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DELIVERY OF REPURPOSED DRUGS FOR CANCER: OPPORTUNITIES AND CHALLENGES

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ABSTRACT

Cancer can be seen as a global burden on the healthcare system as a large number of cases of newly infected as well as mortality rate have been on the rise i.e., 18.1 million cases of new patient's affected from cancer and 9.6 million of peoples died because of this life-threatening disease. Common types of cancers occurring in humans are breast cancer, lung cancer, and colorectal cancer mostly seen in females. There are high chances of death in these cancer patients due to the development of resistance very rapidly against cancer chemotherapies provided cancer heterogeneity as well as chances of metastases. The patients that are suffering from this disease might have chances of developing other morbidities also that can contribute to the severity of the disease. The review majorly focuses on different types of cancer, characterization of biomarkers to determine the severity of the disease, and its therapeutic responses are focused in this review paper. Majorly focusing on repurposing previously existing drugs for their new uses that help raise the treatment spectrum that will be challenging as well as taken as an opportunity for developing the old drugs for their new uses that will ultimately save the cost of research and time to develop a new drug. The severity of the disease and various adverse effects associated with it emerges from the need of repurposing the previously existing drugs for the treatment purpose of this deadly disease to improve the quality of a patient's life. Concluding the work with clinical complications associated with the disease, its etiology, pathophysiology & significance of the treatment that together will provide an effective outcome.

KEYWORDS: Cancer, repurposed drugs, etiology, pathophysiology, drug deliver.

INTRODUCTION

Cancer can be seen as a global burden on healthcare system as large number of cases of newly infected as well as mortality rate have been on the rise i.e., 18.1 million cases of new patient's affected from cancer and 9.6 million of peoples died because of this life threatening disease. This data is reported by International Agency for Research on Cancer (IARC).[1] Common types of cancers occurring in humans are breast cancer, lung cancer and colorectal cancer mostly seen in females. There are high chances of death in these cancer patients due to development of resistance very rapidly against cancer chemotherapies provided cancer heterogenecity as well as chances of metastases. Metastatic tumor/surgically unrespectable cancers have shown mortality rate upto 90% in 5 years in chronic tumors like that of cytogenetically defined high risk acute myeloid leukaemia (AML) & pancreatic cancer till date; therapeutic failure is not the main cause of development of aggressive tumors rather may be due to the crisis of production rate of drugs used for the treatment purpose that took place in the research and development areas of various pharmaceuticals companies[2] and they prepare to the clinic.

In fact, although investment in the last decade.[3] The lack in production of drug and being approved is become more challenging for therapeutic innovates the discovery and development process of therapeutic innovation (new drug) becomes long and expensive with low overall probability of skill. The 70% of project failed in phase-1, phase-2 & phase-3 due to inappropriate response shown by drug molecules under these phases of clinical trials and may be due to various chemical, physical properties of drug that are being examined.[4,5] The failure of drug to deliver its desired response may also be due to inappropriate results due to drugs are not effective as they intended to be on the targeted area to produce a better response and might be the reason for drug withdrawl from the market that are showing very less or very high response than what needed by patients.[6] The possible positive effect is too short to detect the treatment duration and there will be no predictive target pathway related biomarker. This brings the need of new drugs to the research pipeline that are much more

effective against cancer should be developed and bought to market and hence resolving important issues related to the disease.

Cost for developing of new drug is also a major issue in the process of R&D and hence lowering the investment in this area of research and development and this raised the cost of approved novel cancer therapeutics used in the prevention and treatment of patients.[7,8] Recently there is high necessity for an automotive move that will be definitely helpful in reduction cost of these vital lifesaving novel drugs that shows desired therapeutic action against the cancer and these effective therapeutics will shortly will be availed by everyone. These days there are some drugs that are examined for their anti-cancer efficacy as these are already approved by FDA and have been evaluated on all parameters and this also saves lots of time and money; the process is called as drug repurposing or drug repositioning.

