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Clinical Implication of Cyclophosphamide in Oncology, Hematology and Bone Marrow Transplantation (BMT)

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Abstract:- Cyclophosphamide (Cytoxan; Cy) is an alkylating agent with immunosuppressive and cytotoxic action. The origin compound is out of action in vitro and utilizesits biologic activity over metabolites, principally phosphoramide mustard stemming from hepatic microsomal enzymes. The accurate process of cytotoxic and immunosuppressive activity of Cy at the cellular level is not ultimately presumed. Myelosuppression, alopecia, hemorrhagic cystitis, and gonadal disturbance are the main harmful consequence. Applicable information proposesthat Cy has carcinogenic probable in humans. Cy is greatly utilized as chemotherapy for cancer treatment, also as an immunosuppressive chemical, it is profitably used in specific nonmalignant diseases whether autoimmune phenomena are entrenched or suspicious in the pathogenesis of the disease. It is the preferred drug in Wegener's granulomatosis. Broad efforts are being made to generate Cy analogues with higher selective cytotoxic and immunosuppressive activity.

Keywords:- *Cyclophosphamide, cyclophosphamide and cancer, chemotherapy, toxic effect.*

I. INTRODUCTION

Cancer is the most obvious cause of death globally and it is considered the second leading cause of death in the United States. Thesituation is approximated to furtherdeteriorate by 2030 as deaths due to cancer may pass over 13.1 million. The US net consumption on cancer concerns is predicted to shift from 125 billion in 2010 to 156 billion by 2020 (Iqubal et al., 2019). Cyclophosphamide is one of the ultimate outstanding anticancer agents ever synthesized. Even current, greater than 50 years later,its synthesis, cyclophosphamide, is still extensively utilized as a chemotherapeutic agent and in the mobilization and conditioning procedures for blood and marrow transplantation (BMT). Between 1,000 chosen compounds and antibiotics tested in contrast to 33 tumors,phosphamide was the higher effective agent and only four agents were discovered to retain pharmacologic characterstics (Emadi et al., 2009). They are cyclophosphamide (Cytoxan, Cy),trofosfamide, ifosfamide, and sufosfamide. The original clinical investigation of cyclophosphamide forcancer treatment wasaccomplished in 1958, and in 1959 grow into the eighth cytotoxic anticancer chemicalapproved by the FDA. It is also accepted for nephrotic syndrome in children;however, regardless of its widespread utilizationin other autoimmune diseasesand BMT, it has never been approved for these indications.Cyclophosphamide is the precursor of oxazaphosphorines, without absolute alkylating activity (Emadi et al.,2009).The metabolic pathway of cyclophosphamide (Cy) has been broadly investigated. The subsequent scheme was based on experimental investigations.

