International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

Impact of chemotherapy and immunotherapy on patients offering cancer

ProjjalMukhopadhyaya, Sandip Kumar Pahari, ShamboPanda, Sourav Manna, Ujjwal Mahato.

Submitted: 25-06-2021 Revised: 01-07-2021 Accepted: 03-07-2021

ABSTRACT

Cancer is the among of the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer related deaths worldwide. By 2040, the number of new cases per year is expected to rise to 29.5 million and the number of cancer related deaths to 16.4 million. These statistics make it an attractive disease to review and possibly improve therapeutic treatment options. Surgery, radiation, chemotherapy, targeted treatment and immunotherapy are commonly used to treat cancer individually or in combination. However, this type of treatment can lead to various side effects and chemotherapy-based methods seem to have reached a therapeutic plateau. Therefore, effective and better tolerable treatments need to be addressed and hopefully this shock will have to be overcome. Recent advances have enabled better investigations into the potential use of natural compounds for the treatment or control of various cancerous diseases. For the past 30 years, natural compounds have become a pillar of chemotherapy. However, only a few compounds have been tested in cancer patients and only partial evidence of their clinical efficacy has been found.

Side effects of systemic chemotherapy used to treat cancer are often fatal. For decades, oncologists have focused on the treatment of the tumor, which can cause damage to the host that carries the tumor and has immunity. Recently a lot of attention has been paid to the immune system of patients and it is activated through biological treatment. Biological therapies, including immunotherapy and Oncolytic Virus therapy (OV) therapy, are often more physiological and well tolerated. The current review highlights how these treatments work and why these treatments can be better tolerated: i) Immune therapies in contrast to chemotherapy induce a memory function of the adaptive immune system; ii) The goal of immunotherapy is to particularly activate the immune system against cancer; Side effects are less due to immune tolerance mechanisms, which maintain the integrity of the body in the presence of B and T lymphocytes with their antigen receptor properties and; iii) The first type of reactive response, which is caused by OVs, is an ancient congenital immune defense .

The present review I focused on impact of chemotherapy and immunotherapy on patients offering cancer with the aim of reducing side effects and increasing long lasting efficacy in cancer therapy.

INTRODUCTION

Cancer is a disease that involves the growth of abnormal cells, including the possibility of invading or spreading to other parts of the body. In contrast to benign tumors, which do not spread. Possible signs and symptoms include nausea, abnormal bleeding, chronic cough, unexplained weight loss, and changes in bowel movements. Although these symptoms may indicate cancer, there may be other causes. More than 100 cancers affect people.

Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity excessive drinking of alcohol. Other factor includes certain infections and environmental pollutants in the developing world,15% of cancers are due to infections such as Helicobacter pylori, hepatitis B, Hepatitis C, Human papilloma virus infection, Epstein Barr virus and Human immune deficiency virus. These factors act, at least partly, by changing by genes of a cell. Topically, many genetic changes arerequired before cancer develops. Approximately 5-10% of cancers are due to inherited genetic defects. Cancer can be detected by certain signs and symptoms or screening tests. It is then typically further investigated by medical imaging and confirmed by biopsy.

As per GLOBOCAN 2020 an estimated 19.3 million new cancers occurred in 2020 and about 10.0 million cancer deaths. Female breast cancer has surpassed lung cancer as the most common cancer, with an estimated 2.3 million new

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

cases (11.7%) followed by lung (11.4%), colorectal (10.0%), prostate (.3.3). Lung cancer remains the leading cause of cancer deaths due to cancer and stomach (5.6%), with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), and liver (6.3). %), Stomach (7.7%) and female breast cancer (9.9%). The overall incidence was 2-fold to 3-fold higher in transgender versus transgender countries for both sexes, where the mortality rate was <2 times in males and slightly higher in females. However, women's breast and uterine cancer mortality rates were significantly higher in transit vs. transitioning countries (15.0 vs. 12.8 and 100,000 per 12.4 and 5.2, respectively). The global cancer burden is expected to reach 26.4 million cases in 2040, an increase of since 2020, with large changes in transgender (2% to 5 %) countries due to population changes (4% to 9 %). Received, although it may be exacerbated by the risk factors associated with globalization and the growing economy. Efforts to build a sustainable infrastructure for the prevention of cancer and the spread of cancer care in developing countries are important controls for global cancer control.**[1]**

The current review focuses on cancer chemotherapy, a type of standard cancer therapy and a modern biological type of targeted therapy, which is not yet part of standard care. In the late 1970s, there were some drugs used in chemotherapy such as bleomycin, vinblastine and cisplatin; However, they did provoke serious side effects, such as vomiting 12 times. Since antiemetic drugs were not available at this time, patients were expected to tolerate the side effects of invasive chemotherapy.

The US National Cancer Institute (NCI) is involved in the study of cytostatic drugs, resulting in a combination of different drugs for cancer treatment and study plans. By 1979, the NCI had created a network of 20 cancer centers, which was involved in conducting new research on cancer treatment. Clinical boards, which were involved in approving and coordinating studies involving humanities, with the aim of expediting the approval process. However, since these studies often test treatment on humans first without examining the efficacy of animal tumors, errors were often made. In addition, some cytostatic drugs were approved despite their low efficacy and serious side effects.

The current review was generally aimed at focusing on treatment side effects. The World Health Organization (WHO) defines side effects as grades 0-4. The current review mentions that not only cytostatic drugs, but also several novel drugs of the last decade can create serious adverse effects. This review also provided overviews regarding various types of cancer and their therapy and also the important parameters to differentiate chemotherapy, immune therapy and OV therapy.

History of cancer

There have been cancers throughout the recorded history of the human body and other animals. So, it is not surprising that people wrote about cancer from the very beginning of history. Fossil bone tumors, human mummies in ancient Egypt, and some of the earliest evidences of cancer are found in ancient manuscripts.**[2]**Suggestions for an increase in bone cancer called osteosarcoma have been found in mummies. Head and neck cancer has also been found to destroy the skull. The earliest description of our cancer (although the term cancer is not used) was discovered in Egypt and dates back to about 3000 BC. It is called the Edwin Smith Papyrus and is a copy of a part of an ancient Egyptian textbook on trauma surgery. It describes 8 tumor or breast ulcer cases that were carefully removed with the help of a tool called a fire drill. "There is no treatment," the article said.**[3]**

The origin of the word cancer is attributed to the Greek physician Hippocrates (460–370 BC), who is considered the "father of medicine."[**3**] Hippocrates used the terms carcinos and carcinoma to describe non-ulcer formation and ulcer-forming tumors. In Greek, these words refer to a crab, probably because it was applied to a disease because a finger-like projection from cancer resembles a crab shape. The Roman physician Celsus (27-50 BC) translated the Greek word for cancer, the Latin word for crab. Another Greek physician named Galen (130-200 AD) used the term oncos (swollen Greek) to describe tumors**[4]**. Although the crab resemblance of Hippocrates and Celsus is still used to describe malignant tumors, Galen's term is now used as a name for an oncologist.

In the 16th and 17th centuries, it became more acceptable for physicians to disperse corpses to discover the cause of death. German professor Wilhelm Fabry believed that mammalian cancer was caused by the clotting of milk in a mammalian pile. Descartes' follower, the Dutch professor Francois de la BoeSylvieus, believed that all diseases were the result of chemical processes and that acidic lymph fluid was the cause of cancer. His contemporary Nicholas Tilp believed that cancer was a poison that spread slowly and came to the conclusion that it was contagious.**[5]**

The British surgeon Percival Pot, discovered the 1st cause of cancer who in 1775.That testicular cancer was a common disease among chimney sweeps. The work of other individual

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

physicians brings different insights, but when physicians start working together, they can come to a firm conclusion.

With the widespread use of microscopes in the eighteenth century, it was discovered that 'cancer toxins' eventually spread from lymph nodes through primary tumors to other sites ("metastasis"). This view of the disease was first developed by the English surgeon Campbell de Morgan between 1871 and 1874.**[6]**The use of surgery to treat cancer due to hygiene problems had poor results. Renowned Scottish surgeon Alexander Monroe saw only two breast tumor patients out of two surgeries that survived for two years. In the nineteenth century, asepsis improved surgical hygiene and as survival figures increased, surgical removal from tumors became the primary treatment for cancer. With the exception of William Collie, who in the late 19th century realized that healing rates were higher after surgery before asphyxia (and who injected bacteria into tumors with mixed results) That infection stimulates the immune system to destroy left tumor cells. At the same time, the notion that the body was made up of different tissues, made up of millions of cells, rested humor-theories about chemical imbalances in the body.

Classification of cancer

Cancers are mainly classified by their primary site of origin or by their histological or tissue types.

