

# CANCER CHEMOTHERAPY 2012

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# Cancer Chemotherapy - Lecture Outline

1. Targets for cancer chemotherapy
2. Classification of anticancer drugs
3. Cell cycle specificity
4. Drug resistance
5. New approaches

# Introduction

Cancer may be considered to be an unregulated proliferation of cells of which the cardinal features in addition to growth are invasion and metastasis. The microenvironment varies throughout a solid tumor with a tendency for central hypoxia and necrosis. This variability together with the cellular heterogeneity are complications for cancer chemotherapy.

Unlike microbial chemotherapy in which there are marked differences in chemistry from the host cells, the cancer cell provides relatively limited changes from the normal cells and does not offer clear targets for chemotherapeutic attack. Since there is generally negligible immune response to cancer cells it has been argued that there should be complete elimination of neoplastic cells for a cure to be achieved. There is experimental evidence that a single cancer cell may be sufficient to give rise to a fatal response after proliferation.

Further evidence suggests that a given dose of a cancer chemotherapeutic agent causes the death of a constant proportion of cancer cells (first order kinetics). For this reason, the elimination of all cancer cells is more likely to be achieved when the tumor burden is small.

## Inhibition of Growth

Experimental cancer chemotherapy has been largely directed at the inhibition of cellular proliferation with little attention being directed to more difficult models which would detect effects on the invasive and metastatic potential of cancer cells. Perhaps for this reason the greatest success has been achieved against the more rapidly proliferating tumors including certain childhood solid tumors and leukemias and against lymphomas in adults. The major tumors of adults including those of the lung, breast and colon have shown only limited response.

## Inhibition of Growth

Cancer chemotherapy has often been seen as a last resort after surgery and irradiation have failed but there has been a growing use of adjuvant chemotherapy in combined modality treatments. In contrast to microbial chemotherapy, there has been much greater emphasis on combination chemotherapy against cancer. The objectives in combination chemotherapy have been to limit the toxicity of individual agents and to evade drug resistance by exposing the cancer cell to drugs with different modes of action simultaneously.

## Classification of Anticancer Drugs

1. Alkylating agents: chlorambucil, mechlorethamine, cyclophosphamide, melphalan
2. Antimetabolites: methotrexate, pemetrexed (Alimta), 6-mercaptopurine, 5-fluorouracil, capecitabine, cytosine arabinoside, gemcytabine
3. Mitotic inhibitors: vinblastine, vincristine, paclitaxel (Taxol), docetaxel (Taxotere)
4. Antibiotics: actinomycin D, doxorubicin (Adriamycin), daunomycin, bleomycin
5. Nitrosoureas: carmustine (BCNU), lomustine (CCNU)
6. Antibody: trastazumab (Herceptin), bevacizumab (Avastin), cetuximab (Erbix), rituximab (Rituxan)
7. Enzyme: asparaginase
8. Agents that inhibit DNA synthesis (hydroxyurea ) or damage DNA: cisplatin, carboplatin, oxaliplatin

## Classification of Anticancer Drugs

9. Signal transduction inhibitor: imatinib (Gleevec), dasatinib
10. Differentiation agent: all-trans retinoic acid, HDAC inhibitors (Vorinostat)
11. Hormones and hormone antagonists: prednisone, tamoxifen, aromatase inhibitors, abiraterone
12. Proteasome inhibitors: Velcade
13. DNA topoisomerase I inhibitors: camptothecin, irinotecan and topotecan
14. Agents that inhibit DNA repair: PARP inhibitors
15. Arsenic trioxide: increasing the degradation of the PML-RAR $\alpha$  oncoprotein.
16. Inhibitors of DNA methylation: Azacitidine and 5-aza-2'deoxyctidine.
17. Chimeric toxic protein: Ontak (IL2 + Diphtheria toxin)

## Toxicity of Anticancer Drugs

The therapeutic index for cancer chemotherapeutic agents is usually low and the cells of the bone marrow and the gastrointestinal tract are usually the most sensitive normal cells. Some drugs such as the nitrogen mustards are toxic for dividing and non-dividing cells but many cancer chemotherapeutic agents are more effective against dividing cells.