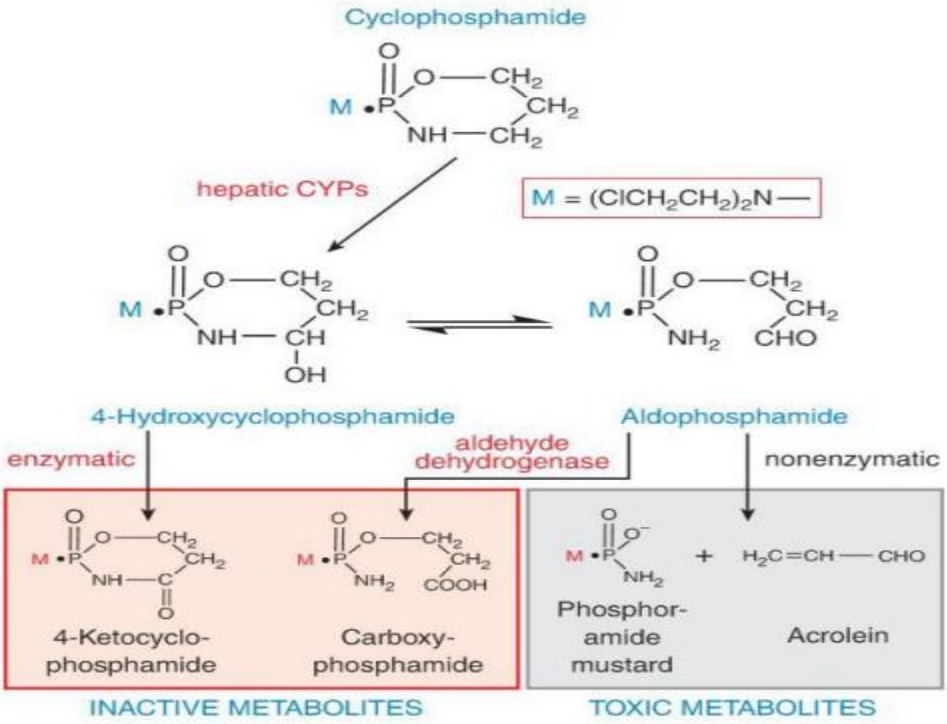

Fig. 1: Schematic illustration of metabolic pathway of cyclophosphamide (Hilal-Dandan and Brunton, 2013)

At physiological pH, phosphoramide mustard is described as a strong alkylating agent and is most likely the most important biologically active alkylating substance obtained from Cy (Colvin et al., 1976). The compound is not extensively bound to circulating albumin and lower than 20% of radiolabel Cy is detected in the urine (Struck et al., 1971) (Bagley et al., 1973). Individual differences in Cy plasma half-life range from 2 to 10 hours have been recorded (Friedman et al., 1976).Furthermore, the precise mechanism of action, specifications of cellular transport and conversion, of Cy at the cellular level are unknown. Phosphoramide mustard has no discernible immunosuppressive properties (Sensenbrenner et al., 1979).Chloroacetaldehyde, a powerful immunosuppressive agent produced during Cy side chain oxidation, is most likely responsible for its immunosuppressive effects (Ahmed and Hombal, 1984).

II. THERAPEUTIC USES

A wide range of human tumors has high response to Cy therapy and this is a reason for the continuous implication of the drug in variety of diseases treatment fifty years after its discovery, such as lung carcinoma, sarcomas, leukemias, many cases of mycosis andfungoides, malignant lymphomas, neuroblastoma carcinomas of the ovary, retinoblastoma and testis, and, multiple myeloma (Emadi et al., 2009).

Cy is typically administered in combination or after treatment with other antineoplastic drugs in cancer management. Many studies have shown its significant anticancer activity and Cy is also applied in the treatment of particular autoimmune diseases, where the body's immunologic surveillance systems are involved in their pathophysiology, as an immunosuppressive agent. It has been depicted that the chemotherapeutic margin of Cy and its powerful immunosuppressive properties are because of a variety of cellular expression of AlDH (Molin et al., 1978).

III.TOXIC EFFECTS OF CYCLOPHOSPHAMIDE

The dosage of cyclophosphamide, and thus its toxicity profile, varies greatly depending on clinical implication. This drug may be prescribed at low dose, 1–3 mg/kg per day (40–120 mg/m2) that is mostly administered orally or pulse dose could be intravenously recommended, 15–40 mg/kg (600–1,500 mg/m2) every 3–4 weeks. Furthermore, in bone marrow transplantation high dose of cyclophosphamide is used, >120 mg/kg (>5,000 mg/m2) which is more frequently administered over 2–4 days as conditioning for BMT. Some acute toxic impacts could be detected with the use of mild to moderate dosage of the drug but chronic toxicity can develop with long term, more than six months, administration of low dose of cyclophosphamide. Contrarily, obvious acute toxic impacts are developed with high dose cyclophosphamide.however, alleviates the risk of prolonged toxicity effects (Brodsky et al., 2004) (Dussan et al., 2008).

