ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Comprehensive Review of the Pharmacological Approach to Cancer Treatment.

Favour Ebube Ugwu*, Richa Singh, and Hyma P.

Department of Pharmaceutics, GITAM School of Pharmacy, GITAM University, Hyderabad Campus, Rudraram, Telangana 502329, India.

ABSTRACT

Cancer has emerged as a very deadly disease, caused as a result of when cells grows uncontrollably and abnormally and spread to other parts of the body, cells and tissues. Cancer cells often grows as tumors and comes with various signs and symptoms which could be discomforting to the individual. Various types of cancers include Carcinoma, sarcomas, Myelomas, leukemia, and lymphomas. Various methods for diagnosis of cancers are Physical Examination, Family History, Family History, Cytological diagnosis and CT Scan. Cancer can be prevented by modifying our lifestyles, having a healthy balanced diet, avoiding smoking tobacco, avoiding abusing of alcohol, protecting our skin from frequent exposure to the sun and screening out skin and ensure safety from cancers. Cancer therapeutic modalities are surgery, chemotherapy, and radiation. Some chemotherapeutic agents used in the treatment of cancers include Alkylating agents like (Mechlorethamine, Melphalan, cyclophosphamide, Busulfan, Thiotepa, Lomustine, Carmustine. Dacarbazine, Temozolomide, and Procarbazine), Anti-Metabolite like (Methotrexate, pemetrexed, 6-Mercaptopurine, 6-Thioguanine, Azathioprine, Fludarabine, 5-fluorouracil, Cytarabine, Capecitabine, Floxuridine), cisplatin, Vincristine, Vinblastine, taxanes, Etoposide, Hydroxyurea. Actinomycin D, and Doxorubicin. These drugs undergo pharmacokinetic actions when they are administered to patients and they are widely distributed to the CNS, they are metabolised and excreted through the urine. These chemotherapeutic agents have some adverse reactions like; causing of Myelo suppression, nausea, mild alopecia, Diarrhea, and vomiting. The Anti-metabolite used in the treatment of cancers causes inhibition of purine synthesis and pyrimidine synthesis. Anti-biotics also aid in the treatment of cancers; it is called anticancer antibiotics; they bind with DNA and result to the formation of complex. They inhibit Topo-isomerase II and produce cytotoxicity and hence interrupt DNA functions. Various uses of anticancer antibiotics are in the treatment of lymphomas and Hodgkin's disease; its side effects includes Anorexia.

Keywords: Cancer, Tumors, Doxorubicin, Breast cancer, Lung cancer.

https://doi.org/10.33887/rjpbcs/2023.14.5.9

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Cancer is one of the world's deadliest diseases. It grows in the body of an individual uncontrollably. Cancer has no known cause, rather it is estimated to be caused as a result of some unfavourable conditions and lifestyles like drinking lots of alcohol, smoking, inadequate and improper diet, bad lifestyles, intake of tobacco, and unhealthy body weight; it is also concluded to be caused by certain changes in the DNA by a process called Mutation [1].

Cancer is known to be an uncontrolled growth of abnormal cells in the body, which contains trillions of cells which, if they are not treated early, can cause the death of a patient. These abnormal cells grows abnormally an invade other parts of the body rapidly without control [2].

These cells need to be examined and controlled by cutting them off through surgery or chemotherapy or radiation [3]. Cancer has no permanent cure but through this method, it can be managed to protect the individual suffering from this [4].

Types Of Tumors

- Benign Tumors: these types of tumors are not cancerous and non-problematic because they do not spread to other sides of the body [5].
- Malignant Tumors: These tumors are cancerous; they invade nearby tissues and spread to other body parts [6].