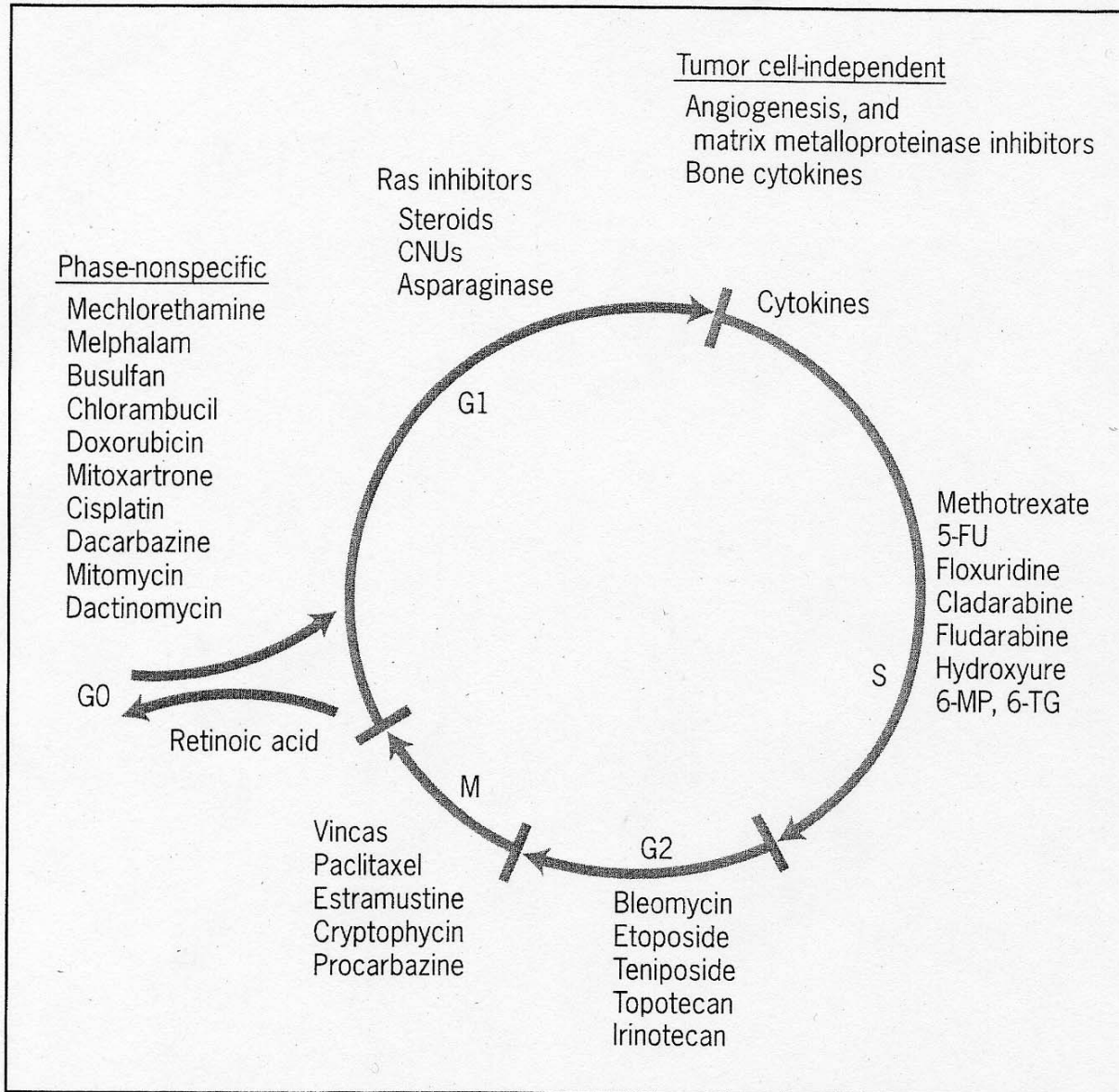
## Toxicity of Anticancer Drugs

For some such drugs the phase of the cell cycle is not critical (cell cycle stage nonspecific) but for others toxicity may be limited to a particular stage in the cell cycle e.g. the S phase. In such cases the degree of synchronization and the timing of therapy will be important.

