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RECENT TRENDS IN THE MANAGEMENT AND TREATMENT OF CANCER-A STATUS REPORT

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ABSTRACT

Cancer is a group of diseases characterized by unregulated cell growth, invasion into new sites and spread of cells from the site of origin to other regions of the body. According to World Health Organisation (WHO) cancer is the second leading cause of death globally. It has claimed 9.6 million lives in the world in 2019 and India's share in it is distressing 8.17%. India ranks third in cancer cases after China and USA. However, the American Cancer Society (ACS) reported in 2018 that cancer mortality was reduced by 1.7% which includes cancer types like, lung, breast, prostate and CRC. This may be due to steady reductions in smoking, and advances in early detection and treatment. The hallmarks of cancer include independence from growth signals, irresponsiveness to signals which halt the cell division, uncontrolled replication and evasion of apoptosis, sustained angiogenesis, and metastasis. Plethora of discoveries and growing understanding of cancer biology needs to be intelligently utilized in order to combat dreaded diseases like, cancer. In spite of accumulation of tremendous knowledge, thanks to substantial funding the incidences of full-blown malignancies have always been on the rise. Serious efforts are being made across the globe by international scientific communities to find out more and more proficient methods of curing cancer. High efficacy, lower costs and least side effects are known to be the main objectives of the researchers. Undoubtedly, conquering the warfare against cancer is and will be the focal point of contemporary medical research. This is a review of the modalities and advancements in finding an elusive yet definitive cancer treatment strategy.

KEYWORDS: Cancer, tumor, metastasis, carcinogenesis, apoptosis, angiogenesis

1. INTRODUCTION

Cancer is the second leading cause of death in the world today just behind cardiovascular disease, which is the number one killer.[1] It is also a global issue majorly affecting people in developing countries. Cancer is not a new disease as it has been afflicting people throughout the world for ages.[2] Only 10% of cancer is inherited, 70% is sporadic and 20% of cancer is caused by pathogens, mainly viruses. Approximately 85% of cancers occur in epithelial cells and are classified as carcinomas. According to ACS, an estimated 606,880 Americans died because of cancer and 1,762,450 new cases are registered in 2019 (Fig.1).[1]

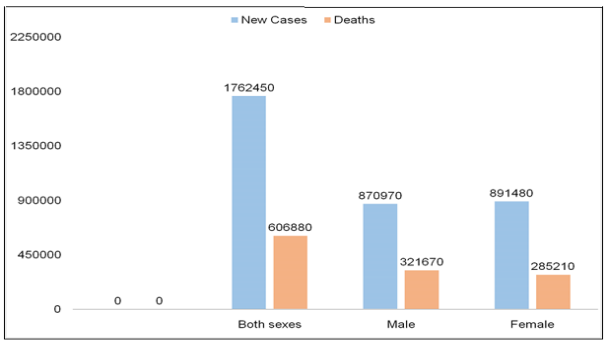

Fig.1: 2019-cancer statistics in USA.

In India as estimated in 2018 about 2.25 million people are living with cancer and 7, 84,821 cancer-related deaths are registered. It is a multifactorial disorder involving complex modifications in the genome affected by the interactions between host and environment. The hallmarks of cancer include independence from growth signals, irresponsiveness to signals which halt the cell division, uncontrolled replication and evasion of apoptosis, sustained angiogenesis, and metastasis, the capacity to penetrate into other tissues.[3] The microenvironment of benign tumor manifests dysregulation of various regulatory proteins and extracellular environment, which plays a vital role in the origin and development of cancers.[4] Plethora of discoveries and growing understanding of cancer biology needs to be intelligently utilized in order to combat dreaded diseases like, cancer. The torrent of inventions especially in the recent times can be used in the first place to prevent cancer as many types of cancers can indeed be prevented. Moreover, cancers can often be nipped in the bud by screening: primary tumors can be detected early and removed before they have metastasized, as in the case of cervical cancer. Many opportunities are there now for better screening, prevention and treatment. Across the globe millions of cancer patients extend their life due to early identification and treatment. For example, by using highly sensitive molecular assays several types of cancers can be straightforwardly diagnosed at the early stages. Advances in these areas offer immediate prospects of reducing the cancer death rate substantially. But screening and prevention so far have never been significantly effective. In spite of accumulation of tremendous knowledge, thanks to substantial funding, the incidences of full-blown malignancies have always been on the rise. This situation is unlikely to change in the near future and the need for the development novel treatment methods will continue to persist for many more years to come. Cancerous cells do not respond to the signals that activate the normal cell cycle because they have a degree of self-sufficiency which leads to the uncontrolled growth and proliferation of transformed cells.[5] If the proliferation of cancerous cells continues, it eventually leads to death. In fact, 90% of cancer related deaths are because of the spread of cancer cells to other tissues, called metastasis.[6] Cancer is an abnormal condition in which a group of cells disregard the physiological rules of the cell division and grow in an uncontrolled manner to form different types of tumors. Tumors are named depending upon the type of cell from which they originate (Table 1). Origin of cancer in man is often associated with viruses. About 15% of the incidences are found to be associated with viral oncogenes. Viruses that are known to cause cancer are, human papillomaviruses (HPVs), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), Merkel cell polyomavirus (MCPyV), HBV and HBC (hepatitis B and hepatitis C virus).[7, 8] Fig. 2. revealed about the percentage occurrences of different cancer types, and it was found that out of different cancer types breast cancer holds the topmsost position.

