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Original article

Proactive nursing interventions on side effects during the treatment of acute promyelocytic leukemia with arsenic trioxide: A mixed-methods study in Piacenza

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Abstract. *Background and aim:* Acute promyelocytic leukaemia (APL) accounts for about 10% of acute myeloblastic leukaemias in adults and has become the most potentially curable subtype. Randomised trials have demonstrated the efficacy and safety of the arsenic trioxide and all-trans retinoic acid (ATO/ATRA) protocol without chemotherapy as first-line therapies in patients with low-risk APL. Despite the progress achieved in the treatment of APL, complications often occur therefore rapid intervention is required. No articles can be found in the literature on the centrality of the nurse in the management of patients in treatment with ATO, but daily experience shows that nursing care also plays a key role in the success of therapy by preventing adverse events. The aim of the study is to find out whether and which proactive nursing interventions can reduce the consequences of major drug side effects on the patient, improve compliance and the patient's course of treatment. *Methods:* This study was carried out through a retrospective survey of medical records combined with qualitative 14 semi-structured interviews with operators and patients at the U.O. Haematology in-patient unit. *Results:* Considering that the patients in this study were hospitalized for an average of 39 days, out of a total of a mean number of 542 interventions carried out during a single 39-day hospitalization, the frequency of autonomous interventions was 395 (73%) compared to 147 (27%) of collaborative interventions. *Conclusions*: Although the results obtained underline the centrality of the nurse and the proactive interventions, the narrowness of the sample makes it necessary to undertake further investigations. (www.actabiomedica.it)

Key words: APL, nurse, arsenic trioxide, proactive interventions, mixed-methods, side effects

Introduction

Acute promyelocytic leukemia (APL) represents approximately 10% of acute myeloblastic leukemias in adults (1,2) and thanks to therapeutic advances, has become the most potentially curable subtype of adult acute myeloid leukemia (AML) (2–4). Its distribution, by age, is different from other forms of LAM; in fact, most patients with APL are adults between the ages of 20 and 50 years (4). APL is pathologically distinguished from other types of acute myeloid leukemias due to its specific morphology and chromosomal abnormality. The pathophysiological picture of the disease is mainly constituted by the suppression of normal hematopoiesis resulting in anemia, granulocytopenia and thrombocytopenia. Signs and symptoms of anemia, infections, fever and hemorrhagic syndrome (purpura, ecchymosis, epistaxis) constitute the most

common initial clinical picture (5). Patients can be divided into three prognostic categories based on white blood cells and platelet count:

- low risk leukocytes <10,000 and platelets >40,000;
- intermediate risk leukocytes <10,000 and platelets <40,000
- high risk leukocytes >10,000(4-5).

The discovery of the molecular pathogenesis has led to the naming of all-trans retinoic acid (ATRA) as the standard care for acute promyelocytic leukemia. In most cases it is associated with anthracycline-based chemotherapy with cure rates above 80% (6). Recently several randomized studies have demonstrated the efficacy and safety of the regimen with arsenic trioxide and all-trans retinoic acid (ATO/ATRA) without chemotherapy, as first-line therapies in patients with low-risk APL (2,7,8). Despite the considerable progress achieved in the therapy of APL, difficult situations arise in which rapid identification is essential to know who correctly manage the toxicities and complications related to the administration of ATO (trade name Trisenox) (2,4,8). In fact, common side effects may occur (nausea, vomiting, asthenia, loss of appetite and muscle pain), but also complications that constitute an important cause of morbidity and mortality, such as leukocyte activation syndrome, consumptive coagulopathy, electrocardiographic anomalies and /or hyperleukocytosis (2,4,9,10). Proactive management of these side effects is necessary to ensure maximum survival for patients with APL. APL is considered a medical emergency and consequently requires timely interventions. In the literature there are no emerging articles about the importance of the nurse in the management of patients being treated with ATO, but daily experience highlights that nursing care also plays a fundamental role in the success of the therapy by preventing adverse events, for example through effective patient education, safe treatment administration, improved management and monitoring of possible side effects.

The aim of this study is to understand if and which proactive nursing interventions can reduce the consequences on the patient of the main side effects caused by the drug, to improve the patient's compliance and therapeutic process through a retrospective investigation of medical records associated with a qualitative investigation through semi-structured interviews from operators and patients at Hematology Departement in Ausl of Piacenza.

