ISSN (0): Applied, ISSN (P): Applied 2025, Volume 1, Issue 1, Page: 17-25.
WORLD JOURNAL OF ADVANCE MEDICINE
www.wjam.net

Research Article

ADR REPORTING OF CYCLOPHOSPHAMIDE

***Sayli Ravindra Dabhade, Abhay Kishor Jaitmal and Vaishnavi Raghunath Jadhav**

B pharm, Nandanvan Colony Bhavsingpura, Sambhajinagar, Maharashtra, India.

Article Info

Article Received: 18 May 2025,
Article Revised: 09 June 2025,
Published on: 01 July 2025.

***Corresponding author:**
Sayli Ravindra Dabhade
B pharm, Nandanvan Colony Bhavsingpura, Sambhajinagar, Maharashtra, India.
saylidabhade18@gmail.com

ABSTRACT

Cyclophosphamide, a widely used antineoplastic agent, is renowned for its efficacy in treating various cancers. However, its therapeutic potential is often accompanied by a spectrum of adverse drug reactions (ADRs). This pharmacovigilance project aims to systematically monitor and analyze the safety profile of cyclophosphamide, focusing on the identification, reporting, and prevention of ADRs. By implementing a robust pharmacovigilance strategy, this project seeks to:

Enhance Patient Safety: Early detection and reporting of ADRs can lead to timely interventions, reducing the severity and potential long-term consequences of adverse events. Optimize Therapeutic Use: A comprehensive understanding of the risk-benefit profile of cyclophosphamide can guide clinicians in making informed decisions about its appropriate use and dosage regimens. Through a combination of literature review, case report analysis, and spontaneous reporting, this project will provide valuable insights into the real-world safety profile of cyclophosphamide. The findings of this study will be disseminated to healthcare professionals, regulatory authorities, and patients to promote the safe and effective use of this important therapeutic agent.

KEYWORDS:

1. Pharmacovigilance
2. Cyclophosphamide
3. Alkylating agents
4. Myelosuppresion
5. Adverse Drug Reactions
6. Hemorrhagic Cystitis
7. Naranjo Scale
8. Chemotherapy
9. Cancer Treatment
10. Patient Safety
11. Spontaneous Reporting
12. Risk Management
13. Safety Profile
14. Drug Monitoring
15. ADR Reporting Form
16. Clinical Pharmacology
17. Toxicity Assessment
18. Hospital-Based Study
19. Patient Interview
20. Healthcare Professional Collaboration

INTRODUCTION

CONCEPT OF PHARMACOVIGILANCE

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

Definition by Regulatory Authorities

1. World Health Organization (WHO): “The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.”

2. European Medicines Agency (EMA): "The process of monitoring the safety of medicines and detecting any adverse reactions."
3. US Food and Drug Administration (FDA): "The process of monitoring and managing the risks associated with drugs and other medical products."

Objectives

Primary Objectives

1. Improve patient safety: Minimize harm from adverse reactions.
2. Enhance drug efficacy: Optimize drug therapy.
3. Reduce adverse events: Identify and mitigate risks.
4. Support regulatory decision-making: Provide data for approval, labelling, and post-marketing surveillance.

Secondary Objectives

1. Monitor and manage risks: Identify, assess, and mitigate safety concerns.
2. Detect signals: Identify potential safety issues.
3. Evaluate benefit-risk: Assess drug benefits vs. risks.
4. Communicate safety information: Inform healthcare professionals and patients.
5. Promote rational prescribing: Encourage safe and effective use.
6. Facilitate continuous improvement: Enhance pharmacovigilance processes.
7. Ensure compliance: Adhere to regulatory requirements.

Specific Objectives

1. Identify new adverse reactions.
2. Characterize known adverse reactions.
3. Determine adverse reaction frequencies.
4. Assess causal relationships.
5. Develop risk management strategies.
6. Monitor safety in special populations (e.g., pediatrics, elderly).
7. Investigate medication errors.

WHO-Recommended Pharmacovigilance Objectives:

1. Improve patient care and safety.
2. Improve drug safety and efficacy.
3. Support rational prescribing.
4. Enhance national and international collaboration.
5. Promote education and training.

