Immediate adverse reactions in the chemotherapy treatment of patients with cancer at an oncology day hospital

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Abstract. A descriptive and cross-sectional study was performed to characterize the degree of immediate adverse reaction and the type of causative antineoplastic drug presented by 371 different patients treated for cancer at the oncology day hospital unit of the San Carlos Clinical Hospital (Madrid, Spain), during the period between January 2015 and December 2019. In the case series, 488 immediate adverse reactions secondary to chemotherapy toxicity were detected. The dominating factors were: Female sex, age from 51-70 years old, skin melanoma and the use of vinca alkaloids and analogs. Among the most frequent adverse reactions, the following stood out: Disorders of the nervous and musculoskeletal systems and of the connective tissue. There was a higher number of moderate adverse reactions (grade 2 according to the Common Terminology Criteria for Adverse Events Version 4.0) between the first and third chemotherapy cycles, with a latency period of between 6 and 15 min., generally lasting less than 30 min. Association with the degree of immediate adverse reaction (grade) has been observed in male subjects over 71 years of age, with soft tissue neoplasm type and monoclonal antibodies therapeutic group.

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Introduction

The demographic transition in developed countries establishes a high increase in the percentage of population >65 years of age. The projections of cancer incidence point to a future increase in figures, due in large part to the aging of population and the increase in life expectancy, which involve a greater exposure to risk factors associated with chronic non-communicable diseases (1).

Some types of tumors have increased rapidly as a cause of morbidity and mortality in an elderly population, a tendency which is associated with changes in lifestyle among a number of other causes. In Spain, with a high life expectancy at birth, there has been an increase in chronic non-communicable diseases including cancer, which is currently the main cause of years of life lost, showing a growing trend in both sexes. The number of cancer cases diagnosed in Spain in the year 2022 is estimated to reach 280,100 cases according to the calculations by the Spanish Network of Cancer Registries (REDECAN). An increase in the incidence of cancer is expected worldwide and, in this context, it is estimated that, in 2040, the incidence in Spain will reach 341,000 cases. In addition, in our country, 60% of new cancer diagnoses occur in individuals >65 years of age and 30% in those over 75 years of age (2).

The Covid-19 pandemic has probably had a significant effect on the number of diagnosed cancer cases in a number of countries during the year 2020 (3). In 2020, Spain was one of the most seriously affected countries by this pandemic during its first wave. Therefore, the number of cancer cases finally diagnosed in 2020 was lower than expected, due to fear of contagion in medical centers or difficulties in accessing the health system during the state of alarm period.

There are four main therapeutic approaches in cancer therapy; surgery, radiotherapy, chemotherapy and immunotherapy. It is important to indicate that two thirds of patients with neoplasms receive chemotherapy to destroy tumor cells at some point during their treatment. Chemotherapy is not exempt from complications and undesirable effects affecting other parts of the body, despite the fact that

Table I. Characterization of immediate adverse reactions.

