaction" OR "adverse drug reactions" OR "adverse drug event" OR "adverse drug events" OR "drug toxicities") AND ("patient safety" OR "patient safeties").

The duplicate references were removed using an appropriate software (EndNote Basic®). All electronic searches in the databases were performed on July 2, 2020.

The selection of studies was made using an online application (Rayyan®, Qatar Computing Research Institute). In the first phase, two researchers (FVA and PEDR) independently analyzed the titles and abstracts of all the studies identified in the electronic databases and selected those that appeared to fulfill the inclusion criteria. Subsequently, the same researchers proceeded to independently read these selected studies in full and excluded those that did not fulfill the inclusion criteria. Any disagreements in the first or second phase were resolved through discussion and consensus between the two researchers.

Eligibility criteria

In this integrative review, original studies published in English, Spanish, or Portuguese, registered in electronic databases in the period 2010-2019, which contained information on adverse events related to systemic antineoplastic treatment in non-hematological neoplasms, strategies for safety in prescribing systemic antineoplastic treatment, and strategies for pharmacovigilance and risk management were included. The exclusion criteria were as follows: studies that did not include information on adverse events related to systemic antineoplastic treatment in non-hematological neoplasms, strategies for safety in prescribing systemic antineoplastic treatment, and strategies for pharmacovigilance and risk management; studies that included patients aged below 18 years; studies in languages that did not belong to the alphabet alphanumeric; studies that addressed hematological tumors; pre-clinical research studies *in vitro* or *in vivo*, clinical research studies in phase I or II; systematic reviews, meta-analyses, abstracts, posters, letters to the editor, opinions, book chapters, case reports, and research protocols.

Categorization of studies

Two researchers (FVA and PEDR) organized and summarized the information about the included studies: characteristics of the study (author, objective, country, and year of publication); characteristics of the population (mean age, n, antineoplastic treatment); study design; main results; and conclusions. Any disagreements were resolved through discussion and agreement between the two researchers.

Evaluation of included studies

The evaluation of the individual methodological quality of the primary studies included in the sample was performed using the *Joanna Briggs Institute (JBI) critical appraisal tools* (Joanna Briggs Institute, 2014) [9] by considering the appropriate tool for the type of design included. Two reviewers independently (FVA and PEDR) evaluated the studies using the checklists corresponding to the design of the included studies. Each of the questions was rated "yes," "no," or "not applicable." The assessment of the methodological quality of a study aimed to determine the extent to which a study addressed the possibility of bias in its design, conduct, and analysis. Thus, they were categorized as follows according to the risk of bias: high, when the study achieved a "yes" score below 49%; moderate, when the study achieved a "yes" score between 50% and 69%; and low, when the study had a "yes" score above 70%. [10]

Interpretation of results and knowledge synthesis

All the studies analyzed evaluated parameters that are considered to improve the quality and safety of the prescription of antineoplastic chemotherapy. Based on the objective of each study, they were divided into three categories. The first category included studies that addressed adverse events related to systemic antineoplastic treatment in non-hematological malignant neoplasms.

The second category included studies that addressed strategies for safety in prescribing antineoplastic treatment. The third category included studies that addressed strategies for pharmacovigilance and risk management.

RESULTS

The initial bibliographic research identified 1,595 studies using three electronic databases. After the removal of the duplicate references, the titles and abstracts of 1,529 studies were analyzed, and 21 potentially relevant studies were selected for a full reading. Of these, 8 studies fulfilled all the eligibility criteria and were included in this integrative review. Figure 1 illustrates the flowchart of the processes of identification, screening, and inclusion of studies.

All studies were published in English from 2015 to 2019 and evaluated systemic antineoplastic treatment. In total, five studies addressed adverse events related to systemic antineoplastic treatment in non-hematological malignant neoplasms, and included 4,970 patients treated with immunotherapy, target therapy, and chemotherapy. [11-15] One study evaluated issues related to the safety of prescribing antineoplastic agents. [4] Finally, two studies included a pharmacovigilance and risk management approach evaluating the adverse effects related to immunotherapy, chemotherapy, and target therapy. [16,17] The characteristics of the studies included in this integrative review are described in Table 1.

