Nursing Management of Patients Receiving EGFR Inhibitors

What are EGFR Inhibitors?

Treatments for cancer have traditionally focused on chemotherapy agents that damage DNA within a cell at various stages of cell development, resulting in cell death. Chemotherapy agents are associated with toxic side effects, often limiting their use and causing patients great discomfort. Over the past five years, we have seen the emergence of targeted therapies on to the oncology scene. These new cancer treatments can inhibit interactions occurring on the cell surface, or inside of, cancer cells, resulting in the blockage of essential biologic pathways and ultimately cell death. They can focus on different targets, such as blocking receptors on the cell surface or interfering with integral intracellular pathways. Some drugs are multi-targeted, meaning they can block multiple targets to work against cancer cell proliferation. A major class of targeted agents is the Epidermal Growth Factor Receptor (EGFR) inhibitors.

These drugs target the EGF receptor, also known as the HER-1 receptor. Scientists have identified a group of protein receptors on cells, known as the HER family, which includes HER-1, HER-2 neu, HER-3, and HER-4. HER-1 (EGFR) is over expressed in many cancers, HER-2 neu can be over expressed in breast cancer, and not much is known thus far about HER-3 and HER-4. On normal cells, these receptors are only expressed at low levels; however, they can be over expressed in cancer cells. When activated by the binding of ligands to the receptor on the cell, downstream signaling occurs. Downstream signaling refers to the process in which a cancer cell communicates actions to result in uncontrolled proliferation, inhibition of apoptosis (planned, necessary cell death), and secretion of vascular endothelial growth factor (VEGF, a substance which recruits a new blood supply). These reactions result in the growth and metastasis of cancer cells.

EGFR inhibitors can work in different ways. Some are formulated as small molecules, meaning that they bind with the EGF receptor on the cell to gain entrance into the cell, and then block downstream signaling at another level. An example of this is the EGFR-Tyrosine Kinase Inhibitors (EGFR-TKI's). They block EGFR activity at the tyrosine kinase domain found just inside the cell. Other EGFR inhibitors are larger molecules, such as monoclonal antibodies. These drugs bind with the actual EGF receptor on the cell surface, preventing the ligand from binding at all. Thus, no downstream signaling can occur. These complicated processes are the foundation for the efficacy of targeted therapies in the fight against cancer.

What are the available EGFR Inhibitors?

The first EGFR-TKI to be approved in the United States in 2003 was gefitinib (Iressa). It was approved for use in metastatic non-small cell lung cancer (NSCLC) after the failure of a platinum-based regimen of chemotherapy, based on phase II data showing some good responses. However, gefitinib was removed from the market in 2004 based on phase III data that showed that gefitinib did not show a statically significant survival over placebo in all-comers with NSCLC. The drug can now only be used in patients who have shown clinical or radiographic benefit from the drug in the past.

Erlotinib (Tarceva) is also an EGFR-TKI approved for the second or third-line use after the failure of a platinum-based chemotherapy regimen in metastatic NSCLC. This received approval in 2004 based on the BR21 trial, showing a modest benefit when used in patients with NSCLC. Patients on erlotinib had a 6.7 month average survival, while only 4.7 months on placebo. At the initiation of the BR21 trial, there was no FDA approved standard treatment for the 2 nd or 3 rd line treatment of NSCLC, and therefore, a placebo control arm was necessary and ethical. The study was randomized at a 2:1 ratio, in favor of receiving the drug based on the idea that the drug did show responses in phase II studies. Also notable about the BR21 trial is that it allowed for patients with an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of up to 3, which is defined as a patient who is in bed more than 50% of the day, but not bedridden and performs limited self care. Many clinical trials limit enrollment to a PS of 2 or less, however, because this study wanted to get a good overall picture of end stage lung cancer patients, it included patients with a PS of 3 or less.

Erlotinib also later gained approval in combination with gemcitabine chemotherapy for the frontline treatment of advanced pancreatic cancer. The PA3 trial showed a slight, but statistically significant survival advantage by adding erlotinib to gemcitabine. It is the first drug, since gemcitabine, to show a survival advantage in pancreatic cancer patients, despite numerous clinical trials of many other agents.