Patients and Methods

The material and methods used for this study is Mixed-Method (MM) and consists of two phases. The first has a retrospective descriptive observational character, the second is qualitative research with a realist Context-Mechanism-Result (CMO) analysis, carried out through the administration of a semi-structured interview. The study started following the approval by the Ethics Committee of the Emilia Nord Area (AVEN) on 25/05/2022, under protocol number 2022/0165836, with the corresponding company authorization on 31/05/2022, resolution number 2022/0169228. The data were extracted from the paper and electronic medical records of the Hematology Unit; for each patient, information was collected regarding the major side effects of ATO and ATRA therapy, as known in literature, which require a central role in early nursing assessment and proactive intervention. Specifically, the following data extracted:

- General anamnesis: age, sex
- Duration of hospitalization
- Predictable side effects that can be evaluated and treated proactively:
  - Mucositis
  - Prolonged QTc interval on the electrocardiogram
  - Hypokalemia and hypomagnesemia
  - Neutropenia
  - Differentiation syndrome: weight gain
  - Differentiation syndrome: leukocytosis o DIC
- Detection of side effects/complications
- Nurse's role: collaboration or autonomy
- Proactive intervention in collaboration with the doctor
- Proactive nursing intervention

The first part of the study is aimed at patients hospitalized at the U.O. Hematology and Transplant Center of the Local Health Authority of Piacenza, suffering from APL and who have carried out and completed treatment with ATO and ATRA. This is a non-probability sample and more precisely a convenience sampling. A non-probability sample was also drawn for the second part of the study. More specifically, it is a proactive sample and is aimed at:

- Patients whose records have been analysed, hospitalized at the U.O. Hematology and Transplant Center of the Local Health Authority of Piacenza, suffering from APL and who have carried out and completed treatment with ATO and ATRA.
- Nurses of the U.O. Hematology and Transplant Center of the Local Health Authority of Piacenza which provided assistance to patients suffering from APL, who underwent treatment with the ATO+ATRA drug.

The method used for the interviews was semi-structured, characterized by a list of questions that could be amended by the researchers during the interviews. The responses were open-ended. The questions were formulated based on the literature reviewed and the data collected from the analysis of nursing records. The interviews conducted with the patients and nurses shared three common questions regarding the understanding of the concept of initiative medicine, the importance of emotional state, and personal considerations on the topics discussed. Patients were asked eleven questions aimed at investigating their awareness of the therapy they were undergoing, the concept of proactivity, the importance of therapeutic education, and the relevance of emotional state during the therapeutic process. The intention was to determine whether the proactive approach was effective in reducing morbidity and discomfort caused by the illness, prolonged hospitalization, and ATO and ATRA therapy, and if there were any nursing activities or interventions that were particularly helpful in coping more calmly with their illness experience. Nurses were asked eleven questions aimed at investigating their awareness of the side effects of the therapy and their role in monitoring and managing them, as well as determining their understanding of the concept of proactivity, how it was applied in clinical practice, and to what extent it helped reduce morbidity and discomfort caused by the illness, prolonged hospitalization, and ATO and ATRA therapy. Additionally, the interview sought to determine whether and how patient behavior and emotional state could influence the care provided by the nurse. To find people suitable for the inclusion criteria and willing to be interviewed, the objectives and characteristics of the study were exposed to the coordinator of the Hematology department and to a nurse who participated in the study from the beginning. After receiving their authorization, some people were identified who, according to the inclusion criteria, would be available. The patients were contacted by telephone, the project was explained to them and, after receiving authorization, it was possible to proceed with the analysis of the records and a date and place were agreed to schedule the interview. To identify the nurses available for the interview, the information sheet relating to the study and a sheet where they could record their availability and their telephone number were delivered to the ward. Subsequently, available people were contacted, and the date, time and place of the interview were agreed. Furthermore, the interview aimed to determine if and how patients' behaviors and their emotional state can influence the care that the nurse provides. In the second phase, the responses from the interviews addressed to patients and nurses were analysed. The interviews were analyzed using a realist synthesis defined as Context-Mechanism-Result (CMO) configuration which allows us to describe "what works, in which circumstances and how" revealing the interaction of specific interventions between context, mechanisms and results of particular interventions (20 –22).

