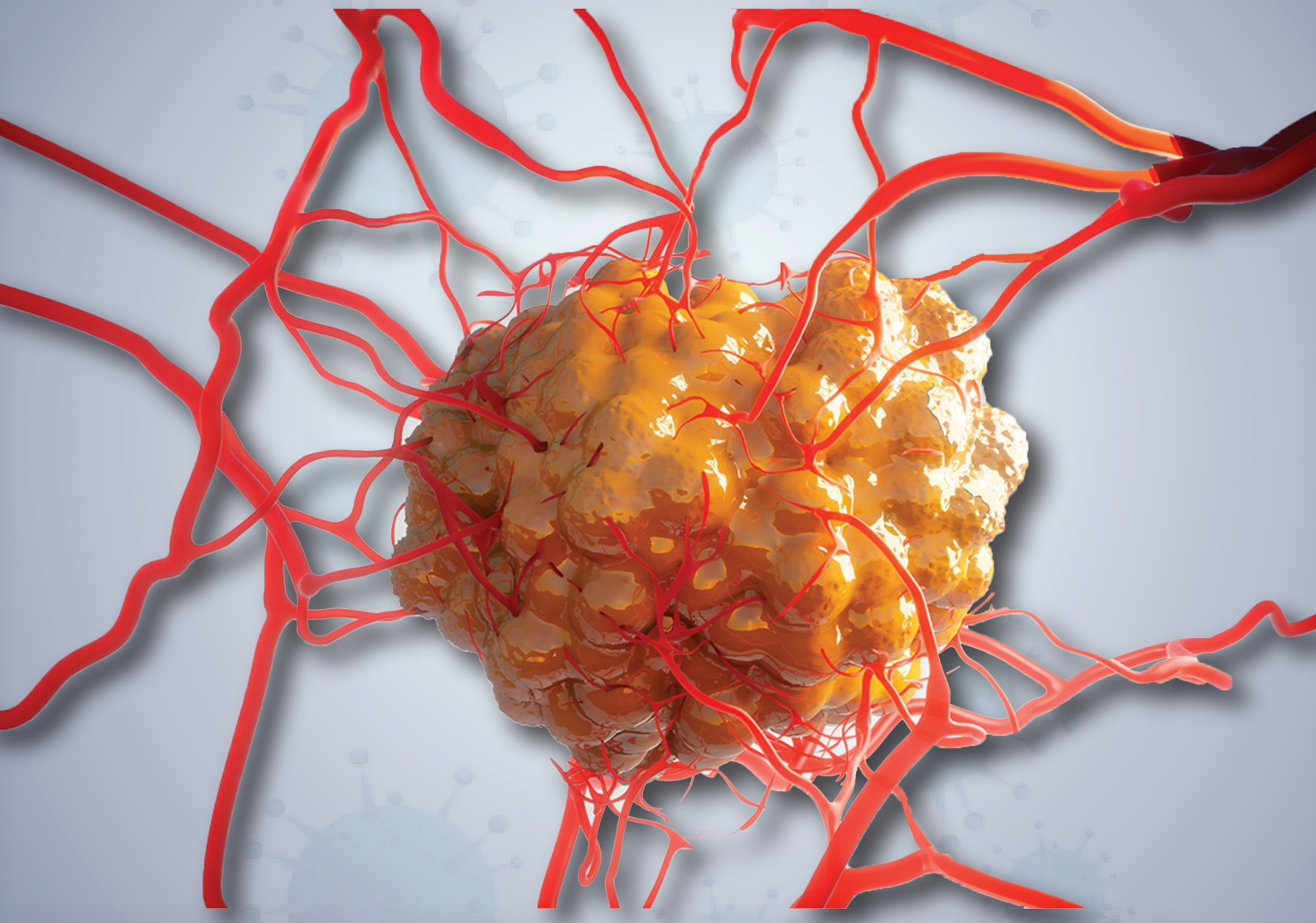
Module in The Area of **Medical Oncology**



Module I

Cancer Biology And Principles Of Cancer Treatment.

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Introduction

Treating cancer is one of the most complex aspects of medical care. It involves a team that encompasses many types of doctors working together (for example, primary care doctors, gynecologists or other specialists, medical oncologists, radiation oncologists, surgeons, and pathologists) and many other types of health care practitioners (for example, nurses, radiation therapists, physiotherapists, social workers, and pharmacists).

Treatment plans take into consideration the type of cancer, including its location, its stage (how large and widespread the cancer is), and its genetic characteristics, as well as specific characteristics of the person being treated.

Treatment decisions also take into account other factors, including

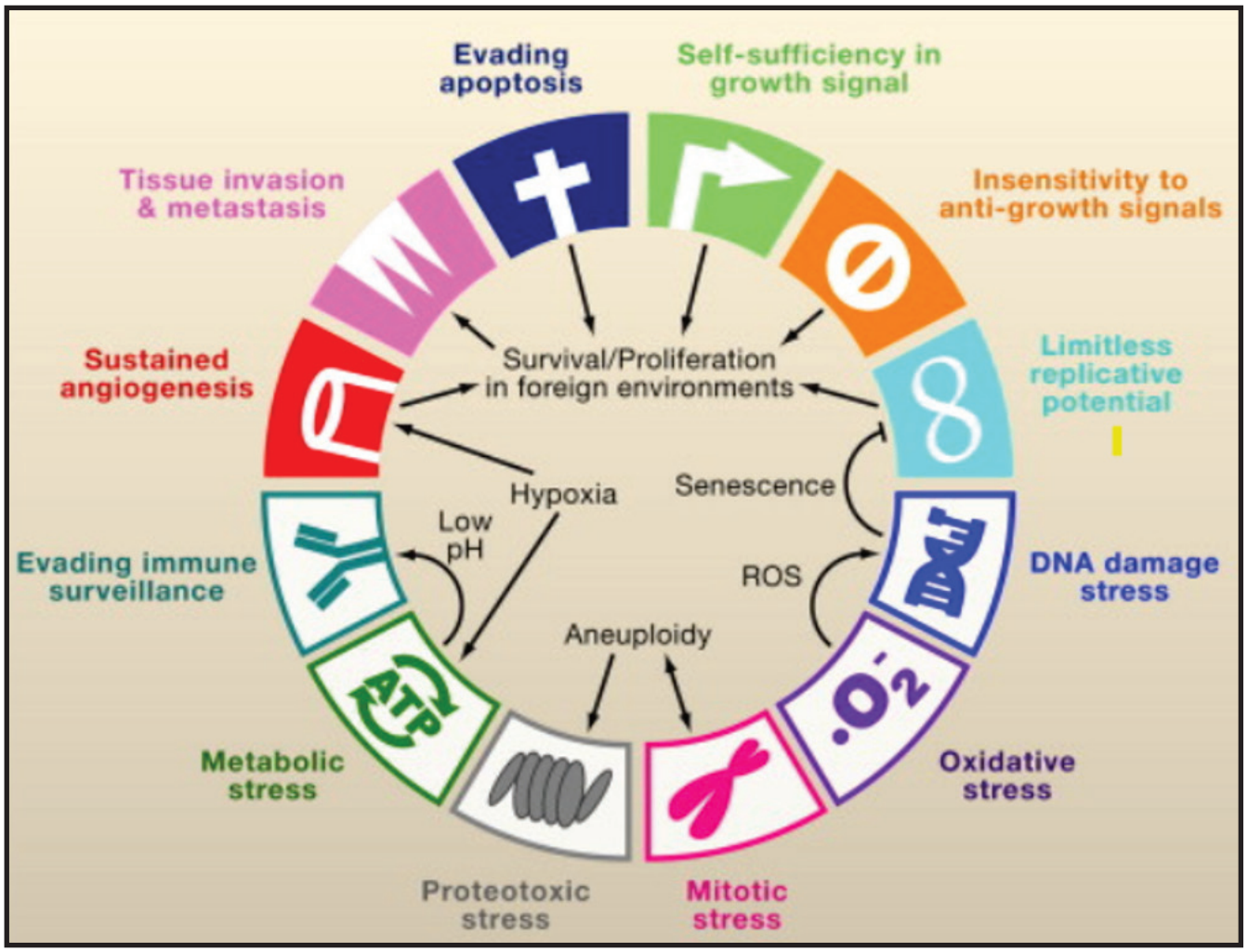
- The likelihood of cure or of prolonging life when cure is not possible
- The effect of treatment on symptoms
- The side effects of treatment
- The person's wishes

People undergoing cancer treatment hope for the best outcome and the longest survival with the highest quality of life. However, people must understand the risks involved with treatment. They should discuss their wishes regarding medical care with all of their doctors and should participate in decisions about treatment When the diagnosis of cancer is first made, the main goal of treatment is to remove the cancer completely if possible (through a single treatment or through a combination of surgery, radiation therapy, chemotherapy, and sometimes other cancer treatments). Treatment sometimes also aims to eliminate cancer cells elsewhere in the body, even when there is no sign of those cells.

