A REVIEW ON TYPES OF CANCERS AND NOVEL THERAPEUTIC OPTIONS FOR PREVENTION AND MANAGEMENT OF CANCER

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Abstract:
Cancer is a large group of diseases that occur when abnormal cells divide rapidly and can spread to other tissue and organs. These rapidly growing cells may cause tumors. They may also disrupt the body's regular function. Cancer is one of the leading causes of death in the world. According to the World Health Organization Trusted Source, cancer accounted for almost 1 in 6 deaths in 2020. Experts are working hard to test out new cancer treatments every day. Differentiating features of malignant and benign lesion are well established; these include rapid growth, increased cell turn-over, invasive growth, metastases, vascular or lymphatic channel invasion for malignant lesions. There are many exceptions to these attributes of cancer. There are overlaps between benign and malignant lesions. The traditional model of cancers envisaged a "normal cell" transformed to "atypical or dysplastic" cell with progression into invasive of malignant cell. This is the model that only assumes stochastic generation of cells capable of the behavior of metastasis and progression and cellular heterogeneity of cancers. Cancer initiation, driver mutations, progression and metastases are common attributes for both stochastic and cancer stem cell models; cancer stem cells possess attributes that enhance survival in all environments hence more suitable as model of cancer. Integrated models that capture every essence of a cancer could enhance the ability to target different components of cancer for maximum therapeutic effect. The prior detection and treatment of cancer could lower the future progression of cancer associated burden in the community.

Keywords: Cancer, tumors, benign lesion, malignant lesion, therapeutic effect.

Introduction

Cancer occurs when genetic mutations in abnormal cells cause them to divide rapidly. Cancer is a large group of diseases that occur when abnormal cells divide rapidly and can spread to other tissue and organs. These rapidly growing cells may cause tumors. They may also disrupt the body's regular function. Cancer is one of the leading causes of death in the world. According to the World Health Organization (WHO) Trusted Source, cancer accounted for almost 1 in 6 deaths in 2020[1-4]. Experts are working hard to test out new cancer treatments every day. Human cancers occur worldwide. In 2008, 12.7 million new cancers and 7.6 million cancers were recorded; incidence and mortality rates varied with regions and levels of income around the world. These results require refocusing on all attributes of cancer.

Differentiating features of malignant and benign lesion are well established; these include rapid growth, increased cell turn-over, invasive growth, metastases, vascular or lymphatic channel invasion for malignant lesions. There are many exceptions to these attributes of cancer. There are overlaps between benign and malignant lesions. Benign (non-malignant) tumors do show chromosome aberrations; uveal melanomas and blue nevi share mutations in G protein [2]. A good example is the recent attempt among dermatopathologists to segregate some melanocytic lesions as atypical melanocytic proliferations with low malignant potential (MELTUMP). Sometimes a cancer at given site/organ is classified as containing two cell types; for example, pancreatic cancer with neuroendocrine and acinar/ductal components. What model can accommodate unclassifiable cancers in a specific location? Cancer classification schemes always reserve a group as unclassifiable. How can this group are eliminated. The last two decades have witnessed the surge in molecular profiling and has already expanded into predictive and diagnostic molecular classification of cancers. As in the diagnosis of cancers, current molecular classification schemes are still dependent on morphologic variables. These classifications schemes use cell of origin as seen by light and electron microscopy. Inherently, all organs can multiple cancer types as multiple cell types exist in these organs- "the holy-grail of all subspecialties". Furthermore, cancer subtypes are generated under the banner of a single, specific cell type of origin concept. Take the example of the common Basal cell carcinoma- it has variants and subtypes such as nodular, superficial, adenoid, morpheaform, infiltrative, keratotic, pigmented, basosquamous, clear cell, granular, eccrine, apocrine, fibroepitheliomatous, adamantoid, and basosebaceous Do these entities have unique biological features or simply morphological variants of interest only to the diagnostic pathologists? Will the "cancer stem cell origin concept" cure this malady. The current move to genomics {(gene and transcripts, kinomes, micro RNAs, single nucleotide polymorphisms (SNPs), gene copy number variation (CNVs) and proteomics (antibody microarray and mass spectrometry)} brings change to the diagnostic information needed for treatment. Along with the genomic profiling, are efforts at targeted and gene therapy. Because of accumulated experience, in diagnosis, classifications and treatment of cancer that depends on morphology, the shift to genomic methods should be comprehensive and adequate for day-to-day clinical use. While future cancer classification schemes or models may not require morphological attributes, current dependencies on morphological phenotype requires its inclusion[5-11]. Morphologic cancer phenotyping does not need to hide the compendium of genetic alterations, interactions with environment and alterations in transcriptional and protein interaction networks that are present in all cancers.

