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Adverse reactions related to checkpoint inhibitors: an integrative review

Reações adversas relacionadas aos inibidores de checkpoint: uma revisão integrativa

Reacciones adversas relacionadas a los inhibidores de checkpoint: una revisión integradora

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ABSTRACT

Objective: to examine for adverse reactions and determine their prevalence in cancer patients using checkpoint inhibitors. **Method**: this integrative literature review used a combination of the descriptors: "immunotherapy" AND "adverse reaction" AND "Neoplasms", in a five-year time frame, in the MEDLINE and Cochrane databases. **Results**: seventeen articles, all in English, were found (14 in MEDLINE and three in CINAHL). The main adverse reactions identified were diarrhea, colitis, pneumonitis, fatigue, rush, hepatic, and endocrine changes. The articles revealed that, when the treatment involved Nivolumab and Ipilimumab together, prevalence of these reactions was higher (from 42% to 57% of patients). **Conclusion**: with the rapid expansion of the use of checkpoint inhibitors, a therapy that increases survival, knowing their adverse events becomes essential for quality care.

Descriptors: Nursing; Neoplasms; Immunotherapy; Drug-Related Side Effects and Adverse Reactions; Toxicity.

RESUMO

Objetivo: analisar as reações adversas nos pacientes oncológicos em uso de inibidores de checkpoint e sua prevalência. **Método**: revisão integrativa da literatura, utilizando a combinação de descritores "Imunoterapia" *AND* "Reação adversa" *AND* "Neoplasias", no recorte temporal de cinco anos, incluindo as bases CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), CINAHL (*Cumulative Index to Nursing and Allied Health Literature*) e Cochrane. **Resultados**: foram encontrados 17 artigos, sendo 14 da base de dados MEDLINE e três da base de dados CINAHL, todos na língua inglesa. As principais reações adversas identificadas foram diarreia, colite, pneumonite, fadiga, *rush*, alterações hepáticas e endócrinas. Os artigos revelaram maiores prevalências dessas reações quando o tratamento está associado às medicações Nivolumabe e Ipilimumabe juntas, sendo observadas em cerca de 42% a 57% dos pacientes. **Conclusão**: com a rápida expansão do uso dos inibidores de *checkpoint*, uma terapêutica que aumenta a sobrevida desses pacientes, conhecer seus eventos adversos torna-se primordial para um cuidado de qualidade.

Descritores: Enfermagem; Neoplasias; Imunoterapia; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Toxicidade.

RESUMEN

Objetivo: analizar reacciones adversas en pacientes con cáncer, utilizando inhibidores de checkpoint y su prevalencia. **Método**: revisión integradora de la literatura, utilizando la combinación de descriptores "Inmunoterapia" *y* 'Reacción adversa" *y* "Neoplasias", en un recorte temporal de cinco años, incluyendo las bases de datos CINAHL (Cumulative Index to Nursing and Allied Health Literature y Cochrane. **Resultados**: se encontraron 17 artículos, siendo 14 de la base de datos MEDLINE y 3 de la base de datos CINAHL, todos en inglés. Las principales reacciones adversas identificadas fueron diarrea, colitis, neumonitis, fatiga, erupción cutánea, alteraciones hepáticas y endocrinas. Los artículos revelaron una mayor prevalencia de estas reacciones cuando el tratamiento se asocia con los medicamentos Nivolumab e Ipilimumab juntos, observándose en alrededor del 42% al 57% de los pacientes. **Conclusión**: con la rápida expansión del uso de inhibidores de checkpoint, una terapia que aumenta la sobrevida de esos pacientes, conocer sus eventos adversos se vuelve fundamental para una atención de calidad.

Descriptores: Enfermería; Neoplasias; Inmunoterapia; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Toxicidad.

