EGYPTIAN DENTAL JOURNAL
www.eda-egypt.org
VOL. 70, 147:164, JANUARY, 2024
PRINT ISSN 0070-9484 • ONLINE ISSN 2090-2360
ORAL MEDICINE, X-RAY, ORAL BIOLOGY AND ORAL PATHOLOGY
Submit Date : 01-11-2023 • Accept Date : 29-11-2023 • Available online: 01-01-2024 • DOI : 10.21608/EDJ.2023.234480.2708

ANTI-CANCER MEDICINS (CLASSIFICATION AND MECHANISMS OF ACTION)

Ahmed M. Hussein*, Khaled A. Hussein**, Hamzah A. Babkair**, *and* Mohamed Badawy***

ABSTRACT

Cancer is one of the chief dying cause in the world, killing roughly 3500 people/million each year. Malignancy is motivated by genetic defect in the cellular material in view of ecological or hereditary roads. Surgical operation and radiation are used as early intervention helped for regional and non-metastatic foreign mass, else are deficient in the neoplasms have diffused through the body. Usage of medications is one of the current choice for curing malignant tissues, since they are able to reach all human organs via the bloodstream. Anti-cancer medicines mainly include chemotherapy, immunotherapy, targeted therapy, and hormonal therapy; may be serviced before or after surgery or radiotherapy. Many kinds of anti-neoplastic compounds are valued alone or in fusion with other treatments. These agents are varying in their chemical forms, their prescription and doses, how beneficial they are in healing diverse sorts of lesions, and their undesirable effects. Medicaments of anti-malignancy are not easily categorized into groups. Several classifications have been proposed and none is totally satisfactory. Thus, drugs have been typed according to their chemical composition, presumed mechanisms of action, and cytotoxic activity to the cell cycle. Each categorizing has merits, but the fact that there are so many ways of grading these agents reflect the disparate origin of anti-cancer remedies, knowledge of their actions, and bases of tumor selectivity.

KEY WORDS: Cancer, Chemotherapy, Immunotherapy, Targeted Therapy, Hormone Therapy.

* Oral and Maxillofacial Pathology Department, Faculty of Dentistry, Assiut University, Assiut, Egypt.
** Division of Oral and Maxillofacial Pathology, Oral and Maxillofacial Diagnostic Sciences Department, College of Dentistry, Taibah University, Madina, Saudi Arabia.
*** Oral Biology Department, Faculty of Dentistry, Assiut University, Assiut, Egypt.

INTRODUCTION

Cancer globally ranks 2nd element in loss of life. It is accountable about one in sex dooms globally [1]. It represents uncontrolled growth of abnormal cells in body catalyzed by a complex genetic disorders, may leading to death. Lifestyle divergences, senility, hormonal disturbance, and exposure to carcinogens; have the main signaling cues for activation of neoplasia in peoples [2]. Generally, the malignant development can be dissected into stages as exposure to carcinogen starts DNA injury due to failure in genetic repair mechanisms, which represented as initiation stage. In promotion stage, the hyper-proliferation, modification, and tissues inflammation of tumor cells occur. Finally, progression, through it, lesion formation beings from pre-neoplastic cells via clonal expansion [3].

Different categories for the malignancy care which include operation, radiation, chemo, immuno, targeted therapies, as well as stem cell transplant [4]. Among these approaches, anti-cancer drugs still remain the efficiently routine to treat numerous kinds of neoplasms. A growing of anti-malignant agents and natural products can hold extension of tumor via different techniques [5]. Several admixtures alter tissue metabolism as work on crucial cellular enzymes. They also can impede against criticizing cellular processes, e.g., DNA replication, apoptosis, resistance to drugs, genetic destruction, or immune responses [6]. These medications have clear ways for exertion several sets of cancer. These treatments alter the cellular proteins quality, rendering them non-functional for physiological pathways [7]. Else, pharmaceuticals interfere with body's metabolism via essential hormones [8]. The 2018 Nobel Prize attributed to pointed up the value for immuno-oncology, which manifested the chance for immune order modulation to manage the malignant conditions and can resist against the disease recurrence [9].

This article reviews several aspects of anti-cancer medication, including mechanisms of action with their applications and the practice chemotherapeutic agents. Furthermore, presented a run-through modern therapies mechanisms; pointing on immuno, targeted therapies, and hormonal medicines.

CHEMOTHERAPY

Over the past decades the chemotherapeutic agents performed the frontline option for malignancies where not advised surgery and/or radiation [10]. The chemotherapy cures are rooted on the harmful mixtures that early arrest the rapid growth of the tumors. It attacks oncocytic cells at variances steps of the proliferation cycle. Knowing how these factors act aids to predict which remedies are likely to run well together [11]. The new cells be liable in cancer lesions in fasts manner than healthy genres and builds them a superior goal for chemotherapy. Although, chemo-treatments cannot differ the clashing between well and abnormal tissues. This indicates that normal cells are harmed as the malignant structures, and result in chemo-care problems. Chemo-drugs are given to realize an equilibrium betwixt damaging malignancy for tissue healing and lessen the side effects for normal cells [12].

Chemotherapeutics can be bisected into 2 classes regarding their nature. They can either be natural or synthetic origin [13]. Intravenous drugs of chemotherapy require straight vein infusion for take minutes to a few hours. Several fluid or pills medications can be given at significant intervals. Other roads of giving chemotherapeutic medications as; intramuscular or intra-abdominal administration have taken for specific locations of tumor mass. However, an advanced technology called pressurized therapy has efficiently deliver intraperitoneally for peritoneal end-stage metastases patients. Further, medicines providing through the skin surface in topical formulas [14, 15].

Chemotherapies can be grouped according their chemical formation, how they operated, and the relationships to one more medicaments. Almost compounds go in more than one way,

and may belong to more than one class. The side effects prediction depending on knowing how the drug works. This helps to select which remedies are performing well together [16]. Depending on their actions, they can be separated, regarding the main common serviced, into; alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic spindle inhibitors, and others [17]. In the next section, an overview provides for comprehensive of different pharmaceutical chemotherapeutic drugs that had served in different cancer sorts in last decades.

Alkylation Chemotherapy

Alkylating agents comprise a major therapeutic modality for many tumors. These physics can bear an alkyl groups to DNA guanine residues or generate intra or inter-strand cross links [18]. The DNA geometry has been damaged via the cross-linking of nucleic acids with proteins or peptides that create erroneous in base pairing, breakage in DNA strand, and in the end put a stop to cellular division. These nostrums toil the cell cycle in all phases, that represent the first agent line of chemotherapy against abnormal varieties. They are the greatest known therapeutic value for slow maturation of neoplasms [19].

Mechanistically, chemical alkylating agents are electrophilic mixes. They can transfer groups of carbon onto nucleophilic atoms of nitrogen or oxygen via bases of DNA[20]. The variety of covalent adducts produced through creation an alkylation related adducts to the reactive sites number in the alkylating agent (bifunctional versus monofunctional) [21]. The bifunctional alkylating compound has more than one reactive site, which can proceed with divided DNA bases to set up cross links or bulky DNA adducts. In addition, an alkylating agent contains one reactive part is monofunctional, either a direct methyl or a multiplex alkyl group. The alkylating substances attack DNA bases via reaction of nucleophilic substitution; monomolecular nucleophilic substitution (S_N1) or bimolecular nucleophilic substitution 2 (S_N2). The alkylating members of S_N2 replay mainly with the N ring atoms, while the alkylating agent S_N1 can move with N and O atoms [22, 23].

The S_N1 alkylating agents are favorable for most oncologist, whereas for relative selectivity; alkylating S_N2 may be advantageous. The N^7-position nucleophilic is high reactivity for DNA guanine bases, nearly the formation of N^7-methylguanine occurs in all monofunctional methylating members induce a key methylation adduct, nearly about 80% of the DNA alkylation lesions. The O^6-position of guanine is the crucial site for methylation by S_N1 alkylating agents to generate methylguanine [24]. (Figure 1)

The alkylating agents can alter different biological molecules to produce a lesions classify which can elicit a number of biological effects. The biological molecules are concern to alkylation impairment, including RNA, protein, lipids, and mitochondrial DNA [25]. In Table; description of the common chemotherapeutic alkylating agents.

