NEW TRENDS IN THE CHEMISTRY OF ANTICANCER DRUGS

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ABSTRACT
The majority of conventional chemotherapeutic agents cause cell death by directly inhibiting the synthesis of DNA or interfering with its function. This means that they are often not tumor-specific and are associated with considerable morbidity. Nowadays there are many trends in the chemistry of anticancer drugs appear and there is no doubt that almost of these trends help each others in order to give good results in anticancer drugs research. This review aims to provide such an overview.

KEYWORDS: Cancer, Molecular Docking, Nanotechnology, Hormonal Therapy.

INTRODUCTION
Cancer is one of the most widespread and feared diseases in the world today, feared largely because it is known to be difficult to cure. The main reason for this difficulty is that cancer results from the uncontrolled multiplication of subtly modified normal human cells. Around the world, tremendous resources are being invested in prevention, diagnosis, and treatment of cancer. One of the main methods of modern cancer treatment is drug therapy (chemotherapy). The development of more effective drugs for treating patients with cancer has been a major human endeavor over the past 50 years, and the 21st century now promises some dramatic new directions.

Cancer
What is cancer? Cancers are a large family of diseases that involves abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth, and will often form a mass or lump.
Cancer Treatments

- The treatment given for cancer is highly variable and dependent on the type, location, the amount of disease and the health status of the patient.
- The treatments are designed to either:
  - Directly kill/remove the cancer cells.
  - To lead to their eventual death by depriving them of signals needed for cell division.
  - The treatments work by stimulating the body's own defenses.

Classical types of cancer treatment

- **Chemotherapy:** A term used for a wide array of drugs used to kill cancer cells. Chemotherapy drugs work by damaging the dividing cancer cells and preventing their further reproduction.
- **Surgery:** Often the first line of treatment for many solid tumors. If the cancer is detected at an early stage, surgery may be sufficient to cure the patient.
- **Radiation:** The goal of radiation is to kill the cancer cells directly by damaging them with high energy beams. The radiation is most commonly low energy x-rays for treating skin cancers, while higher energy x-ray beams are used in the treatment of cancers within the body.\[^1\]

Anticancer Drugs

**Introduction:** It is difficult to assign a date to the beginning of the treatment of cancer with drugs because herbs and other preparations have been used for cancer treatment since antiquity. However, the 1890s, a decade that represents an extraordinarily creative period in painting, music, literature, and technology, encompassed discoveries that were to set the
scene for developments in cancer treatment in the 20th century. The discovery of penetrating radiation, or x-rays, by Roentgen in Germany in 1895 was complemented 3 years later by the discovery of radium by Marie and Pierre Curie. The efficacy of chemotherapy depends on the type of cancer and the stage. In combination with surgery, chemotherapy has proven useful in a number of different cancer types including: breast cancer, colorectal cancer, pancreatic cancer, testicular cancer, ovarian cancer, and certain lung cancers. The overall effectiveness ranges from being curative for some cancers, such as some leukemias,\textsuperscript{2, 3} to being ineffective, such as in some brain tumors.\textsuperscript{4}.

**Categories of anticancer drugs:** Anticancer drugs can be divided into three main categories based on their mechanism of action.

- **Stop the synthesis of DNA molecule building blocks**
  These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some steps in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which are the building blocks of DNA and RNA, can't be synthesized. Thus the cells can't replicate because they can't make DNA without the nucleotides. Examples of drugs in this class include.
  1) Methotrexate (Abitrexate®)
  2) Fluorouracil (Adrucil®)
  3) Hydroxyurea (Hydrea®)
4) Mercaptopurine (Purinethol®)

- **Directly damage the DNA in the nucleus of the cell**

These agents chemically damage DNA and RNA. They disrupt replication of the DNA and either totally halts replication or cause the manufacture of nonsense DNA or RNA (i.e. the new DNA or RNA does not code for anything useful). Examples of drugs in this class include.