Even when a cure is impossible, symptoms resulting from the cancer can often be relieved with treatment that improves the quality of life (palliative therapy). For example, if a tumor cannot be removed surgically, radiation to the tumor may shrink it, temporarily reducing pain and symptoms in the immediate vicinity of the tumor (local symptoms).

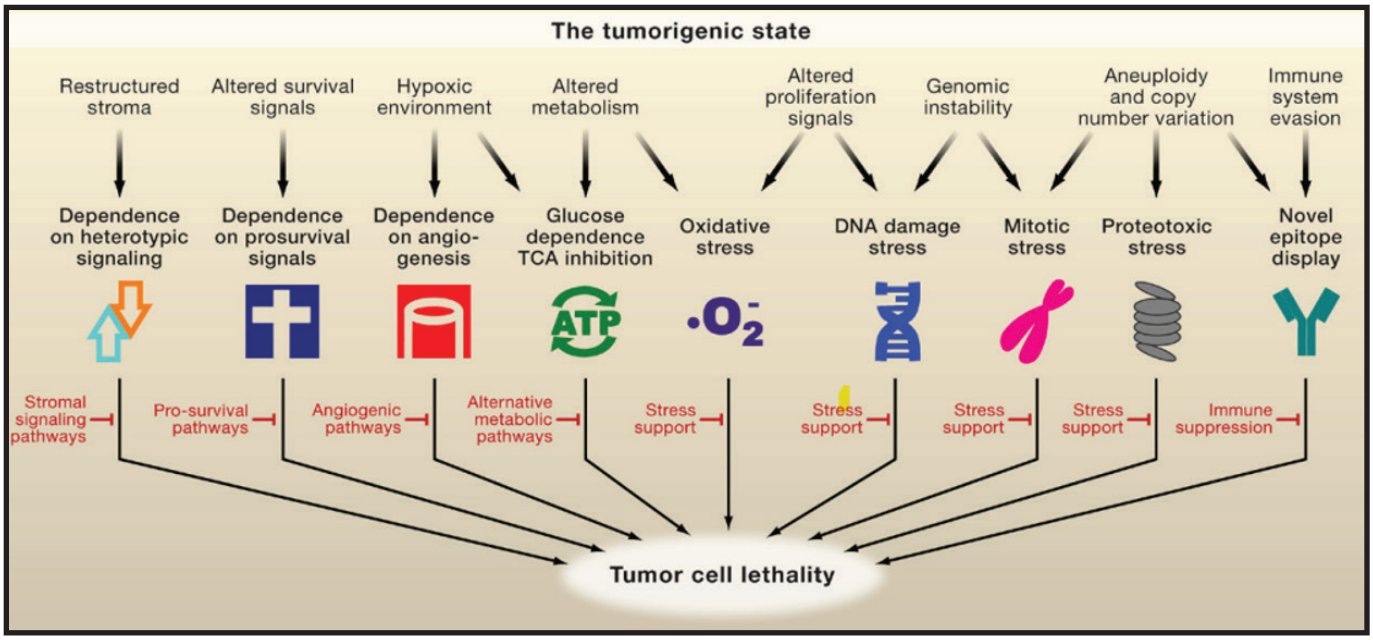
Because treatments are complex, specific approaches to care, called treatment protocols, have been developed to ensure that people receive the safest and most effective care. Treatment protocols ensure that people receive a standard approach derived from careful scientific experiments. Protocols are typically developed and refined through clinical trials. A clinical trial allows doctors to compare new drugs and treatment combinations with standard treatments to determine whether new treatments are more effective. Often, people with cancer are offered the opportunity to participate in such a trial, but not all people with cancer are eligible for a clinical trial.

The Hallmarks of Cancer



Examples of Non-oncogene Addictions in Cancer Cells

The tumorigenic state results in a variety of alterations (shown on top), which are related to the hallmarks described in the Figure below . These alterations give rise to a number of potentially deleterious circumstances or vulnerabilities (detailed in the bottom half) that could be lethal to the tumor cells if left unchecked. The existence of stress support pathways (shown in red) help suppress this lethality. Many of these pathways are examples of non-oncogene addiction (NOA), and therapeutics that interfere with their functions could display synthetic lethality with the tumor genotype/phenotype.



DNA Damage and DNA Replication Stress

Based on karyotypic and mutational analyses, it is clear that tumors, especially solid tumors, pass through stages of extreme genomic instability that result in the accumulation of point mutations, deletions, complex chromosomal rearrangements, and extensive aneuploidy This level of instability is due in part to a constitutive level of endogenous DNA damage, which results in activation of the DNA damage stress response (DDR) pathway Elevated levels of DNA damage observed in early stage tumors are thought to be due to several factors. First, the shortening of telomeres due to replication in the absence of sufficient telomerase activity leads to the appearance of double-strand breaks (DSBs) at telomeric ends. The subsequent fusions of these deprotected ends initiate breakage-fusion-bridge cycles that result in translocations and gene amplification events.

DSBs resulting from replication stress can also lead to breakage-fusion-bridge cycles Additionally, oncogene activation in precancerous lesions has been shown to increase DSBs and genomic instability possibly through DNA hyper-replication Finally, mutation of genes involved in either DNA repair programs (such as excision, crosslink, or mismatch repair) or the DDR pathways (such as ATM and p53 signaling) can lead to increased DNA damage, inappropriate cell-cycle progression, and genomic instability In normal cells, DNA damage signals to halt proliferation, induce cellular senescence, or elicit apoptosis. Cancer cells have evolved to overcome the antiproliferative effects of DNA damage, continuing to replicate in the presence of damage (Figure 1).

Proteotoxic Stress

Tumors exhibit proteotoxic stress evidenced by their frequent constitutive activation of the heat shock response. We think this is due, in part, to the striking degree of aneuploidy (altered chromosome number) often found in solid tumors (Figure 1)

Aneuploidy and gene copy-number changes can alter the relative balance of growth and survival signals, thereby promoting tumorigenesis. However, they also result in corresponding increases and decreases in transcript level that produce imbalances in the stoichiometry of protein complex subunits These imbalances increase the amount of toxic, unfolded protein aggregates in the cell and place additional burdens on the protein folding and degradation machineries This proteotoxic stress is counteracted, in part, by the heat shock response pathway, which promotes the proper folding and/or proteolytic degradation of proteins.

Mitotic Stress

A subset of tumors display increased rates of chromosome mis-segregation, which is referred to as the CIN (chromosome instability) phenotype This instability results in a shifting chromosome distribution, thus allowing tumor cells to rapidly evolve. In principle, CIN phenotypes can result from defects in a variety of pathways involved in mitosis, including defects in mitotic proteins that execute chromosome segregation and defects in the spindle assembly checkpoint, which coordinates anaphase entry with proper alignment of chromosomes on the mitotic spindle In addition, the CIN phenotype could result from the presence of extra centrosomes in tumor cells or from stresses placed on the mitotic apparatus due to the need to segregate supernumerary chromosomes Furthermore, CIN and mitotic stress might arise indirectly as a result of DSBs and genomic instability following oncogene activation, even in lesions where the mitotic machinery is intact. Mutations in certain oncogenes, such as Ras, and tumor suppressors, such as p53, have been suggested to contribute to the CIN phenotype However, the precise cause of mitotic stress is not known for the vast majority of tumors.

Metabolic Stress

Normal cells derive the bulk of their ATP through mitochondrial oxidative phosphorylation. In what has been referred to as the Warburg effect, most cancer cells are found to predominantly produce energy by the less efficient method of glycolysis and secrete a large amount of lactic acid, even under high oxygen conditions Tumor cells exhibit dramatically increased glucose uptake and highly elevated rates of glycolysi This provides the basis for tumor imaging by positron emission tomography (PET) using the glucose analog 18F-2-deoxyglucose. This transition to glycolysis for energy production provides several advantages to the tumor including adaptation to a low oxygen environment and the acidification of the surrounding microenvironment, which promotes tumor invasion and suppresses immune surveillance (Figure 1).