Table 1: Difference Between Benign Tumors and Malignant Tumors

Benign Tumor	Malignant Tumor
Slow growing	Fast growing
Non-invasive	invasive
Small	Large
Well differentiated	Poorly differentiated
Stays Localized	Metastasised

Table 2: Cancer By Cell/Tissue Types

CANCER TYPE	LOCATION (where they occur)
Carcinoma	Epithelial cell
Sarcomas	Bone
Myelomas	Plasma cells
Leukemia	Blood Cells
Lymphomas	Immune system (lymph node, spleen)
Mixed	Derived from multiple tissues or cell types

Signs And Symptoms Of Cancers

Breast cancer: Signs and symptoms of breast cancer include; a change in the texture of the breast, blood discharge from the nipple, and a lump in the breast (most common sign) [7].

Lung Cancer: Most common signs and symptoms of lung cancer are: chest pain, cough coming out with blood, wheezing [8] etc.

Lymphomas: Its signs and symptoms include fatigue, enlarged lymph nodes, weight loss [9], etc.

Leukaemia: The signs and symptoms of this include; bleeding, decreased blood clotting, increased infections, fatigue, weight loss, [10] etc.

ISSN: 0975-8585

Diagnosis Of Cancer Include

Physical Examination: This is a careful examination by observing for cancer growth on the skin, breast, lymph nodes, and lungs [11].

Family History: Doctors frequently ask about the family history of the patients because whatever runs in the bloodline has the probability of repeating again [12].

Haematological diagnosis: This is cancer diagnosis through blood tests [13].

Radiological diagnosis: This type of diagnosis helps to detect the location of the cancer tumor and the damaged tissue [14].

Cytological diagnosis: This diagnosis examines every cell and the affected area of cancer [15].

Molecular diagnosis: This diagnosis helps to determine the likelihood of a person developing cancer. This is known as molecular profiling, to determine whether a person is at risk of developing cancer [16].

Tumor markers: These are also called Bio-markers; they are used in the diagnosis of cancer [17].

CT Scan: This is a painless procedure that helps the doctor to see the shape and size of the tumor. CT Scan is known as Computed Tomography Scan [18].

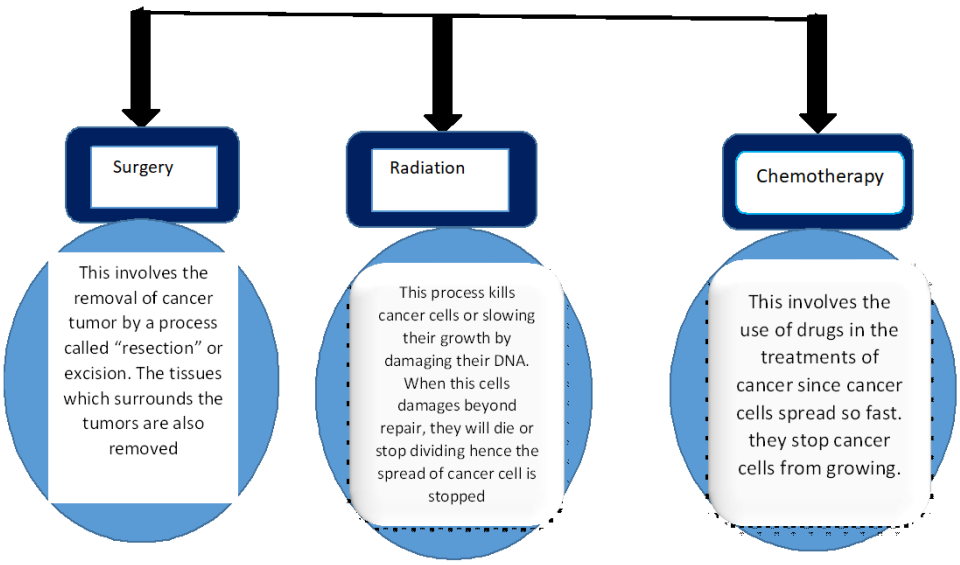
Prevention Of Cancer

- Avoid the use of Tobacco or smoking [19].
- Getting vaccination for Hepatitis B and Human Papilloma Virus.
- Maintain good body weight.
- Exercise frequently.
- Avoid much intake of alcohol.
- Avoid frequent exposure of skin to the sun.
- Avoid polluted environments like air pollution.