The main benefit of this process is cost and time effective over the other clinical trial processes. It minimizes the cost and risk which are involved with drug it also reduces the time interval between discovery of the drug & functionality to patients because of compensability of high amount of patient related data during clinical trial process.[9,10] In the content of oncology its useful mention two additional loss late advantage of drug repurposing in fact when we perform oncology experimentally these offers an uninterrupted new targets validation & sometime drugs reduces the effectiveness of drug discovery process due to drug repurposing the approved drug that strengthens the combinational treatment potential of drug effectiveness which has there already in anti-cancer drugs.[11,12]

In particular, the biomedical community finds stored methods and systems in various regions of the disease, which at first glance no obvious similarities. New uses of old drugs often emerge such an analysis. For example, wound healing / injury. The answer is that it is one immunosuppressive usually when played in a cancerous environment both of the basics - e.g. the tumor overrides its blood supply and its components die - and it undergoes treatment. Drugs that contribute to this well-expressed response such as non-inflammatory drugs, adrenergic blockers, and others may affect the processes and effects of cancer. What are the benefits of repeating the drug over and over the cost? These drugs can be tested quickly, with success rates they are often higher than new growing drugs, probably because their safety record is well known. Indeed, most of the drugs manage an excellent safety profile compared to most drugs in oncologist toolbox. One warning is that these drugs - for cancer use-can be used in different doses or schedules than they are designed for early diagnosis and combined with cancer drugs as well therefore an unexpected poison may arise.[13,14]

Pathophysiology of Cancer

There are various levels & mechanism at which genetic changes takes place. In case there might be an error in the mitosis process, that results in loss/gain of entire chromosome. For example, mutations that can be simply defined as changes in genomic DNA nucleotide sequencing. A small portion of chromosome may either be gained or deleted in the process of large-scale mutations process. When a cell has numerous copies of tiny chromosomal locus resulting in amplification of genome that consist of either single or multiple oncogenes & its surrounding genetic material. There is various mutation process occur in the promoter region like insertion, deletion, point mutations resulting in affecting gene expression, alteration in its functionality, stability of protein products or changes in gene encoding sequence.[15,16]

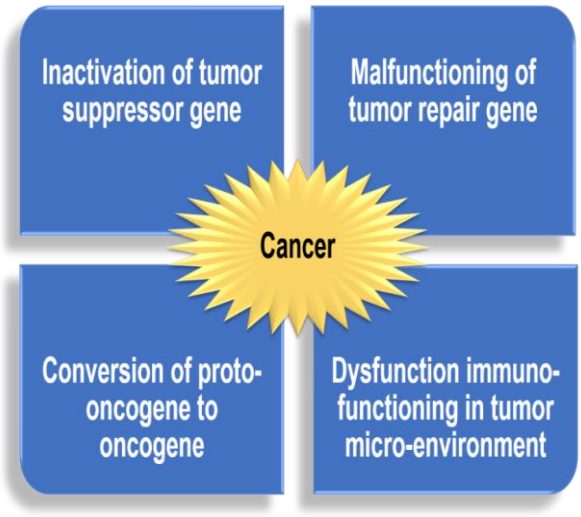

Figure 1: Etiology of Cancer.

Significance of cancer therapy

Since last decade cancer is successful in developing its identity as an organ whose complex approaches were difficult to detect as they have their genetic makeup completely different from that of healthy cells. The biology of cancer cells can only be identified when they are inspected on the individual basis. This also helps to know about the microenvironment that is building around the tumor cells. The mechanism of cancer cells can only be understood by isolating a specific group of homogenous cells and considering property of individual cells in that group. There is a group of cells that contributes to the biology of tumor microenvironment and the signaling system that helps to control the function of individual cells as well as that of the group of cancerous cells. In a deep observation, it is found that there is a compartment formation by neoplastic epithelial cells which is clearly differentiated from mesenchymal cells that are responsible for generation of stroma associated with cancer.[17,18]