A. Hematologic toxic effects

The common side effect of cyclophosphamide is bone marrow suppression and the resulted neutropenia is greatly dose dependent. Despite the low risk of development of significant neutropenia with the use of low dose cyclophosphamide, close monitoring of patients is highly required. High doses of the chemotherapy can develop various hematological issues, such as anemia, leukopenia, and thrombocytopenia. However, patients with normal bone marrow reserve can develop a rapid recovery process within

2–3 weeks regardless of the administrated dose (Emadi et al., 2009).

B. Cardiac toxic effects

Cardiotoxicity impact of cyclophosphamide is mostly dose dependent and it commonly appears after high dose administration (Santos et al., 1972). The toxic effect of the drug on cardiac tissues vary, which ranged from innocuous to fatal. It has been noted that lower than 0.1% patient treated with cyclophosphamide can develop hemorrhagic necrotic perimyocarditis, which is fatal and urgently occurs within few days of drug infusion (Murdych&Weisdorf, 2001) (Cazin et al.,1986).

C. Gonadal toxic effects

Gonadal deterioration is a main obstacle in cyclophosphamide therapy, specifically in women.There are several factors that could have significant impacts in the development of adverse reactions of the drugs, such as patient age, the administration itinerary and the cumulative dose (Watson et la., 1985) (Boumpas et al., 1993). It has been noted that women below 25 years old have 12% risk of the development of continuous amenorrhea with lupus receiving moderate dose of cyclophosphamide and the risk of the event become greatly higher in women 30 years older of more than 50% (Boumpas et al., 1993).

The hazard of the development of ovariandeterioration after the administration ofhigh dose cyclophosphamide seems to be lower than that of intermediatedose. On the other hand, no sign of ovarian deterioration was recorded following administration of high dose of cyclophosphamide after allogeneic BMT for aplastic anemia in women with lower than 26 years old although it wasmostly identified in older women (Sanders et al., 1988).

D. Bladder toxicity

The most obvious and popular form of bladder toxicity following cyclophosphamide administration is hemorrhagic cystitis,but squamouscell carcinoma or bladder fibrosiscan further develop (Stillwell et al., 1988).The development of hemorrhagic cystitis may appear in early stage or might be somewhat delay subsequent to cyclophosphamide administration. The occurrence of the issue in early commencement defect, in the initial few days'later cyclophosphamide therapy, looks to be affected by acrolein (Figure 2) (Cox, 1979). Several aspects can have substantial in the prevention hemorrhagic cystitis, such as potent hydration, mandatory diuresis therapy and administration of MESNA, which produces nontoxic adducts throughout interaction with acroleinand thereby inhibition of hemorrhagic vialimitation of uroepithelialdisclosure to acrolein (Haselberger&Schwinghammer, 1995).