Hallmarks of Cancer Cell

Hanahan and Weinberg (2000) [14, 15] listed the seven attributes of cancer; 1) Self sufficiency in growth signals, 2) Insensitivity to anti-growth signals, 3) Evading apoptosis, 4) Limitless replicative potential, telomerase and telomeres 5) Sustained angiogenesis, 6) Tissue invasion and metastasis, and 7) Genome instability. All seven attributes have received great attention in the past decade. Growth and anti-growth signaling are really complex [13]. Protein-protein interaction and signaling networks, growth signaling pathways, the role of ubiquitination and protein degradation, and dysfunctional protein networks and interactions are complex, described as hubs, modules and motifs. Information on cancer cell death and provocation by drugs and irradiation now requires all cell death types to be considered- apoptosis, necrosis, autophagy. We now must include the pivotal role of microRNAs [21, 22], and methylation patterns. For example, microRNA-185 suppresses cancer growth by interfering with Six1; when absent in cancers leads to increase growth and progression. Recent efforts have uncovered the role of transposons in the induction of cancer in mouse models; the studies are generating previously unknown cancer related genes[12-19]. Class II (DNA transposons) and class I retrotransposons contribute to DNA instability. Cancer cells use aerobic glycolysis to meet energy needs (Warburg effect) and presumed to be a response to hypoxia and tumor micro-environment; changes in metabolic needs of cancer cells such as need for glutamine and activation of hypoxia-inducible-factor (HIF) are interconnected to oncogene activation.

Origin of Cancer Cells

The traditional model of cancers envisaged a "normal cell" transformed to "atypical or dysplastic" cell with progression into invasive of malignant cell. This is the model that only assumes stochastic generation of cells capable of the behavior of metastasis and progression and cellular heterogeneity of cancers. The stochastic model is used to explain heterogeneity in cancers such as in prostate cancer. The stochastic model will have to assume that all genetic aberrations conferring advantages to the cancer cells "must be maintained in all subsequent cells as growth and proliferation continues and some maturation occurs". As cancers can also undergo senescence, apoptosis, autophagy and necrosis, the stochastic model must account for these changes. Cancer senescence occurs via telomere shortening, oxidative stress, and oncogene activation, that can impair cancer progression[20-22].

Causes of cancer

These external causes, called carcinogens, can include:

- physical carcinogens like radiation and ultraviolet (UV) light

- chemical carcinogens like cigarette smoke, asbestos, alcohol, air pollution, and contaminated food and drinking water
- biological carcinogens like viruses, bacteria, and parasites

Risk factors

Certain risk factors may increase your chance of developing cancer. These risk factors can include:

- tobacco use
- high alcohol consumption
- an unhealthy diet, characterized by red and processed meat, sugary drinks and salty snacks, starchy foods, and refined carbohydrates including sugars and processed grains, according to a 2017 review
- a lack of physical activity
- exposure to air pollution
- exposure to radiation
- unprotected exposure to UV light, such as sunlight
- infection by certain viruses including *H. pylori*, human papillomavirus (HPV), hepatitis B, hepatitis C, HIV, and the Epstein-Barr virus, which causes infectious mononucleosis

The risk of developing cancer also increases with age. In general, the risk of developing cancer appears to increase until the age of 70 to 80Trusted Source and then diminish, according to the National Cancer Institute (NCI).