- "Contexts" refer to the background of the research and are understood as any condition that triggers and/or modifies the behavior of a mechanism (23).
- Mechanisms are "underlying entities, processes, or structures that operate in particular contexts to generate results of interest" (24).
- The results derive from the interaction between a mechanism and its deactivation context and

allow us to evaluate the success or failure of interventions and contextual factors. Intervention, mechanism and context are highly intertwined, they interact and influence each other (25).

Ethical Considerations

The study did not guarantee that it would always be possible to obtain written informed consent from enrolled subjects for ethical reasons (e.g., frail middle-aged patients, residents in towns/regions other than Piacenza, or deceased patients) and/or organizational reasons, in line with the provisions of GDPR 679/2016 and General Authorization No. 9/2016, as extended by Provision No. 424/2018. However, as the obligation remains, consent was obtained for patients who could be contacted and/or when it was possible to provide them with adequate information. It was deemed unnecessary to inform the enrolled subject's general practitioner about the proposed study since it was a retrospective observational study. This investigation was conducted according to Good Clinical Practice and the principles set forth in the Declaration of Helsinki.

Rigor

To ensure rigor in the qualitative sections of the research, the principles of credibility, transferability, and reliability were applied. [26] Credibility was ensured through the analysis of the interviews conducted independently by the author and another researcher (M.M). Regarding transferability, the characteristics of the participants and the context in which enrollment took place were described to allow comparisons with studies conducted in different contexts. Finally, to ensure reliability, the supervisor (MG) and another member of the research group (GC) verified and discussed all stages of the data analysis process.

Data collection tool

The data from the records were collected using an Excel table, with patients pseudonymized and recorded with a unique identification code. The Excel file is stored on a company computer protected by a password. The interviews were audio-recorded, with the consent of the patients and nurses, in a private room to ensure privacy, following a brief introduction and explanation of the study's purpose. The audio recordings were pseudonymized.

Results

For the first phase of the study, the medical records of four patients who met the inclusion and exclusion criteria were analyzed. The data were extracted from both paper and electronic medical records of the Hematology Unit; for each patient, information was collected regarding the side effects of ATO and ATRA therapy and the pathology, as known in the literature, that emphasize the importance of early nursing assessment and proactive intervention.

A significant finding connected to literature relates to the total number and type of events observed in the four patients that is in line with what we found in literature. As shown in Table 1, 136 cases of side effects from the disease or therapy were identified, distributed relatively evenly across seven distinct events.

It can be noted that consumption coagulopathy was the most frequently occurring complication among the total complications identified in all 4 patients (136), presenting with a frequency of 40 (29%) and manifesting in 75% of patients. Focusing the analysis on APL

Table 1. Frequency of LPA and ATO+ATRA complications in all patients.

Complications LPA and ATO+ATRA	**Absolute Frequency**
Consumption coagulopathy	40 (29%)
Mucositis	29 (21%)
Leukocytosis	26 (19%)
Severe neutropenia	17 (13%)
Weight gain	12 (9%)
Electrolyte abnormalities	9 (7%)
QTc prolongation	3 (2%)
Total	**136**

Table 2. Data collected from the records revealed the proactive interventions recorded in the nursing diary.

Condition	Nursing Interventions
Mucositis	Daily oral hygiene education and assessment during the morning shift; oral mucosae assessment with VAS and WHO scales; products like sodium bicarbonate and oil-based emollients provided.
QTc Prolongation	Twice-daily monitoring of vital parameters; electrocardiogram twice a week (daily if QTc prolongation detected) reviewed by physician.
Electrolyte Imbalances (Hypokalemia, Hypomagnesemia)	Blood tests every other day to monitor for electrolyte reductions, in collaboration with the physician.
Neutropenia	Twice-daily temperature checks; daily blood tests in collaboration with physician; weekly evaluation of central venous catheter site (or every 3 days with gauze adhesive).
Weight Gain	Daily weight measurement: significant weight gain reported to physician and monitored twice daily for 3 days; daily assessment of lower limb and abdominal edema.
Leukocytosis	Daily blood tests in collaboration with the physician.
Disseminated Intravascular Coagulation (DIC)	Daily monitoring for abnormal bleeding, petechiae, and hematomas; daily coagulation assays in collaboration with the physician.

Table 3. Frequency of autonomous and collaborative interventions in a 39-day hospitalization.