Cancer cells can be removed surgically or destroyed with toxic chemicals or radiation; but it is hard to eradicate every single one of them. Surgery can rarely scrabble out every metastasis, and treatments that kill cancer cells are generally toxic to normal cells as well. If even a few cancerous cells remain, they can proliferate to cause the resurgence of the disease; and, unlike the normal cells, they often evolve resistance to the drugs used against them. In spite of the difficulties, effective cures using anticancer drugs have already been found for some formerly highly lethal cancers—notably Hodgkin's lymphoma, testicular cancer, choriocarcinoma, and some leukemias and other cancers of childhood. Even for types of cancer where a cure at present seems beyond our reach, there are treatments that will prolong life or at least relieve distress. Of late, much thoughtfulness has been given to the immune system of patients and its activation through biological therapies. These methods include immunotherapy and oncolytic virus (OV) therapy, which are more physiological and well tolerated.[9]

Table 1: Types of tumors classified based on the type of tissue from which they originate.

Types of tumors	Characteristic features
Carcinoma	They are formed as a result of altered epithelial cells. They constitute the highest ratio in all types of cancer.
Sarcoma	These are cancer abnormalities found in the bone, muscle, fats, and connective tissue.
Lymphoma	They are formed as a result of malignancy of the lymphatic system or cells which are derived from the bone marrow
Myeloma	They depict the cancers of those particular white blood cells that synthesize antibodies
Leukemia	They are formed as a result of malignancy of the lymphatic system or cells which are derived from the bone marrow

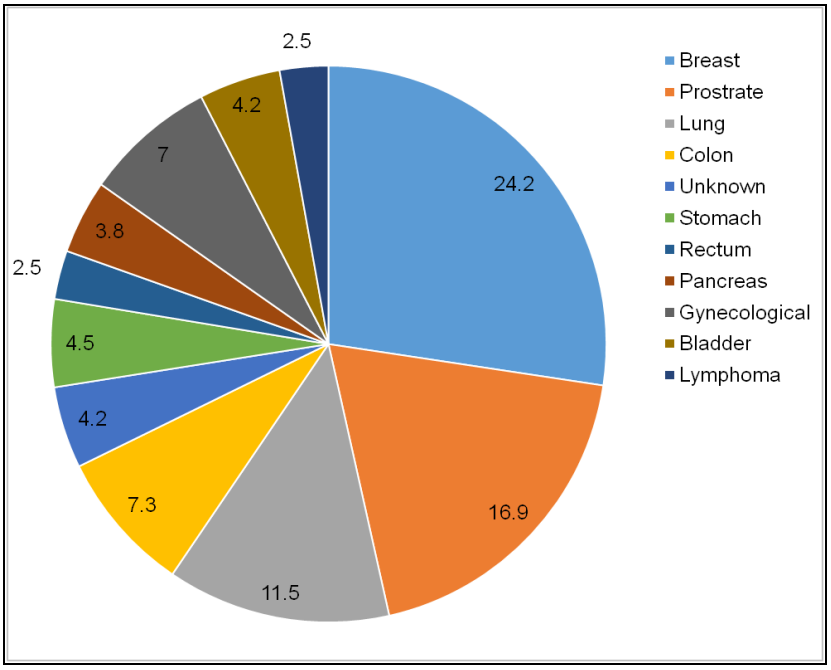

Fig. 2: Percentage of occurrence of Cancer Types.

2.1. Diagnostics, Prognostics and Predictives

These three are distinct and specific initial steps in the treatment of cancer. However, food and drug administration (FDA) always used the term 'diagnostics' in relation to testing, and to cover all the three above categories. Diagnostic tests revealed indicative or characteristic of a disease. There is no doubt that cancer cells evolve through the accumulation of somatic mutations, which extricate normal cells from regular behaviour patterns.[10] It is likely that trace amounts of abnormal proteins and nucleic acids are present in the general circulation even at an early stage in its development. Therefore, the aim of cancer detection is to seek out indirect evidences for the presence of that abnormal growth, preferably earlier rather than later in its journey from the benign to the malignant state. Detecting these molecules pre-supposes that they bear some characteristics that differentiate them from those associated with normal cells, and identifying 'tumor-specific' proteins or other classes of molecule has been the most challenging aspect of the search for circulating or fluid diagnostic markers. Immunodiagnostic approaches representing largest proportion of FDA approved cancer diagnostics. Rapid developments in the use of mass spectroscopy have brought new power to the search for rare molecules or fragments of molecules in fluids. But there are several problems related to their reproducibility and standardization of these techniques. Next generation sequencing (NGS), allows the simultaneous sequencing of many millions of individual DNA molecules.[11] It provides exquisite sensitivity and specificity for the detection of abnormal DNA in solid tissues and in body fluids. Feasibility of using NGS for the detection of somatic mutations are investigating by scientists for the presence of tumor in many genes such as *KRAS,TP53* and *EGFR* in DNA, as surrogate markers.[12] In addition, the sheer capacity of the NGS technique also allows multiplex sequencing of many gene hotspots simultaneously.