A 2020 reviewTrusted Source suggests this may be the result of:

- less effective cell repair mechanisms that come with aging
- buildup of risk factors over the course of life
- duration of exposures to carcinogens

Types of cancer

Cancers are named for the area in which they begin and the type of cell they are made of, even if they spread to other parts of the body. For example, a cancer that begins in the lungs and spreads to the liver is still called lung cancer.

There are also several clinical terms used for certain general types of cancer:

- Carcinoma is a cancer that starts in the skin or the tissues that line other organs.
- Sarcoma is a cancer of connective tissues such as bones, muscles, cartilage, and blood vessels.
- Leukemia is a cancer of the bone marrow, which creates blood cells.
- Lymphoma and myeloma are cancers of the immune system.

Learn more about specific types of cancer with the resources below.

- appendix cancer
- bladder cancer
- bone cancer
- brain cancer
- breast cancer
- cervical cancer
- colon or colorectal cancer
- duodenal cancer
- ear cancer
- endometrial cancer
- esophageal cancer
- heart cancer
- gallbladder cancer
- kidney or renal cancer
- laryngeal cancer
- leukemia
- lip cancer
- liver cancer
- lung cancer
- lymphoma
- mesothelioma
- myeloma
- oral cancers
- ovarian cancer
- pancreatic cancer
- penile cancer
- prostate cancer
- rectal cancer
- skin cancer
- small intestine cancer
- spleen cancer
- stomach or gastric cancer
- testicular cancer
- thyroid cancer
- uterine cancer
- vaginal cancer
- vulvar cancer

The importance of early detection

Early detection is when cancer is found in its early stages. This can increase the effectiveness of treatment and lower the mortality rate[23-29]. Cancer screenings may help detect signs of cancer early. Some common cancer screenings may detect:

- **Cervical cancer and prostate cancer.** Some screenings, such as for cervical cancer and prostate cancer, may be done as part of routine exams.

- **Lung cancer.** Screenings for lung cancer may be performed regularly for those who have certain risk factors.
- **Skin cancer.** Skin cancer screenings may be performed by a dermatologist if you have skin concerns or are at risk of skin cancer.
- **Colorectal cancer.** The American Cancer Society (ACS) Trusted Source recommends regular screenings for colorectal cancer beginning at age 45. These screenings are typically performed during a colonoscopy. At-home testing kits may also be able to detect some forms of colorectal cancer, according to a 2017 review of researchTrusted Source.
- **Breast cancer.** Mammograms to test for breast cancer are recommended for women ages 45 and olderTrusted Source, but you may choose to begin screenings at age 40. In people at a high risk, screenings may be recommended earlier.

Signs and symptoms of cancer can include:

- lumps or growths on the body
- unexplained weight loss
- fever
- tiredness and fatigue
- pain
- night sweats
- changes in digestion
- changes in skin
- cough

Spread of cancer

Abnormal cell division

Normal cells in your body grow and divide. Each one has a life cycle determined by the type of cell. As cells become damaged or die off, new cells take their place. Cancer disrupts this process and causes cells to grow abnormally. It's caused by changes or mutations in the cell's DNA. The DNA in each cell has instructions that tell the cell what to do and how to grow and divide. Mutations occur frequently in DNA, but usually cells correct these mistakes. When a mistake is not corrected, a cell can become cancerous. Mutations can cause cells that should be replaced to survive instead of die, and new cells to form when they're not needed. These extra cells can divide uncontrollably, causing tumors to form[30-33].

Creation of tumors

Tumors can cause health problems, depending on where they grow in the body.. Not all tumors are cancerous. Benign tumors are noncancerous and do not spread to nearby tissues.. But sometimes, tumors can grow large and cause problems when they press against neighboring organs and tissue. Malignant tumors are cancerous and can invade other parts of the body.