1) Cisplatin (Platinol®)
2) Antibiotics - daunorubicin (Cerubidine®)
3) Doxorubicin (Adriamycin®)
4) Etoposide (VePesid®)

- **Effect the synthesis or breakdown of the mitotic spindles**

Mitotic spindles serve as molecular railroads with "North and South Poles" in the cell when a cell starts to divide itself into two new cells. These spindles are very important because they help to split the newly copied DNA such that a copy goes to each of the two new cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division. Examples of drugs in this class.

1) Vinblastine (Velban®)
2) Vincristine (Oncovin®)
3) Pacitaxel (Taxol®).

**Best Selling Cancer Drugs**

Nick Mulcahy wrote in *Medscape Medical News* (http://www.medscape.com) the best selling cancer drugs in 2013 according to data compiled by Evaluate Pharma, a pharmaceutical intelligence company (June 12, 2014).

**Table.1: Best selling cancer drugs in 2013.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sales (in billions)</th>
<th>Cancer Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>$7.78</td>
<td>Non-Hodgkin's lymphoma, chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Avastin</td>
<td>$6.75</td>
<td>Colorectal, lung, kidney, and glioblastoma</td>
</tr>
<tr>
<td>Herceptin</td>
<td>$6.56</td>
<td>Breast, esophageal, and gastric</td>
</tr>
<tr>
<td>Gleevec</td>
<td>$4.69</td>
<td>Variety of leukemias and gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>Neulasta</td>
<td>$4.39</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Revlimid</td>
<td>$4.28</td>
<td>Multiple myeloma, mantle cell lymphoma, myelodysplastic</td>
</tr>
</tbody>
</table>
Table 2: Best selling cancer drugs in 2014

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication(s)</th>
<th>Company</th>
<th>2014 sales ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia</td>
<td>Roche</td>
<td>7546</td>
</tr>
<tr>
<td>Avastin</td>
<td>Colorectal, lung, breast, kidney cancer</td>
<td>Roche</td>
<td>7018</td>
</tr>
<tr>
<td>Herceptin</td>
<td>HER2+ breast cancer</td>
<td>Roche</td>
<td>6863</td>
</tr>
<tr>
<td>Revlimid</td>
<td>Multiple myeloma</td>
<td>Celgene</td>
<td>4980</td>
</tr>
<tr>
<td>Gleevec</td>
<td>Chronic myeloid leukemia/Gastrointestinal stromal tumors</td>
<td>Novartis</td>
<td>4746</td>
</tr>
<tr>
<td>Velcade</td>
<td>Multiple myeloma/Mantle cell lymphoma</td>
<td>Takeda/J&amp;J</td>
<td>3069</td>
</tr>
<tr>
<td>Alimta</td>
<td>Non-small cell lung cancer</td>
<td>Eli Lilly</td>
<td>2792</td>
</tr>
<tr>
<td>Zytiga</td>
<td>Prostate cancer</td>
<td>Johnson &amp; Johnson</td>
<td>2237</td>
</tr>
<tr>
<td>Erbitux</td>
<td>Colorectal, head &amp; neck cancer</td>
<td>Merck KGaA/BMS</td>
<td>1925</td>
</tr>
<tr>
<td>Afinitor</td>
<td>Breast cancer</td>
<td>Novartis</td>
<td>1575</td>
</tr>
</tbody>
</table>