Classification by site of origin:

By primary site of origin, cancer is categorised in few types like breast cancer, lung cancer, prostate cancer, liver cancer renal cell carcinoma (kidney cancer), oral cancer, brain cancer etc.

Classification by tissue types:

Based on tissue types cancers mainly categorised in six major categories:

1.Carcinoma: -This type of cancer arises from the epithelial layer of cells that form the lining of the outer parts of the body or the inner lining of the internal organs of the body. Carcinomas, abnormalities of epithelial tissues, contribute 80 to 90 percent to all cases of cancer because epithelial tissues are present in the skin of the body in abundance in the lining of the fingers and lining such as the gastrointestinal tract. Carcinoma usually affects the secretory organs or glands, including the breast, lungs, bladder, colon, and prostate.**[7]**

2.Sarcoma: -These cancers originate in connective and connective tissue, including muscle, bone, cartilage, and fat. Bone cancer is one of the sarcomas known as osteosarcoma. It affects young people the most. Sarcomas appear as their raised issue.

Other examples include the chondrosarcoma (of the cartiledge), leomyosarcoma (smooth muscle), Ryabadomyosarcoma (skeletal muscle), mesothelial sarcoma or mesothelioma (body cavity membrane layer), Fibrosarcoma (fiber issues), Angiosarcoma or hemangioendothelioma (blood vessels), Myxosarcoma (primitive embryonic connective tissue) and Mesenchymous or mixed mesodermal tumors (mixed connective tissue types).

3.Myeloma: -These originate in the plasma cells of bone marrow. Plasma cells are capable of producing various antibodies in response to infections. Myeloma is a type of blood cancer.

4.Leukemia: -It is a group of cancers that are grouped into blood cancers. These cancers affect the bone marrow which is the site for blood cell production. With cancer, the bone marrow begins to produce excessively immature white blood cells that fail to perform their normal function, and the patient is often at risk of infection.There are various types of leukaemia including**;[7]**

i. Acute myelocytic leukemia (AML) – these are malignancy of the myeloid and granulocytic white blood cell series seen in childhood.

ii. Chronic myelocytic leukemia (CML) – this is seen in adulthood.

iii. Acute Lymphatic, lymphocytic, or lymphoblastic leukemia (ALL) – these are malignancy of the lymphoid and lymphocytic blood cell series seen in childhood and young adults.

iv. Chronic Lymphatic, lymphocytic, or lymphoblastic leukemia (CLL) – this is seen in the elderly.

v. Polycythemia vera or erythremia – this is cancer of various blood cell products with a predominance of red blood cells

5. Lymphoma: - These are cancers of the lymphatic system. Unlike the leukemias, which affects the blood and are called “liquid cancers”, lymphomas are “solid cancers”. These may affects lymph nodes a specific sites like stomach, brain, intestines etc. These lymphomas are referred to as extra nodal lymphomas. Lymphomas may be of two types – Hodgkin’s lymphoma and Non-Hodgkin’s lymphomas. In Hodgkin lymphoma here is characteristic presence of Reed-Sternberg cells in the tissue samples which are not present in Non-Hodgkin lymphoma.**[7]**

6. Mixed types: -They contain two or more carcinogens. Some of the examples include mixed mesodermal tumors, carcinosarcoma, adenoscomascarcinoma, and teratocarcinoma.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

Blastomas are another type of tumor that involves fetal tissue.

Therapy of cancer

The goal of any cancer treatment is to remove or destroy the cancer cells without killing the normal cells. The most common types of cancer treatment include surgery, radiation and chemotherapy that can be used alone or with each other or in combination with other therapies. Surgery involves the removal of obviously cancerous tissue and is the primary treatment for most cancers, especially hard tumors. Ultrasonic and / or CD scanners are used as diagnostic tools to confirm a biochemical diagnosis and further determine the spread and spread of the tumor. Radiation therapy is the application of high-powered X-rays to shrink the tumor. It is mostly used with surgery or alternative chemotherapy or as a neo-adjuvant therapy to aid in surgery by reducing the size of the tumor and is considered topical treatment as it only affects the tumor area. However, the therapeutic efficacy of radiotherapy for the treatment of locally or regionally advanced cancer is often limited by tumor radio-resistance, systemic tumor progression, and local or distant metastasis. Chemotherapy is discussed below.

Chemotherapy Drugs:

Chemotherapy has been the standard therapy for cancer for decades. Chemotherapy is the application of chemicals or drugs to reduce cancer cells and its effects are systemic. so far, the various activities of different types of anticancer drugs have been based on their mechanisms of action and include the following: a) DNA-damaging alkalizing agents; B) anti-metabolism that replaces common building blocks of RNA and DNA; C) antibiotics that interfere with the enzymes involved in DNA replication; D) topoisomerase inhibitors that inhibit topoisomerase I or II, which are enzymes involuntarily involved in DNA during transcription and transcription; e) mitotic inhibitors that inhibit mitosis and cell division; And f) corticosteroids, which are used to treat cancer and to relieve side effects from other drugs.

Patients with unnecessary and metastatic cancer (palliative) may benefit from chemotherapy. Under current guidelines, first-line chemotherapeutic treatments contain platinum agent-based doublets, e.g., Cisplatin or carboplatin in combination with a third-generation cytoxic drug, gemcitabine, a toxin (paclitaxel, dosatexel), or vinorelbine. Meta-analyzes of randomized clinical trials comparing cisplatin with carboplatin suggest that the clinical results of cisplatin doublet are not associated with serious toxic effects **[8].** Mortality has been reduced. In the late 2006's, Bevacizumab, a single-dose antibody administered against vascular endothelial growth factor (VEGF), was approved for the first-line treatment of patients with non-squamous NSCLC in combination with paclitaxel and carboplatin chemotherapy **[9][10]**. A number of antacid drugs used to treat lung cancer (bleomycin, doxorubicin, etoposide (VP-16), cisplatin and methotrexate) Fas can be mediated through cross linking. Platinum drugs are effective for patients with positive K-rasmutation, while several drugs are not effective for increasing rate-2 expression. In addition, increased expression of p27 enhances efficacy of taxanes**[11]**, while taxanes are ineffective for patients who have positively converted to beta-tubulin. In conclusion, cisplatin and other platinum drugs may not benefit patients with high patient reform protein (ERCC1) expression**[12]** .

1.Cisplatin:-Cisplatin(cis-diamminedichloroplatinum,DDP) is One of the most effective and widely used chemotherapeutic agents for the treatment of hard tumors. It is a platinum-based compound that forms endogenous and interstitial adducts with DNA and is a powerful indicator of cell cycle arrest and apoptosis in most cancer cells**[13]**. Unfortunately, many of these patients eventually become re-infected and become disobedient. (Drug resistant) to chemotherapy either intrinsically (e.g., as observed in patients with colorectal, lung, and prostate cancer) or acquired following cisplatin chemotherapy (as often seen in patients with ovarian cancer)**[14]**. Cancer cells can develop cisplatin resistance through changes in (1) drug transport leading to reduced intracellular cisplatin accumulation, (2) an enhanced drug detoxification system due to elevated levels of intracellular scavengers such as glutathione and/or metallothioneins, (3) changes in DNA repair involving increased nucleotide excision repair, inter-strand crosslink repair or loss of mismatch repair, (4) changes in DNA damage tolerance mechanisms, and finally (5) changes in the apoptotic cell death pathways . Cisplatin resistance might result in conjunction with GSH followed by the inactivation of cisplatin or the prevention of cisplatin-adducts formation. The level of GST-π isoenzyme expression has been found to be significantly associated with intrinsic resistance to cisplatin in lung cancer cell lines**[15]**.

2.Taxanes: -Chemotherapeutic agents known as Taxanes have emerged as one of the most powerful compounds in the fight against cancer, exhibiting a wide range of activities. The tubulin / microtubule

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

complex has been proven to be a useful antitumor target for treatment. Examples of chemotherapeutics that work through the ablation of tubulin polymerization include polyethylene (Taxol®), docetaxel (Taxotere®), vinblastine, and discodermolide. First, docetaxel is a semi-synthetic derivative of paclitaxel. Then, vinblastine, in contrast to the other three compounds that stabilize all microtubules, aggregates tubulin and leads to microtubuledepolymerization**[16][17]**.

Various clinical trials evaluating docetaxel and paclitaxel in a first-line treatment setting for metastatic breast, lung, ovarian, and digestive cancers, as well as in the adjuvant setting for breast cancer, have confirmed that taxanes are leading contributors to the armamentarium of cancer treatments **[18]**. Althoughtaxanes share similar mechanisms of activity, but differences in their molecular pharmacology, pharmacokinetics, and pharmacodynamic profiles are obvious. These differences may indicate differences in their clinical activity and taxes in toxicity.

