Original Article

Clinical profile of cancer patients and hypersensitivity reactions to systemic chemotherapeutic agents

Perfil clínico de pacientes oncológicos e reações de hipersensibilidade aos agentes antineoplásicos sistêmicos

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ABSTRACT | OBJECTIVE: to identify the clinical profile of cancer patients and hypersensitivity reactions to systemic chemotherapeutic agents. **METHOD:** this is a documentary and retrospective study, with data obtained from medical records of cancer patients undergoing chemotherapy. 249 clinical records were analyzed between january 2013 and january 2014 to identify hypersensitivity reactions and extract demographic and clinical data. **RESULTS:** six medical records of patients with episodes of hypersensitivity to chemotherapy were identified. 66,7% were female patients, with an average age of 58,4 years (SD: ± 14,9) and stage III cancer (66,7%), whereas colon and ovarian tumors were the most prevalent types (33,3%). The incidence of hypersensitivity reactions was 2,4%. Of the 12 episodes studied, respiratory distress was the most frequent symptom (58,3%) and hyperemia was the most frequent sign (50%). Rituximab was the antineoplastic agent most associated with such reactions (33,3%), followed by the combination of FOLFOX and bevacizumab (25%). Most episodes occurred in the second chemotherapy cycle (25%). **CONCLUSION:** the hypersensitivity reactions to chemotherapy depends on the drugs selected and the responses developed by the patients, with a wide range of signs and symptoms.

DESCRIPTORS: Chemotherapy. Antineoplastic agents. Drug hypersensitivity.

RESUMO | OBJETIVO: identificar o perfil clínico de pacientes oncológicos e reações de hipersensibilidade aos agentes antineoplásicos sistêmicos. **MÉTODO:** trata-se de um estudo documental e retrospectivo, com dados obtidos de prontuários clínicos de pacientes oncológicos em tratamento quimioterápico. Foram analisados 249 prontuários clínicos entre janeiro de 2013 e janeiro de 2014 para identificar reações de hipersensibilidade e extrair dados demográficos e clínicos. **RESULTADOS:** foram identificados seis prontuários de pacientes com episódios de hipersensibilidade aos quimioterápicos. Na amostra 66,7% foram pacientes do sexo feminino, com idade média de 58,4 anos (DP: ± 14,9) e câncer em estágio III (66,7%), sendo os tumores de cólon e ovário os tipos mais prevalentes (33,3%). A incidência de reações de hipersensibilidade foi 2,4%. Nos 12 episódios estudados, o desconforto respiratório foi o sintoma mais frequente (58,3%) e hiperemia foi o sinal mais frequente (50%). O rituximabe foi o agente antineoplásico mais associado a tais reações (33,3%), seguido pela combinação de FOLFOX e bevacizumabe (25%). A maioria dos episódios ocorreram no segundo ciclo quimioterápico (25%). **CONCLUSÃO:** as reações de hipersensibilidade à quimioterápicos sistêmicos dependem dos fármacos selecionados e das respostas desenvolvidas pelos pacientes, com ampla variação de sinais e sintomas.

DESCRITORES: Quimioterapia. Antineoplásicos. Hipersensibilidade a drogas.

Submitted 04/17/2020, Accepted 10/01/2020, Published 10/27/2020
J. Contemp. Nurs., Salvador, 2020 October;9(2):185-191
Doi: 10.17267/2317-3378rec.v9i2.2876 | ISSN: 2317-3378

How to cite this article: Barbosa-Lima R, Kameo SY, Vassilievitch AC, Fonseca TV, Silva GM, Sawada NO. Clinical profile of cancer patients and hypersensitivity reactions to systemic chemotherapeutic agents. J Contemp Nurs. 2020;9(2):185-191. doi: 10.17267/2317-3378rec.v9i2.2876

Introduction

Adverse reactions to drugs can be understood as negative and exacerbated responses evoked by a pharmacological agent used conventionally in the treatment of any disorder or disease. These events occur in significant portions of patients hospitalized and treated in outpatient clinics, frequently associated with morbidities and mortality, seen as a challenge for public health[1-2].

