Anti-cancer Therapy: Antimitotic Agents

Edy Suwarso
Discussion Points

• What is cancer?
• Mitosis and mitotic checkpoints
• How deregulation of the above contributes to cancer formation
• Antimitotic agents as a treatment
• Taxanes

• Vinca alkaloids
• Colchicine
• Problems with antimitotics overall
• What's new with antimitotics?
What is Cancer?

• Cancer is the deregulation of normal cellular processes. Cells that have been transformed tend to proliferate in an uncontrolled and deregulated way and, in some cases, to metastasize (spread).

• Cancer is not one disease, but a group of more than 100 different and distinctive diseases.

• Cancer can involve any tissue of the body and take on many different forms in each area.

• Cancer is the 2nd leading cause of death in the U.S., surpassed only by heart disease.
What Happens in Cancer Cells?

• Cancer cells become deregulated in many different ways.
  • One way: Mutations in one or more mitotic checkpoints allow the cell to move from one phase of mitosis to another unchecked.
  • Another way: Mutations in cellular machinery itself so that mitotic errors are not properly detected/repaired, and the cell is allowed to move through mitosis unchecked.

• But what is ‘mitosis?’
What is Mitosis?
“It’s been so long, I’ve forgotten...”

• Here’s a video to remind everybody exactly what mitosis, also known as the ‘Cell Cycle,’ entails:

  • Short video first
    http://youtube.com/watch?v=eFuCE22agyM

  • More detail
    http://www.youtube.com/watch?v=VlN7K1-9QB0&NR=1
Stages of Mitosis

• Interphase: Technically not part of mitosis, but rather encompasses stages G1, S, and G2 of the cell cycle which prepare the cell for mitosis.

• Prophase: Chromatin in nucleus condense; nucleolus disappears. Centrioles begin moving to opposite ends of the cell and fibers extend from the centromeres.

• Metaphase: Spindle fibers align the chromosomes along the middle of the cell nucleus. This line is referred to as the ‘metaphase plate.’

• Anaphase: The paired chromosomes separate at the kinetochores and move to opposite sides of the cell. Motion results from the physical interaction of polar microtubules.
Stages of Mitosis (cont.)

- Telophase: Chromatids arrive at opposite poles of cell, and new membranes form around the daughter nuclei. The chromosomes disperse.

- Cytokinesis: Results when a fiber ring composed of a protein called actin around the center of the cell contracts, pinching the cell into two daughter cells, each with one nucleus.
Mitosis Summary

- Mitosis is the process by which a cell duplicates the chromosomes in its cell nucleus in order to generate two, identical, daughter nuclei.
- It is followed immediately by cytokinesis, which divides the nuclei, cytoplasm, organelles and cell membrane into two daughter cells containing roughly equal shares of these cellular components.
- Mitosis and cytokinesis together define the mitotic (M) phase of the cell cycle.
- Mitosis is a normal cellular process necessary to sustain life, but its deregulation in one form or another is found in all cancer cells.
- Mitosis can often become abnormal by the change in, or absence of, the normal mitotic checkpoints.
Mitotic Checkpoints

• Mitotic checkpoints are points in the cell cycle which act to ensure correct transmission of genetic information during cell division. These checkpoints look for abnormalities within the cycle, specifically chromosomal aberrancy.

• Checkpoints take place towards the end of each phase of mitosis and must be passed before the cell can get clearance to enter into the next stage of mitosis.

• If errors are found during checkpoints, the cell acts quickly to correct them, arresting cell growth and not proceeding with mitosis until the error has been fixed.

• If these errors cannot be fixed, the cell normally undergoes apoptosis, or programmed cell death.
How ‘Cancer’ Arises

• The cell is allowed to move through the cell cycle and grow unchecked, and more mutations are accumulated over time that extend past the cell cycle to the cellular machinery itself.

• These mutations, in combination with the genetic mutations accrued through abnormal mitotic progression, eventually cause the cell to be completely deregulated in its growth and proliferation.

• It becomes unstoppable and even immortal.