Table 8-1. *Some characteristics of commonly used antineoplastic drugs*

Drugs that specifically inhibit enzymes or biochemical processes required only at one point in the cell cycle are usually schedule dependent whereas those that exhibit multiple cytotoxic mechanisms are generally schedule independent. See bibliographic citations for detailed information about these drugs. Drugs that affect cells at several points in the cell cycle are active against several types of cancer (indicated by \*). Nucleophilic targets include both macromolecules and small biochemicals like glutathione. The  $G_1$  phase remains underutilized as a target.

Phase of the cell cycle	Name of drug product	Common name	Molecular target
$G_0 \rightarrow G_1$	Taxol*	paclitaxel	microtubules
$G_1$	none		
$G_1 \rightarrow S$ transition	Hycamtin, Camptosar	topotecan, CPT-11	topoisomerase I
S phase	Cytosar, Cladribine	ara-C, 2-chlorodeoxyadenosine	DNA synthesis
$S \rightarrow G_2$ transition	Etoposide	VP-16	topoisomerase II
$G_2$	Blenoxane	bleomycin	??? DNA
M	Oncovin, Taxol*	vincristine, paclitaxel	microtubules
nonspecific	Platinol*	cisplatinum	nucleophiles
nonspecific	Adriamycin*	doxorubicin	topoisomerase II, DNA
nonspecific	Cytoxan*	cyclophosphamide	nucleophiles



**Figure 9-5.** Cell cycle and phase specificity of anticancer drugs. During G1, there is normal cellular growth and accumulation of DNA synthesis metabolites. In S-phase, DNA synthesis (chromosomal duplication) takes place. G2 is the premitotic phase, during which validation of chromosomal duplication takes place. M-phase indicates mitosis. 5-FU—5-fluorouracil; 6-MP—6-mercaptopurine; 6-TG—6-thioguanine; CNU's—nitrosoureas.

## **Mechanisms of Drug Resistance**

1. The cell membrane is impermeable
2. The drug is actively pumped out of the cell by the P-glycoprotein
3. The drug is not metabolized to an active form
4. The drug is inactivated
5. The drug target is increased e.g. increased level of enzyme or gene amplification
6. Mutation in a target protein decreases the affinity for the drug
7. Alternative biochemical pathways are increased
8. There is a decrease in topoisomerase II and DNA breaks
9. DNA damage is repaired

**TABLE 20-6.** Mechanisms of Drug Resistance to the Commonly Used Anticancer Agents

<b>DRUG</b>	<b>MECHANISM OF RESISTANCE</b>
Methotrexate	Decreased influx Decreased polyglutamylation Increased polyglutamate hydrolase Increased DHFR activity Altered DHFR
Fluorouracil	Decreased activation Decreased incorporation in RNA Increased thymidylate synthase Altered thymidylate synthase Increased breakdown of nucleotide Decreased nucleotide formation
6-Mercaptopurine	Increased breakdown of nucleotide Decreased activation to nucleotide
Cytosine arabinoside	Decreased uptake Increased breakdown Poor nucleotide formation
Alkylating agents	Poor uptake (nitrogen mustard) Increased catabolism or inactivation Increased repair of DNA damage
Cisplatin	Poor uptake Increased catabolism or inactivation Increased repair of DNA damage
Doxorubicin	Increased efflux (MDR) Altered topoisomerase II binding
Vinblastine, vincristine	Increased efflux (MDR) Decreased binding to tubulin Increased breakdown
Taxol	Increased efflux (MDR) Decreased binding to tubulin
Etoposide	Increased efflux (MDR) Altered topoisomerase II binding
Nitrosoureas	Repair of alkylated DNA (O <sup>6</sup> -methyl transferase)
L-Asparaginase	Increased asparagine synthetase

Abbreviations: DHFR, Dihydrofolate reductase; MDR, multidrug resistance.

# I. ALKYLATING AGENTS

The alkylating agents either spontaneously or after metabolism yield an unstable alkyl group,  $R-CH_2^+$ , which reacts with nucleophilic centers on proteins and nucleic acids. In most cases they may be considered to be cell cycle nonspecific agents. Many are bifunctional and can cross-link two DNA chains.