Nitrosoureas, are a special alkylating agents' family. The nitrosoureas alkylating model can travel into the brain, but other types do not able that. Through the blood brain barrier area; nitrosoureas can enter the brain, that area keeps the medications out of brain. This action objected these agents as definite statues in treating brain tumors. Nitrosoureas products include: carmustine, lomustine, and streptozocin [27].

Antimetabolites Chemotherapy

Antimetabolites are a division of substances that compete, replace, or impede the specific cellular metabolism. Their agents belong to certain phases of cell cycle; which has G1, S, G2, and M phases. The antimetabolites focus in blocking DNA synthesis of tumor cells during DNA replication[28]. These atoms possess a formula like a cellular metabolite or enzyme substrate to meet the tissue needs.

TABLE: Listing the Common Chemotherapeutic Anti-Cancer Drugs [18, 22, 25, 31, 41].

Drug class	Subgroup	Drug	Cell cycle specificity	Mechanism of action
Alkylating agents	Oxazaphosphorines	Cyclophosphamide Ifosfamide	Nonspecific	Alkylation of DNA/RNA and cross-links DNA at guanine N–7 lead to decrease DNA replication.
	Nitrogen mustards	Chlorambucil Melphalan		
	Imidazotetrazines	Temozolomide		
	Nitrosoureas	Carmustine Lomustine Streptozocin		Alkylation of DNA/RNA and cross-links between DNA lead to decrease DNA synthesis.
	Alkyl sulfonate	Busulfan		Cross-links between DNA strands lead to decrease DNA replication.
	Hydrazines	Procarbazine		Inhibition of transmethylation of methionine into transfer RNA lead to decrease DNA, RNA, and protein synthesis.
	Platinum-based agents	Cisplatin Carboplatin Oxaliplatin		Cross-links between DNA strands lead to decrease DNA replication.
Antimetabolites	Antifolates	Methotrexate	S phase	Displacement of dihydrofolate decreased the formation of pyrimidine and purine nucleotides lead to decrease DNA synthesis.
		Pemetrexed		Multitargeted antifolates.
	Pyrimidine antagonists	Cytarabine		Inhibits DNA polymerase.
		5-Fluorouracil		Incorporation of pyrimidine analog into DNA and RNA decreased DNA and RNA synthesis.
		Capecitabine		
		Gemcitabine		Incorporation of pyrimidine analog into DNA decreased DNA synthesis.
	Purine antagonists	6-Mercaptopurine Azathioprine		Incorporation of purine analog (thiol analog) into DNA lead to decrease DNA synthesis.
		Fludarabine		Incorporation of purine analog into DNA lead to decrease DNA and RNA synthesis.
		Cladribine	Nonspecific	Inhibits DNA polymerase
	Ribonucleotide reductase inhibitors	Hydroxyurea (hydroxycarbamide)	S phase	Inhibition of ribonucleotide reductase decreased DNA replication (S phase) and massive cytoreduction.
Topoisomerase inhibitors	Topoisomerase I inhibitors	Irinotecan Topotecan	S and G2 phase	Inhibition of topoisomerase I decreased DNA unwinding and lead to decrease DNA replication and DNA degradation.
	Topoisomerase II inhibitors	Etoposide Teniposide		Inhibition of topoisomerase II decreased DNA degradation and DNA replication.
Mitotic inhibitors	Vinca alkaloids	Vincristine Vinblastine Vinorelbine	S and G2 phase	Binding of β-tubulin and inhibition of β-tubulin polymerization into microtubules lead to prevention of mitotic spindle formation result in mitotic arrest of the cell in metaphase.
	Taxanes	Docetaxel	M phase	Hyperstabilization of polymerized microtubules lead to decrease mitotic spindles breakdown then, mitotic arrest in metaphase (not proceeding to anaphase).
		Paclitaxel	Late G2 mitotic phase	
	Nontaxane microtubule inhibitors	Eribulin	G2/M phase	Inhibition of mitotic spindle formation lead to mitotic blockage then, cell cycle arrest at the G2/M phase.
		Ixabepilone Epothilone	M phase	Binding to β-tubulin lead to hyperstabilization of the microtubules then decreased the breakdown of mitotic spindles breakdown with mitotic arrest in metaphase.

Antibiotics	Bleomycin		G2 phase	Induces formation of free radicals with breakage of DNA strand lead to cell cycle arrest at G2 phase.
	Actinomycin D		Nonspecific	DNA intercalation with interference with DNA transcription lead to decrease RNA synthesis.
	Anthracyclines • Doxorubicin • Daunorubicin • Idarubicin			Inhibition of topoisomerase II decreased DNA degradation (dsDNA breaks) and DNA replication. Formation of free radicals lead to breakage of DNA strands.
	Mitomycin			Cross-linking between DNA strands lead to decrease DNA and RNA synthesis.
Protein kinase inhibitors (e.g., tyrosine kinase inhibitors)	BCR-ABL tyrosine kinase inhibitors and c-KIT tyrosine kinase inhibitors	Imatinib Dasatinib Nilotinib	G0/G1 phase	Inhibition of autophosphorylation and activation of multiple proteins by tyrosine kinases
	EGFR tyrosine kinase inhibitors	Erlotinib Gefitinib Afatinib Osimertinib	G0/G1 phase	Inhibition of HER1/EGFR tyrosine kinase with blockage of intracellular phosphorylation lead to cell death
	VEGFR tyrosine kinase inhibitors	Cabozantinib Pazopanib Sunitinib Sorafenib Tivozanib Axitinib		Inhibition of VEGF tyrosine kinase lead to multimodal change to tumor microenvironment via antiangiogenic effect, effects on vessel function, and immune modulation.
	ALK tyrosine kinase inhibitors	Alectinib Crizotinib		Inhibition of the anaplastic lymphoma kinase.
	V600E mutated-BRAF oncogene inhibitor	Dabrafenib Vemurafenib Encorafenib		Selective inhibition of BRAF oncogene with V600E mutation lead to inhibition of cancer cell growth.
	MEK inhibitors	Trametinib		Inhibition of MAP kinase signaling pathway lead to inhibition of cancer cell growth and induction of apoptosis.
	Bruton tyrosine kinase inhibitors	Ibrutinib Acalabrutinib	G1 phase	Inhibition of Bruton tyrosine kinase lead to growth inhibition of malignant B cells.
	Janus kinase inhibitors	Ruxolitinib	G1/S phase	Inhibition of JAK1 and JAK2 kinase reduced activation of hematopoietic progenitor cells.
	CDK inhibitors	Palbociclib		Inhibition of cyclin-dependent kinase 4 and 6 lead to inhibition of cancer cell growth and induction of apoptosis.
Other	Enzymes	L-asparaginase	G1 phase	Cleavage of the amino acid L-asparagine by L-asparaginase lead to decrease asparagine source for leukemic cells with cytotoxicity specific to leukemic cells.
	Proteasome inhibitors	Bortezomib Carfilzomib Ixazomib	G2/M phase	Inhibition of ubiquitinated apoptotic protein degradation (e.g., of p53) lead to arrest in G2/M with apoptosis.
	PARP inhibitors	Olaparib	G2 and S phase	Inhibition of poly (ADP-ribose) polymerase decreased the repair of single-strand DNA breaks.