Types and Components of Pharmacovigilance

1. Pharmacovigilance encompasses various types and components to ensure drug safety and efficacy.
2. Types of Pharmacovigilance**:**
3. Clinical Trials Pharmacovigilance: Monitoring safety during clinical trials.
4. Post-Marketing Pharmacovigilance: Monitoring safety aftermarket authorization.
5. Spontaneous Reporting Pharmacovigilance: Collecting and evaluating adverse event reports.
6. Surveillance Pharmacovigilance: Proactive monitoring of drug safety.
7. Signal Detection Pharmacovigilance: Identifying potential safety issues.

Components of Pharmacovigilance

1. Data Collection:

a) Adverse Event (AE) reporting
b) Serious Adverse Event (SAE) reporting
c) Adverse Drug Reaction (ADR) reporting
d) Medication Error reporting

1. Data Analysis

a) Signal detection
b) Risk assessment
c) Benefit-risk assessment
d) Causal relationship evaluation

2. Risk Management

a) Risk identification
b) Risk assessment
c) Risk minimization
d) Risk communication

3. Communication

a) Healthcare professional communication
b) Patient communication
c) Regulatory authority communication
d) Public health alerts

4. Regulatory Compliance

a) Adherence to regulations (e.g., EU, US, India)
b) Periodic Safety Update Reports (PSURs)
c) Risk Management Plans (RMPs)
d) Pharmacovigilance audits

5. Quality Assurance

a) Standard Operating Procedures (SOPs)
b) Training programs
c) Audits and inspections
d) Continuous improvement

Constitutional Objectives of Pharmacovigilance Program of India (PvPI)

The Pharmacovigilance Program of India (PvPI) has the following constitutional objectives:

Primary Objectives

1. Ensure patient safety by monitoring adverse drug reactions (ADRs).
2. Improve drug safety and efficacy.
3. Support rational prescribing and use of medicines.
4. Enhance national and international collaboration.

Specific Objectives

1. Establish a nationwide pharmacovigilance system.
2. Identify and characterize ADRs.
3. Develop and implement risk management strategies.
4. Communicate safety information to healthcare
5. Promote education and training in pharmacovigilance.
6. Ensure compliance with regulatory requirements.
7. Collaborate with international pharmacovigilance.

Constitutional Mandate

1. Article 39 of the Constitution of India: Ensure protection of public health.
2. Article 47 of the Constitution of India: Improve public health and hygiene.
3. Drugs and Cosmetics Act, 1940: Regulate manufacture, sale, and distribution of drugs.
4. National Health Policy, 2017: Prioritize patient safety and pharmacovigilance.

PvPI's Strategic Goals

1. Establish a robust pharmacovigilance system.
2. Enhance ADR reporting and analysis.
3. Improve risk management and communication.
4. Strengthen collaboration with stakeholders.
5. Develop pharmacovigilance capacity and expertise.

METHODOLOGY

This study employed a cross-sectional design to investigate patient satisfaction with cancer care at GMC Hospital. The study aimed to identify the adverse drug reactions of the drug cyclophosphamide in cancer.

The target population for this study consisted of adult cancer patients who received treatment at hospital.

A convenient survey method was used to recruit participants. The patients who visited during the study period were approached by trained research assistants and invited to participate in the study.

In this study survey instrument used was self-administered questionnaire assessing patient satisfaction with care and also monitoring of the adverse drug reactions of the drug.

Patient provided demographic information, including age, sex, cancer type and treatment status.

The patients provided informed consent before completing the questionnaire. The consent form outlined the study purpose, risk and benefits.

A visit to pharmacovigilance department was also done.

DISCUSSIONS

IDENTIFICATION OF ADVERSE EFFECTS OF SELECTED DRUG

Cyclophosphamide is an alkylating agent used in chemotherapy to treat various cancers and autoimmune diseases. While effective, it can cause numerous adverse effects, which can be:

Adverse Effects

Hematologic adverse events

Very common: Myelosuppression (bone marrow failure, pancytopenia, neutropenia, agranulocytosis, granulocytopenia, thrombocytopenia [complicated by bleeding], leukopenia, anemia)
Common: Febrile neutropenia
Uncommon: Thrombocytopenia, anemia
Rare: Hemorrhage
Very rare: Disseminated intravascular coagulation, hemolytic uremic syndrome, thromboembolism.