The next EGFR inhibitor to gain approval was cetuximab (Erbitux), a monoclonal antibody given intravenously (IV) as opposed to the EGFR-TKI's, which are orally administered. In 2004, cetuximab was approved for use in colorectal cancer either as monotherapy, or in combination with irinotecan chemotherapy. Initially, practitioners had to prove that the tumor over-expressed EGFR by performing FISH (Fluorescent in situ hybridization) testing of the cancer cells, however, this practice is no longer necessary for administration. The original trial enrolled patients who had become refractory to irinotecan alone, and compared cetuximab and irinotecan together versus cetuximab alone. In the combination arm, 22.9% of patients achieved tumor shrinkage, lasting about 4 months. Patients in the cetuximab monotherapy arm achieved response rates of 10.8%.

Cetuximab received approval in 2006 for the treatment of squamous cell carcinoma of the head and neck (SCCHN), in combination with radiation. It was also approved for metastatic or recurrent SCCHN refractory to cisplatin-based chemotherapy. The cetuximab plus radiation trial showed a 20 month median survival advantage over radiation alone. In the study of cetuximab monotherapy, approval was based on a 13% tumor shrinkage rate and a 6 month progression free survival. A phase III randomized study was presented at ASCO (American Society of Clinical Oncology) 2007, demonstrating patients with metastatic or recurrent SCCHN had a significant survival benefit when using cetuximab in addition to first line standard chemotherapy.

Panitumumab (Vectibix), a fully human EGFR monoclonal antibody, received FDA approval in 2006 for single agent use in metastatic colorectal cancer, for patients who have failed multiple lines of chemotherapy. The approval was based on a study of over 400 patients receiving panitumumab, showing that they had an improvement in time to disease progression over best supportive care and an 8% tumor shrinkage rate.

The most recent drug in this category to gain FDA approval is lapatinib (Tykerb) in the treatment of HER2 over expressing breast cancer. This drug is a multi-targeted oral agent, which targets the EGFR-TK domain as well as the EGFR2 (also known as the HER2) receptors. It is approved for use in combination with capecitabine (Xeloda) for trastuzumab (Herceptin) refractory patients. When studied in a randomized clinical trial, the lapatinib arm showed an improvement in time to progression and improved response rates.

There are many other multi-targeted agents approved, or in active research studies, which look to inhibit other receptors on cancer cells. The EGFR class of drugs has become a mainstay in the treatment of many common cancers, and targeted agents are certainly the foundation for the future of cancer treatment. They also provide for a less toxic treatment regimen, allowing patients to have a chance of receiving the optimal doses over longer periods of time. Nurses will continue to see more of these targeted agents approved, either alone, or in addition to chemotherapy or radiotherapy, causing new side effect profiles that will need to be monitored.

What are the side effects EGFR Inhibitors?

While the targeted agents are desirable because they do not exhibit many of the traditional toxic chemotherapy side effects, they carry their own unique side effects, many of which are new to oncology nurses. The EGFR inhibitors are most commonly associated with a distinctive rash, occurring mostly on the face. They can also cause diarrhea, infusion reactions, inflammatory lung disease, hair and nail changes, dry skin, and some changes in lab values. While these side effects are usually quite manageable, they can be quite severe and affect quality of life.

Rash

EGFR inhibitors are known for the ability to cause a dry, erythematous, papulo-pustular eruption occurring on the face, neck, chest, back, and sometimes the trunk and limbs. It can occur in up to 85% of patients receiving these drugs. But the more severe, grade 3 or 4 rash occurred in only 9% of patients in the erlotinib BR21 study and 17% of head and neck patients receiving cetuximab with radiation. Rash was the most common reason in these two studies for patients to require dose reductions or delays. Grade 3 or 4 rash was seen in 5.2% of colorectal cancer patients in the cetuximab monotherapy study. While the rash may be concerning to patients, it is important to note that development of the rash and the severity of the rash were associated with the presence of a response to the EGFR treatment in the BR21 trial. For this reason, management of the

EGFR rash has become an important initiative in oncology nursing.

The pathobiology of this rash is not well understood. EGF receptors are expressed in keratinocytes and sebaceous glands, located in the many layers of the epidermis. When giving drugs to block EGFR, it is thought that there is an alteration in normal replication and secretion, causing the papulopustular reaction to occur. Skin samples taken in erlotinib studies showed inflammatory infiltrates and follicular rupture.