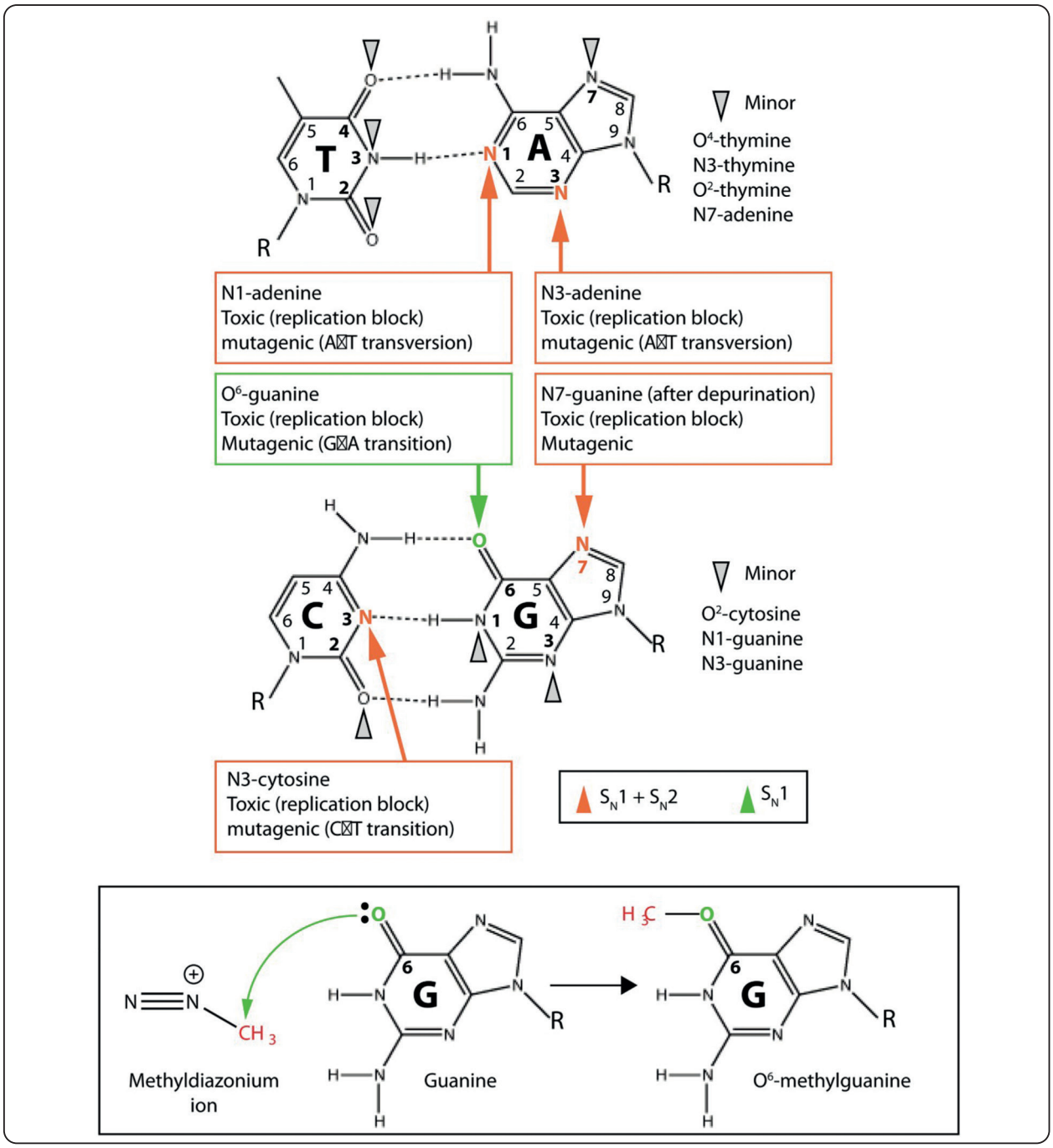

Fig. (1): Alkylation Sites on Bases of DNA [26].

These drugs reacting via replacement the ideal building blocks of RNA and DNA. After this occurs, a malignant cell cannot reproduce because the DNA has not make copies [29].

Antimetabolites can be arranged into several grades: pyrimidine and purine antagonists; which stand against the DNA synthesis. Antifolates; block folic acid activity, which is essential for precursors of DNA and RNA. Additionally, ribonucleotide reductase inhibitors; which reduce production of deoxyribonucleotides. These anti-cancer drugs break the DNA strand formation through particular suppression enzymes or constituting of wrong pyrimidine/purine structural analogues into DNA [30, 31]. A common antimetabolites detailed description is comprehensively provided in the Table.

Topoisomerase Inhibitors

These potions are interfering with topoisomerases enzymes, which assist in easing single-strands separation of DNA. Topoisomerases are essential enzymes to carry out multiplex interconversions of DNA supercoils, knots, and catenane. These enzymes act for inducing break DNA strands during replication. Topoisomerase II enzymes result in splitter of both strands to roll a double strand break [32].

Topoisomerase I inhibitors; are a natural long-known topoisomerase inhibitory. In later years, more synthesized derivatives inhibitors are being used in therapy [33]. The accepted drug in this class; topotecan, was profited to fit the high grade ovary, lung, and cervical malignancy. Sudden stop of DNA replication and transcription via block of topoisomerase I lead to causing tumor widening stop [34]. The coupling site of topotecan obstructs with the topoisomerase I while reiterating the scratched DNA strand in the wake of releasing the strain. Such intercalation traps the topoisomerase I in the cleavage composite bound to the DNA. Other accepted cure of this family is irinotecan; it was success with colorectal carcinoma in advanced, lung, cervix, ovary, and colon cancers [35].

Topoisomerase II inhibitors; also, called podophyllotoxins as a semi-synthetic etoposide imitative of a plant glycoside. It purposes DNA erosion by posing G2 cell cycle arrest through altering DNA topoisomerase II function (Figure 2). Creating a ternary combination between DNA and the topoisomerase II complex by etoposide stop binding of DNA strands, makes degeneration to DNA constitutions [36]. Cancer cell depends on this enzyme as it splits more quickly; although, it determines apoptosis via promoting defects in DNA synthesis. Etoposide has a success with high grade malignancies as Ewing's or Kaposi's sarcomas, lung masses, testicular lesions, non-lymphocytic leukemia, and lymphoma [37].

Mitotic Spindle Inhibitors

They are a plant alkaloids inhibitors which job via stop cells dividing, in all phases as arresting cell enzymes from production the needed proteins for reproduction [38]. These medicaments as vinca alkaloids and taxanes modify the spindle microtubules function through mitotic metaphase arrest, result in cell demise (Figure 2). The electronically N-carbonyl acridness stopped tubulin polymerization, which producing a high anti-proliferation activity against glandular mammary lesions [39, 40].

Paclitaxel/taxol, is a complex drug of diterpene taxane ring has activity via a cytotoxic novel suit. It increases tubulin polymerization, thereby motivating a technique opposite to that of the aforementioned alkaloids. It has shown efficacy against the advanced head and neck carcinomas, lung lesions, esophageal adenocarcinoma, and prostate cancers [41]. Docetaxel, is a high powerful paclitaxel with an equivalent activity. It provides benefits against the ovarian neoplasms had resistant to first line chemotherapeutic medicines [42].

Vinca alkaloids, are cell division suppressors, that obstruct the protein tubulin polymerization and leading to stop mitotic activity. The regular chromosomes spit does not occur regularly during cellular division, leading to capture of metaphase. Vincristine and vinblastine were the first samples of this grain had divergent degrees of anti-tumor activity. Cancers treated with these consolidations include Hodgkin's/non-Hodgkin's lymphomas, leukaemias, rhabdomyosarcoma, Ewing's sarcoma, neuroblastoma, miscellaneous myeloma, thyroid neoplasms, brain lesions, and several blood related disorders [43, 44]. The Table provided a description details of the anti-neoplastic agents.

Anti-Tumor Antibiotics

They are not like an antibiotic that operated for bacterial treatment. These drugs can run by altering the DNA of cancer tissues to prevent them from thickening and replication[45]. The anti-cancer anthracyclines antibiotic interacts with DNA copying enzymes during cell cycle (Figure 2). They bind DNA to prevent it from making copies and reproduce. They are utilized widely to different lesions [46]. Examples include: adriamycin, epirubicin, idarubicin, daunorubicin, doxorubicin liposomal, and valrubicin. A concernsd key for these pharmaceuticals in high doses administration, that they cause heart damage. Thus, limitation for dose lifespan must set on these medications. Other anti-cancer antibiotics are: bleomycin, dactinomycin, mitomycin-C, and mitoxantrone [47].