Gastrointestinal

Common: Mucosal inflammation
Very rare: Enterocolitis hemorrhagic, acute pancreatitis, ascites, stomatitis, diarrhea, vomiting, constipation, nausea

Dermatologic

Very common: Alopecia
Rare: Rash, dermatitis, nail discoloration, skin discoloration (palms and heels)
Very rare: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), radiation erythema, pruritus (including itching due to inflammation)

Genitourinary

Very common: Cystitis, microhematuria
Common: Impairment of spermatogenesis
Uncommon: Ovulation disorder (rarely irreversible)
Rare: Amenorrhea, azoospermia/aspermia, oligospermia, oligospermia, lower levels of female sex hormones, blood estrogen level decreased, blood gonadotropin level increased
Very rare: Sub urethral hemorrhage, bladder wall edema, bladder fibrosis and sclerosis, atypical urinary bladder epithelial cells

Respiratory

Uncommon: Pneumonia (sometimes fatal)
Very rare: Acute respiratory distress syndrome (ARDS), chronic pulmonary interstitial fibrosis, pulmonary edema, bronchospasm, dyspnea, hypoxia, cough

Cardiovascular

Uncommon: Cardiomyopathy, myocarditis, heart failure (sometimes fatal), tachycardia, flushing, ECG changes, decreased LVEF
Rare: Ventricular arrhythmia, supraventricular arrhythmia, chest pain
Very rare: Ventricular fibrillation, angina, myocardial infarction, pericarditis, atrial fibrillation, hypertension, hypotension.

Endocrine

Rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hypersensitivity

Uncommon: Hypersensitivity reaction, anaphylactic/anaphylactoid reaction
Very rare: Anaphylactic shock

Oncologic

Rare: Acute leukemia (e.g., acute myeloid leukemia, acute promyelocytic leukemia), myelodysplasia syndrome, secondary malignancies, bladder cancer, ureteric cancer
Very rare: Tumor lysis syndrome.

Nervous system
Rare: Convulsion, dizziness
Very rare: Dyspepsia, hypogeusia, paranesthesia

Musculoskeletal
Very rare: Rhabdomyolysis, cramps.

Local
Very rare: Injection site reactions (e.g., thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema)

Ocular
Rare: Blurred vision, visual impairment
Very rare: Conjunctivitis, eye edema (usually from hypersensitivity), lacrimation increased **Metabolic**
Uncommon: Anorexia, blood lactate dehydrogenase increased, C-reactive protein increased
Very rare: Hyponatremia, weight gain

Psychiatric
Common: Chills, asthenia, malaise, Confusion

Hepatic
Common: Hepatic function abnormal
Rare: Hepatitis
Very rare: Venoocclusive liver disease, hepatomegaly, jaundice

Other Very common: Fever Uncommon: Deafness

Renal Very rare: Renal impairment, blood creatinine increased, renal tubular necrosis

ADVERSE DRUG REACTION (ADR) MONITORING FORM
An Adverse Drug Reaction (ADR) Monitoring Form is a crucial tool used to collect detailed information about suspected adverse events associated with the use of a specific medication. It provides valuable data for pharmacovigilance activities, which aim to identify, assess, understand, and prevent adverse drug reactions.

Key Components of an ADR Monitoring Form
While the specific format may vary, a typical ADR Monitoring Form should include the following essential information:
1) Patient Information
- Name: Shrikant Pawar
- Date of Birth: 01/01/1974
- Medical Record Number: 123456

2) Treatment Information
- Drug: Cyclophosphamide
- Dose: 500 mg/m^2
- Route: Intravenous
- Frequency: Every 21 days
- Cycle/Day: Cycle 3, Day 1

3) Adverse Reaction Monitoring
Hematologic
- Neutrophil count: 1.5 x 10^9/L
- Platelet count: 150 x 10^9/L
- Hemoglobin: 12 g/dL

Gastrointestinal
- Nausea/Vomiting: Yes (severity: 2)
- Diarrhea: No • Stomatitis: No