Management Of Cancer

These are the Cancer therapeutic modalities [20]

Figure 1: Cancer therapeutic modalities



ISSN: 0975-8585

Current Drugs On The Treatment Of Cancer

Current drugs used in the chemotherapy of cancer helps to kill cancer cells and stop them from dividing and spreading to different parts of the body. Below is the classification of drugs used in the current treatment of cancer based on their mechanism of action [21].

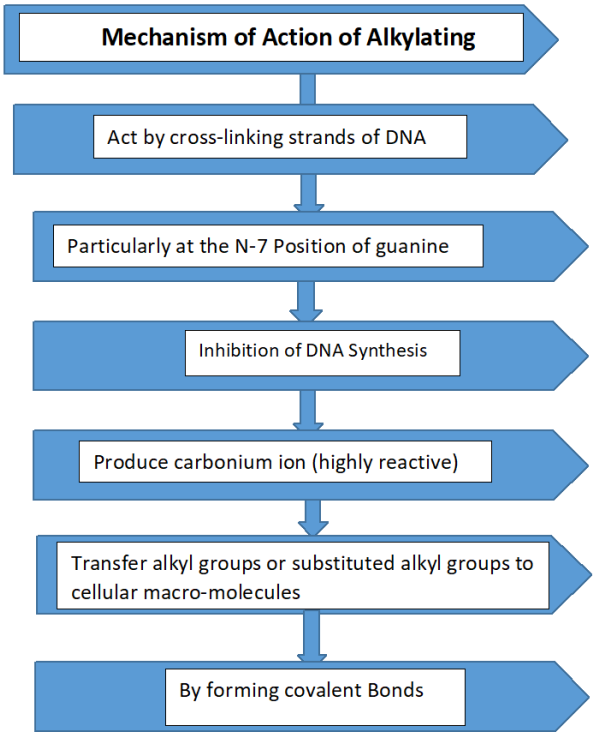
Table 3

Classifications	Examples of drugs
1. Alkylating Agents	(I). Nitrogen Mustard: Mechlorethamine, Melphalan, cyclophosphamide, ifosphamide. (ll). Alkyl Sulfonate: Busulfan (lll). Ethylenimines: Thiotepa (lV). Nitrosoureas: Lomustine, Carmustine. (V). Triazine: Dacarbazine, Temozolomide. (VI). Methyl Hydrazine: Procarbazine.
2. Anti-Metabolite	(l). Folate Antagonoist: Methotrexate, pemetrexed. (ll). Purine Antagonist: 6-Mercaptopurine, 6-Thioguanine, Azathioprine, Fludarabine. (lll). Pyrimidine Antagonist: 5-fluorouracil, Cytarabine, Capecitabine, Floxuridine
3. Platinum coordination complexes [22]	(l). Cisplatin (ll). Carboplatin (lll). Oxaliplatin
4. Plant-derived products	(l). Vince Alkaloids (Vincristine, Vinblastine). (ll). Taxanes: Paclitaxel, Docetaxel
5. Antibiotics	(l). Actinomycin D. (ll). Doxorubicin (lll). Bleomycin. (lV). Mitomycin C.
6. Hormones & Related Drugs	(l). progestins
7. Drugs that alter Hormone	(l). Glucocorticoid: Prednisolone (ll). Estrogen: Diethylstibestreol (lll). Androgen: Testosteron (lV). Aromatase inhibitors: Letrozole, Exemestane, Anastrozole. (V). GnRH Analogues: Leuprorelin, Nafarelin (VI). SERMs: Tamoxifen, Toremifene (VII). SER-down Regulator: Fulvestrant
8. Monoclonal Anti-bodies	(l). Trantuzumab (ll). Rituximab
9. Topo-Isomerase-1-Inhibitors	(l). Topotecan (ll). Irinotecan
10. Topo-Isomerase-2-Inhibitors [23]	(l). Etoposide
11. Miscellaneous	(l). Hydroxyurea (ll). L-Asparaginase (lV). Tretinoin (V). Arsenic Trioxide