Cancer is a disease treatable by several approaches, including the use of specific drugs. An exponential increase in new cancer cases worldwide is expected, approximately 70% in the next two decades, accompanied by millions of annual deaths[3]. With the advancement of this condition, new therapeutic strategies, including drugs, have been developed and improved over the years[3-4].

The systemic drugs used to treat cancer, known as antineoplastic agents, have the potential to trigger hypersensitivity reactions in cancer patients due to the immune response that these drugs can evoke in the body. The raise in the production and use of these drugs, justified by the increase in cancer cases, has elevated the frequency of these reactions in these individuals. Understanding, reporting and monitoring these events can contribute to avoid complications related to hypersensitivity reactions[3-5].

Hypersensitivity reactions can manifest themselves acutely and late in several degrees of severity, according to the dose of the drug administered in the blood plasma. These reactions can lead patients to not undergo chemotherapy or to force the use of second-class drugs that are less effective in the treatment, in addition to being associated with higher death rates and decreased quality of life. However, it is important to note that all antineoplastic agents can evoke such reactions[5-6].

When hypersensitivity reactions occur during the first hour after infusion of an antineoplastic drug, they can be classified as immediate, whose main signs and symptoms are bronchospasm, urticaria, angioedema and anaphylactic reactions. After this time, they are classified as late, whose main symptoms are dermatitis, maculopapular eruptions, vasculitis and rashes. This variation occurs due to the hypersensitivity mechanism caused by the drug in the body[3,7].

Risk factors to development of hypersensitivity reactions involve recurrent exposure to other drugs with high molecular weight, history of allergies, genetic aspects, female sex and viral infections, such as the Epstein-Barr virus. Concomitant use of different drugs is also associated with an increase of hypersensitivity reactions[7].

In addition, drug hypersensitivity reactions can also be classified according to severity and need for treatment at grade 0 (no occurrence / no intervention), grade 1 (mild / basic intervention), grade 2 (moderate / non-invasive intervention), grade 3 (severe / invasive intervention), grade 4 (risk of death / intensive care) and grade 5 (death)[6,8].

Research on the occurrence of hypersensitivity reactions has made significant progress in recent years, promoting greater safety in the use of antineoplastic agents[2]. However, hypersensitivity reactions affect approximately 7% of patients undergoing drug treatment and between 10 and 20% of hospitalized patients. The risk of lethal outcomes associated with these reactions can limit the use of antineoplastic agents and requires extensive investigations into the manifestation of these episodes[5].

Given this context, the objective of this study is to identify the clinical profile of cancer patients and hypersensitivity reactions to systemic chemotherapeutic agents.

Method

This is a documentary, retrospective, descriptive and quantitative study carried out with collection and

analysis of data from conventional (non-electronic) medical records of patients linked to a private oncology outpatient clinic located in the northeastern city. The outpatient clinic studied was chosen because it is an oncology service with a considerably high flow of patients and a significant volume of clinical records to analyze. Data collection took place between January 2013 and January 2014. The entire methodological procedure carried out was subject to review and approval by the Research Ethics Committee (CAAE 22939614.0.0000.5546).

All data collection procedures followed the bioethical guidelines for research with human beings and the Informed Consent Form (ICF) was waived due to the documentary nature of the study. There was no direct contact with the patients. The collection of data in the medical records occurred using a pilot form to systematize the data, maintaining the confidentiality of the patients involved.

Patients aged 18 years or over, with cytological or anatomopathological diagnosis of cancer, who underwent chemotherapy treatment between January 2006 and 2014 at the oncology service and who had episodes of hypersensitivity reactions were included. Clinical records duly filled in with patients' demographic and clinical data were eligible, discarding incomplete, illegible and not located.