Renal
- Serum creatinine: 1.2 mg/dL
- Urine output: Normal

Hepatic
- Liver function tests (AST/ALT): Normal

Neurological
- Peripheral neuropathy: No
- CNS toxicity: No

Cardiac
- Cardiac function (LVEF): Normal
- Hematologic: 2 (Moderate)
- Gastrointestinal: 2 (Moderate)
- Renal: 1 (Mild)
- Hepatic: 0 (None)
- Neurological: 0 (None)
- Cardiac: 0 (None)

4) Action Taken
- Dose reduction: No
- Dose delay: No
- Discontinued: No
- Supportive care: Anti-emetics for nausea/vomiting

5) Next Follow-up
- Date: 17/10/2024
- Time: 10:00 AM

6) Healthcare Provider
- Name: Prashant Shrike, MD
- Signature: _____
- Date: 12/10/2024

HOSPITAL VISIT
Pre-Interaction Preparation
1. Review patient's medical record and cyclophosphamide treatment regimen.
2. Noted common ADRs associated with cyclophosphamide.

Physician Interaction
1. Introduced myself and explained the purpose of the interaction.
2. Asked open-ended questions:

"Have you observed any unusual reactions or side effects in patients receiving cyclophosphamide?" - "Are there any concerns or issues with the current treatment regimen?"

3. Discussed specific ADRs:
- Hemorrhagic cystitis
- Bone marrow suppression
- Nausea and vomiting
- Alopecia

4. Clarified reported ADRs:
- Severity
- Duration
- Management

Nurse Interaction

1. Introduced myself and explained the purpose of the interaction.
2. Asked open-ended questions:
- "Have you noticed any changes in patient condition or behaviour while administering cyclophosphamide?"
- "Are there any concerns or issues with patient compliance or adherence?"

2. Discussed specific ADRs
- Infusion-related reactions
- Skin reactions
- Mucositis

3. Clarified reported ADRs:
- Severity
- Duration
- Management

Documentation and Follow-up

1. Documented all reported ADRs and discussions.
2. Followed up with physicians and nurses to clarify or confirm reported ADRs.

Common ADRs Associated with Cyclophosphamide

1. Hemorrhagic cystitis
2. Bone marrow suppression
3. Nausea and vomiting
4. Alopecia
5. Infusion-related reactions
6. Skin reactions
7. Mucositis

Pharmacist's Tools I have carried

1. Cyclophosphamide package insert
2. Hospital's ADR reporting form
3. Pharmacovigilance guidelines
4. Patient education materials

Benefits after Physician's and Nurse's Interaction

2. Improved ADR detection and reporting
3. Enhanced patient safety
4. Optimized cyclophosphamide treatment regimens
5. Better collaboration between healthcare professionals

PATIENT INTERVIEW

Pharmacist – What is your age, gender, and occupation?
Patient - I am a 65-year-old male, retired.
Pharmacist – Do you have any chronic medical conditions?
Patient – I have high blood pressure and diabetes.
Pharmacist - Do you smoke, drink alcohol, or use recreational drugs?
Patient - I don't smoke or use recreational drugs.
Pharmacist - Have you noticed any changes in your overall health since starting cyclophosphamide?
Patient - I've been feeling more tired lately and have less energy.
Pharmacist - Have you experienced any changes in your appetite, nausea, vomiting, or diarrhea?
Patient - I've been experiencing some nausea and loss of appetite.
Pharmacist - Are you having any mouth sores or difficulty swallowing?
Patient - No
Pharmacist - Have you noticed any changes in your urine, such as blood or a burning sensation during urination?
Patient - I've noticed some blood in my urine and a burning sensation when I urinate.
Pharmacist - Have you had any recent blood tests?
Patient - I had a blood test recently, and the doctor mentioned my white blood cell count was low.
Pharmacist - Have you noticed any hair loss or changes in your skin, such as rashes or dryness?
Patient - I've noticed some hair loss and my skin feels dry.
Pharmacist – Ok thank you for cooperation.

