

Side Effects of Targeted Molecular Agents Vary According to Mechanism of Action

By Sarah Bronson

The main side effects of cytotoxic chemotherapy are notorious. But the side effects of newer, targeted molecular agents are less well known, so patients receiving such drugs may not know what to expect and may require additional guidance from physicians.

Targeted molecular therapy is designed to disrupt oncogenic signaling pathways while leaving normal functions intact and has improved the treatment of many types of cancer. However, targeted agents frequently interfere with pathways necessary for the growth of normal cells as well as cancer cells, leading to “off-target” effects. Most of these toxic effects differ in character from those of conventional cytotoxic drugs.

Many widely used targeted drugs share common side effects. Among the most frequently seen side effects are fatigue and rashes, which can result from a wide range of targeted drugs. Gastrointestinal effects, especially diarrhea, and mouth sores, often in the form of stomatitis or mucositis, are also typical with many targeted drugs. Diarrhea occurs in a large proportion of patients treated with epidermal growth factor receptor (EGFR) inhibitors or agents that inhibit multiple tyrosine kinases. Mouth sores appear in a substantial proportion of patients treated with EGFR inhibitors, mammalian target of rapamycin (mTOR) inhibitors, or agents that inhibit multiple tyrosine kinases.



A papulopustular rash is seen on a patient undergoing cancer treatment with an epidermal growth factor receptor inhibitor. Image courtesy of Dr. Anisha B. Patel.

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Side Effects of Targeted Molecular Agents

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Although some side effects are shared by many targeted agents, each type of targeted drug is associated with specific side effects. Sunil Patel, M.D., an assistant professor in the Department of General Oncology at The University of Texas MD Anderson Cancer Center, said, “Now more than ever, the toxicity profile of a targeted drug can be predicted depending on the class of drug and its mechanism of action.”

EGFR inhibitors and dermatological effects

Most patients receiving EGFR inhibitors (including cetuximab, panitumumab, gefitinib, erlotinib, and lapatinib) will experience similar adverse effects in the skin. Red acneiform papules and pustules, sometimes with pain and itching, are typical in these patients and usually appear on the scalp, face, and upper trunk.

In patients who have rashes associated with EGFR inhibitors, the affected skin may develop secondary infections. Infections also may develop around the nails of these patients (paronychia).

Grade 1 or 2 rashes are usually treated with topical corticosteroids and topical or oral antibiotics; more severe rashes can be treated with antibiotics, systemic corticosteroids, or isotretinoin. If needed, the EGFR inhibitor dose can be modified. Adequate management of these dermatological side effects can significantly improve quality of life and treatment adherence in patients who receive these drugs.

Antiangiogenic drugs and cardiovascular effects

Another class of drugs with distinct side effects is the targeted antiangiogenic agents, such as the vascular endothelial growth factor (VEGF) inhibitors bevacizumab and aflibercept and the VEGF-targeting multiple tyrosine kinase inhibitors sunitinib, sorafenib, axitinib, cabozantinib, pazopanib, ponatinib, and vandetanib.

Antiangiogenic drugs share a potential for cardiovascular side effects, the most common of which is hypertension. In addition, bevacizumab and some of



Von Frey filaments, which measure sensitivity to touch, are among the tools used to assess neuropathy in a former cancer patient during a follow-up visit. Neuropathy is a common side effect of some targeted molecular agents as well as several cytotoxic chemotherapy drugs.

the tyrosine kinase inhibitors increase the risk of arterial thromboembolic events. Sunitinib and pazopanib can decrease the left ventricular ejection fraction, and vandetanib can significantly prolong the QTc interval.

Because some of the cardiovascular effects associated with angiogenesis inhibitors are potentially serious and even life threatening, patients who receive these drugs should be carefully selected and monitored. Preexisting cardiovascular conditions such as hypertension should be treated before patients receive antiangiogenic agents, and high-risk candidates—such as patients who have previously experienced arterial thromboembolic events—can receive prophylactic treatments such as anticoagulants.

