THINK INDIA JOURNAL ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Recent Advancesin Anti-Cancer Drugs

Neharika Gupta[1], Kadavala Triveni[1],Tejasvi Roy[1], G Arun Kumar Reddy[1], Amarish Kumar Sharma*

Department of Bioengineering &Bioscience, Lovely Professional University, Phagwara, Punjab, India-144411

Corresponding Author E-mail:amarish.19824@lpu.co.in

Introduction:

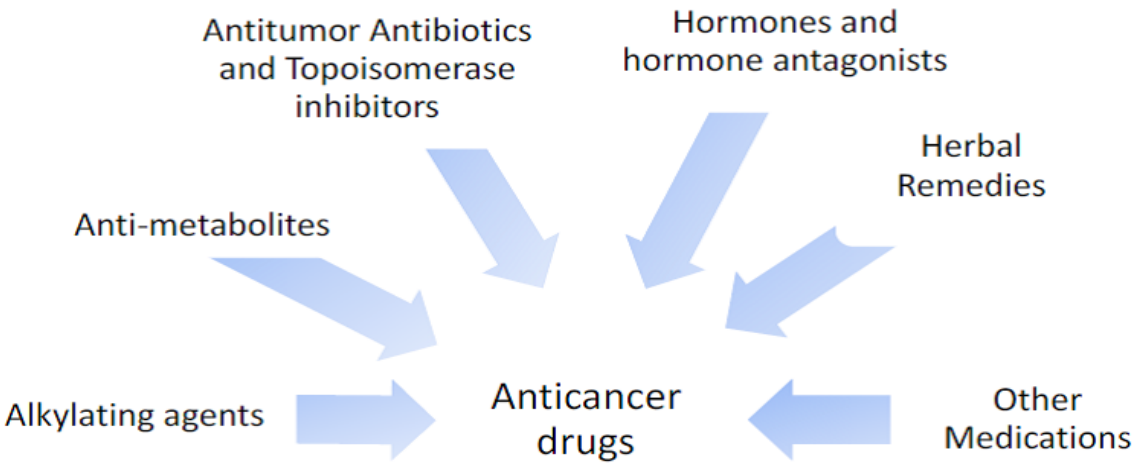
The global scenario of cancer affected patient as per recent data floated by World Health Organization (WHO) is estimated by 18 million new cases and around 10 million casualties leading to death in 2018.Rising work stress and unbalanced food habits globally is hypothesized to be the main reason for the onset of malignancy. At per recent statistical data, one in eight men and eleven women respectively is prone to be malignant. Female breast cancer and common lung cancers are most prevalent and leading form of cancer amounting to 19 percent of global population.In the global scale,9.2 percent of people are affected by colorectal cancer,8.2 percent by stomach cancer and 8.2 percent by hepatic cancer respectively.[1]

Recent development in research & technology in cancer therapeutics have encouraged used of new selective oncology drugs, to which the results are highly promising. U.S Food and Drug Administration (USFDA)has recently approved eight drugs for cancer indications in 2017 and twelve cancer drugs for diverse cellular targets. In recent times, very promising anti-cancer drugs such as IDH2 inhibitor have been approved which can effectively kill carcinogenic cells through blocking their signalling metabolic pathways. The advent of Biosimilar, which is substantially cost effective and equally efficacious as the novel drug, plays a highly significant role in sufficing the need for affordable treatment in developing nations. [2]

Food and Drug administration has granted a very promising anti-cancer biosimilar drug, a tissue agonist with targeted genetic change irrespective of the type of cancer. It is very interesting to note that in 2018,80 percent of the total drugs approved by USFDA,was for cancer therapy. Despite of best of the efforts and millions of dollar invested by pharmaceutical companies and research industries globally, complete cure from cancer through targeted delivery of drugs is still a major challenge. Novel drugs are effective but comes with critical side effects leading to various other subsidiary ailments. Looking into the present challenge in cancer therapy, combinatorial therapy could be the future for oncology patients. [3

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Figure 1:Anticancer Drug Activity Based Classification. [4]



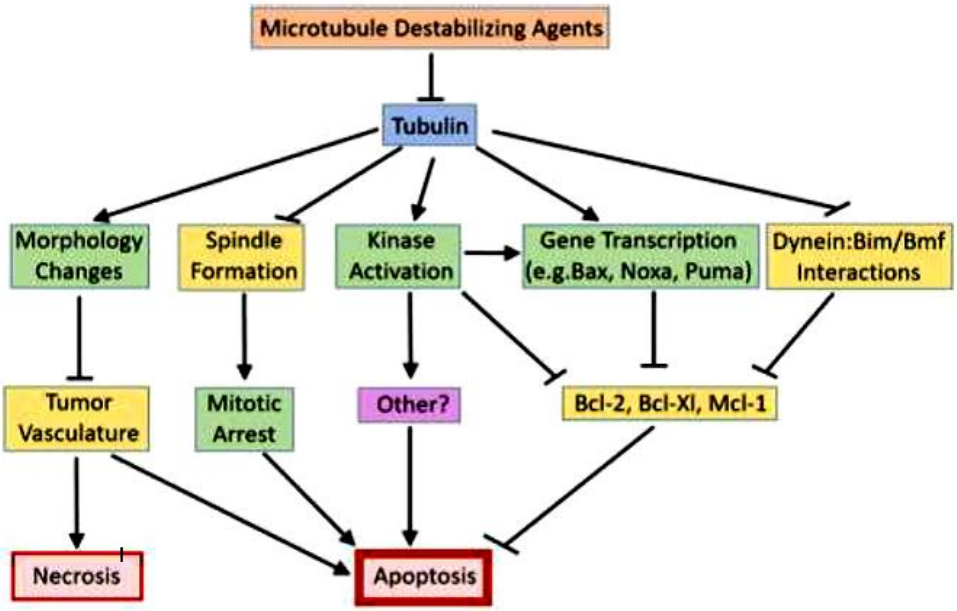
Generally the anti-cancer drugs or the chemo-therapeutics acts on the malignant cells and kill it either through programmed cell death or by arresting their growth cycle. Most of the anti-cancer drugs target the mutagenicity factor and denature them, which promotes uncontrolled cell division. The most prominently affected cellular targets in human system if hematopoietic bone marrow, the prostate and the gastro-intestinal tract. The metabolic organs namely the liver and kidney, which are continuously at work and have very high cellular stress and are mostly deals with addressing cellular toxicity. This could be one of the reason for them to be affected with cellular signalling mismanagement which could lead to carcinoma. [Figure 1]

