Incidence, severity, and outcome of adverse events to chemotherapeutic drugs used in hematological malignancies: Data from a reference center

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Abstract

Objective: The aim of the study was to document the frequency, severity, evolution, and impact of adverse events (AE) on chemotherapy and the clinical evolution of patients with hematologic malignancies. **Material and Methods:** A prospective study was carried out at a hematology reference center in Northeastern Mexico over 1 year. All patients with malignant disease developing adverse chemotherapy events were included in the study. AEs were classified according to Common Terminology Criteria for AEs v5.0. **Results:** One-hundred and seventy-four patients attended the hematology clinic for outpatient chemotherapy. Acute lymphoblastic leukemia accounted for 51.7%, non-Hodgkin's lymphoma 25.9%, acute myeloid leukemia 9.8%, multiple myeloma 6.3%, Hodgkin's lymphoma 5.7%, and chronic myeloid leukemia 0.6% of the cases. A total of 191 AEs, including 79 hospital admissions, were registered in 58 (33.3%) patients. About 62.3% of the cases were Grade 3, in 43.9% of the events complete resolution was achieved, whereas the chemotherapy regimen had to be suspended in 13.6% of the cases. Febrile neutropenia was the main AE, documented in 77.6%; four (6.9%) patients died as a direct consequence of this complication. Thrombocytopenia occurred in 65.5% and anemia in 55.2%, with no deaths. **Conclusions:** AEs secondary to chemotherapeutic drugs used in the treatment of hematological malignancies constitute an important cause of morbidity and occasional mortality and should be closely monitored and documented.

Key words: Adverse event. Hematologic malignancy. Acute leukemia. Lymphomas. Febrile neutropenia.

Introduction

Cancer is the second leading cause of mortality in the world, and almost 1 out of 6 deaths are due to cancer¹. Hematological malignancies have a high incidence and mortality. In Mexico in 2014, hematological malignancies took thirteenth place in mortality, first in ages 5-9 and second in ages 10-14². The dictionary of the National Cancer Institute uses adverse effect and adverse event (AE) as interchangeable concepts, defined as an

unexpected medical problem that happens during treatment with a drug or other therapy³. There is a wide variety of chemotherapeutic agents used in patients suffering hematologic cancer, and the AEs that occur during treatment with these drugs are common. In most cases, patients receive combined chemotherapy schemes, using multiple drugs, thus increasing the risk of toxicity and vulnerability to AEs. The discontinuation of treatment is sometimes necessary for the management of toxicity due to antineoplastic agents, directly

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impacting the quality of life and clinical evolution of these patients⁴. It is important to know the frequency with which AEs occur due to agents currently used in hematology and the treatment strategies for an adequate intervention and resolution. In this respect, pharmacovigilance relates to the detection, assessment, understanding, and prevention of AEs or any other medicine-related problem⁵; this concept has just been introduced in low-middle income countries^{6,7}, and it has become of special importance in oncology due to the new drug therapies being tested and approved. Despite conducting an extensive search in the literature, we were not able to find reports on adverse chemotherapy events in hematology patients. This study is aimed to establish the incidence of AEs secondary to chemotherapy in patients with hematological malignancies and to determine its treatment and influence on clinical paths.

Materials and methods

This was a prospective observational study carried out at the Department of Hematology of the Universidad Autónoma de Nuevo León's, School of Medicine and Dr. José Eleuterio González University Hospital. For the purpose of this study, the term AE was used to include expected AEs secondary to the administration of chemotherapeutic agents. Patients of all ages and both sexes with a diagnosis of hematological malignancy who attended the outpatient clinic for ambulatory treatment and presented an adverse chemotherapy event were included to document the frequency, treatment, evolution, and impact on the chemotherapeutic regimen. Medical records were reviewed, and a database was built, which included demographic information, diagnosis, therapy regimen, and specific documentation of any AE related to the drugs administered, its treatment and clinical outcome; changes in scheduling, composition, and/or intensity of the proposed chemotherapeutic scheme were also documented.