Oxidative Stress

The defining characteristic of oxidative stress is the presence of reactive oxygen species (ROS), and cancer cells typically generate more ROS than normal cells Both oncogenic signaling and the downregulation of mitochondrial function in tumors can contribute to ROS generation. ROS are highly reactive and likely to contribute to the increased levels of endogenous DNA damage observed in cancer cells (Figure 1). In addition, ROS are important signaling mediators, and their presence may contribute to transformation. For example, ROS promote the activation of the transcription factor HIF-1 by hypoxia and HIF-1 can promote the glycolytic switch and angiogenesis observed in tumors.
Attacking the Hallmarks of Cancer Any therapy with the stated goal to treat and possibly cure cancer must show differential toxicity toward tumor cells relative to normal cells. Implicit in this statement is that some unique properties of cancer cells not shared by normal cells, such as those depicted in Figure 1, must be exploited to the specific detriment of cancer cells, i.e., the concept of synthetic lethality. In principle, cancer can be treated by inducing cancer cells to undergo apoptosis, necrosis, senescence, or differentiation. These changes can be brought about by disrupting cancer cell-autonomous processes, by interfering with autocrine/paracrine signaling within tumors, or by blocking heterotypic signaling between tumor cells and the surrounding stromal tissue or blood vessels. Enhancing immune surveillance against cancer cells expressing novel antigens is also an attractive approach that has shown efficacy in specifically killing cancer cells Experiments aimed at either suppressing oncogene activity or restoring tumor suppressor function have revealed that such intervention is highly deleterious to the cancer cell. The heightened state of dependency of cancer cells on oncogenes and the loss of tumor suppressors led to the terms "oncogene addiction" (OA) and "tumor suppressor gene hypersensitivity" These alterations are necessary for both the establishment and maintenance of the oncogenic state and therefore are logical drug targets. Indeed, much effort has been extended to pharmacologically inhibit oncoproteins. What is thought to underlie the phenomenon of oncogene addiction is the observation that oncogenes elicit strong, opposing prosurvival and proapoptotic signals in cancer cells that favor growth and survival, and the acute inhibition of oncogene function tilts this balance toward cell death To bring about their phenotypic manifestations, oncogenes rely on extensive adaptations in cellular processes that are themselves not oncogenic. In addition, cancer cells may also display an increased dependence on the normal cellular functions of certain genes that act in oncogenic pathways but are not themselves classical oncogenes. For example, mutations in many genes in a given oncogenic pathway are unable to directly promote tumor formation because, despite being required for their pathway, they cannot increase the overall activity of the pathway because they are not rate-limiting. However, a reduction in the activity of many such genes can become rate-limiting to the pathway in question, and thus, they represent potential drug targets. By this rationale, cancer cells are addicted to both oncogenes and non-oncogenes. To describe this addiction of cancer cells to the functions of non-oncogenes, we have termed this phenomenon "non-oncogene addiction," NOA Although NOA genes, like oncogenes, are required for maintenance of the tumorigenic state, NOA genes do not undergo oncogenic mutations or functionally significant genomic alterations in tumors. The concept of non-oncogene addiction underscores the important contribution of these supporting networks to oncogenesis and highlights the potential of non-oncogenes as points of intervention for cancer therapeutics.

Whereas some gene classes and pathways fall neatly into the OA or NOA designations, others are more difficult to categorize because they exhibit characteristics of both phenomena. For example, interferon regulatory factor 4 (IRF4) is oncogenic and overexpressed due to translocations in some multiple myelomas. However, it is also required for the survival of myelomas lacking IRF4 translocations or overexpression Should it be considered as an example of OA in the latter cases? Also, should a protein that is directly activated by an oncogene and required for tumorigenesis—but is otherwise not mutated in cancer—be considered an example of NOA when it is so clearly linked to an oncogene? Both examples are clear if one adheres to a strict definition of NOA stating that NOA genes do not undergo oncogenic mutations in tumors. However, these examples often run counter to our overall intuitive sense of the different categories. Regardless, although the OA and NOA designations are not perfect, they provide a useful intellectual framework for thinking about cancer cell vulnerabilities and the principles of cancer therapies. Below, we will discuss examples of oncogene and non-oncogene addiction and describe how modern tools are being applied to identify these classes of genes for possible therapeutic exploitation.

Oncogene Addiction and Tumor Suppressor Gene Hypersensitivity Despite the multitude of genetic and epigenetic alterations found across cancers, a given tumor is likely to be driven by only a select few changes—those that result in the gain of an oncogene or the loss of a tumor suppressor. The phrase "oncogene addiction" was coined to describe the observation that tumor maintenance often depends upon the continued activity of certain oncogenes This phenomenon has been demonstrated in vivo for several oncogenes. For example, mouse models using an inducible MYC oncogene have shown that MYC-driven skin papillomas, lymphomas, and osteosarcomas can all be reversed upon MYC withdrawal In human colorectal cancer cells bearing a KRAS mutation, somatic knockout of the KRAS oncogene results in reversion of the transformed phenotype and abrogates the ability of these cells to form tumors in nude mice The subset of oncogenes whose inhibition can lead to tumor cell death, differentiation, arrest, or senescence is of great clinical interest as targets for cancer therapeutics (Table 1). This strategy has proven successful for the protein kinase oncogenes BCR-ABL (imatinib/Gleevec), EGFR (gefitinib/Iressa, erlotinib/Tarceva), and HER2 (trastuzumab/Herceptin) and efforts toward inhibition of BRAF, MDM2, and the lipid kinase PI3K are underway. Targeting non-kinase oncogenes such as RAS and MYC, however, has proven more difficult.

Table 1Cancer Therapies Targeting Various Hallmarks of Cancer

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
17AAG (small molecule)	HSP90	NOA		A geldanamycin analog that binds to the ATP-binding pocket of HSP90 and inhibits its catalytic activity	Whitesell and Lindquist, 2005

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
1MT, MTH-Trp (small molecule)	IDO	NOA		Inhibits tryptophan catabolism in tumor microenvironment to allow T cell proliferation	Muller and Scherle, 2006
5-fluorouracil (small molecule)	DNA	NOA		Inhibits pyrimidine metabolism, incorporation in to DNA and RNA causes cell-cycle arrest	Longley et al., 2003
ABT-737, ABT-263 (small molecule)	BCL-XL, BCL-2	OA		Bind to the BH3 pocket of Bcl-XL and inhibit its antiapoptotic function	Stauffer, 2007
Alvocidib, PD 0332991 (small molecule)	CDKs	OA		Inhibit CDKs and induce cell-cycle arrest	Lee and Sicinski, 2006
AP 12009 (antisense oligo)	TGFβ 2	NOA		Inhibits tumor autocrine and paracrine signaling, reverses immune suppression in the tumor microenvironment	Muller and Scherle, 2006
AZD2281, AG014699 (small molecule)	PARP1	NOA		Inhibit base excision repair in homologous recombination repair-deficient cancer cells	Bryant et al., 2005 , Farmer et al., 2005
Bevacizumab (antibody)	VEGF	NOA		Inhibits endothelial cell recruitment and tumor vasculature	Folkman, 2007
BEZ235 (small molecule)	PI3K	OA		Causes cell-cycle arrest in tumor cells and inhibits tumor angiogenesis	Maira et al., 2008
Bortezomib	Proteasome	NOA		Inhibits the catalytic activity of 26S proteasome	Roccaro et

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
(small molecule)				and induces apoptosis	al., 2006
Celecoxib (small molecule)	COX2	NOA		Reverses immune suppression in the tumor microenvironment, inhibits tumor autocrine and paracrine signaling	Muller and Scherle, 2006
Cisplatin and analogs (small molecule)	DNA	NOA		Induces DNA crosslinks	Siddik, 2003
Erlotinib, Gefitinib (small molecule)	EGFR	OA		Inhibit EGFR tyrosine kinase by competing with ATP binding	Sharma et al., 2007
GRN163L (modified oligo)	hTERT	OA		Mimics telomere sequence and inhibits the hTERT active site	Dikmen et al., 2005 , Harley, 2008
GRNVAC1 (cell therapy)	hTERT	OA		Autologous dendritic cells transduced to express an hTERT-LAMP fusion protein to elicit T cell response to hTERT + tumor cells	Harley, 2008 , Su et al., 2005
GV1001 (peptide)	hTERT	OA		A short immunogenic peptide from hTERT designed to elicit T cell response against hTERT + tumor cells	Harley, 2008 , Nava-Parada and Emens, 2007
Imatinib, Dasatinib (small molecule)	BCR-ABL, c-Kit, Src, PDGFR, other TKs	OA		Tyrosine kinase inhibitor with multiple targets	Quintas-Cardama et al., 2007

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
Mapatumumab, Lexatumumab (antibody)	TRAIL receptor	NOA		Bind and activate TRAIL receptors to induce apoptosis	Carlo-Stella et al., 2007
Methotrexate (small molecule)	DHFR	NOA		Inhibits thymidine biosynthesis and induces replicative stress	McGuire, 2003
Nutlin-3 (small molecule)	HDM2	OA		Binds to HDM2 and inhibits the binding and ubiquitination of p53	Vassilev, 2007
Oblimersen (antisense oligo)	BCL-2	OA		Inhibits the expression of BCL-2 by blocking translation of its mRNA	Moreira et al., 2006
Paclitaxel, Vinblastine (small molecule)	Mitotic spindle	NOA		Interfere with dynamics and stability of mitotic spindles, activate mitotic checkpoints, and induce chromosome mis-segregation	Weaver and Cleveland, 2005
PF-00477736 (small molecule)	Chk1	NOA		Prevents activation of the DNA damage response, leading to persistent DNA damage and replication stress	Ashwell and Zabludoff, 2008
PRIMA-1, MIRA-1 (small molecule)	Mutant p53	TSGH		Reactivate the function of mutant p53	Selivanova and Wiman, 2007
Rapamycin, RAD001, Temsirolimus (small molecule)	mTOR	NOA		Inhibit protein synthesis	Guertin and Sabatini, 2007
Retinoic acid (small molecule)	RAR, RXR	OA		Induces cellular differentiation	Spira and Carducci, 2003

