Oncology Update: Targeted Cancer Therapies & Patient Management

1 Contact Hour

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Purpose and Objectives

The purpose of this continuing nursing education course is to provide healthcare professionals with information about targeted cancer therapies and management of patients receiving these therapies.

After successful completion of this course, you will be able to:

1. State the definition of targeted cancer therapy.
2. Describe 3 types of targeted cancer therapy.
3. Discuss the mechanism of action of targeted cancer therapies.
4. Discuss management of common side effects of targeted cancer therapy.

Glossary

Angiogenesis: The growth of new blood vessels.

Apoptosis: Cell death that eliminates cells without releasing harmful substances into the surrounding area.

Biological response modifiers: Substances that stimulate the body's response to disease.

Carcinogenesis: Process by which normal cells are transformed into cancer cells.

Dimerization: The activation of a receptor by the pairing of 2 monomers that are side to side on the cell surface.

Epidermal Growth Factor Receptor (EGFR): A protein on the surface of many cells to which epidermal growth factor binds. The binding triggers intracellular signaling for the cell to divide. It may also be referred to as HER1 or ErbB1.

Heterodimerization: The pairing of 2 different receptors that have been bound by ligands.

Homodimerization: The pairing of 2 of the same type receptors that have been bound by ligands.

Ligand binding: The process by which the molecule attaches to the receptor and activates it.

Ligands: Molecules that activate receptors on the cell surface.

Monoclonal antibodies: Antibodies that are identical because they are produced by a single type of immune cell. As a targeted cancer therapy, they are directed against molecules found only in overexpressed or mutated in cancer cells.

Monomer: Single inactivated receptor.

Overexpress: Making too many copies of a protein or gene.

Phosphorylation: The transfer of chemicals (phosphates) from one molecule in the signaling pathway to the next.

Signal transduction: The process by which a molecular or physical signal interacts with a receptor on the cell surface and sends a message down a relay team of messengers inside the cell ultimately effecting the function of the cell.

Small molecule inhibitors: Drugs that interfere with tyrosine kinases.

Tyrosine kinase: An enzyme that can transfer a phosphate group from adenosine triphosphate to a protein in the cell and then trigger cell signaling.

Introduction

The goal of targeted therapy in cancer treatment is to create a “magic bullet” that goes straight to the cancer cells, bypassing normal cells. These therapies do this by interfering with one of the specific molecules in the cancer cell that are involved with tumor growth and progression. Thus, they are referred to as “molecularly targeted therapies,’’ “molecularly targeted drugs,” or just “targeted therapies.”

Targeted therapies lead to the individualization of cancer treatment, referred to as personalized medicine, as they enable doctors to tailor cancer treatment based on the individual characteristics of the patient’s cancer. All healthcare professionals need to be familiar with the concept behind these therapies so that they can educate patients, help them make decisions, and monitor side effects and interactions with other treatments.

The mechanisms and actions of these agents differ from traditional chemotherapy. They are usually better tolerated, but are associated with their own set of adverse reactions.

Targeted therapy can be a stand-alone treatment or used with other modalities.

Key Point: targeted cancer therapies are agents that interfere with specific molecules involved with cancer cells to stop its growth and progression (National Cancer Institute NCI, n.d).

Definition of Targeted Cancer Therapy

Targeted cancer therapies are agents (drugs or other substances) that “target” select pathways involved in carcinogenesis (process by which normal cells are transformed into cancer cells).

The molecular targets are identified through research. They are chosen deliberatively to interact with specific molecules in order to block a target in the cell signaling pathway that leads to cancer cell division, growth, and travel throughout the body. They can also lead to apoptosis, which is programmed death of the cancer cell.

How Do Targeted Therapies Differ from Standard Chemotherapy?