MicrotubuleInhibitors

Microtubulesareanimportantandeasytargettokilltumourcellsbecausetheyplayamainrolein mitosisandifmitosisisnotcarriedoutinawaythatisrequiredfornormaldivision,itmatleadtoap optosis.Themicrotubuleinhibitorsareagroupofcompoundsthatinhibitthefunctionalityof cellularmicrotubules.Microtubuleinhibitorsforexamplevincaalkaloids,epothilonesandtax anesinterfereswiththedynamicsofthemicrotubuleeitherbystabilizingordestabilizingthem,t hereby
hinderingthemicrotubulefunctionneededforitspropermitoticactivity.Thisinturnblocksthec ell cycle and leadingtocelldeathofthecellsviaaprocessknownas apoptosis. Microtubulesplayavarietyoffunctionslikecellshapemaintenance ,cellsignalling,mitosis, intracellulartransportandpolarity.Inmitosis,microtubulesleadstotheformationofspindlefib res,
whosemainfunctionistoseparatedaughterchromosomes,towardsoppositeendsofthedividin g
cell.Thismajorpropertyofmicrotubulesmakesthemaneasytargetfortheproductionofchemo - therapeuticdrugs againsttumorcells.[5]

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Figure 2: Microtubule destabilising agents in Cancer models. [6]



MicrotubuleStructure

Themicrotubulestructureiswell-defined. Theyarecomposedofpolymersoftubulin.Microtubules arepolymersofα-andβ-tubulinheterodimer,joinednon-covalentlyandformsatube-likestructure.Themolecularweightofthetubulinsubunitsisapprox.50kDaandare~50%identicaltoeachother.Thepolymerizationtakesplacebyaphenomenonknownasnucleation-elongation.During thisprocessthedimersareaddedattheendofashortstretchofmicrotubuletermedasnucleus.Aheadtotailarrangementisseenduringpolymerisation,specifyingα-tubulinofonedimerjoinedtotheβ-tubulinofthefollowingdimer.Thestructureformedafterthisarrangementisknownas protofilaments,whichisthebackboneofthehollow,tube-likemicrotubule.Thehead-tail configurationofthedimersgivespolaritytothemicrotubule.Oneextremeisencircledwithα-tubulinandtheotherextremeiscoveredwithβ-tubulin,conferring-and+charge.Theseextremesaresonamedas(−)and(+)terminalsrespectively.Thereisaregion knownasthemicrotubuleorganizingcenter(MTOC),mainlycomposedofproteins,wherethe microtubulesareanchored.The(−)extremeofmicrotubuleisconnectedtotheMTOCandthe(+)extremeisfree.Amajorpropertyofthemicrotubulesisthattheyexistinadynamicconditioni.e. elongationandcontraction takesplacebyreversibleassociationanddissociationofα/β-tubulinatbothterminals.The- terminal is less dynamicandthe+terminalismoredynamic.ThereisaGTPbindingsiteateachsubunit,knownasthenon-exchangeableregioninαsubunitand theexchangeableregioninβsubunit.GTPbindingtoα-subunitisstablewhereastheGTPbinding toβ-subunitisunstableandhydrolyzedtoGDPafterpolymerization.Therateatwhichtubulingetsaddedisfasterthantherateatwhich GTPgetshydrolysed.[6]

ThebindingofGDPorGTPonthe exchangeablesitedecidesthestabilityofthemicrotubule.AGTP-boundmicrotubuleismorestable thanamicrotubuleboundtoGDP.GrowthofmicrotubuleincludesthebindingofGTPand shortening includes thebreakdownofGDP-bound units.

Thepolymerizationanddepolymerizationofthemicrotubulesshowstwocharacters:treadmillinganddynamicinstability.Treadmillingreferstothenetadditionofdimerstothe+terminalandsimultaneoussubtractionofatubulinsubunitatthe−terminal.Spindlemicrotubulesaremoredynamicascomparedtotheinterphasemicrotubulesforfastassociationanddissociationof microtubulesduringseparationofthehomologouschromosomestowardstheoppositeendofthe dividing cell.Dynamicinstabilityrepresentsswitchingofmicrotubulesbetweenphasesofslowgrowth, fast shorteningandpausedmicrotubule(neitherpolymerisingnordepolymerization).catastropheisthetransitionofmicrotubulesfromgrowthphasetoshorteningphaseandrescueistheswitching of microtubules from ashorteningphasetogrowthphase.[7]

ChemotherapeuticdrugsusedagainstmicrotubulesworksbyarrestingthecycleintheG2/Mphase and leading to apoptosis.Microtubuleinhibitorsaregroupedasfollows:destabilizingandstabilizingagents. Microtubule-destabilizingagentscomprisesofvincaalkaloidsandtheirmainfunctionistodepolymerizethe microtubules. .Stabilizingagentscomprisesofepothilonesandtaxanes.Theyactbyenhancingthepolymerizationprocess. [8]

Microtubule-DestabilizingAgents

Vincaalkaloidswerepreviouslyextractedfromaplantknownas*Vincarosea*.Vinblastineand vincristinewerethefirsttwovincaalkaloidstobeidentified.Theyonlydifferinawaythatinvincristinetheformylgroupisattachedtothedihydroindolenitrogenandinvinblastinemethyl group is present at the sameposition.Vinorelbineisanothervincaofsemisyntheticnature.

Thevinca-bindingregiononβ-subunitissituatedclosetotheexchangeableGTP-bindingregion. Therearetwodifferentbindingsitesonmicrotubules:onebindingwithhighaffinitytotheendsof thesubunitsandotherbindingwithlowaffinityalongthesidesurfaceofmicrotubule.Thisalso enhancethetendencyofthesubunitstoself-associate,formingspiralaggregates.Vincascause microtubuledepolymerizationsotheyaretermedasdestabilizingagents.Otherreasonsinclude suppressing dynamic instabilityandtreadmilling,inhibitingmitosisandfinally apoptosis. [9]

Microtubule-StabilizingAgents

Paclitaxelisanaturaltaxaneisolatedfromaplantknownas*Taxusbrevifolia*.Docetaxel,ontheotherhand,isasemisynthetictaxane.Taxaneisaditerpenehavingatetracycliccoremadeupof two cyclohexanes, a cyclooctane,andanoxetane.

Boththedrugsi.e.paclitaxelanddocetaxelinhabitthesamebindingregionontheβ-subunitoftubulinwitharatio1:1.Thetaxanebindingsiteissituatedontheinnersideofthemicrotubules,sothemicrotubulesgetstabilized,thusincreasingpolymerizationandinterferenceindynamicsof

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

the microtubule, resultinginarrestofthecellcyclein the G2/M phase andcelldeath.[10]