ISSN: 0975-8585

Alkylating Agents

Figure 2



Nitrogen Mustard

Mechlorethamine

Uses of Mechlorethamine

- Used in ailment of Hodkin's disease
- Treatment of Leucopenia
- Treatment of Lymphomas.
- Treatment of Thrombocytopenia

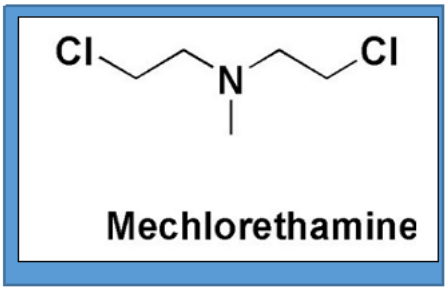


Figure 3

Chlorambucil

MOA of Chlorambucil

- Radiomimitic
- Interferes with DNA replication.
- Damages DNA in cells

ISSN: 0975-8585

Uses of Chlorambucil

- Used as an immunosuppressant [24].
- To be used in the treatment of chronic Lymphatic
- To be used in the treatment of Malignant Lymphomas

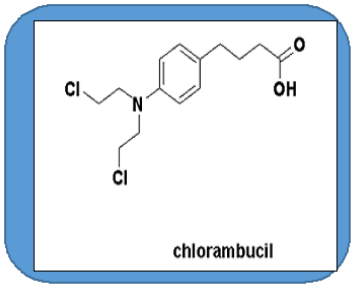


Figure 4

Busulfan

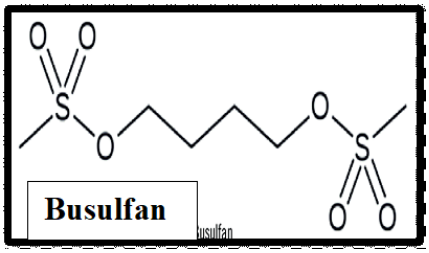


Figure 5

Uses of Busulfan

- Used to treat chronic granulocytic leukemia.
- Used as immunosuppressant on bone marrow.

Thiotepa

Uses of Thiotepa

- Treating Breast Cancer
- Treating ovarian cancer
- Treating Bladder Cancer
- Treating lymphomas.

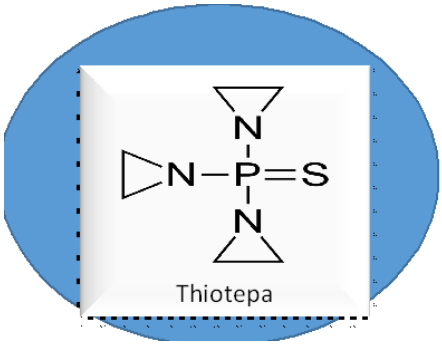


Figure 6

ISSN: 0975-8585

Melphalan

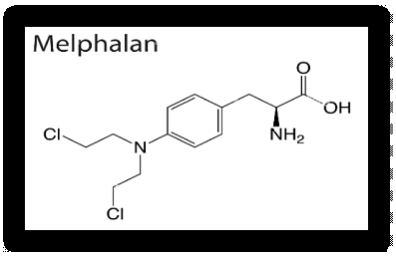


Figure 7

Uses of Melphan

- Treatment of Breast Cancer.
- Treatment of Ovarian Cancer [25].

Cyclophosphamide [26]

Uses of Cyclophosphamide

- Used in ailment of Hodgkin's disease.
- used in ailment of Breast cancer.
- Used in ailment of Lung cancer
- Used in the treatment of Leukemia.
- Used in the treatment of Lymphomas.

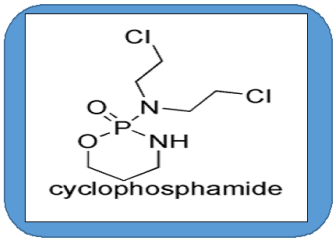


Figure 8

Pharmacokinetics of Alkylating Agents.