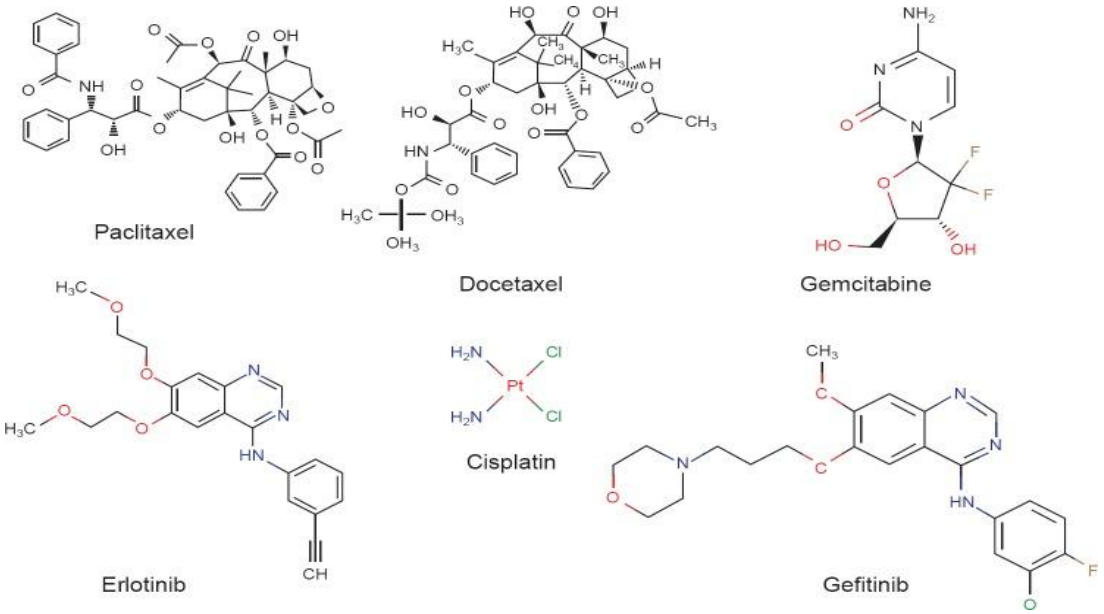

Fig 1: Chemical structures of anti-tumor agents with clinical agents

3.Paclitaxel: -Paclitaxel is used as a first-line chemotherapy treatment for NSCLC, but the acquired resistance of patients becomes a complex problem. Tubulin is the "building block" of microtubules and agents that bind to tubulin block cells at the metaphase-anaphase junction of mitosis by interfering with mitotic spindle activity and blocking cell division. Microtubules are complex structures involved in numerous cellular activities, including cell shape maintenance, intracellular transport, secretion, and neurotransmission. Moreover, microtubules are highly dynamic and unstable structures that continuously integrate free dimers and release dimers into soluble tubulin pools. A 24-hour dosage of paclitaxel for advanced and metastatic NSCLC treatment and received a response rate of 21% and 24%, respectively, while a short transition schedule for 3 hours and 1 hour yielded the same results**[19][20].**Docetaxel ß-shows greater affinity for tubulin, targets centrosome organization, and acts on cells at three stages of the cell cycle (S / G2 / M), while paclitaxel affects cell age at G2 and M phases, mitotic spindles, cell cycle, and pack Early in the S stage of maximum resistance. A recent report found that a concentration of Paclitaxel> 10 nm inhibits endothelial cell proliferation through a G2-M arrest and induces subsequent cell death by apoptosis, similar to its effects on tumor cell lines. Over the past decade, the additional activity of taxol has been described in many ways, including taxon-induced phosphorylation of IBB, while several studies have further shown that taxol directly buys survival pathways such as BCL-2, ACT, COX-2, mitogen activated proteins, etc. Different from NF-κB.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

Phosphorylation of BCL-2 is seen as a feature of cell death transmitted by paclitaxel, but the correlation between this event, mitotic arrest, and apoptosis remains controversial. Preliminary reports suggest that phosphorylation of BCL-2 leads to inactivation of itsantiapoptotic function. Currently, the molecular mechanism by which apoptosis is caused by paclitaxel-induced mitotic arrest is not clear, although evidence has been shown to involve several signaling pathways, including mitogen-activated protein kinases (MAPKs), actions of various protein kinases, such as serine. Its thrombin-induced phosphorylation and p53 pathway lead to Caspase-9/Apaf-1/cytochrome C apoptosome activation of the mitochondrial dependent apoptotic pathway towards Caspase-3 activation. Ofir et al. (2002) also found that propaspase-9 is not activated after taxol treatment in MCF-7 breast cancer and SKOV3 ovarian cancer cell lines and that the drug induces apoptosis independently in caspase-3 and -9**[21]**. However, during taxol-transmitted apoptosis (Human Caucasian Acute Lymphoblastic Leukemia) in CCRF-HSB-2 cells, Caspase-3 is activated but remains independent of Caspase-9. It appears that the effect of taxol on Caspase-9 activation is also cell-type-specific; For example, taxolinduced apoptosis in human leukemia HL-60 cell line has been observed to induce cytosol release in cytosol C and induce APAF-1-mediated caspase-3 and -9 activity. Parks et al. (2004) and Lin et al. (2000) demonstrated taxol-induced apoptosis in human lymphoblastic leukemia cells and hepatoma cells via a ROS-independent pathway**[22][23]**.

Prevention of paclitaxel is defined as progression of the disease during treatment, failure to achieve tumor regression after at least four courses of therapy, or recurrence of the disease within 6 months of completion of paclitaxel therapy. The radio-sensitive effects of docetaxel related to paclitaxel have been evaluated in intro-comparative analysis using three human cancer cell lines (uterine cancer, mesothelioma, and lung cancer). The results showed that the three cell lines were more sensitive to docetaxel than paclitaxel and that mesothelioma cells were individually resistant to both radiation and toxins, but with regional administration of docetaxel before radiation the immune system was defeated. Nevertheless, most patients with advanced lung cancer develop resistance to taxol. In another study, it was shown that paclitaxel, combined with apoptin, can significantly inhibit expression as a result of addictive cytoxic activity in osteosarcoma and NSCLC cells.

Involvement of caspases in taxane-induced cell death is cell line-dependent. Resistance to Caspase 1 and Caspase 3 has been observed in mouse cell lines to prevent docetaxel-induced DNA fragmentation **[24]**. However, the pan caspase inhibitor failed to reduce cell function by docetaxel in gastric cancer cells. Moreover, toxins have been shown to cause apoptosis in caspase 3-deficient MCF-7 breast cancer cells. Paclitaxel activates Caspase 8 in human colon cancer cells, suggesting a potential interaction between the built-in and extrinsic apoptotic pathways.

4.Gefitinib: - Gefitinib is an oral agent used to target epidermal growth factor receptor tyrosine kinase and has a specific efficacy against non-small cell lung cancer. EGFR-TKIs, Gefitinib-IRESSA has been shown to inhibit cell proliferation that exceeds EGFR with some ER-negative cell lines. In the first stage of the test, various types of oral Gefitinibtumors are found to be cancerous. In a second-stage study, oral gefitinib was used to treat breast cancer at 500 mg / day and showed similar tolerances at 250 and 500 mg / day at NSCLC; However, in the case of NSCLC, less tolerance has been found in lower doses **[25][26]**. Gefitinib reduces tumor thyroid cancer cell growth in vitro and in vivo that exceeds EGFR. Since 2003, the FDA has approved three generations of EGFR tyrosine kinase inhibitors (TKIs), including Gefitinib, Erlotinib, Afatinib and Osimertinib **[27]**. Gefitinib is a specific EGFR-TKI that is widely used in clinical practice for the treatment of small lung cells. With the change of Giftinib EGFR as the choice of first line therapy, NSCLC has significantly improved the survival rate of patients. Nevertheless, the resistance achieved after Gefitinib therapy is almost irreversible and limits the success rate of treatment. To overcome the resistance of EGFR-TKIs, a combination of other compounds with them must be designed **[28]**.

5.Gemcitabine: -In vitro gemcitabine and first-stage studies have demonstrated activity against a variety of tumors. However, the development of higher cytotoxic and innate or acquired drug resistance has made this drug a major challenge in gemcitabine therapy and has managed to reduce the survival rate of cancer patients**[29]**. It is being used in combination with other drugs to treat locally developed or metastatic non-small-cell lung cancer, bladder cancer, and ovarian cancer. Gemcitabine treatment shows more inhibitory activity against breast cancer cells. In prostate cancer cells, the combination of gemcitabine with compounds αM and γM showed anti-cancer effects. The combination of gemcitabine with other capecitabines, as in patients with stage III

pancreatic cancer, shows a slight synergistic effect**[30]**. Thus, the development of the use of natural compounds to increase gemcitabine in the treatment of cancer is urgently needed.