MECHLORETHAMINE (Nitrogen mustard, Mustargen, Mustine)

1. CHEMICAL NATURE:  $Cl-CH_2-CH_2-N(CH_3)-CH_2-CH_2-Cl$ . Decomposes rapidly in water.
2. MECHANISM OF ACTION: Bifunctional alkylating agent.
3. RESISTANCE: Increased proficiency of DNA repair
4. CELL CYCLE SPECIFICITY: Nonphase specific but mitosis and G1 are most sensitive
5. TOXICITY: Nausea and vomiting, myelosuppression, local vesicant action

## CYCLOPHOSPHAMIDE (Cytosan)

1. MECHANISM OF ACTION: Bifunctional alkylating activity, inhibition of DNA synthesis
2. RESISTANCE: Increased proficiency of DNA repair
3. CELL CYCLE SPECIFICITY: Causes more cytotoxicity during S phase
4. TOXICITY: Nausea and vomiting, thinning of the hair, cystitis
5. METABOLISM AND EXCRETION: For activity the drug must be metabolized in the liver to give the metabolites phosphoramidate mustard and acrolein. Excretion is primarily via the kidneys.



### CARMUSTINE (BCNU, Bis-Chlorethyl Nitrosourea)

1. CHEMICAL NATURE:  $\text{Cl-CH}_2\text{-CH}_2\text{-N(NO)-CO-NH-CH}_2\text{-CH}_2\text{-Cl}$
2. MECHANISM OF ACTION: Has both alkylating and carbamoylating action. Crosses the blood brain barrier.
3. RESISTANCE: May include increased cellular levels of glutathione
4. CELL CYCLE SPECIFICITY: Cell cycle nonspecific
5. TOXICITY: Nausea and vomiting, Myelosuppression
6. THERAPEUTIC USE: Multiple myeloma, brain cancer, lymphoma, melanoma.
7. METABOLISM AND EXCRETION: Forms alkyl group and 2-chlorethyl isocyanate. There is rapid renal excretion of metabolites.

### LOMUSTINE (CCNU, Chloroethyl Cyclohexyl Nitrosourea)

1. CHEMICAL NATURE:  $\text{Cl-CH}_2\text{-CH}_2\text{-N(NO)-CO-NH-C}_6\text{H}_5$
2. MECHANISM OF ACTION: Has both alkylating and carbamoylating action. Crosses the blood brain barrier
3. RESISTANCE: May include increased cellular levels of glutathione
4. CELL CYCLE SPECIFICITY: Cell cycle nonspecific
5. TOXICITY: Nausea and vomiting, Myelosuppression
6. THERAPEUTIC USE: Brain cancer, small-cell lung cancer, lymphoma, colorectal cancer



## II. ANTIMETABOLITES

### METHOTREXATE (Amethopterin)

1. MECHANISM OF ACTION: Analog of folic acid which inhibits dihydrofolate reductase and thereby inhibits one carbon transfers required for nucleic acid synthesis. Selective rescue of normal cells may be achieved with leucovorin (citrovorum factor).

2. RESISTANCE:

- a. Decreased transport
- b. Decreased affinity of target enzyme
- c. Gene amplification and increased synthesis of target enzyme

3. CELL CYCLE SPECIFICITY: Kills cells in S phase but also slows entry of cells into S phase

4. TOXICITY: Myelosuppression, Mucosal ulceration in GI tract, Nausea

## 5-FLUOROURACIL (5-FU)

1. CHEMICAL NATURE: structural analog of thymine
2. MECHANISM OF ACTION: 5-fluorouracil is metabolized to ribo and deoxyribonucleoside phosphates. There is inhibition of thymidylate synthetase by 5-fluoro-2'- deoxyuridine-5'-monophosphate. In addition there is incorporation of 5-fluorouridine triphosphate into RNA.
3. RESISTANCE: Multiple mechanisms including increased synthesis or altered affinity of target enzymes, decreased activation and increased catabolism
4. CELL CYCLE SPECIFICITY: cells are killed throughout the cell cycle
5. TOXICITY: Myelosuppression, Nausea and vomiting, Anorexia, Alopecia
6. THERAPEUTIC USE: GI tract adenocarcinomas, in combination protocols for breast cancer, topical application for premalignant keratoses
7. METABOLISM: Similar to uracil after action of dihydrouracil dehydrogenase in the liver.