Variable	Number (n=488)	Percentage (%)
Sex		
Male	113	22.7
Female	375	76.4
Age		
≥50	134	27.5
51-70	270	55.3
≥71	84	17.0
Type of medication (antineoplastic agents and immunomodulators; ATC code)		
Nitrogen mustard analogs (Cyclophosphamide)	1	0.2
Nitrosoureas (Streptozocin)	1	0.2
Vinca alkaloids and analogs (Vinorelbine)	1	0.2
Podophyllotoxin derivatives (Etoposide)	4	0.9
Taxanes (Paclitaxel, Doxetaxel, Cabazitaxel)	247	50.7
Anthracyclines and related substances (Doxorubicin)	13	2.8
Platinum compounds (Cisplatin, Carboplatin, Oxyplatin)	176	36.2
Monoclonal antibodies (Trastuzumab, Cetuximab, Bevacizumab, Panitumumab, Pertuzumab, Trastuzumab Emtansine, Atezolizumab, Pankomab)	39	7.2
Other antineoplastic agents (Irinotecan)	5	1.3
Cytokines (Interferon α-2b)	1	0.2
Number of chemotherapy cycles		
1st-3rd cycle	315	64.5
4th-6th cycle	84	17.2
7th cycle onwards	89	18.2
Grade of adverse reaction (CTCAE criteria)		
Grade 1. Mild adverse event	17	3.4
Grade 2. Moderate adverse event	328	67.3
Grade 3. Severe adverse event	119	24.3
Grade 4. Adverse event with risk of mortality or disability	24	4.9
Grade 5. Mortality associated with an adverse event	0	0.0
Duration of adverse reaction		
3 to 30 min	282	57.7
31 to 60 min	128	26.2
61 to 120 min	55	11.2
121 to 180 min	15	3.1
181 to 240 min	5	1.1
>241 min	3	0.6
Latency period		
2 to 5 min	89	18.2
6 to 15 min	146	29.9
16 to 30 min	91	18.7
31 to 60 min	63	12.9
61 to 120 min	71	14.6
121 to 360 min	28	5.6
Signs and symptoms of adverse reaction (SOC code)		
Cardiac disorders	15	1.1
Ear and labyrinth disorders	1	0.1
Eye disorders	26	1.9
Gastrointestinal disorders	119	8.7
General disorders and disturbances in the area of administration	53	3.9

Table I. Continued.

Variable	Number (n=488)	Percentage (%)
Musculoskeletal and connective tissue disorders	138	10.1
Nervous system disorders	151	11.1
Respiratory. thoracic and mediastinal disorders	278	20.5
Skin and subcutaneous tissue disorders	396	29.1
Vascular disorders	182	13.4

Table II. How the reactions were resolved by the health team.

Action	Percentage
Required pharmacological treatment	97.7
Infusion stopped	85.5
Infusion restarted at a lower speed	42.2
Patient needed observation	39.5
Infusion was not restarted	24.40
Dose was reduced	0.4

technological advances are allowing increasingly personalized treatments.

The characteristics of patients with cancer differ between age groups, due to the pathophysiological changes it causes in the human body in the different stages of life. The lack of knowledge about the frequency and magnitude of the adverse effects that antineoplastic drugs can cause in the human body has been the reason for conducting the present study.

The objectives were to characterize the immediate adverse reactions produced by the antineoplastic drugs administered at the day hospital and to analyze what factors can contribute to the degree of the adverse reaction.

Materials and methods

Design, participants and context. A descriptive and cross-sectional study was performed to characterize the immediate adverse reactions secondary to chemotherapy treatment that appeared in 371 different cancer patients treated at the oncology day hospital unit of the San Carlos Clinical Hospital, between January 2015 and December 2019.

Measurements. The measurement instruments used were the International Code of Diseases, 10th edition (ICD-10), for the type of neoplasm (4); the Anatomical, Therapeutic, and Chemical Classification System (ATC) (5), for the type of medication; and the classification by groups and systems (SOC), for signs and symptoms of the adverse reaction (6). The Naranjo algorithm was used to assess causality (7).

Variables. Among the variables analyzed, the following elements were prominent: Sex, age, type of neoplasm, type of drug, number of chemotherapy cycles, degree of adverse reaction, duration of treatment, latency period and signs and symptoms exhibited.

Data sources. Data were obtained from the review of all the records of suspected immediate adverse reaction to antineoplastic drugs during their administration. The criteria for inclusion of patients were: >18 years of age, having an active oncological disease, receiving intravenous antineoplastic chemotherapy as the sole treatment at the time of the adverse reaction and having the suspected adverse reaction symptoms develop during the patient's stay at the oncology day hospital unit. In addition, the information was completed with the clinical history of the patients and with the data provided by the hospital pharmacy service. All patient data were completely anonymized in compliance with the current data protection law.

Statistical methods. Frequency and percentage were used as descriptive summary measures and the χ^2 test with Yates correction was used to determine the differences between the independent variables and the degree of the immediate adverse reaction, which was considered as a dependent variable. $P<0.05$ was considered to indicate a statistically significant difference, equivalent to a confidence level of 95%. SPSS 23.0 (IBM Corp.) statistical was used for the analysis.