Daunorubicin agencies DNA strand break and producing free radicals by actuating topoisomerase II. It relieved to treat cancer broadening in leukemia and Kaposi's sarcoma[48]. Daunorubicin impedes the complex of topoisomerase II; then unties the DNA chain for repetition and suppress the DNA double helix from resealing and act against the proliferation proceed[49]. **Bleomycin** is needed against lymphoma, ovarian, and testicular tumors. It produces superoxide radicals of copper or iron, and interacts with strands of DNA objects chain breakage. Emerging

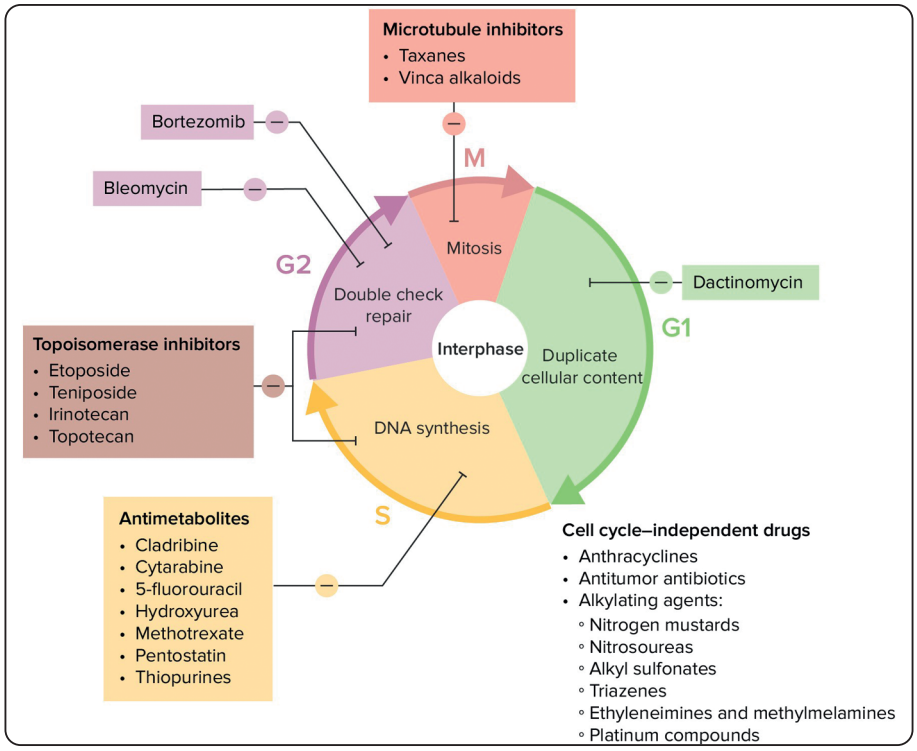

Fig. (2): Diagram Showing Chemotherapy Agents in Relation to the Cell Cycle [57].

indicator suggests that bleomycin else hinders the consolidation of DNA thymidine into strands, and the cleavage of DNA relies upon oxygen and metal particles [50]. This remedy has been effectual against different carcinomas of skin, oral cavity, throat, and genitourinary tract [51].

Dactinomycin-D is a chromo-peptide transcription inhibitor molecule attach DNA during being initiation multiplex and restrains elongation steps of RNA. It ideally intercalates between DNA cytosine and guanidine, or secure the strands grooves to produce a highly stable DNA drug, that preventing unwinding of DNA and thus stalling RNA progress [52]. Dactinomycin identified as an antibiotic agent, which initially obtained from Streptomyces species, but laterally recognized anti-tumor activity. It was inducted as an anti-cancer antibiotic to treat Ewing's sarcoma, rhabdomyosarcoma, trophoblastic neoplasm, testicular, and ovarian lesions [53]. Mitomycins derived from Streptomyces as a strain of natural quinones. It known as anti-neoplastic agent to slow down fibroblast germination in glaucoma [54]. These bio-reductive alkylating types (as mitomycin-C derivatives) are fitted as anti-malignant therapy via their modification in structural obstructs G1 and S phase transitions of the cell cycle. Its depletion lead to N-alkylation of DNA bases. The DNA replication prevented with cross-linking at N^6 adenine and O^6 and N^2 guanine. It is beneficially in the sedative drug in different solid tumors of lung, breast, colorectal, esophageal, pancreatic, and cervical origins. Porfiromycin is mitomycin-C derivative in an N-methyl form, that is found functional against lesions of head and neck regions [55].

Head and Neck Cancer Chemotherapy

Head and neck localized malignancy is usually treated with surgery and/or chemo-radiotherapy in a multidisciplinary manner. Chemo-cures for neoplasms of this region need a controlling actions to strike tumor cells. Medications are often given during or prior radiation to enhance the advantageous of care. The commonly practiced drugs against head and neck lesions include platinol, aluodrucil, carboplatin, abraxane, onxol, docefrez, and erbitux [56].

Cancers might start from one genus mutation follow multiple genetic abnormalities accumulation to activate the tumor progress. This lead to tumor heterogeneity. The lesion mass nature developing a resistance against the anti-cancer medications [58]. Long-term treatment cases enormous toxicity with severe injury or multiple organs failure. This creates a patient physiological and psychological stress under chemotherapeutic medication. The anti-malignant medicines mainly interrupt the pathways of cell division; therefore, the affected organs early include the tissues which dividing continuously, such as hair, skin, oral mucosa, and intestinal linings [59]. The utmost of chemotherapy drugs affects these organs in a dose-dependent manner; though, there are dissimilarity in their individuals' sensitivity, in that enormous aspects as hereditary role, metabolic regulation, other medication, and external factors [60].

The toxicity of chemotherapeutic cures, the destruction of normal cells, and the drug resistance, support the needing for new drugs based on molecular biology changes in the tumor tissues. These novel therapies by FDA approved cancer medicaments in fresh years, block biologic transduction pathways and/or specific malignant proteins to induce the killing of affected cells through stimulation of the immune system and apoptosis, minimizing the undesirable chemotherapy problems [61].

CANCER IMMUNOTHERAPY

Immunotherapy can be done by contrasting ways to stimulating the natural defenses so it performs harder to find tumor cells. Additionally, making substances just like immune components and using them to support the immunity for attack malignancy [62]. Supplementing immune regulation via devising immunotherapy rods is a specific and a promising

approach to neoplasms in a late stage. A lot of styles were developed to modify an immune system to identifying the transformed abnormal cells in the body through recognizing specific markers. The immunotherapy regime has significantly success of the chemo-potions in many malignant sets [63].

The immune cells have a time to marking the neoplastic cells; because malignancy actually start in normal cells, which does not always recognize them as foreign. The tumor tissues usually recognized by the immune system, but with no strong response to destroy them. Malignant cells can produce substances that blind immunity from finding and attacking them [64]. For solve this, there are several prime natures of immuno-oncology benefited to treat malignancy (Figure 3).

Checkpoint inhibitors are a category of immunotherapy that block checkpoint proteins. They are medicines that release the brakes on immune system. They block the proteins programmed cell death (PD-1), programmed cell death ligand (PD-L1), cytotoxic T lymphocyte antigen 4 (CTLA-4), and killer immunoglobulin-like receptor (KIR) on the immune cell surface, to let them go after pullulating the cancerous. Examples include PD-1 inhibitors as pembrolizumab, nivolumab, and cemiplimab. The PD-L1 inhibitors like atezolizumab, avelumab, and durvalumab. Besides, CTLA-4 inhibitor as ipilimumab (yervoy). Finally, TF inhibitor (tivdak) [65].

Adoptive cell therapies (ACT) is an ex vivo strategy in which tumor-specific T cells are expanded by mixes them with a virus that learn it how to attach neoplasm; then returned to the case to kill neoplastic cells and generate a long-lasting theoretic memory against recurrence. It is a possible care for children with leukemia and some adults with lymphoma. Examples as tisagenlecleucel (kymriah) and axicabtagene ciloleucel (yescarta) [66].