1. **Rituxan® (Rituximab)** The first selling cancer drug in 2013 and 2014, our top contender is made by Roche Company. Rituxan is primarily found on the surface of immune system B cells. Based on its safety and effectiveness in clinical trials,[5] Rituxan was approved by the U.S. Food and Drug Administration in 1997 to treat B-cell non-Hodgkin lymphomas (NHLs) resistant to other chemotherapy regimens.[6] It was the first monoclonal antibody drug, meaning that the drug was the first oncology drug developed to target a specific protein or cells, which may then stimulate the body’s immune system to attack those cells. Rituxan is used to treat cancers of the white blood system such as leukemias and lymphomas, including non-Hodgkin's lymphoma and lymphocyte predominant subtype of Hodgkin's Lymphoma.[7]
2. **Avastin® (Bevacizumab)** The second selling cancer drug in 2013 and 2014. Another of Roche’s long standing cancer blockbusters. Avastin is produced in a mammalian (Chinese Hamster Ovary cell) expression system in a nutrient medium. Avastin, like most of the medicines on our list, has now been on the market for a decade. The drug, which is known generically as Bevacizumab, is used primarily to treat colon cancer, has gained several new expansions in the years since its initial approval in 2003, and is now used to treat lung, breast, and kidney cancers. Clinical trials are underway to test an intra-arterial technique for delivering the drug directly to brain tumors, bypassing the blood–brain barrier.\(^8\) Avastin has also demonstrated activity in glioblastoma multiforme.\(^9\)

3. **Herceptin® (Trastuzumab)** The third selling cancer drug in 2013 and 2014. Herceptin, generically known as Trastuzumab and developed by Genentech (Roche), is one of the most widely used breast cancer treatments currently on the market. The biotech company Genentech developed Herceptin jointly with UCLA and gained FDA approval in September 1998.

4. **Revlimid® (Lenalidomide)**

![Revlimid](image)

**Fig. 3: Revlimid [Systematic (IUPAC) name: (RS)-3-(4-Amino-1-oxo 1,3-dihydro-2H-isooindol- 2-yl)piperidine-2,6-dione]**

The sixth selling cancer drug in 2013 and the fourth selling cancer drug in 2014. Like several other drugs on this list, Revlimid is an older medicine, first approved by the FDA in 2006. Revlimid has significantly improved overall survival in myeloma (which generally carries a poor prognosis), although toxicity remains an issue for users.\(^{10}\) It costs $163,381 per year for the average patient.\(^{11}\) Revlimid is one of the novel drug agents used to treat multiple myeloma. It is a more potent molecular analog of Thalidomide, which inhibits tumor angiogenesis and tumor proliferation.\(^{12, 13}\) Revlimid synthesized as below.\(^{14}\)
5. Gleevec® (Imatinib)

The fourth selling cancer drug in 2013 and the fifth selling cancer drug in 2014. Gleevec was first approved in 2001, often called a “wonder drug” or “miracle drug”. Because the BCR-Abl tyrosine kinase enzyme exists only in cancer cells and not in healthy cells, Gleevec works as a form of targeted therapy, only cancer cells are killed through the drug’s action. In this regard, Gleevec was one of the first cancer therapies to show the potential for such targeted action, and is often cited as a paradigm for research in cancer therapeutics. [15]

A 2012 economic analysis funded by Bristol-Myers Squibb estimated that the discovery and development of Gleevec and related drugs had created $143 billion in societal value at a cost to consumers of approximately $14 billion. The $143 billion figure was based on an estimated 7.5 to 17.5 year survival advantage conferred by Gleevec treatment, and included the value of ongoing benefits to society after the Gleevec patent expiration. [16] After the Philadelphia chromosome mutation and hyperactive BCR-Abl protein was discovered, the investigators screened chemical libraries to find a drug that would inhibit that protein, they identified 2-phenylaminopyrimidine. This lead compound was then tested and modified by the introduction of methyl and benzamide groups to give it enhanced binding properties, resulting in Gleevec. [17]
6. Velcade® (Bortezomib)

Fig. 6: Velcade [Systematic (IUPAC) name: \[(1R)-3-methyl-1-\{(2S)-3-phenyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl\}amino\}butyl\]boronic acid]

The eighth selling cancer drug in 2013 and the sixth selling cancer drug in 2014. The drug was approved as a first line treatment for the blood cancer by the UK’s National Institute for Health and Care. In May 2003, seven years after the initial synthesis, Velcade was approved in the United States by FDA for use in multiple myeloma.\[18\]