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
SAHBs (stapled peptide)	BCL-XL, BCL-2	OA		Stapled BH3 domains that bind to BCL-2 family members and promote apoptosis	Verdine and Walensky, 2007
Sorafenib, Sunitinib (small molecule)	Multiple kinases (VEGFR, RAF, c-Kit, PDGFR)	NOA		Inhibit endothelial cell recruitment and tumor vasculature	Folkman, 2007
Topotecan, Irinotecan (small molecule)	Topo-isomerase I	NOA		Induce DNA breaks	Pommier, 2006
Trastuzumab (antibody)	ERBB2	OA		Inhibits ERBB2 activation and induces immune destruction of cancer cells	Hynes and Lane, 2005

Principles of treatment of cancer

Therapeutics are selected based on the diversity of their chemical structures, the hallmarks they attack, and their cellular targets. These agents are either investigational drugs or approved for selective oncology indications. Abbreviations: OA, oncogene addiction; NOA, non-oncogene addiction; TSGH, tumor suppressor gene hypersensitivity. Symbols for each hallmark refer to those used in figure
In contrast to oncogenes, tumor suppressor genes act to provide the cellular restraints necessary to prevent aberrant growth and survival or genomic instability. Loss of tumor suppressor genes through deletion, inactivating mutation, or epigenetic silencing results in the removal of these restraints leading to tumorigenesis. Reintroduction of a tumor suppressor gene into a tumor lacking that gene can result in tumor regression. This concept has been recently demonstrated by reactivation of p53 in mouse tumor models. Pharmacological exploitation of tumor suppressor mutations, however, has lagged behind efforts aimed at oncogenes because it is often difficult to use a small molecule to either restore or mimic the function of a protein that is either mutated or absent. In cases where a tumor suppressor negatively regulates the activity of a proto-oncogene, drugs targeting the corresponding proto-oncogene should prove efficacious in treating tumors lacking that tumor suppressor. For example, tumors that have lost the tumor suppressor and lipid phosphatase PTEN, which normally acts to constrain PI3K signaling, are likely to be sensitive to PI3K inhibitors. Similarly, loss of Rb, p16, p21, or p27 all result in upregulation of cyclin-dependent kinase (CDK) activity, which drives cell-cycle entry. In principle, tumors resulting from these lesions might be more sensitive to CDK inhibitors. Whether such predictions prove true will only become apparent from clinical trials employing PI3K and CDK inhibitors. In many other cases, however, such as those involving loss of the tumor suppressors p53 or ARF, there is no obvious positive signaling pathway to target, and alternative therapeutic strategies must therefore be considered.

Targeting Non-oncogene Addiction for Cancer Therapy We proposed the concept of non-oncogene addiction (NOA) based on the understanding that the tumorigenic state depends on the activities of a wide variety of genes and pathways, many of which are not inherently oncogenic themselves Importantly, these genes and pathways are essential to support the oncogenic phenotype of cancer cells but are not required to the same degree for the viability of normal cells. From a purely genetic point of view, these dependencies should provide an ample number of drug targets that when inhibited will constitute synthetic lethality with the underlying tumor genotype. Gene interaction studies in yeast have provided precedence for this notion. For example, most mutations exhibit enhanced growth defects when paired with certain other mutations, and one study in yeast identified an average of six genetic interactions per gene As a tumor contains many genetic alterations, each of these changes provides an opportunity to pair with the loss of function of a second gene to result in a severe and possibly lethal growth and survival phenotype. Furthermore, if this second gene is targeted with a drug that inhibits its protein, then a potential cancer therapy can result.

Assessment of the tumor(Watson, Max,et al)

Assessment of the tumour:

Histological nature of the tumour:

Tumour specimens, usually obtained through fine-needle biopsy, core biopsy, surgical biopsy, or excision of a mass or lesion, are examined to confirm:
High grade, poorly differentiated tumours tend to have a poorer outcome than low-grade, well-differentiated tumours.

Biological behaviour of the tumour:

Tumour markers produced by cancers may be a useful adjunct to histological classification and staging and can be used to influence and monitor efficacy of treatment–Table 4.1. tumour markers can be ↑ in many non-malignant conditions.
Tumour markers and associated conditions.

Anatomical extent of the tumour:

Usually determined through a combination of clinical, radiological (Table 4.2), biochemical and surgical assessment. Routine blood tests including liver function tests and bone profiles may also indicate the presence of metastases.

Response to Cancer Treatment

A **complete response (remission)** occurs when a cancer disappears for any length of time after treatment. Doctors regularly monitor people who are being treated or have been treated for cancer. This usually consists of imaging tests and or laboratory tests to monitor the cancer's response to treatment and to identify cancer quickly if it returns.
Some cancers produce proteins that are detectable in the bloodstream. These substances are called tumor markers. An example is prostate-specific antigen (PSA). PSA levels increase in men with prostate cancer. Most tumor markers are not specific enough to be useful in screening (detecting a cancer before a person develops symptoms) or diagnosing cancer because a number of disorders other than cancer can cause these substances to appear in the blood. However, tumor markers (such as PSA and cancer antigen [CA] 125 for ovarian cancer) can help doctors assess a person's response to treatment. If the tumor marker was present before treatment but no longer appears in a blood sample after treatment, the treatment has probably been successful. If the tumor marker disappears after treatment but later reappears, the cancer has probably returned.

Cure is obviously the most successful outcome. A cure means that all evidence of cancer disappears and does not return over a long period of observation. With some forms of cancer, doctors consider people cured if they remain disease-free for 5 years or longer. With other forms, a longer period is required before the person is considered cured.

With a **partial response**, the size or extent of a cancer (for example, as seen on imaging studies such as x-rays, computed tomography [CT], and positron emission tomography [PET]) is reduced by more than half, although cancer remains visible on imaging studies. With a partial response, the person usually has fewer symptoms and may have a prolonged life, although the cancer grows back in most cases. The duration of response is measured from the time of the partial response to the time when the cancer begins to enlarge or spread again.

In some people, treatment does not lead to a complete or partial response, but the cancer may not grow or spread and the person may experience no new symptoms for an extended period of time. This response is also considered beneficial. In the least successful response, the tumor continues to increase in size or new sites of disease appear despite treatment.

Relapse occurs when a cancer that has completely disappeared returns later.
The **disease-free interval** is the interval between the time cancer completely disappears and when it returns.

Total survival time is the interval from diagnosis of cancer to the time of death.
Some types of cancer, such as breast cancers or lymphomas (tumors of the lymph nodes), are termed responsive because they tend to respond well to chemotherapy or radiation therapy. Other cancers, such as pancreas or brain cancers, are termed resistant because most do not respond to chemotherapy or radiation therapy. Some tumors, such as many in the digestive tract and lungs, often respond to chemotherapy at first but later become resistant. Metastatic cancers (cancers that have spread to other sites) are largely incurable.

Surgery for Cancer

Surgery is a traditional form of cancer treatment. It is the most effective in eliminating most types of cancer before it has spread to lymph nodes or distant sites (metastasized). Surgery may be used alone or in combination with other treatments, such as radiation therapy and chemotherapy Doctors may give these other treatments:

- Before surgery (neoadjuvant therapy) to reduce the size of the tumor before surgery

- After surgery (adjuvant therapy) to ensure that as many cancer cells as possible are eliminated

If the cancer has not metastasized, surgery may cure the person. However, it is not always possible to be sure before surgery whether the cancer has or has not spread. During surgery, doctors often remove lymph nodes near the tumor (sentinel nodes) to see whether the cancer has spread to them. If so, the person may be at a high risk of having the cancer recur and may need chemotherapy or radiation therapy after surgery to prevent a recurrence.

Surgery is not the preferred treatment for all early-stage cancers. Some cancers grow in inaccessible sites. In other instances, removing the cancer might require removing a necessary organ, or surgery might impair the organ's function. In such cases, radiation treatment with or without chemotherapy may be preferable.

Surgery is not the main treatment once a cancer has metastasized. However, surgery is sometimes used to reduce primary tumor size (a procedure called debulking), so that radiation therapy and chemotherapy may be more effective. Or surgery may be done to relieve symptoms, such as the severe pain or nausea or vomiting caused when a tumor blocks (obstructs) the intestine. Surgically removing metastases rarely results in a cure because finding all the tumors is difficult. Tumors that remain usually continue to grow. However, in certain cancers (such as renal cell cancer) that have a very small number of metastases, particularly to the liver, brain, or lungs, surgical removal of the metastases can be beneficial.