Cancer vaccines learn immune systems to tackle the transformed cells. The vaccines are made

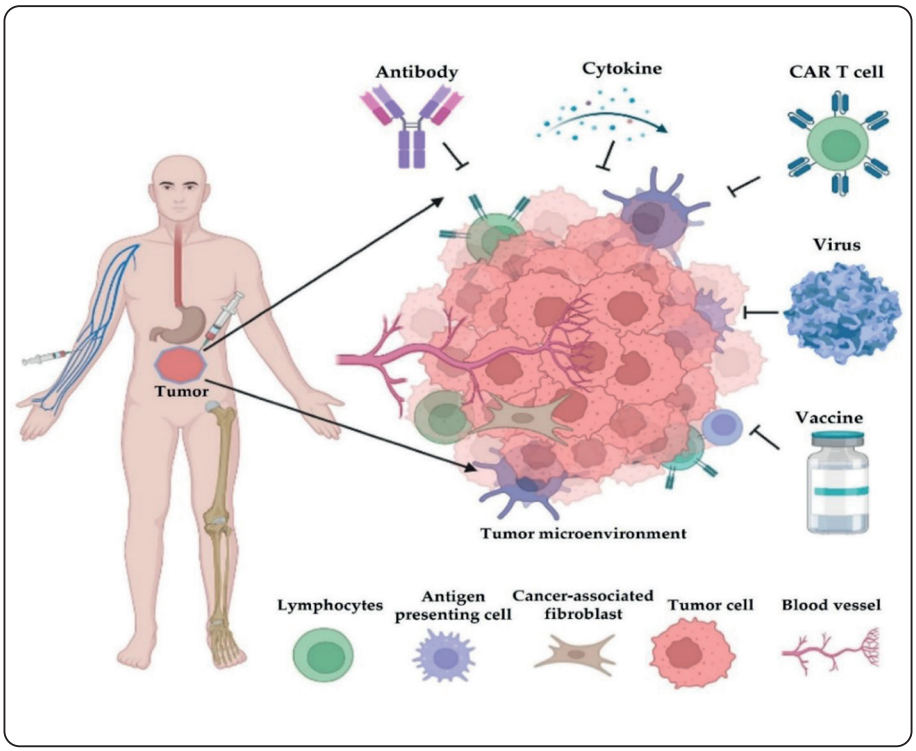

Fig. (3): Kinds of Immunotherapy; A Blockade Immune Checkpoints, Adoptive Transfer of Engineered Cells, Cytokine Therapy, Oncolytic Viruses, and Cancer Vaccines [77].

from defunct malignant tissues, proteins from tumor matter, or immune cells [67]. Cervarix, gardasil, and gardasil-9 are the approved vaccines to prevent malignancy which were developed versus the human papillomavirus, that links to different cervix, throat, vagina, vulva, anus, and penis neoplasms. Also, vaccine of hepatitis B against HBV infections that may spring liver lesions. Others vaccines are accepted for oncology treatment as sipuleucel-T, treats advanced prostate cancer. Talimogene laherparepvec, treats skin melanoma that has spread. Bacillus calmette-guerin, against first stage bladder diseases [68].

Monoclonal antibodies (mAbs) are immune version proteins. The mAbs is seeing to strike a fixed part of a malignant cell. They run in divergent ways. Naked monoclonal antibodies are the common shape, which they unattached to anything. The response from these antibodies block the antigens which help the lesion swell and metastases. A radioactive particle or chemotherapy agent are attached to conjugated monoclonal antibodies which directly attached the cancerous tissues. This action assists chemo and radiation treatments go better with reducing their side effects. Moreover, two proteins are attached at once in bispecific monoclonal antibodies. Some bind an oncocytic cell and an immune one, which associates the immunity attack the neoplasm. The blinatumomab drug fastens to a protein on leukemia cells, and to a protein on T-cells [69- 71].

Oncolytic viruses which modify to kill proven tumor cells without harming the healthy tissues. They have the potential to large malignant lesions through direct lysis of neoplastic cells, whilst stimulating an immune response to clear any cancer cell remnants. The first oncolytic virus has been approved, which derived from a herpes simplex virus type 1, is talimogene laherparepvec (TVEC). It has been engineered to replicating in oncocytic cells and activating anti-malignant immune response [72].

Cytokines services to stimulate the immune cells to attack neoplasia. These medications fall into two sets. **Interleukins** as IL-2 which rise T-cells and natural killer (NK) cells numbers in the body. The IL-2 aldesleukin is confirming in treating late stage tumor of kidney and metastatic melanoma. **Interferons** are a generation of cytokine that forcing immunity for more activity against malignancy. IFN-alfa aids in treating leukemia, sarcoma, lymphoma, and melanoma [73, 74].

Immunomodulators: are variety of medicaments regularly boosts against particular strains of malignancy through the immune system. They include: imiquimod, lenalidomide, pomalidomide, and thalidomide [75].

Head and Neck Cancer Immunotherapy

Immunotherapy empower human immunity for fighting cancer to be a very potent in treating advanced lesions, among other diseases. Two checkpoint inhibitors were confirmed by FDA for head and neck squamous cancers that can stopped the responding for chemotherapy as a standard treatment. The mediations are called nivolumab and pembrolizumab; they block a PD-1 protein which found on immune cells. The PD-1 makes an immune system brake, which down the responses. They release this brake to allowing the immune cells to mount a stronger attack against head and neck malignancy [76].

TARGETED THERAPY

The non-specificity to directly objet cancerous cells is the prime obstacle of chemotherapeutic ministrations plans. Therefore, a big limit in therapy due to drug failure for local delivering to the tumor mass. Many constituted strategies have been tested to give hopes for future medicaments delivery [78]. Delivery of nanoparticle techniques, targeted antibodies, aptameric functionalization, and specific agents give promise that can get success in the coming years. Neoplastic cell directed

antibodies are a method for medicine delivery which have accelerated the hunt for more effective approaches [79]. Nanodrugs formulations disported in nanocarriers have improved the treatment delivery to the malignant cells. For minimize the toxicities to adjacent tissues and organs is the significant advantage of this therapy. Otherwise, many effective delivery lines are still under clinical evaluation [80]. These therapies operate via finding specific proteins substances or a receptor that lesions have. This line of cure can be utilized by itself or in fusing with other medical interventions, such as traditional chemotherapy, surgery, or radiation. Targeted remedies can be occasioned after healing to control the tumor or prevent it from back again [81].

Neoplastic cells typically have genes changes produce dissimilarity from healthy tissues. These genes represent a DNA section which notify cells to do specific things. Several specific forms of proteins or enzymes in malignant neoplasms have messages for tumor tissue to inform thriving and copy itself. This knowledge advice the need for development of target drugs that can block these proteins or enzymes to preventing the messages for being sent [82].

The multiple targeted medicaments function in more than one way to control cancer cells and also be considered immunotherapy since they boost the immune framework. Their actions aid to treat malignancy via interfering with proteins

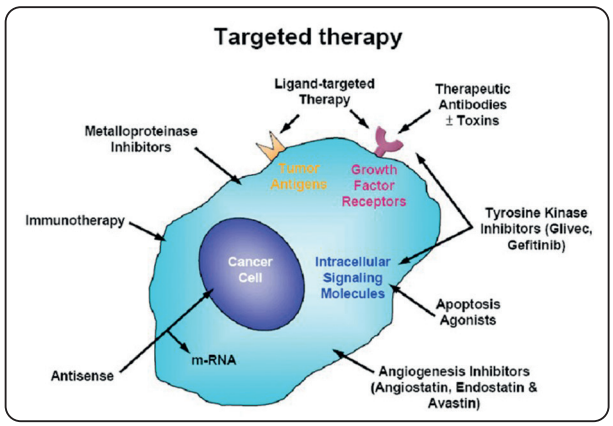

Fig. (4): Ways for Target Therapy [95].

that assist tumors sprouting throughout the body [83]. The following explains the ways for oncology treatments (Figure 4). Targeted therapies can mark malignant cell so it is easier to find and destroy by the immune cells. Different treatments helpmate immune system to go better against metastases [84]. A lot of malignant lesions have changes in the proteins of cell surface which notify them to part whether or not signals are present. Multiple therapies interfere with these proteins for inhibiting the cells to split. This role relief a slow cancer shooting up [85].

