ROLE OF PHARMACOVIGILANCE IN MANAGEMENT OF CHEMOTHERAPY INDUCED ADVERSE EFFECT

ANKITA BHOSALE[1*], PRITAM SALOKHE[2], DR. NILESH CHOUGULE[3], PRANALI LAD[1], UNNATI KUNDAP[1], AVDHUT PATIL[1]

[1]Student, Ashokrao Mane Institute of Pharmacy, Ambap, Maharashtra, India. 416112

[2] Assistant Professor, Ashokrao Mane Institute of Pharmacy, Ambap, Maharashtra, India. 416112

[3] Principal, Ashokrao Mane Institute of Pharmacy, Ambap, Maharashtra, India. 416112

Abstract

Pharmacovigilance is essential for keeping track on the safety and efficacy of anticancer drugs. This review article examines the adverse drug reactions (ADRs) associated with various anticancer medications, focusing on their toxic effects and the importance of continuous monitoring. By analyzing data from multiple studies and clinical reports, the review identifies common ADRs and their impact on different physiological systems. The findings underscore the need for robust pharmacovigilance practices to detect, assess, and prevent ADRs, thereby enhancing patient safety and therapeutic outcomes. The review also highlights the necessity of personalized medicine and careful drug selection to minimize toxic effects and optimize treatment efficacy in cancer patients.

Keywords: Pharmacovigilance, Adverse drug reactions, Efficacy, Cancer, Treatment

1. Introduction:

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug related problems. [1]

Adverse Drug Reaction (ADR) has been defined by the World Health Organization (WHO) as the reaction to a drug that is noxious, unintended and occurs at doses used for disease prophylaxis, diagnosis or treatment. [2]

Cancer stem cells (CSCs) are a small population of cancer cells with the capability of renewal themselves and possess high tumor-promoting and invasive ability. [3]

Chemotherapy medications that effectively destroy cancer cells might harm healthy cells and have unintended consequences.[4]

Clinicians frequently describe chemotherapy side effects in clinical trials, and they may underreport the frequency and intensity of side effects in comparison to patient accounts.[5]

Adjuvant chemotherapy is most effective when administered prior to or following radical local therapy (e.g., adjuvant chemotherapy in breast, colon, and pediatric malignancies).[6]

Combination chemotherapy is frequently used to get satisfactory results as well. By encouraging cytotoxicity in both resting and dividing cells, they seem to stop the formation of resistant clones.[7]

1.Signal information that was previously unknown or insufficiently recorded regarding a possible cause-and-effect link between a drug and an adverse event. Medication errors are any preventable situations that could lead to inappropriate pharmaceutical use or patient harm when the medication is being administered by the patient or healthcare professional or Problems in control over customers throughout the ordering or medical intervention procedure

2. For several years, evaluate the efficacy of drugs and monitor their adverse effects from the lab to the pharmacy and beyond.

3. Pharmacovigilance keeps an eye out for any serious adverse drug reactions.

4. Enhance public safety and health with regard to medication use.

5. Participate in the evaluation of risk, effectiveness, harm, and benefit

II. NEED FOR PHARMACOVIGILANCE

Reason 1: Humanitarian concern - Insufficient evidence of safety from clinical trials Animal experiments Phase 1-3 studies prior to marketing authorization.

Reason 2: Medicines are supposed to save lives Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.

Reason 3: ADR-related cost to the country exceeds the cost of the medications themselves.

Reason 4: Promoting rational use of medicines and adherence.

Reason 5: Ensuring public confidence.

Reason 6: Ethics, to know of something that is harmful to another person who does not know, and not telling, is unethical.[8]

III. National Programme of Pharmacovigilance:

The Pharmacovigilance Programme of India (PvPI) is an Indian government organization which identifies and responds to drug safety problems.[9]

Its activities include receiving reports of adverse drug events and taking necessary action to remedy problems.[10]

History: Many developed countries set up their pharmacovigilance programs following the Thalidomide scandal in the 1960s,[11]

India set up its program in the 1980s. [12]

This general concept of drug safety monitoring went through different forms, but the Central Drugs Standard Control Organisation established the present Pharmacovigilance Program of India in 2010.[13]

Now the program is well integrated with government legislation, a regulator as leader, and a research center as part of the Indian Pharmacopoeia Commission.[14]

It gave us to Information about rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions is often incomplete or not available. Certain adverse drug reactions may not be detected until a very large number of people have received the medicine.

Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use.

Providing information to users to optimise safe and effective use of medicines.

Monitoring the impact of any action taken.[15]

IV. Conducting of PV activity:

Activities**:** Pharmacovigilance is a specialized discipline of medical science dealing with activities linked to the detection, assessment, understanding and prevention and control of adverse effects or any other possible drug-related problems.[16]

As of 2018 there were 250 centers in India capable of responding to reports of major adverse reactions.[17]

One of the problems of the organization is training doctors and hospitals to report adverse drug reactions when patients have them.[18]

Although the Pharmacovigilance Program generates these reports, any clinic would be a good place to start.[19]

Promoting a culture and social expectation of reporting drug problems is the goal of the Pharmacovigilance Program.[20]

The establishment of the Pharmacovigilance Program made India a more attractive international destination for foreign companies to bring clinical trials research[21]

Understanding the quality of India's pharmacovigilance programme is key to international The establishment of the Pharmacovigilance Program made India a more attractive international destination for foreign companies to bring clinical trials researchresearchers conducting trials in India.[22]

The program collaborates both in India and internationally with the World Health Organization on projects for safe medication.[23]

As a collaborating center, the Pharmacovigilance Programme assists the WHO in developing international policy for other countries to manage their own drug safety programs.[24]

While the United States and Europe have pharmacovigilance systems which are developed well in some ways, the Indian programme has more and specialized expertise to apply.[25]

V. Cancer and Severity of cancer in India.

Breast cancer (BC) is the commonest malignancy among women globally. It has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases .[26]

Epidemiological studies have shown that the global burden of BC is expected to cross almost 2 million by the year 2030.[27]

In India, the incidence has increased significantly, almost by 50%, between 1965 and 1985.[28]

World Health Organization: Estimated number of new cancer cases in 2020, worldwide-

The estimated number of incident cases in India in 2016 was 118000 (95% uncertainty interval, 107000 to 130000), 98.1% of which were females, and the prevalent cases were 526000 (474000 to 574000). Over the last 26 years, the age-standardised incidence rate of BC in females increased by 39.1% (95% uncertainty interval, 5.1 to 85.5) from 1990 to 2016, with the increase observed in every state of the country.[29,30]

In India in 1990, the cervix was the leading site of cancer followed by BC in the registries of Bangalore (23.0% vs 15.9%), Bhopal (23.2% vs 21.4%), Chennai (28.9% vs 17.7%) and Delhi (21.6% vs 20.3%), while in Mumbai, the breast was the leading site of cancer (24.1% vs 16.0%). By the years 2000-2003, the scenario had changed, and breast had overtaken as the leading site of cancer in all the registries except in the rural registry of Barshi (16.9% vs 36.8%). In the case of BC, a significant increasing trend was observed in Bhopal, Chennai and Delhi registries.[31]

When it comes to the 5-year overall survival, a study reported it to be 95% for stage I patients, 92% for stage II, 70% for stage III and only 21% for stage IV patients.[32]

According to the World Cancer Report 2020, the most efficient intervention for BC control is early detection and rapid treatment.[33]

V. What do you mean by chemotherapy?

Chemotherapy:

The term “chemotherapy” was coined by German chemist Paul Ehrlich who investigated the use of drugs to treat infectious diseases. He was also the first scientist to study animal models to screen a series of chemicals regarding their potential activity against diseases. Historical documents suggest the use of arsenicals started in the 1900s. Radiotherapy ad surgery were the mainstays of cancer management in the 1960s. As micrometastases and recurrence of cancer after surgery and radiation therapy became evident, combination chemotherapy started gaining significance.[35]

Chemotherapy is one of the most important tools in the management of metastatic cancer.[36]

Chemotherapeutic drugs affect rapidly proliferating cancer cells but, unfortunately, damage normal bystander cells and also select drug resistance.[37]