• You get CANCER!
Antimitotic Agents: One Possible Treatment

- Antimitotic agents: Anti-tumor agents that inhibit the function of microtubules through the binding of their subunits or through direct cessation of their growth.
- What are microtubules (MTs)? Protein polymers formed by α-Tubulin and β-tubulin heterodimers that play an important role in critical cell functions such as movement, phagocytosis and axonal transport. They also play a key role in the formation of the mitotic spindle apparatus and cytokinesis at the end of mitosis.
- In normal cells, microtubules are formed when a cell starts dividing during mitosis. Once the cell stops dividing, microtubules are broken down or destroyed.
- The crucial involvement of MTs in mitosis makes them a prime target for anti-cancer agents.
Antimitotic Agents

• Three distinct classes of antimitotic agents have been identified thus far.
  1.) **Taxanes**; include: paclitaxel and docetaxel.
  2.) **Vinca alkaloids**; include: vincristine, vinblastine, vindesine, and vinorelbine.
  3.) **Colchicine**.

• All must be administrated via intravenous infusion.
Taxanes (First Antimitotic Group)

- Prevent the growth of cancer cells by affecting microtubules.
- Overall, they encourage microtubule formation, then they stop the microtubules from being broken down so that the cells become so clogged with microtubules that they cannot continue to grow and divide. This results in the cell’s arrest in mitosis.
- Eventually, cell DEATH by apoptosis.
Taxanes: History

• Isolated from the bark of the Western yew tree in 1971, this compound became useful in the treatment of cancer when it was discovered that it possessed the unique ability to promote the formation of microtubules by binding to their B-tubulin subunit and antagonizing their disassembly.

• However, the amount of paclitaxel in yew bark was small, and extracting it was a complicated and expensive process. In addition, bark collection was restricted because the Western yew is a limited resource located in forests that are home to the endangered spotted owl.

• As demand for paclitaxel grew, government agencies and the pharmaceutical company Bristol-Myers Squibb, worked to increase availability and find other sources of paclitaxel besides the bark of the Western yew tree.

• This work led to the production of a semi-synthetic form of paclitaxel (docetaxel) derived from the needles and twigs of the Himalayan yew tree Taxus bacatta, which is a renewable resource. The FDA approved docetaxel in the spring of 1995.
Taxanes: Paclitaxel

- Paclitaxel [Taxol] was the first compound of the series to be discovered and used in cancer treatment.


- Side effects include: bone marrow loss, hypersensitivity, muscle aches, peripheral neuropathy, bradycardia and tachycardia.
Docetaxel [Taxotere] is a partially-synthetic derivative of Taxol and results from the modification of paclitaxel’s side chain. While it is paclitaxel’s structural analog, it is much more potent in terms of potential patient toxicity. It acts to kill cancer cells in the same way as paclitaxel.
Taxanes: Docetaxel (cont.)

- Useful in the treatment of: mainly prostate cancer, but also breast, ovarian and lung cancer.
- Must be co-administered with dexamethasone to prevent progressive, often disabling, fluid retention in the peripheries, lungs and abdomen.
- Side effects are more severe but more short-lived than Taxol and include: leukopenia, peripheral edema, neutropenia.
Taxanes: Complicating Factors

• Resistance to taxanes is a complicating factor to successful treatment and is often associated with increased expression of the *mdr-1* gene and its product, the P-glycoprotein.

• Other resistant cells have B-tubulin mutations which inhibit the binding of taxanes to the correct place on the microtubules; this renders the drug ineffective. In addition, some resistant cells also display increased aurora kinase, an enzyme that promotes completion of mitosis. Some cells display a heightened amount of survivin, an anti-apoptotic factor.

• Side effects can be debilitating.

• These drugs are very expensive and must be administered in large amounts at once due to the fact that much of the drug is excreted in the urine or allocated to the plasma. This large administration volume cannot be tolerated in many patients.
Vinca Alkaloids (Second Antimitotic Group)

- The Vincas work through their ability to bind to the B-tubulin subunit of microtubules, blocking their ability to polymerize with the α-tubulin subunit to form complete microtubules. This causes the cell cycle to arrest in metaphase because, in absence of an intact mitotic spindle, duplicated chromosomes cannot align along the division plate. The ultimate fate of such cells is to undergo apoptosis.

- The Vinca alkaloids are all derived from the Madagascan periwinkle plant, *Vinca rosea*. The plant was reputed to be useful in the treatment of diabetes. Attempts to verify the antidiabetic properties of the plant’s extracts in the 1950’s led instead to the discovery and isolation of vinblastine.

- Scientists first observed its anticancer properties in a lab in 1962 with the observation of regression of lymphocytic leukemia in rats.