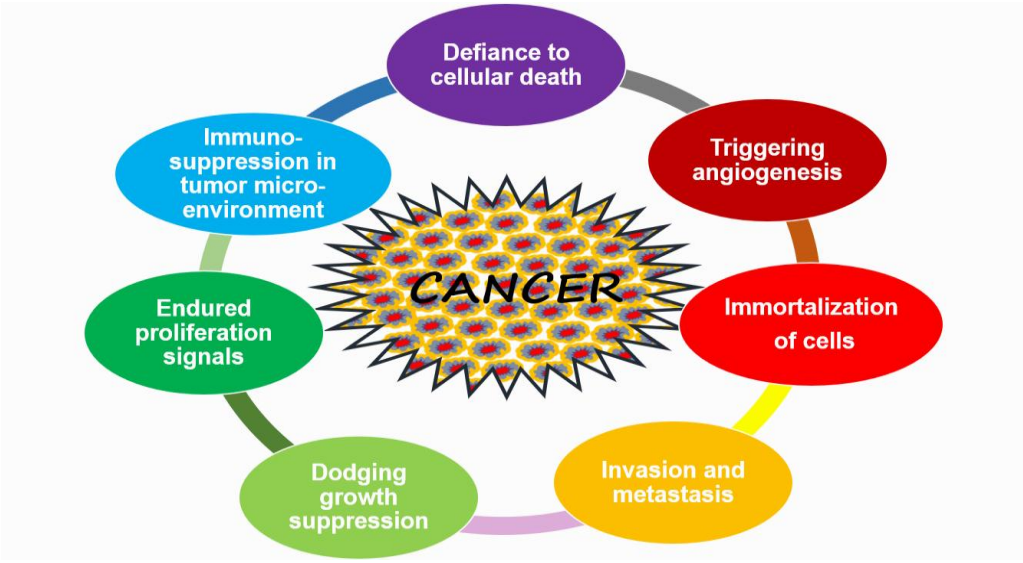

Figure 2: Hallmarks of cancer.

Cancer cells and cancer stem cells: The foundation or strength of this disease is the type of cells it produces that remains unidentified due to constant change in their genetic makeup and surviving for contributing in severity of disease. From traditional times the hologenetic cell population is one of the reason for progression of cancer. This process starts when an increase is seen in unstable spawn clonal population that is combined with hyperproliferation of cells.

This shows clonal heterogenicity in cancer cells. In some tumors it is found that histopathology of human cancer is very vast and diverse, differentiated by degree of growth, vascularity, proliferation property, invasiveness and production of severe inflammation at the site of attack. In a current research, it is also found that cancer cells have a property of intra-tumor heterogenicity i.e., formation of sub-group of cancer cells that shows more complexity in revelation of their genetic makeup and this property gives birth to a sub-class of cancer cells that are known as cancer stem cells (CSCs). Hence, the research is still going, it is not yet confirmed that these cancer sub-cells are sub-part of all cancer cells, but it is assured that it is found as a part of most of the tumor cells. In a study it is found that these cancer stem cells can be easily identifies by their property of giving rise to new stem cells when they are inoculated in the host mice model in the laboratories.[19,20]

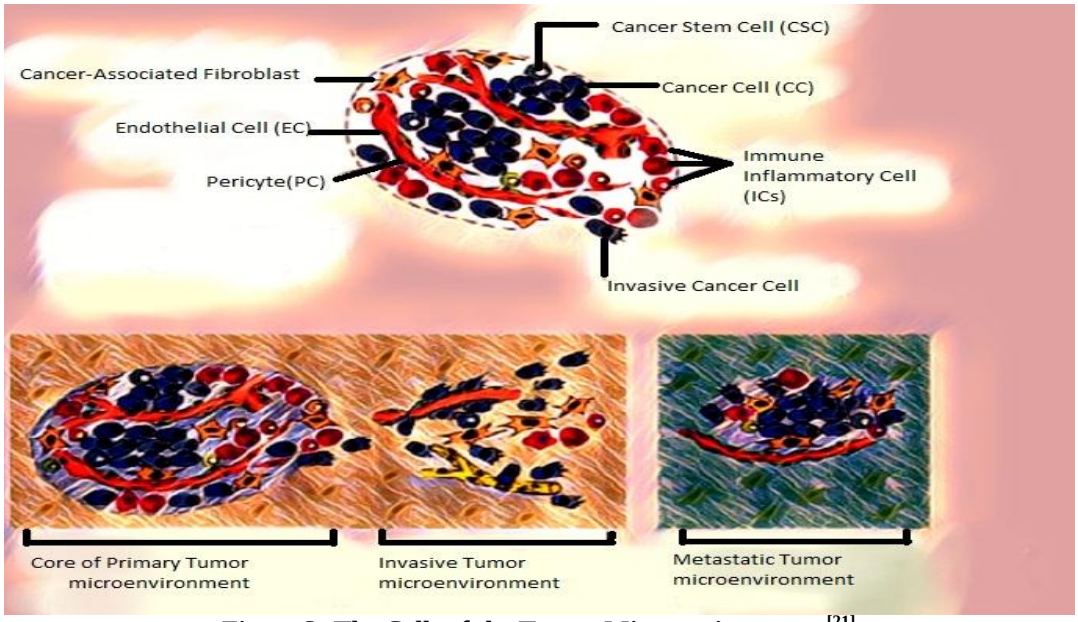

Figure 3: The Cells of the Tumor Microenvironment.[21]

Immune inflammatory cells: These sub-class of cancer cells are rarely seen with identical profile that justify their designation of cancer stem cells that vary in their genetic material hence much more difficult to identify and target easily. The variability of cancer stem cells is not yet very cleared with solid tumors because of their

property of changing genetic makeup from one cell to another cancer cell. There are some cancer cells that are not well differentiated transit amplifying cells and those cells are termed as progenitor cells. These cells are not fully differentiated because these possess more likely to that of stem cells and have undergone only initial phase of oncogenic transformation.

