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Patterns of Care in Medical Oncology

Management of Toxicities Associated with Anticancer Therapies

Side Effects Associated with Endocrine Therapy; Use of Bisphosphonates

Chemotherapy-Associated Side Effects

Dermatologic Toxicities

Cardiotoxicity, Thrombosis and Bleeding

Psychological Aspects of Medical Oncology; Role of Second Opinions

Editor

Neil Love, MD

Results of a National Survey Evaluating Treatment Practices of Medical Oncologists

CME Certified

FROM THE PUBLISHERS OF:

Breast Cancer® UPDATE | Colorectal Cancer™ UPDATE | Lung Cancer™ UPDATE | Hematologic Oncology™ UPDATE | Prostate Cancer™ UPDATE | Renal Cell Cancer™ UPDATE

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Continuing Medical Education (CME) Information

OVERVIEW OF ACTIVITY

It is important for practicing oncologists to be aware of similarities and differences between their treatment patterns and those of other oncologists. It is also important for cancer care specialists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence to definitively support a single strategy.

This program focuses on the self-described practice patterns of randomly selected medical oncologists related to key clinical issues in supportive cancer care. Also included are clinical investigator commentary and excerpts from select publications addressing these topics. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

LEARNING OBJECTIVES

- Compare and contrast self-reported supportive care management strategies utilized by community oncologists when addressing toxicities related to the endocrine treatment of breast cancer.
- Maintain effective anticancer regimens by employing prophylactic and acute supportive care strategies that minimize the incidence and severity of aromatase inhibitor-associated joint discomfort and bone loss.
- Identify premedication regimens to reduce the risk of hypersensitivity and emetogenic reactions among patients receiving systemic chemotherapy.
- Recall the chemical entities that are associated with chemotherapy-induced peripheral neuropathy, and utilize practical interventions to abrogate this toxicity without compromising the efficacy of primary anticancer treatments.
- Describe the incidence and clinical presentation of cutaneous side effects accompanying specific cytotoxic agents and EGFR and multitargeted tyrosine kinase inhibitors, and incorporate evidence-based management strategies into routine patient care.
- Develop a cardiovascular risk-reduction strategy and monitoring plan to reduce the incidence of short- and long-term toxicity associated with anti-angiogenic and anti-HER2 therapies.
- Recognize the signs of cancer-related depression and recommend medical and behavioral alternatives for affected patients.
- Delineate the complementary and alternative practices employed by cancer specialists to support oncology patients undergoing conventional antineoplastic treatments.

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COMMENTS IN THIS MONOGRAPH

To highlight the practice issues presented in this survey, a number of excerpts are included from CME publications. For the related audio programs from Research To Practice, please visit **www.ResearchToPractice.com**.

ABOUT THIS SURVEY

This survey was completed in August 2008 by 100 community-based medical oncologists in the United States. The community-based oncologists were selected from a proprietary mail list used by Research To Practice for distribution of its CME programs.

interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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Editor's Note: The new toxicology of solid tumor oncology

This issue of *Patterns of Care* continues our efforts to quantitatively assess clinical practice patterns in a number of different areas of oncology. For this unique foray — our first ever into supportive care — we commissioned a web-based survey of 100 US-based medical oncologists with the goal of better understanding how these individuals manage the side effects and complication risks associated with many common systemic agents used to treat solid tumors, particularly and specifically, "targeted biologic agents."

The snapshot that emerges suggests that the recent introduction of a litany of new therapies and regimens has forced oncologists to suddenly wear a number of new primary care hats in order to manage a spectrum of novel toxicities. Below find a few thoughts on the challenges associated with administering a number of these agents and combinations that were not widely used prior to the year 2000, along with some related "stat bites" from the survey.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com

Select Oncology Agents and Regimens Widely Introduced Since 2000 for Solid Tumors

Drug class	Agents/regimens
Tyrosine kinase inhibitors	Lapatinib, sunitinib, sorafenib, gefitinib, erlotinib, imatinib mesylate
mTOR inhibitor	Temsirolimus
Anti-VEGF antibody	Bevacizumab
Anti-EGFR antibodies	Cetuximab, panitumumab
Anti-HER2 antibody	Trastuzumab (adjuvant)
Aromatase inhibitors	Anastrozole, letrozole, exemestane (adjuvant)
Chemotherapy agents/ regimens	Oxaliplatin, docetaxel/cyclophosphamide (TC), paclitaxel/carboplatin/trastuzumab (TCH), nanoparticle albumin-bound (*nab*) paclitaxel, pemetrexed disodium

1. The many and sometimes not so purely targeted TKIs

91% *Percent of oncologists who have prescribed sunitinib or sorafenib (Figure 30).*

50% *Median estimate by oncologists of the percent of patients experiencing dermatologic toxicity while receiving erlotinib (Figure 19).*

The good news is that many of these oral agents are associated with impressive efficacy, and the associated risks are rarely life threatening. The less-than-good news is that it takes meticulous attention and constant vigilance to keep patients on these therapies because of a number of side effects, including fatigue, hand-foot syndrome and diarrhea. It will be fascinating to see how these challenging toxicities impact the current adjuvant renal cell cancer trial comparing one year of sunitinib to sorafenib to placebo in a double-blind design. Investigators tell us that it's pretty clear who is receiving an active drug, and many patients have difficulties reaching the one-year point.

Despite these challenges, the TKIs are having a significant impact in a number of interesting tumor types. In hepatocellular cancer, after more than 100 Phase III randomized trials of systemic therapy failed to change the outcome of these patients, for the first time sorafenib has been demonstrated to improve survival, and this agent is now the standard first-line systemic therapy. It is now being investigated in combination with local treatments such as RFA (radiofrequency ablation) or TACE (transarterial chemoembolization).

Similarly, clinical investigators specializing in renal cell cancer tell me their waiting rooms are now much more crowded, in part because patients are living longer as a result of the impact of sunitinib as the standard first-line therapy for metastatic disease. Waterfall plots are equally impressive, demonstrating benefits for most patients.

In breast cancer, lapatinib is a welcome new alternative for patients with HER2-positive disease, although recent reports of significant diarrhea and skin rash when combined with paclitaxel have led to modifications of the designs of a number of new adjuvant and neoadjuvant trials.

Perhaps the most exciting TKI story (in solid tumors anyhow) is in non-small cell lung cancer, in which approximately 10 percent of patients — mostly nonsmokers — have EGFR tumor mutations that predict exquisite sensitivity to erlotinib or gefitinib. While these agents also often bring with them a troublesome rash and even a strange abnormal eyelash growth, the response in these patients is about as close as we've come in solid tumors to the magic that is imatinib in CML.

2. Bevacizumab

23% *Percent of oncologists who consider primary tumor location of a non-small cell lung cancer to be the most important risk factor for bevacizumab-associated hemoptysis (Figure 34).*

Bevacizumab — a highly interesting anti-VEGF antibody — has been a major topic of discussion since Herb Hurwitz's stunning ASCO 2003 presentation demonstrating a progression-free and overall survival advantage to adding this agent to chemotherapy (IFL) in metastatic colon cancer.

Bev is now out there in breast, lung and colon cancer and a bunch of other less common tumors, but I still don't hear any-

one — not even Lee Ellis or Rakesh Jain — explaining for sure how this agent works. We also have yet to find an effective predictor of response or toxicity, although emerging evidence about hypertension and SNPs — as discussed in a fascinating paper by Schneider et al in the October 1st issue of *JCO* — are at least providing some hints.

One of the most important qualities of bev is that it doesn't seem to make many patients feel more ill, and while hypertension and proteinuria are not infrequent, these problems are reported to be relatively easy to control for most patients. Serious complications with bev are uncommon, and the modest increase in arteriovenous events associated with the agent needs a lot more definition.

The scariest acute bev toxicity is the pulmonary hemorrhage seen in lung cancer. This event — which may be part of a brisk tumor response — is, thankfully, quite infrequent (one to four percent) and may be less of a concern in a clinical scenario (metastatic non-small cell) in which more than 80 percent of patients will die within two years despite "standard treatment." It's interesting that a quarter of docs believe that central tumor location is the most important predictor of this potentially catastrophic event, although Alan Sandler, the principal investigator of ECOG trial E4599, the seminal bev study in metastatic lung cancer, repeatedly has rejected this association.

The toxicities of this agent will be totally reexamined if it works in the adjuvant setting, a question being addressed in breast and lung cancer, but most critically, in the colossally important NSABP-C-08 trial and the AVANT study, arguably the most important current oncology trials currently complete and waiting for results.

3. Cetuximab/panitumumab

56 *Mean number of patients with colorectal cancer treated with cetuximab in the past year by clinical investigators in GI cancer (For oncologists in practice, this number was 16.)*

80% *Median estimate by oncologists of the percent of patients who experience dermatologic toxicity while receiving cetuximab (Figure 19).*

As of ASCO 2008, this class of agents is now a consideration for the most common solid tumor, as discussed on the *Lung Cancer Update* audio series by the principal investigator of the FLEX trial, Dr Robert Pirker, and the ASCO discussant of this historic study, Dr Tom Lynch. As noted in the above stat bite, oncologists in community practice know a lot about cetuximab and its cousin, panitumumab, from treating colorectal cancer, and a major quality of life concern is dermatologic toxicity.

All docs in practice are eager for effective solutions to this visible and disturbing problem. One strategy that would certainly help alleviate this problem would be to clone Dr Mario Lacouture, a dermatologist at Northwestern University who focuses his entire practice and clinical research on EGFR-related dermatologic side effects. Mario treats this dilemma as both an art and a science, and perhaps as an alternative to genetic engineering, we can help him encourage and train other dermatologists to give up a few cosmetic procedures and develop expertise in this area.

4. mTOR inhibitor (temsirolimus……TEM-sir-OH-li-mus)

11% *Percent of oncologists who can correctly pronounce temsirolimus (kidding)*

It took me a while to get the hang of pronouncing the name of this recently introduced agent, but finally, just like bevacizumab and trastuzumab before it, temsirolimus started flowing out naturally. Most docs in practice have only used temsirolimus (got the hang of it yet?) a couple of times, considering that it is both new and so far confined only to advanced renal cell cancer.

However, as time passes and this interesting agent enters into other treatment areas, along with brethren like everolimus (I actually prefer the initial moniker, the super techno-sounding "RAD 001"), the metabolic changes seen with these agents, such as hyperglycemia and hyperlipidemia, may end up challenging even the most seasoned clinicians.