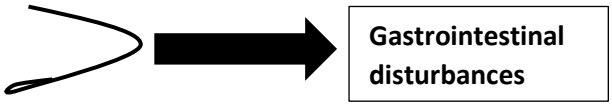
Absorption: they are administered orally and well absorbed orally [27].

Distribution: it is widely distributed to the CNS.

Metabolism & Excretion: The metabolites and the parent compound are excreted in the urine.

Adverse Effects of Alkylating Agents

- Myelo suppression
- Mild Alopecia
- Nausea
- Vomiting
- Diarrhea



Antibiotics

This is a substance derived from a micro-organism or produced synthetically to kill the growth of microorganisms [28].

ISSN: 0975-8585

Mechanism Of Action Of Antibiotics On Treatment Of Cancer

- Acts by binding to DNA
- By intercalation and strand breakage
- Inhibit cell replication
- Blocking the transcription of RNA and DNA.

Doxorubicin

This is a cytotoxic anthracycline antibiotic [29].

Uses of Doxorubicin

- Used in the treatment of Leukemia.
- Used in ailment of breast cancer.
- Used in ailment of bladder cancer
- Used in the treatment of Lymphoma.
-

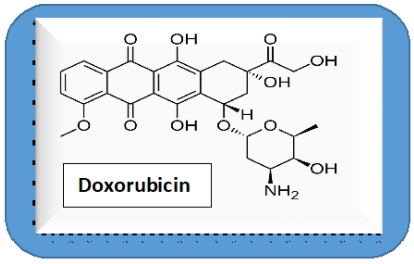


Figure 9

Bleomycin

This consists of Bleomycin A_2 and Bleomycin B_2. It is obtained from Streptomyces Verticulus.

Uses of Bleomycin

- Used in the treatment of carcinoma of the cervix, neck, head, and penis
- Used in the treatment of bronchus, trachea and Lungs.

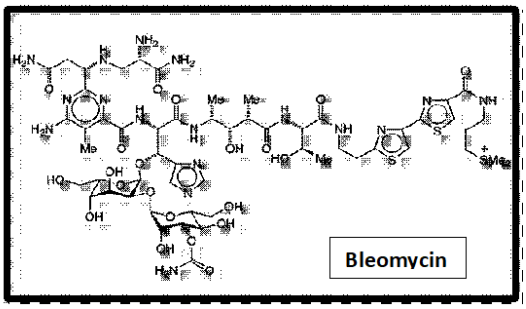


Figure 10

Platinum coordination complexes (cisplatin).

Mechanism of Action Cisplatin

- It is a chemotherapy medication used to several number of cancers [30].
- It is a platinum-based antineoplastic medication.
- It binds to DNA and inhibit its replication.

ISSN: 0975-8585

Uses of Cisplatin

- used in the ailment of breast cancer.
- Lung cancer treatment.
- Bladder cancer treatment.

Adverse Effect of Cisplatin

- Bone marrow suppressant
- Hearing Problem
- Kidney problem
- Heart Disease

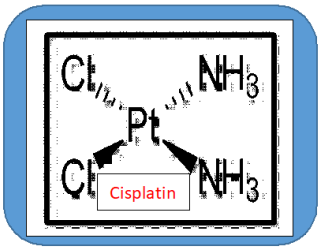


Figure 11

Plant products in the treatment of cancer (Plant-Derived products)

Plant medicines are essential in preventing and treating cancer because they are derived from plants and have lesser side effects. Vince Alkaloids (Vincristine, Vinblastine) are the major plant products used to treat cancer [31].

Mechanisms of Action of Vinca Alkaloids

- Binds to microtubular protein tubulin in a dimeric form.
- The forming end of the drug is enhanced by the tubulin complex,
- Microtubule to terminate assembly,
- Depolymerization of the microtubules occurs.

Uses of Vinca Alkaloids

- It is used in the treatment of breast cancers
- Treatment of Testicular cancers
- Treatment of Hodgkin's Lymphomas
- Treatment of Lymphocytic Leukemia.