Demographic and clinical data extracted from the included medical records were: sex, age, cancer diagnosis, chemotherapy agents experienced, cycle in which the adverse reaction occurred and the signs and symptoms presented. In addition to these, the procedures adopted in the face of hypersensitivity reactions were evaluated.

The data extraction was carried out by two independent researchers and trained through their own pilot form based on the desired demographic and clinical data. After the two evaluators selected the scope of medical records for inclusion, collected data were crossed to identify errors and minimize selection bias. After selection, data were stored in tables for further analysis and interpretation.

The statistical analysis was performed with the aid of Microsoft Excel software (2010). Descriptive statistics were performed to obtain means and frequencies of hypersensitivity reactions to systemic chemotherapy agents.

Results

249 clinical records of cancer patients undergoing chemotherapy were eligible. Of this total, six (2,4%) reported adverse reactions during the administration of antineoplastic drugs and were included in these results. In the six evaluated patients, 12 episodes of hypersensitivity to the administered antineoplastic agents were observed.

There was a predominance of female patients (66,7%), with a mean age of 54,8 years (SD: ± 14,9). Regarding the diagnosis, two patients had a colon tumor (33,3%), two ovarian tumors (33,3%), a non-Hodgkin lymphoma (16,7%) and a lung tumor (16, 7%). As for the clinical stage of the disease, four patients (66,7%) were in stage IV and two patients (33,3%) in stage III.

Regarding the antineoplastic agents of the twelve identified hypersensitivity reactions, four occurred during the administration of rituximab (33,3%), three during the administration of FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) and bevacizumab (25%), two during the combined administration of carboplatin and paclitaxel (16,7%), one during the administration of cisplatin (8,3%), one during the administration of carboplatin (8,3%) and one during the administration of bevacizumab (8,3%). Table 1 presents these findings in relation to the chemotherapy cycle in which they occurred.

Table 1. Frequency of hypersensitivity reactions according to the cycle and the antineoplastic drug, Aracaju, Sergipe, Brasil, 2014

Chemotherapy cycle	N	%	Antineoplastic drugs
I	1	8,3	FOLFOX + bevacizumab
II	3	25	FOLFOX + bevacizumab carboplatin bevacizumab
III	2	16,7	FOLFOX + bevacizumab cisplatin
IV	1	8,3	rituximab
V	1	8,3	rituximab
VIII	2	16,7	rituximab carboplatin + paclitaxel
IX	2	16,7	rituximab carboplatin + paclitaxel
Antineoplastic drugs	**N**	**%**	**Chemotherapy cycle**
Rituximab	4	33,3	IV / V / VIII / IX
FOLFOX + bevacizumab	3	25	I / II / III
Carboplatin + paclitaxel	2	16,7	VIII / IX
Carboplatin	1	8,3	II
Cisplatin	1	8,3	II
Bevacizumab	1	8,3	II

Source: data collected from clinical records.

Considering the clinical signs and symptoms presented during hypersensitivity reactions, the main manifestation observed was respiratory distress, occurring in seven of the 12 episodes (58,3%) identified in the sample. Other manifestations observed were hyperemia (50%), tremors and chills (33,3%), decreased oxygen saturation (33,3%), skin rash (25%), pain (16,7%), nausea (16,7%), changes in blood pressure (16,7%), changes in heart rate (16,7%) headache (8,3%), psychomotor agitation (8,3%) and hyperthermia (8,3%).

Furthemore, regarding the procedures adopted by the outpatient service professionals, the infusion of antineoplastic drugs was stopped immediately when the clinical signs and symptoms of hypersensitivity reactions were observed. Nine of the 12 cycles that presented such reactions were restarted after the clinical improvement of the patients, without new episodes of hypersensitivity after the reinfusion of the antineoplastic agent. However, three cycles were suspended after the improvement of the condition, considering the individualities of each patient, as well as three cycles had the infusion time recalculated and increased after the occurrence of the hypersensitivity reaction.