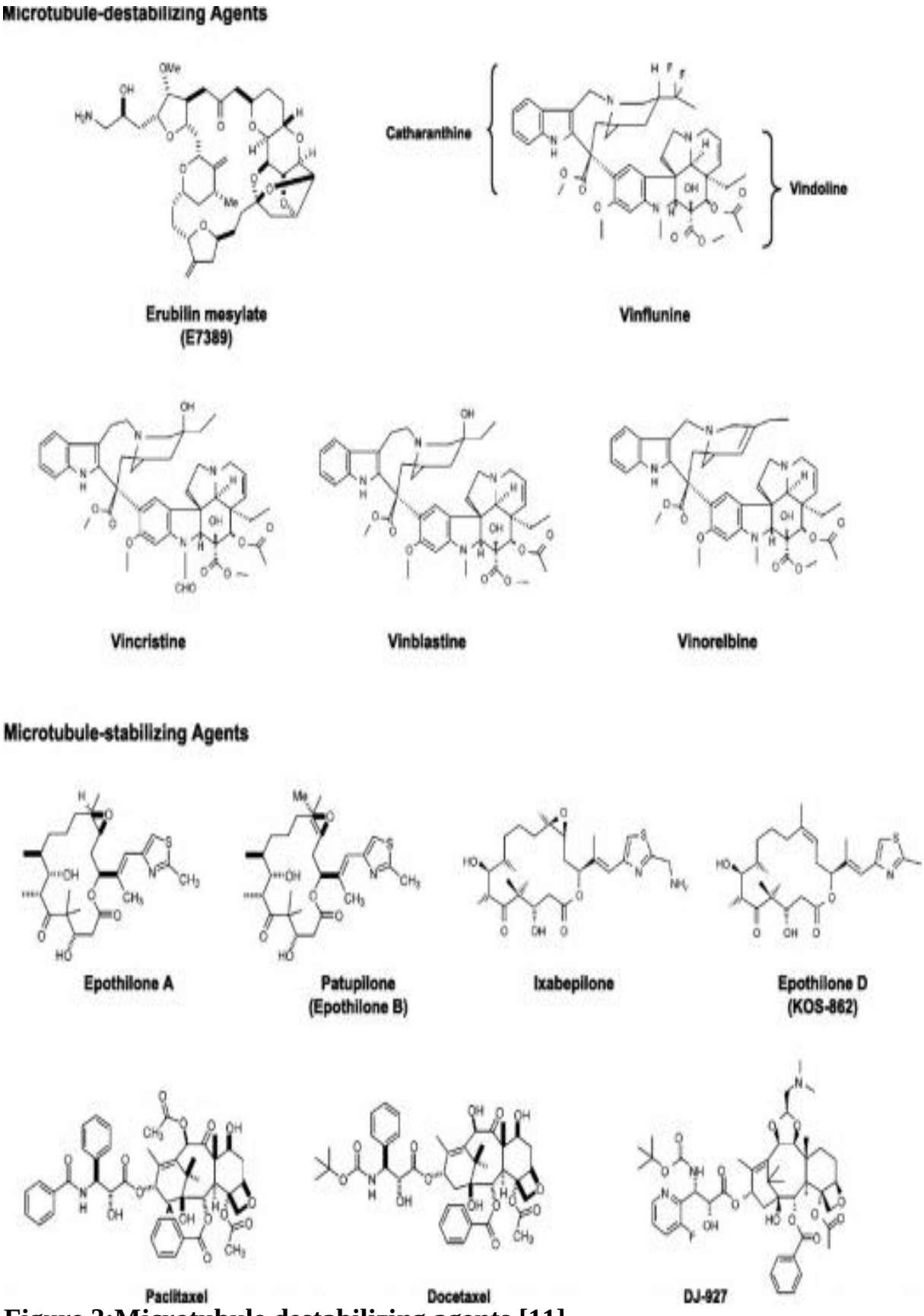


Figure 3:Microtubule destabilizing agents [11]

Epothilones

TheEpothilonesarecharacterizedas16-memberedmacrolides.EpothilonesAandBweretwotypes ofepothiloneswhichwereearlierextractedfromamyxobacterium.Boththetypesshareacommon structure,exceptforthesubstitutionofahydrogenforamethylgroupatC-12positioninthe epothilone B.

Liketaxanes,epothilonesshowsimilarmechanismofaction,includingstabilization,non-functionalityofmicrotubuledynamics,increasedpolymermassathighconcentrationsandtubulin polymerization.Epothilones,duetoitsaction,causesmitotic(cellcycle)arrestintheG2/Mphase, resultingincelldeath.Someuniquemolecularinteractionsareresponsibleforthebindingof epothiloneswithβ-subunitoftubulin.ThebenzoylphenylresiduesoftypeAissituatedinaregion oftheβ-tubulinpocket.Also,someoftheoxygen-containingpolargroupsintypeAshowsspecific interactionswiththeβ-tubulin(unlikepaclitaxel).

Threeuniquemolecularinteractionsare responsible for the binding of typeAwiththepocket.(1)Thr274andArg282ofβtubulinformscooperativehydrogenbondwiththeC3,C5,andC7 oxygen of epothiloneAthatarerequired for binding.(2)Glu292ofβtubulinformsahydrogenbondwithLeu275,requiredforbalancingtheMloopandhydrogen bonding to epothiloneA.(3)Ala231 forms a hydrogen bond with His22 that anchorsepothiloneAwiththepocket.[12]

AlkylatingAgents

Alkylating operators are one of the most crude and primitive category of drugs for treating malignant growth, since 1940's. Cancerous cells are quite delicate to the affliction (harm) to DNA. The working criteria of the alkylating agents is in such a way that they bind or react to the protein whose role is to bond together to frame sensitive double helical structure of DNA particle, in this manner adding an alkyl gathering to a few or every one of the proteins. This restricts these proteins from showing linkage as needed and therefore causing breakage of the DNA strands and, in the long run, leading to the expiration or end of these cancerous cells. This response is basically a transformation that removes the capacity of the malignant growth cell to duplicate. [13]

Alkylation is the process in which transfer of an **alkyl group** takes place from one molecule to another.The alkyl assemblage is moved as an alkyl carbo-cation. In medication, alkylation of DNA is utilized in chemotherapy for DNA damage of malignant growth cells.

Alkylating operators are generally dynamic and most active in the resting period of the cell. These drugs are cell-cycle vague or cell **cycle non-specific**. The following are a few sorts of alkylating operators utilized in chemotherapy medicines: Mustard gas derivatives: **Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, and Ifosfamide.[14]**

There are various alkylating molecules, they function by the above mentioned mode of action. The alkylating molecules used for treatment of chemotherapy have this

particular effect on malignant growth cell during every time of its life cycle, despite the fact that their greatest effect is in the **S-stage**. Oncologists utilize these alkylating molecules for a vast scope of malignancies. As seen, greatest effect is on malignant growths that develop gradually, similar to strong tumors and leukemia, yet they are likewise used to treat lung malignancy, ovarian disease, bosom malignancy, lymphomas, sarcomas, myelomas, and Hodgkin's illness.

Another method by which these alkylating operators can cause DNA damage is by the arrangement of cross-bridges, i.e. bonds are shaped between the bases in the DNA molecule. In this procedure, two bases show linkage by an alkylating molecule which carries two DNA restricting positions. This **cross linkage** keeps the DNA from being isolated for synthesis or its conversion to mRNA. [15]

Mechanism of Action

Alkylating medications utilized for disease treatment are cell-cycle vague operators. They assault the DNA at any phase in the cell cycle. These medications function at subatomic level by linking to negatively charged positions of DNA. This process is known alkylation.

The aftereffect of the reaction is a DNA molecule having DNA particle having an appended chain of carbon group. This additional strand hampers the duplication and division of strands of hereditary issue. The DNA strands can break down, and the cross-connecting required for DNA replication can be restrained.