After a tumor has been removed, additional surgery may be needed to improve the person's comfort or quality of life (for example, reconstruction of a breast after mastectomy).

Radiation Therapy for Cancer

Radiation is a form of intense energy generated by a radioactive substance, such as cobalt, or by specialized equipment, such as an atomic particle (linear) accelerator.
Radiation preferentially kills cells that divide rapidly and cells that have difficulty repairing their DNA. Cancer cells divide more often than normal cells and often cannot repair damage done to them by radiation. Therefore, cancer cells are more likely than most normal cells to be killed by radiation. Nonetheless, cancer cells differ in how easily they are killed by radiation. Some cells are very resistant and cannot be effectively treated with radiation.
(See also Cancer Treatment Principles.)

Types of Radiation Therapy

The **most common form** of radiation therapy used in cancer treatment is

- External beam radiation

Another form of radiation therapy is

- Internal radiation

Radioactive substances can also be attached to proteins called monoclonal antibodies, which seek out cancer cells and attach to them. The radioactive material attached to the antibody concentrates at the cancer cells and destroys them.

External Radiation Therapy

In radiation therapy, a beam of gamma or x-rays, alpha particles, or electrons is aimed at the person's cancer. Radiosurgery is a type of radiation therapy in which very focused beams of radiation are used.

There are several types of external beam radiation, including

- Three-dimensional conformal radiation (3D-CRT)
- Intensity-modulated radiation therapy (IMRT)
- Image-guided radiation therapy (IGRT)
- Tomotherapy
- Stereotactic radiosurgery
- Stereotactic body radiation therapy
- Proton beam radiation
- Electron beam radiation therapy

All types of external radiation are focused on the particular area or organ of the body that contains the cancer. To avoid over-exposing normal tissue, several beam paths are used and surrounding tissues are shielded as much as possible.

Three-dimensional conformal radiation therapy allows doctors to deliver a precise beam of radiation that can be shaped to the contours of the tumor.

Intensity-modulated radiation therapy uses many devices to shape the radiation beam and deliver a dose of radiation. Because so many devices shape the radiation beam, doctors can more precisely control the amount of radiation delivered to specific areas of the tumor, allowing more protection for nearby healthy tissue.

In **image-guided radiation therapy**, imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) are taken during the radiation treatment. These images allow doctors to detect changes in a tumor's size or location during treatment and allow them to adjust the person's position or the radiation dose during the treatment.

Tomotherapy is a combination of image-guided therapy and IMRT. Tomotherapy is given by a machine that combines a CT scanner and a linear accelerator. This machine can obtain very detailed images of the person's tumor, allowing very precise targeting of the radiation beam.

Stereotactic radiosurgery is used to give very high doses of radiation to very small tumors. It can only be used in small tumors that have very clear edges, so it is often used for tumors in the brain and spinal cord. Stereotactic radiosurgery requires that the person be held in a very precise position during treatment, so special head frames and other positioning devices are used.

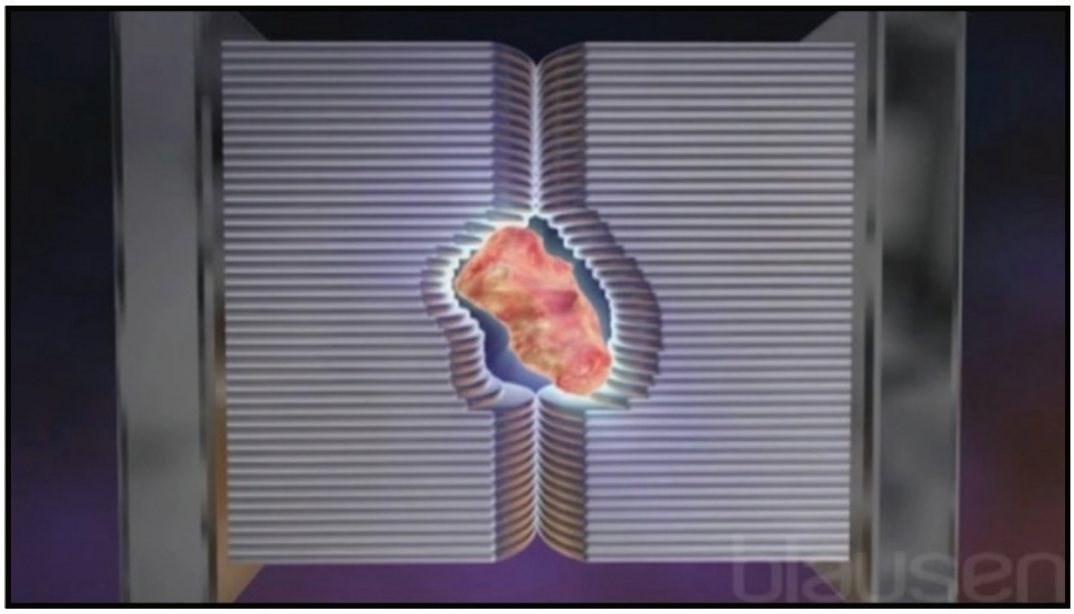
Stereotactic body radiation therapy uses smaller treatment areas (radiation fields) and higher doses of radiation therapy than three-dimensional conformal radiation therapy. It is used to treat small tumors that are located outside the brain and spinal cord.

Proton beam radiation, which can be focused on a very specific area, effectively treats certain cancers in areas where damage to normal tissue is a particular concern, such as the eyes, brain, prostate, or spinal cord.

Electron beam radiation therapy is used to treat tumors near the surface of the body such as skin cancers.

The choice of technique often depends on tumor location.

Intensity-Modulated Radiation Therapy



VIDEO

External beam radiation therapy is given as a series of equally divided doses over a prolonged period of time. This method increases the lethal effects of the radiation on cancer cells while decreasing the toxic effects on normal cells. Toxic effects are decreased because normal cells can repair themselves quickly between doses while cancer cells cannot. Typically, a person receives daily doses of radiation over a period of 6 to 8 weeks. To ensure that the same area is treated each time, the person is precisely positioned using foam casts or other devices.

Internal Radiation

In other radiation therapy strategies, a radioactive substance may be injected into a vein to travel to the cancer (for example, radioactive iodine used in treatment of thyroid cancer). Sometimes, a radioactive substance is attached to a monoclonal antibody (an antibody manufactured in a laboratory) that is designed to attach directly to cancer cells. In another technique, people may swallow the radioactive substance.
Brachytherapy uses small pellets ("seeds") of radioactive material placed directly into the cancer (for example, radioactive palladium used for prostate cancer). These implants provide intense radiation to the cancer, but little radiation reaches surrounding tissues. Implants contain short-lived radioactive substances that stop producing radiation after a period of time.

Uses for Radiation Therapy

Radiation therapy plays a key role in curing many cancers, including Hodgkin lymphoma, early-stage non-Hodgkin lymphoma, squamous cell cancer of the head and neck, seminoma (a testicular cancer), prostate cancer, early-stage breast cancer, some forms of non–small cell lung cancer, and medulloblastoma (a brain or spinal cord tumor). For early-stage cancers of the windpipe (larynx) and prostate, the rate of cure is essentially the same with radiation therapy as with surgery. Sometimes, radiation therapy is combined with other forms of treatment. Certain kinds of chemotherapy drugs, such as cisplatin, enhance the effectiveness of radiation therapy, and these drugs may be given with radiation treatments.

Radiation therapy can reduce symptoms when a cure is not possible, such as for bone metastases in multiple myeloma and painful tumors in people with advanced lung, esophageal, head and neck, and stomach cancers. By temporarily shrinking the tumors, radiation therapy can relieve symptoms caused by spread of cancer to bone or brain.

Side Effects of Radiation Therapy

Radiation can damage normal tissues near the tumor. Side effects depend on how large an area is being treated, what dose is given, and how close the tumor is to sensitive tissues. Sensitive tissues are those in which cells normally divide rapidly, such as skin, bone marrow, hair follicles, and the lining of the mouth, esophagus, and intestine. Radiation can also damage the ovaries or testes. Doctors try to accurately target the radiation therapy to prevent damaging normal cells.

Side effects depend on the area receiving radiation and may include

- Fatigue
- Mouth sores

- Skin problems (such as redness, itching, and peeling)
- Painful swallowing
- Lung inflammation (pneumonitis)
- Liver inflammation (hepatitis)
- Gastrointestinal problems (such as nausea, loss of appetite, vomiting, and diarrhea)
- Urinary problems (such as increased frequency and burning during urination)
- Low blood cell concentrations, leading to anemia (which causes fatigue and weakness), easy bruising or bleeding, and risk of infections

Radiation to head and neck cancers often causes damage to the overlying skin as well as the salivary glands and the lining of the mouth and throat. Doctors try to identify and treat such symptoms as early as possible so the person remains comfortable and can continue with treatments. For example, a variety of drugs can reduce the diarrhea caused by radiation therapy to the abdomen.