Complications	Autonomy	39 days	Collaboration	39 days
Leukocytosis	0		Blood tests 1/day	39
Weight gain	Weight 1/day	78	0	
DIC	Abnormal bleeding evaluation 1/day	39	Blood tests 1/day	39
Mucositis	WHO 1/day, VAS 1/day, Oral hygiene 1/day	117	0	
QTc	Vital signs 2/day	78	ECG 2/week	11
Electrolytes	0		Blood tests every other day	19
Neutropenia	Temp 2/day, CVC/PICC site evaluation 1/week	83	Blood tests 1/day	39
Total	**395 (73%)**		**147 (27%)**	

complications, it is possible to observe that about half (46%) of such complications are of the DIC (Disseminated Intravascular Coagulation) type. Instead, if we focus on the side effects of ATO and ATRA therapy, it is evident that leukocytosis was the most frequently occurring event with a frequency of 52%, while QTc interval prolongation was the least common with a frequency of 6%. Next, proactive interventions implemented for the previously reported events were analyzed. The data collected from the records revealed that the proactive interventions recorded in the nursing diary include we reported in Table 2.

Considering that the patients in this study were hospitalized for an average of 39 days, out of a total of a mean number of 542 interventions performed during a single 39-day hospitalization, the frequency of autonomous interventions was 395 (73%) compared to 147 (27%) collaborative interventions (Table 3).

For the second phase of the study, a total of 14 interviews were conducted, including 4 patients and 10 nurses who met the inclusion and exclusion criteria. The interviews were audio-recorded, transcribed verbatim, and after a process of synthesis and abstraction (Tables 4 and 5), 3 main CMO

Table 4. Contexts, mechanisms, and results for individual interviews.

Contexts	Mechanisms	Results
PZ1	- Long therapy/hospitalization - Specific therapy, low awareness - Physical isolation, loneliness - Limited external and family contacts - Characteristics of the hospital room - Vulnerable emotional state: worry, sadness	- Empathy, familial approach - Constant contact with the patient - Availability to explain and answer questions - Attention to every detail - Encouragement - Participation in the management of one's health
PZ2	- Long therapy/hospitalization - Specific therapy, low awareness - Potentially lethal condition - Physical isolation, loneliness - Patient's unsociable approach	- Availability to explain and answer questions - Personalized approach and interventions - Empathy, familial approach - Practical and pragmatic advice - Attention to every detail - Step-by-step explanations with professionalism and clarity - Flexibility - Reassurance - Participation in the management of one's health
PZ3	- Long therapy/hospitalization - Specific therapy, low awareness - Potentially lethal condition - Physical and mental isolation, loneliness - Limited external and family contacts - Severe physical distress - Vulnerable emotional state: worry, sadness	- Availability and listening - Personalized approach and interventions - Empathy, familial approach - Practical advice (oral hygiene) - Constant contact with the patient - Step-by-step explanations with professionalism and clarity - Participation in the management of one's health
PZ4	- Long therapy/hospitalization - Vulnerable emotional state: worry, sadness - Severe physical distress: asthenia, stress - Positive and serene work environment	- Empathy, familial approach - Listening and dialogue - Step-by-step explanations with professionalism and clarity - Constant contact with the patient - Attention to every detail - Respect for privacy
IN1	- Long therapy - Young patient - Vulnerable emotional state: worry, sadness - Collaboration - Potentially lethal condition - Severe physical distress: asthenia, stress	- Timely education - Retraining - Simple and patient-appropriate language - Assessment of patient understanding - Assessment of autonomy - Reinforcement of deficiencies - Correction of erroneous behaviors - Use of specific products
IN2	- Long therapy - Young patient - Specific therapy, low awareness - Specific therapy, numerous side effects - Vulnerable emotional state: worry, sadness - Receptive patient - Unreceptive patient - Calm environment	- Education during moments of patient calm and listening - Simple and patient-appropriate language - Assessment of understanding - Assessment of autonomy - Encouragement and reassurance - Positive attitude - Maintenance of habits - Use of specific products
IN3	- Long therapy - Young patient - Physical and social isolation: distance from family, loneliness - Vulnerable emotional state: worry, sadness - Collaboration - Nurse as the figure with the most contact	- Education during moments of patient calm and listening - Simple and patient-appropriate language - Retraining - Listening, dialogue, relationship - Collaboration
IN4	- Long therapy - Young patient - Physical and social isolation: loneliness, distance from family - Vulnerable emotional state: worry, sadness - Collaboration	- Continuous monitoring - Daily education - Retraining - Listening, dialogue, relationship - Reporting of anomalies by the patient
IN5	- Long therapy - Specific therapy, low awareness - Specific therapy, numerous side effects - Vulnerable emotional state: worry, sadness - Physical and social isolation: distance from family - Collaboration - Nurse as the figure with the most contact	- Continuous monitoring - Daily education - Clarity - Simple and patient-appropriate language - Collaboration among colleagues
IN6	- Long therapy - Specific therapy, numerous side effects - Vulnerable emotional state: worry, sadness - Condition with severe physical distress: asthenia	- Continuous monitoring - Step-by-step explanation - Listening, dialogue, relationship - Support, stimulation, motivation - Concreteness
IN7	- Long therapy - Young patient - Specific therapy, numerous side effects - Vulnerable emotional state: worry, sadness - Physical and social isolation: distance from family - Collaboration - Condition with severe physical distress: asthenia - Desire for autonomy	- Continuous monitoring - Daily education - Assessment of understanding - Assessment of autonomy - Listening, dialogue, relationship - Support, stimulation, motivation - Intervention planning - Personalized assistance - Familiality