INTRODUCTION

According to the National Cancer Institute[1], cancer is considered the main public health problem in the world, being among the four main causes of premature death (before 70 years of age) in most countries. There has been an increase in the incidence and mortality from cancer around the world. This fact is related to aging, population growth and the change in the distribution and prevalence of cancer risk factors, especially those associated with socioeconomic development.

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It was estimated in 2020 that one in five people in the world had a cancer diagnosis during their lifetime, considering the increase in life expectancy. These numbers could double by 2040, with a greater increase in low- and middle-income countries[2].

The estimate for each year of the 2020-2022 triennium in Brazil indicates that there will be 625,000 new cases of cancer (however, this number drops to 450,000 excluding non-melanoma skin cancer). The most incident will be non-melanoma skin cancer with 177 thousand new cases, followed by breast and prostate with 66 thousand new cases each, then colon and rectum with 41 thousand, lung with 30 thousand, and stomach with 21 thousand[1].

Despite the great evolution in treating cancer, especially in chemotherapy and radiotherapy, many adverse reactions are observed in patients, as these are therapies which affect both cancer cells and normal ones. Thus, target-specific therapeutic actions which are less aggressive and with fewer adverse events have been studied[3].

It is observed that immunotherapy has been used more in cancer treatment in recent years, given its therapeutic action against the large number of tumors[4]. This type of treatment is based on using the immune system itself to induce an antitumor response.

The immune system plays a fundamental role in preventing, controlling and eliminating cancer cells[5]. However, it is noteworthy that there are several immune suppression and evasion mechanisms which occur within the tumor microenvironment, thus allowing cancer cells to grow and spread in the body.

This modality was consolidated as a therapeutic pillar for cancer in the last decade after years of basic and clinical research on the role of immune system modulation in cancer treatment. Monoclonal antibodies targeting inhibitory co-receptors involved in immune synapse modulation have been approved in Brazil for clinical use. For example, ipilimumab (anti CTLA-4 agent) for melanoma patients; nivolumab and pembrolizumab (anti PD1 agents) for patients with lung cancer, melanoma and more recently, renal carcinoma and PD-1 ligand (PD-L1) blockers such as atezolizumab, avelumab and durvalumab[6].

There are immune system pathways that regulate the immune response which are the immunological checkpoints[7]. The same authors reported that these checkpoints modulate the immune response to reduce damage to healthy tissues when the immune response is no longer needed. However, it is known that cancer cells can use these pathways to bypass the immune response and proliferate. Thus, with the discovery of these important immunological checkpoints in the early 1990s, researchers investigated ways to inhibit checkpoints to fight malignancy.

Checkpoints are receptors for blocking the activity of immune cells, being a non-specific active immunotherapy approach. Tumors use these receptors as a strategy to evade immune surveillance, commanding them and using them to block the immune response. As a result of this blockade, “brakes” are released on the cells of the immune system, increasing their ability to destroy tumor cells[6]. This type of cancer therapy shows promising results, in addition to observing a constant evolution in its use. Therefore, oncology nurses need to stay up to date with these new immunomodulatory therapies. This includes understanding its effectiveness, thus managing side effects[7].

Due to the rapid clinical development of this class of drugs, knowledge of adverse reactions and their pathophysiological mechanisms becomes essential in view of their specific characteristics, which differ from those observed in conventional cytotoxic chemotherapy[6]. In view of the above, this article aims to analyze the adverse reactions in cancer patients using checkpoint inhibitors and their prevalence.

METHOD

This is an integrative review of the available literature which was developed based on the following steps: establishing the hypothesis and objectives of the integrative review; establishing inclusion and exclusion criteria for articles (sample selection); defining the information to be extracted from the selected articles; analyzing the results; discussion and presenting results; and the last step consisted of presenting the review[8].