Prognostics tests provide information as to the likely future course and outcome of a disease. Once the presence of a tumor is diagnosed and the disease is staged using standard clinico-pathological criteria, the oncologist will have a judicious idea of the prognosis without resorting to molecular tests.[13] *OncotypeDx*™ test is one of the prognostic tests that is based on the analysis of expression of 21 genes. It quantifies the likelihood of disease recurrence in women with early-stage hormone receptor-positive breast cancer, and as such is prognostic.[14] It also been proved to be useful in assessing the likely benefits of chemotherapy. These types of prognostic tests are required to be developed for all types of cancers.

Predictive tests provide information on the likely response of a patient to a drug or therapy. Predictives include finding biological markers that predict probable response to a drug or treatment. The most uncomfortable part of this step is the cost of developing a new drug.[13] The cost of a single, new anti-cancer drug from discovery to licensing is currently estimated to be more than US$1 billion. To add to the misery, time taken and the risk of taking these drugs to licensing is unduly high. Most of these often fail at the II, III and transition phases. Between 1990 and 2006 there were a total of 920 candidate therapeutics; of which 45% of these had been completed by 2007, but only 32 had been approved by the FDA. This equates to a startlingly low overall success rate of 8%.

2.2. Emergence of resistances in cancer cells to treatments

Nearly all of the molecular faults present in cancer cells may boost their sensitivity to cytotoxic agents, but unluckily others may increase their resistance to drugs. For example, much of the cell death induced by DNA damage occurs through apoptosis, so cancer cells that harbour defects in their cell death programs can sometimes escape the effects of cytotoxic therapy. Cancer cells vary widely in their response to radiation and to the different kinds of cytotoxic drugs. [15] It seems likely that this difference reflects the particular kind of defect that they have in DNA repair, cell-cycle checkpoints, and apoptosis pathways. Genetic instability itself can be both good and bad for anticancer therapy. Unfortunately, genetic instability can also make eradicating cancer more difficult.[16] Because of the abnormally high mutability of many cancer cells, most malignant tumor cell populations are heterogeneous in many respects, which may make them difficult to target with a single type of treatment. Moreover, this mutability allows many cancers to evolve resistance to therapeutic drugs at an alarming rate.

To make matters worse, cells that are exposed to one anticancer drug often develop a resistance not only to that drug, but also to other drugs to which they have never been exposed. This phenomenon of multidrug resistance is frequently correlated with amplification of a part of the genome that contains a gene called *Mdr1*. This gene codes for a plasma-membrane-bound transport ATPase. The overproduction of this protein or some other members of the same family can prevent the intracellular accumulation of certain lipophilic drugs by pumping them out of the cell. The amplification of other types of genes can likewise give the cancer cell a selective advantage: thus the gene for the enzyme dihydrofolate reductase (DHFR) often becomes amplified in response to cancer chemotherapy with the folic-acid antagonist methotrexate.

2.3. Trends in the modalities of cancer treatment

Side effects and lack of accuracy are the major disadvantages of conventional methods of cancer treatment. Search is in progress to develop treatment methods with least amount or without any disadvantages that are seen in conventional methods. Presently, more than 60% of all ongoing medical quality treatment trials globally are focused on cancer.[17] The range of treatment and management methods rely on the cancer type, location, stage and progression of the disease. Chemotherapy, irradiation, surgical operation, and surgical knives based on radiation are the most commonly used methods of treatment. Surgical operations are carried out in order to remove the tumor without unnecessary risk of tissue damage. Different kinds of radiation linked surgical options are available depending upon various factors. Stereotactic radiosurgery (SRS), Gamma Knife technique (GKT) and Linear accelerator (LINAC) are the three most commonly used Radiation-based surgical knives. SRS is a kind of radio-knife in which ionizing radiations are used for the destruction and damage of tumor. This technique exposes a small area of the body to a very high dose of radiations. In this case there is no cutting or blade is used.[18] It is chiefly employed in circumstances where conventional surgical techniques are hard or unsafe. For example, in case of brain tumors. Similarly, GKT uses Gamma rays.[19] LINAC uses high-energy X-rays and it can destroy bigger tumors as compared to GKT.[20]

