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Introduction to Cancer and the Multiple Protein and Enzymes to Be Used to Treat the Cancer: A Review

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ABSTRACT

Any of the several illnesses characterised by the growth of aberrant cells that divide out of control and have the capacity to invade and destroy healthy bodily tissue are referred to as cancers. The propensity of cancer to spread throughout your body is common. Two-thirds of the 145,000 deaths and 270,000 new cases that occur each year globally take place in developing nations. Cancer can produce a range of signs and symptoms, depending on which part of the body is afflicted. Research on corresponding and substitute medicine that covenants with cancer controlling has recently received more attention. Since its inception, the Indian traditional medicine known as Ayurveda has had great success employing plant-based medicines to prevent or suppress a variety of cancers. There are numerous cellular and metabolic targets drawn to enhance by many ways to cure cancer and also boost the action of target protein.

INTRODUCTION

One of the important feared diseases of 20th century, Cancer is now one of the most prevalent in the 21st. Cancers are any of the many diseases that are characterised by the expansion of abnormal cells that uncontrolled dividation, have ability to pierce, and cause harm to good physiological tissue. Cancer has a tendency to spread throughout your body. 6.7 million individuals worldwide pass away from cancer every year. Two-thirds of the 145,000 deaths and 270,000 new cases that occur each year globally take place in developing nations. It is viewed as a rival to modernity and the sophisticated sociocultural pattern dominated by western medicine. The best scientific research across disciplines is being done to battle this disease, but the perfect cure is not yet to be brought into world medicine.[1]

Cancer can produce a range of signs and symptoms, depending on which part of the body is afflicted. Here are some general signs and symptoms of cancer that are not specific to this illness:

• Fatigue.

• Feelable lump or region of thickening below the skin.

• Change in weight, involving an unexpected losing or gaining.

•Skin colour changes, such as skin may be turning yellow/darkening of skin or modifications to existing moles.

• Modifications in bowel patterns.

• Continuing cough or issues in breathing.

• Difficulty in swallowing.

By abstaining from the risk of emerging definite cancers can be abridged by quitting smoking, sustaining a weight, restrictive alcohol consumption, eating fruits, root vegetable, and whole grains, getting immunised beside particular transferrable diseases, preventive consumption of managed meat and red meat, and restraining disclosure to direct sunlight.

Environmental variables that underwrite to cancer mortality include disclosure to a variety of chemical agents, environmental toxins, poor diet and corpulence (30–35%), infections (15–20%), and radiation. The use of tobacco is responsible for 25–30% of cancer deaths.

The various types of cancers are:

1. **Breast Cancer:** Breast cancer is another most frequent cancer in women in United States, after skin cancer.

The yearly new cases anticipated are in women: 268,600 & in male: 2,670. The estimated annual death is in women: 41,760 and in male: 500. The rate of 5-year survival is 90% of people are women (2008–2014).

2. **Lung Cancer:** Lung cancer, the second most frequent malignancy, is the main reason for cancer-related death.

There are 228,150 projected new cases each year out of which around 142,670 people die each year. The five-year survival rate is 23% (2008–2014).

3. **Prostate Cancer:** Prostate cancer, the furthermost prevalent cancer and another leading reason of cancer mortality in American men, is typically slow-growing.

There are approximately 164,690 new cases every year out of which approximately 29,430 deaths occur each year and there is 98% of survivorship after five years (2008–2014).

4. **Rectal and Colon Cancer:** Cancers of the colon or rectum are referred to as colorectal cancer. They combine to form the big intestine.

The yearly projected new cases are 145,600 and projected annual deaths are 51,020 & survival rate after five years: 64% (2008–2014).

5. **Melanoma (Skin):** Cancer that starts in the specialised cells that yield the pigment that provides skin its colour is called a melanoma (melanin).

There are 96,480 projected new cases each year and annual estimated death toll: 7,230. The Survival rate after five years is 92% (2008–2014).

6. **Leukemia (All types):** Cancers called leukemias start in the bone marrow, which produces blood.

Large numbers of aberrant white blood cells accumulate in the blood and bone marrow to the point where they push out healthy blood cells, which is a characteristic of many tumours. The body finds it more difficult to control bleeding, deliver oxygen to its tissues, and fight infections as a result.