Standard Chemotherapy	Targeted Therapy
Found by trial and error	Found via deliberate research
Kill all rapidly dividing cells	Carefully chosen to interact with specific pathways
Collateral damage appears in healthy tissue that is rapidly dividing e.g., • Circulatory system • Immune system • Digestive system	Because damage to normal cells is limited or non-existent, there are less, fewer and less toxic side effects

Types of Targeted Therapies

There are 3 main categories of targeted cancer therapies:

- **Small Molecules:** Can easily cross cell membranes so they are used to interfere with proteins both on the inside and outside of the cell. Often they modify enzyme activity of the cell or its ability to interact with other molecules. Usually these are oral medications with half-lives of only hours so need to be given daily.
- **Monoclonal Antibodies (MoAbs):** Antibodies usually work outside the cell; they bind to the receptors on the cell surface and prevent them from being activated. They can also be used inside the cells as a delivery vehicle; they can deliver radioactive molecules or chemotherapy into the cell. They are usually given intravenously. Their half-lives range from days to weeks so they only have to be given every 1-4 weeks.
- **Vaccines:** The immune system does not do a good job fighting cancer because it does not usually recognize cancer cells as foreign. Some cancers even inhibit the ability of the immune system to work. Vaccines try to activate the immune system and make it recognize cancer cells as foreign so it will attack them. Their action on cancer cells is thus indirect; they do not act on a specific cancer cell pathway like small molecules and antibodies do. Vaccines are usually given parentally: intramuscularly, subcutaneously, or intravenously.

  (NCI, n.d).

What Is Cell Signaling?

Cell signaling is a complex network of biochemical and molecular messaging that regulates all cell processes. When a signal is generated, it produces a cascade of reactions that travel down a pathway to the cell nucleus; this is referred to as **signal transduction.**

When the signal arrives at the nucleus of the cell, it directs the activities of the cell. These activities include cell growth and division (proliferation), programmed cell death (apoptosis), and growth of new blood vessels) (NCI,n.d; Polovitch et al, 2009).

The website of the National Cancer Institute (http://www.cancer.gov).

Processes Involved in Carcinogenesis: How Cancer Cells Bypass Normal Cell Processes

Cancer cells bypass normal cell processes in a number of different ways

- **Acquisition of autonomous proliferative signaling:** This results when proto-oncogenes are activated into oncogenes. Proto-oncogenes are developmental genes expressed during early embryonic development to regulate normal growth and development. If activated later in life, they become oncogenes which are abnormal, mutated genes responsible for the transformation of a normal cell into a cancer cell. These cancer cells have the ability to grow and multiply (proliferate) without needing any other signals to do so.

- **Inhibition of tumor growth signaling:** Tumor suppressor genes contain the genetic portion of DNA that stops or inhibits normal cell growth and division. If these genes are inactivated or

mutated, the normal controls on cell growth are removed, and cell proliferation beyond the normal needs of the body is allowed.

- **Evasion of programmed cell death or apoptosis:** Normally cells that are not needed or are mutated (have DNA damage) are instructed to die. This is called programmed cell death or apoptosis. Cancer cells gain the ability to resist apoptosis and continue cell division.

(Bayon, Chaturvedi, Shah, & Wenig, 2011, Polovich et al, 2009)

Processes Involved in Carcinogenesis: How Cancer Cells Bypass Normal Cell Processes (Cont.)

- **Immortalization:** Normally cells are programmed to divide a set number of times and then undergo apoptosis, i.e., they are “mortal.” Cancer cells can divide an infinite number of times, i.e., they are “immortal.”

- **Angiogenesis:** This is the growth of new blood vessels. Tumors less than 1 cubic millimeter (mm) get their nutrition from diffusion. Once tumors reach this size, they must build new blood vessels in order to obtain the nutrition they need. To do this, they secrete tumor angiogenic factor (TAF). This is also referred to as vascular epidermal growth factor or VEGF. VEGF stimulates the growth of new blood vessels which allow the tumor to continue growing.

- **Tissue invasion and metastasis:** Cancer cells are able to break away from parent cells, invade surrounding tissue by direct extension, seeding, or gaining access to lymph or blood system. Thus they are able to invade various tissues and sites in the body.

(Bayon et al, 2011, Polovich et al, 2009)

How Do Targeted Therapies Stop This?

Targeted therapies can interfere with the cancer cells ability to bypass normal cell regulatory mechanisms in several ways. The goal is for them to stop the impaired part of the regulatory system from talking to rest of the pathway. One way they do this is by blocking receptors from being activated. Receptors are activated when 2 receptors are paired (dimerization); or, when a molecule that activates receptors, called a ligand, attaches to a specific receptor site.

The website of the National Cancer Institute (http://www.cancer.gov)

How Else Do Targeted Therapies Stop This?