Treatment protocols and outcomes for malignant hematology diseases in our population have been published⁸⁻¹⁶. For diagnosis and classification of the severity of AEs pertinent to this study, the Common Terminology Criteria for AEs v5.0¹⁷ were used. Patients with anemia and thrombocytopenia were included if they presented bleeding in the case of thrombocytopenia or anemic syndrome in the case of anemia, and/or those who required transfusion despite not presenting clinical manifestations. Evaluation after the management of AEs was classified as complete resolution, partial resolution, persistence, or death.

In the case of febrile neutropenia, complete resolution was defined as the complete absence of fever and total recovery of the neutrophil count after management. Partial recovery: the resolution of fever, without recovery of the neutrophil count; Persistence: the persistence of fever, without recovery of the neutrophil count. Death: the cause of death was directly related to the episode of fever and neutropenia.

In patients who presented thrombocytopenia, complete recovery was defined as the recovery of the platelet count and the absence of bleeding. Partial recovery: the absence of bleeding with the persistence of the platelet count below the lower limit of normal but with an increase in the numbers after the transfusion. Persistence: persistence of bleeding and a platelet count below the normal limit, with no increase in the post-transfusion count. Death: the cause of death was directly related to the presence of bleeding associated with thrombocytopenia.

In patients with anemia, complete recovery was defined as total recovery of hemoglobin levels and the absence of anemic syndrome. Partial recovery: the absence of anemic syndrome, with the persistence of the hemoglobin level below the lower limit of normal but with an increase after packed red blood cells transfusion. Persistence: persistence of the anemic syndrome and a hemoglobin figure below the limit of normality, with no increase after transfusion. Death: the cause of death was directly related to the presence of anemia.

For data analysis, the statistical package SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used; descriptive analysis was performed. Categorical data were reported as counts and percentages while continuous data were reported as means and standard deviations or medians and ranges. Informed consent was obtained from all individual participants included. The protocol was approved by the Ethics and Research Committee at the Institution.

Results

One-hundred and seventy-four patients attended the outpatient hematology clinic for ambulatory chemotherapy during the study period; 80 (46%) females and 94 (54%) males with a median age of 22.5 years (2-93). A total of 191 AEs were reported in 58 (33.33%) patients receiving treatment with antineoplastics, with an incidence of 3 (range 1-11) adverse chemotherapy events per patient; their median of age was 22 years (2-86); and a sum of 79 admissions was documented with a median of 1 (range 1-5) admission per patient.

Table 1. Severity of 191 adverse events in 58 patients with hematological malignancy receiving chemotherapy over a year. There was a median of three events per patient

Adverse event	Patient ^a	Events	Severity n (%) ^b				
	n (%)	n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Febrile neutropenia	45 (77.59)	55 (28.80)	0	0	48 (87.28)	3 (5.45)	4 (7.27)
Thrombocytopenia	38 (65.51)	44 (23.03)	0	21 (47.70)	23 (52.30)	0	0
Anemia	32 (55.17)	38 (19.90)	0	2 (5.26)	34 (89.48)	2 (5.26)	0
Nausea	12 (20.69)	12 (6.29)	9 (75)	3 (25)	0	0	0
Vomit	11 (18.97)	11 (5.76)	7 (63.64)	4 (36.36)	0	0	0
Constipation	5 (8.62)	5 (2.62)	1 (20)	2 (40)	2 (40)	0	0
Oral mucositis	13 (22.41)	13 (6.80)	1 (7.70)	8 (61.54)	4 (30.76)	0	0
Anal and oral mucositis	3 (5.17)	3 (1.57)	0	1 (33.33)	2 (66.64)	0	0
Tumor lysis syndrome	1 (1.72)	1 (0.52)	0	0	1 (100)	0	0
Hepatic toxicity	1 (1.72)	1 (0.52)	0	0	1 (100)	0	0
Exanthema	2 (3.45)	2 (1.05)	1 (50)	0	1 (50)	0	0
Cytosine arabinoside syndrome	1 (1.72)	1 (0.52)	c	-	-	-	-
Differentiation syndrome	2 (3.45)	2 (1.05)	0	0	2 (100)	0	0
Headache	3 (5.17)	3 (1.57)	0	3 (100)	0	0	0

^aA single patient can have more than one adverse chemotherapy event over time. ^bSeverity according to common terminology criteria for adverse events (CTCAE) Version 5.0. (17). ^cThe classification of this adverse event is not specifically described in the CTCAE manual.