Effects in other classes of targeted agents

Also linked to cardiotoxicity are human epidermal growth factor receptor 2 (HER2) inhibitors. In particular, the HER2 inhibitor trastuzumab carries a modest risk of decreased left ventricular ejection fraction and a small risk of heart failure.

Patients treated with mTOR inhibitors such as everolimus can develop elevations in blood sugar and, as mentioned above, often experience mouth sores as well as fatigue. Pneumonitis is another potential toxic effect of mTOR inhibitors.

Managing side effects

The toxic effects from targeted drugs are managed in the same way as those from cytotoxic drugs. Low-grade toxic effects that do not limit a patient's daily life or threaten his or her health can be managed with basic interventions. For

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– Dr. Sunil Patel

example, diarrhea can be treated with loperamide, deodorized tincture of opium, or octreotide. Higher-grade effects, however, can require a reduction in the targeted agent's dose or, in some cases, a break in therapy.

In patients with preexisting comorbidities, certain toxic effects need to be anticipated. Depending on a patient's baseline physical status and the planned treatment, specific conditions may need to be managed before treatment begins. For example, if echocardiography shows that a patient has a high risk of heart failure, then that patient needs to begin treatment with medications to optimize his or her cardiac function before starting a targeted drug that could cause cardiotoxicity.

The combined influence of comorbidities and toxic effects may influence which drugs are chosen to treat a patient's cancer. Similarly, the toxic effects from other modalities of treatment may overlap with those of targeted therapy and should be planned for.

Because most targeted drugs have

existed for only a few years, researchers lack data on the long-term toxic effects of these drugs. In general, however, the toxic effects subside when treatment with the targeted drug comes to an end. An exception is peripheral neuropathy, which is associated with the use of certain targeted drugs, such as the protease inhibitor bortezomib, as well as with several cytotoxic drugs. While most cases of drug-related neuropathy resolve or improve over time, neuropathy may linger 6–12 months after the end of treatment or become a lifelong issue. Chronic neuropathy can be managed with physical therapy, analgesic creams, non-steroidal anti-inflammatory drugs, and opioids but cannot be reversed.

Different approach, different effects

Although some side effects, such as neuropathy and fatigue, can be caused by targeted or cytotoxic drugs, the differences between the toxicity profiles of targeted drugs and cytotoxic agents

“[T]hese effects aren't necessarily less than those of cytotoxic drugs; targeted therapy just has a different side effect profile.”

– Dr. Charles Cleeland

can have clinical implications.

For patients who have experienced cytotoxic chemotherapy before but are new to targeted therapy, some of the differences may be unexpected. For instance, although cytotoxic agents will often decrease white blood cell counts, some targeted drugs have no effect on blood counts. For this reason, infection risk is less of a concern during treatment with some targeted drugs than with cytotoxic drugs.

In contrast, the side effects from

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IN BRIEF

Study Finds Less Frequent Bisphosphonate Treatment Equivalent to Standard Regimen

A regimen of less frequent bisphosphonate treatments appears to be just as effective as the standard bisphosphonate regimen in preventing skeletal events in patients with bone metastases from breast cancer after the first year of monthly administration, according to a recent study.

Bisphosphonates such as zoledronic acid reduce the occurrence of skeletal events such as bone pain, osteoporosis, spinal cord compression, and increased calcium levels in patients with bone metastases from breast cancer by limiting the activity of osteoclasts, the cells that break down bone to release calcium. There is also evidence that metastatic breast cancer cells are attracted to areas with active osteoclasts; therefore, limiting osteoclast activity with bisphosphonate treatment may decrease the risk of additional bone metastases.

The standard bisphosphonate treatment regimen for breast cancer patients with bone metastases is monthly intravenous infusions for life. To determine whether this is the optimum dosing schedule for bisphosphonates, a phase III clinical trial called OPTIMIZE-2 was conducted at The University of Texas MD Anderson Cancer Center and other institutions.