They can blocks signals from being transmitted by keeping the receptor in the "off" position.

Or they can block any of the “relay” participants along the path to the nucleus.

The website of the National Cancer Institute (http://www.cancer.gov)

How Are Targets Chosen?

The best target would be something present in cancer cells and absent in normal cells

This ideal target is difficult to find, possibly because cancer cells develop from normal cells. Targets need to be involved in the carcinogenesis pathway, and they need to be detectable and measurable

in tumor tissue (Bayon et al., 2011; NCI, n.d).

How Else Are Targets Chosen?

If an “ideal” target cannot be found, scientists will look for something that is present more often in the cancer cell. Often the molecule may be over-expressed (more made than normal) or mutated in the cancer cell. For example, a mutated molecule can keep the growth receptors in the “on” position at all times.

The website of the National Cancer Institute (http://www.cancer.gov)

How Else Are Targets Chosen?

A less optimal choice, but one that still has benefit, would be to choose a target that is present in the cancer cell and the normal cell, but the patient is able to replace any normal cells that get destroyed.

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Target Cell Surface Receptors: Trastuzumab

Trastuzumab (Herceptin®): Trastuzumab targets the growth factor receptor HER2 which is found on cell surfaces. It is a monoclonal antibody that binds to the receptor so that it cannot dimerize with another HER2 receptor. Thus, the receptor is unable to stimulate the pathways that promote growth and division of certain cancer cells. Overexpression of HER2 receptors is found in about 20-25% of breast cancers and in many gastro-esophageal junction and gastric cancers (Gerber, 2008; NCI, n.d).

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Target Cell Surface Receptors: Imatinib

Imatinib (Gleevec®): Imatinib is a small molecule that works inside the cell to prevent certain proteins in the cell from functioning in the cell signaling relay team. Imatinib does this by preventing phosphorylation. (The transfer of chemicals [phosphates] from one molecule in the signaling pathway to the next.)

Two of the proteins it inhibits are involved in the signaling of cell growth. They are called abl and c-kit.

Patients with chronic myelongenous leukemia (CML) have a mutant form of the abl protein. The mutant form is called Brc-abl. Brc-abl fuels cancer growth by always being in the “on” position.

Imatinib also targets the protein c-kit. Stopping this protein from signaling helps patients with unresectable or metatasitc gastrointestinal stromal tumors (GIST).

Therapies that Promote Cell Death

Normally the number of cells in the body stay fairly constant due to a balance of cell pathways for cell survival and cell apoptosis. Cancer cells are able to tip the balance toward cancer cell survival. Therapies that target apoptosis try to tip the balance back toward death for the cancer cells.

Signals for apoptosis can come from outside or inside the cell. Inside the cell, anti-apoptotic proteins may be overproduced. Overexpression of the protein Bcl-2 helps some cells evade apoptosis.

Outside the cell a signaling molecule binds to one of 2 “death” receptors: Death Receptor 4 or Death Receptor 5. These receptors tend to be overexpressed in cancer cells. One of these signaling molecules is tumor necrosis factor related-apoptosis-inducing ligand or TRAIL.

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Promote Cell Death: HGS-ETR1 and HGS-ETR2

HGS-ETR1 (mapatumab) and HGS-ETR2 (lexatumumab) are monoclonal antibodies undergoing clinical trials. One binds to Death Receptor 4 and the other binds to Death Receptor 5. They mimic the signaling molecule TRAIL and trick the receptors into thinking that TRAIL has stimulated them, thus they activate the pro-apoptotic pathways and cause death of the cancer cells. Since there are more Death Receptors in cancer cells, it is hoped that these drugs will only minimally affect normal cells.

In addition to killing cells themselves, it is hoped these drugs will make the cancer cells more receptive to other treatments.

HGS-ETR1 is being tested in patients with refractory or relapsed multiple myeloma. HGS-ETR2 is being tested in pediatric patients with refractory or relapsed lymphoma and some solid tumors (NCI, n.d).

Therapies that Prevent Angiogenesis

Normal angiogenesis takes place during very early growth and development and later in life only to aid in wound healing or support female reproduction as needed. When cells become oxygen deprived, they release proteins that find and bind on receptors of the endothelial cells that make blood vessels. These proteins stimulate the endothelial cells to secrete matrix metalloproteinases or MMPs. MMPs allow endothelial cells to travel to the cell that needs to form new blood vessels.