The replacement of the antineoplastic drug to prevent new episodes of hypersensitivity only occurred in one cycle. After management and clinical improvement of the patient, the combination of carboplatin and placitaxel was replaced by liposomal doxorubicin. After the replacement of chemotherapy, no new episodes of hypersensitivity were observed and the patient completed the cycle.

Discussion

Unlike our results, Bertolazzi and collaborators (2015) found a higher incidence of facial hyperemia (23,5%), followed by respiratory changes (20,9%) during hypersensitivity reactions to antineoplastic agents. In addition, paclitaxel was the antineoplastic agent most involved in these episodes, followed by oxaliplatin (23,1%). Hypersensitivity reactions affected only 0,24% of the investigated patients[6].

In fact, paclitaxel is an antineoplastic drug that is often associated with hypersensitivity reactions and is not well tolerated by patients. However, due to its high effectiveness in several tumors, it is still widely spread and prescribed, especially in cases of breast and ovarian cancer[9]. The same still occurs with rituximab, which was the antineoplastic drug most associated with adverse reactions in our results. With high efficacy in lymphoid neoplasms, rituximab has been used in immunochemotherapies in an increasing way in the last decade, although it is highly related to hypersensitivity reactions[10].

Clinical signs and symptoms of hypersensitivity reactions to rituximab can range from respiratory changes to chills and tremors, being expected in more than half of the patients who use this agent. On the other hand, new strategies involving biosimilars and desensitization techniques have reduced the occurrence and severity of reactions involving rituximab[10-11].

Hypersensitivity reactions evoked by the administration of this antineoplastic drug are rarely severe, frequently affecting the respiratory system and the main signs and symptoms are cough, rhinitis, bronchospasm, hypotension, dyspnoea and sinusitis. This symptomatological cluster is consistent with our findings, however, a point in which there is a difference refers to hypotension, since an increase in blood pressure was observed after the eighth cycle in one of the cases[11-13].

Although there is no consistent evidence for some classes of antineoplastic drugs, desensitization is an alternative to avoid hypersensitivity reactions, that is, patients are exposed to premedications and attenuated doses of the antineoplastic agent, inducing the body to tolerate it until the necessary therapeutic dose is reached. This technique is considered safe and with significant success rates, however, it needs more clinical evidence for some antineoplastic drugs[5,14].

Hypersensitivity to platinum agents is often reported in the scientific literature. For oxaliplatin, reactions can occur in several cycles of chemotherapy treatment. For cisplatin and carboplatin, reactions commonly occur in advanced stages of treatment. For platinum agents, the signs and symptoms of hypersensitivity are similar and skin tests are useful to project the risk of hypersensitivity reactions and indicate desensitization protocols[15-16].

Recently, Chung and collaborators (2018) evaluated a new desensitization protocol for platinum (oxaliplatin, carboplatin and cisplatin). In their results, the authors reported that pre-medication with histamine receptor blockers (H1 and H2) associated with Montelukast medication was effective in reducing the incidence of hypersensitivity reactions in patients with a history after administration of any platinum derivative[17].

In fact, despite the significant increase in hypersensitivity reactions to antineoplastic drugs worldwide, desensitization techniques can reduce their occurrence, being considered a safe procedure that allows the administration of the most effective therapeutic doses of drugs, avoiding interruptions in the treatment and improving prognosis[18-19].

The management of hypersensitivity reactions and their risks are important points in oncology services. In these places, all the equipment and medicines needed to revert the clinical conditions must be on standby, as well as a clinical protocol for systematizing care in the face of hypersensitivity reactions are essential, and all professionals must be accustomed with the conducts[20-21].