5. Advances in antiemetics

55% *Percent of oncologists using a regimen with a second-generation 5-HT3 antagonist to prevent emesis when prescribing cisplatin/gemcitabine (Figure 7).*

Aprepitant, palonosetron and other 5-HT3 receptor antagonists have made the use of traditional chemotherapies a less toxic experience and this has, for example, greatly facilitated the rapidly emerging use of adjuvant chemotherapy in non-small cell lung cancer — particularly with cis-based regimens. In our survey, the dichotomy of how physicians approach premedication with common regimens such as FOLFOX and GEM/cis suggests that a significant fraction are either overtreating or undertreating this classic, highly disturbing, traditional chemotherapy side effect.

6. New chemo regimens: TC (docetaxel/cyclophosphamide) for breast cancer

59% *Percent of oncologists who believe that TC has a more favorable safety/toxicity profile than AC (Figure 8).*

We have tracked the TC story since Steve Jones first presented this important data set at San Antonio several years ago. Steve was a central figure in the creation of "AC" but now finds it somewhat amusing and apropos that his new US Oncology study — at least in his mind — has helped send AC out to pasture.

Dr Jones is pleased that in its place is a less cardiotoxic,

leukemogenic and emetic regimen that also seems to be associated with fewer cancer relapses and resulting deaths, and TC has been rapidly incorporated into the treatment landscape of breast cancer.

Questions remain about indications for prophylactic myeloid growth factors with this regimen, but my sense is that there are a few too many neutropenic infections out there that might be prevented. With the recent emergence of the "TIC-TAC-TOE" trial, it could be that five years from now, TC/bevacizumab might be the way to go for many patients as adjuvant therapy.

7. New chemo regimens: FOLFOX (oxaliplatin)

74% *Fraction of GI cancer investigators who would generally recommend FOLFOX to an 84-year-old patient with Stage III disease and 15/25 positive nodes (27% of practicing docs would make the same recommendation.)*

44% *Percent of oncologists who start patients on magnesium and calcium to manage oxaliplatin-related neuropathy (Figure 17).*

I had the good fortune and honor to interview Dr Aimery de Gramont at the 2003 ASCO meeting, right after he presented for the first time the MOSAIC trial results, demonstrating an advantage to FOLFOX compared to 5-FU as adjuvant therapy for colon cancer. I had held my breath in anticipation of Dr de Gramont's arrival at our temporary recording studio in New Orleans that day, as a fulminant thunderstorm flooded the streets and pounded the area.

After the soggy but smiling Parisian investigator showed up, we chatted not only about the MOSAIC efficacy findings with FOLFOX but also about the reported incidence of neurotoxicity. A few years later, this critical issue has been muddied by the confusing sequence of events related to the potential preventive role of magnesium and calcium. Another issue is the split between clinical investigators and practicing docs on the use of this agent in older patients, and new studies attempting to reduce the number of treatment cycles to six may lead to a considerable reduction in this important treatment risk.

8. New chemo regimens: *Nab* paclitaxel

27% *Percent of oncologists who use corticosteroid premedication with* **nab** *paclitaxel (Figure 12).*

62% *Percent of oncologists who believe nab paclitaxel has a more favorable safety/toxicity profile than paclitaxel (Figure 13).*

I regularly ask investigators and practicing docs for their thoughts on this controversial agent. What I have commonly found is that most physicians — community-based or academic — believe that in breast cancer, *nab* offers some advantages compared to its Cremophor®-bound cousin, and if cost and reimbursement were the same, plain old paclitaxel might have a minimal role in community practice. What that means and how this information should be applied to patient care I have no idea, but I am sure that some health economist somewhere has managed to put a price tag on the potential avoidance of infusion reactions, insomnia and agitation. It is also somewhat concerning that a significant fraction of medical oncologists report using steroid premedications with this agent, a practice not done in trials evaluating this taxane and not done by clinical investigators.

9. Targeted adjuvant therapies of breast cancer (trastuzumab, aromatase inhibitors)

65% *Percent of oncologists who believe that TCH has a better safety/toxicity profile compared to an anthracycline-containing anti-HER2 regimen (Figure 27).*

37% *Percent of oncologists who check cardiac function six months after initiating adjuvant trastuzumab (Figure 24).*

The spectacular 2005 ASCO presentations on adjuvant trastuzumab instantly created 10,000 new cardiologists or, more specifically, medical oncologists who now had to ramp up their knowledge base to deal with a serious cardiac threat for curable patients. The rapid acceptance of TCH (docetaxel, carboplatin, trastuzumab), which does not seem to increase the risk of cardiac dysfunction as much as anthracycline regimens, while providing the same antitumor effect, has resulted in a lot less stress for patients and oncologists. However, our survey suggests that docs are being less meticulous about cardiologic monitoring, maybe because they are less concerned about complications with no anthracycline involved.

73% *Percent of oncologists who would consider continuing an AI after five years for a patient who is tolerating it well (Figure 2).*

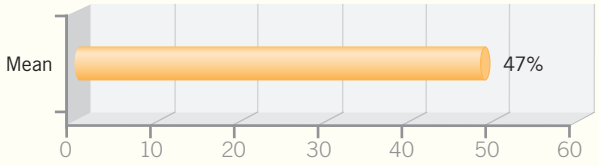
8% *Mean estimate by oncologists of the percent of patients with "severe" arthralgias on AIs (Figure 1).*

The poor AIs have been getting roughed up a lot in publications and meetings lately because of their propensity to cause arthralgias. That may now change instantly with a profoundly interesting *Lancet* paper just published by Jack Cuzick and colleagues demonstrating a fascinating correlation between vasomotor symptoms and/or arthralgias and relapse rate in patients treated in the ATAC trial. One wonders if the perspective on these symptoms might now change in the same manner as rash with EGFR inhibitors, where docs try to ameliorate this side effect but encourage patients that this may be a sign that the agent is working more effectively.

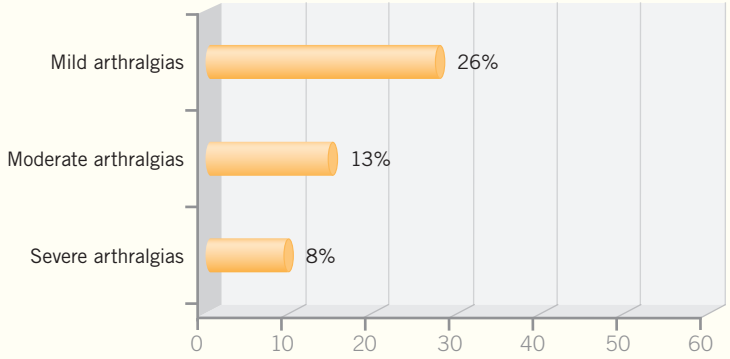
Management of Side Effects Associated with Endocrine Therapy; Use of Bisphosphonates

FIGURE 1

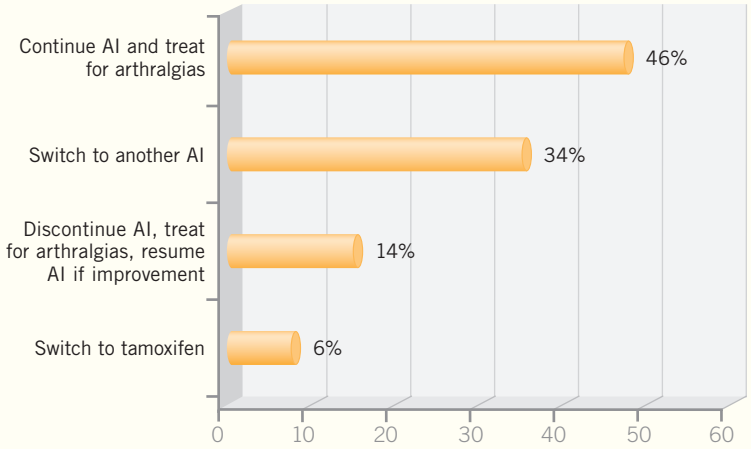
Approximately what percent of your patients who receive aromatase inhibitors (AIs) develop arthralgias?



Approximately what percent of your patients who receive AIs experience...



*What is generally your first-line approach in managing **severe** arthralgias in postmenopausal women receiving adjuvant AIs?*



Breast Cancer Update Issue 7, 2007

CHARLES L VOGEL, MD: My experience with the arthralgias associated with the aromatase inhibitors has been highly variable. Approximately 30 percent of my patients have to be switched to another therapy or discontinue the aromatase inhibitor. Aman Buzdar and I had an agreement not to agree. He told me, "It is a class effect. If you get it with one aromatase inhibitor, you will get it with another." I absolutely do not agree because I have seen patients respond to a second aromatase inhibitor.

Breast Cancer Update Think Tank Issue 2, 2008

DANIEL F HAYES, MD: Many of us underestimated the issue of aromatase inhibitor-associated arthralgias during the early clinical trials and when they were first reported. Increasingly in practice, many of us are beginning to see arthralgias as a major issue.

In a prospective trial we have in our consortium of breast cancer pharmacogenomics, COBRA, we found in the first 100 patients we put on a randomized trial comparing exemestane to letrozole that 15 percent of patients quit taking the drug because of joint symptoms.

In a study by Morales and colleagues reported in the *Journal of Clinical Oncology*, they assessed tendon synovial changes serially with MRI and observed carpal tunnel thickening in many patients who were receiving the AIs and in fewer patients who were receiving tamoxifen.

We don't know why this happens, but physicians need to be aware of it. I have seen a few patients who started out at baseline with low-level carpal tunnel syndrome and ended up requiring surgery. That may have happened anyway, but it seemed as if it was hastened by the aromatase inhibitor therapy.

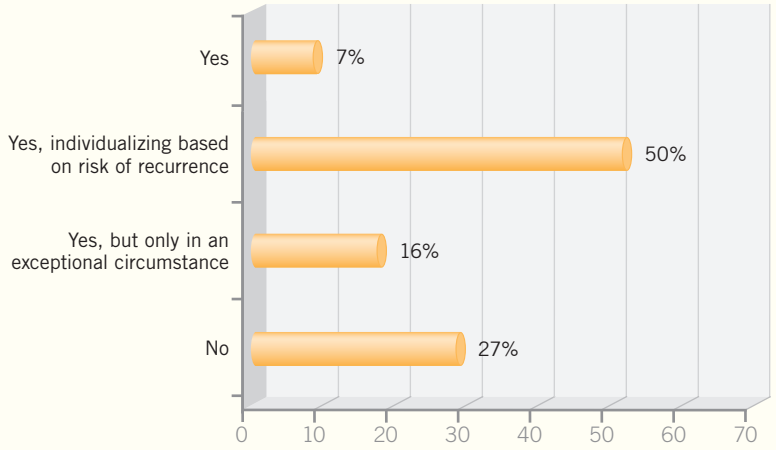
Breast Cancer Update Issue 5, 2008

NANCY E DAVIDSON, MD: Lynn Henry published data from the first 100 patients in a clinical trial evaluating the pharmacogenomics of adjuvant exemestane and letrozole, and a large proportion saw a rheumatologist because they crossed a predefined symptomatology threshold.