Assessment of the rash is according to grading scales. The most common grading scale is the NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) grading scale. This scale was developed and is revised periodically by oncology experts to grade toxicities and side effects of cancer drugs used in clinical trials. The grades are meant to guide the use of the drugs, including any necessary dose reductions. The scale uses grades 1-4, with grade 1 being minor toxicity, not affecting daily functioning, to grade 4, which is considered life threatening and usually requires the drug to be stopped. An alternate grading scale was devised to create an easy to use scale for oncologists to grade and treat this rash. The scale utilizes a mild, moderate, and severe grading scale. Either grading scale is appropriate to use to describe this rash, but should be used uniformly within your institution.

Treatment of the rash caused by EGFR inhibitors is an area in need of nursing support and research. So far, there has not been any successful published research supporting a proven treatment algorithm. This is partly due to the fact that you would have to conduct a randomized trial with a control arm. Because skin types differ, the control arm would ideally be on the same subject. This would require using half of the face for the treatment arm and withholding the treatment to the other half of the face. This strategy has been attempted in clinical trials, but has been unsuccessful due to poor patient compliance and low enrollment. There is also no validated quality of life tool available to accurately measure the impact of rash on quality of life for a cancer patient, though one is currently under development and validation.

A couple of treatment algorithms have been published based on best practice models. One is an algorithm derived from the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and KinaseS) clinic at Northwestern University, headed up by Dr. Mario Lacouture. This clinic has devoted its time to studying and treating the EGFR inhibitor rash. This algorithm suggests the use of oral tetracyclines at the start of the rash and adding topical agents such as clindamycin gels or pimecrolimus cream. Another treatment algorithm published in *The Oncologist* in 2006 recommends a stepwise approach based on the grading of the rash. For instance, if the nurse or practitioner considers the rash mild, then you would start with topical steroids, clindamycin gel, or nothing at all if the patient is not bothered by it. If the rash is moderate, adding in oral tetracyclines and/or pimecrolimus cream. Then, if the rash worsens or presents as severe, dose reduction coupled with the addition of steroids is the recommended treatment.

It is important to remember that neither of these treatment algorithms have been validated or tested in a randomized setting, and that they were developed by oncology and dermatology health care professionals looking to help others manage the rash in order for patients to maintain quality of life while on these medications. There was a small study presented at ASCO 2007, looking at giving pre-emptive oral tetracycline to hopefully reduce rash development. Results showed that up front tetracycline did not reduce the development of the rash, however, it did show that the rash was less severe in patients who were on the treatment arm at 4 weeks. Other initiatives being studied are the use of topical Vitamin K, various creams and cleansers to improve EGFR rash management. The rash continues to be an area of concern and discomfort for patients, and with more targeted therapies in development, this will continue to be an important subject for toxicity management.

Diarrhea

Diarrhea is the second most common side effect noted in clinical trials with EGFR-TKI's. The grading of diarrhea also uses grades 1 through 4, with grades 1 and 2 meaning that a patient has an increase in stools of 1-6 per day but not interfering with activities of daily living (ADL's). Grades 3 and 4 are associated with requiring intravenous fluids, hospitalization, or causing interference with ADL's. Diarrhea occurred in 55% of patients taking erlotinib in the BR21 trial, but only 6% encountered grade 3 or 4 diarrhea.

The diarrhea is typically manageable with diet changes and oral anti-diarrhea medications. Most commonly practitioners will try over the counter medications such as loperamide first, and if that is not enough, prescribing Lomotil® (diphenoxylate/atropine) will generally alleviate symptoms.

Hypersensitivity

Hypersensitivity reactions are most common with the monoclonal antibodies (cetuximab and panitumumab). However, since panitumumab is a fully human antibody, there are fewer, if any hypersensitivity reactions. With cetuximab, this reaction occurs because it is a part human and part mouse antibody. Because it can look like a foreign protein to the body's immune system, the body sometimes responds with a hypersensitivity reaction. The reaction is rare, with only 4 out of 211 patients (1.9%) in the Bonner, et al, head and neck cancer cetuximab study having to discontinue cetuximab due to severe hypersensitivity. This was slightly higher (3.5%) in the Cunningham, et al, cetuximab trial of colorectal cancer patients. Treatment of the reaction consists of pre-medicating with antihistamines, and if a reaction occurs, stopping the drug and following standard anaphylaxis procedure.