Metastasis

Some cancer cells can also spread through the bloodstream or lymphatic system to distant areas of the body. This is called metastasis. Cancers that have metastasized are considered more advanced than those that have not. Metastatic cancers are often harder to treat and more fatal.

Treatment

Cancer treatment can include different options, depending on the type of cancer and how advanced it is.

- **Localized treatment.** Localized treatment usually involves using treatments like surgery or local radiation therapy at a specific area of the body or tumor.
- **Systemic treatment.** Systemic drug treatments, such as chemotherapy, targeted therapy, and immunotherapy, can affect the entire body.
- **Palliative treatment.** Palliative care involves relieving health symptoms associated with cancer, such as trouble breathing and pain.

The most common types of treatment are[34-39]:

Surgery

Surgery removes as much of the cancer as possible. Surgery is often used in combination with some other therapy in order to make sure all of the cancer cells are gone.

Chemotherapy

Chemotherapy is a form of aggressive cancer treatment that uses medications that are toxic to cells to kill rapidly dividing cancer cells. It may be used to shrink the size of a tumor or the number of cells in your body and lower the likelihood of the cancer spreading.

Radiation therapy

Radiation therapy uses powerful, focused beams of radiation to kill cancer cells. Radiation therapy done inside of your body is called brachytherapy, while radiation therapy done outside of your body is called external beam radiation.

Stem cell (bone marrow) transplant

This treatment repairs diseased bone marrow with healthy stem cells. Stem cells are undifferentiated cells that can have a variety of functions. These transplants allow doctors to use higher doses of chemotherapy to treat the cancer. A stem cell transplant is commonly used to treat leukemia.

Immunotherapy (biological therapy)

Immunotherapy uses your body's own immune system to attack cancer cells. These therapies help antibodies recognize the cancer, so they can use your body's natural defenses to destroy cancer cells.

Hormone therapy

Hormone therapy removes or blocks hormones that fuel certain cancers to stop cancer cells from growing. This therapy is a common treatment for cancers that may use

hormones to grow and spread, such as certain types of breast cancer and prostate cancer.

Targeted drug therapy

Targeted drug therapy uses drugs to interfere with certain molecules that help cancer cells grow and survive. Genetic testing may reveal if you are eligible for this type of therapy. It may depend on the type of cancer you have and the genetic mutations and molecular characteristics of your tumor.

Clinical trials

Clinical trials investigate new ways to treat cancer. This may include testing the effectiveness of drugs that have already been approved by the Food and Drug Administration (FDA) but for other purposes. It can also include trying new drugs. Clinical trials can offer another option for people who may have not seen the level of success they wanted with conventional treatments. In some cases, this treatment may be provided for free.

Alternative medicine

Alternative medicine may be used to complement another form of treatment. It may help decrease symptoms of cancer and side effects of cancer treatment, such as nausea, fatigue, and pain. Alternative medicine for cancer can include:

- acupuncture
- yoga
- massage
- meditation
- relaxation techniques

Prevention

Knowing the factors that contribute to cancer can help you live a lifestyle that decreases your cancer risk.

Preventive measures to reduce your risk of developing cancer can include:

- avoiding tobacco and secondhand smoke
- limiting your intake of processed meats
- eating a diet that focuses mainly on plant-based foods, lean proteins, and healthy fats, such as the Mediterranean diet
- avoiding alcohol or drinking in moderation
- maintaining a moderate body weight and BMI
- doing regular moderate physical activity for 150 to 300 minutesTrusted Source per week
- staying protected from the sun by avoiding direct sun exposure and wearing a broad spectrum sunscreen, hat, and sunglasses
- avoiding tanning beds
- getting vaccinated against viral infections that can lead to cancer, such as hepatitis B and HPV.