There are 61,780 new cases are anticipated each year and approximately 22,840 fatalities per year. The Survival rate after five years is 61.4% (2008–2014).

Various Targets of Cancer:

Research on corresponding and substitute medicine that covenants with cancer controlling has recently received more attention. Since its inception, the Indian traditional medicine known as Ayurveda has had great success employing plant-based medicines to prevent or suppress a variety of cancers.

There are numerous cellular and metabolic targets drawn to enhance by many ways to cure cancer and also boost the action of target protein.

There are many targets to cure Cancer:

1. Anaplastic lymphoma kinase[2]
2. Topoisomerase[3]
3. XIAP Protein (X-linked inhibitor of apoptosis protein) [4]
4. hnRNP-K protein [5]
5. HER2 [6]
6. Src family kinases (SFKs) [7]
7. Cyclin D-cyclin-dependent kinase 4 (CDK4) [8]

1. Anaplastic Lymphoma Kinase:

Lung carcinomas, which are formed from epithelial cells, make up the great majority of primary lung malignancies. The most frequent type of cancer-related death among men is lung cancer and the cause of 1.3 million fatalities worldwide is women as per every year as of 2004. [9]Difficulty to breath, coughing, and weight loss are the supreme typical symptoms.

Receptor for epidermal growth factor (EGFR), an often-over expressed receptor tyrosine kinase in lung cancer that is not tiny cell (NSCLC). [10]

Because the activation of phosphorylated EGFR results which are in the phosphorylation of downstream proteins important for cell attack, metastasis, and apoptosis, these receptors are essential for the survival of tumour cells. Expression seems to depend mostly on histological types, which are often expressed not only in large cell carcinomas and adenocarcinomas but also in squamous cell carcinomas.

Anaplastic lymphoma kinase gene activating mutations or translocations have been connected to anaplastic large-cell lymphoma [11], neuroblastoma [12,13], provocative bowel disease, and other malignancies (ALK), Myofibroblastic tumour and lung cancer. Cancer is associated with an unusual protein called EML4-ALK fusion gene-encoded protein has kinase activity. There are many distinct EML4-ALK chimeric alternatives that show *in vitro* transformation breakpoints in various EML4 exons.

Preclinical examines of more than 600 tumorous human cell lines and a selective ALK inhibitor under study specifically compact the growth of cells with inherited ALK modifications, demonstrating the validity of ALK as a pharmacological target and demonstrating its role in the proliferation of malignant cells. Crizotinib (PF-02341066, Pfizer) and Sunitinib malate are oral ATP-competitive selective inhibitors of the ALK and MET tyrosine kinases that block ALK activation by inhibiting tyrosine phosphorylation at nanomolar levels.[14,15]

2. Topoisomerase:

DNA topoisomerases, which are widely distributed enzymes that unlink DNA, are essential for numerous biological activities requiring DNA. DNA topoisomerases come in type I and type II varieties. Duplex DNA's one DNA strand is broken by type I topoisomerases, allowing either the rotation of the downstream DNA duplex about the break or passage of the other DNA strand the strand once it has broken, and then reseal it. Therefore, they change the connecting number in increments of one.[16,17] Type I topoisomerases come in three different subtypes: type IA, type IB, and type IC. To bind to DNA, type IA topoisomerases need a nick or a single-stranded region.

One strand of duplex DNA is cleaved, the site of tyrosine which is active is covalently attached to a 50-phosphoryl group, and the 'strand' is then used. DNA topology can be

changed by passage's process. Types IB and IC topoisomerases, in contrast covalently bind the active-site tyrosine of one duplex DNA strand to a 30-group phosphoryl, relax DNA supercoils by using the "swivel" mechanism. Microbiological topoisomerase I (Top 1) and Top 3 are examples of type IA topoisomerases. Eukaryotic Top 1 is a type IB organism. Topoisomerase V, a member of the archaeal genus Methanopyrus, is the sole known subtype of type IC member. It is noteworthy that type IB topoisomerases are found in some bacteria.

When catalysing the process using the "strand passing" method, type II topoisomerases undergo a number of significant conformational changes. During the cleavage of two DNA strands by type II topoisomerases, phosphotyrosyl bonds are created between the two active-site tyrosines and a pair of 50 phosphates are required to ensure that DNA's integrity can be recovered. Type II topoisomerases come in type IIA and type IIB subtypes. [18]All other type II topoisomerases fall within the type IIA subtype, while topoisomerase VI belongs to the type IIB subtype. Each topoisomerase subtype is structurally and functionally distinct and constitutes a family of proteins.