The findings are all over the map, and no single explanation for these symptoms is clear to me. What to do about them is also complicated, and one purpose of our

FIGURE 2

In general, do you continue an aromatase inhibitor (AI) in a patient who is completing the fifth year of an adjuvant AI and is tolerating it well?



study is to determine whether it is possible to predict which aromatase inhibitor a patient will tolerate better or perhaps to identify patients who are more prone to these musculoskeletal symptoms.

I believe these symptoms were underreported in the large, randomized aromatase inhibitor trials. Now that we are paying attention to this side effect, we are recognizing that the problem is critical to address because compliance is important with these drugs.

Breast Cancer Update Issue 5, 2007

JACK CUZICK, PHD: Not surprisingly, we see somewhat but not enormously higher rates of arthralgias with anastrozole than with tamoxifen in the ATAC trial. The rate is 30 percent with tamoxifen and 36 percent with anastrozole, so the effect is real, but it's a small effect compared to the fact that arthralgia is not uncommon in the early postmenopausal years anyway.

So, to some extent, the aromatase inhibitors are being blamed for some arthralgias that they don't cause. They do increase the risk, but a lot of arthralgias will occur anyway. We will learn more about that from the IBIS-2 study because we'll be comparing anastrozole to placebo, and there's no doubt that a fair amount of arthralgia is occurring in the placebo arm.

D Cella et al. Quality of life of postmenopausal women in the ATAC ("Arimidex", tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. Breast Cancer Res Treat 2006;100(3):273-84.

These are the first HRQoL data to become available that cover the entire 5-year treatment period in the primary adjuvant setting for an aromatase inhibitor.

Although it was not necessarily expected, results from the 5-year HRQoL analysis are broadly similar to those of the 2-year analysis. For both the anastrozole and tamoxifen treatment groups, the good HRQoL of patients at baseline was maintained and perhaps even improved overall throughout the treatment period...

Vaginal discharge was less frequently bothersome with anastrozole but vaginal dryness, decreased libido, and dyspareunia were more frequently bothersome with anastrozole compared with tamoxifen. HRQoL should play a role in informed consent and patient-reported data of this nature add important information beyond the traditional end points to be considered when making decisions about therapeutic options and appropriate supportive measures.

C Derzko et al. Management of sexual dysfunction in postmenopausal breast cancer patients taking adjuvant aromatase inhibitor therapy. Curr Oncol 2007;14(Suppl 1):20-40.

Clinical evaluation of AI therapy-associated signs and symptoms of urogenital atrophy, vaginitis, dyspareunia, and loss of sexual interest demonstrates several similarities with natural age- and menopause-related gynecologic events associated with diminished estrogen levels. Management of these events through a combination of lifestyle modification, counselling, and hormonal and non-hormonal interventions can therefore improve quality of life significantly for patients...

In view of recent findings raising concerns over elevated circulating estradiol levels in breast cancer patients on AI therapy who are using transvaginal estrogenic preparations, non-hormonal therapies including regular application of vaginal moisturizers and lubricants are recommended and certainly should be first-line therapy. In addition, pelvic therapy for pelvic tone awareness and pelvic floor exercises (for example, Kegel exercises) and lifestyle modification are preferred and should be considered early.

Breast Cancer Update Issue 4, 2008

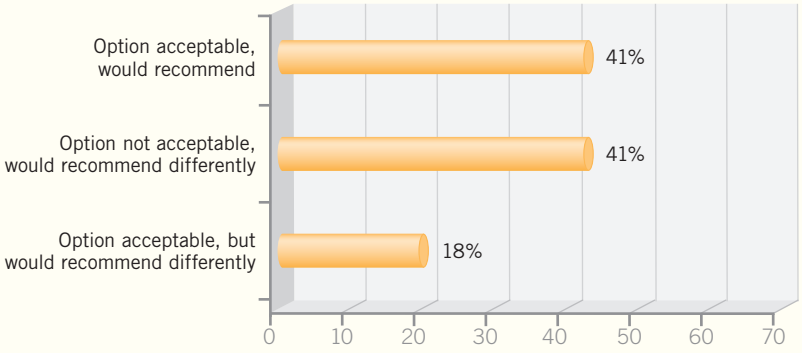
MICHAEL GNANT, MD: The ABCSG-12 trial, evaluating adjuvant endocrine therapies in premenopausal women, addressed both the issue of endocrine therapy and the use of bisphosphonates. The bone substudy data reported in 2004 revealed that the bisphosphonates completely reversed bone loss from aromatase inhibitors. We then increased the trial size from 1,250 to 1,800 to answer the antitumor question regarding bisphosphonates.

We administered four milligrams of zoledronic acid every six months, for a total of seven infusions over three years. At five years of follow-up, we observed only 137 disease-free survival events. We saw a 36 percent improvement in disease-free survival, translating to at least a nonsignificant trend toward better over-

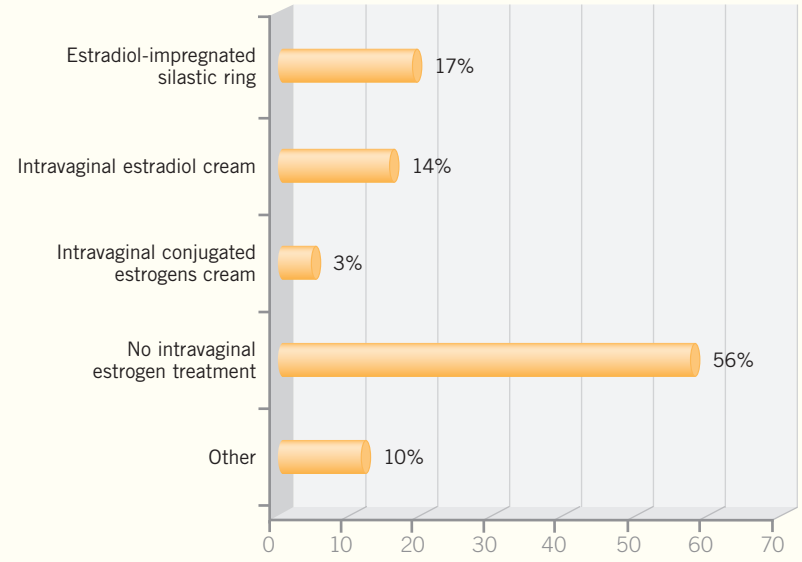
FIGURE 3

A sexually active 70-year-old woman is receiving adjuvant anastrozole after adjuvant chemotherapy/trastuzumab for ER-positive, HER2-positive breast cancer. She is experiencing vaginal dryness, dyspareunia and frequent urinary tract infections, with no relief from long-acting vaginal moisturizers and lubricants. Her gynecologist prescribed intravaginal estrogen tablets.

What would you tell this patient regarding the recommendation?



If you would recommend something different, what would you recommend?



all survival. That's an accomplishment usually observed with interventions such as taxane chemotherapy. We observed that efficacy with an acceptable side-effect profile.

More importantly, we also saw benefit in various event subcategories, including locoregional recurrence, contralateral breast cancer and distant metastasis outside of the bone (such as liver or lung disease). That's something most of us did not expect.

When we started the trial in 1999, nobody was aware of osteonecrosis of the jaw (ONJ). When the first reports were published, we made an effort to educate physicians and patients. We identified three suspected cases and examined the original dental films. We did not find evidence of a single case of confirmed ONJ. This is in line with what is known about that dose and frequency of administration of zoledronic acid.

Basically, all the reports suggest that ONJ with IV bisphosphonates occurs with more intense regimens or higher-dose schedules. I would say that ONJ is not a problem in the adjuvant treatment setting. I believe it's prudent for patients to see a dentist prior to initiating bisphosphonate therapy to ensure that they don't have any major problems.

DM Reid et al. Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treat Rev 2008;34(Suppl 1):3-18.

In postmenopausal women, the use of aromatase inhibitors increases bone turnover and induces bone loss at sites rich in trabecular bone at an average rate of 1-3% per year leading to an increase in fracture incidence compared to that seen during tamoxifen use...

Randomised clinical trials in postmenopausal women indicate that bisphosphonates prevent the bone loss and accelerated bone turnover associated with aromatase inhibitor therapy and are a promising strategy for the prevention and treatment of osteoporosis in this setting. Treatment initiation recommendations are based on a combination of risk factors for osteoporotic fracture and BMD levels. Bisphosphonates, along with a healthy lifestyle and adequate intake of calcium and vitamin D are the treatments of choice to prevent bone loss.

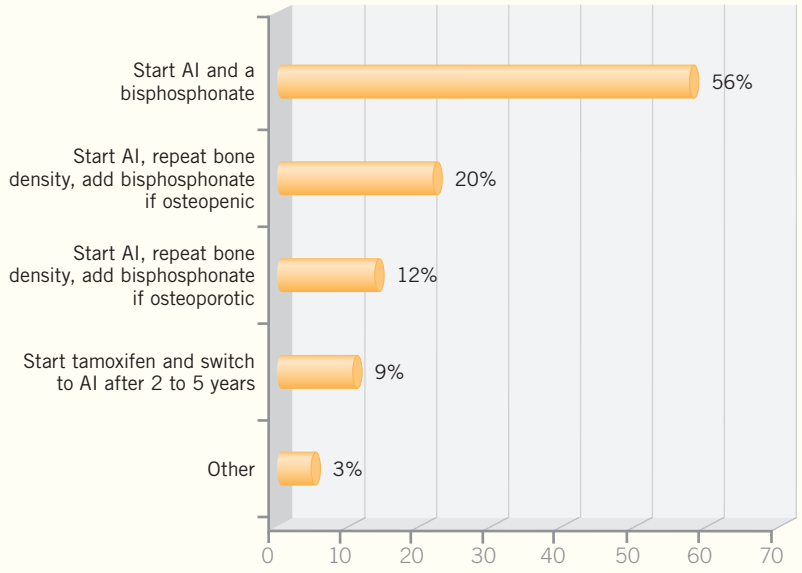
Due to the rate of bone loss associated with breast cancer treatments, and uncertainties about the interaction between aromatase inhibitor use and BMD for fracture risk, the threshold for intervention has been set at a higher level than that generally recommended for postmenopausal osteoporosis.