6.Erlotinib: - Erlotinib, a small molecular agent like Giftinib that is used to target epidermal growth factor receptors (EGFRs) and has become a major target for the treatment of EGFR-resistant advanced non-small cell lung cancer**[31]**. However, it is expensive and its effectiveness is limited by primary or secondary drug resistance, which develops over an extended period of treatment. Mixed mir-34a and EGFR-TKI both attach to EGFR wild-type and mutant NSCLC cells**[32]**.

Natural compounds:-

Natural compounds have long been a source of anticancer compounds. For many years, traditional Chinese medicine (TCM) has been used to treat cancer in China and beyond**[33]**. Herbal medicines are usually low cost, in abundance and show very little toxicity or side effects in clinical practice. Most valuable compounds (such as paclitaxel and vinca alkaloids) were discovered serendipitously or from slow and laborious in the case of in vivo screening. Most of the current research in cancer therapeutics develops drugs or vaccines targeting key molecules that can inhibit tumor cell growth, metastasis, and proliferation. Including anti-metastasis reactions usually have their effects targeting specific key replicating factors.

1.Wortmannin and Roscovitine: -Purine analoguesRoscovitine is a small molecule that inhibits the activity of cyclin-dependent kinases (CDKs) through direct competition at the ATP-binding site. It is particularly active against CDK1 (CDC2), CDK2, and CDK5 and induces G1 and G2-M cell cycle arrest**[34]**.Roscovitine has been shown to have antitumor effects on various cancer cell lines. Similarly, roscovitine induces apoptosis in A549 cells in a dose-dependent manner. Meanwhile, wortmannin, a fungal metabolite, is a potent specific PI3K inhibitor, which binds to the P110 catalyst subunit of PI3K and inhibits the enzyme irreversibly, which can chemo synthesize three tumor cell lines (A549, HCT116 and HELLA cells)**[35]**. In A549 cells, wortmannin enhances roscovitine-induced apoptosis in a dose-dependent manner, which is associated with inhibition of phosphorylated PKB / ACT levels. Wortmannin significantly decreases mitochondrial membrane potential (MMP) and increases cytochrome C release and activated Caspas-3, as well as enhances the effects of Roscovitine, as well as increases box and bed activation, including back oligomerizationand mitochondrial translocation. Taken together, these results provide evidence of the potential application of a combination of roscovitine and wortmannin in the clinical treatment of solidtumors.

2.Cordyceps militaris: -Cordyceps militaris is well-known as a traditional herbal medicinal mushroom and a potentially attractive candidate for cancer treatment use. Water extract of C. militaries (WECM) induce the apoptosis of A549 cells through a cascade of signals of death receptor-mediated extrinsic and mitochondria-mediated internal caspase pathways. It also concluded that apoptotic events due to WECM are mediated with reduced telomerase activity through the prohibition of hTERT transcriptional activity**[36]**.

3.Resveratrol: -Resveratrol has been evaluated in more than 110 clinical trials, such as in patients with DM and metabolic syndrome, and in patients with certain types of cancer. Resveratrol (3,5,4 '-trihydroxy-stilbene) is a phytoalexin found in red wine and various plants, including grapes, peanuts, algae and lemons, and is produced due to stress, injury, fungal infections or UV exposure**[37]**. Resveratrol has also been shown to induce antioxidant and anti-inflammatory effects and inhibit the proliferation of various cancer cells. What's more, resveratrol inhibits platelet aggregation and also has antioxidant properties. Resveratrol has been reported to have protective effects against lung cancer; It alters large amounts of genes and proteins and inhibits cell proliferation, inhibits apoptosis, and inhibits A549 cell proliferation by altering the intracellular memory signals of the TGF-β pathway**[38]**. Resveratrol has already been established as an inhibitory agent in A549 human lung cancer cells and this effect has been associated with phosphorylation of Arabic proteins and suppression of transcription components of nuclear factor-kB (NF-kB) and activator protein-1. It has been found that resveratrol administration in colorectal adenocarcinoma patients reduces tumor cell proliferation**[39]**.

4.OSU03013: -OSU03013 is a derivative of Celecoxib. Although celecoxib is an inhibitor of cyclooxygenase (COX) -2, significant data suggest that celecoxib-induced apoptosis cell death occurs via a COX-2-isolated pathway. 1 (PDK1) / can induce one through a signaling pathway and inhibit cell growth more strongly than celecoxib. Furthermore, OSU 03013 has been used in the treatment of breast cancer and has been shown to have higher cytotoxicity, especially in breast cancer cells with excessive expression of the epidermal growth factor receptor (HER) -2. Tong et al. (2006)

discovered that 10 μM A549 of OSU03013 may induce cytochrome C-mediated apoptosis in lung cancer cells, especially for its low concentration of externally expressed ones**[40]**.Similarly, Tan et al. (2008) found that OSU03013 can affect several pathways such as cAMP-dependent protein kinase (PKA) and W / H catechin pathway and cause ER stress-induced apoptosis at a dose as low as 2 μM in lung cancer cells**[41]**.

5.Myricetin: -Myricetin is a flavonoid it is commonly found in tea, wines, berries, fruits and medicinal plants. It has been reported to possess antioxidative,antiproliferative and anti-inflammatory qualities. Previous studies have shown that myricetin exerts an antiproliferative effect on lung, oesophageal, leukemia, and prostate cancer cells**[42]**. Myricetin may act as a direct antioxidant that scavenges or quenches oxygen free radicals, and as an indirect antioxidant that induces antioxidant enzymes to protect cells against H2O2-induced cell damage**.**

6.Berberine: -Barberine is an isoquinoline derivative alkaloid that is isolated from many medicinal plants, such as Hydrastis canadensis, Cortex phellodendri, and Rhizoma coptidis. It is widely used in conventional Chinese medicine for the treatment of inflammatory diseases and anti-microbial activities**[43]**. Barberine has been reported to have a variety of pharmacological effects, including interaction with DNA for complex formation, inhibiting DNA and protein synthesis, an arresting effect on cell cycle progression, inhibiting tumor cell proliferation, and an anticancer effect. Barberine has been shown to reduce c-Fos, C-Jun, and NF-κB activation, reduce the motility and invasion of small lung cancer cells, and inhibit the uPA, MMP2 protein. Berberine exerts an antitumor effect by inhibiting cell proliferation and incorporating apoptosis into ovarian cancer cells. Curcumin and berberine have been shown to have synthetic chemopreventive effects on breast cancer cell lines through caspase-dependent apoptosis and autophagy cell death via the ERK and JNK / Beclin 1 / BCL-2 signaling pathways, respectively**[44]**.

7.Antroquinonol: -Antroquinonol, a ubiquinone derivative isolated from Mycelia, and a. Effective bodies of camphor have been shown to demonstrate cytotoxic activity with cancer cell lines MCF-7, MDA-MB-231, HEP3B, HEP G2, and DU-145, LNCaP. IC 50 values range from 0.13 to 6.09 μm. Among other groups, we found that Antroquinonol AMP-activated protein kinase (AMPK) or phosphadylinositol-3-kinase (PI3K) / rapamycin (mTOR) modified the pathway of mammalian targets and lung cancer**[45]**. Recent studies have shown that anthraquinone induces apoptosis and autophagy of pancreatic cancer cells. In colon cancer, ANQPI3K / AKT / β-catechin signalling has been shown to suppress stem cell-like features.

Adverse effects of chemotherapy

Chemotherapy is associated with many serious side effects, including immediate symptoms of poisoning and late signs of chronic poisoning. Their severity can be mild (Grade 1), moderate (Grade 2), severe (Grade 3), or fatal or disabled (Grade 4), according to the WHO classification. Immediate effects can be observed on skin and hair, bone marrow and blood, gastrointestinal tract and kidneys. All parts of the body can be affected, including the heart, lungs, and brain. Grade 3 and 4 neurotoxicity can induce opacity, paraesthesia, paralysis, ataxia, spasms, and coma. Also, the long-term effects of chemotherapy include drug resistance, carcinogenicity, and infertility Most side effects go away after treatment. But some continue, come back or develop later**[46][47]**.