Contexts	Mechanisms	Results
IN8	- Young patient - Long therapy - Physical and social isolation - Specific therapy, particular: numerous side effects - Emotional state: anxiety and fear.	- Continuous monitoring - Daily education - Reporting of anomalies by the patient - Assessment of autonomy - Clarity - Concreteness - Support, stimulation, motivation
IN9	- Long therapy - Vulnerable emotional state: worry, sadness - Physical and social isolation: reduced - Freedom - Severe physical distress	- Continuous monitoring - Daily education - Assessment of autonomy - Reporting of anomalies by the patient - Reinforcement of deficiencies - Personalized assistance - Simple language - Kindness and familiality - Team approach
IN10	- Long therapy - Young patient - Physical and social isolation - Vulnerable emotional state: worry, sadness	- Continuous monitoring - Personalized assistance - Familiality - Listening, dialogue, relationship - Daily education - Assessment of understanding - Assessment of autonomy

Table 5. Identified contexts, mechanisms, and results.

Contexts	Mechanisms	Results
- Long therapy/hospitalization - Specific therapy, low awareness - Potentially lethal condition - Characteristics of the hospital room - Physical isolation, loneliness, limited external contacts - Young patient - Collaboration - Receptive patient - Nurse as the figure with the most contact - Positive work environment - Physical distress - Emotional vulnerability	- Availability, constant contact with the patient - Step-by-step education, clarity, professionalism, concreteness - Personalized assistance - Retraining - Simple language - Maintenance of habits - Assessment of understanding - Assessment of autonomy - Correction, reinforcement of deficiencies - Specific products - Reporting of anomalies by the patient - Collaboration - Empathy, familial approach - Relationship: listening, dialogue - Shared planning - Reassurance, motivation - Respect for privacy - Continuous monitoring	- Awareness of one's health, therapy, and interventions - Collaboration/active participation - Responsibility - Reduction of morbidity - Patient-centered care - Calmer approach to the condition - Trust relationship between nurse and patient - Control and reduction of side effects

(Context-Mechanism-Outcome) configurations were identified in line with the study objectives. These are presented and described below and summarized in Table 6.

First of all, it should be noted that the 3 CMOs are not mutually exclusive, with contexts and/or mechanisms that influence and feed into others or become outcomes of third parties. Specifically, most interventions occurred in the contexts of "young patient" and "long therapy/hospitalization." This is confirmed by the data collected from medical records, where it is observed that the 4 patients, when hospitalized in the Hematology ward, were aged between 27 and 55 years and that the duration of hospitalization was always over 35 days, with an average of 39 days. Additionally, regarding outcomes, "active participation" is common to all CMOs and is therefore favored by multiple educational, relational, and personalized care interventions.