7. Alimta® (Pemetrexed)

Fig. 7: Alimta [Systematic (IUPAC) name: \(2\)-\{2-\{2-aminooxy-1,7-dihydro pyrrolo [2,3-\text{d}]pyrimidin-5-yl\}ethyl\}benzoyl\}amino\}pentanedioic acid]

The seventh selling cancer drug in 2013 and 2014. First developed to treat mesothelioma and later also approved for the treatment of lung cancer. On September 2008, the FDA granted approval as a first-line treatment, in combination with Cisplatin, against lung cancer.\[19, 20\]

8. Zytiga® (Abiraterone)

Fig. 8: Zytiga [Systematic (IUPAC) name: \(3\beta\)-17-(pyridin-3-yl)androst-5,16-dien-3-ol]

The tenth selling cancer drug in 2013 and the eighth selling cancer drug in 2014. In the early 1990s, Mike Jarman, Elaine Barrie and Gerry Potter of the Cancer Research UK Centre for
Cancer Therapeutics within the Institute of Cancer Research in London set out to develop drug treatments for prostate cancer. Zytiga was first approved in 2011.

9. **Erbitux® (Cetuximab)** The *ninth* selling cancer drug in 2013 and 2014. Erbitux developed as part of a partnership between Merck and Bristol-Myers Squibb Company. The drug, used in the treatment of colon, head, and neck cancers is specialized; however, Merck has done little to expand the drug to new indications, resulting in a steady drop-off in sales. Erbitux only works on tumors that are not mutated. \(^{[21]}\)

10. **Afinitor® (Everolimus)**

Fig. 9: Afinitor [Systematic (IUPAC) name: dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone]

The *tenth* selling cancer drug in 2014 but didn't find in the list of best selling anticancer drugs in 2013. Afinitor (everolimus) is a cancer medicine that interferes with the growth of cancer cells and slows their spread in the body.

11. **Neulasta® (Pegfilgrastim)** The *fifth* selling cancer drug in 2013 but didn't find in the list of best selling anticancer drugs in 2014. Neulasta (pegfilgrastim) is a man-made form of a protein that stimulates the growth of white blood cells in the body. White blood cells help the body fight against infection.

**New Trends In The Chemistry Of Anticancer Drugs**

1- **Molecular Docking**

*Introduction*: The field of molecular docking has emerged during the last three decades, driven by the needs of structural molecular biology and structure-based drug discovery. It has been greatly facilitated by the dramatic growth in the availability and power of computers, and the growing ease of access to small molecule and protein databases. \(^{[22–25]}\) Docking is a
method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. \cite{26} Hence docking plays an important role in the rational design of drugs. \cite{27}

**Theory:** There are a number of excellent reviews of molecular docking methods \cite{28, 29} and a large number of publications comparing the performance of a variety of molecular docking tools. \cite{30–37}

![Fig. 10: A typical docking workflow. This flowchart shows the key steps common to all docking protocols.](image)

**Methods:** No matter which docking method is selected, the user needs to prepare the appropriate input files. This will depend on the docking method used. The number of docking programs currently available is high and has been steadily increasing over the last decades. The following list presents an overview of the most common protein-ligand docking programs, \cite{38} with indication of the corresponding year of publication and country of origin. This list is comprehensive but not complete.