Most common adverse effects in patients occurred by chemotherapy are shortly discussed below,

1.Fatigue: -Fatigue is feeling tired or exhausted almost all the time. This is the most common side effect of chemotherapy. Even if you get enough rest and sleep it is a feeling of physical, mental and emotional fatigue. Cancer-related fatigue can affect your daily life. It can affect mood and emotions, daily activities, relationships with family and friends, hope for the future, and so on. Cancer fatigue usually occurs a few days after chemotherapy treatment or a few weeks after the start of radiotherapy. Other mind-body techniques such as touch therapy, music therapy, massage, relaxation, cancer fatigue can be overcome after taking proper diet, medication and supplements and talking to a consultant and consulting doctors.

2.Pain: -Some of the pain caused by chemotherapy may include headaches, muscle aches, abdominal pain, pain from nerve damage such as burning, numbness or shooting pain, usually between the fingers and toes. Most types of pain associated with chemotherapy go away or go away in treatment. However, nerve damage is often worse with each dose. Many times, the cause of nerve damage is to stop the medication. It can take months or years for the nerve damage to improve or go away from chemotherapy. In some people it never goes away perfectly. Treatment of pain often differs depending on the cause. In addition to chemotherapy, there may be other causes of pain, such as cancer itself. If the pain is related to

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

chemotherapy, doctors can treat the pain signals by giving painkillers, treating the pain signals from the nerves in the brain by treating the spinal cord or nerve blocks, and adjusting the doses of chemotherapy.

3.Mouth and throat sores: -Chemotherapy can damage cells inside the mouth and throat. It causes painful sores in these areas known as mucus inflammation. Mouth sores usually occur 5 to 14 days after treatment. The wound may be infected. Eating a healthy diet and keeping your mouth and teeth clean can reduce your risk of getting mouth sores. When the treatment is over, the sores on the face usually go away completely.

4. Nausea and vomiting: -Nausea and vomiting are sometimes serious side effects of cancer treatment. Chemotherapy, radiation therapy and other treatments for cancer can cause nausea and vomiting. These symptoms can be mild or severe. Mild nausea and vomiting can be uncomfortable but usually does not harm your health. Excessive nausea can cause other health problems such as dehydration, weight loss and fatigue. It is important that nausea and vomiting are controlled and managed. If not, these problems can delay the patient's daily life, mental health, physical health and even treatment. Physicians may prescribe medications called "antiemetics" to treat nausea and vomiting. Giving the right medication before and after each dose of chemotherapy can usually prevent nausea and vomiting.

5.**Blood disorders: -**The bone marrow is the spongy tissue inside the bone. It makes new blood cells. Chemotherapy affects this process, so the patient may have side effects due to having too few blood cells. Normally the number of blood cells becomes normal after the completion of chemotherapy. During treatment, however, low blood counts can cause problems and must be looked at closely.

A complete blood count (CBC) test shows the level of red blood cells and white blood cells in the blood. Adequate red blood cells do not cause a condition called anemia. Symptoms include fatigue, dizziness, and shortness of breath. A condition called **leukopenia** is not caused by insufficient white blood cells. This increases the risk of infection. When a patient has low white blood cells, the infection can be serious. If this happens, the patient needs antibiotics as soon as possible.

Platelet count. This test measures the number of platelets in your blood. Platelets are cells that stop bleeding. They do this by plugging damaged blood vessels and helping blood form clots. Platelet count. This test measures the number of platelets in your blood. Platelets are cells that stop bleeding. They do this by plugging damaged blood vessels and helping blood form clots. Not having enough platelets causes a condition called **thrombocytopenia.** Patients can bleed and bruise more easily than normal.

Doses of chemotherapy can often be adjusted to prevent low blood counts. The ESA includes drugs such as epothin alpha (Epogen, Procrit, Retacrit) and drugs such as darbepoetin and oprelvekin (Neumega) and some other drugs prescribed by doctors to treat blood disorders through chemotherapy. The drugs help the bone marrow to make more blood cells.

6.**Nervous system effects: -** Drugs like Taxotere, Taxol, Abraxane, oncovin, velban causes nerve damage. This can cause nerve or muscle symptoms like tingling, burning, weakness or numbness in the hands, feet, or both. Weak, sore, tired, or achy muscles. Loss of balance, headache, problems in seeing,hearing,walking. These symptoms usually get better with a lower chemotherapy dose or after treatment. But damage is sometimes permanent.

7.Memory and concentration problems: -Some people have problems with short-term memory, concentration and attention span during chemotherapy. As you can see, routine tasks take much longer than usual. It is unclear why this happens, but symptoms usually improve after treatment. After using lists, posting notes, calendars and reminders, your mobile phone can help. Doing some mental exercises, eating well and getting enough rest can also be effective.

8.Hair loss: - Some types of chemotherapy drugs such as Hexalen, Para platin, Platinol, 5-FU, Allocrest, Nevelbine etc. damage the hair all over the patient's body. It may come out a bit at once or in a larger jolt. Hair loss usually begins after the first few weeks of chemotherapy. It takes 1 to 2 months for treatment. Physicians can predict the risk of hair loss based on the medications and doses taken. The medical term for hair loss is **alopecia**. An over-the-counter medication called minoxidil can help thin hair from hormone therapy or targeted therapy. It can also help if your hair does not come back completely after chemotherapy, radiation therapy or stem cell / bone marrow transplantation. There are also other medications that you can take orally. These include spironolactone (aldactone) and finasteride (propecia, proscar). Some patients shave their heads before starting treatment to avoid hair loss or thinning hair.

9.Appetite loss: -You may eat less than usual, not feel hungry or feel full after eating small amounts. If you continue this treatment, you may lose weight and may not get the nutrition you need. You can

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

lose muscle mass and strength. These problems can slow recovery and cause a break in treatment. Patients should consult a registered dietitian for advice on diet plan and symptom management. A dietitian may also decide that the patient may benefit from nutritional supplements or digestive enzymes. Medicinal herbs like Ovavan, Prasad, Amen, Provera etc. can be used by physicians for treatment related to loss of appetite and weight loss.

10.Sex and fertility issues :-Many lose interest in sex during chemotherapy. It is usually temporary and the patient should return to the patient's sex drive gradually after the end of treatment ome Some chemotherapy drugs can reduce fertility in men and women. It is often temporary but can be permanent in some cases. The patient should consult with the team to take care of her fertility issues that may occur during treatment. Females may later be able to freeze eggs for use in IVF. Men may be able to keep a sample of their sperm frozen so it can be used for artificial insemination at a later date. Patients should avoid getting pregnant or having a baby during treatment because chemotherapy drugs can harm the baby. Patients use condoms as a barrier method to avoid this particular risk factor.

Current trends in therapy of cancer

Side effects of systemic chemotherapy used to treat cancer are often fatal. For decades, oncologists have focused on treating the tumor, which can cause damage to the host that carries the tumor and its immunity. Recently, much attention has been paid to the immunity of patients and its activation through biological treatment. Biological treatments are often physiological and well tolerated. Biological and physiological therapies, which support the immune system, may therefore be beneficial in the treatment of cancer with the goal of reducing side effects and increasing long-term efficacy in the treatment of cancer.

The goal of cancer biological therapy is to induce the patient's immune system to detect and kill cancer cells. The patient's immune system fights off invaders, such as germs, throughout the patient's body. The immune system should also recognize cancer cells as abnormal but it does not always do so. Cancer cells can develop the ability to hide from immune cells. Or cancer cells may inactivate or prevent the cells of the immune system from acting**[48].**

1.Immune checkpoint inhibitors: - Immune checkpoints are a common part of the immune system. Their role is to prevent the immune response from becoming so strong that it destroys the body's healthy cells. Immune checkpoints are involved when the surface proteins of the immune cells are called T cells and bind the partner proteins to other cells, such as the cells of some cells. These proteins are called immune checkpoint proteins. When the checkpoint and partner proteins are bound together, they send an "off" signal to the T cells. It can prevent the immune system from destroying cancer. Immunotherapy drugs Immune checkpoint inhibitors work by preventing checkpoint proteins from binding to their partner proteins. This offer allows the cancer cells to be killed and prevents the "off" signal from being sent. One such drug works against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors work against a checkpoint protein called PD-1 or its partner protein PD-L1. Some tumors reverse the T cell response by producing large amounts of PD-L1.

Immune checkpoint inhibitors are approved to treat some patients with a variety of cancer types, including Breast cancer, bladder cancer, cervical cancer, colon cancer, liver cancer, Hodgkin lymphoma etc.

2.T-cell transfer therapy: -It is a treatment that enhances the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Most active against your cancer they are selected or modified in the lab to better attack your cancer cells, grow in larger batches and return to your body through a needle in a vein. The process of growing your T cells in the lab can take 2 to 8 weeks.