- Several years later, the successful purification of the plant’s alkaloids yielded three other active dimers: vincristine, vinorelbine, vinrosidine.
Vinca Alkaloids: Vinblastine

- Vinblastine [Velban] was the first of the Vincas to be used in the treatment of cancer.
- Side effects include: leukopenia, GI disturbances, cellulitis, phlebitis.
Vinca Alkaloids: Vincristine

- Vincristine [Oncovin]
- Better tolerated by children than adults.
- Side effects: myelosuppression, hyponatremia, numbness/tingling of extremities, loss of deep tendon reflexes, and loss of motor function.
- Intrathecal administration results in fatal central neurotoxicity.
Vinca Alkaloids: Vinorelbine

- Vinorelbine [Navelbine]
- Used in the treatment of: lung carcinoma, breast cancer.
- Side effects include: granulocytopenia, thrombocytopenia, myelosuppression, and less neurotoxicity than all of the other Vincas.
Vinca Alkaloids: Vindesine

- Vindesine [Eldisine]
- Side effects: immunodeficiency, anemia, myalgia, fatigue, mouth ulcers, GI upset.
Vinca Alkaloids: Complicating Factors

• Resistance to the Vinca alkaloids comes in the form of cross-resistance due to the structural similarity of the four compounds, and their antitumor effects are blocked by multidrug resistance in which tumor cells become cross-resistant to a wide variety of agents after exposure to a single drug. Resistant cells can also display chromosomal abnormalities consistent with gene amplification, and these cells contain increased levels of the P-glycoprotein. Other forms of resistance stem from mutations in B-tubulin that prevent the binding of the inhibitors to their target.

• Also, because of the heavy concentration of microtubules in the brain and the drug’s disruption of this, patients treated with Vinca alkaloids can experience severe neurotoxicity.
Colchicine (Third Antimitotic Group)

- Colchicine was originally extracted from plants of the genus *Colchicum* and used to treat rheumatic complaints, specifically gout.
- The colchicine alkaloid was initially isolated in 1820 and was found to bind tubulin, the protein subunit of MTs.
- It is a relatively small molecule and inhibits its target in a mechanism similar to the taxanes: by binding to the colchicine binding site of microtubules and promoting their polymerization, thus causing cell clogging and eventually apoptosis.
Colchicine (cont.)

• While it has been shown to kill cancer cells, the drug’s usefulness in the treatment of cancer is hindered by its cytotoxicity; in addition, it is a known emetic and teratogen.
• Colchicine has proven to have a fairly narrow range of effectiveness as a chemotherapy agent, so it is only FDA-approved to treat gout.
• Currently, investigation of colchicine as an antimitotic agent is underway.
Drug Resistance is a **REAL Problem** for Cancer Patients

- Multidrug resistance is a major drawback of cancer chemotherapy and can result in patients becoming immune to the effects of many different drugs at once.
- A major mechanism of multidrug resistance occurs via an over-expression of ATP transmembrane efflux pumps which pump the drug outside of the cell after its entrance.
- Resistance can often result in patient death as a result of lack of effective treatment available.
- This remains a problem with all anti-cancer therapies.
More Problems With Antimitotic Agents

• Side effects with antimitotic agents, as with many chemotherapies, can be debilitating and even fatal. Chemotherapy targets rapidly-dividing cells, which includes cancer cells but also hair and gut cells. This results in hair loss and nausea in patients. Much research remains to be done in this area of cancer treatment to minimize toxicity.

• There are many drug interactions with antimitotic agents, so patients can often only take these drugs alone.
What’s New - Antimitotic Agents

- New taxanes and Vinca alkaloids with oral bioavailability are currently undergoing clinical testing.
- Inhibitors of mitotic kinesin motors, such as KSP-1A and monastrol, are currently being tested and could soon become the newest members of the antimitotic drug family.
- A less toxic form of colchicine is currently being investigated.
- Drugs specifically targeting the Aurora kinase are in various stages of clinical development. One is MK-0457 in Phase II clinical trials at Merck.
- Drugs formulated specifically to target CNEP-E, a mitotic kinase that is responsible for the segregation of chromosomes during mitosis, are currently in the making; one is GSK-923296 at GlaxoSmithKline.
References

- http://en.wikipedia.org/wiki/Mitosis
THANKS FOR YOUR ATTENTION