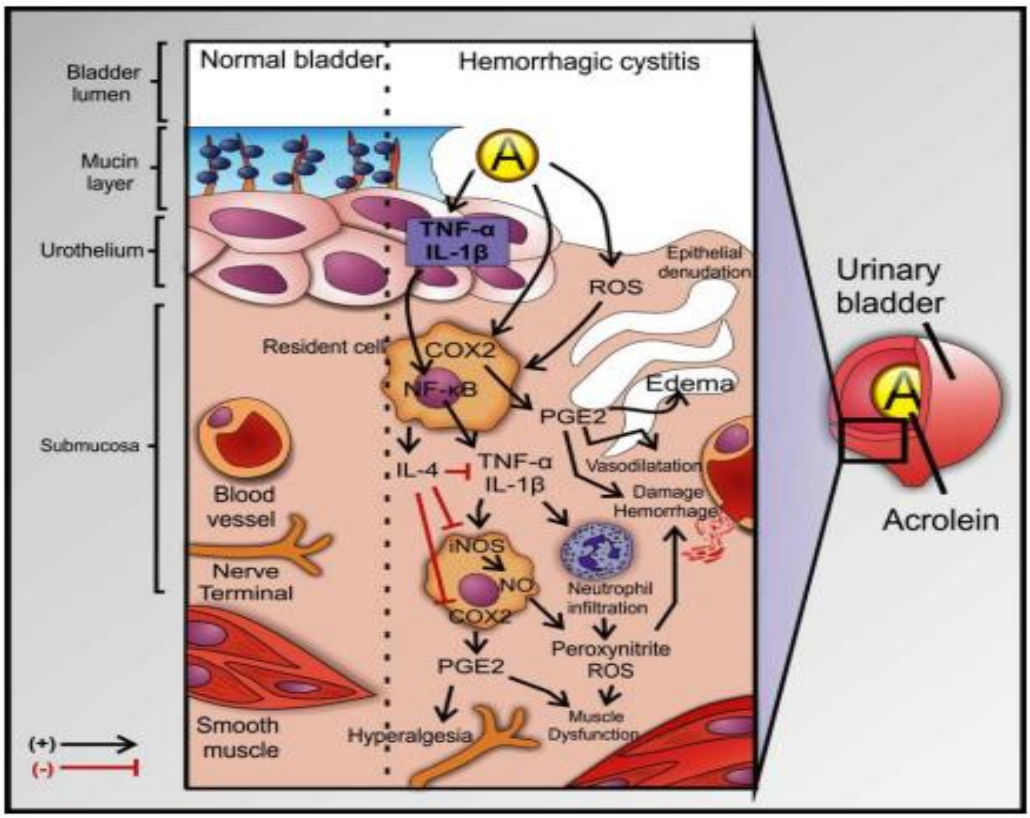

Fig. 2: The detail of suggested pathways for pathogenies of hemorrhagic cystitis (Ribeiro et al., 2012)

Hemorrhagic cystitis can develop weeks to months after therapy in 20–25% of patients who receive high doses of cyclophosphamide (Bedi et al., 1995) (Apperley et al., 1987). Additionally, continuousminimum-dose cyclophosphamide has been associatedwith late-onset hemorrhagic cystitis, which has been associated with the BK virus. Most cases of cyclophosphamideconvinced bladder cancer have been recorded in patients who received the drug orally for further than 1 year. A cumulative dose of further than 20g is the outstanding risk circumstance (Kempen et al., 2008).

IV. CARCINOGENICITY OF CYCLOPHOSPHAMIDE

This chemotherapy has been classified as a carcinogenic agent that can cause the development of various cancers, such as skin cancer, which is the most popular malignancy, post cyclophosphamide management, secondary acute leukemia, and bladder cancer. Generally, the rate of malignancy acquiring related to cyclophosphamide therapy is directly correlated to the cumulative dose of the drug and the length of exposure. It has been recorded that about 2% of treated patients with cyclophosphamide, especially those who have been administrated the drug for a period more than one year can develop therapy related leukemia despite that the development of leukemia-related treatment has been recorded after the implication of high dose of the drug for conditioning regimen for BMT (Levine, E. G. & Bloomfield, 1992).The resulted leukemia from the usage of cyclophosphamide can be attributed to chromosomal 5 and 7 abnormalities, or might be due to complex cytogenetic abnormalities which most frequently occur after long term therapy of 3-10 years (Stone, 1994).

A. Other toxic effects

Similar to the most chemotherapiesnausea and vomiting are obvious adverse reaction that can be noted after the administration of moderate to high dose of cyclophosphamide and the use of (5HT3) receptor antagonists, like ondansetron or dolasetron, as prophylaxis medication can control this side effect successfully. Alopecia is another popular adverse reaction, particularly with large dose therapy regiment of cyclophosphamide. Oral administration of this chemotherapy has a low risk of occurrence of diarrhea, but it may be common with high dose therapy. The administration of this chemotherapy can develop low to moderate levels of hyponatremia due to central pontine myelinolysis and improper antidiuretic hormone which result in from implication of cyclophosphamide (Jayachandran et al., 2008).

B. Miscellaneous toxic effects

The use of parenteral cyclophosphamide at a dose greater than 50 mg/kg can cause various degree of water intoxication due to impaired water excretion and this syndrome is mostly self-limited. Hepatotoxicity after the administration of Cy has been also recorded and furthermore several rare adverse reactions with use of Cy have been reported, such as transient cerebral dysfunction, anaphylaxis, nail pigmentation, mucosal ulceration, acute oropharyngeal dysesthesias, skin pigmentation, and urticarial (Ahmed and Hombal, 1984).