Tumor cells also release MMPs. They can be targeted with agents to interfere with their activity. Many tumors also release a lot of other proteins such as vascular endothelial growth factor (VEGF) that also binds to endothelial cells and stimulates the growth of new blood vessels. **This is the primary driver of tumor angiogenesis.** Overexpression of VEGF has been demonstrated in many solid tumors and has been shown to negatively affect survival. Drugs can also be created to interfere with this step.

Angiogenesis inhibitors do not interfere with already existing blood vessels. They only affect the ability to make new blood vessels (NCI, n.d).

Therapies that Prevent Angiogenesis Bevacizumabs

Bevacizumab (Avastin®) is a monoclonal antibody that directly targets and binds to VEGF so that it cannot attach to receptors on the endothelial cells. New blood vessels are not able to form. Bevacizumab is approved for use with specific chemotherapy agents in patients with metastatic colorectal cancer; unresectable; locally advanced, recurrent or metastatic non-squamous-non-small cell lung cancer; metastatic renal cell cancer in combination with interferon alpha; and as a single agent in glioblastoma after progression of first line therapy (NCI, n.d), www.fda.gov 2007).

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Prevent Angiogenesis Sorafenib

Sorafenib (Nexavar®) is a small oral molecule that inhibits multiple kinases (proteins involved in cell signaling). Some of these kinases are receptors found on the cell surface, some are enzymes found inside the cell. Blocking these kinases can inhibit growth and stop the movement of endothelial cells to the cells that are signaling that they need new blood vessels.

Some of the kinases inhibited are needed by normal cells also. Thus, the drug may have some effect on normal cells.

Sorafenib is approved for the treatment of advanced renal cell cancer and as first line therapy for liver cancer (NCI, n.d, www.fda.gov, 2077).

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Trigger an Immune Response Against Cancer Cells: Rituximab

Rutiximab (Rituxan®) is a monoclonal antibody (MoAb) that can activate the immune system. Mature B lymphocytes (B cells) have a surface protein called CD20. Rutiximab binds to CD20 and initiates the activation of the body's immune system enabling it to kill cancer cells.

Immune cell such as natural killer cells, T cells, and macrophages bind to rituximab and release chemicals that lyse the cells. This is called **antibody-dependent cell-mediated cytotoxicity.**

Additionally rituximab attracts some proteins found in the blood that help fight diseases. These are called complement proteins. This joining together allows disruption of the cell's plasma membrane which then causes cell lysis. This is called **complement-dependent cytotoxicity.**

There is some evidence that rituximab may also directly cause the target cells to undergo apoptosis as well as make them more susceptible to chemotherapy.

CD20 is present on normal and cancer cells. However when patients are given their own or transplanted stem cells, they can make new normal B cells (NCI, n.d).

Therapies that Trigger an Immune Response Against Cancer Cells: Rituximab Uses

Rituximab, in combination with chemotherapy, has been approved for the treatment of certain type of non-Hodgkin lymphomas which are CD20 positive. It is also approved for use in chronic lymphocytic leukemia (www.fda.gov, 2010).

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Trigger an Immune Response Against Cancer Cells: Radioimmunotherapy

Example: Tositumomab (Bexxar®) is referred to as a radioactive immunotoxin. It is a combination agent. It is a MoAb that has radioactive iodine attached to it. The MoAb binds to CD20 and then releases the radioactive iodine directly into the cell. The doses of the radioactive iodine are high

enough to kill the cell. Like with rituximab, normal cells are killed also, but patients can create new B cells from stem cells.

This drug is presently used to treat patients with non-Hodgkin lymphoma whose disease no longer responds to rituximab or who have a recurrence after chemotherapy.

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Trigger an Immune Response Against Cancer Cells: Immunotoxins

MoAbs can be used to deliver other toxic molecules also. Examples are antibiotics and chemotherapy.

Example: Gemtuzumab (Mylotarg®) is a MoAb that binds to the protein CD33 that is found on the surface of cancer cells of patients with acute myeloid leukemia (AML). This therapy works in a still different manner. Gemtuzumab causes the plasma cell membrane to bend inside the cell and this allows the MoAb into the cell. Once inside the cell, gemtuzumab releases a cytotoxic antibiotic. This antibiotic causes breaks in the DNA. If the cell cannot repair the breaks, the cell dies.