CMO1 - Information/Therapeutic education: To increase patients' awareness of their health status and side effects, information and instructions are adapted and personalized based on the patient to whom they are provided, considering the patient's context, reality, and level of understanding. Nurses, in order to make patients active participants in their healthcare, state that one should always consider their willingness to learn and their ability to effectively apply the teachings. Therefore, it is important for all interviewed nurses to identify and intervene on possible individual learning barriers, particularly on emotional vulnerability, which is often present in patients undergoing long and complex, debilitating therapies.

Table 6. Identified CMO Configurations.

CMO Title	CMO 1: Information/Therapeutic Education	CMO 2: Relationship	CMO 3: Personalized Care
Context	If the patient is young and receptive patient, undergoing long therapy/ hospitalization, specific therapy and low awareness, nurse-patient trust relationship	If the patient undergoing long therapy/hospitalization, young patient, isolation, emotional vulnerability, nurse with more frequent contact	If the patient undergoing long therapy/hospitalization, young patient, specific therapy with many aspects to monitor
Mechanism	Then the use of step-by-step education/ information, retraining, simple and clear language, concreteness, evaluation of autonomy and understanding	Then use a familial and empathetic approach, listening and motivation, physical contact, shared care planning	Then promote evaluation of autonomy, continuous monitoring, shared care planning, collaboration
Results	Make you gain awareness of one's health status, therapy, and interventions, responsibility, active participation, reduction of morbidity, personalization, more serene approach to the disease, strengthening of weaknesses	Make You gain more serene approach to the disease, more receptive patient, greater hope, active participation, nurse-patient trust relationship, collaboration	Make You gain nurse-patient trust relationship, patient as protagonist, reduction of morbidity, active participation, more serene approach to the disease

"... of course, 'retraining' must be done the right way, making the person unique, taking into account the patient's ability to learn because there's the elderly gentleman with whom you need to speak in simple terms, making it easy to learn the behavior, while there's the professional with whom you can perhaps use the same technical terms without any problem..."

Finally, all patients and most nurses emphasized the importance of simplicity, clarity, and concreteness with which nurses educate and respond to their questions, not only for better understanding but also to face the treatment process more calmly.

"... so being clear is the only way to make myself understood and to try to have some compliance, which, I assure you, isn't always there..."

"... then I think education can help reduce the anxiety and fear that one might have, anyway these are things that give an extra sense of security..."

CMO2 - Relationship: All patients reported experiencing several moments of loneliness and sometimes fear. At these times, they appreciate not only the emotional but also the physical proximity of the nurse, "capable of conveying availability and closeness."

"Sometimes it happens that you have a crisis and cry and everything, and the very fact that they come to you with their hand, stand by your side, gives you more human contact. It's not just the amount of time the nurse dedicates to you, but also the ability to sense the moment when you need it most."

When patients perceive this attention, they do not feel alone or abandoned. Both nurses and patients have highlighted that establishing a trust relationship reduces anxiety, encourages greater participation in self-care, and increases the sense of security and protection.

"... there was really attention to the person and a very familiar relationship. They often stopped by to chat, to exchange a few words, so to talk about themselves or ask about me, and this really created a very strong human bond. This helped me a lot in my recovery. Even if I was feeling bad, I felt at home, it was a wonderful feeling."

CMO3 - Personalized care: The interviews with nurses revealed that the most used educational strategy is personalized care. This is based on careful patient evaluation, considering their autonomy and needs. These mechanisms allow for the establishment of a trust relationship between nurse and patient, who actively participates in their care process.

"... when you make the patient aware, you make them responsible... it's your health, it's your life in the

end. You don't feel like an object in someone else's hands, you feel like the protagonist of your health, your well-being, and for me, that was fundamental..."

During the interviews, in addition to the previously mentioned outcomes, an important aspect emerged investigating the awareness of nurses and patients about the concept of "initiative medicine" or "proactivity." Among the nurses, 1 reported having heard of it and being aware of it, 3 had heard of it but were not aware, and 7 had never heard of it. Among the patients, 1 had heard of it but was not aware, and 3 had never heard of it.

It is worth noting that the 3 CMOs do not exclude each other, with contexts and/or mechanisms influencing and fueling others or becoming results of third ones. Specifically, most interventions occurred in the "young patient" and "long therapy/hospitalization" contexts. This is confirmed by data collected from medical records showing that the 4 patients were between the ages of 27 and 55 when hospitalized in the Hematology Unit, and the duration of hospitalization was always more than 35 days with an average of 39.