TIL therapy uses T cells called tumor-infiltrating lymphocytes that are found in your tumor. Doctors examine these lymphocytes in the lab to find out which ones are best known to your tumor cells. Then, these selected lymphocytes are treated with a substance that makes them grow rapidly in large numbers.

CAR T-cell therapy is similar to TIL therapy, but your T cells are changed in the lab to make a type of protein known as CAR before they grow and return to you. CAR means chimeric antigen receptor. CARs allow T cells on the surface of cancer cells to attach to specific proteins, thus improving the ability of cancer cells to invade.

T-cell transfer therapy was first studied for the treatment of metastatic melanoma because melanoma often develops a strong immune system and often contains many TILs. The use of TIL therapy is effective for some people with melanoma and has yielded promising results in other cancers such as cervical squamous cell carcinoma and cholangiocarcinoma. However, this treatment is still experimental

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

3. Monoclonal antibodies: -Monoclonal antibodies are immune system proteins made in the lab. Antibodies are produced naturally by the patient's body and the immune system helps to detect germs that cause and destroy diseases such as bacteria and viruses. Like the body's own antibodies, monochromatic antibodies detect specific targets. Some monoclonal antibodies are also immunotherapy because they help change the immune system against cancer. For example, some monoclonal antibodies identify cancer cells so that the immune system can better detect and destroy them. An example of this is rutuximab, which binds to a protein called CD20 in B cells and some types of cancer cells, causing the immune system to kill them. B cell is a type of white blood cell. Other monochromatic antibodies bring the T cells closer to the cancer cells, helping the immune cells to kill the cancer cells. For example, Blinatumomab (Blincyto®), which binds to both CD19, is a protein found on the surface of leukemia cells and C3, a protein found on the surface of T cells. This process helps T cells to respond to leukemia cells and kill them. Different types of cancer are detected through this therapy.

4.Anticancer vaccines: -The goal of therapeutic dendritic cell (DC) vaccines in cancer immunotherapy is to activate CTLs to detect and attack tumors. Even when the T-cell response was already initiated by antigen activation, there is a complex balance between costly and co-inhibitory signals in DCs resulting in T-cell activation or T-cell tolerance**[49]**. Immunosuppressive indications in tumor microenvironments are currently the main cause of disruption in the application of DC vaccines. It has been suggested that four different types of tumor microenvironments exist based on the presence or absence of TIL and PD-L1 expressions. The ideal combination of cancer treatments based on tumor immunology is to find an optimal niche between maximum antitumor immunity and minimal autoimmunity. This is especially true for the application of checkpoint inhibitors, which interfere with immune control. Advanced prostate cancer, advanced melanoma skin cancer is basically treated with this type of cancer with anti-cancer vaccine.

5.Oncolytic virus therapy (OVs): -This therapy has been described several times as a type of cancer treatment vaccine. It uses an oncolytic virus that is a virus that infects and breaks down cancer cells but does not harm normal cells.

The first FDA-approved oncolytic virus therapy is talimogenelaherperepvec (T-VEC, or Imlygic®). It is based on the herpes simplex virus type 1. Although this virus can infect both cancer and normal cells, normal cells are able to kill the virus when cancer cells cannot.

T-VEC is injected directly into the tumor. The virus makes more and more copies, causing the cancer cells to rupture and die. Dead cells release new viruses and other substances that can build up immunity against cancer cells throughout the body.

Successful biological therapies of cancer

There are numerous examples of successful biological therapies of cancer, including:

i. Development of MABs, which is a product of B lymphocytes. One of the first FDA-approved MABs is trastuzumab (Herceptin), which targets the cell surface receptor HER2 that can be expressed by cancer cells, including breast cancer cells. There are currently dozens of completed MAB applications for patients with various types of cancer

ii. Recent developments in MABs target immune-regulating receptors (checkpoints) in T-cells such as CTLA-4 and PD-1. These receptors provide a negative signal to the active T-cells to stop their activity at the end of their antigenic response. Tumors often use this physiological regulatory mechanism to prevent resistance, which in turn stops the TILs antitumor response. Clinical application of checkpoint inhibitory MABs, which interferes with this tumor prevention mechanism, has resulted in improved survival in a proportion of patients with melanoma and carcinoma.

iii. In 2018, for their work in cancer immunotherapyJames P. Allison and TasukoHonjo were awarded the Nobel Prize in Physics or Medicine. JP Allison's team discovered the TCR in 1982 and was going to develop the area of checkpoint blockade; This leads to the breakthrough drug epilimumab. The group of Honjo discovered an enzyme important for the mechanism involved in the protein-blockade of PD1 and PD1 checkpoints, as well as the class-switch redesign of antibodies.

iv. Adaptive T-cell therapy is an example of which involves the transfer of donor cells from allogeneic peripheral blood to achieve a graft-versus-leukemia (GVL) effect in patients with leukemia. A GVL animal model was developed for advanced metastasized cancer in 201. Immunotherapy usually works in the early stages but rarely in late-stage disease. In this model, tumor-resistant MTCs was used instead of normal T-cells. After single transplantation of allogeneic MTCs into 5 guy irradiated cationic rats with large tumor burden and metastasis to the liver and kidneys, complete cancer was observed. Later, in this model it was observed that tumor-resistance MTCs from the bone marrow

are higher than those from the spleen; They use GvL without inducing a graft-versus-host response. The process involved in this effective immunotherapy has been explained for over 10 years and has recently been summarized.

v. In 2001, Ferrer et al **[50]** described the treatment of human tumors in NOD / SCD rats with reactive MTC obtained from patients with bone marrow. A single intervertebral transfer of such cells induces resistance to subcutaneous atlas tumorgenotransplants. Tumor regression was associated with infiltration by human T-cells and DC, and with tumor cell apoptosis and necrosis. Reactivating T-cells from peripheral blood in the same patients showed much less antitumor response. Shortly afterwards, Feuerer et al demonstrated T-cell priming in the bone marrow in response to blood-borne antigens. This phenomenon has the potential to awaken long-lasting immune resistance.

vi. The Immunological and Oncological Center Cologne (IOZK, Cologne, Germany) has developed a second generation ATV-NDV vaccine [consisting of three components: autologous DC, TAA and NDV]. The second two components were derived from an oncolysis of atherosclerotic NDV-infected tumor cells. IOZK succeeded in producing these components at the highest quality level (Good Manufacturing Practice, GMP). IOZD was the first global company to produce NDV according to GMP standards. Therefore, the company has received official approval for its products on a compassionate basis.

vii. Since 2015, IOZK has provided a viral oncolysis-pulsed DC vaccine (VOL-DC). Also, it provides an innovative multimodal strategy of cancer immunotherapy combined with hyperthermia / oncolytic NDV pretreatment with specific autologous antitumor vaccines.An overview of chemotherapy and biological therapy.

An overview of chemotherapy and biological therapy

An overview of the innovative forms of cancer therapy in recent decades is presented in Table-1. Briefly, the following eight types of agents are listed: i) Chemotherapeutic cytostatic drugs, e.g., docetaxel, capecitabine, gemcitabine, irinitocan, ixabepilone or pemetrexed. ii) Chemically synthesized SMIs, such as imatinib or sanitinib, which target KIT oncogenic signal transduction pathways with specific targets of cancer, such as gastrointestinal stromal cancer or chronic malignant leukemia. iii) MABs that target tumor cells, e.g., those that express growth factor receptors [Human Epidermal Growth Factor Receptors (HR) -1 and HR-2] or oncogenes (RAS). iv) MABs that target the vascular endothelium to inhibit tumor-related angiogenesis. v) Cells that target barrier receptors in T-cells and interfere with immune control. vi) Genetically modified T-cells for acceptable T-cell therapy; These atolls, however, reveal an artificial CAR with a combination of antibody-binding sites and a T-cell signaling chain. vii) Antitumor vaccines for active specific immunotherapy. viii) OV, which exhibits tumor cellulitis and induces tumor cell death (oncolysis); These agents induce immunogenic cell death (ICD) and positively affect patients' immunity**[51]**.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

Type of therapy	Chemical or Biological	Mechanism of action	Physiological	Side effects
Cytostatic drugs	Chemical	Interfere with cell proliferation	No	Grade 1-4
Small molecule inhibitors[a]	Chemical	Targeted therapy: Interfere with oncogenic signal transduction	Yes	Grade 1-4
Antitumor MAbs[b]	Biological	Targeted immunotherapy	Yes	Grade 1-3
Anti-angiogenesis MAbs [c]	Biological	Inhibit angiogenesis	Yes	Grade 1-3
Checkpoint inhibitor MAbs [d]	Biological	Immune regulation	No	Grade 1-4
CAR-T cells	Biological	Targeted cytotoxic T lymphocytes	No	Grade 1-3
Antitumor vaccines	Biological	Active specific vaccination	Yes	Grade 0-2
Oncolytic viruses[e]	Biological	Oncolysis, induction of immunogenic cell death	Yes	Grade 0-2