Cancer incidence is rising and so too is the proliferation of high-cost, life-extending cancer drugs,[38]

Cancer is a very complex genetic, epigenetic and environmental disease and has great diversity in tissue, tumor and cellular levels. Diversity can lead to inappropriate treatments.[39]

Chemotherapy drugs work by targeting cells that reproduce quickly, which is a characteristic of cancer cells.[40]

VI. Common prescribed medicine used for chemotherapy

1. Alkylating Agents

Alkylating agents work by attaching an alkyl group to DNA, which prevents the cancer cells from multiplying.[41] They are among the oldest chemotherapy drugs and are used to treat various types of cancer, including leukemia, lymphoma, and breast cancer.[42] Common examples include Cyclophosphamide (Cytoxan) and Ifosfamide (Ifex).[43]

2. Antimetabolites

Antimetabolites mimic the building blocks of DNA, interfering with the cancer cell's ability to replicate4. They are effective in treating cancers like breast cancer, colorectal cancer, and lung cancer.[45] Methotrexate (Trexall) and 5-Fluorouracil (Adrucil) are well-known antimetabolites.[46]

3. Topoisomerase Inhibitors

Topoisomerase inhibitors block the action of topoisomerases, enzymes that help unwind DNA during replication.[47] By inhibiting these enzymes, these drugs prevent cancer cells from dividing and lead to cell death.[48] Etoposide (VePesid) and Irinotecan (Camptosar) are examples of topoisomerase inhibitors.[49,50]

4. Antitumor Antibiotics

Antitumor antibiotics are not like the antibiotics used to treat infections.[51] Instead, they are derived from natural substances produced by bacteria and work by interfering with the DNA inside cancer cells.[52] Doxorubicin (Adriamycin) and Bleomycin (Blenoxane) are commonly used antitumor antibiotics.[53,54]

5. Mitotic Inhibitors

Mitotic inhibitors disrupt the process of cell division (mitosis) by interfering with microtubules, which are structures that pull the cell apart during division.[55] They are particularly effective

against cancers that divide rapidly, such as breast cancer and lung cancer.[56] Paclitaxel (Taxol) and Vinorelbine (Navelbine) are examples of mitotic inhibitors.[57]

6. Targeted Therapies

Targeted therapies focus on specific genetic mutations in cancer cells.[58] These drugs are designed to target and block the growth and spread of cancer cells while minimizing damage to normal cell.[59] Imatinib (Gleevec) and Trastuzumab (Herceptin) are examples of targeted therapies 2021.

Each of these medications has its own set of potential side effects, which can vary from patient to patient. It's important to discuss with a healthcare provider to determine the most appropriate treatment plan. [52,53,54]

VII. Pharmacoviglance study on Common prescribed medicine used for chemotherapy

Careful study of adverse drug events may identify diagnostic features, syndromes or pathogenic mechanisms. Moreover, clinical, pathological and epidemiological information relating to adverse reactions is necessary for a full understanding of the nature of an adverse reaction and for identifying patients at risk.

Although spontaneous reporting is the mainstay of passive surveillance, the information obtained is inherently limited and likely to be insufficient for regulatory and clinical decisions. Active or intensive surveillance programmes for addressing serious safety concerns have had success in identifying and quantifying drug safety issues, using case control networks, hospital-based intensive monitoring systems, record linkage systems, epidemiological studies…ect

Information received from pharmacovigilance centres should feed directly into drug policy and drug utilization practice. Safety information from National Centres has a bearing on essential drugs programmes, standard treatment guidelines, and national and institutional formularies. Measuring the impact of such information on drug utilization and on the quality of patient care has considerable research potential.

It is necessary that drug regulatory decisions should be based on safety information that reflects national as well as international experience, and that this has been thoroughly and expertly reviewed. Drug utilization patterns also need to be taken into account ADRs have the potential to provide insights into structure-activity relationships, pharmacokinetic, pharmacodynamic and genetic factors affecting the action of medicines.