## CYTARABINE (Cytosine arabinoside, ara-C)

1. CHEMICAL NATURE: 1-beta-arabinofuranosylcytosine (analog of the pyrimidine nucleoside, cytosine, with substitution of arabinose for ribose)
2. MECHANISM OF ACTION: The triphosphate metabolite inhibits DNA polymerase
3. RESISTANCE:
  - a. Decreased kinase activity required for activation
  - b. Increased inactivation by deaminase
4. CELL CYCLE SPECIFICITY: S-phase specific, blocks progression from G1 to S
5. TOXICITY: Myelosuppression, Nausea and vomiting
6. METABOLISM AND EXCRETION: Excreted chiefly as the noncytotoxic metabolite, uracil arabinoside. Deamination can be inhibited by tetrahydrouridine.

### III. PLANT ALKALOIDS

#### VINBLASTINE (Velban)

1. CHEMICAL NATURE: Vinblastine sulfate is the salt of a dimeric alkaloid from the plant *Vinca rosea*
2. MECHANISM OF ACTION: Binds to tubulin and interferes with spindle assembly in mitosis
3. RESISTANCE: Decreased cellular uptake or increased efflux
4. CELL CYCLE SPECIFICITY: Mitosis, but at high concentrations inhibits S and G1
5. TOXICITY: Leukopenia, nausea and vomiting

#### VINCRISTINE (Oncovin)

1. CHEMICAL NATURE: Vincristine sulfate is the salt of a dimeric alkaloid from the plant *Vinca rosea*. It differs from Vinblastine in the substitution of an aldehyde for a methyl group.
2. MECHANISM OF ACTION: Binds to tubulin and interferes with spindle assembly in mitosis
3. RESISTANCE: Decreased cellular uptake or increased efflux
4. CELL CYCLE SPECIFICITY: Mitosis
5. TOXICITY: Numbness and tingling of fingers and toes, hair thinning, minimal myelosuppression

## **ETOPOSIDE (VP-16-213)**

1. **CHEMICAL NATURE:** semi-synthetic alkaloid derived from podophyllotoxin
2. **ACTION:** Binds to tubulin but this is not believed to be important for the therapeutic effect. May stimulate topoisomerase II to cleave DNA
3. **CELL CYCLE SPECIFICITY:** Greatest lethality seen in S and G2 phases
4. **TOXICITY:** Leukopenia, nausea and vomiting more common with oral administration, alopecia

## IV ANTIBIOTICS

### DACTINOMYCIN (Actinomycin D, Cosmegen)

1. CHEMICAL NATURE: An antibiotic from a Streptomyces species. It contains two cyclic polypeptides which are linked by a chromophore moiety.
2. MECHANISM OF ACTION: Binds noncovalently to DNA. Intercalates between adjacent G C base pairs. It inhibits RNA polymerase more than DNA polymerase
3. RESISTANCE: Decreased ability of cells to take up or retain the drug.
4. CELL CYCLE SPECIFICITY: Cell cycle stage-nonspecific
5. TOXICITY: Nausea and vomiting, local vesicant, myelosuppression, redness of skin where radiation has been given, alopecia

### **DAUNORUBICIN (Daunomycin, Rubidomycin)**

1. CHEMICAL NATURE: An anthracycline glycoside isolated from a Streptomyces species, red color
2. MECHANISM OF ACTION: Intercalates between base pairs of DNA and inhibits RNA synthesis
3. RESISTANCE: Decreased uptake or more rapid removal of the drug
4. CELL CYCLE SPECIFICITY: Cell cycle stage-nonspecific
5. TOXICITY: Nausea and vomiting, Myelosuppression, Cardiomyopathy, Alopecia

### **DOXORUBICIN ( Adriamycin)**

1. CHEMICAL NATURE: Same as Daunorubicin except there is an additional hydroxyl group
2. MECHANISM OF ACTION: As for Daunomycin
3. RESISTANCE: As for Daunomycin
4. CELL CYCLE SPECIFICITY: Cell cycle stage-nonspecific but greater efficacy in S
5. TOXICITY Similar to daunomycin
6. THERAPEUTIC USE: Acute leukemias, lymphomas, many solid tumors including sarcomas