Breast Cancer Update Issue 3, 2008

JOHN F FORBES, MD: The data on bone

FIGURE 4

A 65-year-old woman with ER-positive, HER2-negative breast cancer is ready to begin anastrozole following chemotherapy. Baseline bone mineral density after completing the chemotherapy shows osteopenia with a T-score of -1.9. The patient exercises and has been receiving calcium and vitamin D supplements and has no other risk factors for osteoporosis. Which of the following would you most likely recommend?



fractures from the long-term follow-up of the ATAC trial are informative and pleasantly surprising. For a number of years, we've been aware of the increased risk of fractures associated with the aromatase inhibitors compared to tamoxifen. What was surprising was that upon completion of the treatment, no difference was detectable in the risk of fractures with anastrozole compared to tamoxifen.

It is interesting that no detrimental carryover effect is evident here. Almost as soon as you stop the treatment — within one year — the difference is gone. I believe we need to be a little cautious about leaping to safety reassurance at this point, however, because the types of fracture risk may vary: Hip fractures may well be different from vertebral fractures. These are different types of bone, and I believe we need much longer follow-up to be sure that there isn't some unsuspected, longer-term effect on hip fractures.

The bone substudy in ATAC was designed to evaluate the effect of anastrozole on bone density and potential longer-term strategies to correct it. We learned that women who started out with a normal bone density may develop osteopenia but will not develop osteoporosis.

Breast Cancer Update Issue 3, 2007

ANTHONY HOWELL, MD: The important clinical point from the bone data in the ATAC trial was that if the patients started treatment with a normal bone density, none of them became osteoporotic over the five years. In addition, we're seeing a lot of data on the effectiveness of bisphosphonates in preventing bone loss associated with therapy.

The most important data remain those from the Austrian study, which was published in the *Journal of Clinical Oncology* in 2007. They show that zoledronic acid at four milligrams administered every six months completely abrogated the bone loss from goserelin with either tamoxifen or anastrozole.

Breast Cancer Update Issue 5, 2007

ROWAN T CHLEBOWSKI, MD, PHD: I believe it's clear now that almost no one needs annual bone mineral density testing. I expect the recommendation will be every two years. In addition, if the baseline test is normal and insurance issues exist, I believe you can wait longer. As for prophylactic bisphosphonates, the question is, where do you draw the line? Some clinicians might choose to initiate bisphosphonates at a T-score of -1.5, based on Coleman's data, and that's probably reasonable.

R Weitzman et al. Critical review: Updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients — May 2006. Crit Rev Oncol Hematol 2007;62(2):148-52.

It is recommended that patients be encouraged to receive a dental examination prior to initiating bisphosphonate therapy and, if possible, complete any necessary dental procedures (eg, tooth extraction) prior to initiating bisphosphonate therapy. Patients should receive regular dental visits during bisphosphonate therapy.

Patients should be encouraged to practice good oral hygiene and minimize possible jaw trauma. If possible, patients should avoid dental surgery during treatment with bisphosphonates. If exposed bone is observed or reported in the oral cavity at any time (suspected ONJ), refer the patient to a dental professional immediately.

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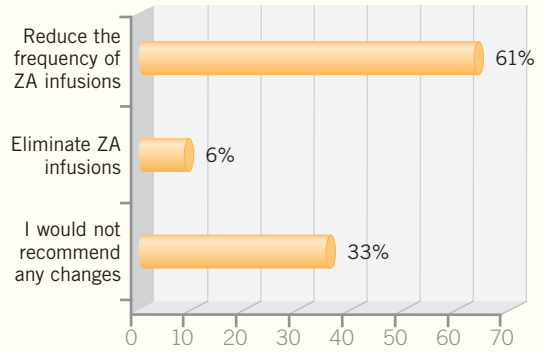
Burstein HJ. **Aromatase inhibitor-associated arthralgia syndrome.** *Breast* 2007a;16(3):223-34. Abstract

Burstein HJ, Winer EP. **Aromatase inhibitors and arthralgias: A new frontier in symptom management for breast cancer survivors.** *J Clin Oncol* 2007b;25(25):3797-9. No abstract available

FIGURE 5

A patient with metastatic cancer in the bone is responding to anticancer treatment and monthly zoledronic acid (ZA) infusions and is expected to live for more than 2 years. Which of the following would you most likely recommend?



After how many months would you reduce the frequency of zoledronic acid infusions?

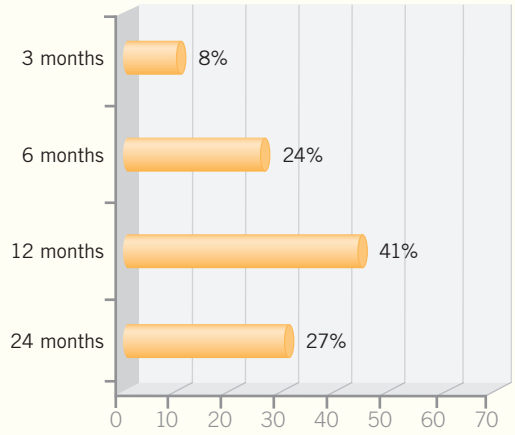
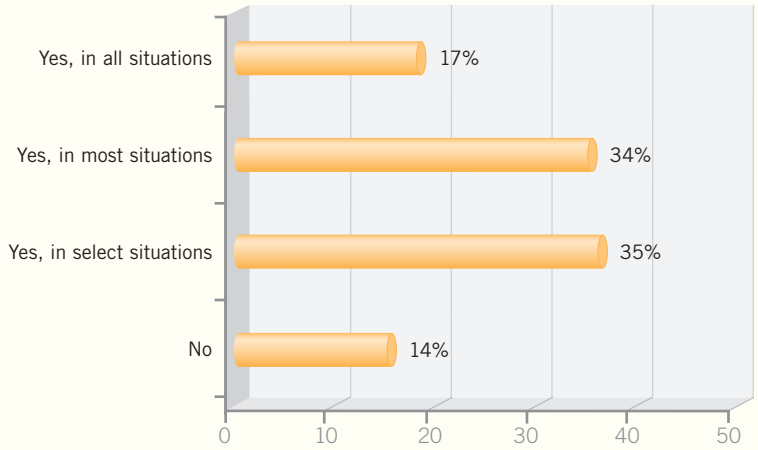


FIGURE 6

In general, when starting a patient with metastatic disease on an intravenous bisphosphonate, do you first have the patient go to a dentist or oral surgeon for an initial evaluation?



Cella D et al. **Quality of life of postmenopausal women in the ATAC ("Arimidex", tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer.** *Breast Cancer Res Treat* 2006;100(3):273-84. **Abstract**

Coleman RE et al. **Aromatase inhibitor-induced arthralgia: Clinical experience and treatment recommendations.** *Cancer Treat Rev* 2008;34(3):275-82. **Abstract**

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Glaus A et al. **Fatigue and menopausal symptoms in women with breast cancer undergoing hormonal cancer treatment.** *Ann Oncol* 2006;17(5):801-6. **Abstract**

Gnant M et al. **Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy.** *Lancet Oncol* 2008;9(9):840-9. **Abstract**

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Hershman DL. **Getting a grip on aromatase inhibitor-associated arthralgias.** *J Clin Oncol* 2008;26(19):3120-1. No abstract available

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Morales L et al. **Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome.** *J Clin Oncol* 2008;26(19):3147-52. **Abstract**

Presant CA et al. **Aromatase inhibitor-associated arthralgia and/or bone pain: Frequency and characterization in non-clinical trial patients.** *Clin Breast Cancer* 2007;7(10):775-8. **Abstract**

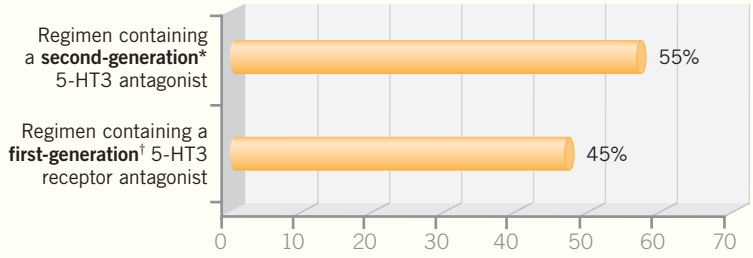
Reid DM et al. **Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group.** *Cancer Treat Rev* 2008;34(Suppl 1):3-18. **Abstract**

Ruggiero SL et al. **Practical guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaw in patients with cancer.** *J Oncol Prac* 2006;2(1):7-14. Available at: **http://jop.state-affiliates-asco.org/JanuaryIssue/7.pdf**. Accessed January 5, 2007.

FIGURE 7

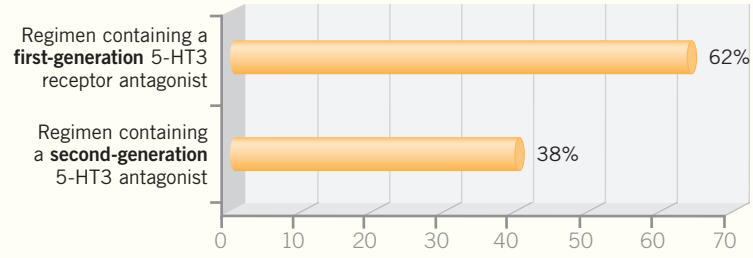
Which of the following acute chemotherapy-induced emesis (CIE) prevention medications do you generally recommend for the following chemotherapy regimens?

Gemcitabine/cisplatin (high emetic risk)

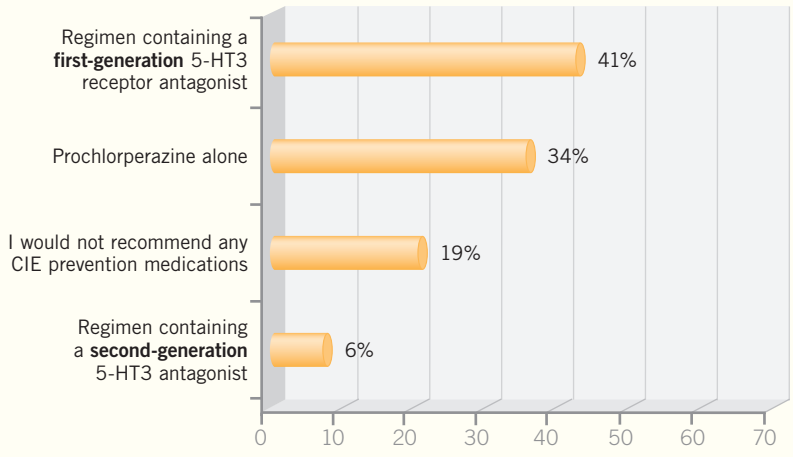


* Palonosetron; † Dolasetron, granisetron, ondansetron
Regimens contain a combination of 5-HT3 antagonists, corticosteroids, NK-1 antagonist, prochlorperazine

FOLFOX (moderate emetic risk)



5-FU/LV (low emetic risk)



A Naeim et al. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol 2008;26(23):3903-10.