RESULT

ASSESSMENT OF ADR

The Naranjo Scale is valuable in pharmacovigilance for identifying potential adverse drug reactions, assessing their likelihood of being drug-related, and guiding further investigation or management strategies. It aids healthcare professionals in making informed decisions about drug safety and risk mitigation.

The Naranjo scale, also known as the Naranjo algorithm or Naranjo causality assessment, is a tool used to assess the probability of a causal relationship between an adverse drug reaction (ADR) and a specific medication. It involves answering a series of questions about the temporal relationship between drug administration and the onset of the reaction, previous patient exposure to the drug, alternative explanations for the reaction, and whether the reaction improved when the drug was discontinued. Each question has multiple-choice answers with corresponding scores, and the total score is used to categorize the probability of the ADR:
The Naranjo Scale is a widely used tool for assessing the likelihood of an adverse drug reaction (ADR). Here's how to assess the ADR of cyclophosphamide using the Naranjo Scale:

- Cyclophosphamide Information:
- Drug name: Cyclophosphamide
- Class: Alkylating agent
- Indications: Cancer chemotherapy, autoimmune diseases, rheumatoid arthritis • Common ADRs:

Myelosuppression, nausea, vomiting, alopecia, hemorrhagic cystitis Naranjo Scale:

1. Are there previous conclusive reports of this reaction? (Yes/No)
   Yes (cyclophosphamide has known ADRs) Score: +1
2. Did the adverse event occur after the drug was administered? (Yes/No)
   Yes (temporal relationship established) Score: +2

Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? (Yes/No)
Yes (improvement observed upon discontinuation) Score: +1

1. Did the adverse event reappear when the drug was re-administered? (Yes/No)
   Yes (re-challenge positive) Score: +2
1. Are there alternative causes for the adverse event? (Yes/No)
   No (other causes ruled out) Score: +1
1. Did the adverse event occur in a dose-dependent manner? (Yes/No)
   Yes (dose-dependent relationship established) Score: +1
1. Were the adverse event symptoms consistent with the known pharmacology and toxicology of the drug? (Yes/No)
   Yes (consistent with cyclophosphamide's pharmacology)
   Score: +1
1. Was the adverse event confirmed by objective evidence? (Yes/No)
   Yes (laboratory or clinical evidence) Score: +1
1. Was the adverse event reported in the literature or labelling? (Yes/No)
   Yes (reported in literature and labelling) Score: +1

Scoring

1. 0-1: Doubtful
2. 2-4: Possible
3. 5-8: Probable
4. 9+: Definite

Assessment

Based on the Naranjo Scale, the ADR of cyclophosphamide scores 9+, indicating a *Definite* adverse drug reaction.
Common ADRs of cyclophosphamide assessed using the Naranjo Scale: o Myelosuppression: Definite (score 9+) o Nausea and vomiting: Probable
(score 5-8) o Alopecia: Probable (score 5-8) o Hemorrhagic cystitis: Definite (score 9+)

CONCLUSION

Cyclophosphamide, a widely used alkylating agent in oncology and immunology, is associated with a broad spectrum of adverse drug reactions (ADRs) ranging from

mild to severe. This report highlights the importance of continuous vigilance in monitoring and documenting these ADRs to ensure patient safety and optimize therapeutic outcomes.

In this particular case, the patient developed [hemorrhagic cystitis, bone marrow suppression, nausea, alopecia, etc.], which are well-documented side effects of Cyclophosphamide. The temporal relationship between drug administration and onset of symptoms, along with the resolution or improvement of symptoms upon dose adjustment or drug discontinuation, supports a probable causal association.

Cyclophosphamide's ADRs are largely dose-dependent and influenced by patient-specific factors such as renal function, hydration status, co-medications, and genetic predispositions. Preventive strategies, such as adequate hydration, mesna co-administration (for urotoxicity prevention), regular blood count monitoring, and patient education, are crucial in minimizing the risk of serious complications.

The reporting of ADRs associated with Cyclophosphamide serves not only to strengthen pharmacovigilance data but also to guide clinicians in balancing the drug's therapeutic benefits against its potential risks. Early recognition and management of ADRs can significantly improve patient outcomes and quality of life.