For cancer stem cells to produce their differentiated derivatives as spawn, firstly there is need of formation of primary tumors. The neoplastic cancer stem cells also form a bulk of these differentiate cancer cells. During constant increase of distinct classes of neoplastic stem cells, it remains stable when there is inception and multiple progression subsequently in case of tumors. And, produce the cancer stem cells that are found in fully developed tumors that are main threat to patient's life and very rarely have effect of any treatment therapy on them.[22,23]

Hence, it is received as an outcome of one of the finding of researchers that these cancer stems are self-renewal in nature and have association with antigenic phenotypes with that of normal as well as cancer stem cells.[24,25]

Stem and progenitor cells of tumor stroma: The self-renewal property of cancer stem cells helps cancer cells to physically differentiate from primary cancer cells and this property is very crucial during the subsequent formation of cloned expansion at dissemination site. For creation and maintenance of the cancer stem cells, it is important that there should be release of heterotype signals basically triggered by activated inflamed stroma. It is reported during a study that at the time of xenotransplantation in mice that there is increase in the population of human tumors that have sub population as the property of cancer stem cells. This can only be explained by their tumor generation capabilities.[26,27]

Metastasis of cancer: A graphic depiction relating networking of microenvironment signal interactions is still having to be accomplished because of large amount of signaling molecules having remarkable complexity that is critically important to the pathogenesis of cancer.

In the figure depicted below, showing hints for such interactions. These fully established examples justify the exemplification of these signaling network of remarkable complexity that are critically important in the pathogenesis of tumor.[28]

There is progressive change of neoplastic and stromal cells that are present around the stromal cells during a multistep transformation process of normal cells to melanomas of higher grade. This progression of histopathological changes that must be reflecting the heterotypic signaling between stroma and parenchyma cancer cells.[29] As depicted in the figure, the depending of stepwise progression might be on back-forth reciprocal interaction between supportive stromal cells and neoplastic cells. This particular model of reciprocal heterotypic signaling might be lengthened for encompassing the final stage of multistep cancer progression i.e., metastasis.[30]

This logic is not applicable at all places and is only implemable in few cases of metastasis and in others as described earlier due to various reasons different tissue microenvironments already supports fresh seeding tumor cells and these are sites permissible that are termed as "metastatic niches". It is clear from above mentioned findings that signaling interactions between supporting stromal cells and tumor cells comes into existence during the multiple tumor stage development process that complicates the goals of elucidating the cancer pathogenesis mechanism.[31,32]