There are many types of neuroreceptors that are involved in the emetic response, including serotonin (5-hydroxytryptamine-3 [5-HT3]), dopamine, corticosteroid, and neurokinin-1 receptors; therefore, antiemetic agents often target different neuroreceptors and can behave synergistically when used in combination. Without the use of prophylactic antiemetic therapy, some highly emetic types of chemotherapy, such as cisplatin, would almost universally result in nausea and/or vomiting, but with the use of optimal antiemetic therapy, clinicians can reduce the prevalence to approximately 25% of patients on highly emetic therapy. Therefore, appropriate pharmacologic prevention and management are essential.

PJ Hesketh. Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358(23):2482-94.

Four groups (the Multinational Association of Supportive Care in Cancer, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the European Society for Medical Oncology) have recently published updated antiemetic guidelines. There is broad agreement among these groups on most key issues. The treatment recommendations that follow reflect a composite of the consensus recommendations of these groups...

High Emetic Risk

The combination of a 5-HT3 antagonist, dexamethasone, and aprepitant is recommended before the administration of chemotherapy that is associated with a high risk of emesis... Patients receiving chemotherapy with high emetogenic potential should receive a combination of aprepitant on days 2 and 3 and dexamethasone on days 2 to 4...

Moderate Emetic Risk

In patients receiving treatment with an anthracycline and cyclophosphamide, a combination of a 5-HT3 antagonist,

FIGURE 8

How would you compare docetaxel/cyclophosphamide (TC) to AC in terms of safety and tolerability?

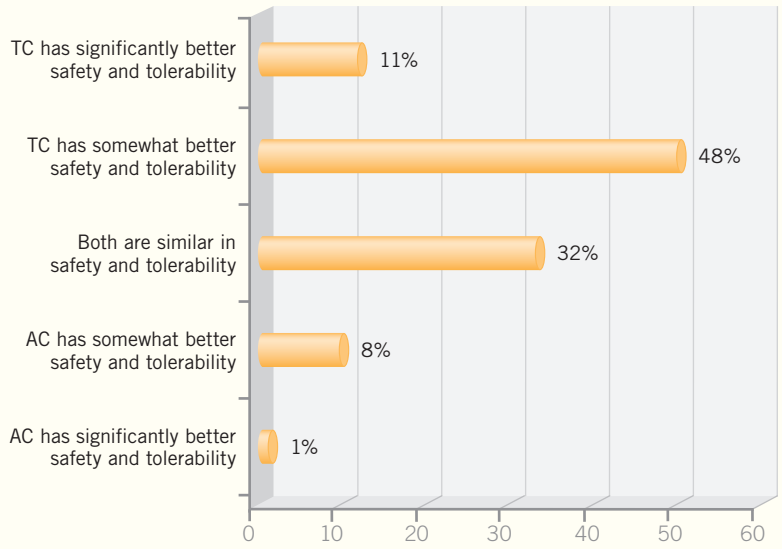
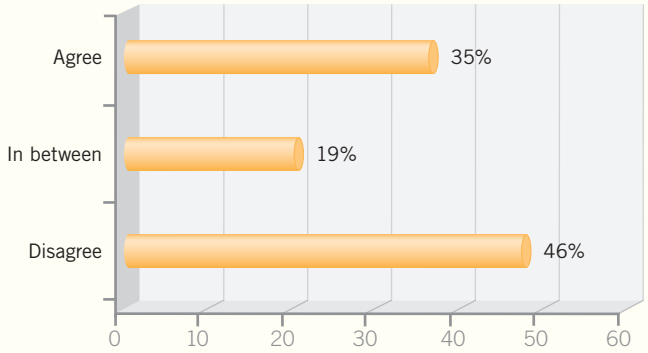


FIGURE 9

In my practice, when aprepitant is used in combination with a 5-HT3 receptor antagonist and dexamethasone, I use a lower dose of dexamethasone compared to that used with a 5-HT3 receptor antagonist and dexamethasone alone.



n = 94 who use aprepitant

dexamethasone, and aprepitant is recommended before chemotherapy. Because this chemotherapeutic regimen has a moderate potential for delayed emesis, aprepitant should also be administered on days 2 and 3...

Low Emetic Risk

A single dose of dexamethasone before chemotherapy is recommended for agents associated with a low risk of emesis. A single dose of a dopaminergic antagonist is another reasonable preventive option. No routine prophylaxis for delayed emesis is indicated...

Minimal Emetic Risk

No routine prophylaxis for acute or delayed emesis is warranted for chemotherapeutic agents that are associated with a minimal risk of emesis.

Breast Cancer Update Issue 2, 2007

FRANKIE A HOLMES, MD: I've started to incorporate the TC regimen much more frequently in my practice, especially in situations in which I have concerns about chemotherapy tolerance. However, at this time, I have not given up on the standard AC taxane regimen for my patients with node-positive disease. AC is now recognized as a highly emetogenic regimen, and patients may experience delayed nausea and vomiting. I was once on a panel discussing emesis, and someone said, "Oh, that's just AC." AC is associated with a lot of delayed nausea and vomiting. You find considerable hidden toxicity if you step into the shoes of a patient. It can be incapacitating. With TC, you don't have that level of burden of emesis and nausea.

Breast Cancer Update Issue 2, 2008

STEPHEN E JONES, MD: We examined the database from the US Oncology adjuvant trial evaluating TC versus AC for long-term potential toxicities and identified three fatal events: congestive heart failure in a woman younger than age 50, myelodysplastic syndrome and myelofibrosis. Those three patients received AC chemotherapy, and we saw nothing similar in the TC arm.

These are the concerns with anthracyclines. They adversely affect the heart, a fact that has been underappreciated. We are beginning to understand this effect better, particularly in older patients. Data from MD Anderson and the SEER and Medicare databases demonstrate that the occurrence of congestive heart failure may be in excess of 10 or 20 percent among women older than age 65 when treated with anthracyclines.

That's scary, and I wonder, did I contribute to this? It would be nice to have a treatment that eliminated doxorubicin,

FIGURE 10

A patient with metastatic cancer receives paclitaxel qwk and has not shown any signs of hypersensitivity on a premedication regimen of dexamethasone/diphenhydramine/famotidine. Treatment will be administered indefinitely if stable or responding. Which of the following would you most likely recommend regarding the use of dexamethasone?

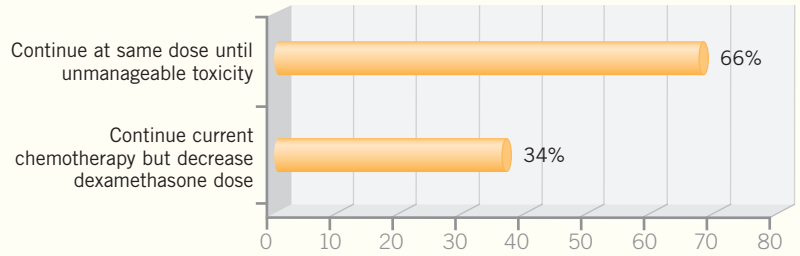
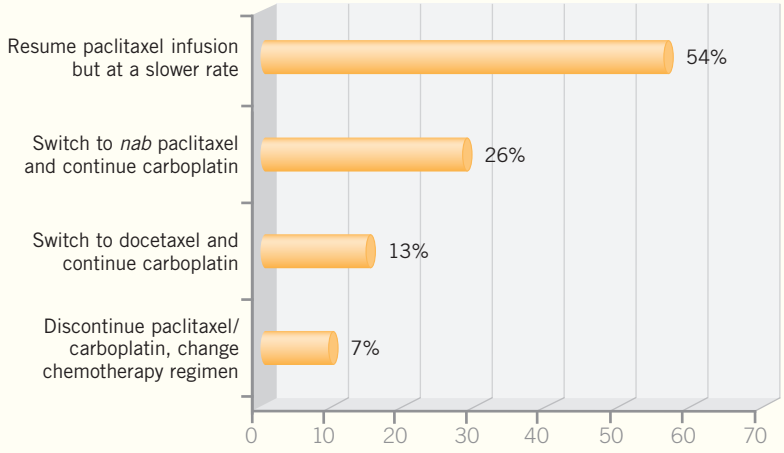


FIGURE 11

A 60-year-old man with metastatic carcinoma of unknown primary is receiving his second cycle of paclitaxel/carboplatin with standard paclitaxel premedication. He experienced a clinical response after the first cycle. Ten minutes into the second paclitaxel infusion, he develops chest tightness and shortness of breath. The paclitaxel infusion is stopped, and methylprednisolone/diphenhydramine is administered. After 45 minutes, the patient's symptoms have abated, although he is still anxious. What do you do now?



which may be responsible for some of the late congestive heart failures.

The anthracyclines also increase nausea and vomiting. In our original report, significantly less Grade III/IV nausea and vomiting was recorded with TC versus AC, and more antiemetics had to be used for those patients with delayed nausea and vomiting.

NCCN Clinical Practice Guidelines in Oncology: Antiemesis — v.3.2008

The development of the 5-HT3-receptor antagonists (such as ondansetron, granisetron, dolasetron mesylate, palonosetron) represents a significant advance in antiemetic therapy. All of these agents have been shown to be effective in controlling the acute nausea and/or vomiting associated with cancer chemotherapy.

Palonosetron is a 5-HT3 antagonist with an approximately 100-fold higher binding affinity for the 5-HT3 receptor compared to the other serotonin antagonists (ie, ondansetron, granisetron, and dolasetron). It has a half-life of approximately 40 hours, which is significantly longer than other commercially available 5-HT3 antagonists... It is recommended (category 1) for acute and delayed emesis prevention when using moderate emetic risk chemotherapy...

In March 2003, the Food and Drug Administration (FDA) approved aprepitant (oral), which selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system. Thus, aprepitant provides a different and complementary mechanism of action to all other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3 receptor antagonists and the corticosteroid dexamethasone to inhibit both acute and delayed cisplatin-induced emesis.

Breast Cancer Update Issue 3, 2008

JULIE R GRALOW, MD: *Nab* paclitaxel does not require premedications, has a faster infusion time and has the ability to deliver somewhat higher doses of the drug. I believe we are seeing a dose-response effect above what we've traditionally observed with paclitaxel. Certainly the data with every three-week *nab* paclitaxel versus paclitaxel are in favor of *nab* paclitaxel.

We have randomized Phase II data showing that when administered weekly, *nab* paclitaxel may be as good as, if not better than, docetaxel. It's a fascinating drug, and I like using it a lot. I like not having to administer steroids and antihistamines and the markedly reduced chance of allergic reactions. I'm excited about trials moving *nab* paclitaxel into the adjuvant setting.