Many anticancer and antibacterial medications have type IIA topoisomerases in mind when designing their therapeutic targets. The role of topoisomerases in cells topoisomerases of type IB is eukaryotic Top 1's swivel action is necessary to relieve DNA superhelical stress that develops during both DNA transcription and replication. Topoisomerases of type IIA the only topoisomerase that can create negative supercoils is DNA gyrase.

3. XIAP Protein (X-linked inhibitor of apoptosis protein):

The caspases-3, caspase-7, and caspase-9 are all neutralised by the X-linked inhibitor of apoptosis protein (XIAP), is an adherent of the IAP family. The apoptotic process in the cell was slowed down by the protein's overexpression, which prevented the growth of cancer. The again fourth common reason of cancer deaths internationally is hepatocellular carcinoma (HCC), one of the most collective types of prime liver cancer. Hepatitis B and C virus,[19] alcohol intake, fatty liver disease, and other variables are all linked to the development of liver cancer. Low rates of early detection make it difficult to treat cancer once it has progressed and developed symptoms to cure.

The most popular methods for treating HCC are liver transplantation, surgery, radiation, and chemotherapy, however failure rates for cancer treatments in advanced stages are higher. Early detection of liver cancer and more effective substances that can stop HCC from

growing are crucial for increasing survival rates by identify the disease connected to HCC to lessen it. [20]

A sort of planned cell death called apoptosis aids multicellular organisms in getting rid of surplus cells. IAPs are a major cause of cancer because they impair apoptosis in the cells. One of the most important anti-apoptotic proteins in the IAP family, XIAP, has a BIR3 domain that can inhibit caspase-9 whereas a BIR2 domain can inhibit caspases-3 and 7, respectively. Cancer cells can evade drug-induced cell death brought on by pro-survival protein overexpression or pro-apoptotic death regulator deficiencies this is one of the primary causes of chemotherapy's failure. Oncogene neutralisation has demonstrated the capacity to shorten the time-consuming chemotherapy procedure, which is helpful in lowering the amount and dose of medications used in cancer treatment. As a result, XIAP-based targeted therapies would be excellent for treating a variety of cancer disorders, such as hepatocellular carcinoma.

Clinical antisense technology, SMAC mimics, and siRNA have all attempted to reduce the overexpression of XIAP; however, due to their neurotoxicity, antisense-based therapies (such as AEG35156) have been discontinued from Phase-I clinical trials. The antisense-based therapy works by decreasing stem cell XIAP mRNA levels and boosting apoptotic cell death. The most common type of important chemicals that operate against the IAP family can also neutralise the XIAP. There are several amino acids in the the N-terminus of SMAC/proline Diablo's is able to interact with the binding groove of concurrent use of the XIAP-BIR2 and XIAP-BIR3 domains. [21]

4. hnRNP-K Protein:

Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a broad family of RNA-binding proteins (RBPs) that are elaborate in the ruling of transcription and translation as well as alternative splicing, mRNA stability, and other aspects of nucleic acid metabolism. In the nucleus of a eukaryotic cell, many ribonucleoproteins (RNPs) assemble on to newly generated transcripts. The heterogeneous nuclear ribonucleoproteins are a subset of these RNPs (hnRNPs). They help to regulate translation, stabilise mRNA during cellular transport, and help newly generated heterogeneous nuclear RNAs (hnRNAs/pre-mRNAs) mature into messenger RNAs (mRNAs). Given their variety of functions and complexity, hnRNPs are essential proteins for cellular nucleic acid processing.

There are many different types of head and neck cancers (HNC), and each one has unique characteristics and treatment options. In spite of advancements in diagnosis, high recurrence, and local management, patient long-term survival rates have not greatly risen in recent years. hnRNP-K protein, involved in splicing and cell cycle progression.[22]

Less is known about the other key hnRNP proteins' involvement in splicing, mostly because to the small number of cases. It is debatable if hnRNP C plays a role in splicing because the early reports were never verified. Splicing efficiency and one instance of alternative splicing control in vivo utilising a minigene have both been linked to hnRNP K. In 293T cells, overexpression of hnRNP M can facilitate exon inclusion and exon skipping events in a few alternative exons.