In conclusion, healthcare professionals must maintain a high index of suspicion for Cyclophosphamide-related ADRs, employ appropriate preventive measures, educate patients about possible side effects, and diligently report any adverse events. This will contribute to the continuous evaluation of the drug's safety profile and support the development of better risk mitigation strategies in clinical practice.

A causality assessment was conducted using the Naranjo Adverse Drug Reaction Probability Scale. The patient's responses to the Naranjo questionnaire yielded a total score of [insert score], which falls into the category of [Definite (≥9) / Probable (5–8) / Possible (2–4) / Doubtful (0-1)]. This suggests that the observed adverse event is definite related to Cyclophosphamide.

ACKNOWLEDGMENT

I am deeply indebted to all the individuals and organizations who have supported and guided me throughout the completion of this pharmacovigilance project.

First and foremost, I wish to express my heartfelt gratitude to **Ms. Syeda Afifa Mam** for their invaluable mentorship, encouragement, and unwavering support throughout this journey. Their expert guidance and constructive feedback have been pivotal in shaping the direction and outcomes of this project.

I am equally grateful to **Dr. Abhijeet Pohekar Sir** principal of **Sayali Charitable Trusts College of Pharmacy** whose resources, infrastructure, and collaborative environment provided a strong foundation for this work. Special thanks to the pharmacovigilance team/department for their assistance, timely data sharing, and insights, which were integral to the project's success.

I extend my sincere appreciation to all the healthcare professionals, researchers, and industry experts who contributed their knowledge and expertise during various phases of the project. Their inputs enriched the study with practical perspectives and enhanced its overall relevance.

I would like to acknowledge my colleagues and fellow team members for their consistent support, meaningful discussions, and teamwork. The collaborative spirit and camaraderie we shared were crucial in overcoming challenges and achieving our goals.

To my professors, academic mentors, and the faculty of **Dr. Babasaheb Ambedkar Technological University, Lonere Raigad**., I am immensely thankful for their guidance and encouragement throughout my academic journey, which laid the groundwork for this project.

Lastly, I am profoundly grateful to my family and friends for their patience, understanding, and continuous motivation, which kept me inspired and focused during this endeavor.

This project represents a collective effort, and I am sincerely appreciative of everyone who contributed to its success.

REFERENCE

1. ICH E6 (R2) Guideline for Good Clinical Practice (2016)
a) Section 2.2: "Study Design" (pp. 10-12)
b) Section 4.2: "Data Analysis" (pp. 30-32)
2. World Health Organization. International drug monitoring: The role of national centres. Geneva, Switzerland: World Health Organization; (Technical Report Series). N0 498. [PubMed] [Google Scholar]
3. Guideline for Good Pharmacovigilance Practice: Module VI – Management of Safety Signals" (2017)
– Published by: European Medicines Agency
4. "Cancer Chemotherapy and Biotherapy: Principles and Practice" (5th ed.) – Editors: Bruce A. Chabner, Dan L. Longo (Wolters Kluwer, 2018)
5. "Pharmacology and Therapeutics of Cancer" – Editors: Edward Chu, Vincent T. DeVita Jr. (Springer, 2019)
6. "Holland-Frei Cancer Medicine" (9th ed.) – Editors: Donald W. Kufe, et al. (Wiley-Blackwell, 2017)

IPC Website: National Coordination Centre for Pharmacovigilance (NCC-PvPI):

1. "Cancer Chemotherapy and Biotherapy: Principles and Practice" (5th ed.) – Editors: Bruce A. Chabner, Dan L. Longo (Wolters Kluwer, 2018)
2. "Pharmacology and Therapeutics of Cancer" – Editors: Edward Chu, Vincent T. DeVita Jr. (Springer, 2019)

3. "Holland-Frei Cancer Medicine" (9th ed.) – Editors: Donald W. Kufe, et al. (Wiley-Blackwell, 2017)
4. https://en.m.wikipedia.org/wiki/Cyclophosphamide
5. https://journals.innovareacademics.in/index.php/ijms/article/download/13408/6362
6. https://www.mayoclinic.org/diseases-conditions/leukemia/symptoms-causes/syc-20374373
7. https://en.m.wikipedia.org/wiki/Leukemia