The PICO strategy was used to construct the question, adapted to PIO. In this case, P (population) was cancer patients, I (intervention) was the use of checkpoint inhibitors, and O (outcome) was observed adverse reactions and prevalence. Given the above, the following question culminated: “What are the main adverse reactions presented in cancer patients using checkpoint inhibitors and their prevalence?”. Next, three databases were used to select the articles: CINAHL (Cumulative Index to Nursing and Allied Health Literature), MEDLINE (Online Medical Literature Analysis and Retrieval System) and Cochrane, during the period from 03/31/2019 to 06/02/2019.

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The following inclusion criteria were subsequently considered to verify compliance with the eligibility criteria: articles adhering to the theme, published in Portuguese, English and Spanish, with abstracts available in the selected databases, in a five-year time frame (2015 to 2020), as this is a more up-to-date survey. Publications of editorials, dissertations and theses were defined as exclusion criterion, as well as repeated/duplicate articles, keeping only the one present in a database.

The search was performed by crossing the following exact Health Sciences Descriptors (DeCS): "*Imunoterapia*" AND "*Reação adversa*" AND "*Neoplasias*" and the following Medical Subject Descriptors (MeSH): "Immunotherapy" AND "Neoplasms" AND "Adverse drug reaction" OR "Drug toxicity". Titles were initially identified and abstracts were later identified in order to select the articles which met the inclusion criteria.

The scientific articles were read by two independent reviewers in order to verify the fit with the eligibility criteria. A third reviewer was requested if there was any divergence in the article selection.

The analysis was performed using a synthetic table specifically built for this purpose which included the following aspects: title; authors; year; results/considerations; and evidence level. Thus, the data extracted from the selected studies was synthesized descriptively, enabling a more in-depth and specific view of the subject.

Next, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) international guide was used in order to further improve the data presentation obtained from surveying the articles; the PRISMA Statement consists of a checklist with 27 items in a four-step flowchart in order to help authors improve the reporting of systematic reviews and meta-analyses[9].

The design of each selected study was subsequently observed to identify the evidence level, and the following levels were assigned: level I for systematic reviews and meta-analysis of randomized clinical trials; level II for randomized clinical trials; level III for non-randomized controlled trials; IV for case-control or cohort studies; V for systematic reviews of qualitative or descriptive studies; VI for qualitative or descriptive and VII for articles of opinion from authorities and/or expert committee reports. Thus, a classification of strong evidence level is given to studies of levels I and II, moderate for those from levels III to V, and weak comprises those from levels VI to VII[10].

RESULTS

A total of 27 articles were located in the MEDLINE database. Then, a sample of 14 articles was obtained after critical and reflective reading of the titles and abstracts. Furthermore, three articles were found in Cochrane, however one was not eligible, while two were duplicates from the MEDLINE database. Next, eight articles were found in CINAHL, one of which was repeated as it was in the MEDLINE database, and four were not eligible. Therefore, the final sample of this review consisted of 17 articles, all in English, as illustrated in the flowchart below in Figure 1.

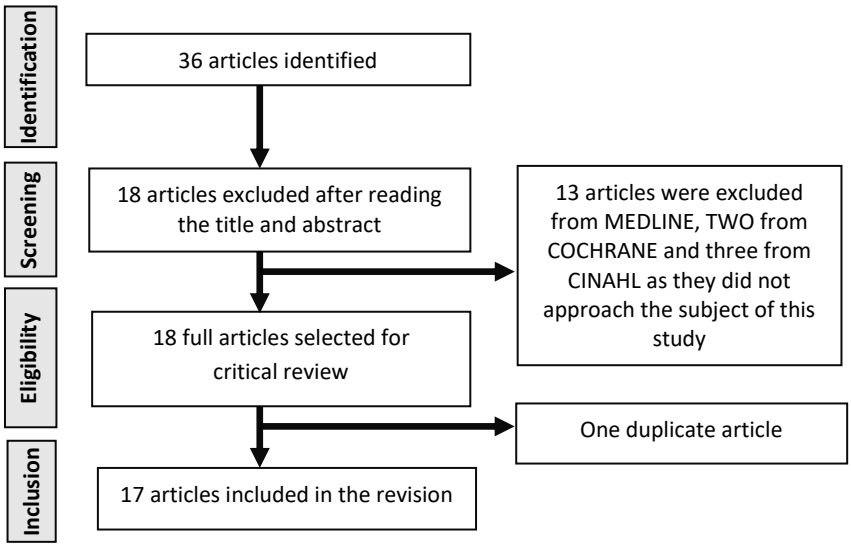

FIGURE 1: Flowchart of articles obtained from the databases used. Niterói, RJ, Brazil, 2020.
Source: Prepared by the authors.