They may provide leads for other novel, indications. This is why it is important for the negative connotation of an ADR to be removed and for systems to be developed that enable medical,

pharmaceutical and chemical information to be applied constructively to a better understanding of how drugs work.[55,56]

1. Adverse Drug Reactions (ADRs)

Adverse Drug Reactions are unintended and harmful reactions to a drug. In chemotherapy, ADRs can range from mild to severe and include symptoms like nausea, vomiting, hair loss, fatigue, and bone marrow suppression. Serious ADRs may require dose adjustments, additional medications to manage symptoms, or even discontinuation of treatment. Identifying and managing ADRs promptly is crucial for patient safety and treatment effectiveness.

2. Ensuring Drug Safety

Ensuring drug safety involves continuous monitoring and evaluating the risk-benefit profile of chemotherapy drugs. This process includes pre-clinical and clinical trials, post-marketing surveillance, and real-world evidence collection. Safety data is analyzed to detect any new or previously unknown adverse effects, leading to updated treatment guidelines and safety measures.

3. Improving Treatment Outcomes

Pharmacovigilance aims to enhance treatment outcomes by minimizing adverse effects and optimizing therapeutic benefits. By monitoring patient responses and adjusting treatment protocols as needed, healthcare providers can improve patient quality of life and increase the chances of successful cancer remission or cure.

4. Regulatory Compliance

Regulatory bodies like the FDA, EMA, and WHO require stringent pharmacovigilance practices to ensure the safety and efficacy of chemotherapy drugs. Compliance involves adhering to guidelines for adverse event reporting, risk management plans, and periodic safety updates. Regulatory compliance is essential for maintaining market approval and public trust in chemotherapy treatments.

5. Adverse Event Reporting

Adverse Event Reporting is the process of documenting any unintended medical occurrence in a patient receiving chemotherapy. Reports are submitted by healthcare providers, patients, and pharmaceutical companies to national and international pharmacovigilance databases. These reports help identify trends, detect rare adverse effects, and provide critical data for safety assessments.

6. Risk Management Plans

Risk Management Plans (RMPs) are comprehensive strategies designed to identify, assess, and mitigate risks associated with chemotherapy drugs. RMPs include measures to prevent or minimize adverse effects, such as dose adjustments, patient education, and regular monitoring. Effective RMPs contribute to safer and more effective chemotherapy treatments.

7. Patient Education

Educating patients about potential side effects and the importance of reporting adverse reactions is a key aspect of pharmacovigilance. Patients are informed about how to recognize and manage side effects, when to seek medical attention, and how to report their experiences. Patient education empowers individuals to take an active role in their treatment and safety.

8. Post-Marketing Surveillance

Post-Marketing Surveillance involves the continuous monitoring of chemotherapy drugs after they have been approved for use. This phase captures data from real-world use, identifying long-term and rare adverse effects not detected in clinical trials. Surveillance helps update safety profiles, improve treatment guidelines, and ensure ongoing patient safety. [57,58,59]

VIII. What research concludes on pharmacovigilance activity on chemotherapeutic agent?

Salu Sunny the author of research work Assessment of Adverse Effects of Most Commonly Prescribed Anticancer Drugs in a Tertiary Care Teaching Hospital has studied pharmacovigilance activity of some common anticancer drugs. In that study A prospective observational study was conducted on 200 patients taking chemotherapy in oncology unit. Patient information was obtained using a data collection form and data was collected using a structured questionnaire.

By this study he conclude that Most of the anticancer drugs were prescribed in combination for a better therapy. Among 41 anticancer drugs, cyclophosphamide was the most commonly prescribed. Chemotherapy has a high potential to cause ADR in cancer patients. Most frequently observed ADRs were gastrointestinal and haematological reactions. Most common adverse effect was vomiting. Vomiting can be preventable, so there is a need to improve the management of vomiting, since the rates of prevention of these adverse effects were poor. In the present study, causality of adverse effects was poor due to the presence of co administered drugs. Since cancer chemotherapy has a high potential to cause ADRs, measures need to be put

into place to reduce the physical, emotional and economic burden on the patient due to adverse drug reactions. There is a need for vigilant ADR monitoring to decrease morbidity and mortality due to ADRs, which requires further studies on larger population. This study demonstrated that monitoring of chemotherapy related ADRs are feasible in a cancer ward and can facilitate quality improvement initiatives, as well as potentially improve patient care. Measures to improve detection and reporting of ADRs should be taken to enhance our understanding the nature and impact of these ADRs. By implementing the ADR monitoring and reporting system, pharmacists can promote drug safety and thereby assist health care professionals for a better patient care. [60]