The website of the National Cancer Institute (http://www.cancer.gov)

Therapies that Target the Immune System: Vaccines

Remember, vaccines are a different type of targeted therapy. They do not act directly on cancer cells. Rather they “target” the immune system. Since they target the whole immune system they are said to “work systemically.” Their goal is to restore or stimulate the body's immune system so it can protect itself from the damage caused by cancer cells. Thus, they are referred to as **biological response modifiers**.

Vaccines are usually made from antigens that are weak, killed, or very similar to the disease causing antigen. The antigen stimulates the body to recognize it as foreign and destroy it. In addition, the body learns to recognize the antigen when it sees it again.

There are two types of cancer vaccines: prophylactic and therapeutic. In the United States, there are three vaccines approved to prevent cancer from developing and one approved for treatment (NCI, n.d, NCI, 2011a, NCI, 2011b).

Therapies that Target the Immune System: Prophylactic Vaccines

Prophylactic cancer vaccines are similar to traditional vaccines. They target infectious agents that have been identified to contribute to the development of cancer. They are based on the antigens that are found on the infectious agents that the immune system can recognize as foreign. The vaccines used in the United States target human papillomavirus (HPV) and hepatitis B virus (HBV).

Gardasil® (manufactured by Merck & Company) and Cervarix (manufactured by GlaxoSmithKline) protect against infection by the human papillomavirus (HPV) types 16 and 18 that cause about 70% of cervical cancer worldwide. They have also been identified as causative agent in some oropharyngeal, vaginal, vulvar and penile cancers.

Hepatitis B vaccine protects against HBV infection. Chronic infection with HBV often leads to liver cancer (NCI, n.d, NCI, 2011a).

Therapies that Target the Immune System: Therapeutic Vaccines

Therapeutic vaccines are more difficult to develop. Cancer cells do have cancer antigens, but they also have normal self-antigens so that the immune system does not recognize the cancer cells as foreign. Sometimes cancer cells even mutate or undergo genetic changes that make them lose the cancer antigens. Additionally, as mentioned before, cancer cells can send messages to turn off cells. One of the messages they send is to turn off the T cells, which are killer cells.

Therapeutic cancer vaccines have to not only stimulate an immune response against a specific target, but they also must be powerful enough to overcome the mechanisms the cancer cell use to protect themselves from attack by the immune system (NCI, 2011a).

Therapies that Target the Immune System: Therapeutic Vaccines Sipuleucel-T

The FDA approved the first therapeutic cancer vaccine in 2010. It is called sipuleucel-T (Provenge®, manufactured by Dendreon). It is a treatment for some men with metatastic prostate cancer. The antigen prostatic acid phosphatase (PAP) is found on most prostate cancer cells. The cells that present this antigen (antigen presenting cells or APCs) can be isolated and grown in culture with a special protein that contains PAP and granulocyte macrophage colony-stimulating factor (GM-CSF). The vaccine is then injected intravenously into the patient. It is thought that the cells that take up the PAP-GM-SF are then able to stimulate the killer cells of the immune system (T cells) to kill the cells that express PAP.

The vaccine is manufactured individually for each patient. Leukapheresis is required before each dose can be manufactured in order to obtain the patient cells. Patients usually receive three treatments at two week intervals (NCI, 2011a, www.provenge.com).

Summary

This has been an overview of targeted cancer therapies. Many other specific targeted cancer therapies that have been approved can be found at resources such as http://cancer.gov/cancertopics/factsheet?Therapy/targeted.

Researchers are experimenting every day to identify molecules and pathways that they think may make a good target. They first experiment on cancer cells. If they see any promising results indicating that the therapy can slow or stop cancer's progress without destroying too many normal cells, they will test the therapy in animal models. If results still look positive, scientists can test the drug in the appropriate patient populations. Right now, there are targeted therapies in all different phases of clinical study.

As more patients are diagnosed with cancer and as patients live longer, primary care and other health care providers will be more and more involved with the care of these patients. Targeted therapies are generally better tolerated than chemotherapy, but do have their own undesirable effects. Therefore an understanding of their side effects and other toxicities is important for optimum patient management. Management of some of these side effects that may be seen by non-oncology health care providers will be discussed next.