V. METHODOLOGY

The writing of this review article were particularly performed which includes therapeutic uses of cyclophosphamide and consequent toxic effects of the drug implication. The preparation of current work has been carried out by searching Google Scholar, ResearchGate, PubMed, databases to obtain open access articles from 1970-2019 from various articles and studies. The key words that have been used were “cyclophosphamide, toxicity of cyclophosphamide, therapeutic uses of cyclophosphamide, alkylating agent, carcinogenicity of cyclophosphamide, hemorrhagic cystitis.

A. Criteria for exclusion

All citations relating to the, clinical pharmacokinetics of cyclophosphamide, post-transplanthigh dose cyclophosphamide, the effect of cyclophosphamide on immune system, cyclophosphamide administration routine, cyclophosphamide analogue, cyclophosphamide for rheumatoid arthritis, cyclophosphamide for multiple sclerosis, cyclophosphamide versus ifosfamide, cyclophosphamide teratogenesis were excluded.

B. Inclusion criteria

Inclusion criteria includes published articles in reviewed journals relevant to alkylating agents such as clinical trials, review articles, case reports and books.

VI. DISCUSSION

Cyclophosphamide is classified as one of the most applicable broad spectrum antineoplastic agents. Despite its efficiently as monotherapy for cancer management, it is mostly used in combination therapy with various anticancer agents. Although the induction of various newer antineoplastic agents, for instance, targeted therapies and Taxanes, develops an idea that these newer agents could substitute cyclophosphamide, the significant effectiveness of the drug in the treatment of different malignancies minimizes the inferiority of the newer accession (Emadi et al., 2009).

A. Lymphomas

Cyclophosphamide-based treatment is applied broadly for lymphomas and is usually effective therapy for aggressive non-Hodgkin lymphoma, especially with Burkitt lymphoma (Magrath et al., 1996). Despite that newer management regiments use intense cyclophosphamide-based combination chemotherapy, RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) considers the most prevalent protocol for treatment of non- Hodgkin lymphoma, with about 30–40% cure rates. Several newer approaches to cyclophosphamide-based combination therapy have been proposed for the management of aggressive non-Hodgkin lymphoma. However, none of these proposed protocols have shown superiority over CHOP. (Fisher et al., 1993). Indolent lymphomas mostly appear in adults over 50 years old, alongside follicular lymphomas developing in the vast majority of cases. Furthermore, lympho plasma cytoid lymphoma, small lymphocytic lymphoma (sll), mycosis fungoides, chronic lymphocytic leukemia (Cll), and marginal zone lymphoma are all distinct entities. Cyclophosphamide as monotherapy or in combination therapy with various agent considered a standard treatment for these lymphomas. It has been detected that complete remission rates can be achieved in patients with sll or Cll who have previously been untreated and those with relapsed and refractory disease via implication FCR (fludarabine, cyclophosphamide and rituximab) protocol (Keating et al., 2005) (Wierda et al., 2005).

Various attempts to exclude cyclophosphamide from chemotherapy protocols via rising purine nucleoside dose have failed, which is elucidated that cyclophosphamide is an essential therapy element for patients with Cll (Kay et al., 2008). In addition, cyclophosphamide can be employed in multidrug combination therapy with different anticancer agents in the treatment protocols for lymphocytic leukemia in children and adults (Gokbuget et al., 2009).

B. Solid tumors Breast Cancer

The combination therapy of cyclophosphamide with other antineoplastic agents has been significantly used as fundamental of adjuvant management protocols of breast cancer as well as metastatic stage of the disease, for instance FEC (5 fluorouracil, epirubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate, 5 fluorouracil) have been applied for decades. Furthermore, many studies conducted by Separate National Surgical Adjuvant Breast and Bowel Project (NSABP) suggested that the combination therapy of AC, doxorubicin, cyclophosphamide, was identical to half year of classic CMF. In addition, the consolidation chemotherapy of paclitaxel and AC regiment has tolerable toxicity for the adjuvant ambience (Fisher et al., 1990) (Fisher et al., 2001).