We have examined the individual abilities of several of the major hnRNP proteins to influence the generation of splice isoforms in order to regulate the kind of action of the key hnRNP proteins that operate in mRNA processing and to explore the potential function of the others.

5. HER2

The second most leading reason of cancer decease for women in the United States, cancer of breast is the most prevalent malignancy. In 2015, it is predicted that over 40,000 women will pass away from the disease and around 231,000 women will identify with breast cancer. 25–30% of breast tumours exhibit HER2 positive, which can be identified by protein overexpression, gene amplification, or both. HER2 positive, [23] regardless of stage, is linked to more aggressive tumour behaviour and significantly reduced germ-free and overall existence in the nonappearance of HER2 targeted therapy.

HER2-positive One kind of breast cancer is HER2-positive (human epidermal growth factor receptor type 2) i.e. (HER2). This protein promotes the growth of cancer cells. Despite adjuvant trastuzumab-based therapy, a quarter of patients with HER2+ early breast cancer immobile involvement relapse, and HER2+ metastatic breast cancer (MBC) is still a fatal disease. HER2 is a potent healing target that is significant through the disease's progression. [24]

Lapatinib, a novel anti-HER2 monoclonal antibody, Pertuzumab, a minor molecule tyrosine kinase inhibitor of HER2 and the epidermal progress factor receptor, and ado-trastuzumab emtansine (T-DM1), a novel antibody-drug conjugate,[25] are just a few of the novel HER2

targeted drugs that have recently become accessible and offer additional treatment options. Recent clinical trials have shown that using Pertuzumab or T-DM1 in combination with traditional HER2 targeted therapy results in better outcomes.

6. Src Family D Kinases (SFKs)

During the growth of tumours, Src family kinases (SFKs) are essential for cell connection, incursion, propagation, survival, and angiogenesis. Nine family members that make up SFKs have a similar structure and function. In tumour tissues, SFKs are typically overexpressed or highly activated, and they serve as key mediators in a number of signalling pathways crucial to oncogenesis. Tyrosine kinase receptors like the EGFR and the VEGF receptor are capable of interacting with SFKs. [26] Through the Ras/ERK/MAPK way, SFKs can influence cell proliferation, and through transcription factors like STAT molecules, they can control gene expression. Through interactions with integrins, actin, GTPase-activating proteins, like p130CAS and paxillin, and kinases like principal adhesion kinases, SFKs can also influence cell adhesion and migration.

By turning on the genes for angiogenic growing factors such fibroblast growth factor, VEGF, and interleukin 8, SFKs can also regulate angiogenesis. These important findings have led to the expansion of small-molecule SFK inhibitors that are currently experiencing initial stage clinical testing. In preclinical studies, these medications have demonstrated the ability to reduce tumour development and metastasis. The compounds seem to be safe for individuals and may expand the arsenal of treatments for particular cancer types. [27,28]

7. Cyclin D–cyclin-dependent Kinase 4 (CDK4):

Sideways with the other D-type cyclins to a slighter extent, Cyclin D1 is commonly dysregulated in cancer and is a biomarker of cancer phenotype and disease progression. The ability of these cyclins to activate CDKs CDK4 and CDK6 is the most well-established mechanism of their carcinogenic effects, making them a desirable therapeutic target. CDK4 or CDK6 activation indorses cell cycle development by phosphorylating substrates like RB and transcription factors involved in proliferation and discrepancy. [29]

These kinase multiplexes also mark molecules involved in cytoskeletal modelling, cell adhesion and motility, mitochondrial function, and cell development. D-type cyclins interact with chromatin-modifying enzymes and other transcription factors, such as steroid hormone receptors, to regulate the transcription of families of genes intricate in explosion and

differentiation without catalysing any reactions. The D-type cyclins not only support efficient DNA repair but also incidentally activate CDK2 by securing CDK inhibitors in addition to directly activating CDK. [30]

Potential therapeutic targets include cyclin D1 and the CDKs it is linked to. Early CDK inhibitors showed promising outcomes in laboratory systems, but there was no indication of their efficacy in human studies. Poor pharmacokinetics, ineffective dosage regimens, and clinical testing in unselected patient populations are potential causes of this dismal result. Clinical trials for CDK4 and CDK6 second-generation, more focused inhibitors are currently being conducted.

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