FIGURE 12

If you use nab *paclitaxel, generally how often do you use steroids as part of your routine premedication regimen? (n = 81)*

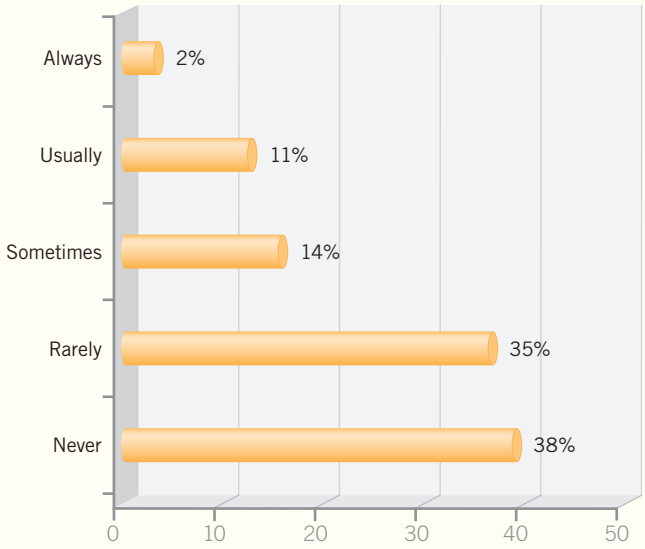
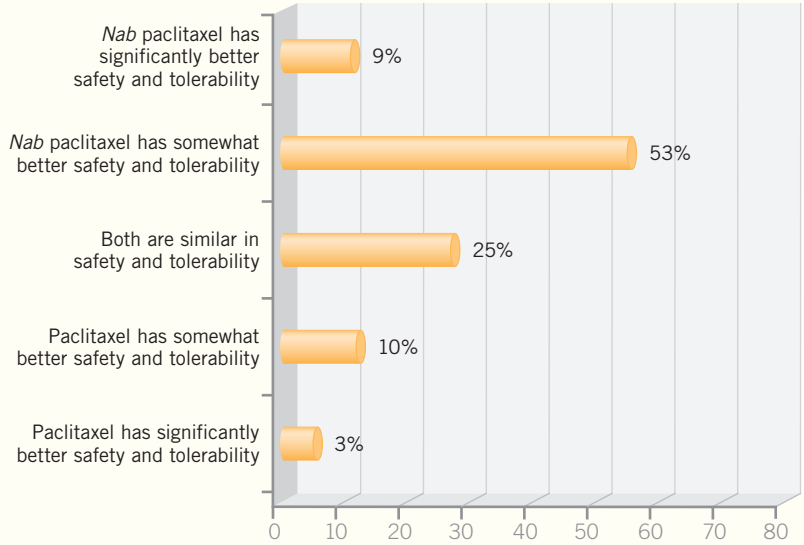


FIGURE 13

How would you compare the safety/tolerability of nab *paclitaxel to paclitaxel?*



Breast Cancer Update Issue 2, 2007

DR HOLMES: I administer *nab* paclitaxel in preference to paclitaxel, period, for patients with metastatic disease. It's a huge advantage. Patients have a life. They have kids. They have day care. At its best, getting through the clinic is difficult. I have emergencies, so I'm backed up. There are all kinds of built-in delays.

We all think we know what it is to go through therapy from the patient's standpoint, but it's hard to remember all the delays, all the problems: "Oh gosh, counts aren't up today. You have to come back later." To begin with, these people have a life, and their time is valuable. In addition, not having to take the dexamethasone is a huge benefit. How many people are hyperactive? They can't sleep that first night. They have to take the steroids and then take lorazepam or something else to relax them. Finally, we all know that patients gain weight on adjuvant chemotherapy.

Apparently, they do not eat more, and their energy intake isn't increased, but their energy expenditure is decreased. Add this anabolic agent on top of that, and we know that some women are sensitized to this. Then there's that minority of patients who develop acne from the dexamethasone. Really, less is more, and avoiding premedication is a tremendous advantage.

Breast Cancer Update Issue 2, 2008

JOYCE O'SHAUGHNESSY, MD: One of the main advantages of *nab* paclitaxel is that you don't need steroids. Steroids weren't used in the *nab* paclitaxel trials, and an increasing body of anecdotal evidence suggests that patients who suffer reactions with paclitaxel or docetaxel can receive *nab* paclitaxel without having anaphylactoid problems. I don't know of any reason to administer steroids to them.

Breast Cancer Update Issue 5, 2007

SHARON GIORDANO, MD, MPH: We've conducted exploratory work examining cognitive dysfunction secondary to chemotherapy. It's difficult to get information from databases because most of the treatment-related cognitive changes are subtle, and I don't believe most physicians would notice them during a routine office visit.

The cognitive changes are important to the patient in terms of memory-only

FIGURE 14

Approximately what percent of the patients in your practice who receive adjuvant chemotherapy develop the following conditions? (Median)

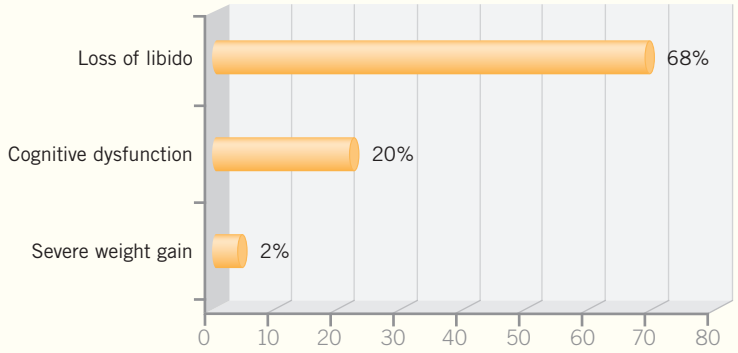
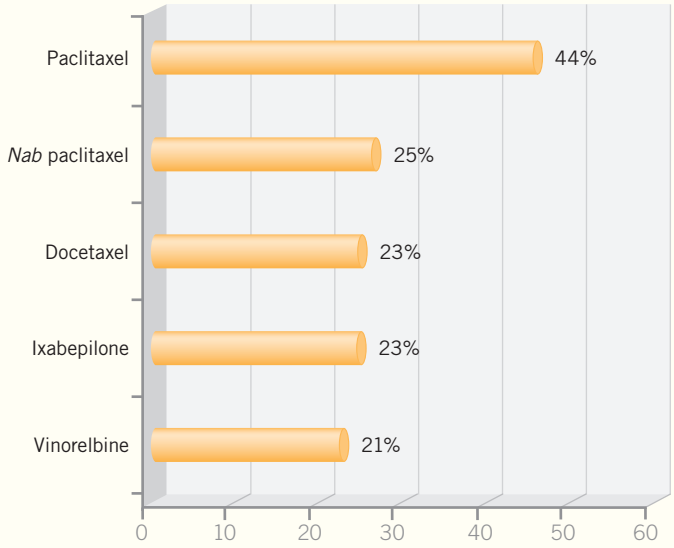


FIGURE 15

Approximately what percent of your patients receiving each of the following therapies experience chemotherapy-related neuropathy? (Mean)



span or recall, attention span, but these are picked up on careful neurocognitive testing.

Clearly, a number of issues exist in the patient's life at the time of diagnosis and treatment, including an enormous amount of stress, possible cytokines released by the cancer that may cause cognitive changes even before starting chemotherapy, the effects of chemotherapy, the effects of menopause in women and the effects of estrogen blockade. So many different things are going on that it's hard to tease out how much each contributes to the dysfunction.

It clearly is a real phenomenon for some patients. One of my young patients in her thirties received chemotherapy, then had difficulty remembering people's names at the day care center she operates. When I saw her a year later at follow-up, it seemed to be getting better. I believe real changes occur, but only some patients are strongly affected in this way.

Colorectal Cancer Update Issue 3, 2008

STEVEN R ALBERTS, MD: The CONcePT trial was designed to evaluate intermittent versus continuous oxaliplatin, with chemotherapy, and the use of calcium and magnesium to decrease oxaliplatin-induced peripheral neuropathy.

The Data and Safety Monitoring Committee halted the trial based on an early analysis that suggested calcium and magnesium were causing some detrimental effect in terms of the response rate, as well as potentially progression-free survival. An independent review group examined the outcomes and it now appears that patients receiving calcium and magnesium were not harmed by it and, indeed, they seem to have a better response rate and a longer duration of disease control.

However, because the trial was stopped early, there's still some concern regarding whether we can rely on the data. Meanwhile, the North Central Cancer Treatment Group (NCCTG) was evaluating calcium and magnesium in a symptom-control trial. The analysis from that trial also suggested there wasn't any potential harm in terms of response rates. In addition, the NCCTG and the CONcePT trials both showed some benefit from calcium and magnesium in controlling treatment-induced peripheral neuropathy.

Colorectal Cancer Update Issue 5, 2007

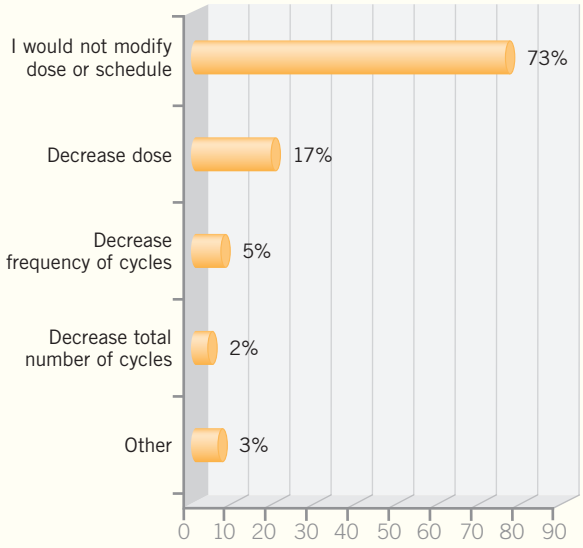
HERBERT I HURWITZ, MD: One approach to maximize the treatment benefit from oxaliplatin in the metastatic setting is to be preemptive through the use of a calendar schedule. This is the OPTIMOX approach, by which stopping and starting treatment are based as much on the calendar as they are on the patient's symptoms or disease control.