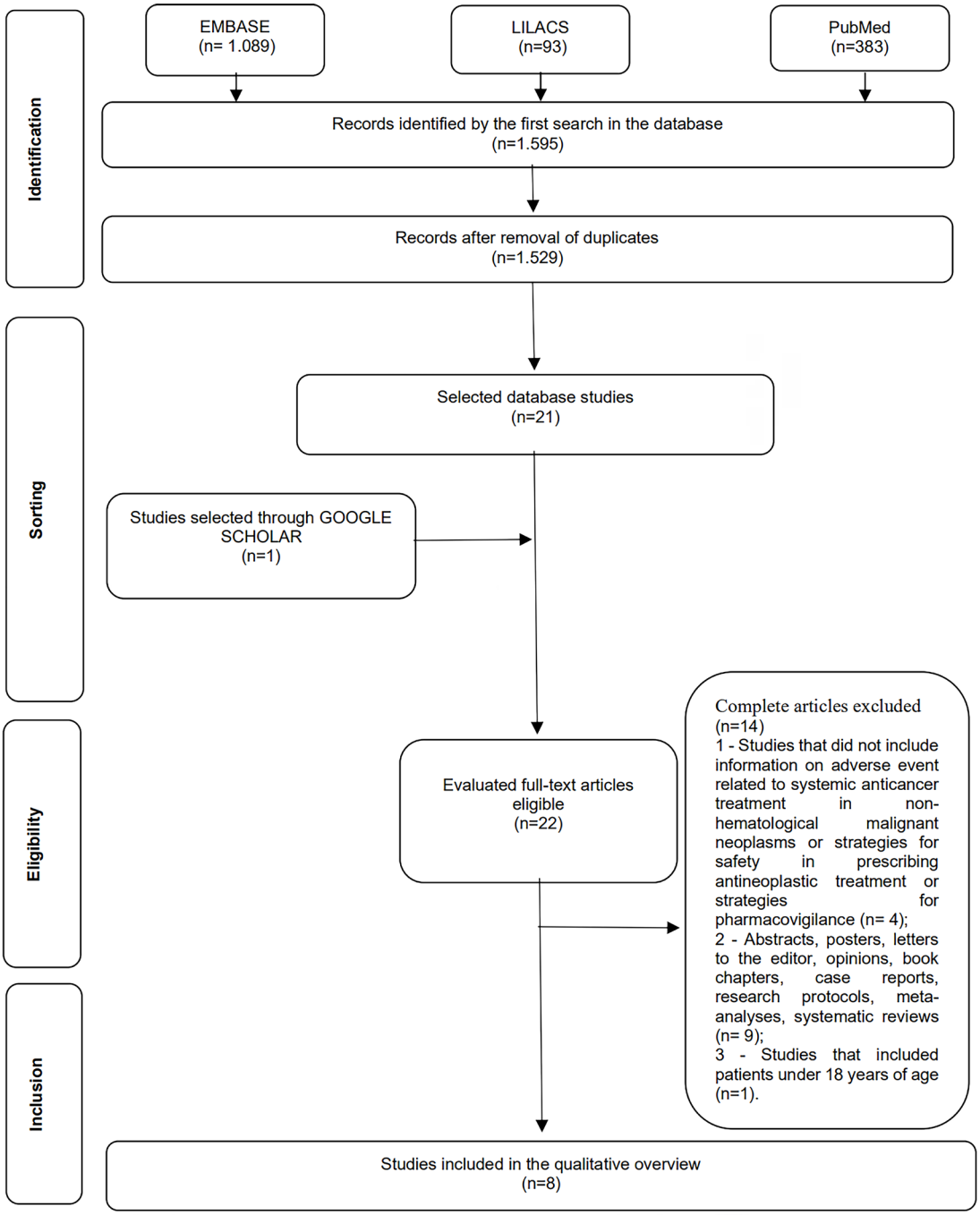

Figure 1 - Flow chart of search criteria and literature selection (adapted from *Preferred Reporting Items for Systematic Reviews and Meta-Analyzes* - PRISMA).