Docetaxel and cyclophosphamide enhancesickness-free survival correlated to paitents that treated with AC which is well toleratedin aged patients (Jones et al., 2007).The induction of cyclophosphamide to docetaxel and doxorubicin regiment to make TAC can still be used in the adjuvant ambience. However, there is a need of granulocyte colony stimulating factor (GCsF) or granulocyte–macrophage colony stimulating factor (GMCsF) bolster (Martin et al., 2005).

The administration of cyclophosphamide with vincristine and dactinomycin (VAC) is utilized as a substitutedprotocol for the management of ovarian germcell cancersfor patients with the diseasewho have enduring or recurrent ovarian tumor after different chemotherapy regiments (Slayton et al., 1985).

C. Bone and soft tissue sarcomas

It has been suggested that cyclophosphamide is the mainstay of therapeutic effectiveness of chemotherapyregiment for various recentlyrecognized and recurring pediatric cancers. Consolidation chemotherapyof etoposide, carboplatin, vincristine, cyclophosphamide and doxorubicin (CAdo), displayed 5-year comprehensive and it was shown that child withlocalized neuroblastoma have more than 90% disease free survival rates as well as leading to consequent surgical ablation (Rubie et al., 2001).

The induction of Cyclophosphamide in various chemotherapy protocols as an adjunct to radiation and surgery has also been utilized in a different types of cancers, for example ewing sarcoma, wilms tumor and retinoblastoma (Emadi et al., 2009).

D. BMT conditioning regimens

Total body irradiation (TBI) is used as an evidence modality for refractory leukemias and lymphomas in clinical conditioning BMT protocols due to both antineoplastic and immunosuppressive properties of the medicine. It has been developed BMT conditioning that did not apply TBI because of toxicity issues and minimal accessing to the provided facilities with TBI. As a consequence of dual antineoplastic and immunosuppressive activity of cyclophosphamide, it was successfully used as substituted therapy of TBI (Sandberg et al., 1971). From animal experiments, high dose of cyclophosphamide explores an optimum immunosuppressant and as result it is considered the most obvious chemotherapy applied in BMT conditioning protocol for aplastic anemia (Thomas et al., 1972). It has been suggested that due to high relapse rates the implication of monotherapy of cyclophosphamide or TBI for BMT in malignant illness do not consider as suitable management regiment (Brodsky and Jones, 2005). On the other hand, the combination of high dose of cyclophosphamide with other anticancer agent, such as busulfan or TBI, shows an effective treatment in highly risk of many hematologic malignancies and importantly many of these case reach a curable state. Therefore, there is great implications of these protocols in conditioning of myeloblative BMT. Recently the usage of intermediate dose of cyclophosphamide with fludarabine has introduced as a standard conditioning protocol for nonmyeloablative allogeneic BMT (Thomas et al., 1975).

VII. CONCLUSION

For more than 50 years, cyclophosphamide has been used in clinical trials to treat malignant disease. Cytoxan, a nitrogen mustard alkylating agent from the oxazophorines group, is a synthetic antineoplastic drug. Cyclophosphamide is still a viable therapeutic option.

REFERENCES

[1.] Ahmed A. and Hombal S. (1984). Cyclophosphamide: A review on relevant pharmacology and clinical uses. *Journal of the American Academy of Dermatology*, 70, 539-540.

[2.] Apperley, F. et al. (1987). Late-onset hemorrhagic cystitis associated with urinary excretion of polyomaviruses after bone marrow transplantation. *Transplantation*, 43, 108–112.

[3.] Bagley, M., Bostick, W. and DeVita, T. (1973). Clinical pharmacology of cyelophosphamide. *Cancer Res*, 33, 226-233.