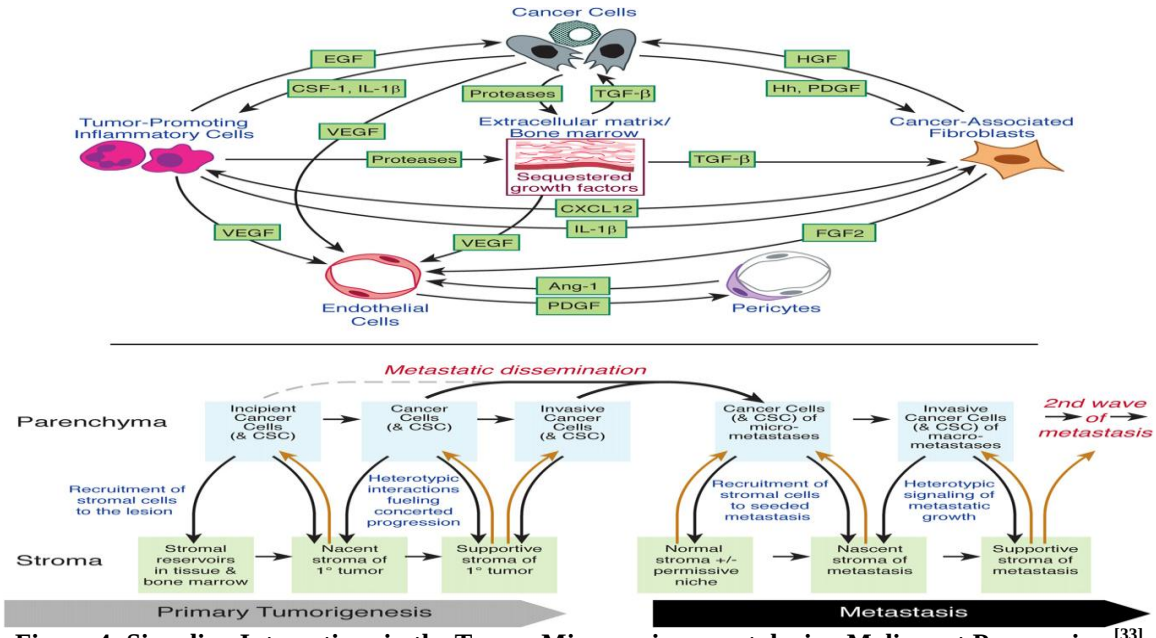

Figure 4: Signaling Interactions in the Tumor Microenvironment during Malignant Progression.[33]

Therapeutic targeting: Targeted therapies for the treatment of tumor has proven fruitful in the past three decades. These are solely mechanism-based therapies for targeting human cancer and has shown effectiveness in possessing therapeutic efficacy against human cancer. The therapies that are not fully developed or are under clinical trial phase are not considered for the treatment purpose. The fast-growing medical techniques and advances in medication system is very reliable for focusing targets according to their capability against different hallmarks and it is explained better in the figure below. According to a certain observation, it is observed that in each case, there is validation of particular activity to know whether it is effective against biology of cancer cells or not, if so then it should impair cancer growth and progression on its inhibition.[34,35]

Specific molecular targets are engaged in a way or other way to enable specific capabilities that are directed towards specified molecular targets. Growing experimental proofs from interpretation of history states that the capabilities of hallmarks are partially regulated by signaling pathways.[36] Consequently, when there is inhibition of main pathway of tumor by targeted therapeutics, it is not mandatory that it completely wave off the capability of hallmark and resulting in survival of few tumor cells to survive till they are not burden under pressure enforced by cancer therapy. Renewed cancer growth, clinical relapse and functional capabilities can be achieved by mutation, remodeling microenvironment of stromal cells and epigenetic reprogramming.[37,38]

There should be limited number of signaling pathway that are parallel supporting a hallmark. To avoid development of adaptive resistance, all possible targets that helps in restricting the adaptive resistance development. As a result of cancer therapy, the tumor cells minimize their dependency of specific hallmarks of cancer and focuses on other. This also shows slightly different form of resistance of acquired drugs. It is predictively seen that inhibition of angiogenesis effectively can portray the normal function of tumor cells and may help in the dissolution of tumors.[39,40] In the coming future to have a significant advancement in a better understanding of the metastasis and invasion process. And also, the aerobic glycolysis role in the malignant growth of tumors can be described more accurately in the near future.[41,42]