The component of activity or action of alkylating operators as chemotherapeutic medications have begun from their capability to irreversibly tie to DNA and, after thebinding is done, the modified particle disturbs the common movement is and replication of the DNA strand.The mechanism of action or activity of alkylating agents as chemotherapeutic drugs medications are originated from their capacity to irreversibly bind to DNA and, when bound, the altered molecule disrupts the typical activity is and replication of the DNA strand. [16]

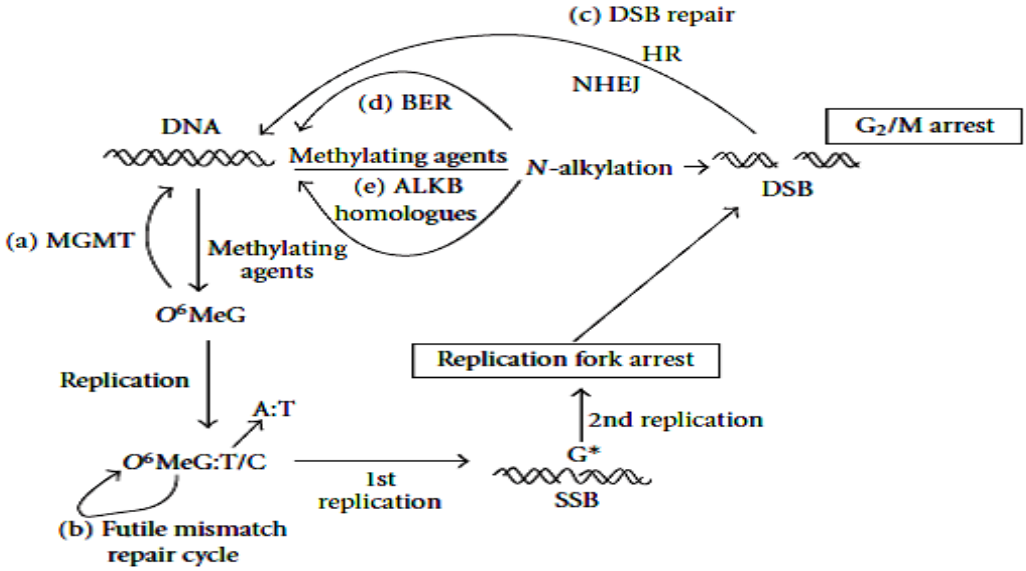
Guanine N7 portion is defenseless or is particularly powerless. These specialists(alkylating operators) advance the intra-and between DNA strand interfacing at guanine bases on the strand. Right when alkylation occurs at a couple of spots along the DNA molecule, the natural mechanisms of the cell are interfered. This prompts to either modified cell demise (apoptosis) or if nothing else a capture or catch in cell replication. In either case, when applied to malignant cells, alkylating operators can limit tumor advancement and cause tumor destruction.

Neoplasms can create opposition or assurance to alkylating operators. This opposition has been connected, at any rate to a limited extent, to the statement of a catalyst known as **MGMT (O6MethylguanineDNAmethyltransferase).**

MGMT is being able to fix the blunders in DNA due to alkylating operators. Taking the example of temozolomide which is a drug which that causes a potential cytotoxic sore in oxygen 6 of the nucleotides of guanine in DNA. [17]

In comparison to cancerous cells the normal cells holds this component of blunder fix is quite a benefactor. A cellular mechanism to avoid the disturbance of DNA in cells that are typical physiologically. Cancer or tumors are in like manner prepared to express this protein (and perhaps overexpress it) subsequently rendering certain

alkylating masters incapable.These operators that show inhibition in the activity of MGMT can or might be utilized as an adjunct to alkylating specialists aiming to conquer this obstruction and enhance the tumor-murdering impact.The broadly used



platinum drugs act as catalysts for the induction of cross-linking of DNA, despite the fact that they probably won't give an alkyl gathering. [18]

Alkylating operators can likewise cause **secondary malignancies**. The widely recognized one is **Acute Myeloid Leukemia** that can appear quite a while after treatment stops. At certain times during extreme conditions, organ damage occurs with the association of alkylating specialists. Aspiratory fibrosis and veno-occlusive sickness of the liver have been seen over a wide range of medications inside the class. The utilization of nitrosoureas has been related with renal disappointment.

Every so often extreme organ harm additionally happens with the organization of alkylating operators. Pneumonic fibrosis and veno-occlusive illness of the liver have been seen over a wide range of medications inside the class. The utilization of nitrosoureas has linkage with renal disappointment.The central nervous system is also influenced alkylating agents as well, as the affect can be seen. Notwithstanding extreme sickness and retching regular to the class, particular operators (for example Ifosfamide) are very neurotoxic, prompting intense disarray and insanity, seizures, loss of motion, and trance state. [19]

Alopecia (male pattern baldness) is known to occur with alkylating operators. Even sex organs are not saved—women that are treated with alkylating specialists may experience permanent amenorrhea (nonappearance of monthly cycle) and in men, sperm creation may stop. They should never be used on pregnant women since they lift the danger of birth surrenders. [20]

Figure:4 Alkylating agents[21]

Figure 1: Methylating agent signalling pathways affecting DNA damage.Methyl adduct is abstracted from *O*6MeG in step (a)by *O*6-methylguanine-DNA methyltransferase (MGMT).Mismatch pairs namely *O*6MeG: C or *O*6MeG: T can

form,if left unrepaired. A: Tmutation (transition state) occurs in the next round of replication of *O*6MeG: T pairs. In step (b),the mismatch repair(MMR) system recognizes *O*6MeG:T and *O*6MeG:C pairs, creating single strand breaks resulting in arrest in cell replication arrest further promoting double strand break. The cell cycle arrest is observed in G2-M phase in the second cell cycle instead if first cell cycle. In the step (c), the repair of double strand breaks is promoted by homologous recombination and non-homologous end joining. Base excision repair or alpha ketoglutarate dependent hydroxylase (AlkB) do the repairing of N-alkylation and if repair is not furnished, double strand break occurs.

Antimetabolites

These are the substances that are often analogous in structure to the natural metabolitethat they inhibit with. These resemble structurally with natural substrates, but differ intheir function and hence interfere with their metabolism**.**Usually, antimetabolites induce cell apoptosis during s phase of cell cycle when incorporated into RNA and DNA of cell .These substances have two distinctive characteristics.(i) Antimetabolites resemble in chemical structure with naturally occurring substances or metabolites that are essential for living processes.(ii) They inhibit the biological action of natural metabolites. [22]Anti-metabolites are used in cancertreatment as chemotherapy medication.As they can interfere with DNA synthesis, and inhibit the cell division, hence the growth of tumour is inhibited. As cancer cells divide more rapidly than normal cells, inhibiting cell division harms cancer cells more than the normal cells.so antimetabolites affect cancer cell division more than affecting normal cell division.These are used for treating variety of cancers, such as leukaemia, pancreatic, ovarian, gastro-intestinal and breast cancer. [23]

Antimetabolites mainly falls into two types.**Base analogues (alters nucleobases)** – these are the substances that can substitute for a natural nucleobase present in nucleic acids like DNA and RNA. This means that these substances are structurally analogue to the nucleobases of DNA. However, since they are slightly different in function from the normal bases, the DNA production is inhibited and effects the cell cycle and eventually the cell dies by apoptosis. P**urine analogues** – thesesubstances are structurally similar with the metabolic purines (adenine and guanine).Examples: Fludarabine, thiopurines, andAzathioprine. P**yrimidine analogues** – these substances arestructurally similar with the metabolic pyrimidines (thymine and cytosine).Examples: Cytarabine, Gemcitabine and 5-Fluorouracil. [24]