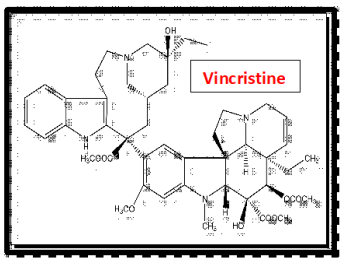


Figure 12

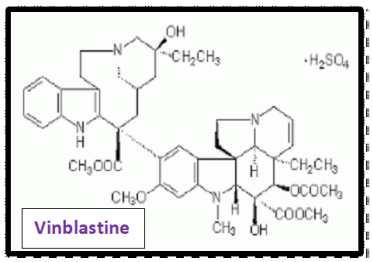


Figure 13

Anti-Metabolite

Mechanism of Action of Anti-Metabolite

- Inhibit purine synthesis [32]

ISSN: 0975-8585

- Inhibit pyrimidine synthesis.

Mercaptopurine

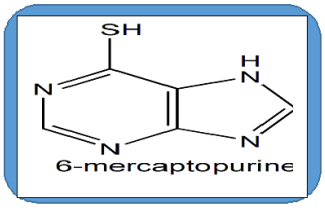


Figure 14

Mechanism of Action Mercaptopurine

- It is metabolized into 6-MPMP (6-Thioinosinate) by HGPRT (Hypoxanthine Guanine Phosphoribosyl Transferase).
- Inhibit conversion of ionisine acid to adenylic acid and xanthylic acid.
- Prevent the purine biosynthesis.

Uses of Mercaptopurine

- Used in the treatment of acute monocytic Leukaemia.