**Table 3: List of Protein-Ligand Docking Software**

<table>
<thead>
<tr>
<th>Program</th>
<th>Country of Origin</th>
<th>Year Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>AADS</td>
<td>India</td>
<td>2011</td>
</tr>
<tr>
<td>ADAM</td>
<td>Japan</td>
<td>1994</td>
</tr>
<tr>
<td>AutoDock</td>
<td>USA</td>
<td>1990</td>
</tr>
<tr>
<td>AutoDock Vina</td>
<td>USA</td>
<td>2010</td>
</tr>
<tr>
<td>BetaDock</td>
<td>South Korea</td>
<td>2011</td>
</tr>
<tr>
<td>DARWIN</td>
<td>USA</td>
<td>2000</td>
</tr>
<tr>
<td>DOCK</td>
<td>USA</td>
<td>1988</td>
</tr>
<tr>
<td>Glide</td>
<td>USA</td>
<td>2004</td>
</tr>
<tr>
<td>EADock</td>
<td>Switzerland</td>
<td>2007</td>
</tr>
<tr>
<td>eHiTS</td>
<td>UK</td>
<td>2006</td>
</tr>
<tr>
<td>EUDOC</td>
<td>USA</td>
<td>2001</td>
</tr>
</tbody>
</table>
Docking may be useful for comparing drugs with each other in order to know which drug more active, for example: Ambrish KS. et al in 2015 studied the molecular docking of Thalidomide, Lenalidomide (The sixth selling cancer drug in 2013 and the fourth selling cancer drug in 2014) and Pomalidomide with human activated C-protein, which is responsible for multiple myeloma and noticed that Pomalidomide binds more efficiently than Lenalidomide.\[39\]

![Schematic structures of Thalidomide (a), Lenalidomide (b) and Pomalidomide (c).](image1)

**Fig. 11:** Schematic structures of Thalidomide (a), Lenalidomide (b) and Pomalidomide (c).

![Representative structure of human activated C-protein (a), docked with Thalidomide (b), Lenalidomide (c) and Pomalidomide (d). The docking region is encircled by white color.](image2)

**Fig. 12:** Representative structure of human activated C-protein (a), docked with Thalidomide (b), Lenalidomide (c) and Pomalidomide (d). The docking region is encircled by white color.
2- Nanotechnology

What is Nanotechnology? Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers. Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science, and engineering. One of the most active research areas of nanotechnology is nanomedicine, which applies nanotechnology to highly specific medical interventions for the prevention, diagnosis and treatment of diseases. [40, 41]

How it Start? The ideas and concepts behind nanoscience and nanotechnology started with a talk entitled “There’s Plenty of Room at the Bottom” by physicist Richard Feynman at an American Physical Society meeting at the California Institute of Technology on December 29, 1959. In his talk, Feynman described a process in which scientists would be able to manipulate and control individual atoms and molecules. Nanotechnology as defined by size is naturally very broad, including fields of science as organic chemistry and molecular biology, etc. [42]

Fig. 13: Richard Feynman (born in May 11, 1918, Queens, New York, United States, died in February 15, 1988 (aged 69) Los Angeles, California, United States)

Nanocarriers Conventional chemotherapy employs drugs that are known to kill cancer cells effectively. But these cytotoxic drugs kill healthy cells in addition to tumor cells, leading to adverse side effects such as nausea, hair-loss and fatigue. Nanoparticles can be used as drug carriers for chemotherapeutic to deliver medication directly to the tumor while sparing healthy tissue. Nanocarriers have several advantages over conventional chemotherapy. They can.
- Protect drugs from being degraded in the body before they reach their target.
- Enhance the absorption of drugs into tumors and into the cancerous cells themselves.
- Prevent drugs from interacting with normal cells, thus avoiding side effects.

**Targeting Strategies** Two basic requirements should be realized in the design of nanocarriers to achieve effective drug delivery (Fig.14). First, drugs should be able to reach the desired tumor sites. Second, drugs should only kill tumor cells without harmful effects to healthy tissue. [43] These requirements may be enabled using two strategies: passive and active targeting of drugs. [44]

![Fig. 14](https://example.com/fig14.png)

- **Passive Targeting** Passive targeting takes advantage of the unique pathophysiological characteristics of tumor vessels, enabling nanodrugs to accumulate in tumor tissues. Typically, tumor vessels are highly disorganized and dilated with a high number of pores. The 'leaky' vascularization, which refers to the EPR effect, allows migration of macromolecules up to 400 nm in diameter into the surrounding tumor region. [44–46]