Out of the 58 patients in this group, 25 (43.1%) were females and 33 (56.9%) males, ($p = 0.591$). The frequency of hematological malignancy in descending order was documented as follows: acute lymphoblastic leukemia (ALL) (24, 41.4%), acute myeloid leukemia (AML) (14, 24.1%), non-Hodgkin's lymphoma (NHL) (13, 22.4%), multiple myeloma (4, 6.9%), and Hodgkin's lymphoma (3, 5.2%), no AE was reported in patients with chronic myeloid leukemia. The highest percentage of AEs (96, 50.26%) and hospital admissions (41, 51.90%) occurred in 24 pediatric patients (< 16 years), followed by 84 AEs and 33 hospital admissions in 30 adults (16-64 years) and finally 11 AEs and 5 hospital admissions in four geriatric patients (≥ 65 years). Most of the patients were receiving chemotherapy alone ($n = 48$, 82.8%), 10 received a combination of chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation.

Out of the 58 patients who presented AEs, 16 (27.6%) had one or more associated comorbidities, including arterial hypertension in five patients, type 2 diabetes mellitus in four, and kidney disease in four patients. Twelve (20.7%) patients were receiving concomitant pharmacotherapy at the time of the admission,

including antihypertensive drugs, insulin, and calcium channel antagonists.

Febrile neutropenia was the main AE reported with a total of 55 episodes (28.8%) and with a Grade 3 severity in 87.3% of the cases. Two 6-year-old patients with a diagnosis of ALL B, a 15-year-old patient with NHL, and a 52-year-old patient with AML, all females, died of sepsis as a direct consequence of this AE; the responsible agents in the first two were *E. coli*, *corynebacterium* spp. in the NHL patient, and in the fourth case, fungal pneumonia was suspected, with no specific agent identified.

Thrombocytopenia (23%) followed in frequency, with 47.7% of events classified as Grade 2 and 52.3% as Grade 3. No deaths were directly associated with this event. Anemia ranked third in frequency (19.9%); 89.5% of the episodes were classified as Grade 3, with no associated deaths. The rest of the AEs reported, their frequency and severity throughout the study are shown in [table 1](#).

Medical management of febrile neutropenia was based on antibiotics, mainly third-generation cephalosporin and aminoglycosides; antifungal drugs were also used to cover frequent microorganisms and treatment was subsequently adapted to clinical evolution and results of cultures. Granulocyte-colony stimulating factor

Table 2. Clinical evolution of 191 adverse events in 58 patients with hematological malignancy receiving chemotherapy