Synthesis of Mercaptopurine

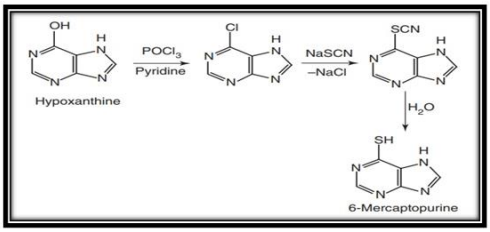


Figure 15

Methotrexate

Mechanism of Action of Methotrexate

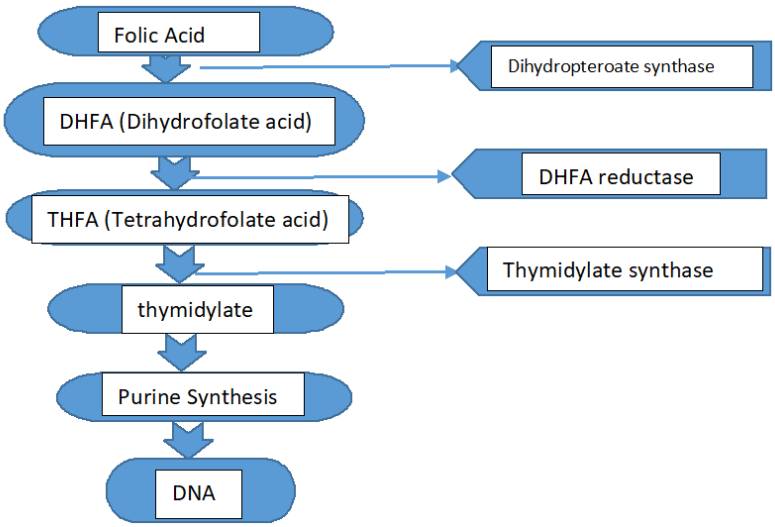


Figure 16: Mechanism of action of methotrexate

Synthesis of Methotrexate

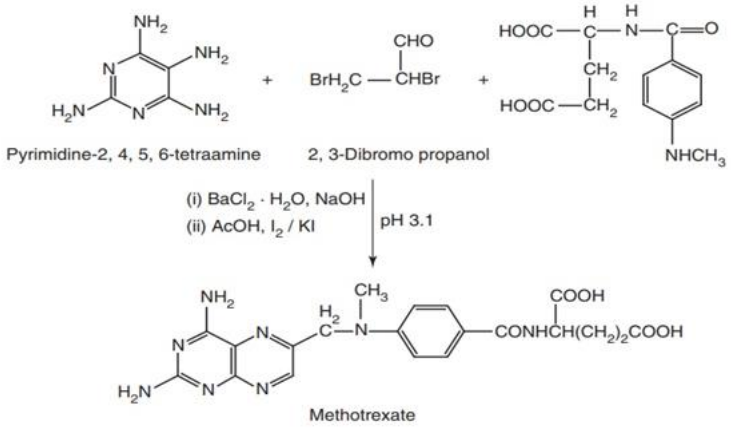


Figure 17

Pharmacokinetics of Methotrexate

Absorption: Oral Absorption, Enteric transport, Enteric metabolism.

Distribution: Intra-vascular space, extravascular space, and protein linkage.

Metabolism: Hepatic influx transport, Phase 1 metabolism, Phase 2 metabolism,

Excretion: Renal Excretion (Efflux transport), Intestinal excretion, and Biliary excretion (by efflux transport).

Floxuridine

Mechanism of Action of Floxuridine

- Inhibition of enzyme thymidylate synthase
- Inhibit DNA synthesis
- Increase anti-cancer activity in 5-fluorouracil

Uses of Floxuridine

- Used in ailment of kidney cancer
- Treatment of colorectal cancer

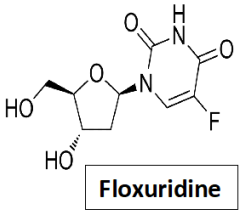


Figure 18

CONCLUSION

We have studied in detail about cancer, its signs & symptoms, its causes, prevention and detailed study on its chemotherapy, along with the pharmacokinetics of these drugs, uses and adverse effects in detail. We hope this article gives you good insight on cancer and its pharmacological and medicinal approach.

REFERENCES

[1] Aida T, Takebayashi Y, Shimizu, T, Okamura C, Higasimoto M, Kanzaki A, et al. Expression of copper-transporting P-type adenosine triphosphatase (ATP7B) as a prognostic factor in human endometrial carcinoma. Gynecol Oncol 2005; 97:41–45.

[2] Kyle RA. Multiple myeloma: review of 869 cases. Mayo Clin Proc 1975; 50:29–40.

[3] Felix CA. Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta 1998; 1400:233–255.

[4] D Addio A, Curti A, Worel N, Douglas K, Motta MR, Rizzi S et al. The addition of plerixafor is safe and allows adequate PBSC collection in multiple myeloma and lymphoma patients poor mobilizers after chemotherapy and G-CSF. Bone Marrow Transplant 2011; 46: 356–363.

[5] Tinnemans JGM, Wobbes T, Holland R, et al: Mammographic and histopathologic correlation of nonpalpable lesions of the breast and the reliability of frozen section diagnosis. Surg Gynecol Obstet 1987; 165:523-569.

[6] Schreiber MH, Winslade WJ: Rights, roles, and responsibilities in radiology. Radiology 1987; 163:269-270.

[7] Roe FJC, Lee PN, Conybeare G, Tobin G, Kelly D, Prentice D and Matter B, Risks of premature death and cancer predicted by body weight in early adult life, Hum Exp Toxicol 1991; 10: 285–8.

[8] Chen, A.M., Zhang, M., Wei, D.G., Stueber, D., Taratula, O., Minko, T., He, H.X. Co-delivery of doxorubicin and Bcl-2 siRNA by mesoporous silica nanoparticles enhances the efficacy of chemotherapy in multidrug-resistant cancer cells. Small 2009;5 :2673–2677.

[9] Okamoto, K, and Ogura, R: Effects of vitamins on lipid peroxidation and suppression of DNA synthesis induced by adriamycin in Ehrlich cells. J Nutr Sci Vitaminol 1985;31:129–137.

[10] Erhola, M, Kellokumpu-Lehtinen, P, Metsa-Ketela, T, Alanko, K, and Nieminen, MM: Effects of anthracyclin-based chemotherapy on total plasma antioxidant capacity in small cell lung cancer patients. Free Radic Biol Med 1996; 21:383–390.