Table:1
Note:
[a]e.g. KIT inhibitors, such as sunitinib, imatinib, sorafenib and lapatinib;
[b]e.g. cetuximab, trastuzumab, panitumumab (targets include HER-1, HER-2 and RAS);
[c]e.g. bevacizumab (Avastin; targets VEGF-L), ramucirumab (Cyramza; targets VEGF receptor 2);
[d]e.g. ipilimumab (targets cytotoxic T-lymphocyte-associated protein 4), nivolumab (targets programmed cell death protein 1), atezolizumab and durvalumab (targets programmed death-ligand 1);
[e]e.g. RNA viruses, including Newcastle Disease Virus from attenuated natural wild type strains.
HER, human epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Chemotherapeutic cytostatic drugs and SMIs are chemical treatments, whereas other therapies are biological. The efficacy and side effects of these drugs are presented in Table I. Notably, the side effects of most of the new approved drugs from this type of therapy, whether chemical or biological, were severe (grades 1-4). Only antitumor vaccines and OVs with side effects between grades 0 and 2 are well tolerated.

The difference between chemical or biological cancer therapies is therefore not enough to explain why any treatment is well tolerated or can be done. Therefore, it may be suggested that any other parameters be introduced, such as whether any therapy is physiological. Physiological means physiological according to the functioning of the human body as a complex process at multiple levels (including cells, tissues, organs and organ systems, cardiovascular, respiratory, gastrointestinal, renal, endocrine, reproductive or nervous system). However, determining whether a therapy is physiological is not so easy; Side effects may be effective in this definition, as they can be used to determine if a therapy is not physiological. The first table includes a column on whether therapies are considered 'physiological'. Regarding SMIs, it was concluded that they were physiological, since SMIs represented a tumor-targeted approach; However, normal cells can also be infected. Regarding checkpoint inhibitor MABs, it was concluded that they are not physiological, as interventions in immune control also interfere with the autoimmune response. With regard to CAR-T cells, it was concluded that they were not physiological, as the receptor is artificial and all cells have the same receptor.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July2021, pp: 497-514www.ijaem.net ISSN: 2395-5252

The difference between physiological and non-physiological treatment is very significant. Significantly, meta-analyzes of toxicity of novel drugs approved by the Food and Drug Administration (FDA) were conducted between 2000 and 2010. The drugs in the novel were approved on the basis of somewhat accurate estimates of benefits but on the basis of less specific estimates of harm**[52][53]**. Analyzes revealed that novel drugs were associated with a significantly higher risk of harm compared with the control group treated with standard therapy; This was true for toxic deaths, discontinued treatment, and grades 3 or 4. The most common serious side effects are fatigue, diarrhea, nausea / vomiting, febrile neutropenia and rash. Studies with 4 studies and an analysis of> 46,000 patients have concluded that immunotherapy seems to have better protection and tolerability than other treatments.

Important parameters of chemotherapy, immunotherapy and OV therapy

A summary of important parameters of chemotherapy, immunotherapy and OV therapy is presented in Table II. Tumor specificity is higher for immunotherapy and OVT but less for chemotherapy. All three therapies show toxicity to the proliferation of tumor cells, while other-proliferative tumor cells (e.g., tumor stem cells and dormant tumor cells) can be leased only through immunotherapy and OV therapy. In contrast, chemotherapy uses unwanted toxic activity against normal proliferating cells (e.g., bone marrow and endothelium) inside the body, but not in the case of immunotherapy and OV therapy.

Table: ii

Parameter	Chemotherapy	Immunotherapy	OVtherapy
Tumor specificity	Low	High	High
Toxicity towards proliferating TCs	+	+	+
Toxicity towards nonproliferating TCs	-	+	+
Toxicity towards normal proliferating cells	+	-	-
Effects on the immune system	Negative	Positive	Positive
Optimized by evolution	No	Yes	Yes
Associated with self-tolerance	No	Yes	Yes
Associated with a memory function	No	Yes	Yes
Approved for application in patients with cancer	Yes[a]	No[b]	No[c]

Note:

[a]Since the 1970s.

[b]With the exception of monoclonal antibodies and checkpoint inhibitors in certain cases.

[c]With the exception of T-VEC approved for melanoma immunotherapy and Newcastle disease virus in Germany with a permit for compassionate use. CT, chemotherapy; IT, immunotherapy; OVT, oncolytic virus therapy; TCs, tumor cells.

Chemotherapy has a negative effect on the immune system, while immunotherapy and OV therapy have a positive effect on the immune system. Immunotherapy and OV therapy are based on systems adapted to evolution, while chemotherapy was originally invented by chemists. The immune system has developed sophisticated methods of self-tolerance to prevent self-immune responses and maintain body integrity. Chemotherapy is toxic to normal cells causing deadly A.E. In addition, the immune system has a memory function, which is important for achieving long-term therapeutic effects; It lacks chemotherapy.

Though immunotherapy and OV therapy have many advantages but these therapies are not yet part of standard cancer therapy; there are only a few exceptions.

CONCLUSION

Systematic methods of cancer treatment are necessary in the stage of cancer transformation, when it is transformed from local to systemic form of the disease through metastasis. Systematic forms of cancer treatment are prophylactic (e.g., in an operative postoperative situation) or therapeutic. The primary goal of chemotherapy is to reduce tumor burden, whereas the goal of immunotherapy is to build resistance to systemic resistance. The focus carries the tumor or the host organism's tumor and its immunity.

The aim of this review was to present the concepts of the novel, which may reduce side effects from the treatment of systemic cancer. Targeted therapy with chemically designed SMIs has higher tumor specificity than conventional chemotherapy; However, the side effects are the same. The majority of novel concepts are derived from biological types of therapy (**Table 1-2**); Some of these biological treatments show considerable side effects. In contrast, conventional immunotherapy with vaccines and OV therapy shows only mild side effects and is well tolerated.

Significantly, a combination of cancer immunotherapy and OV therapy was randomized to controlled trials. This previous study evaluated the efficacy of operative vaccination with ATV-NDV at the stage of fourth CRC patients after liver metastasis. The results revealed that a significant survival benefit of 10 years was found in about 30% of patients with colon cancer. Its tendency is found in melanoma patients treated by IFB. The side effects of these two approaches, however, were different: grades 0–2 for immunization studies compared to grades 1–4 for ICB studies.

Related to future developments, it has been suggested to effectively combine vaccine immunotherapy to expand, expand and facilitate vaccines, OV and immune checkpoint inhibitors. The key findings of this review are: i) Inclusion in standard care may be beneficial to immunotherapy. Evidence-based drug regulations should be consistent with the study of personalized immunotherapy as well as multimodal therapy in general. ii) Recommendations for the use of cytostatic drugs that produce serious side effects and low efficacy should be reviewed by internal medicine associations.

REFERENCES

[1]. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countrieshttps://pubmed.ncbi.nlm.nih.gov/33538338/

[2]. Sudhakar. A, History of Cancer, Ancient and Modern Treatment Methods. https://edisciplinas.usp.br/pluginfile.php/118662/mod_resource/content/2/hystory_cancer_2.pdf

[3]. Early history of cancer, American cancer research society.https://www.cancer.org/cancer/cancer-basics/history-of-cancer/what-is-cancer.html

[4]. Karpozilos A, Pavlidis N (2004). "The treatment of cancer in Greek antiquity". European Journal of Cancer. 40 (14): 2033–40. doi: 10.1016/j.ejca.2004.04.036. PMID 15341975

[5]. Marilyn Yalom "A history of the breast" 1997. New York: Alfred A. Knopf. ISBN 0-679-43459-3

[6]. Grange JM, Stanford JL, Stanford CA (2002). "Campbell De Morgan's 'Observations on cancer', and their relevance today". Journal of the Royal Society of Medicine. 95 (6): 296–9. doi:10.1258/jrsm.95.6.296. PMC 1279913. PMID 12042378.

[7]. A text book of Pathophysiology, Dr. Madan Kaushik.

[8]. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst. 2007; 99: 847-57.