[4.] Bedi, A. et al. (1995). Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. *J. Clin. Oncol*., 13, 1103–1109.

[5.] Boumpas, T. et al. (1993). Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann. Intern. Med.*, 119, 366–369.

[6.] Brock, N. &Wilmanns, H. (1958). Effect of a cyclic nitrogen mustard-phosphamidester on experimentally induced tumors in rats; chemotherapeutic effect and pharmacological properties of B518 ASTA [German]. *Dtsch. Med. Wochenschr*., 83, 453–458.

[7.] Brodsky, A., Chen, R., Brodsky, I. & Jones, J. (2004). High-dose cyclophosphamide as salvage therapy for severe aplastic anemia. *Exp. Hematol.*, 32, 435–440.
[8.] Brodsky, A. & Jones, J. (2005). Aplastic anaemia. *Lancet*, 365, 1647–1656.
[9.] Cazin, B. et al. (1986). Cardiac complications after bone marrow transplantation. A report on a series of 63 consecutive transplantations. *Cancer*, 57, 2061–2069.
[10.] Colvin, M., Brundrett, B., Kan, N., et al. (1976). Alkylating properties of phosphoramide mustard. *Cancer Res*, 36,1121-1126.
[11.] Cox, J. (1979). Cyclophosphamide cystitis—identification of acrolein as the causative agent. *Biochem. Pharmacol*., 28, 2045–2049.
[12.] Dessalvi, M., Deidda, D., Mele, P., Bassareo, R., Esposito, C., Santoro, M., Lembo, M., Galderisi, G. and Mercuro, G. (2018). Chemotherapy-induced cardiotoxicity: new insights into mechanisms, monitoring, and prevention, *Journal of Cardiovascular Medicine*, 19, 315-323.
[13.] Dussan, B., Magder, L., Brodsky, A., Jones, J. & Petri, M. (2008). High dose cyclophosphamide performs better than monthly dose cyclophosphamide in quality of life measures. *Lupus*, 17, 1079–1085.
[14.] Emadi, A. et al. (2009). Cyclophosphamide and cancer: golden anniversary. *Nat. Rev. Clin. Oncol*, 6, 638–647.
[15.] Fisher, B. et al. (1990). Two months of doxorubicincyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J. Clin. Oncol.*, 8, 1483–1496.
[16.] Fisher, B. et al. (2001). Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. *J. Clin. Oncol*., 19, 931–942.
[17.] Fisher, I. et al. (1993). Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N. Engl. J. Med.*, 328, 1002–1006.
[18.] Friedman, M., Wodinsky, I. and Myles, A. (1976). Cyclosphosphamide (NSC-26271)-related phosphoramide mustards-recent advances and historical perspective. *Cancer Treat Rep*, 60, 337-346.
[19.] Gokbuget, N. &Hoelzer, D. (2009). Treatment of adult acute lymphoblastic leukemia. *Semin. Hematol.*, 46, 64–75.
[20.] Haselberger, B. &Schwinghammer, L. (1995). Efficacy of mesna for prevention of hemorrhagic cystitis after high-dose cyclophosphamide therapy. *Ann. Pharmacother*., 29, 918–921.
[21.] Hilal-Dandan, R. and Brunton, L. (2013). Goodman and Gilman Manual of Pharmacology and Therapeutics, Second Edition. McGraw-Hill Professional.
[22.] Iqubal, A., Iqubal, K., Sharma, S., Ansari, A., Najmi, K., Ali, M., Ali, J. and Haque, E. (2019). Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. *Life Sci*., 218, 112-131.
[23.] International Agency for Cancer Research: Cyelophosphamide. Monograph, vol. 26, pp. 165-205. Switzer- /and, 1981, World Health Organization.
[24.] Jayachandran, v., Chandrasekhara, K., Thomas, J., Agrawal, S. &Narsimulu, G. (2008). Cyclophosphamide-associated complications: we need to be aware of SIADH and central pontine myelinolysis. *Rheumatology (Oxford)*, 48, 89–90.
[25.] Jones, S. et al. (2007). Extended follow-up and analysis by age of the US Oncology Adjuvant Trial 9735: docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophoshamide and is well tolerated in women 65 or older [abstract]. San Antonio Breast Cancer Symposium a12.
[26.] Kay, E. et al. (2008). Cyclophosphamide remains an important component of treatment in CLL patients receiving pentostatin and rituximab based chemoimmunotherapy. *Blood*, 112, 43.
[27.] Keating, J. et al. (2005). Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J. Clin. Oncol.*, 23, 4079–4088.
[28.] Kempen, H. et al. (2008). Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. *Am. J. Ophthalmol.*, 146, 802–812.
[29.] Levine, G. & Bloomfield, D. (1992). Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. *Semin. Oncol*., 19, 47–84.
[30.] Magrath, I. et al. (1996). Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J. Clin. Oncol.*, 14, 925–934.
[31.] Martin, M. et al. (2005). Adjuvant docetaxel for nodepositive breast cancer. *N. Engl. J. Med.*, 352, 2302–2313.
[32.] Molin, L., Thomsen, K., Volden, G., et al. (1978). Epipodophyllotoxin (VP-16-213), in Mycosis fungoides: A report from the Scandinavian Mycosis Fungoides Study Group. Acta*DermVenereol (Stockh)*, 59, 84-87.
[33.] Murdych, T. &Weisdorf, J. (2001). Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977–1997. *Bone Marrow Transplant.*, 28, 283–287.
[34.] Ribeiro, R., Roberto, P., et al. (2012). Chemotherapy-induced hemorrhagic cystitis: pathogenesis, pharmacological approaches and new insights. *Journal of Experimental and Integrative Medicine*, 2, 95-112.
[35.] Rubie, H. et al. (2001). Localised and unresectableneuroblastoma in infants: excellent outcome with primary chemotherapy. Neuroblastoma Study Group, SocieteFrancaised'OncologiePediatrique. *Med. Pediatr. Oncol.*, 36, 247–250.
[36.] Sandberg, S., Owens, H. & Santos, W. (1971). Clinical and pathologic characteristics of graft-versus-host