Hormone-based therapy, anti-angiogenic modalities, stem cell therapies, immunotherapy, and dendritic cell-based immunotherapy are also used but that often. Hormonal treatment is effective in the treatment of cancer without any cytotoxicity which is associated with chemotherapy.[21] The socalled novel modalities of treatment focus on areas like targeted designer drugs, immunotherapy, RNAi techniques, angiogenic ability, oncolytic virotherapy, genetic control of apoptosis and tumor-attacking. These treatments are employed against the cancer of the cerebrum, prostate, lung, breast, colorectal, pancreatic, liver, head and neck, bladder, skin, ovarian, and renal malignancy.[22] Biological therapies, including immunotherapy and oncolytic virus are far better methods of cancer treatment. Immunotherapies induce memory functions of the adaptive immunity system. They are involved in precisely stimulating the immune system against cancer. The ill effects are very 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 specificities and the responses of interferon.[9] In recent years, two novel types of immunotherapy have had a marked impact on oncology: Checkpoint inhibitory MAbs and chimeric antigen-specific receptor (CAR)-transfected T-cells (CAR-T cells).[23] Antitumor vaccines and oncolytic viruses (OVs), are the two other types of biological therapies that have been developed in recent decades. These types of therapy are physiological and well tolerated.[24]

DNA microarray is an important diagnostic technique and, in this case, the analysis the mRNA present in a tissue is done and the levels of expression of thousands of genes can also be determined simultaneously in a particular sample. Further, it is matched with the levels in standard control tissue. Each cancer type has its own gene expression profile. When the profiles of numerous patients are matched then they can be congregated into a smaller number of discrete classes whose members share similar characteristics. The dissimilar classes of gene expression profiles, reflecting the consequences of dissimilar sets of oncogenic mutations, correlate with different prognoses and different responses to therapy.

2.4. Chemotherapy

Before Y2K, chemical drugs were being used for killing cancer cells. Chemotherapy is considered to be very effective and widely used method used for treating most types of cancers. The drugs that are used in this method target the cancer tissue and mainly produce ROS (reactive oxygen species) which basically exterminate tumor cells by the means of geno-toxicity.[25] Over the years, use of many chemotherapy drugs has resulted in the successful treatment of many types of cancers. New classes of drugs like aromatase inhibitors and LHRH analogs are being used to treat prostate and breast cancers. The disadvantage with chemotherapy is, it damages normal cells that lead to various dose dependent side effects.[26] such as hair loss, exhaustion, biliousness, and vomiting.[27] Regrettably chemical used also kill normal cells and have a greater adverse effects on the health of cancer patients. The World Health Organization (WHO) has defined side effects as grades 0-4.[28] In the course of time, researchers developed novel combination methods for cancer by combining surgery with chemotherapy and/or radiation.[2] Chemotherapeutic drugs may be cytostatic (biological drugs) or/and cytotoxic. There are different classes of these drugs used singly or in combination. Alkylating agents cause direct damage of DNA and stop division of cancer cells. Many cancer types such as lymphoma, leukemia, multiple myeloma, Hodgkin's disease, sarcomas and cancers of the ovary, breast, and lungs have been cured successfully by using this method.[29] A class of antibiotics called anthracyclines is used against replication related enzymes and arrest cell cycle. But these antibiotics are known to cause serious heart damage. Mitoxantrone actinomycin, doxorubicin D+, bleomycin, and mitomycin C are the other antibiotics that are often used to treat cancer. Topoisomerase inhibitors, mitotic inhibitors and proteasome inhibitor are other chemicals that are generally used in chemotherapy. Antimetabolites are the other class of chemical drugs that target purine or pyrimidine metabolic enzymes, whereas alkaloids target the cytoskeleton (β-tubulin) and mitosis.[28] In the late 1970s, bleomycin, vinblastine and cisplatin were novel drugs used in chemotherapy. But they induced severe side effects, such as vomiting more than 12 times per day.[30]

The overall contribution of chemotherapy to 5-year survival was estimated to be only 2.3% in Australia and 2.1% in the USA. The five most 'chemo-sensitive' cancers, namely testicular cancer, Hodgkin's and non-Hodgkin's lymphoma, cervical cancer and ovarian cancer, accounted for 8.4% of the total cancer incidence in Australia in 1998.[31]

2.5. Radiation therapy

Radiation therapy is based upon the use of physical entities like electrons, protons, and various ions to kill the cancerous cells. The mechanism behind radiation therapy is that high energy radiations halt the cell division and block their ability to proliferate by damaging their genetic material. If it is done before surgery, radiation therapy is given with the intention to shrink the tumor. If done after surgery, radiations will destruct the left behind tumor cells and reduce the cancer relapse.[32] The year 2011 was declared as the "Year of Radiation Therapy" in UK owing to its extensive use in Medical sciences. Now radiation oncology is a very specialized field in medicine.[33] The hostile consequence of this method is that it also can knockout healthy cells lying around the tumor. Nonetheless, better-quality imaging and accurate targeting can decrease the damage of normal cells done by radiation.[34] 3D conformal radiotherapy (3DCRT), Intensity-modulated radiation therapy (IMRT) and Image-guided radiotherapy (IGRT) are the most used irradiation techniques now.