I find that adjustment based on the patient's symptoms — as long as the threshold of symptoms is lowered — ends up being a nearly identical approach. I have a bias to try to adjust based on

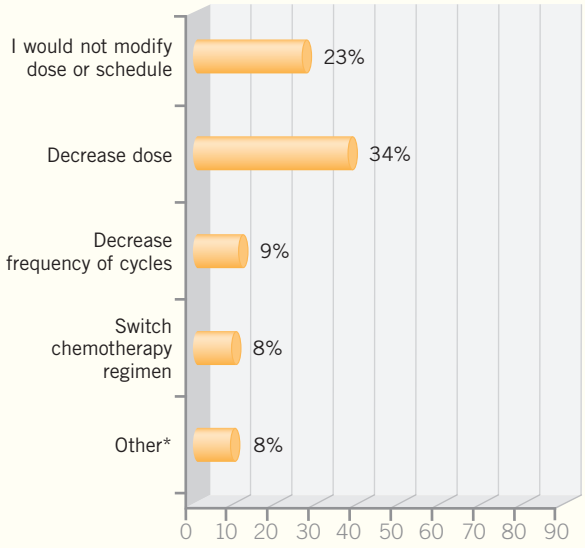
FIGURE 16

Which of the following is your most common approach to chemotherapy-related neuropathy in the curative setting?

Grade I: Loss of reflexes or paresthesia without pain or loss of function, or subjective weakness but no objective findings

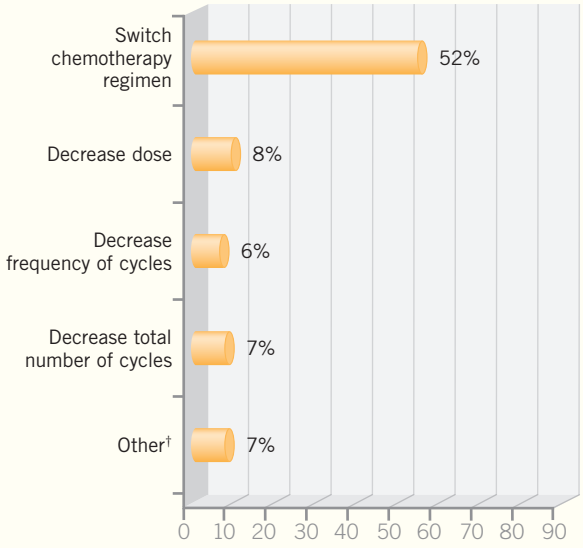


Grade II: Objective sensory loss or paresthesia or motor weakness interfering with function but not activities of daily living



* Decrease dose and/or frequency and/or number of cycles (18%)

Grade III: Objective sensory loss or paresthesia or motor weakness interfering with activities of daily living



† Decrease dose and/or frequency and/or number of cycles and/or switch regimen (20%)

Grade IV: Paralysis or permanent sensory loss that interferes with function

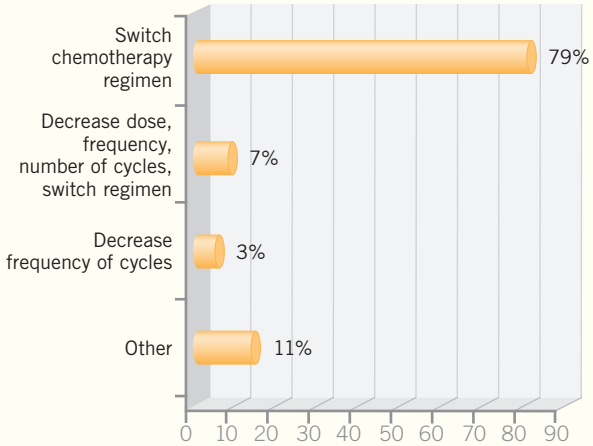


FIGURE 17

A 58-year-old diabetic is on her sixth of 12 planned cycles of modified FOLFOX with bevacizumab for first-line treatment of Stage IV colon cancer. She is responding to treatment but has developed painful persistent tingling in fingers and toes but no interference with activities of daily life. What would be your most likely recommendation at this time?

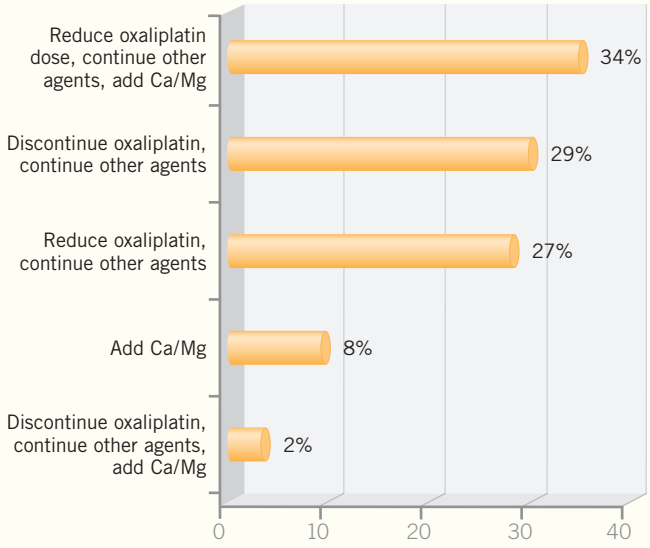
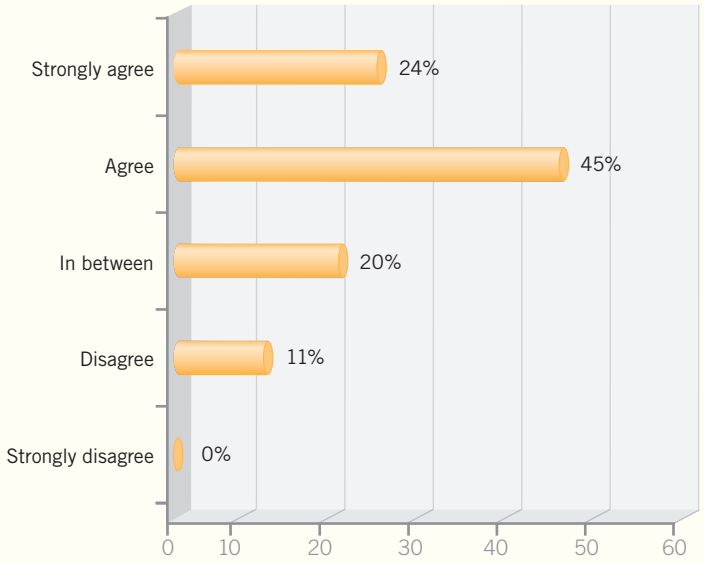


FIGURE 18

Chemotherapy-free intervals are a reasonable option when administering FOLFOX for metastatic colon cancer.



how the patient is faring rather than the calendar, but in practice, the two approaches are most likely similar.

Currently my algorithm is to reduce or stop only the problem agent and to continue the portions of therapy that seem to help, as long as they're well tolerated. For patients who need a break for personal reasons or for asthenia, I believe stopping even the fluoropyrimidine and bevacizumab for a period of several weeks to two months is a reasonable approach, as long as the disease burden and patient symptoms allow for the holiday.

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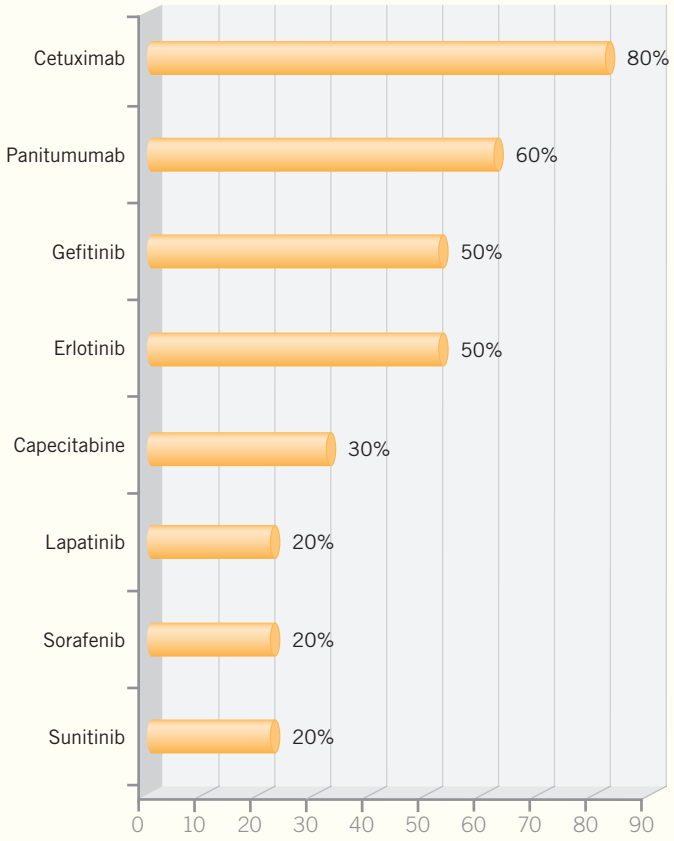
FIGURE 19

Approximately what percent of your patients receiving the following anticancer agents experience dermatologic side effects? (Median)



Lung Cancer Update Issue 3, 2008

THOMAS J LYNCH, MD: We are accruing to a study evaluating two years of adjuvant erlotinib for patients with EGFR mutations (NCT00567359). We know the response rates in this population are extraordinarily high. The issue is, we don't know what the long-term side effects are or the optimal duration of therapy. Patients develop significant rash. For patients who are really benefiting, the rash will burn out. It will not stay at that same level of intensity that you find in the first two months. In advanced disease, I have patients who have been on gefitinib and erlotinib for four, five, six or seven years.

Breast Cancer Update Issue 2, 2008

NANCY U LIN, MD: Some patients receiving the combination of capecitabine and lapatinib report fatigue or mild nausea, and there is the acneiform rash that is typical of any of the EGFR inhibitors. Typically, it appears over the lower part of the face and the upper chest.

Whether the rash is responding to treatment or going away on its own is hard to say, but we've used topical antibiotics with good results.

You definitely see hand-foot syndrome with capecitabine, and trial data suggest it may be worse with the addition of lapatinib.

Breast Cancer Update Issue 3, 2008

DR GRALOW: The rash we have seen secondary to lapatinib is located on the face and trunk. My group treats only patients with breast cancer, so we don't have much experience with EGFR-targeted therapy. We've learned of some topical treatments that we can use. We don't usually use oral antibiotics, but we have done so.

We're getting better at managing the rash. From the patients' standpoint, the rash is visible. They can tolerate it on their chest if they can cover it. When it's on their face, however, they don't like to be labeled or have people ask about it.

Renal Cell Cancer Update Issue 2, 2007

MARIO E LACOUTURE, MD: Dermatological side effects secondary to sorafenib and sunitinib are seen with high frequency. Data from Phase III randomized studies indicated that sorafenib led to a hand-foot skin reaction in 30 percent of patients, with Grade III to Grade IV severity in only five percent. With sunitinib, the development of the hand-foot skin reaction occurred in 20 percent of patients, and of those cases only five percent were Grade III to IV in severity.

Hand-foot syndrome also occurs with other agents, such as fluorouracil or pegylated doxorubicin. However, these seem to be clinically and histologically distinct from the hand-foot skin reaction occurring with sorafenib and sunitinib.