disease produced in cyclophosphamide-treated adult mice. *J. Natl Cancer Inst.*, 46, 151–160.
[37.] Sanders, E. et al. (1988). Ovarian function following marrow transplantation for aplastic anemia or leukemia. *J. Clin. Oncol*., 6, 813–818.
[38.] Santos, W. et al. (1972). The use of cyclophosphamide for clinical marrow transplantation. *Transplant. Proc.*, 4, 559–564.
[39.] Sensenbrenner, L., Marini, J. and Colvin M (1979). Comparative effects of cyelophosphamide and phosphoramide mustard on murine hematopoietic and immunocompetent cells. *J Natl Cancer Inst*, 62, 975-981.
[40.] Slayton, R. E. et al. (1985). Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). *Cancer*, 56, 243–248.
[41.] Stillwell, J. & Benson, C. (1988). Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. *Cancer*, 61, 451–457.
[42.] Stone, M. (1994). Myelodysplastic syndrome after autologous transplantation for lymphoma: the price of progress. *Blood*, 83, 3437–3440.
[43.] Struck, F., Kird, C., Mellett, B., et al. (1971). Urinary metabolites of antitumor agent eycIophosphamide. *MolPharrnaeol*, 7,519-529.
[44.] Thomas, D. et al. (1972). Aplastic anaemia treated by marrow transplantation. *Lancet*, 1, 284–289.
[45.] Thomas, D. et al. (1975). Bone-marrow transplantation (first of two parts). *N. Engl. J. Med.*, 292, 832–843.
[46.] Watson, R., Rance, P. & Bain, J. (1985). Long term effects of cyclophosphamide on testicular function. *Br. Med. J. (Clin. Res. Ed.)*, 291, 1457–1460.
[47.] Wierda, W. et al. (2005). Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J. Clin. Oncol*., 23, 4070–4078.