Considering the complications related to hypersensitivity reactions, it is essential to know the most used antineoplastic drugs and the signs and symptoms associated with their use. Prevention and management actions should be guided according to the characteristics of the drug and the patient involved

in each episode of hypersensitivity, considering the pharmacological history in relation to the use of antineoplastic agents, previous adverse reactions, skin tests and desensitizing therapies[21-23].

Thus, it is important that equipment and support resources are available in the environment in which the administration of antineoplastic drugs will be performed, such as defibrillators, oxygen and the drugs used to reverse adverse clinical conditions, especially epinephrine, antihistamines and bronchodilators. When a hypersensitivity reaction is identified, as the first action, the infusion of the chemotherapy should be stopped immediately, followed by placing the patient in the supine position and checking his vital signs[24].

In addition, patients undergoing chemotherapy must receive all information relevant to the use of antineoplastic agents. Side effects and the possibility of developing hypersensitivity reactions to the drugs used are part of the scope of information that must be told to patients before starting treatment[25].

Conclusion

The hypersensitivity reactions identified in the sample show a wide range of drugs, signs and associated symptoms according to the individual immune response of each patient. However, the occurrence was considered low and no lethal events were identified. In the face of drugs frequently associated with hypersensitivity reactions, the development of prevention and clinical management strategies can reduce their impact on cancer treatment.

Author contributions

Kameo SY and Sawada NO participated in the study design, data collection, statistical analysis, interpretation, writing and approval of the final version. Barbosa-Lima R, Vassilievitch AC, Fonseca TV and Silva GM participated in the study design, statistical analysis, interpretation, writing and approval of the final version.

Competing interests

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to, grants and funding, participation in advisory council, study design, preparation of manuscript, statistical analysis, etc.).

References

1. Regateiro FS, Faria E. Immunopathological mechanisms of drug hypersensitivity reactions. Rev Port Imunoalergologia. 2016;24(2):63-78.

2. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127(3):S74-81. doi: 10.1016/j.jaci.2010.11.048

3. Giavina-Bianchi P, Patil SU, Banerji A. Immediate Hypersensitivity Reaction to Chemotherapeutic Agents. J Allergy Clin Immunol Pract. 2017;5(3):593-599. doi: 10.1016/j.jaip.2017.03.015

4. Waheed A, Hill T, Dhawan N. Drug Allergy. Prim Care Clin Office Pract. 2016;43(3):393-400. doi: 10.1016/j.pop.2016.04.005

5. Babaie D, Shamsian BS, Momtazmanesh N, Godarzipour H, Amirmoini M, Bashardoust B et al. Rapid Desensitization for Hypersensitivity Reactions to Chemotherapeutic Drugs; A Case Series. Iran J Pharm Res. 2019;18(2):1047-1051. doi: 10.22037/ijpr.1999.1100664

6. Bertolazzi LG, Lanza MVC, Bitencourt EC, Canille RMS, Pereira LPS, Oliveira KA et al. Incidence and characterization of immediate side effects to infusion of chemotherapeutic at a sentinel hospital. Arq Ciên Saúde. 2015;22(3):84-90.

7. Dykewicz MS, Lam JK. Drug Hypersensitivity Reactions. Med Clin North Am. 2020;104(1):109-128. doi: 10.1016/j.mcna.2019.09.003

8. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [Internet]. 2010. [acesso em 2020 abr 16]. Disponível em: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

9. Chou PL, Huang YP, Cheng MH, Rau KM, Fang YP. Improvement of Paclitaxel-Associated Adverse Reactions (ADRs) via the Use of Nano-Based Drug Delivery Systems: A Systematic Review and Network Meta-Analysis. Int J Nanomedicine. 2020;15:1731-1743. doi: 10.2147%2FIJN.S231407

10. Prakash G, Malhotra P, Khadwal A, Lad D, Suri V, Kumari S et al. Infusion Related Hypersensitivity Reactions with Biosimilar Anti CD-20 Monoclonal Antibody Rituximab in Indian Patients: A Retrospective Study. Indian J Hematol Blood Transfus. 2018;34(2):273-277. doi: 10.1007%2Fs12288-017-0885-x