Results

From the total number of cancer patients treated with chemotherapy drugs during the study period, a total of 488 immediate adverse reactions were detected, corresponding to 371 different patients included in the research. The total number of sessions performed during the period under study was 11,098 antineoplastic chemotherapy sessions, adding up all the different cycles. This corresponds to 4.40% of the sessions. Table I shows that women had a more than three times higher number of immediate adverse reactions (76.4%), in which the predominant age range was middle age and the elderly (72.3%). Breast and female genital cancer were the most frequent malignant lesions (57.8%). The drugs most frequently implicated were taxanes (50.7%) and platinum compounds (36.2%). Immediate adverse reactions appeared mainly in the first three cycles (64.5%) and it is noteworthy that >90% of these adverse reactions were of moderate and severe magnitude (91.6%) and 5% were life threatening for the patient. Almost half of the reactions occurred within the first 15 min (48.1%) and almost all of them were resolved within the first hour (83.9%). Dermatological reactions (29.1%) and respiratory reactions (20.5%) appeared in half of the cases (49.6%).

Table II shows how the reactions were resolved by the health team. Medication was administered in 97.7% of the cases. Hydrocortisone 100 mg was used in 420 cases and dexchlorpheniramine was administered in 229 of them.

Table III. Risk factors associated with the degree of the adverse reaction (moderate-severe) and chemotherapy treatment.

Associated factor	χ^2	P-value	Highest risk group (appearance of moderate-severe reaction)
Sex	4.95	0.043	Male
Age	7.62	0.022	>71 years
Type of neoplasm	47.97	0.0001	Neoplasm of connective and soft tissues
Therapeutic group	22.16	0.0001	Monoclonal antibodies
Reason of care	7.72	0.020	Low complexity chemotherapy
Discharge reason	117.04	0.001	Urgent admission due to immediate adverse reaction
Therapeutic action against adverse reaction	30.64	0.001	Discontinuation of chemotherapy treatment

Table IV. Protection factors associated with the degree of adverse reaction (moderate-severe) and chemotherapy treatment.

Associated factor	χ^2	P-value	Higher protection group (appearance of none-mild reaction)
Type of neoplasm	47.97	0.001	Malignant neoplasm of the mouth and pharynx Neoplasm of male genital organs
Therapeutic group	22.16	0.0001	Anthracyclines
Toxic habits (alcoholism and smoking)	22.78	0.0001	No toxic habits

Table V. Causal relationship between the administered chemotherapeutic drug and the degree of immediate adverse reaction.

			None + Mild		Moderate + Severe		
Causality	χ^2	P-value	(n)	(%)	(n)	(%)	Total (n)
Final	4.49	0.069	17	85.0	3	15.0	20
None or possible			445	95.5	21	4.5	466
Total	-	-	462	95.1	24	4.9	486

Table III shows that a statistically significant association (P≤0.05) was found between the degree (grade) of the immediate adverse reaction (moderate or intense) and the following variables: Male, >71 years old, having a type of neoplasm affecting connective tissues and soft tissues, using monoclonal antibodies as a chemotherapy therapeutic group, remaining in a low-complexity administration protocol (expected duration of 1 or 2 h), being transferred to the emergency department after a discharge from the oncology day hospital and having to stop chemotherapy treatment in order not to re-expose the patient to the drug for any reason.

It can be observed that Table IV has highlighted the association between the degree (grade) of immediate adverse reaction (none-mild) and not having toxic habits (alcoholism and smoking). In addition, there is an association between mouth and pharynx malignant neoplasms and male genitalia malignant neoplasms with the therapeutic group of anthracyclines (P≤0.001), which behave as protective factors against intensity (moderate-severe) in the immediate adverse reaction to antineoplastic treatment.

Table V shows that in moderate-intense reactions there is a greater probability of them having a causal relationship with the administered drug (15%), expressing an association that, although not statistically significant, does have clinical relevance.