## BLEOMYCIN (Blenoxane)

1. CHEMICAL NATURE: Bleomycin sulfate is a mixture of 13 different bleomycin peptides derived from a Streptomyces species
2. MECHANISM OF ACTION: Inhibits DNA synthesis. Binds to DNA and causes DNA strand breaks
3. RESISTANCE: Increased hydrolase activity, decreased uptake and increased efflux
4. CELL CYCLE SPECIFICITY: Increased sensitivity in G2
5. TOXICITY: Fever, dermatologic reactions, pulmonary toxicity and fibrosis, minimal myelosuppression



## **Gleevec (imatinib mesylate, also known as STI-571)**

In 2001 the Food and Drug Administration announced the approval of Gleevec (imatinib mesylate, also known as STI-571), as a promising new oral treatment for patients with chronic myeloid leukemia (CML).

FDA approved the drug for treating patients with three stages of CML: CML myeloid blast crisis, CML accelerated phase, or CML in chronic phase after failure of interferon treatment. Gleevec has been shown to reduce substantially the level of cancer cells in the bone marrow and blood of treated patients..

Chronic myeloid leukemia occurs when pieces of two different chromosomes break off and reattach on the opposite chromosome, forming the so-called “Philadelphia” chromosome. This chromosome translocation leads to a blood cell enzyme being “turned on” all the time. As a result, potentially life-threatening levels of both mature and immature white blood cells occur in the bone marrow and the blood.

Gleevec acts as a relatively specific inhibitor of the tyrosine kinase coded by the *abl* gene but also inhibits the *kit* gene product.

## IRESSA, TARCEVA AND ERBITUX

In 2003, the Food and Drug Administration (FDA) announced the approval of Iressa (gefitinib) tablets as a single agent treatment for patients with advanced non-small cell lung cancer (NSCLC), the most common form of lung cancer in the US. Iressa was approved as a treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy, two drugs that were the standard of care in this disease.

The mechanism by which Iressa exerts its clinical benefit is not fully understood. However, Iressa was developed to block growth stimulatory signals in cancer cells. These signals are mediated in part by tyrosine kinases. Iressa blocks several of these tyrosine kinases, including the one associated with Epidermal Growth Factor Receptor (EGFR).

## IRESSA, TARCEVA AND ERBITUX

Tarceva (erlotinib HCl) is a drug with a similar mechanism of action. Tarceva is designed to block tumor cell growth by inhibiting the tyrosine kinase activity of the HER1/EGFR receptor, thereby blocking the HER1/EGFR signaling pathway inside the cell.

In 2010, the FDA approved the use of erlotinib as a treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

EGFR is also the target of a monoclonal antibody, Erbitux (cetuximab) which has been approved for the treatment of colorectal cancer.

## ESTROGEN RECEPTOR ANTAGONISTS AND AROMATASE INHIBITORS

Estrogen receptor antagonists such as **tamoxifen** are useful for the treatment of estrogen receptor-positive breast cancer.

Aromatase inhibitors prevent androgen from being converted to estrogen. That results in less estrogen reaching estrogen receptors to stimulate growth. **Arimidex** (generic name: anastrozole), **Femara** (letrozole), and **Aromasin** (exemestane) are the aromatase inhibitors in current use, primarily for post-menopausal women with metastatic breast cancer. In the past, these medications were most commonly used by women who may have already tried other anti-estrogen therapies, such as tamoxifen, and whose cancer was no longer controlled by those drugs. Now with the results of new studies, many doctors recommend an aromatase inhibitor BEFORE tamoxifen for post-menopausal women with metastatic disease.

Reference: Web page: [breastcancer.org](http://breastcancer.org)

## Abiraterone (Zytiga)

April 28, 2011 — The US Food and Drug Administration (FDA) approved abiraterone acetate (Zytiga) in combination with prednisone for the treatment of metastatic, castration-resistant prostate cancer in men who have received prior docetaxel chemotherapy.

Abiraterone is an inhibitor of cytochrome P450 17A1 a 17 $\alpha$  hydroxylase and C17,20 lyase and thereby inhibits testosterone synthesis in all tissue including tumors.