In the OPTIMIZE-2 study, 403 women with bone metastases from breast

cancer who had completed 1 year of monthly treatment with zoledronic acid were randomly assigned to continue monthly treatment or receive treatment every 3 months. The study found no significant difference in efficacy between the two treatment arms; skeletal events occurred in 22% of patients treated monthly and 23% of those treated every 3 months.

The results of this trial, which could lead to a change in the standard of care for patients with bone metastases from breast cancer, were presented in June at the Annual Meeting of the American Society of Clinical Oncology by Gabriel Hortobagyi, M.D., a professor in the Department of Breast Medical Oncology. Dr. Hortobagyi said, “In general, in breast cancer we're getting to the point where our patients are doing well enough that we can begin reducing the treatments they receive, as we're likely over-treating the majority of our patients—and this study is an example of that.” ■

“[I]n breast cancer we're getting to the point where our patients are doing well enough that we can begin reducing the treatments they receive.”

– Dr. Gabriel Hortobagyi

RAS Mutation Status May Predict Outcomes After Surgery for Colorectal Cancer Liver Metastases

By Joe Munch

Emerging evidence suggests that *RAS* mutation status in patients with colorectal cancer liver metastases provides valuable prognostic information and helps determine which patients will most likely be cured by aggressive surgery.

“Unlike most other solid tumors, whose more disseminated spread often precludes any chance for a cure, colorectal cancer has a potential for a cure even after it has spread,” said Scott Kopetz, M.D., Ph.D., an associate professor in the Department of Gastrointestinal Medical Oncology at The University of

Texas MD Anderson Cancer Center. “That cure comes with a combination of chemotherapy and surgery to remove the metastatic disease.”

The standard treatment for colorectal cancer is resection of the primary tumor followed by chemotherapy. In patients who have liver metastases, the

response to chemotherapy helps determine whether the patient is a candidate for liver resection to remove the metastases. According to Dr. Kopetz, 10%–20% of patients with colorectal cancer liver metastases may be candidates for the aggressive surgery.

“These surgeries are becoming increasingly safe; they have less morbidity, a lower complication rate, and a shorter postoperative stay than they did even 10 years ago. So there are now fewer barriers to offering the surgery to patients,” Dr. Kopetz said. “But although the risks of these procedures are much lower, the percentage of patients who benefit remains small. We are in need of biomarkers to help determine whether the surgery will result in a cure.”



In patients with colorectal cancer metastases to the liver, RAS mutation status is associated with the risk of recurrence following liver resection, which may be performed laparoscopically (as shown here) or as an open procedure.

A new role for RAS

One such potential biomarker is RAS mutation status. Currently, RAS mutation status is predominantly used to assess the sensitivity of colon cancer to epidermal growth factor receptor inhibitors such as cetuximab and panitumumab; patients with RAS mutations have disease that is resistant to such therapy. However, a spate of recent studies showed that RAS mutations—primarily KRAS and NRAS mutations—also independently predict worse overall and disease-free survival outcomes following resection for colorectal cancer liver metastases.

In one of these studies, which was led by Jean-Nicolas Vauthey, M.D., a professor in and chief of the liver and pancreas section in the Department of Surgical Oncology, researchers investigated the relationship between RAS mutation status and survival outcomes in nearly 200 patients who underwent potentially curative hepatectomy for colorectal cancer liver metastases. They found that RAS mutation status was an independent predictor of overall survival, recurrence-free survival, and lung recurrence-free survival but not liver recurrence-free survival.