Table 1. Summary of the characteristics of studies included in this integrative review (n=8)

Year, author, country	Objective	Number of patients or adverse event(n)	Antineoplastic treatment	Study design	Main results	Main findings
Studies that addressed adverse events related to systemic antineoplastic treatment in non-hematological neoplasms (n=5)						
2018, Aguiar et al Portugal[11]	To characterize adverse events of immunotherapy and target therapy reported in patients with locally advanced or metastatic melanoma	111 patients 61 year-old	Immunotherapy Target Therapy	A prevalence study in the period 2011-2017	Most received immunotherapy (63.1%). The frequency of adverse events was lower in the anti-PD-1 group. Adverse events of grade 3 to 4 occurred in 15.3% of the cases, being more common in the target therapy group	It is suggested that adverse events related to immunotherapy and target therapy be identified using the Cancer Registry database. Underreporting of adverse events in cancer can have potential implications for the patient's quality of life
2019, Canale et al Itália[12]	To evaluate the association between cardiovascular risk factors and cardiac toxicity in patients treated with anthracyclines with or without trastuzumab	610 patients	ChT Target Therapy	A prevalence study in the period 2008-2016	The frequency of cardiac toxicity was higher in the group that presented cardiovascular risk factors (4.7%) than in the control group (3.2%). All patients in the control group who developed late cardiac toxicity presented cardiovascular risk factors at the time of toxicity not previously reported	Cardiovascular risk factors can predict late cardiac toxicity and their control should be part of the oncologic follow-up program
2019, Desjardin et al França[13]	To investigate factors associated with hepatotoxicity due to preoperative ChT in patients operated for liver metastasis from colorectal cancer	147 patients	ChT	A retrospective study from January 2003 to May 2015	ChT was based on oxaliplatin (40.1%), irinotecan (55.8%), or both (4.1%). The specialist pathologist described 38.8% of vascular lesions, including dilation, nodular regeneration, and peliosis. Steatohepatitis was observed in 10.2% of patients, most frequently after irinotecan and in patients with body mass index > 25 kg/m2	There is a likely association between nonalcoholic steatohepatitis (NASH) and irinotecan. Oxaliplatin seems to lead to upper vascular lesions
2015, Dranitsaris et al Canadá[14]	To determine whether the patient's individual risk factors could worsen NVChT	152 patients	ChT	RCT. Patients scheduled to receive anthracycline-based adjuvant ChT were categorized between low or high risk for NVChT	High-risk patients were 2–4 times more likely to suffer from acute nausea, despite the addition of aprepitant, long-term dexamethasone, and low-dose olanzapine	Despite the addition of aprepitant, dexamethasone, and olanzapine, patients at high risk of NVChT due to personal risk factors were unable to achieve good control of nausea

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Year, author, country	Objective	Number of patients or adverse event(n)	Antineoplastic treatment	Study design	Main results	Main findings
2019, Tervonen et al Austrália[15]	To evaluate the risk of emergency hospital admission and survival outcomes of 5 years after adjuvant ChT for early-stage breast cancer	3.950 patients	ChT Target Therapy	A retrospective study from January 2008 to May 2012	A total of 30.6% of the patients were hospitalized, the most common causes being neutropenia (30.8%), fever (8.6%), and infections (8%). Hospitalizations were more common in women using protocols containing docetaxel. Overall survival over 5 years was similar for women who were (92.2%, 95% CI 90.7–93.8) and were not hospitalized (93.1%, 95% CI 92.1–94.1)	Emergency hospitalizations after ChT were relatively common. Neutropenia was the most common diagnosis in admissions, indicating that these admissions may be related to ChT. The 5-year survival results were good, with no difference between the need for hospitalization
Study that addressed the strategies for safety in prescribing antineoplastic treatment (n=1)						
2019, Patel, Gurumurthy Índia[4]	To detect and monitor adverse ChT reactions and evaluate the impact of clinical pharmacists' interventions in minimizing these reactions	1.133 patients	ChT	Single-centre quasiexperimental study with the first phase of adverse reaction data collection from 2013 to 2014, followed by an intervention phase over 2 years (2014 to 2016)	The most common reactions were vomiting (23.22%), alopecia (9.53%), diarrhea (8.67%), and myelosuppression (7.42%). Inadequate administration of antiemetics (22%), suboptimal support treatment (18%), and administration errors (16%) was identified as avoidable contributing factors. The percentage of avoidable contributing factors was 81% during year 1 (pre-intervention), and 45% and 34% in year 2 and year 3, respectively (postintervention)	The interventions of clinical pharmacists helped to minimize the avoidable adverse reactions of ChT
Studies that addressed pharmacovigilance and risk management strategies (n=2)						
2017, Ali and Watson Estados Unidos da América[16]	To characterize the safety profile of ICI treatment regarding immune-mediated reactions	1,018 immunemediated adverse reactions 62 years	Immunotherapy	A prevalence study that analyzed adverse event reports submitted to the Food and Drug Administration's Adverse Event Notification System between 2011 and 2015	The most frequent reactions were colitis (51%), endocrinopathies (16%), pneumonitis (12%), hepatitis (11%), infusion-related reactions (4%), nephritis (3%), and other reactions (3%)	Checkpoint inhibitors are associated with adverse immune-mediated reactions, particularly colitis and pneumonitis. Pharmacoepidemiological studies are needed to assess the signs identified
2016, Belachew et al Etiópia[17]	To assess the pattern of adverse drug reactions in patients with cancer treated with ChT	203 patients 43,3 years	ChT	A prevalence study from September 2013 to August 2015	The most frequent reactions were nausea and vomiting (18.9%), infections (16.7%), neutropenia (14.7%), fever and/or chills (11.3%), and anemia (9.3%). 65.8% were grade 3–4 (severe), 29.9% were grade 1- 2 (mild), and 4.3% were grade 5 (toxic)	The high incidence of chemotherapyrelated adverse reactions among cancer patients is of concern. However, early detection can help minimize the damage, either by modifying the dose or by making auxiliary and support therapies available