Radiation therapy can increase the risk of developing other cancers years after the initial cancer was treated. The risk depends on the person's age at the time of treatment and the part of the body that received the radiation.

Chemotherapy and other treatments for cancer

Systemic treatments are those that have effects throughout the body rather than being applied directly to the cancer. Chemotherapy is a form of systemic treatment that uses drugs to kill cancer cells or to stop them from growing.
Systemic cancer therapy includes

- Hormonal therapy
- Chemotherapy (anti-cancer drugs)
- Targeted drug therapy
- Immune therapy
- Gene therapy
- Various other drugs for cancer

Immunotherapy is a systemic cancer treatment that stimulates the body's immune system against cancer The number of approved cancer therapies is increasing rapidly. The National Cancer Institute maintains an up-to-date list of drugs used to treat cancer. The list provides a brief summary of each drug's uses and links to additional information.

Not all cancers respond to chemotherapy. The type of cancer determines which drugs are used, in what combination, and at what dose and schedule. Chemotherapy may be used as the sole treatment or combined with radiation therapy, surgery, or immune therapy.

Hormonal Therapy for Cancer

Hormones are proteins produced by endocrine glands that affect activities of target tissues and organs. Hormones serve as messengers, controlling and coordinating activities throughout the body. Some cancers grow and spread more when they are exposed to certain hormones. Consequently, reversing the effects of these hormones may control some hormone-dependent cancers. However, these drugs also can cause symptoms of hormone deficiency.

For example, prostate cancer grows faster when exposed to the male sex hormone testosterone and other androgenic steroids. Thus, anti-androgen therapy is commonly used to treat prostate cancer. Some anti-androgen drugs, such as leuprolide, goserelin, and others, prevent the pituitary gland from stimulating the testes to make testosterone. Other hormonal therapy drugs, such as flutamide, bicalutamide, and nilutamide, are used to block the effects of testosterone. These hormonal therapy drugs do not cure prostate cancer, but they can slow the growth and spread of prostate cancer. However, these drugs also may cause symptoms of testosterone deficiency, such as hot flashes, osteoporosis, loss of energy, reduction in muscle mass, fluid weight gain, reduction of libido, decrease in body hair, erectile dysfunction, and breast enlargement.

Some breast cancers grow faster when exposed to the female sex hormones estrogen and/or progesterone. Drugs such as tamoxifen and raloxifene bind to estrogen receptors and inhibit the growth of breast cancers with estrogen receptors. These drugs also reduce the risk of developing breast cancer. Aromatase inhibitors, such as anastrozole, reduce the production of estrogen and have a similar benefit.
Hormonal therapy may be used alone or combined with other types of cancer therapy.

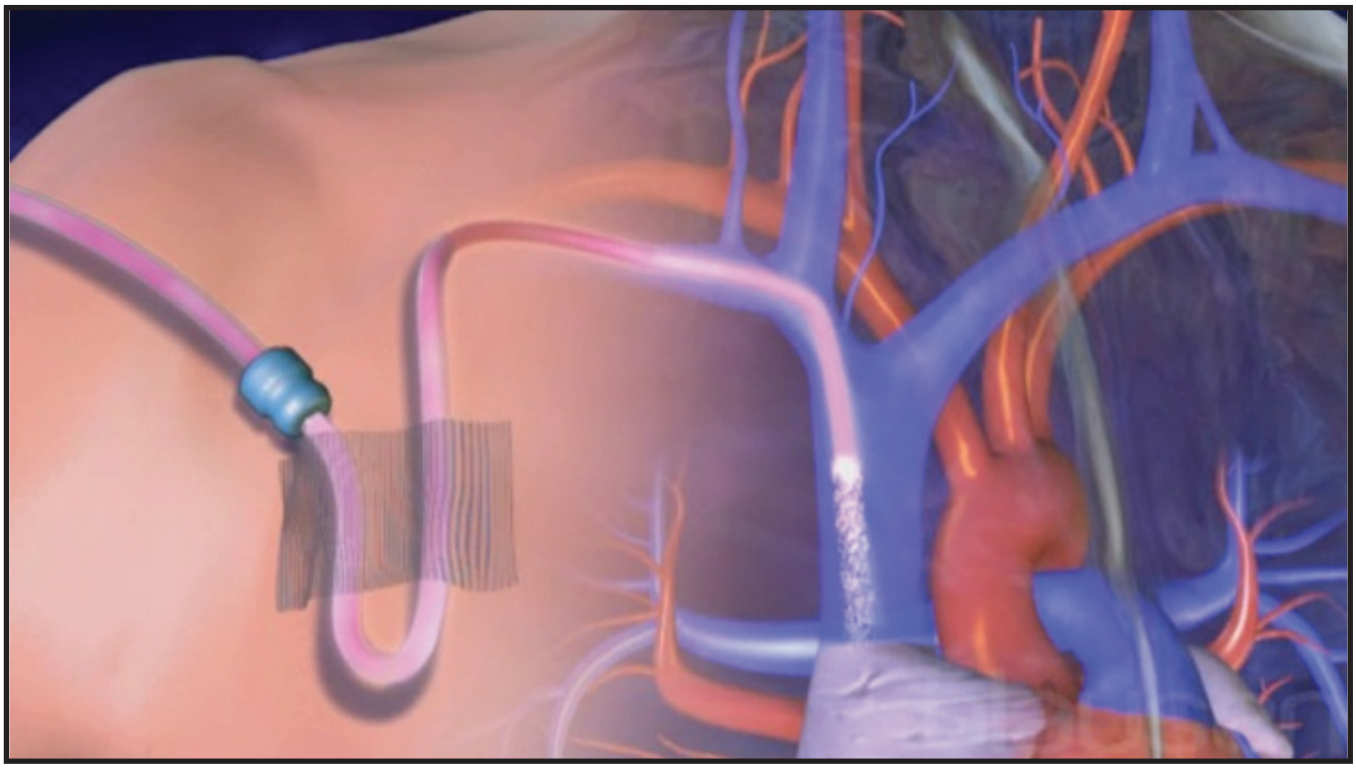
Chemotherapy

Chemotherapy involves the use of drugs to destroy cancer cells. Although an ideal drug would destroy cancer cells without harming normal cells, most drugs are not that selective. Instead, drugs are designed to inflict greater damage on cancer cells than on normal cells, typically by using drugs that affect a cell's ability to grow. Uncontrolled and rapid growth is characteristic of cancer cells. However, because normal cells also need to grow, and some grow quite rapidly (such as those in the bone marrow and those lining the mouth and intestine), all chemotherapy drugs affect normal cells and cause side effects.
Chemotherapy is used to cure cancer. It may also decrease the chance that cancer will return, slow the growth of a cancer, or shrink tumors that are causing pain or other problems.

Although a single chemotherapy drug may be effective against some types of cancer, often doctors give several chemotherapy drugs at the same time High-dose chemotherapy In an attempt to increase the tumor-destroying effects of cancer drugs, the dose may be increased. Sometimes the rest period between cycles of chemotherapy may be decreased. High-dose chemotherapy, with shortened rest periods, is routinely used in many cancers such as leukemias, lymphomas, lung cancers, pancreas cancers, digestive system cancers, breast cancers, and others.

High-dose chemotherapy is sometimes used to treat people whose cancer has recurred after standard-dose chemotherapy, particularly for people with myeloma, lymphoma, and leukemia. However, high-dose chemotherapy can cause life-threatening injury to the bone marrow. Therefore, high-dose chemotherapy is commonly combined with strategies to protect the bone marrow (rescue). In bone marrow rescue, bone marrow cells are harvested before the chemotherapy and returned to the person after chemotherapy. In some cases these cells can be isolated from the bloodstream rather than from the bone marrow and can be infused back into the person after chemotherapy to restore bone marrow function.

Central Venous Catheter/Peripherally Inserted Central Catheter



Targeted Drugs

One approach to increase efficacy uses drugs that target specific mutations in cancer cells. These drugs control cancer cells by targeting specific pathways and processes vital to the cancer cells' growth and survival Imatinib and other drugs that inhibit the enzyme tyrosine kinase,are highly effective in chronic myeloid leukemia and certain cancers of the digestive tract. Erlotinib, gefitinib, and osimertinib target mutations in the epidermal growth factor receptor (EGFR) and are used to treat lung cancers with this mutation. Molecularly targeted drugs have proven useful in treating many other cancers, including other leukemias, and breast and kidney cancers.

Gene Therapy

Because changes (mutations) of genes cause cancer, researchers are looking at ways to manipulate genes to fight cancer.