- **Active Targeting** One way to overcome the limitations of passive targeting is to attach affinity ligands (antibodies, [47] peptides, [48] or small molecules [49] that only bind to specific receptors on the cell surface) to the surface of the nanocarriers by a variety of conjugation chemistries. Nanocarriers will recognize and bind to target cells through ligand–receptor. In order to achieve high specificity, those receptors should be highly expressed on tumor cells, but not on normal cells. To fully explore the application of targeted drug delivery, we need to investigate whether the specific diseases are the correct application for targeting and whether the properties of the therapeutic drugs, as well as their site and mode of action, are suited for targeting. [50] There are many patents on the clinical use of nanoparticles, for example, Jose P. et.al in 2014 reviewed patents on the
clinical use of nanoparticles for gastrointestinal cancer diagnosis and therapy and to offer an overview of the impact of nanotechnology on the management of this disease.\cite{51}

**Gold Nanoparticles in (Chemotherapy)** A gold nanoparticle in chemotherapy is the use of gold in therapeutic treatments, often for cancer or arthritis. To increase specificity and likelihood of drug delivery.

![Gold Nanoparticles](image)

**Fig. 15: Gold Nanoparticles**

**Gold nanorod technology:** Gold nanorod technology developed by Mostafa A. El-Sayed lab. Mostafa A. El-Sayed (born 8 May 1933) is an Egyptian-American chemical physicist, a leading nanoscience researcher, a member of the National Academy of Sciences and a US National Medal of Science laureate. A major focus of his lab is currently on the optical and chemical properties of noble metal nanoparticles and their applications in nanocatalysis, nanophotonics and nanomedicine. Gold nanoparticles (AuNPs), nanorods, and nanoshells with unique properties\cite{52-54} have been shown to be of potential use in anticancer drug delivery systems and photothermal cancer treatment agents.\cite{55-58}

![Mostafa El-Sayed](image)

**Fig. 16: Mostafa El-Sayed, born in 8 May 1933, Egypt**

**Drug Vectorization** Nanovectors should contain anticancer drug as core nanoparticles, in which it can protect normal cells by storing anticancer drugs inside. Research shows that 80~90% of breast cancer tumor cells have estrogen receptors\cite{59} and 60~70% of prostate
cancer tumor cells have androgen receptors. These significant amounts of hormone receptors play a role in intermolecular actions. This role is now used by targeting and therapeutic ligands on gold nanoparticles to target tissue-selective anti-tumor drug delivery. In order to have multiple targeting and therapeutic ligands bind with gold nanoparticles, the gold nanoparticles have undergone polymer stabilization. For example, anti-estrogen molecules with thiolated PEG bind with gold nanoparticles via Au-S bonds, this process forms thiolate protected gold nanoparticles. For example: In 2009 Mostafa A. El-Sayed et.al synthesized Tamoxifen-poly (ethylene glycol)-thiol gold nanoparticle conjugates and approved that they enhanced potency and selective delivery for breast cancer treatment.

![Fig. 17: Synthesis of Thiol-PEGylated Tamoxifen (TAM-PEG-SH) (a) and Covalent Attachment to 25 nm Gold Nanoparticles (AuNPs) (b)](image)

3-Hormonal Therapy

**What hormones are?** Hormones are natural substances made by glands in our bodies. The network of glands that make hormones is called the endocrine system. Hormones are carried in our bloodstream and act as messengers between one part of our body and another. They have lots of effects and one of these is controlling the growth and activity of certain cells and organs.

**What hormone therapy is?** Some cancers use these hormones to grow. Hormone therapy for cancer is the use of medicines to block the effects of hormones. It does not work for all types of cancer. Doctors use hormone therapy for people with cancers that are hormone sensitive or hormone dependent.
Types of hormone therapy: There are a number of different types of hormone therapy, for example.

- Adrenal steroid inhibitors: This type of hormone therapy interferes with the hormones produced by the adrenal gland. The adrenal glands are located on top of the kidneys. The outer portion of the adrenal gland (the adrenal cortex) produces hormones called corticosteroids. When these corticosteroids are blocked from being made, they are not able to signal the body to produce other hormones such as estrogen and androgens. The resulting decrease of estrogens and androgens interferes with the stimulation of cancer growth in tumors that are influenced by these hormones. For example of adrenal steroid inhibitors.