Management Recommendations: Epidermal Growth Factor Receptor (EGFR) Inhibition

In addition to binding to EGFR receptor sites on cancer cells, EGFR inhibitors also bind to receptors on the surface of normal skin cells and lining of the digestive tract. This may result in many dermatological and gastrointestinal (GI) side effects.

Perhaps one of the more distressing reactions patients have is the development of a dry, erythematous, papulopustular skin rash. Incidence of rash is as high as 85%. The rash is usually mild to moderate in intensity, is self-limiting, and usually resolves without scarring after the EGRF therapy is stopped.

However, 5- 17% of patients will develop a severe, grade 3 or 4, rash. The rash can cause significant pain and pruritis and makes the skin more susceptible to infections which can be serious. The rash usually occurs on the face, upper back, chest and dorsal arms. It can lead to poor patient compliance and/or dose reductions. Interestingly, presence and severity of the rash have been correlated to increased disease responsiveness to treatment. Sometimes knowing this makes it easier for the patients to tolerate the rash (Eaby, 2009, Melosky , Burkes, Rayson, Alcindor, Shear, & Lacouture, 2009).

EGFR Rash

Patients with grade 3 acneiform rash, showing dense pustules with diffuse erythema on the scalp (A) and center of the face (B, C).

Patients with grade 3 acneiform rash, showing dense pustules with diffuse erythema on the scalp (A) and center of the face (B, C) (Scope A et al. JCO 2007;25:5390-5396) (©2007 by American Society of Clinical Oncology).

EGFR Rash (Cont.)

Also, it is important to make sure patients know that the terms ***acneiform*** or acne-like that are used to describe this rash are misleading. These rashes are not like acne and should not be treated as such. Acne treatments are drying and can increase burning and irritation.

Less Frequent Dermatologic Side Effects

Less frequent side effects that may result from EGFR inhibition include such things as xerosis (dry skin), paronychia, hair changes (hirutism, trichomegaly, and alopecia), and hand and foot reactions.

Paronychia are infections along the edges of nails. The finger or toe becomes painful, red and swollen. Fissures are often present. Paronychia usually do not appear until 2-3 months after initiation of therapy. Patients need to keep their nails clean, dry, and filed. If a paronychia appears, soaking the area 2-3 times a day in warm water and then applying an over the counter antibiotic and anti-fungal cream may be all that is needed. If topical agents do not work, oral antibiotics should be used. If the paronychia is still not resolved and appears painful and infected, a nail avulsion (removal of nail) may

be needed. “Skin glue”, a medical grade or liquid Band-Aid, may seal the fissures and provide some comfort (Eaby, 2009, Hirsh, 2011, Lacouture & Melosky, 2007).

Other Less Frequent Dermatologic Effects: HFSR

Hand- foot skin reactions (HFSR) may be referred to as hand-foot syndrome (HFS). These are seen commonly in patients taking drugs that target not only EGFR but other kinase inhibitors such as VEGF and c-KIT as well as multi-targeted kinase inhibitors [MKIs]). This rash appears as erythematous, tender scaling lesions with or without blisters. Dysesthesias (abnormal sensations in the presence of stimuli) and parethesias (abnormal sensations in the absence of stimuli) are often present.

Patients should be taught proactive strategies to prevent/decrease the symptoms:

- Avoid hot showers and hot water when washing dishes. Avoid massaging feet and hands.
- Never walk barefoot.
- Make sure foot wear fits properly and is not too tight, wear shoes with padded or gel inserts and thick socks.
- Wear thick gloves.
- Do not do everyday tasks that cause friction on the skin nor partake in vigorous exercises that stress the hands and feet.
- Use urea containing creams or lotions for removal of areas of thickened, callused skin.

(Eaby, 2009, Hirsh, 2011, Lacouture & Melosky, 2007)

Other Less Frequent Dermatologic Effects: Trichomegaly

Trichomegaly is excessive eyelash growth. The eyelashes are often thick and curly. Trichomegaly can obscure vision and cause eyelid irritation. Eyelash trimming is all the treatment that is needed in most cases. If eye irritation occurs, patient should be referred to an ophthalmologist.