Discussion

The present study showed that the findings of immediate adverse reactions of moderate-severe magnitude are relevant, although, in a similar study the rates found (~75%) were lower than those observed in this one (8). The results of the present study are similar to observational studies performed in cancer patients; it is estimated that the risk of presenting an adverse reaction to a medication is 3 to 10 times higher in the elderly than in the young (9). This is mainly explained by the changes in pharmacokinetics that appear in the patient due to ageing.

The findings of the present study in terms of adverse reactions and the drugs that cause them to coincide with those of

another study in a similar series (10). However, other studies found different results (11,12).

Among the physiological factors related to the appearance of adverse reactions (13,14), being female stands out, perhaps due to the greater susceptibility of women to suffer these reactions due to differences in metabolism and the distribution of body fat. Thus, the action of fat-soluble drugs can last longer, a circumstance favored by estradiol.

Another study agrees that the females are more related prone to adverse effects (65.4%) than males (34.6%) (15). This susceptibility may be due to physiological characteristics of each sex and may be related to mechanisms of interaction between hormones and drugs and, as a result, of changes in pharmacokinetics and pharmacodynamics (16).

Dermatological reactions are very frequent (17). In the present study, skin and subcutaneous tissue disorders were one of the main reactions found.

In the present study, musculoskeletal and connective tissue effects appear frequently. Likewise, monoclonal antibodies prove to be a risk factor for moderate-severe reaction, a fact that other authors have already highlighted due to this therapy becoming a popular option (18).

In relation to the evaluation of the causality of an adverse drug reaction using the Naranjo algorithm (7), it is complicated by the fragility and complexity of the patients and also by the multiplicity of drugs used in the treatments (19). It is recommended to use integrated approaches of detection and evaluation of causality and mitigation. The present study analyzed the causality only with the Naranjo algorithm, which represents a weakness of the present study and is why this statistical analysis was performed. As a limitation in the present study, the determination of the ECOG functional status was not performed, despite being a parameter of interest.

Other limitations of the present study are it being a retrospective study, thus collecting the data from medical records and assuming that the vast majority of the reactions were registered. Also, having considered the patients from a single institution as the population for the study, instead of including patients from several centers in order to expand the number of patients and to improve the perspective and focus of the present study and the representativeness of the sample.

In an observational study performed in different cancer care centers with the aim of collecting all the adverse reactions due to chemotherapy, a group of 441 patients was included, 141 of whom had a diagnosis of colorectal cancer (20). The general characteristics of the patients included in that study were similar to those of the present study.

In conclusion, in the oncology day hospital unit of the San Carlos Clinical Hospital, the number of patients with an adverse reactions produced by vinca alkaloids and analogs was 371 within the five years of the study, with predominantly in women aged between 51 and 70 years old and with a higher incidence of melanoma. The main adverse reactions included disorders of the nervous system, the musculoskeletal system and connective tissue. There was a higher number of moderate adverse reactions, grade 2, between the first and third cycles, with a latency period between 6 and 15 min and a duration of less than 30 min.

Finally, the main risk factors that contribute to the appearance of an immediate adverse reaction during the administration of chemotherapy drugs were identified as: Male, >71 years old, with soft tissue neoplasms and low-complexity chemotherapy treatments with monoclonal antibodies. The protective factors against adverse reaction were not having toxic habits (alcoholism and smoking), being treated with anthracycline agents and mouth and oropharynx malignant tumors or male genitalia malignant neoplasms.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RMMR and ASS performed the planning of the study, the data collection, the review of the files, the presentation of the project to the Hospital Clínico San Carlos Ethics Committee and the preparation of the manuscript. ÁFGM, EOP and MLR performed the statistical analysis, the layout of the text and tables, the bibliographic search and the elaboration of the manuscript. RMMR and ASS confirm the authenticity of all the raw data. EOP and ÁFGM performed the bibliographic search, the first translation of the original draft and text review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval of the present study (approval no. 13/155-E) was obtained from the clinical research ethics committee, San Carlos Clinical Hospital (Madrid, Spain). Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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