- Aminoglutethimide, Mitotane

![Fig. 18: a) Aminoglutethimide, b) Mitotane](image1)

- Androgens: are hormones such as testosterone and androsterone that produce or stimulate the development of male characteristics. In women, these hormones can be converted into estrogen. Androgens as cancer therapy are used to oppose the activity of estrogen, thereby slowing the growth of cancer. For example of androgens.

- Fluoxymesterone, Testosterone, Testolactone

![Fig. 19: a) Fluoxymesterone, b) Testosterone, c) Testolactone](image2)
Antiestrogens: bind to estrogen receptor site on cancer cells thus blocking estrogen from going into the cancer cell. This interferes with cell growth and eventually leads to cell death. For example of antiestrogens.

- Tamoxifen, Toremifene

![Fig. 20: a) Tamoxifen, b) Toremifene](image)

4-Photodynamic Therapy (PDT)

![Fig. 21: Close up of surgeons' hands in an operating room with a beam of light traveling along fiber optics for photodynamic therapy. Its source is a laser beam which is split at two different stages to create the proper therapeutic wavelength. A patient is given a photosensitive drug that is absorbed by cancer cells. During the surgery, the light beam is positioned at the tumor site, which then activates the drug that kills the cancer cells, thus photodynamic therapy (PDT).](image)

What photodynamic therapy is? Photodynamic therapy (PDT), sometimes called photochemotherapy, is a form of phototherapy using nontoxic light-sensitive compounds that are exposed selectively to light, whereupon they become toxic to targeted malignant and other diseased cells. PDT is used clinically to treat a wide range of medical conditions, such as malignant cancers. [63]
**History** While the applicability and potential of PDT has been known for over a hundred years, the development of modern PDT has been a gradual one, involving scientific progress in the fields of photobiology and cancer biology, as well as the development of modern photonic devices, such as lasers and LEDs. It was John Toth as product manager for Cooper Medical Devices Corp/Cooper Lasersonics who acknowledged the "photodynamic chemical effect" of the therapy and wrote the first "white paper" branding the therapy as "Photodynamic Therapy" (PDT).

**How PDT works** When the sensitizing drugs are exposed to their particular light, they produce a type of oxygen that kills nearby cells. PDT directly kills cancer cells. The sensitizing drug may damage blood vessels in the tumor, and stop it from receiving nutrients that it needs. PDT may also trigger the immune system to attack the cancer cells. In order to achieve the selective destruction of the target area using PDT while leaving normal tissues untouched, either the photosensitizer can be applied locally to the target area. For instance, in the treatment of skin conditions, including acne, psoriasis, and also skin cancers, the photosensitizer can be applied locally excited by a light source. In the local treatment of internal tissues and cancers, after photosensitizers have been administered intravenously, light can be delivered to the target area using endoscopes and fiber optic catheters.

**PDT drugs approved in the US to treat cancer** Several photosensitizing agents are currently approved by the US Food and Drug Administration (FDA) to treat certain cancers. For example.

**Porfimer sodium (Photofrin®)**
Porfimer sodium is the most widely used and studied photosensitizer. It’s activated by red light from a laser. It accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect. It is given for obstructing oesophageal cancer and non-small cell lung cancer. The main complications are oesophagitis and photo-reactions. In one case, a 75-year-old man with emphysema and a tumor of the right intermediate bronchus had four months' treatment and the tumor disappeared with no recurrence for three years. It is safe for patients with poor pulmonary function.
CONCLUSION
Cancer is one of the most widespread and feared diseases in the world today, feared largely because it is known to be difficult to cure. The main reason for this difficulty is that cancer results from the uncontrolled multiplication of subtly modified normal human cells. Around the world, tremendous resources are being invested in prevention, diagnosis, and treatment of cancer. One of the main methods of modern cancer treatment is drug therapy (chemotherapy). Nowadays there are many trends in the chemistry of anticancer drugs.

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REFERENCES