Pharmacological treatment

The antineoplastic agents are not easily classified. Historically, they are categorized as (1) alkylating agents, (2) antimetabolites, (3) natural products, (4) hormones and antagonists, and (5) miscellaneous. In recent years, however, the miscellaneous group has come to include some of the most important agents. Anticancer agents can also be classified by indication (lymphoma, leukemia, melanoma, solid tumor), mechanism of action (such as alkylating agents, antibiotics, biological response modifiers, antiandrogens, topoisomerase inhibitors or protein kinase inhibitors), chemical structure (folic acid analog, platinum coordination complex, purine or pyrimidine analog, monoclonal antibody) or as cytotoxic or nonspecific vs noncytotoxic or targeted. The classification used in LiverTox represents a mixture of these systems, which generally follow those given in modern pharmacology textbooks[40-41].

Almost all antineoplastic agents have some degree of hepatotoxicity, and the liver injury is usually due to direct, intrinsic toxicity. The typical manifestation is an elevation in liver enzymes or bilirubin during therapy that reverses rapidly with stopping treatment or dose modification. This type of hepatotoxicity is dose related and generally self-limiting, but can be severe, progressive and even fatal as can occur with sinusoidal obstruction syndrome or acute toxic hepatic injury. The antineoplastic agents often have a narrow toxic-therapeutic ratio, although the usual dose limiting toxicity is myelosuppression. Nevertheless, liver injury also can be dose limiting, which generally becomes clear in early dose finding studies. For this reason, many antineoplastic agents acquire a reputation for hepatotoxicity based upon premarketing studies, but are later found to be reasonably well tolerated and only rare causes of clinically significant liver injury when given in lower doses. Antineoplastic agents that are well known to cause significant direct hepatotoxicity when given in moderate to high doses (particularly when used in myeloablation before hematopoietic cell transplantation) include busulfan, melphalan, cyclophosphamide, dacarbazine, cytarabine, fluorouracil, carboplatin and L-asparaginase. At lower doses, these agents are well tolerated.

Some antineoplastic agents can also cause idiosyncratic liver injury due to immunologic or metabolic idiosyncrasy. Thus, typical drug induced cholestatic liver injury can occur in rare instances after therapy with cyclophosphamide, azathioprine, mercaptopurine, melphalan and temozolomide. Acute hepatocellular injury can occur with flutamide, bicalutamide and thalidomide. Steatohepatitis can occur with L-asparaginase, methotrexate and tamoxifen (although this pattern may be due to direct toxicity rather than idiosyncratic injury). Selected anticancer agents have also been linked to immunoallergic hepatitis or to autoimmune hepatitis-like injury. A distinctive autoimmune pattern is found in rare instances after monoclonal antibody therapies or with the protein kinase inhibitors. The pathogenesis of these

immune reactions is not always well understood. Finally, some antineoplastic agents can cause reactivation of hepatitis B, exacerbations of chronic hepatitis C, or lead to decompensation of an preexisting cirrhosis.

A classification of the antineoplastic agents with listing of individual agents is given below. There has been a steady increase in development of innovative antineoplastic agents in recent years and between 5 and 10 new anticancer agents are approved yearly. The hepatotoxicity of these recently introduced agents has not always been well defined. The following links are to individual drug records for the antineoplastic agents; those that are not underlined have yet to be added.

Antineoplastic Agents[42-46]