“The data suggest that RAS mutations can help us to understand the risk of recurrence and specifically where the cancer is more likely to recur. For instance, a patient with colorectal cancer liver metastases who has a KRAS or NRAS mutation is more likely than a patient without such a mutation to have a recurrence outside the liver, specifically in the lungs,” said Dr. Kopetz, a co-investigator in the study. “This is important because, even after going through a fairly intensive surgery, the majority of patients will still develop a recurrence. We now know that one of the strongest predictors of whether or not there is microscopic disease outside the liver is the KRAS or NRAS mutation status.”

The findings also challenge the wisdom of using only conventional scoring systems to gauge the risk of recurrence in patients with colorectal cancer liver metastases. Developed before the modern chemotherapy era and employing only clinicopathological factors such as the number and size of



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– Dr. Scott Kopetz

metastases, these systems do not consider the biology of the tumor, which varies from patient to patient and has important implications for prognosis. In patients with colorectal cancer liver metastases who are candidates for hepatectomy, RAS mutation status provides additional information about tumor biology to give a clearer picture of each patient’s prognosis.

“Considering RAS mutation status in these patients points to a more individualized approach to determining prognosis,” Dr. Kopetz said.

Further refinement

Although it provides valuable prognostic insight, RAS mutation status alone is not a sufficient determinant of who should or should not undergo surgery for colorectal cancer liver metastases. A patient with a RAS mutation has a lower likelihood of being cured by surgery, but there is no guarantee that surgery would not provide a cure.

The issue, Dr. Kopetz said, is that no matter how good a predictor of outcome RAS—or any biomarker—is, most patients would prefer the risks that come with a potentially curative surgery, even if the chance at a cure offered is miniscule.

“A lot of people would still want the surgery if there’s only a 2% chance of being cured of their terminal disease,” Dr. Kopetz said. “That is a high hurdle for a biomarker; to rule out surgery as an option, you basically have to be able to say that there is no doubt that the cancer would come back after the surgery.”

Until such a biomarker is found, Dr. Kopetz recommends that physicians

continue to refer patients who have colorectal cancer liver metastases to major hepatobiliary surgery centers so they can be considered for hepatectomy.

“Population-based studies suggest that we are missing many patients who could be cured by aggressive surgical intervention, and we need tools that can help us select those patients who are most likely to benefit,” Dr. Kopetz said, “While these biomarkers will help refine that, they are not at the point that they alone would exclude any patient from surgery.”

Still, he said, investigating RAS and other genes to better characterize tumor biology in patients with colorectal cancer liver metastases will help identify a population for whom hepatectomy will likely provide a cure.

“Ultimately, instead of subjecting thousands of patients to aggressive surgery only to see the majority of them develop a recurrence, our goal is to be able to identify those patients who will clearly benefit from the major surgery.” ■

FOR MORE INFORMATION

Dr. Scott Kopetz.....713-792-2828

FURTHER READING

Vauthey JN, Zimmitti G, Kopetz S, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg.* 2013;258:619–626.

HPV Test Does Not Replace Pap Test for Cervical Cancer Screening

By Bryan Tutt

The recent approval of a human papillomavirus (HPV) test for cervical cancer screening has created confusion within the medical community about appropriate screening guidelines.

In April, the U.S. Food and Drug Administration (FDA) approved the cobas HPV test as a stand-alone screening tool for cervical cancer. HPV tests had previously been approved for cervical cancer screening, but only in conjunction with a Papanicolaou (Pap) test.

Unfortunately, some reports of the cobas HPV test's FDA approval have been misleading. "The media reported this as 'the Pap test is dead,'" said Andrea Milbourne, M.D., a professor in the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. "People are getting the wrong impression." As a result of this confusion, many patients and even some practitioners are uncertain about the screening guidelines for cervical cancer.

Current screening guidelines

MD Anderson follows the guidelines for cervical cancer screening established by the American Society for Colposcopy and Cervical Pathology in conjunction with the American Cancer Society and the American Society for Clinical Pathology. For those without known risk factors for cervical cancer, the guidelines recommend:

- Women 21–29 years old undergo screening with a Pap test alone every 3 years.
- Women 30–65 years old undergo a Pap test and an HPV test every 5 years.
- Women older than 65 years or who have had a hysterectomy for benign disease do not require screening.