Furthermore, regarding the results, "active participation" is common to all CMOs and is therefore fostered by multiple educational, relational, and personalized care interventions.

Discussion

From the analysis of the records of APL patients who received ATO and ATRA, it can be stated that the side effects and complications observed are consistent with those described in current literature. The results show that consumption coagulopathy was the most frequently occurring complication among the total complications identified in all 4 patients. In fact, the presentation of APL is predominantly hemorrhagic, sometimes even with severe hemorrhages that constitute a true hematological emergency (5), requiring adequate and timely supportive transfusion therapy (4). Focusing on the side effects of ATO and ATRA therapy, it is evident that leukocytosis, an abnormal increase in white blood cells, occurred in about 50% of patients treated with ATO and ATRA, with a peak leukocyte count ≥10 x $10^3/\mu L$ (11). Conversely, the least common side effect was QTc interval prolongation. It can therefore be said that the careful monitoring of electrocardiograms and the maintenance of adequate potassium and magnesium concentrations, as reported in the records, allowed for control of this complication. It can be stated that the patients reported a clinical course consistent with what is described in the literature for the same type of patients (4).

The primary objective of the study was to identify the role of the nurse in the proactive prevention and management of complications resulting from the administration of ATO and ATRA, with the aim of improving the therapeutic pathway. For this reason, the proactive interventions implemented for the previously reported phenomena were analyzed. From these results, it can be observed that the interventions the nurse can perform autonomously are more frequent than those that can be performed in collaboration with the physician. In fact, considering that the patients in this study were hospitalized for an average of 39 days, it is noted that out of a total of 542 interventions performed during a single 39-day hospitalization, the frequency of autonomous interventions was 395 (73%) compared to 147 (27%) collaborative interventions. Autonomy in the nursing profession is therefore an indispensable value in daily practice, as stated in the Code of Ethics for Nurses, which in Article 1 reads: "The nurse is the health professional registered with the Order of Nursing Professions who acts consciously, autonomously, and responsibly. He/she is supported by a set of scientific values and knowledge. He/she positions him/herself as an active agent in the social context to which he/she belongs and in which he/she exercises, promoting the culture of care and safety" (12). This underscores and reinforces the importance of acting autonomously and decision-making ability, which are seen today as a true milestone for the nursing profession, once considered an "auxiliary" operator and now defined as a "Health Professional."

Furthermore, the results clearly show that for mucositis, unlike other events, only nursing-managed interventions are implemented. As reported in the records, the nurse daily evaluates the oral mucosa using the WHO scale, which allows for the detection of the presence of erythema, ulcers, and discomfort (19). This is integrated with the assessment of phonation,

swallowing, and pain according to the visual analog scale (VAS) (13). In addition, the nurse educates and evaluates the correct execution of oral hygiene by providing the patient with soft-bristled atraumatic toothbrushes, alcohol-free mouthwashes containing saline solution, and oil-based emollients.

When discussing proactivity, it should be emphasized that the patient does not merely "passively" receive healthcare services but actively and proactively interacts with the multidisciplinary team (14). One of the fundamental aspects of proactive medicine is therefore to equip assisted individuals with the knowledge and skills to contribute to the self-management of their health, such as being able to detect and promptly report any alterations, even those related to the administration of complex, debilitating, and long-term therapies (15) such as ATO and ATRA. To make the patient active and responsible for their health, education and information about the disease and the prescribed treatment are essential. In the analyzed records, there are no tools for reporting these interventions. Therefore, to better understand these phenomena, the first quantitative phase of the study was integrated with a qualitative investigation through semi-structured interviews with 4 patients and 10 nurses. This realist analysis aimed to collect and discuss the interventions that improve the therapeutic pathway of patients and understand the reasons for their success.

The results obtained from the interviews, based on comparison with the literature, positively highlight the role of the nurse and how they are an important tool in the relationship with the onco-hematologic patient, capable of welcoming and guiding them in their clinical and care journey. Specifically, three CMO configurations were identified concerning education, relationship, and personalization of care. It is essential to note that the CMOs do not exclude each other, with contexts and/or mechanisms that fuel others or become the results of others. Specifically, most interventions occurred in the "young patient" and "long therapy/hospitalization" contexts. This is confirmed by the data collected from the medical records, where it is observed that the 4 patients were between the ages of 27 and 55 when they faced hospitalization in the Hematology Unit, and the duration of hospitalization was always more than 35 days with an average of 39. Furthermore, concerning the results, "active participation" is common to all CMOs and is therefore favored by multiple educational, relational, and personalized care interventions.