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Of the 17 articles analyzed, four (23.5%) were developed in France, two (11.7%) in the USA, three (17.6%) in Australia, two (11.7%) in Belgium, one (5, 5%) in China, one (5.5%) in Germany, one (5.8%) in Egypt, one (5.8%) in Lebanon, one (5.8%) in Japan and one in Spain (5.8%).

Figure 2 is the synthesis of the selected articles, emphasizing their considerations about the theme, publication year and the scientific evidence level, showing that most of the selected articles (52.9%) were categorized as evidence level V, which refers to qualitative or descriptive systematic review studies. Three articles (17.6%) were classified as level I for systematic reviews and meta-analysis of randomized clinical trials; three (17.6%) were classified with evidence level VI for qualitative or descriptive studies; one (5.5%) was classified as evidence level II, which corresponds to randomized clinical trials; and one (5.5%) as IV, case-control or cohort studies.

Article title	Year	Evidence level	Adverse reactions evidenced
A1-Neurologic immune-related adverse events associated with immune-checkpoint inhibitors	2017	V	Headache, dizziness.
A2-Recognizing and managing on toxicities in cancer immunotherapy	2017	V	Most common are rush and colitis. The rarest are hypophysitis, pancreatitis, pneumonitis.
A3-New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management	2017	V	Diarrhea, colitis, hypophysis, immune hepatitis and polyarthritis.
A4-Supportive care for patients undergoing immunotherapy	2017	VII	Skin, gastrointestinal, pulmonary, endocrinological, ophthalmological, neurological reactions.
A5-Immune Checkpoint Inhibitor-Induced Colitis: Diagnosis and Management	2017	VII	Gastrointestinal adverse reactions, including diarrhea and colitis.
A6-Acute management of autoimmune toxicity in cancer patients on immunotherapy: Common toxicities and the approach for the emergency physician	2017	V	Diarrhea and colitis, hepatitis; endocrinopathies and pneumonitis.
A7-Immune-related musculoskeletal toxicities among cancer patients treated with immune checkpoint inhibitors: a systematic review	2017	I	Arthralgia and/or myalgia.
A8-Opportunistic autoimmunity secondary to cancer immunotherapy (OASI): An emerging challenge	2017	V	Gastrointestinal (diarrhea and colitis); hepatic; dermatological; joints; pulmonary and endocrine
A9-Update on New Therapies With Immune Checkpoint Inhibitors	2016	V	Diarrhea; elevated liver enzymes; rush; upper respiratory infection; peripheral neuropathy.
A10-Immune checkpoint inhibitors side effects and management	2016	I	Fatigue, decreased appetite, fever, chills, arthralgia and headache, itching.
A11-Dermatologic adverse events of checkpoint inhibitors: what an oncologist should know	2016	V	The main dermatological reactions observed were: rush, itching and hypopigmentation.
A12-Immune-related adverse events with immune checkpoint blockade: a comprehensive review	2016	V	Vitiligo, rush, mucositis, gastrointestinal, endocrine, liver and lung disorders, neurological syndromes, fatigue.
A13-Immune checkpoint inhibitors renal side effects and management	2016	V	Different types of checkpoint inhibitors may have different renal reactions.
A14-Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors A Systematic Review and Meta-analysis	2018	I	Colitis; pneumonitis; hepatitis; hypophysitis; myositis; nephritis; neurological toxicity.
A15- Phase I study of Nivolumab, an anti-PD-1 antibody, in patients with malignant solid tumors	2016	II	Constipation, diarrhea; cardiac toxicity; fatigue; erythema; itching; rush; decreased appetite.
A16- Pembrolizumab: a case of drug-induced autoimmune diabetes mellitus and colitis	2018	VII	Adverse reactions presented: loss of appetite and diarrhea.
A17- *Prognostic implications of co-occurring dermatologic and gastrointestinal toxicity from immune checkpoint inhibition therapy for advanced malignancies: a retrospective cohort studyImplicações*	2020	IV	Dermatologic and gastrointestinal reactions (irAEs) are among the most common and early toxicities.