2.6. Targeting genetic instability and failure of cell\ cycle control

The life of a cell is naturally programmed; it divides only about 50 times, and then it dies by apoptosis and is replaced by a new cell. This natural phenomenon is called programmed cell death (PCD). Whereas cancer cells lack PCD and contact inhibition ability, leading to the formation of unwanted mass of cells.[35] Anticancer therapies are based on properties of cancer cells that differentiates them from normal cells. Genetic instability is one such property that is characterized by the loss of DNA repair mechanism and chromosome maintenance. Traditional anticancer therapies typically depend on chemical agents, drugs and irradiation that target DNA and genetic machinery that maintains chromosomal integrity. Such treatments specially eradicate certain cancer cells because they have a weakened capacity to survive the DNA damage. Normal cells, when treated with radiation, on the other hand, will suffer DNA damage, but will arrest their cell cycle until the DNA is repaired. Tumor cells that have defects in various cell-cycle checkpoints, however, lose the capability to halt the cell cycle in these conditions, and so continue to reproduce even after irradiation. All such cells will consequently die after a few days on account of the calamitous DNA damage, but they can survive if they attempt to divide even with defective chromosomes. Thus, one of the main principles developed to treat cancer is based on cell cycle control. The decision within a cell concerning growth or quiescence, cellular senescence or programmed cell death (PCD) is taken at restriction point R, during G1 phase of the cell cycle.[36]

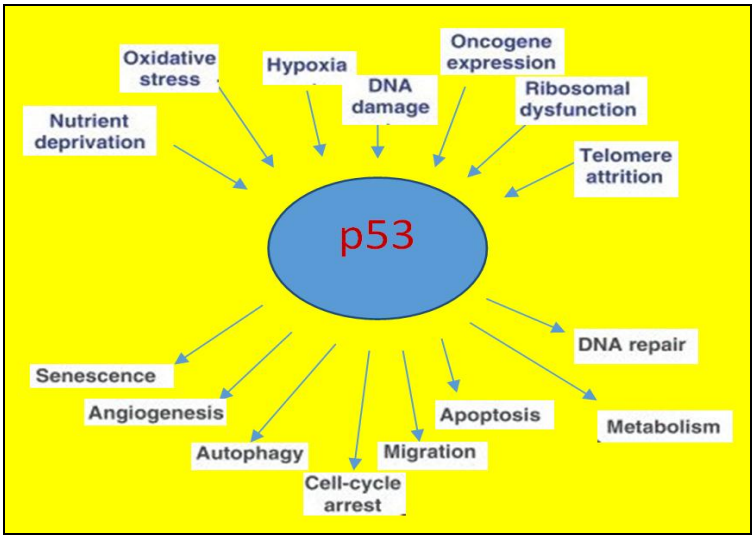

Fig.3: Activators and activities of p53; Top-Signals activating p53; Bottom-Activities and roles of p53.

2.7. Attacking p53 Deficient Cells

Considering biochemical pathways, the most important component of carcinogenesis is the P53 gene. Its normal function is associated with gene transcription, DNA synthesis, apoptosis, and DNA repair (Fig. 3).[37] Alterations and mutations in p53 provoke the progress of primary tumors. Viral onco-proteins bind with the p53 and upset its interactions with other cellular protein components.[38] Thus, certain treatment strategies target defective properties or molecules that tumor cells possess. One of the inventive techniques to target tumor cells is by exploiting the loss of p53. Certain viruses, including the papillomaviruses and the adenoviruses, encode proteins that bind to and inactivate the p53. This enables viruses to outwit the p53-mediated defenses of the host cell and replicate their own genomes freely inside it. As part of their lytic life style, adenoviruses replicate nonstop inside the vulnerable cell, and then surge out when their numbers are ample, killing the cell and infecting it's surrounding cells. An adenovirus has been created that lacks the gene that encodes the p53-blocking protein; this defective virus can therefore only reproduce in cells in which p53 is previously deactivated—including numerous kinds of cancer cells. If this altered adenovirus is inserted into a tumor, the virus might be anticipated to reproduce in and destroy only the cancer cells that lack p53, leaving normal cells undamaged. Fig. 4 showing the effects of energetic stress and DNA damage on p53 gene.