Antifolates are the chemicals that inhibits the functions of folic acid (vitamin B9). folic acid is a chemical which is essential for DNA and RNA synthesis.Example – Methotrexate .Cytarabine, an antimetabolite drug, interferes with dihydrofolate reductase, which is required for the synthesis of tetrahydrofolate and subsequently inhibits synthesis of the folic acid needed for DNA formation. [25]

Table 1: [26]

Antimetabolites	Mode of action

Anti-folates	Displacement of Dihydrofolate due to inhibition of dihydrofolatereductase stops the formation of purine nucleotides.
Pyrimidine antagonists	DNA replication stops due to incorporation of false pyrimidine analogs into DNA
Purine antagonists	DNA replication is arrested due to incorporation of false purine analogs.
Purine analogs	DNA strand breaks due to inhibition of DNA polymerase

Mechanism of action

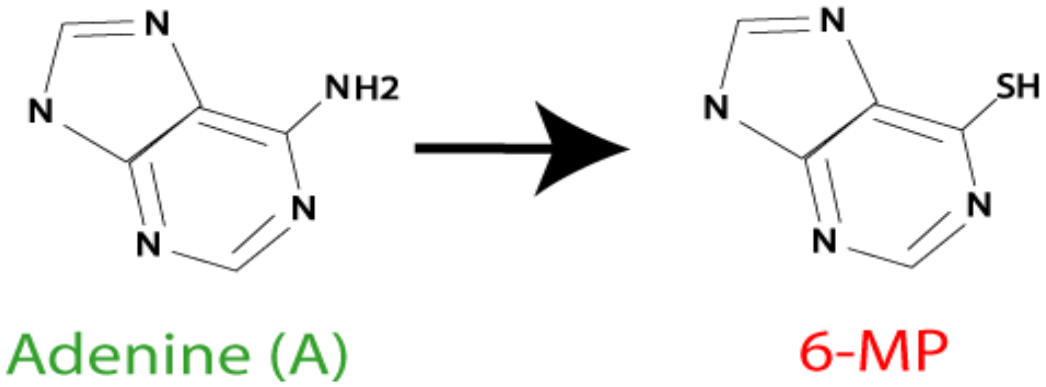
The mechanism of action of pyrimidine and purine antimetabolites is same. Thesesubstances enters into cells by different pathways via, a membrane transporter and mimics the structure of cellular nucleotides by the pyrimidine or purine metabolicpathway enzymes. These metabolites then inhibit enzymes that are necessary for DNA synthesis,damaging DNA replication, eventually causing cell death (apoptosis).

Purines (guanine and adenine) are the substances used for nucleotides synthesis. These are basic components of nucleotides, pre-mitotic division, it must replicate its DNA content, to as to give each daughter cell a complete set of genetic information. In the DNA duplication process, the nucleotides are assembled with each other and forms the new DNA strands. Sugar molecules along with Phosphate groups are joined together to the long strands of newly synthesised DNA of chromosomes. The growth of the DNA is inhibited by Incorporation the purine antagonist and hence prevents cell division. [27]

In two different ways the purine antagonists inhibit the DNA synthesis. (1)The production of nucleotides having purine bases adenine and guanine is inhibited by the purine antagonist. These substances mimic the structure of natural purines. Due to lack of sufficient amounts of purine bases, the DNA replication is halted and the cell cannot duplicate its DNA content. (2). during DNA synthesis Phase they may be incorporated in to cell. The presence of the antimetabolites can thus inhibit the cell division**.**Pancreatic cancer can be treated using purine antagonist which includes **6-mercaptopurine (6-MP).[28]**

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

MERCAPTOPURINE

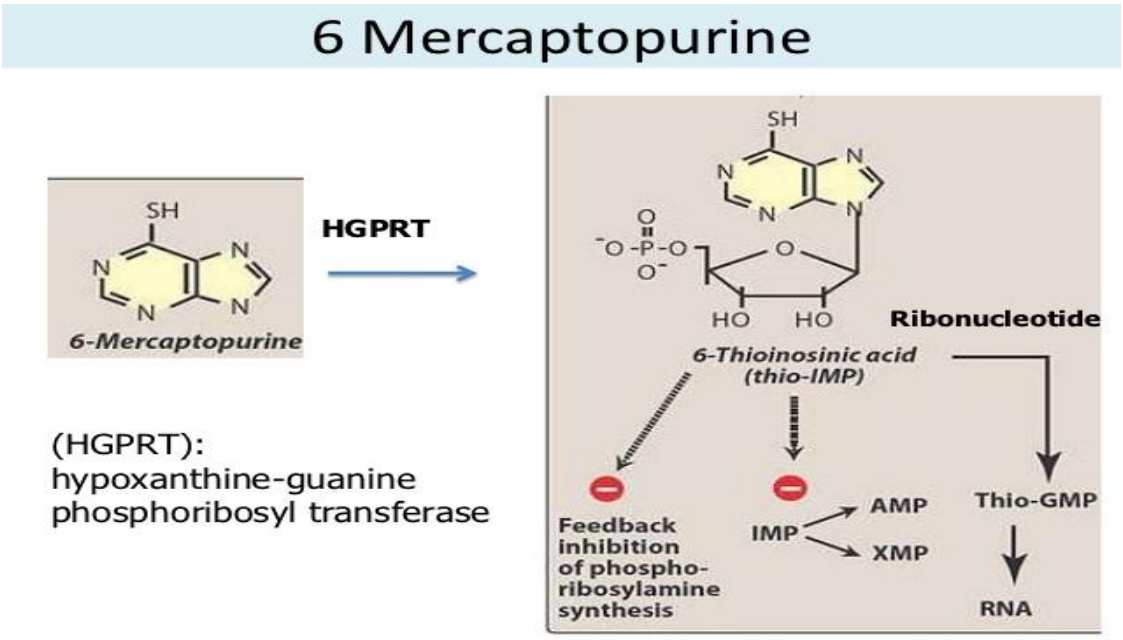


Mercaptopurine (6-MP) competes with the enzyme Hypoxanthine-guaninephosphoribosyl transferase, (this enzyme helps in catalyses conversion of hypoxanthine (a purine derivative) to inosine monophosphate and guanine (a purine) to guanosine monophosphate) and is transforms itself to thio inosine monophosphate (TIMP).