To achieve effective mechanisms and interventions that ensure positive outcomes, it is essential, as most of the literature has stated (16), to establish a good trust relationship so that the patient feels more in control of themselves and their health, promoting the improvement of their functional status and sense of well-being. To achieve a relationship with a positive therapeutic outcome, effective communication is required (17), as reported in CMO 1, using simple, clear, and concrete terms. Easily understandable language allows for the early recognition of the first signs of therapy-related toxicity and its subsequent management. As emerged in CMO 2, all patients reported having experienced several moments of fear and loneliness due to the disease, isolation, and limited external contact. It is precisely in these contexts that patients appreciate the proximity of the nurse, not only emotionally but also physically, capable of conveying availability and closeness. When patients perceive these attentions, they do not feel alone or abandoned. Finally, the questions that investigated the understanding by the nursing staff and openness to dialogue are almost entirely positive, indicating that the nurse was able to adopt good clinical practice, taking into account the patient's psychological reactions.

CMO 1 and 2, as previously mentioned, present contexts, mechanisms, and results that intertwine with those of CMO 3 (personalization of care). In fact, when asked what the most used educational strategy was, most nurses reported, in addition to simple language and a trust relationship, the personalization of care based on a careful patient evaluation, i.e., aimed at the person understood in their entirety and uniqueness, considering their autonomy and needs. Therefore, it is important to identify and intervene on possible individual barriers to learning, particularly on emotional vulnerability.

As some authors recommend (18), it can be concluded that all the strategies and mechanisms addressed in the three CMO configurations represent the "empowerment" philosophy, which ultimately aims at the patient's responsibility for proactive participation in the care pathway related to their needs.

Limitations

The study has some limitations, one of which is the sample in the first phase of the study, as it is not probabilistic but one of convenience and therefore not representative of the entire population. Moreover, it is also relatively small due to the specificity and low frequency of APL, so the results are quantitatively less comparable and do not allow for a precise understanding of the phenomena analyzed. The number of participants in the second part of the study is also limited. Additionally, through the administration of the questionnaire, limitations emerged regarding the time elapsed between the patients' hospitalization and the moment of the interview. This did not allow patients to respond fully to all the questions. Finally, the literature has few studies on proactivity in hematologic patients, which did not provide a specific framework and hindered a more in-depth discussion of the results.

Conclusions

This study aimed to understand whether and which proactive nursing interventions can reduce the consequences of the main drug-related side effects and determine which strategies can influence patient adherence to therapy and their active participation in managing therapy and its complications. Overall, it can be stated that the side effects observed are consistent with what is reported in the literature, namely: consumption coagulopathy, mucositis, weight gain associated with DS, leukocytosis, QT interval prolongation, and neutropenia. Additionally, the study shows that nurses, in monitoring and managing complications caused by the disease and therapy, perform the majority of interventions autonomously; therefore, they play a significant role in the care of these patients. Beyond these aspects, proactivity encompasses other phenomena essential to ensuring active participation by those receiving care. These include therapeutic education based on effective communication that uses simple, clear, and concrete terms; a trust-based relationship that conveys availability and physical and emotional closeness; and personalized care that addresses the person in their entirety and uniqueness, considering their autonomy and needs. It can therefore be stated that these interventions promote personal empowerment, a process that ultimately aims at patient responsibility for proactive participation in the care pathway, gaining greater control over decisions and actions regarding their health. Despite the positive results highlighting the centrality of the nurse in managing such debilitating conditions, the limited sample size necessitates further investigations and future studies on the phenomena studied in this research, perhaps considering a less specific and more common onco-hematological condition. Another implication for the future could be the identification of a tool for recording and evaluating the educational strategies implemented and the patient's coping mechanisms, to make them more aware, cooperative, and engaged in managing their health. Given the importance of proactive actions in hematological diseases, it would be beneficial to inform and raise awareness among the care team about this aspect to intervene with greater awareness and thus attention in providing care.

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Declaration on the use of AI: We declare that no chatbot has been used, only ChatGPT for the English grammar error.

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