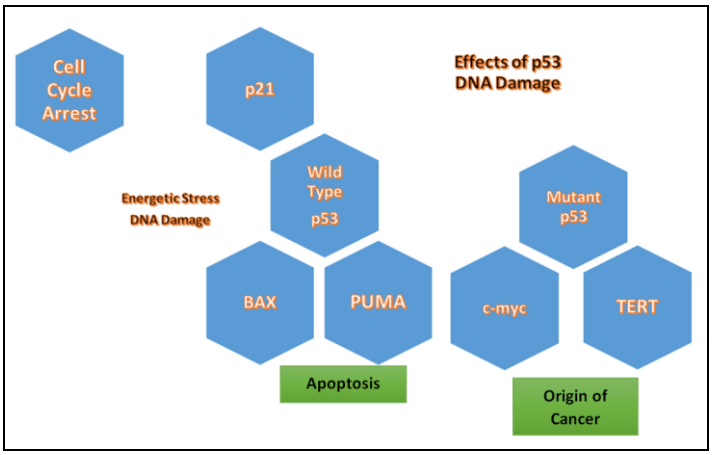

Fig.4: Effects of energetic stress and DNA damage on p53 gene and two alternate consequences.

Blocking Angiogenesis

Another promising approach to destroy tumors is by blocking of angiogenesis. This concept was not recognized till 2004, when the first angio-inhibitor drug, bevicizumab was approved for clinical use by FDA. At present there are more than 25 endogenous angio-inhibitors in clinical trials and many more in preclinical studies for the treatment of cancer.[39] This method does not directly target cancer cells at all. Tumors need the establishment of new blood vessels to propag0ate to more than a millimeter. Treatments that block angiogenesis will prevent tumor growth in numerous diverse kinds of cancer. The development of fresh vessels necessitates local signals, angiogenic growth factors and the action of the angiogenesis inhibitors is utilized so that angiogenesis can be

selectively gridlocked. Clinical trials are completed with angiogenesis inhibitors and they are already being used now. Endothelial cells that are in the process of forming new vessels also turn out to express distinctive cell-surface markers, providing a promising way in which they might be attacked without harming the existing blood vessels in non-cancerous tissues.

Inactivation of Specific Oncogenic Proteins by Designer Molecules

Synthetic drug molecules that can impede the activity of protein kinases upsurges extraordinary optimisms on account of its dramatic success. In more than 95% cases, leukemia (chronic myelogenous) with a specific chromosomal translocation, noticeable as a typical aberration in the karyotype of the *Philadelphia* chromosome. This occurs due because of chromosome breaking and reunion at the sites *Abl* and *Bcr*genes. The union of these two specific genes generates a "hybrid-gene" which produces a chimeric protein, containing N-terminal piece of Bcr bonded to the C-terminal piece of Abl. Abl is a protein tyrosine kinase associated with cell signaling. The replacement of the Bcr piece for its normal N terminus makes it overactive, so that it kindles unsuitable propagation of hematopoietic precursor cells that contain it and prevents these cells from getting killed by PCD or apoptosis, which many of them would normally do. The chimeric Bcr-Abl protein is an apparent goal for therapeutic attack. Synthetic drug molecules, called STI-571 (Imatinib mesylate) and now renamed *Gleevec* can inhibit the activity of protein kinases as it blocks Bcr-Abl. When this molecule was given to 54 patients suffering from leukemia (chronic myelogenous) that had resisted other treatments, all but one of them showed an excellent response, with return of their white blood cell counts to normal. After a year of treatment, 51 out of the initial 54 patients were still well. Results were not so good for patients who had already progressed through further mutations to the acute phase of leukemia, where genetic instability has set in and the march of the disease is far more rapid. These patients showed a response at first and then relapsed: in these cases the cancer cells were able to evolve a resistance to the *Gleevec*. Nevertheless, the extraordinary success of *Gleevec* for the patients in the chronic but early stage of the disease is enough to prove the principle. Once we understand precisely what genetic lesions have occurred in a cancer, we can begin to design effective rational methods to treat it.

Anticancer vaccines

Anticancer vaccines are designed to provide tumor-associated antigens (TAA) in connotation with costimulatory molecules. Their function is to be immunogenic and to overcome T-cell non-responsiveness (anergy) in patients with cancer [9]. TAAs can be cell surface macromolecules that are detected by antibodies, or they can be pMHC complexes from intracellular proteins that are detected by T lymphocytes. Immunosuppressive cues in the tumor microenvironment are major factors currently hampering the application of dendritic cell (DC) vaccination. There are four different types of tumor microenvironments that exist based on the presence or absence of tumor-infiltrating T cells (TILs) and PD-L1 expression [32]. Ideal combination cancer therapies based on tumor immunology have to find an optimal niche between maximal antitumor immunity and minimal autoimmunity. This is particularly true for the application of checkpoint inhibitors, which interfere with immune regulation. The aim of therapeutic DC vaccines in cancer immunotherapy is to activate cytotoxic T-lymphocyte proteins (CTLs) to recognize and attack tumors. Even when the T-cell response is already initiated by antigen engagement, it is the complex balance between costimulatory and co-inhibitory signals on DCs that results in either T-cell activation or T-cell tolerance [40]. Principles of biological and physiological cancer therapies aim at achieving a balance between different entities: ntitumor immunity, autoimmunity and antiviral immunity. Thierry Boon's group described the molecular nature of the first human TAA. Now there are hundreds of TAAs discovered and identified as pMHC complexes.