This new formed substance thus further inhibits several chemical reactions involving inosinemonophosphate (IMP), IMP is the first nucleotide formed during purine synthesis including the conversion of IMP to xanthylic acid(XMP) and the conversion of IMP to adenylic acid (AMP)is inhibited. Adenine and guanine are the building blocks for RNA and DNA.methylation of TIMP forms 6-thylthioinosinate (MTIMP)these two substances MTIMP and TIMP has been reported to inhibit glutamine-5-phosphoribosylpyrophosphate aminotransferase, the first precursor enzyme for the de novo pathway of purine ribonucleotide synthesis, by incorporation in to the nuclei acid.Mercaptopurine interacts with glycoprotein synthesis and nucleotide interconversion. This results in non-functional RNA and DNAradiolabelled mercaptopurine can be extracted from the DNA in the form of deoxy thioguanosine. [29]

Figure: Mechanism of action of 6 Mercaptopurinedrug [29]

ISSN: 0971-1260
Vol-22-Issue-17-September-2019



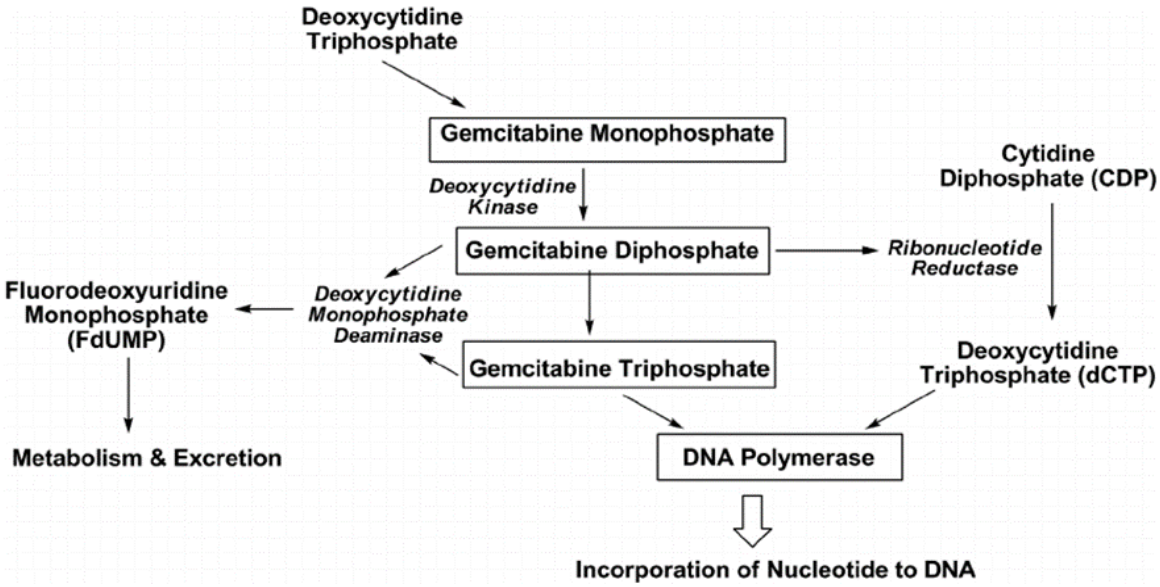
Pyrimidine Antagonists

Mechanism of action the pyrimidine antagonists is similar to purine antagonists. But acts on the pyrimidine containing nucleotides synthesis that is Cytosine and Thiamine in DNA; Cytosine and Uracil in the case of RNA to block their synthesis. These substances resemble the pyrimidine nucleotides. They can inhibit the production of the fully synthesised nucleotides. They effect the pathway in different steps or directly inhibit the enzymes involved. The pyrimidine antagonist can also be incorporated directly into a growing DNA chain and thus lead to DNA synthesis termination. For a cell to reproduce, replicate of the all DNA has to be done. During DNA synthesis, pyrimidine and purine molecules must be available for the synthesis of new nucleotide.The availability of pyrimidine decreased by pyrimidine antagonists, leads to DNA synthesis inhibition and stops cell division and eventually cell dies by apoptosis.Their action can be either accomplished by (a).Incorporation as false purine antagonist in DNA or RNA (b) Through effecting of proteins involved in nucleotide metabolism.Pyrimidine antagonists currently used to treat pancreatic cancer includes **5-fluorouracil, Capecitabine and Gemcitabine.[30]**

GEMCITABINE

Figure 4:Mechanism of action of gemcitabine [31]

ISSN: 0971-1260
Vol-22-Issue-17-September-2019



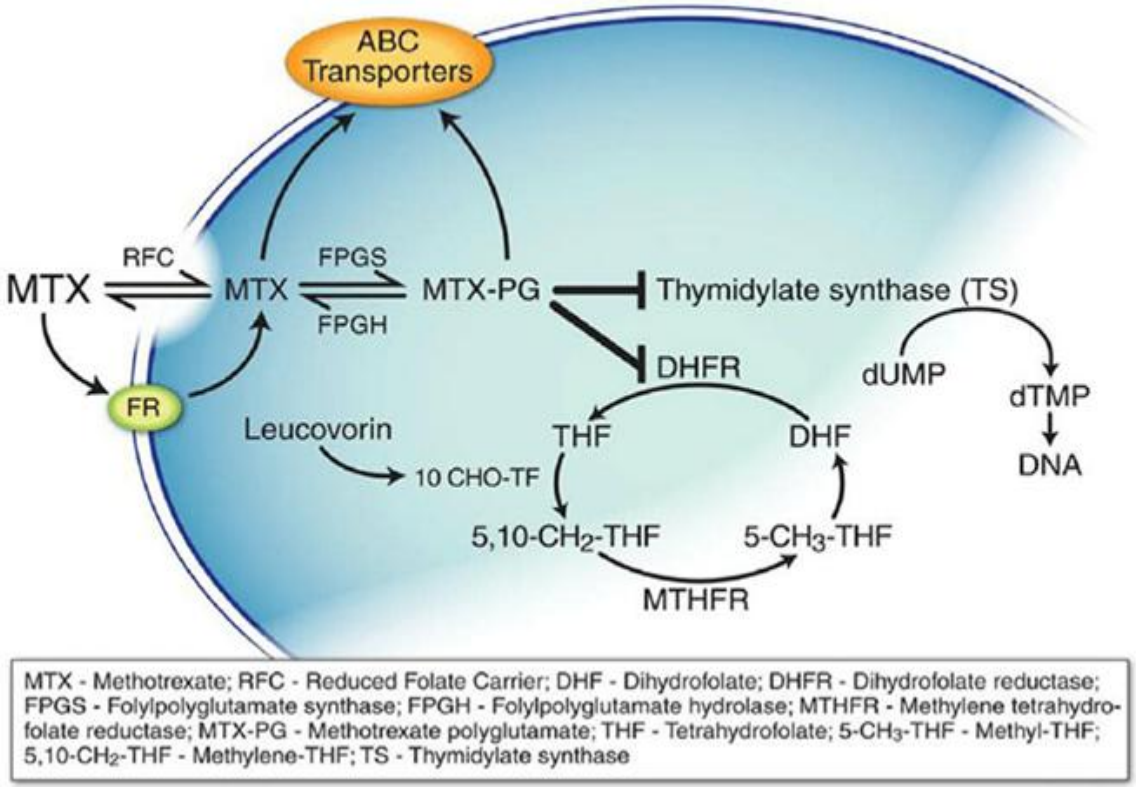
Folate Antagonists

Folate antagonists also identified as antifolates inhibits the function of folic acid that is required for the formation of nucleotide bases by inhibiting dihydrofolate reductase (DHFR) enzyme. When this enzyme is inhibited, nucleotide base formation is altered, and thus interrupts DNA replication process and eventually cell division stops and cell apoptosis occurs.Folate antagonists currently used to treat pancreatic cancer includes Methotrexate. [32]