FIGURE 2: Sample summary according to title, year, evidence level and evidenced adverse reactions. Niteroi, RJ, Brazil, 2020.

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Figure 3 shows the prevalence of immune-related reactions reported in the selected studies, divided by selected article, according to the medications used and the respective degrees of adverse reactions described.

ARTICLE	PREVALENCE
A1	Grades 3, 4 and 5: 10 - 16% with anti-PD-1 Nivolumab and Pembrolizumab. 10 - 42% with anti CTLA4 Ipilimumab and 55% with the combination of Nivolumab and Ipilimumab.
A2	Grade 3-4 colitis with Ipilimumab: 6% - 14%. Diarrhea and colitis: 21% in melanoma patients who received Nivolumab. Diarrhea and colitis: 17% in patients with NSCLC who received Nivolumab. Dermatological: related to the use of Nivolumabe - 28% to 36%.
A3	Ipilimumab: up to 85%. PD1 inhibitors: up to 70%. Pneumonitis: higher incidence (5% to 10%) was reported in the combination of Nivolumab with Ipilumumab.
A4	Grade 3-4 toxicities have been reported at approximately 21%. Dermatological: with Nivolumab (42%), with Ipilimumab (55%) and with two (59%-71%). Diarrhea and colitis: about 30% who received Ipilimumab. Hepatotoxicity: 3-9% with Ipilimumab. Pneumonitis and endocrine toxicities: less than 10%.
A5	Grade III and IV toxicities are seen in up to 10%. Diarrhea: up to 30% in all grades. Colitis: 0.3% - 7%.
A6	Ipilimumab with Nivolumab: 42%-57% in grades 3-4. Nivolumab: 10%-20%. Ipilimumab: 20%-27%.
A7	Arthritis/arthralgia: with the use of Ipilimumab (22%) and with Nivolumab (1%). Myositis with the use of Pembrolizumab: between 0.4% to 6%.
A8	Nivolumab and Pembrolizumab: reactions in about 70%. Ipilimumab: reactions in about 90%. Gastrointestinal events (grade 3-4): less than 10% in patients who received Nivolumab and Pembrolizumab.
A9	Nivolumab: 41%. Pembrolizumab: 36%. Ipilimumab: 64%.
A10	Ipilimumab: 15-43% for fatigue; 24-25% for pruritus; 23-27% for diarrhea; 8-13% for colitis. Nivolumab: 20-33% for fatigue; 10-17% for pruritus; 3-16% for diarrhea. Pembrolizumab: 11-12% for fatigue; 14-23% for pruritus; 12-21% for rush; 8-20% for diarrhea. Ipilimumab with Nivolumab: 35-39% for fatigue; 40-41% for rush; 44-45% for diarrhea.
A11	Ipilimumab: dermatological reactions (45%).
A12	Ipilimumab: about 90%. Nivolumab/Pembrolizumab/Atezolizumab/Durvalumab: about 70%.
A13	Ipilimumab/Nivolumab: 3.2% renal toxicity.
A14	Ipilimumab: fatal adverse effects (colitis/diarrhea: 70%). Nivolumab or Pembrolizumab: fatal adverse effects (pneumonia: 35%). Ipilimumab/Nivolumab: fatal adverse effects (colitis: 37%).
A15	Nivolumab: lymphopenia in 58.8%.
A16	Pembrolizumab: hypothyroidism (7.4%); pneumonia (2.6%); hyperthyroidism (2.4%).
A17	Of the 67 patients with colitis, 28 (42%) also developed cutaneous toxicity.