Abnormal findings on a Pap test may require a second Pap test, an HPV test, or an immediate colposcopy, depending on the grade of the lesion.

Proposed screening algorithm

Dr. Milbourne said that in its application for FDA approval, Roche, the manufacturer of the cobas HPV test, proposed the following screening algorithm:

- Women begin screening with an HPV test alone at age 25 years.
- Women with negative tests are retested in 3 years.
- Women who test positive for HPV-16 or HPV-18—the two most common oncogenic strains of the virus—undergo a colposcopy.
- Women who test positive for any of the other 12 oncogenic HPV strains undergo a Pap test.

This screening algorithm was found to be equivalent to cervical cancer screening by Pap test alone in the clinical study that led to the recent approval of the cobas HPV test. However, several

issues need to be addressed before the new algorithm can replace or be integrated into the current screening guidelines.

Limitations of screening with HPV test only

One concern about the proposed screening algorithm is that the clinical study compared this algorithm to Pap tests alone rather than the combination of Pap tests and HPV tests currently recommended for women 30 years and older.

Another concern is the limited reliability of HPV testing in women younger than 30 years. "The reason we don't routinely test for HPV in women under 30 years old is that almost everyone gets exposed to HPV with their first or second sexual encounter," Dr. Milbourne said. "However, most people in this age group who test positive have transient HPV infections that will resolve without intervention."

Furthermore, according to Dr. Milbourne, HPV testing is often used inappropriately. "Only about 20% of providers use HPV tests according to FDA-approved guidelines," Dr. Milbourne said, citing information discussed at the 2014 Biennial Meeting of the American Society for Colposcopy and Cervical Pathology.

Dr. Milbourne said that some providers are inappropriately recommending HPV tests for women younger than 30 years whose Pap tests show

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"As a triage tool, an HPV test should be done when a Pap test shows atypical squamous cells of undetermined significance."

– Dr. Andrea Milbourne

Advance Directives Make Patients' Wishes Known

Types of advance directives and their functions



Most healthy people don't spend much time thinking about how decisions would be made about their medical care if they were unable to communicate, but there are major benefits to being prepared for such an occurrence.

Considering what kind of medical care you would want if you were unable to make your wishes known and then completing legal documents to record your wishes can provide vital information to your family members and your health care providers.

Making these decisions is never easy, but delaying the process until you are seriously ill can make the task overwhelming. Taking these steps while you are healthy gives you time to consider your options and then discuss your wishes with your loved ones.

Types of advance directives

A written statement about the kinds of medical treatment a person does or does not want in the event he or she is not able to communicate is called an advance directive. Although the laws governing such documents vary from state to state, the most common types of advance directives are living wills, do-not-resuscitate (DNR) orders, and medical powers of attorney.

Living wills

A living will, also known as a directive to physicians and family or surrogates, is a legal document that describes the kinds of medical care, especially life-sustaining care, the patient wants or does not want if he or she becomes terminally ill. A living will takes effect only when the patient is unable to state his or her wishes.

Common issues addressed in a living will are whether the patient wants his or her health care provider to use life-sustaining equipment, such as a dialysis machine or ventilator, and whether the patient wants to receive artificial hydration and nutrition (tube feeding).

Do-not-resuscitate orders

A DNR order is a form signed by the patient and his or her doctor stating that the patient refuses cardiopulmonary resuscitation if his or her heart stops. There are two types of DNR orders. An out-of-hospital DNR order states that a patient who is not hospitalized does not wish to be resuscitated in a clinic or emergency center. Some people with out-of-hospital DNR orders wear bracelets that make this known to emergency personnel. An inpatient DNR order is discussed at the time of hospital admission and is included in the patient's hospital chart.

Without a DNR order, health care providers are obligated to do everything medically possible to attempt to restart a patient's heart if it stops.