[11] Lammi L, Halonen K, Pirinen S, Thesleff I, Arte S, Nieminen P; A missense mutation in PAX9 in a family with distinct phenotype of oligodontia. Eur J Hum Genet 2003; 11:866– 871.

[12] Reya T, Morrison SJ, Clarke MF, Weissman IL: Stem cells, cancer, and cancer stem cells. Nature 2001; 414:105-111.

[13] Goel IP, Didolkar MC. Elias EG. Primary malignant tumors of the small intestine. Surg Gvnecol Ohsiri 1976; 143:717-719.

[14] Litherland JC, Dobson HM. Symptomatic women with normal screening mammograms: is assessment by the breast screening programme justifiable? The Breast 2001;10:58–60.

[15] Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine 1990; 69:1–33.

[16] Pollock BH, DeBaun MR, Camitta BM, Shuster JJ, Ravindranath Y, Pullen DJ, et al. Racial differences in the survival of childhood Bprecursor acute lymphoblastic leukemia: a paediatric oncology group study. J Clin Oncol 2000; 18:813–23.

[17] Friese CR, Earle CC, Magazu LS, et al. Timeliness and quality of diagnostic care for medicare recipients with chronic lymphocytic leukemia. Cancer 2011; 117(7): 1470–1477.

[18] Cheetham S, Gruhl F, Mattick J, Dinger M. Long noncoding RNAs and the genetics of cancer. Br J Cancer 2013; 108: 2419–2425.

[19] Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. Journal of the National Cancer Institute 1981; 66: 1191–308.

[20] Cherny NI, Coyle N, Foley KM. Suffering in the advanced cancer patient: a definition and taxonomy. J Palliat Care 1994; 10: 57–70.

[21] Gregory RK, Smith IE. Vinorelbine - a clinical review. Br J Cancer 2000; 82:1907-13.

[22] Johnson C Platinum alone for chemotherapy for ovarian cancer? Lancet 1998, 352 1567-8.

[23] Hande, K.R. Etoposide: Four decades of development of a topoisomerase II inhibitor. Eur J Cancer 1998; 34:1514–1521.

[24] Goff, R. D.; Thorson, J. S. Assessment of chemoselective neoglycosylation methods using chlorambucil as a model. J Med Chem 2010; 53:8129–8139.

[25] Mistry P, Kelland LR, Abel G et al The relationships between glutathione, glutathione-S-transferase and cytotoxicity of platinum drugs and melphalan in eight human ovanan carcinoma cell lines. Br J Cancer 1991; 64:215-20.

[26] Piccart MJ, Bertelsen K, James K et al Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer Three-year results J Natl Cancer Inst 2000;92: 699-708.

[27] Lee FYF, Coe P, and Workman P. Pharmacokinetic basis for the comparative antitumor activity and toxicity of chlorambucil, phenylacetic acid mustard and fÃ-.fÃ--difluorocnlorambucil(CB 7103) in mice. Cancer Chemother Pharmacol 1986; 17: 21-29.
[28] Li H, Jiao S, Li X, Banu H, Hamal S, Wang X. Therapeutic effects of antibiotic drug tigecycline against cervical squamous cell carcinoma by inhibiting Wnt/beta-catenin signaling. Biochem Biophys Res Commun 2015;467:14–20.
[29] Box V. The intercalation of DNA double helices with doxorubicin and nagalomycin. J Mol Graph Mod 2007;26:14-19.
[30] logs. In Prestayko AW, Crooke ST, Carter SK, eds. Cisplatin, Current Status and New Developments. New York, Academic Press, 1980, 183-192.
[31] Maryam Moudi, Rusea Go, Christina Yong Seok Yien, Mohd Nazre. Vinca Alkaloid. Int J Prev Med 2013; 4(11):1231-1235.
[32] Abelson HT, Kufe DW, Skarin AT et al. Treatment of central nervous system tumors with methotrexate. Cancer Treat Rep 1981;65(suppl 1): 137–140.