One form of gene therapy involves genetically modifying T cells (a type of immune cell)—see also Modified T cells. Doctors remove T cells from a person's blood and genetically modify them to recognize that person's specific cancer. When the modified T cells, called chimeric antigen receptor cells or CAR-T-cells, are put back in the person's bloodstream, they attack the cancer. CAR-T-cells can be used in people with acute lymphoblastic leukemia, multiple myeloma, and lymphoma.

New, still-experimental, techniques allow scientists to insert new genes into a cells, switch off abnormal genes, or increase the activity of helpful genes .Doctors hope these techniques may one day be useful for treating cancer.

Other Drugs

Cancer cells are immature and grow rapidly, so one type of drug promotes the more rapid maturation (differentiation) of cancer cells to slow the growth of the tumor. These differentiating drugs may only be effective for a short time, so they are often used in combination chemotherapy.

Anti-angiogenesis drugs prevent a tumor from forming new blood vessels. If blood vessel growth is prevented, the cancer will lack the blood supply needed to grow. Some drugs can block blood vessel formation to cancer cells. Bevacizumab is a monoclonal antibody that blocks a growth factor needed by blood vessels. It is effective against kidney cancers and colon cancer. Other drugs, such as sorafenib and sunitinib, block the receptor for the blood vessel growth factor. These may be effective in kidney and liver cancers.

Still other drugs target the pathways cancer cells use to signal additional cells to form or grow.

Chemotherapy related side effects

Chemotherapy refers to drugs given to kill or slow the growth of cancer cells. However, because chemotherapy drugs work throughout the body (for example on all cells in a particular stage of development), healthy cells are attacked as well as cancerous ones. Because healthy cells are also damaged during chemotherapy, side effects are likely.

Chemotherapy commonly causes nausea, vomiting, loss of appetite, weight loss, fatigue, and low blood cell counts that lead to anemia and increased risk of infections. People also often lose their hair, but other side effects vary according to the type of drug.

Targeted Drugs

Gastrointestinal (digestive tract) effects are very common and include

- Loss of appetite
- Nausea and vomiting
- Diarrhea

These effects also may be caused by the cancer itself

Loss of appetite is common and may cause weight loss. People who lose more than 10% of their ideal body weight do not do as well as those who are able to maintain their weight or lose less weight. Doctors encourage people to maintain good nutrition. There are several drugs that increase appetite, but it is not clear whether they actually can reverse weight loss, improve quality of life, or prolong survival.

Nausea and vomiting greatly harm quality of life. People often think all cancer drugs cause nausea and vomiting, but these symptoms are more likely with certain drugs and with certain situations. Nausea and vomiting can usually be prevented or relieved with drugs (antiemetics), particularly with granisetron, ondansetron, or aprepitant. Doctors may give these drugs before a dose of chemotherapy as well as to treat nausea and vomiting after it has started. Nausea may also be reduced by eating small meals and by avoiding foods that are high in fiber, that produce gas, or that are very hot or very cold. In some states, marijuana can be prescribed to relieve nausea and vomiting caused by chemotherapy.

Diarrhea is common after treatment with chemotherapy drugs or with targeted therapy drugs (and after radiation therapy). Diarrhea is usually treated with the drug loperamide

Low Blood Cell Concentrations

Cytopenias, a deficiency of one or more types of blood cell, can develop because of the toxic effects that chemotherapy drugs have on the bone marrow (where blood cells are made). For example, a person may develop abnormally low numbers of

- Red blood cells (anemia)
- White blood cells (neutropenia or leukopenia)
- Platelets (thrombocytopenia)

Red blood cells carry oxygen from the lungs to all the cells of the body. Without enough red blood cells, people may be pale or have fatigue or weakness. People with more severe anemia may have dizziness, thirst, sweating, or even shortness of breath and chest pain. If anemia is severe, packed red blood cells can be transfused. A red blood cell growth factor, erythropoietin, also can be given, but transfusion is preferred because there is less risk of a blood clot.

A person with neutropenia is at increased risk of developing an infection because white blood cells are an essential defense against infection. A fever higher than 100.4° F (38° C) in a person with neutropenia is treated as an emergency. Such a person must be evaluated for infection and may require antibiotics and even hospitalization. White blood cells are rarely transfused because, when transfused, they survive only a few hours and produce many side effects. Instead, certain substances (such as granulocyte-colony stimulating factor) can be administered to stimulate white blood cell production.

Platelets are small cell-like particles in the blood that help it to clot when there is a cut or broken blood vessel. A person without enough platelets (thrombocytopenia) is likely to bruise and bleed easily. If thrombocytopenia is severe, people may have severe digestive tract bleeding or bleeding into their brain. Platelets can be transfused to treat or help prevent bleeding.

Chemotherapy-Induced Thrombocytopenia

Mouth Sores

Many people develop inflammation or even sores of the mucous membranes, such as the lining of the mouth. Mouth sores are painful and can make eating difficult. Various oral solutions (usually containing an antacid, an antihistamine, and a local anesthetic) can reduce the discomfort. On rare occasions, people need nutritional support by a feeding tube that is placed directly into the stomach or small intestine or even by vein.

Depression

Depression may be the result of cancer therapy as well as the cancer itself.

Organ Damage and Other Cancers

Sometimes chemotherapy drugs may damage other organs, such as the lungs, heart, or liver. For example, anthracyclines (such as doxorubicin), a type of topoisomerase inhibitor, cause heart damage when used in high total doses.

People treated with chemotherapy, particularly alkylating agents, may have an increased risk of developing leukemia several years after treatment. Some drugs, especially alkylating agents, cause infertility in some women and in most men who receive these treatments.

Tumor Lysis Syndrome and Cytokine Release Syndrome

Tumor lysis syndrome may occur after chemotherapy because, when cancer cells are killed, they may release their contents into the bloodstream. These contents may damage the kidneys or heart. Tumor lysis syndrome occurs mainly in acute leukemias and non-Hodgkin lymphomas but can also occur after treatment of other types of cancer. Sometimes doctors are able to prevent tumor lysis syndrome by giving allopurinol before and during chemotherapy. Doctors may also give fluids by vein to cause the kidneys to excrete these toxic products quickly.

Cytokine release syndrome is related to but distinct from the tumor lysis syndrome. Cytokine release syndrome occurs when large numbers of white blood cells are activated and release inflammatory substances called cytokines. It is a frequent complication of cell-based therapies such as those using CAR-T-cells and some monoclonal antibodies. Symptoms include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, rapid breathing, headache, confusion, and hallucinations. In general, treatment for mild cytokine release syndrome is supportive and involves relieving symptoms like fever, muscle pain, or fatigue. Oxygen therapy, fluids and drugs to raise blood pressure, and drugs to decrease inflammation may be needed in people with more severe cytokine release syndrome.

Stem Cell Transplantation

Stem cells are unspecialized cells that have the capability to become many different types of cells. Stem cells in the bone marrow are the source of all the different normal blood cells. High doses of chemotherapy drugs or radiation therapy can kill cancer cells but often also kills the person's stem cells, which prevents the bone marrow from producing normal blood cells.

Stem cell transplantation replaces the killed stem cells with healthy stem cells from a donor. Donors can be the person with cancer (an autotransplant) or another genetically matched related or unrelated person (an allotransplant). The stem cells may be taken from a donor's bone marrow, but it is easier and almost as effective to get the stem cells from the donor's blood. Stem cell transplants allow doctors to give high doses of chemotherapy to treat leukemias and some lymphomas.

Immunotherapy

Immunotherapy is used to stimulate the body's immune system against cancer. These treatments target specific genetic characteristics of the tumor cells. The genetic characteristics of tumors do not depend on what organ in the body the cancer develops. So these drugs may be effective against many types of cancer. There are several different types of treatments that doctors use to stimulate the immune system. And this area of cancer treatment is being intensively studied. The National Cancer Institute maintains an up-to-date list of immunotherapy drugs (as well as other drugs used to treat cancer). The list provides a brief summary of each drug's uses and links to additional information.

Monoclonal antibodies
Monoclonal antibody therapy involves the use of antibodies produced in a laboratory to target specific proteins on the surface of cancer cells. There are many such antibodies available, and others are currently being studied. Trastuzumab is one such antibody, which attacks the HER-2/neu receptor present on the surface of cancer cells in 25% of women with breast cancer. Trastuzumab enhances the effect of chemotherapy drugs.
Rituximab is highly effective in treating lymphomas and chronic lymphocytic leukemia. Rituximab linked to a radioactive isotope can be used to deliver radiation directly to lymphoma cells.

Gemtuzumab ozogamicin, a combined antibody and drug, is effective in some people with acute myeloid leukemia.