11. Ataca P, Atilla E, Kendir R, Bavbek S, Ozcan M. Successful desensitization of a patient with rituximab hypersensitivity. Case Reports Immunol. 2015;2015:524507. doi: 10.1155/2015/524507

12. Young JS, Simmons JW. Chemotherapeutic Medications and Their Emergent Complications. Hematol Oncol Clin North Am. 2017;31(6):995-1010. doi: 10.1016/j.hoc.2017.08.005

13. Pierpont TM, Limper CB, Richards KL. Past, Present, and Future of Rituximab-The World's First Oncology Monoclonal Antibody Therapy. Front Oncol. 2018;8:163. doi: 10.3389/fonc.2018.00163

14. Picard M, Castells MC. Re-visiting Hypersensitivity Reactions to Taxanes: A Comprehensive Review. Clin Rev Allergy Immunol. 2015;49(2):177-91. doi: 10.1007/s12016-014-8416-0

15. Otani IM, Wong J, Banerji A. Platinum Chemotherapy Hypersensitivity: Prevalence and Management. Immunol Allergy Clin North Am. 2017;37(4):663-677. doi: 10.1016/j.iac.2017.06.003

16. Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin hypersensitivity: evaluation, implications of skin testing, and desensitization. J Allergy Clin Immunol Pract. 2014;2(1):40-5. doi: 10.1016/j.jaip.2013.08.011

17. Chung SJ, Kang SY, Kang RY, Kim YC, Lee KH, Kim TY et al. A new non-dilution rapid desensitization protocol successfully applied to all-grade platinum hypersensitivity. Cancer Chemother Pharmacol. 2018;82(5):777-785. doi: 10.1007/s00280-018-3662-0

18. Bonamichi-Santos R, Castells M. Diagnoses and Management of Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: Reactions to Taxanes and Monoclonal Antibodies. Clin Rev Allergy Immunol. 2018;54(3):375-385. doi: 10.1007/s12016-016-8556-5

19. Bano N, Najam R, Qazi F, Mateen A. Clinical Features of Oxaliplatin Induced Hypersensitivity Reactions and Therapeutic Approaches. Asian Pac J Cancer Prev. 2016;17(4):1637-41. doi: 10.7314/apjcp.2016.17.4.1637

20. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. Clin Transl Immunology. 2015;4(7):e39. doi: 10.1038%2Fcti.2015.14

21. Cáceres MC, Guerrero-Martín J, Pérez-Civantos D, Palomo-López P, Delgado-Mingorance JI, Durán-Gómez N. The importance of early identification of infusion-related reactions to monoclonal antibodies. Ther Clin Risk Manag. 2019;15:965-977. doi: 10.2147%2FTCRM.S204909

22. Silva P, Heck AP, Silva BT, Azambuja AA. O manejo das reações agudas em quimioterapia. Acta Méd. 2015;36:6.

23. Souza NR, Melo JTS, Freire DA, Souza MAO, Oliveira MPB, Bezerra DM. Nursery and importance of professional qualification in radiotherapy services. Rev Enferm UFPI. 2016;5(3):18-23. doi: 10.26694/reufpi.v5i3.5496

24. Kobayashi T, Masaki T, Kogawa K, Matsuoka H, Sugiyama M. Hemoptysis and acute respiratory syndrome (ARDS) as delayed-type hypersensitivity after FOLFOX4 plus bevacizumab treatment. Int Surg. 2013;98(4):445-9. doi: 10.9738/INTSURG-D-12-00020.1

25. Beaver CC, Magnan MA. Managing Chemotherapy Side Effects: Achieving Reliable and Equitable Outcomes. Clin J Oncol Nurs. 2016;20(6):589-591. doi: 10.1188/16.CJON.589-591