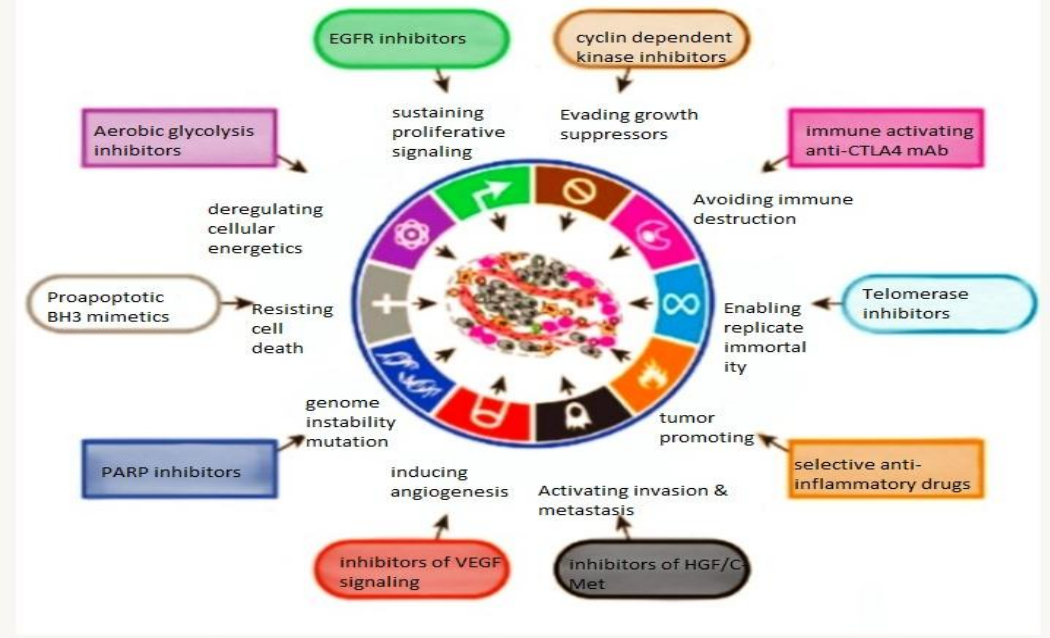

Figure 5: Therapeutic targeting of the hallmarks of cancer.[43,44]

Repurposing drugs as cancer therapeutics: The conventional process for designing and developing of a new drug molecule is so tedious and expensive too and needs plenty of time. The drug discovery process of a new drug approximately requires 12-15 years and cost of development is so high around 800 million dollars. Paul et al., conducted a survey based on industry output that average development duration is around 14 years and it cost upto 1.8-2 billion dollar to be in the market for sales and consumer use. For reducing the time as well as cost of drug discovery and development, there are two process like drug repurposing & drug repositioning that are based on finding new uses of the drug that has been well established in the market already that minimizes the need of performing stability and toxicity studies again that relatively supports rapid bench-to-bedside transition.[45,46]

1. **Metformin-** P. Nowak-sliwinska et.al., 2019 metformin, the recent cohort studies with over "forty-seven thousand participants designed to degree those biases revealed that long- term use of metformin appeared to be associated with the reduced risk of colorectal cancer." To administrated

metformin in the population significantly suppressed the no. of intestinal polyps formed in the both models, not only urine, but also in rats.[47]