Angiogenesis inhibitors block formation of the new blood vessels that sustain the malignancy. Angiogenesis start via signals from tumor cells. The direct interfering with these signals prevent forming a blood supply which lead to the lesions stay small. Besides, if a neoplasm already has a blood supply, these therapies motive the dying of blood vessels, which results the tumor mass has been shrink [86]. Angiogenesis inhibitors interfere with the blood vessel growing as some monoclonal antibodies that specifically recognize and bind to vascular endothelial growth factor (VEGF). When VEGF is fixed to these panaceas, it is unable to activate its receptor. Blocking their activities done by some inhibitors bind to VEGF receptor and other receptors on the endothelial cells surface as well as to the downstream proteins signaling pathways. Other are agents of immunomodulatory which suppress the immune orders of antiangiogenic properties. They appear to be helpful in several neoplasms, when combined with additional therapies. Because angiogenesis inhibitors slowing or stopping tumor maturation without killing cells. Approved types as: axitinib, bevacizumab, cabozantinib, lenalidomide, lenvatinib mesylate, ramucirumab, vandetanib, and ziv-aflibercept [87, 88].

Monoclonal antibodies are combination substances of cell-killing as chemotherapy cures, radiation or toxins. Once they attach to targets on the cancer cells surface, they take up the cell-killing substances, causing them to die. These might de-

liver molecules via themselves or molecules with medicines into or onto the tumor tissue to kill it. Examples: cetuximab for colorectal, lung, head, and neck lesions. alemtuzumab for chronic leukemias, trastuzumab for breast neoplasms. Multiple monoclonal antibodies are referred to as targeted medicament as they have a specific mark on a malignant cell that they pointed to discover, join, and attack. Other monoclonal antibodies move like immunotherapy which inform the body for better respond to attack neoplastic points more forceful [89, 90].

Proteasome inhibitors disrupt normal functions of cell causing cancer die. Normal cells dying occur in programmed way when become harmed or are no longer needed. Tumor tissues have different manners for avoiding this killing process. The targeted therapies can stimulate malignant content to die via this process of cell death, called apoptosis. Example: bortezomib for multiple myeloma [91].

Signal transduction inhibitors change the creation of the tumor tissues through disrupt the cell signals. Multiple breast and prostate neoplasms need proven hormones for development. Hormone therapies are a sort of cancer medicine that can labor in two ways. Several therapies prevent the body from making specific hormones or prevent the hormones from acting. Example: imatinib for chronic leukemias [92].

Head and Neck Cancer Targeted Therapy

Several molecular goals were implicated against head and neck lesions, including epidermal growth factor receptor, VEGF and phosphatidiylinositol 3-kinase (PI3K). Molecular profiling is a genomic testing which looking at the tumor cells; if there are any genetic mutations that could be linked to the disease. Genomic testing can aid to personalize the ideal care. It can rule out therapies that not well act. An example, round about 13% of head and neck neoplasms have a mutation in the PIK3CA gene. The higher percentage is related to human papillomavirus diseases. This exploring new approaches targeting that mutation [93, 94].

HORMONE THERAPY

Hormone therapy is practiced against neoplasms that need hormones to sprout. Medications in this category are operated to sedate the flourishing of certain breast, prostate, and uterine lesions, that physical enlarge in response to normal hormones. Drug action run via making the malignant cells disable for hormone handling that they need to broaden, or by preventing the hormone making[96]. Therapy by hormones can functionally make a tumor compacted before radiation or surgery; called neoadjuvant treatment. As well, further down the risk that malignancy will recurrence back after the significant ministrations; called adjuvant treatment. In addition, damage metastatic cells that have returned or metastases to other body parts [97].

There are several lines of hormone medicaments might be valued to treat breast lesions through aromatase inhibitors as exemestane, anastrozole, and letrozole. Selective estrogen receptor modulators like tamoxifen and raloxifene. Estrogen receptor antagonists via fulvestrant and toremifene. Luteinizing hormone-releasing hormone agonists as goserelin, leuprolide, and triptorelin. Moreover, prostate hormonal therapy via anti-androgens such as apalutamide, enzalutamide, darolutamide, and nilutamide. The CYP17 inhibitors like abiraterone and ketoconazole. Luteinizing hormone-releasing hormone agonists and antagonists through goserelin, leuprolide, and degarelix. Adrenal tumor drugs as adrenolytics, estrogen receptor antagonists (fulvestrant and toremifene), and selective estrogen receptor modulators (tamoxifen and raloxifene) [98- 102].

Corticosteroids, merely named steroids, are naturalistic hormones and hormone-like physics which are operated in the curing of sets of lesions. These pharmaceuticals are objected as a cure division; they are considered chemotherapy treatment. Examples of corticosteroids include: prednisone, methylprednisolone, and dexamethasone. Steroids are else commonly called to prevent nausea and vomiting rooted by chemo cure. They are wonted before some molds of chemo to prevent severe allergic reactions, too [103].

CONCLUSIONS

Chemotherapy is inspected largely and clinically valued in cancer therapeutics. The review briefed the status of present chemo-agents currently booked in the hospital practice. New trends and derivatives of old medicaments with potent efficacy and little toxicities. The compounds which naturally derived from microbial, plants, as well as naturalistic roots fitted as chemotherapeutic agents had a lot of merits over synthetic types, owing to their low cytotoxicity, production price, and modest extraction/ manufacture methods [(104)]. Therefore, the key point in determining the success of its drug regimens depend on the recognition and attenuation of its toxicity. In the future, the clinical strategies should be revising that mixture therapy could emerge as a promising therapeutic approach to heal a diverse malignancy. Synthesis regimes comprise an obvious overlap of the chemo-strategies with the targeted delivery, personalized cure, and immunotherapy. Improving the efficacy of enrolled care can elicit the sense of certain lesions towards their therapeutic targeting[(105)]. Among these, personalized incorporation therapies that mark individual tumor shapes based on their molecular signatures may offer a great promise. Thus, conventional chemotherapy beyond its clinical efficacy can improved by combination with other therapies. The clinical translation of these combination manners is still need complete success and thus warrants more investigations [(106)].

REFERENCES

1. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J (Engl). 2021;134(7):783-91.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3(4):524-48.
3. Hausman DM. What is cancer? Perspect Biol Med. 2019;62(4):778-84.
4. Islami F, Ward EM, Sung H, et al. Annual report to the nation on the status of cancer, part 1: National Cancer Statistics. J Natl Cancer Inst. 2021;113(12):1648-69.
5. Chamberlin SR, Blucher A, Wu G, et al. Natural product target network reveals potential for cancer combination therapies. Front Pharmacol. 2019;10:557.
6. Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. Nat Rev Mol Cell Biol. 2020;21(11):678-95.
7. Laplagne C, Domagala M, Le Naour A, et al. Latest advances in targeting the tumor microenvironment for tumor suppression. Int J Mol Sci. 2019;20(19):4719.
8. Salvadori G, Mirisola MG, Longo VD. Intermittent and periodic fasting, hormones, and cancer prevention. Cancers (Basel). 2021; 13(18):4587.
9. Huang PW, Chang JW. Immune checkpoint inhibitors win the 2018 Nobel Prize. Biomed J. 2019;42(5):299-306.
10. Galmarini D, Galmarini CM, Galmarini FC. Cancer chemotherapy: a critical analysis of its 60 years of history. Crit Rev Oncol Hematol. 2012;84(2):181-99.
11. Park JH, Pyun WY, Park HW. Cancer metabolism: phenotype, signaling and therapeutic targets. cells. 2020; 9(10):2308.
12. Zecha JA, Raber-Durlacher JE, Nair RG, et al. Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer. 2016;24(6):2781-92.
13. Gavrilas LI, Cruceriu D, Mocan A, et al. Plant-derived bioactive compounds in colorectal cancer: insights from combined regimens with conventional chemotherapy to overcome drug-resistance. Biomedicines. 2022;10(8):1948.
14. Trinh LD, Wong JT, Sullivan PA, et al. Impact of a chemotherapy workload and productivity dashboard on pharmacy technician turnover. Am J Health Syst Pharm. 2019;76(13):992-7.
15. Oh S, Paik H, Park SJ, et al. Pressurized intraperitoneal aerosol chemotherapy for recurrent ovarian, fallopian or primary peritoneal cancer with peritoneal carcinomatosis: a narrative review. Gland Surg. 2021;10(3):1244-51.
16. Timin AS, Peltek OO, Zyuzin MV, et al. Safe and effective delivery of antitumor drug using mesenchymal stem cells

impregnated with submicron carriers. ACS Appl Mater Interfaces. 2019;11(14):13091-104.