- Alkylating Agents
  Altretamine, Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Lurbinectedin, Mechlorethamine, Melphalan, Procarbazine, Streptozocin, Temozolomide, Thiotepa, Trabectedin
- Platinum Coordination Complexes
- Carboplatin, Cisplatin, Oxaliplatin
- Antibiotics, Cytotoxic
  Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Valrubicin
- **Antimetabolites**
  Antifolates: Methotrexate, Pemetrexed, Pralatrexate, Trimetrexate
- **Purine**
  Analogues: Azathioprine, Cladribine, Fludarabine, Mercaptopurine, Thioguanine
- **Pyrimidine**
  Analogues: Azacitidine, Capecitabine, Cytarabine, Decitabine, Floxuridine, Fluorouracil, Gemcitabine, Trifluridine/Tipracil
- **Biologic Response Modifiers**
  - Aldesleukin (IL-2), Denileukin Diftitox, Interferon Gamma
- **Histone Deacetylase Inhibitors**
  - Belinostat, Panobinostat, Romidepsin, Vorinostat
- **Hormonal Agents**
  Antiandrogens: Abiraterone, Apalutamide, Bicalutamide, Cyproterone, Enzalutamide, Flutamide, Nilutamide
- Antiestrogens (including Aromatase Inhibitors): Anastrozole, Exemestane, Fulvestrant, Letrozole, Raloxifene, Tamoxifen, Toremifene
- Gonadotropin Releasing Hormone Analogues: Degarelix, Goserelin, Histrelin, Leuprolide, Triptorelin
- Peptide
  Hormones: Lanreotide, Octreotide, Pasireotide
- Monoclonal Antibodies
  Alemtuzumab, Atezolizumab, Avelumab, Bevacizumab, Blinatumomab, Brentuximab, Cemiplimab, Cetuximab, Daratumumab, Dinutuximab, Dostarlimab, Durvalumab, Elotuzumab, Gemtuzumab, Inotuzumab
  Ozogamicin, Ipilimumab, Mogamulizumab, Moxetumomab
  Pasudotox, Necitumumab, Nivolumab, Ofatumumab, Olaratumab, Panitumumab, Pembrolizumab, Pertuzumab, Ramucirumab, Rituximab, Teclistamab, Tositumomab, Trastuzumab, Tremelimumab
- **Protein Kinase Inhibitors**
  Abemaciclib, Acalabrutinib, Afatinib, Alectinib, Alpelisib, Axitinib, Binimetinib, Bortezomib, Bosutinib, Brigatinib, Cabozantinib, Carfilzomib, Ceritinib, Cobimetinib, Copanlisib, Crizotinib, Dabrafenib, Dacomitinib, Dasatinib, Duvelisib, Enasidenib, Encorafenib, Entrectinib, Erdafitinib, Erlotinib, Fedratinib, Futibatinib, Gefitinib, Gilteritinib, Glasdegib, Ibrutinib, Idelalisib, Imatinib, Infigratinib, Ivosidenib, Ixazomib, Lapatinib, Larotrectinib, Lenvatinib, Lorlatinib, Midostaurin, Neratinib, Nilotinib, Niraparib, Olaparib, Osimertinib, Palbociclib, Pazopanib, Pemigatinib, Pexidartinib, Ponatinib, Regorafenib, Ribocicib, Rucaparib, Ruxolitinib, Selumetinib, Sonidegib, Sorafenib, Sunitinib, Talazoparib, Trametinib, Vandetanib, Vemurafenib, Vismodegib, Zanubrutinib
- **Taxanes**
  - Cabazitaxel, Docetaxel, Paclitaxel
- Topoisomerase Inhibitors
  - Etoposide, Irinotecan, Teniposide, Topotecan
- **Vinca Alkaloids**
  - Vinblastine, Vincristine, Vinorelbine
- **Miscellaneous**
- Asparaginase
  (Pegaspargase), Bexarotene, Eribulin, Everolimus, Hydroxyurea, Ixabepilone, Lenalidomide, Mitotane, Omacetaxine, Pomalidomide, Selinexor, Tagraxofusp, Telotristat, Temsirolimus, Thalidomide, Venetoclax

Conclusion

The cancer cells are endowed with capacities for uninhibited proliferation, invasion and metastasis. Cancer initiation, driver mutations, progression and metastases are common attributes for both stochastic and cancer stem cell models; cancer stem cells possess attributes that enhance survival in all environments hence more suitable as model

of cancer. Integrated models that capture every essence of a cancer could enhance the ability to target different components of cancer for maximum therapeutic effect. Family physicians are at the forefront of cancer diagnosis. Following the stepwise approach outlined will make diagnosis, staging, and referral more efficient, decreasing the diagnostic interval and improving patient care by addressing issues such as fertility, vaccinations, and smoking cessation. The timely workup of new malignancies will help preserve the patient-doctor relationship, and, if patients are referred at an earlier stage of disease, might result in improved survival rate of the cancer patients.

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