Instructions not to resuscitate might also be included in a patient's living will, but unlike a living will, which goes into effect when the patient is unable to make his or her wishes known, a DNR order is in force as soon as it is signed by the patient and doctor.

Medical powers of attorney

A medical power of attorney is an advance directive that lets the patient name another person to make decisions about the patient's medical care if the patient is unable to communicate or make such decisions. The document is also called a health care proxy, durable power of attorney for health care, or appointment of health care agent.

Usually the person chosen to make medical decisions on a patient's behalf is a close relative: a spouse, parent, son, or daughter. However, the patient may choose any adult he or she knows and trusts to be his or her agent. The agent has the same decision-making power the patient would have in agreeing to or refusing medical treatment or life support.

The patient can limit his or her agent's decision-making authority by stipulating in the document his or her specific wishes, such as which medica-

tions or treatments the patient wishes to receive, which doctor the patient wants to be treated by, or which hospitals the patient prefers to be treated in. The agent is obligated to follow these guidelines. While the patient is able to communicate, he or she still has the power to make decisions about his or her own care and can take away the agent's authority at any time, orally or in writing.

Although a medical power of attorney gives decision-making authority to one person, it cannot tell that person what to do in every possible situation. Similarly, while a living will can give the patient's doctors and loved ones an idea of what the patient wants, it does not indicate what should be done in every circumstance. A good option for many people is to set up both a medical power of attorney and a living will. This allows the agent to make medical decisions based on the requests stipulated in the living will.

Preparing an advance directive

Anyone 18 years or older can prepare an advance directive. You can get the appropriate forms from your physician, hospital, or state health department; or you can simply write your wishes down yourself. These directives don't have to be complicated or written by an attorney, but they must comply with the patient's state's laws.

Be sure to discuss your wishes with your family and health care providers, and provide them with copies of your advance directives. If you find it too hard to have this talk, it may help to plan a family meeting and invite a social worker or member of your faith community to help guide the discussion. ■

— K. Stuyck

FOR MORE INFORMATION

- Ask your physician
- Visit www.mdanderson.org
- Call MD Anderson's Department of Social Work at 713-792-6195

Side Effects of Targeted Molecular Agents

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targeted therapy should not always be expected to differ from those of chemotherapy in severity. Charles Cleeland, Ph.D., a professor in and chair of the Department of Symptom Research, said, "We're realizing that these effects aren't necessarily less than those of cytotoxic drugs; targeted therapy just has a different side effect profile."

The key to navigating the breadth of targeted drugs that are becoming available, Dr. Patel said, is knowing the pathways

that lead to cancer. "In the end, understanding what pathways are turned on and off in various cancer cells, regardless of the tissue of origin, will not only drive our treatment approaches but also determine many of the off-target effects we will need to manage." ■

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HPV Test Does Not Replace Pap Test

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high-grade squamous intra-epithelial lesions. "Women with high-grade Pap results should immediately undergo colposcopy," she said. "As a triage tool, an HPV test should be done when a Pap test shows atypical squamous cells of undetermined significance. If the HPV test is positive, the patient should undergo colposcopy."

Looking ahead

Even as clinicians and researchers work to clarify the roles of the Pap test and HPV tests in cervical cancer screening, HPV vaccination is changing the patient population. Dr. Milbourne said it will take decades to determine the full effect of HPV vaccination on cervical cancer. "It's new territory," she said. "We don't know how sensitive the Pap test is going to be

in a vaccinated population. Theoretically, we will need a more sensitive test to screen for cervical cancer as the incidence of HPV gets lower." ■

FOR MORE INFORMATION

Dr. Andrea Milbourne.....713-745-6986

CERVICAL CANCER SCREENING

For details about the current guidelines for cervical cancer screening, visit MD Anderson at www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/prevention-and-screening/cancer-screening-guidelines/cervical-cancer.html.

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