METHOTREXATE used for treating pancreatic cancer, Methotrexate is the primary folate antagonist medication used as a chemotherapeutic agent.Methotrexate is aantifolate antimetabolite. It shows it effect on cancer cells by different pathways. Methotrexate alters the function of dihydrofolate reductase (DHFR) enzyme by competitive inhibition [an enzyme that participates in the tetrahydrofolate synthesis] by tightly binding, or though reversibly binding to DHFR and making it non-functional or inactive.Methotrexate enters the cell by different pathways through, reduced folate carriers, low pH folate transporter, or specific folate receptors.[33]

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Figure 5: Methotextrate anti-cancer mechanism of action [34]



Once, methotrexate enters the cell, it binds to DHFR. Because of this binding, the amount of DHFR available to the cell decreases, and due to this unavailability of DHFR the reduction of the tetrahydrofolate precursors stops, that is folic acid and dihydrofolic acid. Folic acid is essential for the de novo synthesis of the nucleoside thymidine, folate is essential for purine and pyrimidine base biosynthesis.so by inhibiting the function of folic acid stops the synthesis of DNA, RNA, thymidylates, and proteins. Without active folate, (tetrahydrofolate) the cell cannot produce new purine and thymidine nucleotides for DNA synthesis. Without DNA synthesis, cell growth or cell division does not occur. [34]

Immunotherapy

Pancreaticductaladenocarcinoma(PDAC)isoneofthelargestcausesofdeathbyacancerwith lowprognosislevel.Thepurposeofthisarticleistoreviewtheimmunotherapeuticapproachest otreat cancer. The environment of PDAC may be housingvarioustypesof cells that are helpful in maintainingtheimmunityofthebody.Maincelltypesaremyeloidderivedsuppressorcells,ma crophagesTcells andmastcells.Presenceofthesedifferenttypesofcellsinthepancreaticstromaisresultedin immuno tolerancetotumorcells.
Mastcellsarefilledbasophillsgranulesandreleasehistaminesubstancesduringallergicandinf lammatoryreactions.Thecountofthesemastcellsarefoundtobeincreasedduringthe

conditionsofthepancreaticadenocarcinoma.Theyalsohelpinremodellingoftissue, tumor growth(gilfillanandbeaven2011).PDACcellsgivesignalsthatmayincreasethesemastcellsin fluxintothemicroenvironmentofPDAC(strouchetal,2010).andthesemastcellsbyaMatric Metallo-
Proteinasedependentmanner(MMP)foundtoincreasetheinvasionofpancreaticcancer cells(strouchetal2010).Itisalsofoundthattheprecursorsofthesemastcellsareattracted towardsthepancreaticstromaandtheyexpressthestemcellfactorreceptorwhichleadstotheinf luxofmastcellstowardstumor.Themastcellsgetactivatedintumormicroenvironmentand secretesmanytypesofInterLeukins,VascularEndothelialGrowthFactorsandTumorNecrosi sFactorwhicharebelievedtoincreasetumorgrowth.SimultaneouslythemastcellssecreteTre gsandInterLeukin10whichmainlyfavorstheimmunosuppressioninthetumormicroenviron ment (Ribatti and Crivellto,2011. [35]

Myeloid Derived Suppressor Cells

MastcellspromotesMyeloidDerivedSuppressorcellrecruitmenttowardsthetumorsiteviath e productionof5-lipoxygenaseandIL-17(YangZ.,B.Zhang,D.Li,M.Lv,C.Huang,G.-X.Shen,
B.Huang.2010andCheonE.C.,K.Khazaie,M.W.Khan,M.J.Strouch,S.B.Krantz,J.Phillips, N.R.Blatner,L.M.Hix,M.Zhang,K.L.Dennis,etal.2011).TheMyeloidderivedSuppressor cellsareimmaturemyeloidcellsthatarecapableofincreasingthetumorinvasionbyenhancing angiogenesisofvascularsystem.Thesesuppressorcellsarealsocapableofsuppressingthe immunesystem(ostrandrosenbeergandsongs,2009,ochandoandchen,2012).TheseMyeloi dDerivedSuppressorcellsinhibitactivationofTcellsbyproducingreactiveoxygenspecies (kusmartsevetal2004)andTcellregulation.TheseMyeloidDerivedSuppressorcellsreduceth e
cytotoxicactivityofNKcellsandpromotetheproliferationofTregs(regulationTcells)(ostran dRosenbergetal2012).TheseMyeloidDerivedSuppressorcellsarefoundtoalterthesurfaceof MHCclass1expressedonthetumorcellswhichpreventsbindingofpeptidethatisprocessed which may if binds activatectlCD8+pathway (loetal2011). [36]
ThisCD8+andCD4+tcellsplaymajorroleinhelpingtheligationofCD40ligationwithits ligand.This
CD40regulatestheimmunitybothcellularandhumoralbyactivatingthantigenpresentingcell s(lanzavecchiaetal1998).TheligationofCD40ligandwithCD40leadstoregulationof costimulatoryandmhcmolecules.Thisleadstoreleaseofcytokininsthatactivatetcells.Recent lyagonistCD40antibodiesarefoundtoprovidethesameeffectwhichotherwiseprovidedbylig ation
ofCD40Ligand(jleukocbiol.2000,Quezada,2004.).CD40mAbimmunotherapyisfollowed by
increaseindepressionofCD86andclass2MHCmoleculesontumorassociatedmacrophagesi n tumor bearing
mice.Macrophagecanbedifferentiatedinto2types:M1likemacrophagesthatpromotetumorc elldeathandM2likemacrophageswhichfavourtumourprogression(ostrand-Rosenbergetal2012;ruffles). [37]

Conclusion:

For the past four decades, the scientific world has witnessed major developments in developing a reproducible understanding in cancer bio-therapeutics. In recent times, many anti-cancer drugs became very popular, as they displayed long term survival of patients post therapy. Tamoxifen is one of such anti-cancer drug, against breast cancer, which is very popular due to the above mentioned reason.Imatinib, a biological anticancer drug, is very successful against myeloid leukaemia.The cumulative success rate of in anti-cancer new chemical entities or biosimilar drugs is tentatively at around 10 percent and covering the business totalling one billion dollars globally.