Conclusion:

The pharmacovigilance study on anticancer drugs highlights the critical importance of continuous monitoring and evaluation of adverse drug reactions (ADRs) to ensure the safety and efficacy of cancer therapies. This review identifies common ADRs associated with various anticancer medications, affecting multiple physiological systems. The findings emphasize the need for robust pharmacovigilance practices to detect, assess, and mitigate toxic effects, thereby enhancing patient safety and improving therapeutic outcomes. Personalized medicine and careful selection of anticancer drugs are essential to minimize ADRs and optimize treatment efficacy for cancer patients. The study underscores the ongoing need for pharmacovigilance to adapt to emerging treatments and evolving patient needs, ultimately contributing to better cancer care and patient well-being.

References:

1. World health organization collaborating centre for international drug monitoring (2007). The importance of pharmacovigilance available at http://www.who_umc.org cited 18 December 2007
2. Organization WH. International Drug Monitoring: The Role of National Centers, Report of a WHO Meeting [Held in Geneva from 20 to 25 September 1971]. World Health Organization; 1972
3. Najafi M, Mortezaee K, Majidpoor J. Cancer stem cell (CSC) resistance drivers. *Life Sci* (2019) 234:116781. doi: 10.1016/j.lfs.2019.116781
4. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html
5. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. Di Maio M, Gallo C, Leighl NB, et al. J Clin Oncol. 2015;33:910–915. doi: 10.1200/JCO.2014.57.9334
6. Pinedo HM, Longo DL, Chabner BA, eds. Cancer chemotherapy and biological response modifiers. Amsterdam: Elsevier Annual 17 (in press)
7. Baserga R. The cell cycle. N Engl J Med. 1981 Feb 19;304(8):453-9
8. SCHOOL OF BIO AND CHEMICAL ENGEERING DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES (INTERNATIONAL RESEARCH CENTRE
9. Indian Pharmacopoeia Commission (2014). "Guidance Document for Spontaneous Adverse Drug Reaction Reporting

10. Indian Pharmacopoeia Commission (2014). "Guidance Document for Spontaneous Adverse Drug Reaction Reporting
11. Thatte, Urmila M.; Chaudhari, Nayan L.; Gogtay, Nithya J. (October 2018). "Pharmacovigilance Program of India: history, evolution and current status". *Adverse Drug Reaction Bulletin*. **312** (1): 1207–1210. doi:10.1097/FAD.0000000000000036. S2CID 81421623
12. Thatte, Urmila M.; Chaudhari, Nayan L.; Gogtay, Nithya J. (October 2018). "Pharmacovigilance Program of India: history, evolution and current status". *Adverse Drug Reaction Bulletin*. **312** (1): 1207–1210. doi:10.1097/FAD.0000000000000036. S2CID 81421623
13. Thatte, Urmila M.; Chaudhari, Nayan L.; Gogtay, Nithya J. (October 2018). "Pharmacovigilance Program of India: history, evolution and current status". *Adverse Drug Reaction Bulletin*. **312** (1): 1207–1210. doi:10.1097/FAD.0000000000000036. S2CID 81421623
14. Thatte, Urmila M.; Chaudhari, Nayan L.; Gogtay, Nithya J. (October 2018). "Pharmacovigilance Program of India: history, evolution and current status". *Adverse Drug Reaction Bulletin*. **312** (1): 1207–1210. doi:10.1097/FAD.0000000000000036. S2CID 81421623
15. (WHO, Pharmacovigilance: ensuring the safe use of medicines, Geneva: WHO 2004.)
16. Ambrose OT, Sarah GS, Umberto DA. Pharmacovigilance of antimalarial treatment in Africa: is it possible? Malaria J. 2006; 5:50
17. Thatte, Urmila M.; Chaudhari, Nayan L.; Gogtay, Nithya J. (October 2018). "Pharmacovigilance Program of India: history, evolution and current status". *Adverse Drug Reaction Bulletin*. **312** (1): 1207–1210. doi:10.1097/FAD.0000000000000036. S2CID 81421623
18. Kalaiselvan, V; Thota, P; Singh, GN (2016). "Pharmacovigilance Programme of India: Recent developments and future perspectives". *Indian Journal of Pharmacology*. **48** (6): 624–628. doi:10.4103/0253-7613.194855. PMC 5155460. PMID 28066097
19. Kalaiselvan, V; Thota, P; Singh, GN (2016). "Pharmacovigilance Programme of India: Recent developments and future perspectives". *Indian Journal of*