Interstitial Lung Disease (ILD)

ILD is rare, but can occur with the EGFR-TKI agents. It is characterized as a rapid onset of shortness of breath or nagging cough, and some patients will have pneumonitis or pulmonary fibrosis seen on a chest CT scan. There have been a couple of case reports of ILD with cetuximab, but none reported in the clinical trials of the drug. For the EGFR-TKI's the incidence was most common in Japanese trials, with an incidence of up to 4%, however, in the US trials it has remained around 1-2%. In the BR21 erlotinib trial, there was not a statistically significant difference in ILD between the treatment and placebo arm. Treatment is centered on stopping the drug and treating with steroids, sometimes requiring hospitalization.

Hair and Nail Changes

Alopecia can be associated with long-term use of the EGFR-TKI's. Usually it is not full alopecia, but a thinning. Pustular lesions or flaking skin on the scalp can occur. Using a selenium-based shampoo and systemic tetracyclines are a good option to ameliorate these side effects. Hypertrichosis, described as thick and curly eyelashes, can result after long term use of EGFR-TKI's. If let go for too long, they can irritate the cornea. To avoid irritation, keep them trimmed and do not bleach or pluck them.

Paronychias can form on the fingernails and toenails, manifesting as painful erythema and pus around the nail beds. Treatment may involve topical antibiotic or antifungals, warm soaks, or if nothing is helping, possibly nail avulsion (removal of the nail).

Dry Skin

Pruritis is also associated with short and long term use of EGFR-TKI's. Generally dry skin comes with EGFR-TKI use, mostly on the face in the short term. After longer-term use (greater than 3-6 months), it can occur over the whole body. Itching and flaking can occur. Treatment with creams and lotions is recommended and adding oral antihistamines may help with itching.

Lab Value Changes

The EGFR inhibitors can affect lab values. Cetuximab can cause low magnesium levels. Erlotinib can cause elevations in liver function tests. There is a possibility of renal dysfunction with both the EGFR monoclonal antibodies and EGFR-TKI's. Lab values should be monitored while on EGFR therapy.

Nursing considerations for patients receiving EGFR Inhibitors

Nurses treating patients with EGFR inhibitors are found in various clinical settings, affecting their role in side effect management. If a patient is receiving an EGFR-TKI, which are all currently orally administered, the nurse may be managing side effects over the phone or in the clinic area with the physician. Nurses will need to become comfortable evaluating and managing this side effect via telephone. Conversely, if a patient is on an EGFR monoclonal antibody, then the infusion room nurse may have more contact with the patients and bear responsibility for teaching them about side effects.

Nurses need to assess the patient's ability to take an orally administered agent. For example, patients must be able to read the labels and remember to take the drug at the same time each day. Compliance can be an issue, so remind the patient that they may need to set up a pillbox or another method to remember to take the dose each day.

For the rash, nurses should make sure that orally administered agents are being taken on an empty stomach. Food increases bioavailability of the drug, therefore increasing side effects. Patients should be reminded to moisturize their skin and use a sunscreen when being exposed to sunlight. Nurses should remind patients that the rash is not an allergic reaction, but instead, an expected side effect of the drug and to notify the nurse or doctor if the rash is uncomfortable or affects activities of daily living. If a patient calls to report diarrhea, they should be asked about frequency and consistency and oral fluid intake. Age is an important factor, as elderly patients may become dehydrated much quicker, requiring IV fluid hydration. Patients should be taught to use over-the-counter anti-diarrheal medication, but understand that if that is not working, to call the office. Also,

avoiding foods high in fiber and following a bland diet with breads and rices can prevent or lessen diarrhea.

If you are infusing a monoclonal antibody, premedication with antihistamines should be ordered. If an anaphylactic infusion reaction occurs, the drug should be stopped and treatment would include steroids and antihistamines based on your hospital or office protocol. Less commonly, but still important, is assessing for ILD. If a patient reports new onset shortness of breath then pneumonia, pulmonary embolism, and ILD (if on an EGFR-TKI) should be considered. Lab values should be part of the monitoring process and checked regularly while on treatment.

With the many new targeted agents used in treating cancer, nurses must be aware of the unique and ever changing side effects associated with the EGFR inhibitors. The role of nursing is also changing with these drugs, focusing more on dermatologic effects rather than hematologic effects. Nurses play an integral role by staying up to date with side effect management for both oral and intravenous agents.