2. **Celecoxib and rofexcoxib-** P. Nowak-sliwinska et., al; 2019 celecoxib and rofexcoxib celecoxib and rofexcoxib. The use of cox-2 inhibitors celecoxib for "CRC prevention was reported in several clinical trials. A group of 77 patients with familial adenomatous polyposis (FAP) treated with celecoxib (400 mg\daily twice for 6 month)" led to significant reduction in the no. of colorectal polyps.[48-49]
3. **Mesalamine-**P. Nowak sliwinska et. al., 2019 reported that there is reduction in the growth and survival of CRC cells various signaling; pathways moreover; Fina et.al reported that mesalamine enhanced. CRC cells anoikic, a form of programed cell death triggered by the loss of anchorage to the, extracellular matrix.[50]
4. **Epirubicin- P**. Nowak sliwinska et; al 2019: plosker et;al, showed "that a fraction of MCRC patients resistance to "oxaliplatin exhibited DNA TOPOISOMERASE 2-αgene amplificant". Epirubicin a 4epimer of the anthracycline antibiotic doxorubicin, actually targets TOP2α and thus interferes with the synthesis of DNA through intercalation being most active in s-phase of the cell cycle.[51]
5. **Acetaminophen-**web et, al; 2019 acetaminophen there was no association between regular use of acetaminophen and endometrial cancer risk in serval studies with the available information. Stratification by BMI suggested an inverse association among overweight women but no association can be seen with women having normal weight.[52]
6. **Quinacrine-**D.B. OIEN et al., 2019 recently reported that this drug might inhibit the cancer cell growth by various mechanisms involving autophagy regulation, facilitates chromatin transcription, i.e., chromatin trapping & repairing of the DNA process. Additionally, it has been reported that quinacrine is found effective against chemo resistant gynecologic cancer.[53]
7. **Succinimide-** A.D A Qahtani, et.al.'2019: succinimide a succinimide- activated PEG derivative has been used to PEGylate the amino groups of lysine residues' of xanthine Soxide, which mediates anticancer activity because of its ability to generate cytotoxic reactive oxygen species. The resulting construct polyethylene glycols fab had slightly decreased tumor cell toxicity invitro when compared to be free s- fab but increased half- life-12 fold – resulting in effective inhibition of tumor growth in vivo.[54]
8. **Levofloxacin-**Yu et2019; suggested that this class of drug exerts antiproliferative & apoptotic affect in breast cancer cells through inhibiting the biogenesis induced by mitochondrial and thus deactivating the p13/akt/MTOR & MAPR/ERK pathways, that was confirmed by Song et. al., have reported that levofloxacin also exerts antiproliferative activity & apoptotic effect in lung cancer cells via upregulation of free reactive oxygen species (ROS), hydrogen, mitochondrial superoxide & oxidative stress makers (HEL AND 4-HNE).[55]
9. **Methyltransferase-**Niu et. al., 2018 reported that "methyltransferase: the function of m'a modification methyltransferase in human cancer". METTL3 was the major RNA N°-adenosine methyltransferase, that was reported to be associated mainly with the development & genesis of tumor. Chen. et.al., reported that METTL3 war significantly upregulated in knocking down the solid human hepatocellular tumors that would drastically reduce the migration of HCC proliferation, *invitro* formation of cancer cell colony formation & HCC progression is suppressed.[56]
10. **5-Flurouracil-** P. Chandranet: al. 2017 development of "chitosan loaded 5-flurorouracil" nanoparticles, to minimize the toxicity of these powerful pharmaceutical on healthy- cells and concluded that the formulated chitosan nanoparticles improved localization of drug at colon region, which was followed by a sustained release mechanism over a period of 24 hrs. this can also be leaded to a greater vol. of drug is localized in the colorectal cancer.[57]
11. **Doxorubicin-** Chen et.al 2015; he reported a unique architecture, cation polymeric Nano capsule, which had well- defined covalently stabilized biodegradable structures can function as a potentially universal and safe therapeutic nanocarrier for co- delivery of doxorubicin and siRNA targeting interleukin-8.[58]
12. **Paclitaxel-** tarantula et al.2014 reported "the co-delivery of siRNA targeting BCL-2/ MRP-1 and Dox/paclitaxel (TAX) using LHRH (luteining hormone-releasing hormone) conjugated nanostructured lipid carries (NLCS) for lung cancer in vivo. Here the lipid phase consisted of pectoral ATO,5 SQUALENE and soybean phosphatidyl-choline, whereas the aqueous phase was composed of "tween-80, 1,2- dioleoyl 3- trimethylammonium - propane and 1,2di- stearoyl sn-glycero3-phosphoehtanolamine-n- (carboxy (polyethylene gly-col)2000). [59]
13. **Ketoconazole-** In the usual oncologic procedure, the antifungal drug ketoconazole remains an important agent for patients who are resistant to circumcision prostate cancer (CRPC). Its role has been replaced in part abiraterone in recent years, which is a very specific inhibitor of androgen synthesis and has a very positive effect profile (nausea, rash, fatigue / weakness), a few side effects used, and a few drug combinations, but also very expensive. Similar to abiraterone, ketoconazole can cause renal insufficiency, and similar steroid administration is recommended.[60]

Anti-neoplastic properties of psychiatric drugs

Table-2: Psychiatric drugs with potential anti- neoplastic effects.

CLASS DRUG	PRIMARY INDICATIONS	PRIMARY MECHANISM	MEWCHANISM OF ANTI- CANCER EFFECTS	REFERENCES
Valproic acid (valproate, VPA)	Bipolar disorder epilepsy migraine headaches	Blockage of voltage-gate sodium potassium and calcium channels and inhibition the re-uptake of GABA.	Inhibits histone deacetylase to reduce cancer cell proliferation and induce apoptosis; induces differentiation and inhibits angiogenesis.	[75]
Phenothiazines Chlorpromazine Levomepromazine Thioridazine	Schizophrenia Psychosis Antiemetic.	Dopamine receptor antagonists	Promotes cancer stem cell differentiation through dopamine receptor pathway; inhibits mitochondrial DNA polymerase and decreases ATP production with selectively cytotoxicity and antiproliferative activity in leukemic cells. Disrupts cholesterol homeostatic.	[76,77]
Olanzapine pimozide	Schizophrenia Bipolar disorder Tourette syndrome resistant tics	An antagonist of the D2, D3, and D4 receptors and the 5-HT7 receptor		[78,79]
Selective serotonin reuptake inhibitors (SSRI) Citalopram Fluoxetine Paroxetine Sertraline	Depression Generalized anxiety disorder Obsessive-compulsive disorder Eating disorders Stroke recovery Premature ejaculation	Serotonin re-uptake inhibition.	Reduces proliferation and induce apoptosis in cancer cells; down-regulates pAKT to mediate the synergistic anti-proliferative interaction with other chemo-drugs	[82,81]
Tricyclic antidepressants Imipramine Trimipramine amitriptyline	Major depression Attention-deficit hyperactivity disorder insomnia	Serotonin and norepinephrine transporter blockage to enhance neurotransmission.	Inhibit cellular proliferation and induces cell apoptosis in different tumors including neuroendocrine tumors; improves the effectiveness of other chemotherapeutic agents.	[160,174,175]
MAO inhibitors Selegiline Phenelzine Tranylcypromine	Atypical depression Panic disorder Borderline personality disorder.	Inhibition of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmission's.	Inhibits BHC110/LSD1, as an important chromatin modification enzyme capable of demethylating histone.	[83, 84,85]