Braiteh F et al. JCO 2008;26:3460-3462

Management of EGFR GI & ElectrolyteToxicities

Diarrhea is the second most common side effect caused by EGFRs. Up to half of the patients taking these drugs will experience diarrhea. Patients need to be taught not to ignore the symptoms as the diarrhea can usually be managed effectively if treatment is started early. Diarrhea can usually be managed with dietary changes and oral anti -diarrhea medications such as loperimide. Teaching patients to remain well hydrated is also necessary to avoid hospitalizations for dehydration and electrolyte imbalances.

Electrolyte depletion may also be seen with these agents, particularly hypomagnesemia. Patients should be periodically monitored for hypomagnesemia, hypocalcemia and hypokalemia during and for at least 8 weeks after therapy (Hirsh, 2011, Gerber, 2008).

Management of Cardiac Dysfunction Related to the Inhibition of the HER2 Receptor: Heart Failure

Trastuzumab is a monoclonal antibody that targets the HER2 receptor. When these receptors are activated they signal for increased cell proliferation and prevention of apoptosis. The receptors are also found on myocardial cells. When the HER2 myocardial receptors are blocked, the signals for cell growth and protection from apoptosis are blocked and cardiac dysfunction, in the form of CHF or decreased left ventricular ejection fraction, may ensue. The risk of heart damage is between 5 and 30%.

Initially, patients should have cardiac echocardiogram or MUGA scans every few months. In addition, patients need to be taught to call their doctor immediately if they develop any signs of congestive heart failure such as shortness of breath, a fast or irregular heartbeat, difficulty breathing or new onset swelling in their lower extremities.

The cardiac dysfunction induced by trastuzumab generally reverses when therapy is discontinued (Fadol, 2011a).

Management of Cardiac Dysfunction Related to the Inhibition of the HER2 Receptor: Prolonged QT

The oral TKI lapatinab can cause prolongation of the QT interval. Prolongation of the QT interval is a warning signal for the development of ventricular tachycardias such as Torsades de pointes and is considered to be a risk factor for sudden death.

Patients at higher risk for QT prolongation are women; the elderly; those using concomitant drugs that may increase the QT interval (e.g., SSRIs, antiemetics, antifungals); patients with preexisting heart failure; and patients receiving drugs that might cause electrolyte imbalances such as diuretics.

The QT interval is measured from the beginning of the QRS to the end of the T wave. If there is an increased QT interval in a symptomatic patient, the offending drug should be stopped immediately (Fadol & Lech, 2011).

Management Recommendations: Angiogenesis Inhibitors: Hypertension

One of the most common side effects of angiogenesis inhibitors is hypertension (HTN). It is felt that these agents reduce nitric oxide production resulting in vasoconstriction. Depending on the agent, 20-40% of patients will experience some degree of HTN; although only 5 -18% will experience grade 3-4 HTN.

Patients with a history of hypertension or risk factors for hypertension (e.g., obesity, inactivity, increased sodium or alcohol intake, or taking medications such as anti-inflammatory drugs, corticosteroids, oral contraceptives or decongestants) will be at increased risk for this adverse effect.

Patients blood pressure needs to be monitored every 2-3 weeks. HTN can usually be managed with oral antihypertensives. The dosage needs to be increased if the hypertension worsens. If HTN cannot be controlled, the drug needs to be stopped. HTN may persist after discontinuation of the drug so blood pressure needs to be monitored at regular intervals.

Patients also need to be taught to incorporate healthy lifestyle changes into their daily activities (Dell, 2009, Genetech, 2010).

Management Recommendations: Angiogenesis Inhibitors: Proteinuria

Proteinuria is a less common side effect of anti-angiogenesis therapy. It occurs because the Inhibition of VEGF has been shown to impair glomerular function. Nephrotic syndrome occurs in < 1% of patients, but it can be fatal (Genentech, 2010).

Urine dipsticks to detect proteinuria are used to monitor patients. If the protein level > 2+, a 24 hour urine collection should be obtained. If > 2 g per 24 hours proteinuria is present, the drug should be withheld until proteinuria is <2 g per 24 hours (Dell, 2009, Genentech, 2010).