## Antibodies

1. Herceptin (trastuzumab) is an antibody against Her2 receptors and is used in the treatment of breast cancer.

2. The FDA has approved Avastin (bevacizumab) for use in combination with intravenous 5-fluorouracil-based chemotherapy for previously untreated metastatic cancer of the colon or rectum. Avastin is a recombinant humanized antibody to Vascular Endothelial Growth Factor (VEGF). Avastin is designed to bind to and inhibit VEGF, a protein that plays a critical role in tumor angiogenesis.

3. Rituxan recognizes the CD20 antigen and is used in the treatment of B-cell tumors (Weinberg page 711).

## CANCER VACCINES

1. Vaccination with irradiated cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor (GM-CSF) has been reported to stimulate anti-tumor immunity and is in Phase III trials for melanoma (OncoVex GM-CSF).
2. Heat shock proteins from a patient's tumor have been injected back into the patient to stimulate an immune response against cells harboring heat shock proteins. Phase III trials are ongoing against renal cell carcinoma.
3. A canarypox virus carrying the carcinoembryonic antigen (CEA) gene is in Phase II trials against colorectal cancer.
4. In April of 2010 the FDA approved a therapeutic vaccine against prostate Cancer (Provenge, sipuleucel-T). The patient's dendritic cells are exposed to a protein found on most prostate cancer cells and the cells are then reinfused in the patient.
5. Gardasil is a vaccine against human papillomas 6, 11, 16 and 18 intended for immunization against cervical cancer

## PROTEASOME INHIBITORS

The Food and Drug Administration (FDA) has approved the use of Velcade (bortezomib) injection, a new treatment for multiple myeloma, a cancer of the bone marrow.

Multiple myeloma is the second most prevalent blood cancer after non-Hodgkin's lymphoma. It is a cancer of the plasma cell, an important part of the immune system that produces antibodies to help fight infection and disease. There are approximately 45,000 people in the United States living with multiple myeloma and an estimated 14,600 new cases of multiple myeloma are diagnosed each year.

Velcade is the first proteasome inhibitor to receive FDA approval for cancer treatment.

Reference: FDA News, May 13, 2003



## RNAi

**RNA interference** is a gene silencing mechanism that results in sequence specific destruction of mRNAs. Small interfering RNAs consist of 21-25 nucleotide double stranded RNAs (siRNAs). The antisense strand of the siRNA is incorporated into the RNA induced silencing complex (RISC) which contains an RNase.

RNA interference is being investigated as a therapeutic mechanism in the treatment of cancer. One attractive target is the bcr/abl fusion gene transcript. This is present in nearly all chronic myeloid leukemia (CML) patients and 30% of adults with acute lymphoblastic leukemia (ALL). The siRNA-induced reduction of the oncogenic transcript results in the cells becoming more susceptible to apoptosis.

Problems to be address in the RNAi approach include achievement of sufficient concentration, targeting to cancer cells and metabolic stability of the siRNAs.

Reference;Biotechniques 36: 557-561, 2004.

## Maintenance or Activation of p53

The p53 tumor suppressor gene is inactivated in most human tumors. In some cases this results from mutation of the p53 gene. In other cases there is activation of the MDM2 gene resulting in an inhibition of p53. A group at Hoffman-La Roche in Nutley, New Jersey have identified a class of imidazoline molecules that keep MDM2 from binding p53. These molecules have been termed “Nutlins”. Oral administration in tumor-bearing mice has resulted in inhibition of tumor growth by 90%.

Reference: Science 303: 23-25, 2004.

The first commercialized gene therapy is the development in China of an adenovirus vector delivery system expressing the p53 tumor suppressor gene termed Gendicine. This was tested against late-stage head and neck squamous cell carcinoma. In a total of 120 patients, 64% experienced complete regression and 32% experienced partial regression.

Reference; Modern Drug Discovery 7(3): 32-36, 2004.

Nature Reviews Drug Discovery published online 23 March 2006

# Suggested Reading

**Holland-Frei Cancer Medicine, 8th Edition., 2010. Edited by D.W. Kufe et al., Part IV - Therapeutic Modalities**

**Section 12 - Chemotherapy**

**Section 13 - Chemotherapeutic Agents**

**Section 14 - Biotherapeutics**

**Section 15 - Endocrine Therapy**

**Section 16 - Gene Therapy**

**R. Weinberg, The Biology of Cancer, Chapter 16, Garland Press, 2007.**