Radiotherapy- It is one of the cheapest ways to cancer treatment, and more than half of all patients will receive radiotherapy at some point while they are being treated for cancer. 1 Radiotherapy can be used as a single method or combined with alternative therapies in various ways. 40 percent of Cancer can be treated with radiotherapy alone or combined and other cancer treatments. cancer drugs, to bring about a promising combination. Chemotherapy agents include temozolomide, cisplatin, 5-fluorouracil (5-FU), cetuximab, and mitomycin C are individually approved by the Food and Drug Administration (FDA) compliance use with radiotherapy for specific indications. Still, many other FDA-approved drugs for other indications, including many non-cancerous, and / or pipeline have the potential to improve radiotherapy. In particular, he is empowered by broom external radiotherapy tackling the coming cancer crisis in developing countries[88] and the ability to reuse non-patent drugs as stimulants, this the strategy can offer less expensive ways to improve effects of cancer worldwide. Although the main effect of ionizing radiation is considered to be genomic damage and especially the formation of chromosomal DNA double-strand break (DSBs), many features of the tumor and the grip factors determine whether the radiation dose will perform enough, it creates a variety of targets with which they can Repeated drugs can mimic the effects of radiation. Therefore, in addition to agents affecting DNA repair, drugs targeting hypoxia absorption, metabolism, dysfunction, proliferation, angiogenesis, signature survival, and attack / metastasis among others has the potential to improve radiotherapy response.[86]

Repurposing to decreases tumor Hypoxia- Radiation oncology has undergone major changes as well growth in technology development over the past decade. There has been more emphasis on new machines that can accurately place the tissues in the direction directed by the image, and focus on providing a more uniform radiation treatment using intension-modulated, volume-modulated, and proton methods of radiotherapy. Precision radiotherapy cone using beam computed tomography, image-guided radiotherapy uses fiducials included, and / or the inclusion of radiotherapy has become a norm the most common. In addition, there has been an increasing use of deceptive radiotherapy methods using stereotactic surgery for the treatment of stereotactic systemic tissue radiosurgery) and abnormal tissue (stereotactic radiotherapy body). Many payers have adopted supporting payment models the use of this development of radiotherapy. However, it continues **s**lack of emphasis on developing a radiation therapy index using the combination of available drugs.[87,88]

CONCLUSION

On the basis of a report from IARC cancer remains to be a major global healthcare burden as 18.1 million recent cases come into existence & over 9.6 million deaths till 2018. Metastatic tumors or surgical non-respectable tumor have shown 5-year deaths above 90% in case of severe cancer types & at genetically at high risk of acute myeloid leukemia till now not because of failure of therapeutics rather due to shortage of productivity rate in research and development of the drug products. In the long-term process of R&D, the cost productivity is potentially minimizing the cost at least in some areas of the research has drastically increased the cost of novel approved cancer therapeutics is being raised as an important issue. The drug repurposing also helpful to those drug which are present with in the market to improvising the revenue and identification of new indication to extend the years of survival of patients. It also helps to protect the compares from intellectual property against competitors. By the think drug repurposing will set more and more successful stage in future cancer therapeutics scenario which will be effective and useful. Since last decade cancer is successful in developing its identity as an organ whose complex approaches were difficult to detect as they have their genetic makeup completely different from that of healthy cells.

In a current research, it is also found that cancer cells have a property of intra-tumor heterogenecity i.e., formation of sub-group of cancer cells that shows more complexity in revelation of their genetic makeup. Hence, the research is still going, it is not yet confirmed that these cancer sub-cells are sub-part of all cancer cells, but it is assured that it is found as a part of most of the tumor cells. In a study it is found that these cancer stem cells can be easily identifies by their property of giving rise to new stem cells when they are inoculated in the host mice model in the laboratories.

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