Adverse event	Patients ^a	Events	Clinical evolution				Suspension of chemotherapy	
	n (%)	n (%)	Complete resolution	Partial resolution	Persistence	Death	Yes	No
Febrile neutropenia	45 (77.59)	55 (28.80)	19 (34.54)	30 (54.54)	2 (3.63)	4 (7.29)	15 (27.27)	40 (72.73)
Thrombocytopenia	38 (65.51)	44 (23.03)	13 (29.54)	30 (68.20)	1 (2.30)	0	3 (6.82)	41 (93.18)
Anemia	32 (55.17)	38 (19.90)	5 (13.15)	25 (65.80)	8 (21.05)	0	2 (5.28)	36 (94.72)
Nausea	12 (20.69)	12 (6.29)	12 (100)	0	0	0	0	12 (100)
Vomit	11 (18.97)	11 (5.76)	11 (100)	0	0	0	0	11 (100)
Constipation	5 (8.62)	5 (2.62)	5 (100)	0	0	0	1 (20)	4 (80)
Oral mucositis	13 (22.41)	13 (6.80)	8 (61.53)	4 (30.77)	1 (7.70)	0	0	13 (100)
Anal and oral mucositis	3 (5.17)	3 (1.57)	1 (33.33)	1 (33.33)	1 (33.33)	0	0	3 (100)
Tumor lysis syndrome	1 (1.72)	1 (0.52)	1 (100)	0	0	0	1 (100)	0
Hepatic toxicity	1 (1.72)	1 (0.52)	0	1 (100)	0	0	1 (100)	0
Exanthema	2 (3.45)	2 (1.05)	3 (100)	0	0	0	0	2 (100)
Cytosine arabinoside syndrome	1 (1.72)	1 (0.52)	1 (100)	0	0	0	1 (100)	0
Differentiation syndrome	2 (3.45)	2 (1.05)	2 (100)	0	0	0	2 (100)	0
Headache	3 (5.17)	3 (1.57)	3 (100)	0	0	0	0	3 (100)

^aA single patient can have more than one adverse chemotherapy event over time.

was administered in 12.7% of the febrile neutropenia cases. The treatment of patients who presented anemia and thrombocytopenia was supportive. Symptomatic patients (anemic syndrome or bleeding) received transfusion therapy with packed red blood cells and/or platelet concentrates, respectively. Patients without associated symptoms, with platelet and hemoglobin levels below the normal limit, were transfused assessing the patient's clinical situation and the risk of decompensation.

The management of oral mucositis was based on maintaining adequate hygiene, use of solutions in the form of mouth rinses, and pain management; anal mucositis management consisted of cleaning the injured area and evaluation of the lesions to detect any associated complication.

Nausea and vomiting, with a frequency of 6.29% and 5.76%, respectively, were prevented and treated with ondansetron. Constipation, with a low frequency of presentation (**Table 1**), was managed with oral polyethylene glycol.

Tumor lysis syndrome was reported on one patient. Its treatment consisted of the administration of intravenous

fluids as well as the use of allopurinol. Similarly, liver toxicity was reported on one occasion. Its treatment was supportive, associated with the immediate suspension of the chemotherapeutic regimen.

Allergic reactions, manifested as exanthema, had a low frequency with two episodes. Administration of hydrocortisone and chlorpheniramine solved both cases. One case of cytarabine syndrome was reported, which was treated with hydrocortisone and immediate suspension of the drug, although there are no guidelines regarding this complication, a recent case report suggests using corticosteroids as premedication¹⁸. Differentiation syndrome was documented in two acute promyelocytic leukemia patients. Its treatment consisted of the immediate suspension of the drug as well as administration of dexamethasone¹⁹. The evolution of AEs events is shown in **table 2**. The chemotherapeutic scheme was suspended in 26 (13.61%) of the 191 AEs, mainly due to febrile neutropenia (**Table 2**). Due to their relevance and high prevalence, **table 3** and **table 4** provide a description of the clinical and laboratory characteristics observed in the three most frequent AEs

Table 3. Clinical characteristics associated with febrile neutropenia, thrombocytopenia, and anemia in 58 hematological patients