Pharmacology. **48** (6): 624–628. doi:10.4103/0253-7613.194855. PMC 5155460. PMID 28066097

20. Kalaiselvan, V; Thota, P; Singh, GN (2016). "Pharmacovigilance Programme of India: Recent developments and future perspectives". *Indian Journal of Pharmacology*. **48** (6): 624–628. doi:10.4103/0253-7613.194855. PMC 5155460. PMID 28066097
21. Gupta, YK; Padhy, BM (June 2011). "India's growing participation in global clinical trials". *Trends in Pharmacological Sciences*. **32** (6): 327–9. doi:10.1016/j.tips.2011.02.017. PMID 21489644.
22. Dylan Fernandes, S; Anoop, NV; Castelino, LJ; Narayana Charyulu, R (January 2019). "A national approach to pharmacovigilance: The case of India as a growing hub of global clinical trials". *Research in Social & Administrative Pharmacy*. **15** (1): 109–113. doi:10.1016/j.sapharm.2018.03.061. PMID 29602659. S2CID 4507185
23. World Health Organization (2017). "WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services". *World Health Organization*. Archived from the original on 26 February 2018
24. World Health Organization (2017). "WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services". *World Health Organization*. Archived from the original on 26 February 2018
25. Jose, Jobin; Rafeek, Naziya Refi (November 2019). "Pharmacovigilance in India in Comparison With the USA and European Union: Challenges and Perspectives". *Therapeutic Innovation & Regulatory Science*. **53** (6): 781–786. doi:10.1177/2168479018812775. PMID 30554527. S2CID 58768139
26. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209–249. doi: 10.3322/caac.21660
27. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin. 2011;61:409–418. doi: 10.3322/caac.20134

28. Saxena S, Szabo CI, Chopin S, Barjhoux L, Sinilnikova O, Lenoir G, Goldgar DE, Bhatanager D. BRCA1 and BRCA2 in Indian breast cancer patients. Hum Mutat. 2002;20:473–474. doi: 10.1002/humu.9082
29. Breast Cancer Factsheet. Global Cancer Observatory. International Agency for research on cancer. [cited 31 March 2021] Available from: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf
30. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Oncol 2018; 19: 1289-1306 [PMID: 30219626 DOI: 10.1016/S1470-2045(18)30447-9]
31. Takiar R, Srivastav A. Time trend in breast and cervix cancer of women in India - (1990-2003). Asian Pac J Cancer Prev 2008; 9: 777-780 [PMID: 19256775]
32. Arumugham R, Raj A, Nagarajan M, Vijilakshmi R. 327P - Survival Analysis of Breast Cancer Patients Treated at a Tertiary Care Centre in Southern India. Ann Oncol 2014; 25: iv 107 [DOI: 10.1093/annonc/mdu327.72]
33. International Agency for Research on Cancer. World Cancer Report [Internet]. 2020 [cited 4 April 2021] Available from: https://www.iarc.who.int/cards_page/world-cancer-report/
34. Breast Cancer Factsheet. Global Cancer Observatory. International Agency for research on cancer. [cited 31 March 2021]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf
35. DeVita VT, Chu E. A history of cancer chemotherapy. Cancer Res. 2008 Nov 01;68(21):8643-53
36. Carelle, N.; Piotto, E.; Bellanger, A.; Germanaud, J.; Thuillier, A.; Khayat, D. Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer* **2002**, *95*, 155–163.
37. Shaffer, B.C.; Gillet, J.-P.; Patel, C.; Baer, M.R.; Bates, S.E.; Gottesman, M.M. Drug resistance: Still a daunting challenge to the successful treatment of AML. *Drug Resist. Updates* **2012**, *15*, 62–69.
38. Stephens P: Bridging the gap: Why some people are not offered the medicines that NICE recommends. In. Edited by Excellence WPNIoHaC. 210 Pentonville Rd London N1 9JY: IMS Health; 2012: 1–32
39. Guo, Y. and J. Huo, Salvage treatment after chemotherapy drug extravasation: A rare case report. Asian journal of surgery, 2023: p. S1015-9584 (23) 00076-3