PD-1: programmed cell death protein; ChT: chemotherapy; RCT: Randomized Clinical Trial; ICPis: Immune Checkpoint Inhibitors; NVChT: nausea and vomiting induced by chemotherapy; CI: Confidence Interval

Based on the evaluation of the methodological quality using the JBI tool, [10] the total scores of the studies according to their design were as follows: 69.2% for randomized clinical trial (RCT); [14] 80% for the retrospective studies; [13,15] 87,5% a 100% for the prevalence studies [11,12,16,17] and 77,7% for the quasi-experimental study. [4]

Therefore, seven studies [4,11-13,15-17] included in this integrative review presented scores above 70%, reaching the low risk of bias and high methodological quality according to the JBI tool, while one study presented a score of 69.2%, [14] reaching moderate methodological quality, as shown in Table 2.

Table 2. Evaluation of the methodological quality of the studies included according to the JBI critical evaluation checklist study design

Reference	Study design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total	Risk
Aguiar et al., 2018[d 11]	Prevalence	Y	N	Y	Y	Y	Y	Y	Y	NA	-	-	-	-	87,5%	Bass
Ali, Watson, 2017[d 16]	Prevalence	Y	Y	Y	Y	Y	Y	Y	Y	NA	-	-	-	-	100%	Bass
Belachew et al., 2016[d 17]	Prevalence	Y	Y	Y	Y	Y	Y	Y	Y	NA	-	-	-	-	100%	Bass
Canale et al., 2019[d 12]	Prevalence	Y	Y	Y	Y	N	Y	Y	Y	NA	-	-	-	-	87,5%	Bass
Desjardin et al., 2019[b 13]	Retrospective	Y	Y	Y	Y	Y	N	N	Y	Y	Y	-	-	-	80%	Bass
Dranitsaris et al., 2015[a 14]	RCT	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	69,2%	Moderated
Patey, Gurumurthy, 2019[c 4]	Quasi-experimental	Y	Y	Y	N	N	Y	Y	Y	Y	-	-	-	-	77,7%	Bass
Tervonen et al., 2019[b 15]	Retrospective	Y	Y	Y	Y	Y	N	N	Y	Y	Y	-	-	-	80%	Bass

Legend: *Y (yes); N (no); NA (does not apply)*

[a] *What is JBI's tool for RCT: Q1. Has true randomization been used to assign participants to treatment groups? Q2. Has the allocation to treatment groups been hidden? Q3. Were treatment groups similar at baseline? Q4. Were participants blinded to treatment assignment? Q5. Were those administering the treatment blind for treatment allocation? Q6. Were the outcome evaluators blinded to treatment assignment? Q7. Were the treatment groups treated identically except for the intervention of interest? Q8. Was the follow-up complete and, if not, were the differences between groups in terms of follow-up adequately described and analyzed? Q9. Were the participants analyzed in the groups to which they were randomized? Q10. Were the results measured in the same way for the treatment groups? Q11. Were the results measured reliably? Q12. Was an appropriate statistical analysis used? Q13. Was the study design appropriate and were any deviations from the standard RCT design (individual randomization, parallel groups) taken into account in conducting and analyzing the study?*