The advent of System Biology which uses prediction analysis and simulations through mathematical modelling is gaining pace in recent times for screening of target based anti-cancer drug therapy. Quantitative Structure Activity Relationships (QSAR) is one of such technology which is increasingly adopted in recent times to predict the outcome of drug formulation and scale-up.[38]

For an anti-cancer drug to be effective on the human host system few important criteria's need to be considered. This include the clear understanding of pathophysiology of cellular target affected with carcinoma, enhanced expression of target site inducing malignancy, intracellular or intracellular interactions in malignant tissues, the understanding of picking or developing correct animal models for preclinical screening of anti-cancer drugs and looking for target specific biomarker, which can provide a close clue for understanding the pathogenesis and developing a personalized anti-cancer therapy. [39]

References:

1. Meegan, M. J., & O'Boyle, N. M. (2019). Special Issue "Anticancer Drugs".
2. Impact, N. D. T. A. (2018). Available online: https://www. fda. gov/files/drugs/published. *New-Drug-Therapy-Approvals-2018_3. pdf (accessed on 11 September 2019)*.
3. Makharza, S. A., Cirillo, G., Vittorio, O., Valli, E., Farfalla, A., Curcio, M., ...&Hampel, S. (2019). Magnetic Graphene Oxide Nanocarrier for Targeted Delivery of Cisplatin: A Perspective for Glioblastoma Treatment. *Pharmaceuticals*, *12*(2), 76.
4. Gurova, K. (2009). New hopes from old drugs: revisiting DNA-binding small molecules as anticancer agents. *Future oncology*, *5*(10), 1685-1704.
5. Perez EA (2009). Microtubule inhibitors: Differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. Mol Cancer Ther 8: 2086–2095.
6. Nogales, E. (2001). Structural insights into microtubule function. *Annual review of biophysics and biomolecular structure*, *30*(1), 397-420.
7. Desai, A., &Mitchison, T. J. (1997). Microtubule polymerization dynamics. *Annual review of cell and developmental biology*, *13*(1), 83-117.

8. Jordan, M. A. (2002). Mechanism of action of antitumor drugs that interact with microtubules and tubulin. *Current Medicinal Chemistry-Anti-Cancer Agents*, *2*(1), 1-17.
9. Lobert, S., Vulevic, B., &Correia, J. J. (1996). Interaction of vinca alkaloids with tubulin: a comparison of vinblastine, vincristine, and vinorelbine. *Biochemistry*, *35*(21), 6806-6814.
10. Mukhtar, E., Adhami, V. M., & Mukhtar, H. (2014). Targeting microtubules by natural agents for cancer therapy. *Molecular cancer therapeutics*, *13*(2), 275-284.
11. Perez, E. A. (2009). Microtubule inhibitors: Differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. *Molecular cancer therapeutics*, *8*(8), 2086-2095.
12. Nicolaou, K. C., Roschangar, F., &Vourloumis, D. (1998). Chemical biology of epothilones. *AngewandteChemie International Edition*, *37*(15), 2014-2045.
13. Saffhill, R., Margison, G. P., & O'Connor, P. J. (1985). Mechanisms of carcinogenesis induced by alkylating agents. *BiochimicaetBiophysicaActa (BBA)-Reviews on Cancer*, *823*(2), 111-145.
14. Warwick, G. P. (1963). The mechanism of action of alkylating agents.
15. Siddik, Z. H. (2002). Mechanisms of action of cancer chemotherapeutic agents: DNA-interactive alkylating agents and antitumour platinum-based drugs. *The cancer handbook*, *1*.
16. Walpole, A. L. (1958). Carcinogenic action of alkylating agents. *Annals of the New York Academy of Sciences*, *68*(3), 750-761.
17. Esteller, M., & Herman, J. G. (2004). Generating mutations but providing chemosensitivity: the role of O 6-methylguanine DNA methyltransferase in human cancer. *Oncogene*, *23*(1), 1.
18. Lawley, P. D., & Brookes, P. (1963). The action of alkylating agents on deoxyribonucleic acid in relation to biological effects of the alkylating agents. *Experimental cell research*, *9*, 512-520.
19. Reimer, R. R., Hoover, R., Fraumeni Jr, J. F., & Young, R. C. (1977). Acute leukemia after alkylating-agent therapy of ovarian cancer. *New England Journal of Medicine*, *297*(4), 177-181.
20. Simister, J. M. (1966). Alopecia and cytotoxic drugs. *British medical journal*, *2*(5522), 1138
21. Healy, A. R., &Herzon, S. B. (2017). Molecular basis of gut microbiome-associated colorectal cancer: a synthetic perspective. *Journal of the American Chemical Society*, *139*(42), 14817-14824.
22. Peters, G. J., Van der Wilt, C. L., Van Moorsel, C. J. A., Kroep, J. R., Bergman, A. M., &Ackland, S. P. (2000). Basis for effective combination cancer chemotherapy with antimetabolites. *Pharmacology & therapeutics*, *87*(2-3), 227-253.
23. Woolley, D. W. (1952). A study of antimetabolites. *A study of antimetabolites.*
24. Fowden, L., Lewis, D., &Tristram, H. (1967). Toxic amino acids: their action as antimetabolites. *Adv. Enzymol.*, *29*, 89-163.
25. McGuire, J. J. (2003). Anticancer antifolates: current status and future directions. *Current pharmaceutical design*, *9*(31), 2593-2613.
26. Kompis, I. M., Islam, K., & Then, R. L. (2005). DNA and RNA synthesis: antifolates. *Chemical reviews*, *105*(2), 593-620.
27. Fleisher, M. (1993). Antifolateanalogs: mechanism of action, analytical methodology, and clinical efficacy. *Therapeutic drug monitoring*, *15*(6), 521-526.

28. Bertino, J. R. (2009). Cancer research: from folate antagonism to molecular targets. *Best Practice & Research Clinical Haematology*, *22*(4), 577-582.
29. Lennard, L. (1992). The clinical pharmacology of 6-mercaptopurine. *European journal of clinical pharmacology*, *43*(4), 329-339.
30. Maley, F. (1977). Pyrimidine antagonists. In *Chemotherapy* (pp. 327-361). Springer, Boston, MA.
31. Plunkett, W., Huang, P., & Gandhi, V. (1995). Preclinical characteristics of gemcitabine. *Anti-cancer drugs*, *6*, 7-13.
32. Bertino, J. R. (1963). The mechanism of action of the folate antagonists in man.
33. Bischoff, K. B., Dedrick, R. L., Zaharko, D. S., &Longstreth, J. A. (1971). Methotrexate pharmacokinetics. *Journal of pharmaceutical sciences*, *60*(8), 1128-1133.
34. Jolivet, J., Cowan, K. H., Curt, G. A., Clendeninn, N. J., &Chabner, B. A. (1983). The pharmacology and clinical use of methotrexate. *New England Journal of Medicine*, *309*(18), 1094-1104.
35. Steele, C. W., Karim, S. A., Leach, J. D., Bailey, P., Upstill-Goddard, R., Rishi, L., ... &Eberlein, C. (2016). CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. *Cancer cell*, *29*(6), 832-845.
36. Ostrand-Rosenberg, S., & Sinha, P. (2009). Myeloid-derived suppressor cells: linking inflammation and cancer. *The Journal of Immunology*, *182*(8), 4499-4506.
37. Nagaraj, S., &Gabrilovich, D. I. (2010). Myeloid-derived suppressor cells in human cancer. *The Cancer Journal*, *16*(4), 348-353.
38. Taşkın-Tok, T., & Gowder, S. (2014). Anticancer drug—friend or foe. In *Pharmacology and Therapeutics*. IntechOpen.
39. Meegan, M. J., & O'Boyle, N. M. (2019). Special Issue "Anticancer Drugs".