Development of New Therapies

Our growing understanding of cancer cell biology and tumor progression is gradually leading to better methods for treating the disease, and not only by targeting defects in cell cycle arrest and DNA repair processes. Table 2 showing types of therapies, their mechanism of action, side effects and examples.

As a classical example, tamoxifen, an estrogen antagonist that blocks estrogen synthesis is now widely used to prevent or delay recurrence of breast cancer. Scientists are now testing such novel agents to prevent new cancers from arising. Such anti-estrogen compounds do not directly kill off the tumor cells. Nevertheless, they improve the patient's prospect of survival, presumably because estrogens are necessary for the growth of normal mammary epithelium and a proportion of breast cancers retain this hormone dependence.

Endocrine therapy in patients with estrogen receptor (ER)-positive breast cancer has clearly improved patient outcomes. However, endocrine therapy can be accompanied by severe side effects, identification of patients who will benefit most from extended treatment is crucial.[41] Recently, the TKI cabozantinib was approved as a first-line therapy for patients with advanced clear cell Renal Cell Carcinoma ccRCC. Cabozantinib was initially approved for patients previously treated with antiangiogenic therapy based on the phase 3 METEOR study, which demonstrated a clinical benefit compared with everolimus for overall survival (OS), progression-free survival (PFS) and objective response rate.[42]

Table 2: Types of cancer therapies, their mechanism of action, side effects and examples.

Type of therapy	Mechanism of action	Side effects	Examples
Cytostatic drugs	Interfere with cell proliferation	Grade 1-4	azathioprine, cyclophosphamide, hydroxyurea, methotrexate and mercaptopurine
Small molecule inhibitors	Targeted therapy: Interfere with oncogenic signal transduction	Grade 1-4	KIT inhibitors, such as sunitinib, imatinib, sorafenib and lapatinib
Antitumor MAbs	Targeted immunotherapy	Grade 1-3	Cetuximab, trastuzumab, panitumumab
Anti-angiogenesis MAbs	Inhibit angiogenesis	Grade 1-3	Cabozantinib, Bevacizumab (Avastin) and ramucirumab (Cyramza)
Checkpoint inhibitor MAbs	Immune regulation	Grade 1-4	Lpilimumab, nivolumab, atezolizumab and durvalumab
CAR-T cells	Targeted cytotoxic T lymphocytes	Grade 1-3	Axicabtageneciloleucel (Yescarta), Brexucabtageneautoleucel (Tecartus) and Tisagenlecleucel (Kymriah)
Antitumor vaccines	Active specific vaccination	Grade 0-2	Tumor Associated Antigens
Endocrine Therapy	Estrogen receptor specific	Grade 2-4	TKI cabozantinib
Oncolytic viruses	Oncolysis, induction of immunogenic cell death	Grade 0-2	RNA viruses, including Newcastle Disease Virus from attenuated natural wild type strains. B, biological therapy; C, chemoteherapy; HER, human epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

In 1990s scientists produced therapeutic monoclonal antibodies rituximab and trastuzumab that specifically targeted lymphoma and breast cancer cells. At present scientists are developing vaccines to boost the body's immune response against cancer cells. As more is learned about the molecular biology of cancer cell, researchers developed new classes of molecules such as antisense oligodeoxynucleotides and small interfering RNA (siRNA) for the treatment of cancer. RNA expression profiling permits scientists to define relative amounts of numerous RNA molecules at one time. Knowledge about proteins or RNA molecules that are present in cancer cell will reveal the secrets about how a cell is behaving and time and again it can help to forecast which drugs that can be used against a particular tumor.

The paramount hopefulness lies, in discovering a more potent and discerning way to directly exterminate cancer cells. Now that we can pinpoint their genetic lesions, we can now use our knowledge of cell biology to kill them. In recent years, a varied diversity of exploratory new-fangled methods to attack tumor cells have been advocated, several of which have been shown to function only in model systems, characteristically decreasing or precluding tumor progress in mice. Several of these procedures will turn out to be of no medical significance, since they do not work in humans, have ruthless side effects, or simply problematic to use. But some of them are expected to do well even in human systems. It is a well-established fact that, some tumors are profoundly reliant on a specific protein that they overproduce. Obstructing the action of such proteins is actually a good means of handling cancer if it does not unduly damage normal tissues. For example, about 25% of breast tumors express unusually high levels of the Her2 protein, a receptor tyrosine kinase, related to the EGF receptor that normally plays a part in the development of the mammary epithelium. Therefore, fastening off Her2's action is expected to decrease or stop the growth of breast tumors in humans; in fact, this approach is currently being tested with some success in clinical trials, using as the blocking agent a monoclonal antibody that recognizes Her2.