	Febrile neutropenia	Thrombocytopenia		Anemia	
Events	55	44		38	
Patients	45	38		32	
Events per patient [median (range)]	1 (1-4)	1 (1-3)		1 (1-2)	
Sex					
Female	20 (44.44)	19 (50)		15 (46.88)	
Male	25 (55.56)	19 (50)		17 (53.12)	
Hematological diagnosis					
ALL B	19 (42.22)	17 (44.74)		11 (34.38)	
AML	11 (24.44)	12 (31.58)		12 (37.50)	
NHL	9 (20)	5 (13.16)		7 (21.88)	
HL	3 (6.68)	1 (2.63)		0	
MM	2 (4.44)	2 (5.26)		1 (3.12)	
ALL T	1 (2.22)	1 (2.63)		1 (3.12)	
Infectious focus ^a		Bleeding		Anemic syndrome	
Absent	25 (45.45)	Absent	14 (31.80)	Absent	5 (13.15)
Present	30 (54.55)	Present	30 (68.20)	Present	33 (86.85)
Pulmonary	15 (27.30)	Epistaxis	11 (25)		
Gastrointestinal	3 (5.45)	Gingivorrhagia	10 (22.72)		
Soft tissue abscess	6 (10.90)	Hematuria	3 (6.81)		
Sepsis	5 (9.10)	Purpuric syndrome	3 (6.81)		
Herpetic stomatitis	3 (5.45)	Digestive tract bleeding	1 (2.27)		
Sinusitis	1 (1.81)	Metrorrhagia	2 (4.54)		
Osteomyelitis	1 (1.81)	Hemoptysis	1 (2.27)		
Phlebitis	1 (1.81)	Transfusion therapy		Transfusion therapy	
Associated death	4 (6.9)	Yes	40 (90.90)	Yes	38 (100)
		No	4 (9.10)	No	0

^aOne single patient can have more than one infectious focus. ALL B: acute lymphoblastic leukemia type B; AML: acute myeloid leukemia; NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma. MM: multiple myeloma; ALL T: T-cell acute lymphoblastic leukemia. G-CSF: granulocyte-colony stimulating factor.

found in our hematology population, febrile neutropenia, thrombocytopenia, and anemia. Importantly, no clerical errors were documented in the administration of chemotherapy drugs during the period of the study.

Discussion

To the best of our knowledge, this is the first prospective study exclusively aimed at identifying AEs in hematology patients with a diagnosis of malignant disease who are receiving chemotherapy and documenting its treatment and clinical outcome; hematology population is frequently included among malignancies in general²⁰ and even specifically excluded from other AE studies²¹. Although chemotherapeutic agents are

highly cytotoxic, only one-third of our population presented an AE. This can reflect good safety practices for drug administration and the effectiveness of prophylaxis available for expected AEs. The AEs found in our patients with hematological malignancies constituted an important cause of morbidity. Chemotherapy-based treatment is critical for this group of diseases; however, given the disease complexity, most patients receive multidrug regimens. Therefore, the risk of toxicity and AEs is high, and it is difficult to assign the cause to a single drug. In addition to affecting quality of life, AEs influence the clinical evolution of the disease due to the AE itself or the need for delay, reduction of doses, or even suspension of the chemotherapy regimen⁴.

Table 4. Laboratory characteristics associated with febrile neutropenia, thrombocytopenia, and anemia in 58 hematological patients

Febrile neutropenia		Thrombocytopenia		Anemia	
Leukocytes*	1.06 ± 1.11	Platelets*	12.39 ± 13.64	Hemoglobin [§]	6.17 ± 1.14
Neutrophils*	0.107 ± 0.153				
G-CSF use	7 (12.72)				
ANC post G-CSF	1.88 ± 2.24	PC post PT	33.88 ± 22.54	Hb post PRBC	8.54 ± 2.07

*(mean ± SD) k/ μ L, [§](mean ± SD) g/dL. G-CSF: granulocyte-colony stimulating factor; ANC post-G-CSF: absolute neutrophil count after G-CSF administration; PC post-PT: platelet count after platelet transfusion; Hb post-PRBC: hemoglobin after packed red blood cell transfusion; SD: standard deviation.

In more than one-third of AEs hospital admission was required, some patients were admitted repeatedly, and some had more than one AE throughout the study period. Only in 17 (8.9%) out of the 191 episodes presented, there was no improvement after treatment, whereas in 26 (13.6%) cases chemotherapy had to be suspended. This shows the impact that these complications can have on the patients' quality of life, the chance of cure, and the potential danger that they represent.