[b] *JBI tool questions for retrospective study: Q1. Were the groups comparable, except for the presence of disease in the cases or the absence of disease in the controls? Q2. Were the cases and controls properly combined? Q3. Were the same criteria used to identify cases and controls? Q4. Was exposure measured in a standard, valid, and reliable manner? Q5. Has exposure been measured in the same way for cases and controls? Q6. Were confounding factors identified? Q7. Have strategies been established to address confounding factors? Q8. Were the results evaluated in a standardized, valid, and reliable way for cases and controls? Q9. Was the exposure period of interest long enough to be significant? Q10. Was appropriate statistical analysis used?*

[c] *Questions of the JBI tool for quasi-experimental study: Q1. Is it clear from the study what is the "cause" and what is the "effect" (that is, there is no confusion about which variable comes first)? Q2. Were participants included in any similar comparison? Q3. Were participants included in any comparisons that received similar treatment/care, other than the exposure or intervention of interest? Q4. Was there a control group? Q5. Were there multiple measurements of the outcome before and after the intervention/exposure? Q6. Was the follow-up complete and if not, were the differences between groups in terms of follow-up adequately described and analyzed? Q7. Were the results of the participants included in any comparison measured in the same way? Q8. Were the results reliably measured? Q9. Was an appropriate statistical analysis used?*

[d] *Questions of the JBI tool for prevalence study: Q1. Was the sample frame appropriate to address the target population? Q2. Were study participants sampled in an appropriate way? Q3. Was the sample size adequate? Q4 Were the study subjects and the setting described in detail? Q5. Was the data analysis conducted with sufficient coverage of the identified sample? Q6. Were valid methods used for the identification of the condition? Q7. Was the condition measured in a standard, reliable way for all participants? Q8. Was there appropriate statistical analysis? Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?*

Source: Own authorship.

DISCUSSION

Some studies have evaluated the toxicity profile of chemotherapy, target therapy, and immunotherapy in systemic antineoplastic treatment. In a meta-analysis that included 20 RCTs, it was observed that ICPis have a different toxicity profile than chemotherapy (ChT), with programed death (PD)-1/PD-ligand1 inhibitors having fewer adverse events of grade 3, 4, and 5 than ChT (13.8% vs. 39.8%, $p<0.001$) or cytotoxic-T-lymphocyte- associated-antigen-4 inhibitors (13.4% vs. 22.8%, $p<0.001$). [18] Two integrative review studies have reported that ICPis are associated with immune-mediated adverse reactions, with the three main areas of toxicity being endocrine, hepatobiliary, and respiratory disorders. [11,16]

Regarding chemotherapy, the most frequent reactions were nausea and vomiting (18.9%), infections (16.7%), neutropenia (14.7%), fever and/or chills (11.3%), and anemia (9.3%), as reported in another study. [17] In an RCT, it was observed that individual risk factors of the patient, such as nausea before treatment, anxiety, and reduced sleep before the chemotherapy cycle, can worsen nausea and vomiting induced by chemotherapy. [14]

Additionally, in a study evaluating the risk of emergency hospital admission in patients undergoing adjuvant chemotherapy for early-stage breast cancer, it was observed that 30.6% of patients were hospitalized, with the most common causes being neutropenia (30.8%), fever (8.6%), and infections (8%). [15]

One study assessed cardiac toxicity in patients treated with chemotherapy and target therapy, [12] it was observed that cardiovascular risk factors can predict late cardiac toxicity and its control should be a part of the oncologic follow-up program as the incidence of cardiac toxicity was higher in the group that presented cardiovascular risk factors (4.7%) than in the control group (3.2%).