17. Apetoh L, Ladoire S, Coukos G, et al. Combining immunotherapy and anticancer agents: the right path to achieve cancer cure? Ann Oncol. 2015;26(9):1813-23.
18. Peng Y, Pei H. DNA alkylation lesion repair: outcomes and implications in cancer chemotherapy. J Zhejiang Univ Sci B. 2021;22(1):47-62.
19. Kondo N, Takahashi A, Ono K, et al. DNA damage induced by alkylating agents and repair pathways. J Nucleic Acids. 2010;2010:543531.
20. Wróbel A, Drozdowska D. Recent design and structure-activity relationship studies on the modifications of DHFR inhibitors as anticancer agents. Curr Med Chem. 2021;28(5):910-39.
21. Martinez GR, Loureiro AP, Marques SA, et al. Oxidative and alkylating damage in DNA. Mutat Res. 2003;544(2-3):115-27.
22. Hwa Yun B, Guo J, Bellamri M, et al. DNA adducts: Formation, biological effects, and new biospecimens for mass spectrometric measurements in humans. Mass Spectrom Rev. 2020;39(1-2):55-82.
23. Povey AC. DNA adducts: endogenous and induced. oxicol Pathol. 2000;28(3):405-14.
24. Sharma V, Collins LB, Clement JM, et al. Molecular dosimetry of endogenous and exogenous O(6)-methyl-dG and N7-methyl-G adducts following low dose [D3]-methylnitrosourea exposures in cultured human cells. Chem Res Toxicol. 2014;27(4):480-2.
25. Habli Z, Toumieh G, Fatfat M, et al. Emerging cytotoxic alkaloids in the battle against cancer: overview of molecular mechanisms. Molecules. 2017;22(2):250.
26. Fu D, Calvo J.A, Samson L.D. SERIES: Genomic instability in cancer Balancing repair and tolerance of DNA damage caused by alkylating agents. Nat Rev Cancer. 2012;12(2):104-20.
27. Sauter B, Gillingham D. Profiling the nucleobase and structure selectivity of anticancer drugs and other DNA alkylating agents by RNA sequencing. Chembiochem. 2018;19(15):1638-42.
28. Brandes AA, Bartolotti M, Tosoni A, et al. Nitrosoureas in the Management of Malignant Gliomas. Curr Neurol Neurosci Rep. 2016;16(2):13.
29. Mehrmohamadi M, Jeong SH, Locasale JW. Molecular features that predict the response to antimetabolite chemotherapies. Cancer Metabol. 2017;5:8.
30. Sullivan MR, Darnell AM, Reilly MF, et al. Methionine synthase is essential for cancer cell proliferation in physiological folate environments. Nat Metab. 2021;3(11):1500-11.
31. Ayati A, Moghimi S, Toolabi M, et al. Pyrimidine-based EGFR TK inhibitors in targeted cancer therapy. Eur J Med Chem. 2021;221:113523.
32. You F, Gao C. Topoisomerase inhibitors and targeted delivery in cancer therapy. Curr Top Med Chem. 2019;19(9):713-29.
33. Baglini E, Salerno S, Barresi E, et al. Multiple Topoisomerase I (TopoI), Topoisomerase II (TopoII) and Tyrosyl-DNA Phosphodiesterase (TDP) inhibitors in the development of anticancer drugs. Eur J Pharm Sci. 2021;156:105594.
34. Beretta GL, Gatti L, Perego P, et al. Camptothecin resistance in cancer: insights into the molecular mechanisms of a DNA-damaging drug. Curr Med Chem. 2013; 20(12):1541-65.
35. Hart LL, Ferrarotto R, Andric ZG, et al. Myelopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: results from a randomized, double-blind, placebo-controlled phase ii study. Adv Ther. 2021;38(1):350-65.
36. Kciuk M, Marciniak B, Kontek R. Irinotecan-Still an important player in cancer chemotherapy: a comprehensive overview. Int J Mol Sci. 2020;21(14):4919.
37. Infante Lara L, Fenner S, Ratcliffe S, et al. Coupling the core of the anticancer drug etoposide to an oligonucleotide induces topoisomerase II-mediated cleavage at specific DNA sequences. Nucleic Acids Res. 2018;46(5):2218-33.
38. Pommier Y, Leo E, Zhang H, et al. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chem Biol. 2010;17(5):421-33.
39. Sinha D, Duijf PHG, Khanna KK. Mitotic slippage: an old tale with a new twist. Cell Cycle. 2019;18(1):7-15.
40. Ashrafizadeh M, Ahmadi Z, Mohamadi N, et al. Chitosan-based advanced materials for docetaxel and paclitaxel delivery: Recent advances and future directions in cancer theranostics. Int J Biol Macromol. 2020;145:282-300.
41. Asma ST, Acaroz U, Imre K, et al. Natural products/bioactive compounds as a source of anticancer drugs. Cancers (Basel). 2022;14(24):6203.

42. Iiyama S, Fukaya K, Yamaguchi Y, et al. Total synthesis of paclitaxel. Org Lett. 2022;24(1):202-6.

43. Chin K, Yamamoto S, Takahashi M, et al. Effectiveness of taxanes following nivolumab in patients with advanced esophageal squamous cell carcinoma: a retrospective chart review of patients in ATTRACTION-3. Esophagus. 2022.

44. Zhang Y, Yang SH, Guo XL. New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer. Biomed Pharmacother. 2017;96:659-66.

45. Ye X, Wang A, Lin W, et al. The Role of intestinal flora in anti-tumor antibiotic therapy. Front Biosci (Landmark Ed). 2022;27(10):281.

46. Martins-Teixeira MB, Carvalho I. Antitumour anthracyclines: progress and perspectives. ChemMedChem. 2020; 15(11):933-48.

47. Marinello J, Delcuratolo M, Capranico G. Anthracyclines as topoisomerase ii poisons: from early studies to new perspectives. Int J Mol Sci. 2018;19(11):3480.

48. Murphy T, Yee KWL. Cytarabine and daunorubicin for the treatment of acute myeloid leukemia. Expet Opin Pharmacother. 2017;18(16):1765-80.

49. Mayer LD, Tardi P, Louie AC. CPX-351: a nanoscale liposomal co-formulation of daunorubicin and cytarabine with unique biodistribution and tumor cell uptake properties. Int J Nanomedicine. 2019;14:3819-30.

50. Yu Z, Yan B, Gao L, et al. Targeted delivery of bleomycin: a comprehensive anticancer review. Curr Cancer Drug Targets. 2016;16(6):509-21.

51. Chiani M, Azadmanesh K, Shokrgozar MA, et al. Enhanced antitumor effect of targeted nanoliposomal bleomycin. Chem Biol Drug Des. 2017;90(5):953-61.

52. Arndt C, Hawkins D, Anderson JR, et al. Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. J Clin Oncol. 2004;22(10):1894-901.

53. Al-Tarawneh SF, Dahmash EZ, Alyami H, et al. Mechanistic modelling of targeted pulmonary delivery of dactinomycin iron oxide-loaded nanoparticles for lung cancer therapy. Pharm Dev Technol. 2022:1-12.

54. Raoof M, Sullivan KM, Frankel PH, et al. Multicenter dose-escalation Phase I trial of mitomycin C pressurized intraperitoneal aerosolized chemotherapy in combination with systemic chemotherapy for appendiceal and colorectal peritoneal metastases: rationale and design. Pleura Peritoneum. 2022;7(4):169-177.

55. Cheng SY, Delgado-Cruzata L, Clement CC, et al. Cytotoxicity, crosslinking and biological activity of three mitomycins. Bioorg Chem. 2022;123:105744.

56. Rajendra A, Noronha V, Joshi A, et al. Palliative chemotherapy in head and neck cancer: balancing between beneficial and adverse effects. Expert Rev Anticancer Ther. 2020;20(1):17-29.

57. McCreary AC, Muller CP, Filip M. Psychostimulants: basic and clinical pharmacology. Int Rev Neurobiol. 2015;120:41-83.

58. Berrios-Caro E, Gifford DR, Galla T. Competition delays multi-drug resistance evolution during combination therapy. J Theor Biol. 2021;509:110524.