Management Recommendations: Angiogenesis Inhibitors: Bleeding, GI Perforations, and Thromboembolic Events

Bleeding is a common side effect of this class of therapy. Bleeding can range from minor epistaxis (that can be managed by applying pressure) that occurs in about one third of patients to massive, fatal hemoptysis, GI bleeding, or CNS hemorrhage.

Minor bleeding is that which lasts less than 10 minutes and does not require medical intervention. If the bleeding lasts longer or if the patient feels dizzy or faint, they need to know to call their healthcare provider.

Gastrointestinal perforation has been reported in 2-3% of patients. Patients need to report abdominal pain, nausea, vomiting, constipation and/or fever. Emergency surgery may be needed.

Patients who undergo surgery while on an angiogenic inhibitor have a greater incidence of wound healing problems as the tissue needs to make new blood vessels in order to heal. It is suggested that angiogenic inhibitors be suspended for 28 days before elective surgery and not restarted until 28 days after surgery and the wound is fully healed.

Both arterial and venous thrombosis occur more often in these patients. Patients need to report angina, TIAs, and other signs of an impending heart attack or stroke as well as those of a DVT and PE (Dell, 2009, Genetic, 2010).

Monoclonal Antibodies & Infusion Reactions

Monoclonal antibodies are derived from human and mouse combinations.

- Murine: derived from mouse antibody, name will end in -momab
- Chimeric: derived from a combination of mouse and human antibodies, name will end in -ximab
- Humanized: derived mostly from human antibody but contains a small amount of mouse antibody, name will end in -momab
- Human: derived only from human antibodies, name will end in –umab

Nurses administering MoAbs need to be aware of the risk of infusion reactions. The more mouse

content the MoAb has, the more risk there is. These reactions usually occur with the first or second dose. Most are mild and not life threatening, but fatal anaphylaxis can occur. Those administering these agents need to pre-medicate patients at risk and standing orders should be in place to deal with emergencies (Polovich et al., 2009).

Summary

Targeted therapies for cancer have resulted in better patient outcomes in many types of cancer. In order to maximize treatment benefits by minimizing any dose reductions or delays in treatment, it is essential that health professionals are aware of specific side effects and initiate preventive and supportive care measures.

Nurses also need to be cognizant of the fact that most of the small molecule inhibitors are oral drugs that are taken at home on a long term basis. In many cases, cancer has become a chronic disease. Assessing patient adherence to oral cancer treatments needs to be a part of every visit.

Additionally, patients need to undergo periodic regular medication reviews. This is especially important for those on small molecule inhibitors as they are metabolized by cytochrome P450 enzymes. Many medications patients may be on for comorbid conditions are also potentially metabolized by cytochrome P450 enzymes and dose modifications may be necessary (Gerber, 2008).

NCI GRADING	DESCRIPTION	SUGGESTED TREATMENTS
1	Papules or pustules on<10% body, +/- symptoms (tenderness, irritation, burning, itching), does not interfere with ADL	Use hypoallergenic, alcohol free, fragrance free, mild products to clean & moisturize (e.g., Dermablend ® makeup can be used) Moisturize at least 2 x a day No long hot showers, tepid baths are preferred Use sunscreen May use 2% clindamycin & 1% hydrocortisone in lotion base 2 x day Stay hydrated May use cool compresses and/or antihistamines
2	Papules, pustules or both covering 10-30% body, +/- symptoms Associated with psychological impact and limits instrumental ADL	Above + minocyline or doxycylcline for at least 4 weeks and until rash is grade 1
3	Papules, pustules or both covering >30% body, +/- symptoms, Limits ADL, associated with local superinfection	Above + withhold treatment until improvement to grade 1 or 2 May add oral corticosteroid
4	Papules or pustules or both covering any % of body, +/- symptoms, extensive superinfections	Intravenous antibiotics Discontinue drug

	Life threatening	

Hirsh 2011, Melosky, et al,2009, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Conclusion

In this course, you learned:
Targeted cancer therapies are quickly evolving and revolutionizing treatment of the patient with cancer. Care is becoming more personalized or individualized. Scientists have always known that "one size does fit all," but now highly targeted diagnostic and therapeutic regimes are leading to the creation of treatments that are more effective in delaying disease progression, stopping the disease and in some cases even preventing the disease and improving the quality of life.

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