40. Somashekhar, S.P., et al., Toxicity profile of chemotherapy agents used in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies. European Journal of Surgical Oncology, 2020. 46(4, Part A): p. 577-581
41.
42. World health organization collaborating centre for international drug monitoring (2007). The importance of pharmacovigilance available at http://www.who_umc.org cited 18 December 2007
43.
44.
45. Organization WH. International Drug Monitoring: The Role of National Centers, Report of a WHO Meeting [Held in Geneva from 20 to 25 September 1971]. World Health Organization; 1972
46. SCHOOL OF BIO AND CHEMICAL ENGEERING DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES (INTERNATIONAL RESEARCH CENTRE
47. (WHO, Pharmacovigilance: ensuring the safe use of medicines, Geneva: WHO 2004.)
48. Satyajeet Singh*, Jai Prakash, Dr. Naveen Goyal, Rajeev Tomar, Abhishek Chaudhary, REVIEW ON PHARMACOVIGILANCE, WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES, Volume 4, Issue 06, 266-275
49. ..
50. .
51. …
52. H. Qiu, Y. Wang Exploring DNA-binding proteins with *in vivo* chemical cross-linking and mass spectrometry J Proteome Res, 8 (4) (2009), pp. 1983-199
53. *"Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer". Chemical Reviews.* ***109*** *(7): 2880 Lodish* H, Berk A, Zipursky SL, et al. (2000). *Molecular Cell Biology. 4th edition. The Role of Topoisomerases in DNA Replication*. New York: W. H. Freeman, Goodsell DS
54. Yang H, Ganguly A, Cabral F (October 2010). "Inhibition of cell migration and cell division correlates with distinct effects of microtubule inhibiting drugs". *The Journal of Biological Chemistry*. **285** (42): 32242 32250. doi:10.1074/jbc.M110.160820. PMC 2952225. PMID 20696757

55. Rikken F, Vos R. How ADRs can play a role in innovative drug research: Similarities in ADR profiles of captopril and penicillamine. Pharmacy World and Science 1995; 17(6): 195-200.
56. Alkofide H, Almalag HM, Alromaih M, Alotaibi L, Altuwaijri N, Al Aloola N, Alsabhan JF, Bawazeer GA, Al Juffali L, Alfaraj R, et al. Pharmacovigilance Practices by Healthcare Providers in Oncology: A Cross-Sectional Study. *Pharmaceuticals*. 2024; 17(6):683. https://doi.org/10.3390/ph17060683
57. WHO International drug monitoring the role of hospitals technical report series, WHO, Geneva, (1969):425
58. Saini VK, Sewal RK, Ahmad Y, Medhi B. Prospective observational study of adverse drug reactions of anticancer drugs used in cancer treatment in a tertiary care hospital. Indian Journal of Pharmaceutical Sciences. 2015;77(6):687-93
59. Swathi B, Bhavika D, Begum N. Adverse drug reaction profiles of commonly used platinum compounds in cancer chemotherapy. International Journal of Basic and Clinical Pharmacology. 2015;4(2):284-9.
60. Salu Sunny1, Athira Thampi1, Johnkennedy, Prescribed Anticancer Drugs in a Tertiary Care Teaching Hospital, Indian Journal of Pharmacy Practice, Vol 10, Issue 4, Oct-Dec, 2017