FIGURE 3: Summary of the prevalence of immune-related reactions. Niterói, RJ, Brazil, 2020.
Source: Prepared by the authors.

DISCUSSION

It can be said that most of the articles (9) reported general reactions regarding the description of immunorelated adverse reactions, meaning that common reactions were observed in patients using checkpoint inhibitors with a prevalence of about 70% in patients using Nivolumab or Pembrolizumab, and up to 90% in patients treated with Ipilimumab. However, there were articles that exposed specific reactions such as neurological, dermatological, gastrointestinal, musculoskeletal and renal, also highlighting a higher prevalence of gastrointestinal events with about 10% to 30%.

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The most frequently cited gastrointestinal reactions in the selected articles were diarrhea and colitis. It was reported in one of the studies that diarrhea incidence is higher in patients who receive CTLA-4 blockers compared to patients who are treated with PD115 receptor inhibitors.

Dermatological events, such as pruritus and rush, are also highlighted in the articles studied, as they were mentioned in ten of them[15]. It is extremely important that nurses know the specific clinical characteristics for this toxicity, thus making a clinical-pathological correlation, including the detailed history of the treatment and the appearance of these lesions. In turn, a specific diagnosis supports disease prevention, adequate treatment and the possibility of treatment continuity[27].

Rush, itching and hypopigmentation were evidenced in a study which specifically portrays dermatological reactions, being the most frequent and precocious, requiring quick and appropriate management[20].

In one study, it was shown that adverse reactions related to the dermatological and gastrointestinal immune system (irAEs) are among the most common and initial toxicities in patients who use immunological control point inhibitors.

The highest prevalence of adverse reactions was related to the use of protocols with Nivolumab associated with Ipilimumab, in which fatigue can be observed in 35-39% of patients, rush in 40-41%, and diarrhea in 44-45%.

Early identification of any adverse reaction symptom is of fundamental importance so that a quick intervention can be made. This care has the main objective to avoid harm to the patient[28].

All articles portrayed the importance of early management of adverse events, as they can significantly change the quality of life of patients. Clear and effective guidance on immune-related reactions is essential to reduce these events and/or detect them as early as possible.

Only one article reported the role of oncologist nurses in managing the care of patients who use this therapy, emphasizing the importance of being prepared to change the treatment options available to their patients[7].

The engagement of nurses together with the medical and pharmaceutical team in protocol production is of paramount importance for the care of cancer patients, thus resulting in fast and accurate care based on scientific evidence[29].

CONCLUSION

It was observed that all articles found and selected to answer the question of this review are in English, and were conducted in other countries. This points to a gap with regard to national publications on a topic of great importance and such repercussion in the oncology field, thus evidencing a study limitation.

Given the expansion of the use of checkpoint inhibitors, it is essential to know their adverse reactions for quality care, as the growing use of this new class of drugs can interfere with the prevalence of clinical autoimmune diseases.

These immune-related reactions can significantly alter the quality of life of patients. Thus, it is extremely important to carefully monitor and prevent them. The best management of these events is related to the possibility of early identification.

Knowing these new adverse reactions, as well as their prevalence, supports the development of specific treatment strategies for these patients.

The articles selected for this study provide subsidies to continue with research in the area, as it is a therapy which increases the survival of cancer patients and can benefit a significant number of cancer patients.

The Nursing team has a key role in terms of the care of patients undergoing treatment with immunotherapeutics, as they are complex-acting drugs in the body, requiring specialized attention and care. The team needs to be well trained, to understand the action mechanisms and possible adverse reactions, thus preventing clinical complications.

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