59. Yang H, Wang J, Khan S, et al. Selective synergistic anticancer effects of cisplatin and oridonin against human p53-mutant esophageal squamous carcinoma cells. Anticancer Drugs. 2022;33(1):e444-52.

60. Salari N, Rasoulpoor S, Valipour E, et al. Liposomes, new carriers for delivery of genes and anticancer drugs: a systematic review. Anticancer Drugs. 2022;33(1):e9-20.

61. Stine ZE, Schug ZT, Salvino JM, et al. Targeting cancer metabolism in the era of precision oncology. Nat Rev Drug Discov. 2022;21(2):141-62.

62. Abbott M, Ustoyev Y. Cancer and the immune system: the history and background of immunotherapy. Semin Oncol Nurs. 2019;35(5):150923.

63. Shi Y, Lammers T. Combining nanomedicine and immunotherapy. Acc Chem Res. 2019;52(6):1543-54.

64. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020;70(2):86-104.

65. Li B, Chan HL, Chen P. Immune checkpoint inhibitors: basics and challenges. Curr Med Chem.;26(17):3009-25.

66. Met O, Jensen KM, Chamberlain CA, Donia M, Svane IM. Principles of adoptive T cell therapy in cancer. Semin Immunopathol. 2019;41(1):49-58.

67. Saxena M, van der Burg SH, Melief CJM, et al. Therapeutic cancer vaccines. Nat Rev Cancer. 2021;21(6):360-78.

68. Lopes A, Vandermeulen G, Preat V. Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. J Exp Clin Cancer Res. 2019;38(1):146.

69. Waldmann H. Human monoclonal antibodies: the benefits of humanization. Methods Mol Biol. 2019;1904:1-10.

70. Posner J, Barrington P, Brier T, et al. Monoclonal antibodies: past, present and future. Handb Exp Pharmacol. 2019;260:81-141.

71. Gao F, Yang C. Anti-VEGF/VEGFR2 monoclonal antibodies and their combinations with pd-1/pd-l1 inhibitors in clinic. Curr Cancer Drug Targets. 2020;20(1):3-18.

72. Mondal M, Guo J, He P, et al. Recent advances of oncolytic virus in cancer therapy. Hum Vaccin Immunother. 2020;16(10):2389-402.

73. Klein C, Waldhauer I, Nicolini VG, et al. Cergutuzumab amunaleukin (CEA-IL2v), a CEA-targeted IL-2 variant-based immunocytokine for combination cancer immunotherapy: Overcoming limitations of aldesleukin and conventional IL-2-based immunocytokines. Oncoimmunology. 2017;6(3):e1277306.

74. Huang YW, Tsai CY, Tsai CW, et al. Pharmacokinetics and Pharmacodynamics of Novel Long-Acting Ropeginterferon Alfa-2b in Healthy Chinese Subjects. Adv Ther. 2021;38(9):4756-70.

75. Grippin AJ, Dyson KA, Qdaisat S, et al. Nanoparticles as immunomodulators and translational agents in brain tumors. J Neurooncol. 2021;151(1):29-39.

76. Trivedi S, Sun L, Aggarwal C. Immunotherapy for head and neck cancer. Hematol Oncol Clin North Am. 2021;35(5):1021-37.

77. Yang M, Olaoba OT, Zhang C, et al. Cancer immunotherapy and delivery system: an update. Pharmaceutics. 2022;14(8):1630.

78. Perez-Herrero E, Fernandez-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm. 2015;93:52-79.

79. Shariati M, Meric-Bernstam F. Targeting AKT for cancer therapy. Expert Opin Investig Drugs. 2019;28(11):977-88.

80. Karaosmanoglu S, Zhou M, Shi B, et al. Carrier-free nanodrugs for safe and effective cancer treatment. J Control Release. 2021;329:805-32.

81. Luk BT, Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. J Control Release. 2015;220(Pt B):600-7.

82. Lin D, Feng X, Mai B, et al. Bacterial-based cancer therapy: an emerging toolbox for targeted drug/gene delivery. Biomaterials. 2021;277:121124.

83. Srinivasarao M, Low PS. Ligand-targeted drug delivery. Chem Rev. 2017;117(19):12133-64.

84. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565-70.

85. Lee YT, Tan YJ, Oon CE. Molecular targeted therapy: Treating cancer with specificity. Eur J Pharmacol. 2018;834:188-96.

86. Kiselev SM, Lutsenko SV, Severin SE, et al. Tumor angiogenesis inhibitors. Biochemistry (Mosc). 2003;68(5):497-513.

87. Lin Z, Zhang Q, Luo W. Angiogenesis inhibitors as therapeutic agents in cancer: Challenges and future directions. Eur J Pharmacol. 2016;793:76-81.

88. Rani V, Prabhu A. Combining angiogenesis inhibitors with radiation: advances and challenges in cancer treatment. Curr Pharm Des. 2021;27(7):919-31.

89. Silvestre ALP, Oshiro-Junior JA, Garcia C, et al. Monoclonal antibodies carried in drug delivery nanosystems as a strategy for cancer treatment. Curr Med Chem. 2021;28(2):401-18.

90. Tsao LC, Force J, Hartman ZC. Mechanisms of therapeutic antitumor monoclonal antibodies. Cancer Res. 2021;81(18):4641-51.

91. Manasanch EE, Orlowski RZ. Proteasome inhibitors in cancer therapy. Nat Rev Clin Oncol. 2017;14(7):417-33.

92. Davies DM, Sampson JR. Small-molecule signal-transduction inhibitors: targeted therapeutic agents for single-gene disorders. J Med Genet. 2010;47(3):145-9.

93. Alsahafi E, Begg K, Amelio I, et al. Clinical update on head and neck cancer: molecular biology and ongoing challenges. Cell Death Dis. 2019;10(8):540.

94. Liu SY, Chen W, Chughtai EA, et al. PIK3CA gene mutations in Northwest Chinese esophageal squamous cell carcinoma. World J Gastroenterol. 2017;23(14):2585-91.

95. Han-Chung W, Chang DK, Chia-Ting H. Targeted Therapy for Cancer. Journal of Cancer Molecules 2006;2(2).

96. Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors - review of the literature. Pathol Oncol Res. 2020;26(1):63-78.

97. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted

therapy for breast cancer: ASCO guideline. J Clin Oncol. 2021;39(13):1485-505.

98. Kharb R, Haider K, Neha K, et al. Aromatase inhibitors: role in postmenopausal breast cancer. Arch Pharm (Weinheim). 2020;353(8):e2000081.

99. Furman C, Hao MH, Prajapati S, et al. Estrogen receptor covalent antagonists: the best is yet to come. Cancer Res. 2019;79(8):1740-1745.

100. Katzer T, Leite Junior A, Beck R, et al. Physiopathology and current treatments of androgenetic alopecia: Going beyond androgens and anti-androgens. Dermatol Ther. 2019;32(5):e13059.

101. Yin L, Hu Q. CYP17 inhibitors--abiraterone, C17,20-lyase inhibitors and multi-targeting agents. Nat Rev Urol. 2014;11(1):32-42.

102. Malik P, Bhushan R. Development of liquid chromatographic methods for enantioseparation and sensitive detection of β-adrenolytics/β2-agonists in human plasma using a single enantiomer reagent. J Chromatogr B Analyt Technol Biomed Life Sci. 2017;1061-1062:117-22.

103. Hatano Y, Matsuoka H, Lam L, et al. Side effects of corticosteroids in patients with advanced cancer: a systematic review. Support Care Cancer. 2018;26(12):3979-83.

104. Ortiz-Perez E, Rivera G, Salas CO, et al. Natural and synthetic naphthoquinones as potential anti-infective agents. Curr Top Med Chem. 2021;21(22):2046-69.

105. Colli LM, Machiela MJ, Zhang H, et al. Landscape of combination immunotherapy and targeted therapy to improve cancer management. Cancer Res. 2017; 77(13):3666-71.

106. Urquhart R, Cordoba W, Bender J, et al. Risk stratification and cancer follow-up: towards more personalized post-treatment care in Canada. Curr Oncol. 2022;29(5):3215-23.