Several monoclonal antibodies modify the function of immune checkpoints, which help to control the immune system, and in so doing stimulate the body's natural anticancer immunity. Drugs called checkpoint inhibitors may block checkpoints, which are proteins that help turn the immune response off and on. Some cancers activate these checkpoints and turn off the immune system's ability to attack the cancer. Checkpoint inhibitors such as CTLA-4 (ipilimumab and tremelimumab) and PD1 (cemiplimab, dostarlimab, nivolumab, and pembrolizumab) or PD-L1 (durvalumab, atezolizumab, and avelumab) allow the immune system to attack the cancer. For example, pembrolizumab can be used for any advanced cancer with a DNA-repair defect independent of where the cancer is in the body.

Checkpoint inhibitors are sometimes given alone or combined with other anticancer drugs.

Modified T cell are cells of the immune system that can recognize and destroy foreign cells. In this form of cancer treatment, T cells are removed from the blood of a person with cancer. Then in the laboratory, doctors modify these T cells genetically so that they recognize and attack that person's cancer cells. Then they return the modified T cells to the person. The most common example of this strategy is termed chimeric antigen receptor (CAR)-T-cells. CAR-T-cells are an effective therapy in people with acute lymphoblastic leukemia, B-cell lymphomas, and multiple myeloma.

Related techniques involve growing the extracted T cells in a culture and activating them by exposure to a certain signaling substance used by the body's cells. Alternatively, T cells may be extracted from the person's tumor, cultured to create a larger amount, and then reinfused.

Nonspecific immunotherapy Biologic response modifiers stimulate normal cells to produce chemical messengers (mediators) that improve the immune system's ability to find and destroy cancer cells. The effects are generalized and not specific to only certain cancers.

Interferon (of which there are several types) is the best-known and most widely used biologic response modifier. Almost all human cells produce interferon naturally, but interferon can also be made through biotechnology. Although its precise mechanisms of action are not totally clear, interferon has a role in the treatment of several cancers, such as Kaposi sarcoma and malignant melanoma.

Interleukins are messengers produced by certain immune system cells (activated T cells). Giving interleukins can help in the treatment of metastatic melanoma and may be of benefit in kidney cancer. Interleukin 2, which is produced by certain white blood cells, can be helpful in renal cell carcinoma and metastatic melanoma.

Vaccines composed of material derived from cancer cells can boost the body's production of antibodies or immune cells that can attack the cancer. Extracts of weakened tuberculosis bacteria, which are known to boost the immune response, have been successful when instilled into the bladder to prevent recurrence of bladder tumors.

Combination Therapy

Cancer drugs are most effective when given in combination. The rationale for combination therapy is to use drugs that work by different mechanisms, thereby decreasing the likelihood that resistant cancer cells will develop. When drugs with different effects are combined, each drug can be used at its optimal dose, without intolerable side effects.

For some cancers, the best approach is a combination of cancer surgery, radiation therapy, and chemotherapy or other cancer drugs. Surgery or radiation therapy treats cancer that is confined locally, while cancer drugs also kill the cancer cells that have spread to distant sites.

Sometimes radiation therapy or drug therapy is given before surgery to shrink a tumor, thereby improving the opportunity for complete surgical removal (this technique is called neoadjuvant therapy). Radiation therapy and/or drug therapy given after surgery (called adjuvant therapy) help to destroy any remaining cancer cells.

The stage and type of the cancer often determines whether single therapy or combination therapy is needed. For example, early-stage breast cancer may be treated with surgery alone or surgery combined with radiation therapy, drug therapy, or with all three treatments, depending on the size of the tumor and the risk of recurrence. Locally advanced breast cancer is usually treated with chemotherapy, radiation therapy, and surgery.

Sometimes combination drug therapy is used not to cure but to reduce symptoms and prolong life. Combination drug therapy can be useful for people with advanced cancers that are not suitable for radiation therapy or surgical treatment (for example, people with non–small cell lung cancer, esophageal cancer, or bladder cancer that cannot be completely removed by surgery).

Diet and Cancer

Many studies have tried to determine whether specific foods increase or decrease a person's risk of getting cancer. Unfortunately, different studies have had conflicting results, so it is hard to know what effect foods or dietary supplements have on cancer risk. A common problem is that when studies find that people who eat more of a certain food seem to have lower rates of a certain cancer, it can be difficult to tell whether those people also were different in terms of other risk factors (such as where they live, how much they smoke and drink, and so forth).
Often, when doctors do a controlled trial and randomly give some people a seemingly helpful food or supplement, the studies do not show a beneficial effect. Some foods and supplements have been studied more than others, and many studies are ongoing. The most convincing evidence is from studies that show diets low in fiber and high in processed meats increase cancer risk. Obesity, regardless of the type of diet, increases the risk of many cancers.

Alcohol

Alcohol increases the risk of cancers of the mouth, throat, esophagus, liver, breast, and the colon and rectum. People who smoke as well as drink have a much higher risk of these cancers.

Antioxidants

Antioxidants, such as vitamins C and E and beta-carotene (vitamin A), are part of a well-balanced diet. However, studies have not shown that taking supplements containing these antioxidants decreases the risk of cancer. There is some evidence that taking high doses of beta-carotene or vitamin E supplements may increase the risk of certain types of cancer.

Artificial sweeteners

Although some early studies show an increased risk of bladder cancer, brain cancer, and lymphomas with certain sweeteners, these studies were done in animals. No studies in humans show an increased risk of cancer with the use of these sweeteners.

Bioengineered foods (genetically modified [GMO] foods)

Genes from different plants or from certain microorganisms are added to the genes of some plants to increase the plants' hardiness or resistance to pests or to improve them in some other way. No current evidence demonstrates that bioengineered foods have any effect on cancer risk.

Calcium

Some studies have found that higher vitamin D levels and calcium supplements may reduce the risk of precancerous polyps of the colon. However, other studies suggest that a high calcium intake increases the risk of prostate cancer.

Coffee

Although some older studies appeared to show a link between coffee consumption and cancer risk, more recent studies have not shown any connection.

Fiber

Some studies report that a diet high in fiber reduces the risk of cancer, especially colorectal cancer, but these reports controversial.

Fish and omega-3 fatty acids

Some studies in animals suggest that omega-3 fatty acids may stop cancers from growing or slow their growth. However, these findings have not been replicated in humans.

Fluoride

Studies have not shown an increased risk of cancer in people who drink fluoridated water or who use toothpastes or undergo dental fluoride treatments.

Folate

Some evidence indicates a higher cancer risk in people with folate (folic acid) deficiency, but whether the deficiency is the cause of cancer is unknown. In contrast, other less conclusive evidence suggests that excess folate may increase cancer risk. A person eating a normal diet requires no additional folate.

Food additives

Food additives must be approved by the Food and Drug Administration before they are included in foods, so new additives undergo extensive testing. So far, no evidence shows that the levels of additives found in food products increase the risk of cancer.

Garlic

Scientific studies have not shown that garlic is effective in reducing the risk of cancer.

Irradiated foods

Radiation of food, which is sometimes used to kill microorganisms in food, does not increase cancer risk.

Lycopene

Some studies suggest that lycopene, a natural red pigment and antioxidant found mainly in tomatoes, may reduce the risk of some cancers but these data are controversial.

Meats cooked at high temperatures

Eating meat cooked at high temperatures, for example by grilling or broiling, may introduce cancer-causing chemicals and increase cancer risk.

Organic food

There is no evidence that organically grown foods reduce cancer risk more than the same foods grown by other methods.

Overeating

Obese people have higher risks of diverse cancers.

Pesticides

There is no evidence that pesticide residue found in small amounts on foods increases the risk of cancer.

Processed meats

People who eat large amounts of processed meats may be at risk for stomach and colon and rectal cancers. Some evidence suggests that this is caused by nitrates in luncheon meats, hams, and hot dogs.

Saturated fats

Some studies have found higher rates of some types of cancers in countries where fat intake is higher. However, no studies have found that decreasing fat intake decreases the risk of cancer. Of more importance, however, is that foods that contain high levels of saturated fats also contain many calories and may contribute to obesity, which is a risk factor for cancer and other health problems.

Selenium

There is no convincing evidence that selenium reduces cancer risk.

Spices

There is no convincing evidence that spices such as tumeric, capsaicin (red pepper), cumin, or curry decrease cancer risk.

Tea

There is no convincing evidence that regular or green tea decreases cancer risk.

Vitamin D

Vitamin D when taken with omega-3 fatty acid may decrease risk of death from cancer but does not decrease risk of developing cancer. Any potential benefit is greater in Blacks.

Vitamin E

There is no convincing evidence that vitamin E supplements decrease cancer risk, and some evidence suggests an increased risk of prostate and other cancers.

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VITALEDGE ACADEMY OF CLINICAL STUDIES

Office No F-5, C Wing, 1st Floor, Shah Arcade, Rani Sati Marg, Jagruti Stop,
Malad East. Mumbai – 400097

Mob No :8779653812 | Email ID: drprasad.vadde@veacs.co.in | www.veacs.co.in