In two other studies, the high incidence of chemotherapy-related adverse reactions among patients with cancer was evaluated, and it was concluded that early detection can help to minimize the damage, either by modifying the dose or by providing auxiliary and supportive therapies; [17] the importance of detecting and monitoring adverse ChT reactions was also shown since interventions by clinical pharmacists minimize preventable ChT adverse reactions. [4]

The use of chemotherapy and other systemic agents for cancer is changing rapidly. The treatment is improving steadily, the rate of introduction of new drugs is accelerating, and the number of patients benefiting from such treatments is increasing rapidly. However, with these benefits come concerns regarding safety in prescribing systemic antineoplastic treatment and risk management. [19]

International manuals provide information on essential elements that should be incorporated and documented in evaluations of systemic antineoplastic treatment. This information intends to assist health professionals in clinical decision-making, in order to better assess patients who are able to receive the treatment. Therefore, clear documentation of the intention to treat, selection of the treatment protocol, as well as assessment of comorbidities and the patient's nutritional status should be included in the pre-prescription assessment. [20-22]

Elderly patients (≥65 years) who are receiving systemic antineoplastic treatment need careful evaluation to identify vulnerabilities that may not be identified in routine cancer assessments. The guidelines of the American Society of Clinical Oncology (ASCO) recommends using tools such as CARG (Cancer and Aging Research Group) or CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) to obtain estimation of the risk of treatment toxicity. [23]

Prescription safety is a highly significant issue when systemic antineoplastic treatment is used as a treatment modality due to the high potential for damage from these agents and the disease for which they are being used. The complexity of the treatment regimens used to achieve the best therapeutic effect versus an acceptable toxicity leaves a limited margin of error. Overdosage may result in death due to adverse effects of treatment, while under dosage may have significant implications for disease control. [24]

ASCO guidelines recommends not indicating antineoplastic treatment for patients with solid tumors who have not benefited from previous treatment and have an Eastern Cooperative Oncology Group (ECOG) performance status with a score greater than or equal to 3 - that is, a symptomatic patient who is bedridden for more than 50% of the day. [25] The ECOG performance status is related to the attempt to quantify the general well-being of patients and is often used as an indicator to assess whether the patient will be able to tolerate and respond to treatment. [26]

Potential side effects of chemotherapy include nausea and vomiting, mouth ulceration, diarrhea, hair loss, and bone marrow depression. Treatment-related toxicity varies in severity and is classified using the common toxicity criteria. [27] Adjustments in treatment dose and prophylactic use of antiemetics, antibiotics, and bone marrow stimulants have reduced the severity of side effects. However, one of the most serious complications of treatment is neutropenic sepsis. Bone marrow depression leads to a reduction in the number of neutrophils in the peripheral blood, with reduced ability of the immune system to fight infection. Systemic infection as a result of neutropenia can be fatal. [24]

By contrast, immunotherapy has transformed cancer treatment. However, the increasing use of immune-based therapies, including the widely used ICPis, has exposed a group of irAEs. Many of these are controlled by the same immune mechanisms responsible for the therapeutic effects of the drugs, that is, blocking inhibitory mechanisms that suppress the immune system and protect tissues from an acute or unrestricted chronic immune response. [28]

Cutaneous, intestinal, endocrine, pulmonary, and musculoskeletal irAEs are relatively common, while cardiovascular, hematological, renal, neurological, and ophthalmological irAEs occur much less frequently. Most of the irAEs are mild to moderate in severity; however, severe and, occasionally, life-threatening irAEs are reported, and treatment-related deaths occur in up to 2% of patients, varying according to the ICPi. Immune-related adverse events usually have a late onset with prolonged duration compared to adverse events of chemotherapy, and effective management depends on early recognition and immediate intervention using immunosuppression and/or immunomodulatory strategies. [28]

With this, the need for a multidisciplinary approach to recognize, report, and manage specific organ toxicity related to immunotherapy has arisen. Specialist physicians, nurses, and pharmacists familiar with irAEs should be involved at an early stage for early recognition and immediate intervention using appropriate immunosuppression and/or immunomodulatory strategies according to the affected organ and severity of toxicity. [28]

CONCLUSION

Regarding adverse events related to systemic antineoplastic treatment, it was observed that chemotherapy, targeted therapy and immunotherapy have different toxicity profiles. It is important to identify and document these adverse events, because targeted approaches are needed for each type of treatment.

Strategies for systemic antineoplastic treatment prescription safety, such as early detection and monitoring of associated adverse events, help to minimize the damage caused by adverse reactions. A multidisciplinary approach is important to recognize, report and manage the risk of treatment.

The evidence from the studies included in this integrative review is limited; however, it suggests that the evaluation of treatment related adverse events as well as risk management strategies should be considered to improve the quality and safety of the systemic antineoplastic treatment.

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