[9]. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. Oncologist. 2007; 12: 713-8.
[10]. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006; 355: 2542-50.
[11]. Cho JY, Kim JH, Lee YH, Chung KY, Kim SK, Gong SJ, et al. Correlation between K-ras gene mutation and prognosis of patients with non-small cell lung carcinoma. Cancer. 1997; 79: 462-67.
[12]. Britten RA, Liu D, Tessier A, Hutchison MJ, Murray D. ERCC1 expression as a molecular marker of cisplatin resistance in human cervical tumor cells. Int J Cancer. 2000; 89: 453-57.
[13]. Cohen SM, Lippard SJ. Cisplatin: from DNA damage to cancer chemotherapy. Prog Nucleic Acid Res Mol Biol. 2001; 67: 93-130.
[14]. Kartalou M, Essigmann JM. Mechanisms of resistance to cisplatin. Mutat Res. 2001; 478: 23-43.
[15]. Rowinsky EK, Onetto N, Canetta RM, Arbuck SG. Taxol: the first of the taxanes, an important new class of antitumor agents. Semin Oncol. 1992; 19: 646-62.
[16]. Rowinsky EK, Onetto N, Canetta RM, Arbuck SG. Taxol: the first of the taxanes, an important new class of antitumor agents. Semin Oncol. 1992; 19: 646-62.
[17]. Eckardt JR. Antitumor activity of docetaxel. Am J Health Syst Pharm. 1997; 54: S2-6.
[18]. Gligorov J, Lotz JP. Preclinical pharmacology of the taxanes: Implications of the differences. Oncologist. 2004; 9: 3-8.
[19]. Chang AY, Kim K, Glick J, Anderson T, Karp D, Johnson D. Phase II study of taxol, merbarone, and piroxantrone in stage IV non-small-cell lung cancer: The Eastern Cooperative Oncology Group Results. J Natl Cancer Inst. 1993; 85: 388-94.
[20]. Gatzemeier U, Heckmayer M, Neuhauss R, Schluter I, von Pawel J, Wagner H, et al. Chemotherapy of advanced inoperable non-small cell lung cancer with paclitaxel: a phase II trial. Semin Oncol. 1995; 22: 24-8.
[21]. Ofir R, Seidman R, Rabinski T, Krup M, Yavelsky V, Weinstein Y, et al. Taxol-induced apoptosis in human SKOV3 ovarian and MCF7 breast carcinoma cells is caspase-3 and caspase-9 independent. Cell Death Differ. 2002; 9: 636-42.
[22]. Park SJ, Wu CH, Gordon JD, Zhong X, Emami A, Safa AR. Taxol induces caspase-10-dependent apoptosis. J Biol Chem. 2004; 279: 51057-67.
[23]. Lin HL, Liu TY, Chau GY, Lui WY, Chi CW. Comparison of 2-methoxyestradiol-induced, docetaxel-induced, and paclitaxel-induced apoptosis in hepatoma cells and its correlation with reactive oxygen species. Cancer. 2000; 89: 983-94.
[24]. Suzuki A, Kawabata T, Kato M. Necessity of interleukin-1beta converting enzyme cascade in taxotere-initiated death signaling. Eur J Pharmacol. 1998; 343: 87-92.
[25]. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol. 2003; 21: 2237-46.
[26]. von Minckwitz G, Jonat W, Fasching P, du Bois A, Kleeberg U, Luck HJ, et al. A multicentre phase II study on gefitinib in taxane-and anthracycline-pretreated metastatic breast cancer. Breast Cancer Res Treat. 2005; 89: 165-72.
[27]. Shi L, Tang J, Tong L, Liu Z. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials. Lung Cancer. 2014; 83: 231-9.
[28]. Li F, Zhu T, Cao B, Wang J, Liang L. Apatinib enhances antitumour activity of EGFR-TKIs in non-small cell lung cancer with EGFR-TKI resistance. Eur J Cancer. 2017; 84: 184-92.
[29]. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012; 62: 220-41.
[30]. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol. 2007; 25: 2212-7.

[31]. Wang Y, Schmid-Bindert G, Zhou C. Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. Ther Adv Med Oncol. 2012; 4: 19-29.
[32]. Zhao J, Guerrero A, Kelnar K, Peltier HJ, Bader AG. Synergy between next generation EGFR tyrosine kinase inhibitors and miR-34a in the inhibition of non-small cell lung cancer. Lung Cancer. 2017; 108: 96-102.
[33]. Hsiao WL, Liu L. The role of traditional Chinese herbal medicines in cancer therapy--from TCM theory to mechanistic insights. Plan-ta Med. 2010; 76: 1118-31.
[34]. Meijer L, Borgne A, Mulner O, Chong JP, Blow JJ, Inagaki N, et al. Biochemical and cellular effects of roscovitine, a potent and selective inhibitor of the cyclin-dependent kinases cdc2, cdk2 and cdk5. Eur J Biochem. 1997; 243: 527-36.
[35]. Zhang F, Zhang T, Gu ZP, Zhou YA, Han Y, Li XF, et al. Enhancement of radiosensitivity by roscovitinepretreatment in human non-small cell lung cancer A549 cells. J Radiat Res. (Tokyo) 2008; 49: 541-8.
[36]. Park SE, Yoo HS, Jin CY, Hong SH, Lee YW, Kim BW, et al. Induction of apoptosis and inhibition of telomerase activity in human lung carcinoma cells by the water extract of Cordyceps militaris. Food Chem Toxicol. 2009; 47: 1667-75.
[37]. Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res. 2004; 24: 2783-840.
[38]. Whyte L, Huang YY, Torres K, Mehta RG. Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. Cancer Res. 2007; 67: 12007-17.
[39]. Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS, et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res. 2010; 70: 7392-9.
[40]. Tong Z, Wu X, Chen CS, Kehrer JP. Cytotoxicity of a non-cy-clooxygenase-2 inhibitory derivative of celecoxib in non-small-cell lung cancer A549 cells. Lung Cancer. 2006; 52: 117-24.
[41]. Tan YH, Lee KH, Lin T, Sun YC, Hsieh-Li HM, Juan HF, et al. Cytotoxicity and proteomics analyses of OSU03013 in lung cancer. Clin Cancer Res. 2008; 14: 1823-30.
[42]. Lu J, Papp LV, Fang J, Rodriguez-Nieto S, Zhivotovsky B, Holmgren A. Inhibition of Mammalian thioredoxin reductase by some flavonoids: implications for myricetin and quercetin antican-cer activity. Cancer Res. 2006; 66: 4410-8.
[43]. Shvarev IF, Tsetlin AL. [Anti-blastic properties of berberine and its derivatives]. FarmakolToksikol 1972; 35: 73-5.
[44]. Wang K, Zhang C, Bao J, Jia X, Liang Y, Wang X, et al. Synergistic chemopreventive effects of curcumin and berberine on human breast cancer cells through induction of apoptosis and autophagic cell death. Sci Rep. 2016; 6: 26064.
[45]. Kumar VB, Yuan TC, Liou JW, Yang CJ, Sung PJ, Weng CF. An-troquinonol inhibits NSCLC proliferation by altering PI3K/mT0R proteins and miRNA expression profiles. Mutat Res. 2011; 707: 42-52.
[46]. Chemo therapy drugs and side effects. Beaumont https://www.beaumont.org/treatments/chemotherapy-drugs-side-effects
[47]. Managing physical side effects, Cancer.nethttps://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/fatiguehttps://www.healthline.com/health/chemotherapy#procedure
[48]. Immunotherapy to treat cancer, National cancer institute.https://www.cancer.gov/about-cancer/treatment/types/immunotherapy#how-does-immunotherapy-work-against-cancer
[49]. Vasaturo A, Di Blasio S, Peeters DG, de Koning CC, de Vries JM, Figdor CG, Hato SV. Clinical implications of co-inhibitory molecule expression in the tumor microenvironment for DC vaccination: A game of stop and go. Front Immunol. 2013; 4:417. doi: 10.3389/fimmu.2013.00417.
[50]. Feuerer M, Beckhove P, Bai L, Solomayer EF, Bastert G, Diel IJ, Pedain C, Oberniedermayr M, Schirrmacher V, Umansky V. Therapy of human tumors in NOD/SCID mice with patient-derived reactivated memory T cells from bone marrow. Nat Med. 2001;7:452–458. doi: 10.1038/86523.
[51]. Schirrmacher V. Quo Vadis Cancer Therapy? Fascinating discoveries of the last 60 years. Lambert Academic Publishing; 2017. pp. 1–353.

[52]. Niraula S, Seruga B, Ocana A, Shao T, Goldstein R, Tannock IF, Amir E. The price we pay for progress A meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol. 2012;30:3012–3019. doi: 10.1200/JCO.2011.40.3824.

[53]. Niraula S, Amir E, Vera-Badillo F, Seruga B, Ocana A, Tannock IF. Risk of incremental toxicities and associated costs of new anticancer drugs: A meta-analysis. J Clin Oncol. 2014;32:3634–3642. doi: 10.1200/JCO.2014.55.8437.