Febrile neutropenia, thrombocytopenia, and anemia were the most common AEs found in our population, similar to results from solid tumor populations²⁰⁻²². Treatment of the AEs relied on international guidelines²³⁻²⁵, personalized decisions based on an individualized approach of the patient, and the clinical judgment of the physician. In our study, more than 50% of AEs did not have complete recovery. It was necessary to suspend chemotherapy in 27% of the cases, and the four deaths reported were directly related to this complication; their successful treatment requires early recognition and therapy. Thus, the education of the patient and his/her family to recognize signs and symptoms of neutropenia at an early stage is an essential part of early treatment and therefore, of prevention of fatal outcomes. Anemia and thrombocytopenia frequently follow febrile neutropenia as AEs associated with chemotherapy. There are no guidelines on the appropriate management of patients with chemotherapy-induced thrombocytopenia and management consists of supportive treatment, based on delay or dose modification chemotherapy, and platelet transfusion for severe thrombocytopenia^{4,26-28}, although the platelet count at which the transfusion should be given in these circumstances is not established, available literature suggests 20,000/ μ L²⁸. Treatment of chemotherapy-induced anemia was also supportive, based on transfusion therapy according to hemoglobin levels and the patients' clinical situation. Recent guides recommend

the use of erythropoiesis-stimulating agents, iron preparations, or red blood cell transfusions depending on the needs of each patient^{29,30}.

Despite transfusion therapy, platelets and hemoglobin reached normal values in only 13.1% and 29.5% of our cases of thrombocytopenia and anemia, respectively; this was probably due to persistence of chemotherapy myelosuppressive effects and platelet consumption in the presence of fever and infection; therefore, it is important for the physician to adhere to transfusion guidelines strictly.

Although nausea and vomiting not being that common, an important consequence is that they could be associated with malnutrition⁴ and treatment adherence could also be affected. In our center, the prophylaxis and management of these events are given with ondansetron; guidelines also suggest dexamethasone and olanzapine, depending on the anti-neoplastic agent of greatest emetic risk included in the chemotherapy scheme^{31,32}.

Constipation was rare and was managed with an osmotic laxative, the first-line therapy in these cases, which resulted in resolution in all episodes³³. The rest of the AEs secondary to chemotherapy observed in our population had a much lower frequency; however, they negatively affected the patient's quality of life and could be a cause of temporary suspension of the treatment. More than one in four of our patients had associated comorbidities, and one in five received concomitant pharmacological treatment. This could lead to interactions that may cause a decrease in treatment efficacy and an increase in the risk of presenting an AE³⁴.

An important aspect of underscoring is the skills, experience, and training of the nursing personnel since they are responsible for the correct administration of chemotherapy schemes. A recent study demonstrated that the implementation of medication safety practices decreased the incidence of AEs related to chemotherapy

in pediatric patients with ALL³⁵. Our nursing personnel has 20 years of experience and certified training in hematological oncology, which may have positively influenced our results. Specific training for nurses is recommended to reduce the risk of presenting AEs³⁵.

The lack of preventive guidelines regarding some of the AEs, and the inadequate implementation of the existing ones may contribute to the incidence found in this report, besides a number of these events may be under registered. The reporting of AEs by treatment cycle and the use of patient-reported outcomes on the evaluation of anticancer drugs have been proposed to improve their safety, collection, and analysis³⁶.

Conclusions

From these results, some conclusions can be reached: attention should be paid to the correct application of existing treatment guidelines for AEs. Training of health personnel is crucial to reduce AEs it is critical, to educate hematology patients and family members about the risks and possible complications associated with the chemotherapy scheme, their treatment, and situations in which a visit to the hospital is required. The health personnel must perform intentional questioning in search of associated AEs, which sometimes do not directly threaten the patient's life but cause deterioration in the quality of life and can interfere with the chemotherapy scheme. Additional AE studies and improved therapeutic strategies for neutropenic fever in hematology patients are needed.

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Conflicts of interest

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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