A different methodology to terminate tumors aims at the delivery of a drugs straight into the cancer cells by taking advantage of key proteins that are plentiful on the surface of tumor cells. Antibodies counter to such proteins can be equipped with a toxic chemical, or made to transport an enzyme that slices an harmless 'prodrug' into a toxic molecule. In the second instance, the enzyme can then produce an enormous amount of toxic drug molecules. A beneficial feature of this stratagem is that the toxic chemical produced enzymatically can then spread to adjoining cancer cells, increasing the odds that they too will be destroyed, even if the antibody is not bound to them directly. Undoubtedly, conquering the warfare against cancer is and will be the focal point of contemporary medical research. Making a single "cure-all" drug for cancer is the dream of cancer biologists. It

has not yet been developed, even though many new cancer treatment methods and drug targets have been discovered. More research studies and diverse clinical trials are the key to find a definitive remedy for cancer. The complexity of cancer is such that it entails intense scientific battle to fight against it in all disciplines (See, Table-2 for the list of therapies).

CONCLUSION

Positive medical advancements always depend on clear-cut diagnosis. If the disease is not identified decorously, we cannot determine its causes, envisage its consequence, choose the suitable treatment for a given patient, or conduct trials on a population of patients to judge whether a proposed treatment is effective or not. Cancer is a strangely heterogeneous assemblage of diseases. Nevertheless, new techniques provide tools to make diagnosis unambiguous, accurate and explicit. We have the means now to characterize each individual tumor at a molecular level with unprecedented details. These technologies are now being established as there are some modifications required for improving the efficacy and reproducibility.

With our greatly increased understanding of molecular genetic mechanisms, we can now, aim to determine for each type of cancer, the precise defects in the structure, biosynthesis, alterations, recombinations, maintenance, repair and whole lot of biological activities of nucleic acids. Cell cycle checkpoints help tumor cells to procure the manifold mutations essential for tumor formation, development and intrusiveness. These flaws are making the cancer bizarrely sensitive and defenceless to specific types of attack on the biological activities of nucleic acids. The view is supported by the fact that tumorous cells are destroyed quiet effortlessly by radiation and chemo therapies. More effective method of cancer treatment would be achieved by designing accurately directed drugs that makes use of a specific flaw in cancer cells than the conventional and traditional methods of treatments. There by it would be possible to exterminate the cancer cells more effectively. In order to accomplish this feat, the molecular analysis of cancer tissue is inexorable. This will promise to renovate cancer treatment by empowering scientist to design a tailor-made strategy, which obviously will be much more accurate to treat any individual cancer patient.

We are not in the groping in the dark era anymore, thanks to the unearthing of an array of genes which are critically connected to cancer. Molecular basis of cancer is more or less established. It is quiet promising to learn that some the fundamental principles and the crucial genetic abnormalities are common for many types of the cancer. However, it is still a distant dream to have a complete understanding of the most common types of cancers. Most of the physiological functions and sequences of many genes related cancer are known to us now. Hence, it has become increasingly easier to invent and make precisely targeted, rational treatments. Especially when modern technologies like, Mass Spectroscopy, DNA Microarray, CADD (Computer Aided Drug Designing), QSAR (Quality Structure Assisted Rationality), High-throughput analysis and Next Generation Sequencing (NGS) are in our hands. But, a better knowledge of how the relevant molecules interact to govern the behavior of the individual cell, a better understanding of the sociology of cells in tissues, and a critical information regarding various progressions that rule the origin and blowout of cancerous tissue via though a series of mutations and also the general process of natural selection.

According ACS, the overall cancer death rate dropped continuously from 1991 to 2016 by a total of 27%, translating into approximately 2,629,200 fewer cancer deaths than would have been expected if death rates had remained at their peak [1].Cancer biologists are apparently hopeful of a certain breakthrough in the discovery of sure shot method to control and manage this ever-growing and menacing disease. The history of cell biology reveals the speed and descent progress in the recent past. The aspiration to comprehensively deciphering the codes of cancer drives basic research, which will certainly disclose and open up novel ways to use our knowledge of the cell for finding a wide-ranging treatment strategy.

Apparently plant based therapeutics will dominate in the 21st century. Discovery of plant derived cancer drugs is an important and necessary strategy in improving chemotherapy. Natural drugs have found direct medical application as drug entities, they also will serve as chemical models or templates for the design, synthesis, and semisynthesis of novel substances, such as Paclitaxel (Taxol), Vincristine (Oncovin) and Camptothecin.[43]

Changes occur regularly and invariably all the time in a very high pace in the route of developing a cancer drug. It is always in a critically dynamic situation. Humanitarian concern is more important than economics. I believe a change in priority and perspective should change. Drug companies are not ready to give up making targeted drugs in favour of diagnostic tests. But, it is often opined that the targeted drug therapy is fundamentally flawed and it may be time to go back to the beginning. As we have gone ahead too far without properly strengthening our fundamentals completely. More and more resources should be provided to develop early detection techniques. Conceivably it is time to change prominence from treatment to precise and accurate detection. Undoubtedly, the most critical stage in the treatment of cancer is diagnostics. It needs additional support and incentivizing at all levels, especially at the level of fundamental research. Better sense should prevail: prevention is better than cure.

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