With more conventional agents, you have swelling, redness and pain diffusely through the palms and soles. With sorafenib and sunitinib, you have a thickening of the skin. This thickening, when it is subject to pressure, leads to bleeding underneath the thickened areas, causing significant pain for the patient.

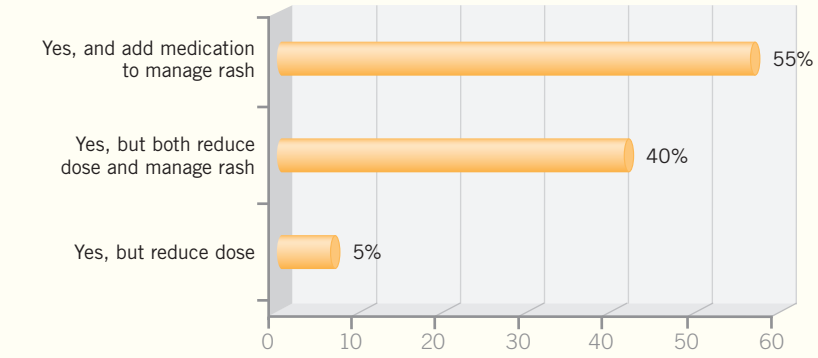
Colorectal Cancer Update NSABP Education Session 2006

MICHAEL J O'CONNELL, MD: The toxicity associated with panitumumab, like cetuximab, is a cutaneous eruption —

FIGURE 20

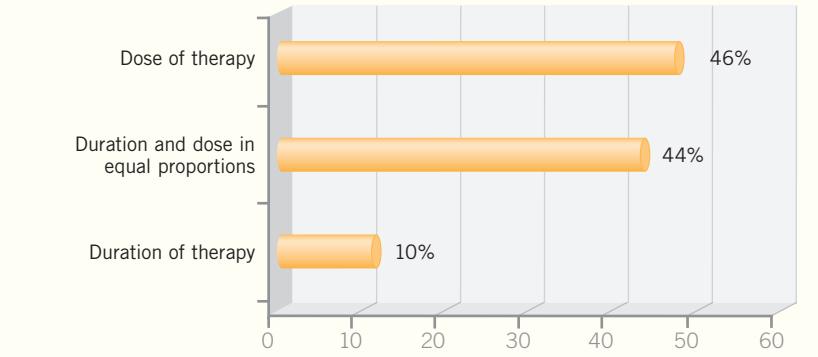
A 48-year-old man is receiving irinotecan/cetuximab as third-line treatment for metastatic colorectal cancer and is responding to therapy. He is due for his fourth week of treatment but presents with a Grade II acneiform rash (macular or papular eruption or erythema without associated symptoms).

Would you recommend continuing with cetuximab?

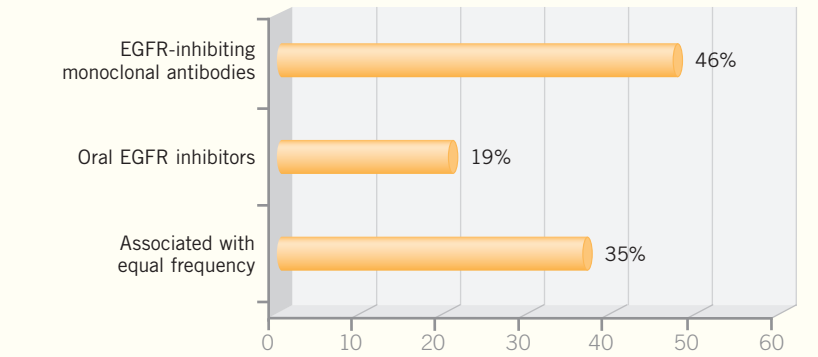


n = 83 who responded "yes"

In your experience, which of the following has the greatest impact on dermatologic side effects from EGFR inhibitors?



In your experience, with which EGFR inhibitors are dermatologic side effects more frequently associated?



acneiform skin rash. Nearly 100 percent of the patients receiving panitumumab are reported to have some degree of skin rash. Infusion reactions have been uncommon with panitumumab. A variety of other side effects are seen infrequently — diarrhea, fatigue — but the major dose-limiting side effect has been skin rash.

TJ Lynch et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: An evolving paradigm in clinical management. Oncologist 2007;12:610-21.

If patients develop EGFRI-associated dermatologic toxicity, the following interventions are suggested, based on severity of the reaction:

Mild toxicities: Patients may not require any form of intervention; however, it may be appropriate to treat some mild toxicities with topical hydrocortisone (1% or 2.5% cream) or clindamycin (1% gel). The EGFRI dosage should not be altered for mild toxicities.

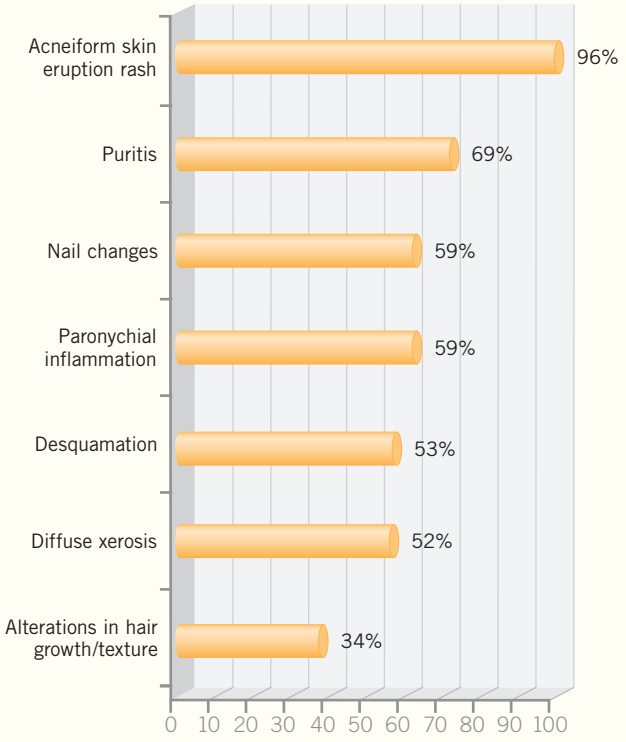
Moderate toxicities: Treatment is hydrocortisone (2.5% cream), clindamycin (1% gel), or pimecrolimus...(1% cream), with the addition of either doxycycline (100 mg, po twice a day [bid]) or minocycline (100 mg, po bid). The EGFRI dosage should not be altered for moderate toxicities.

Severe toxicities: A reduction in the EGFRI dose is recommended. Concomitant intervention is the same as for moderate toxicities — ie, hydrocortisone (2.5% cream), clindamycin (1% gel), or pimecrolimus (1% cream), with the addition of either doxycycline (100 mg, po bid) or minocycline (100 mg, po bid) — but with the addition of methylprednisolone dose pack. If toxicities do not sufficiently abate at 2-4 weeks, despite treatment, then interruption of EGFRI therapy is recommended, in accordance with prescribing information.

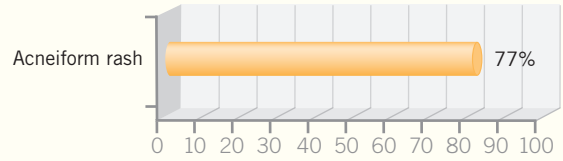
It is important to note that intervention for cutaneous toxicities needs to be maintained even when EGFRI therapy is decreased or is interrupted, because EGFRI-associated toxicities may have a very long duration, analogous to the prolonged tissue half-life of EGFRIs. Once the cutaneous reactions have sufficiently

FIGURE 21

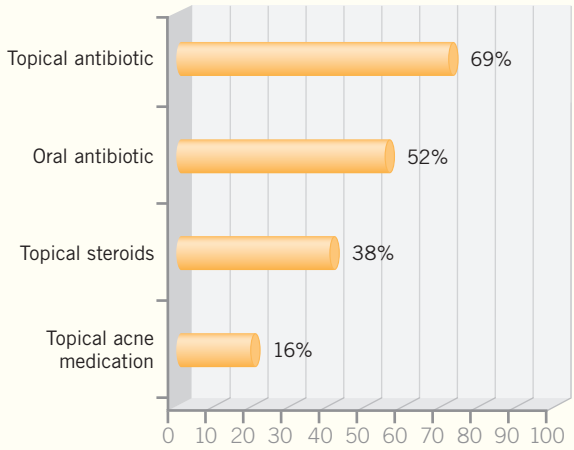
Which of the following dermatologic side effects of EGFR inhibitors have your patients experienced? (Check all that apply)



Which dermatologic side effects do your patients experience most frequently?



How do you generally treat patients who present with significant rash secondary to treatment with erlotinib or cetuximab? (Check all that apply)



diminished in severity, or resolved, then EGFRI therapy may typically be re-escalated or restarted with a good degree of confidence that cutaneous toxicities may be more easily managed.

RTP Satellite Symposium: Molecular Oncology 101 2008

DR LACOUTURE: I believe that — at least for most of the EGFR inhibitors right now — the possibility of having the discontinuation of these agents and the toxicities and reverting to a normal state would be better with the oral agents as opposed to the monoclonal antibodies.

We do seem to achieve a higher inhibition of the EGFR pathway with monoclonal antibodies, which may have greater antitumor activity by internalizing the receptor and, therefore, degrading it, and something that can also occur in skin. That may explain why we see a 17 to 20 percent rate of Grade III rash in the patients receiving the EGFR-inhibiting monoclonal antibodies versus approximately nine percent with the use of tyrosine kinase inhibitors.

Might I add that there's a consistent story emerging across several classes of biologics, and that is that a pretty good link is evident between class-specific toxicity and efficacy. For example, with tamoxifen there is now evidence that if a patient experiences hot flashes, she has a better likelihood of getting benefit.

We have growing evidence with VEGF-targeting agents that hypertension is associated with survival. And, of course, with EGFR inhibitors, we've got evidence from multiple agents that rash is associated with improved outcome, so I believe the toxicities are becoming pretty good pharmacodynamic indicators of benefit.

Lung Cancer Update Issue 2, 2008

ROMAN PEREZ-SOLER, MD: The RADIANT study is evaluating adjuvant chemotherapy followed by erlotinib administered for two years to patients with non-small cell lung cancer (NSCLC) who have EGFR-positive disease as determined by IHC or FISH. The issue will be whether a patient can receive erlotinib for two years — if that would be tolerable. I believe it will be tolerable for most patients.

The first two months may be rough, but after two months of erlotinib, the majority will find that the toxicity sub-

FIGURE 22

Which of the following dermatologic toxicities from the multitargeted tyrosine kinase inhibitors sorafenib and sunitinib do your patients...

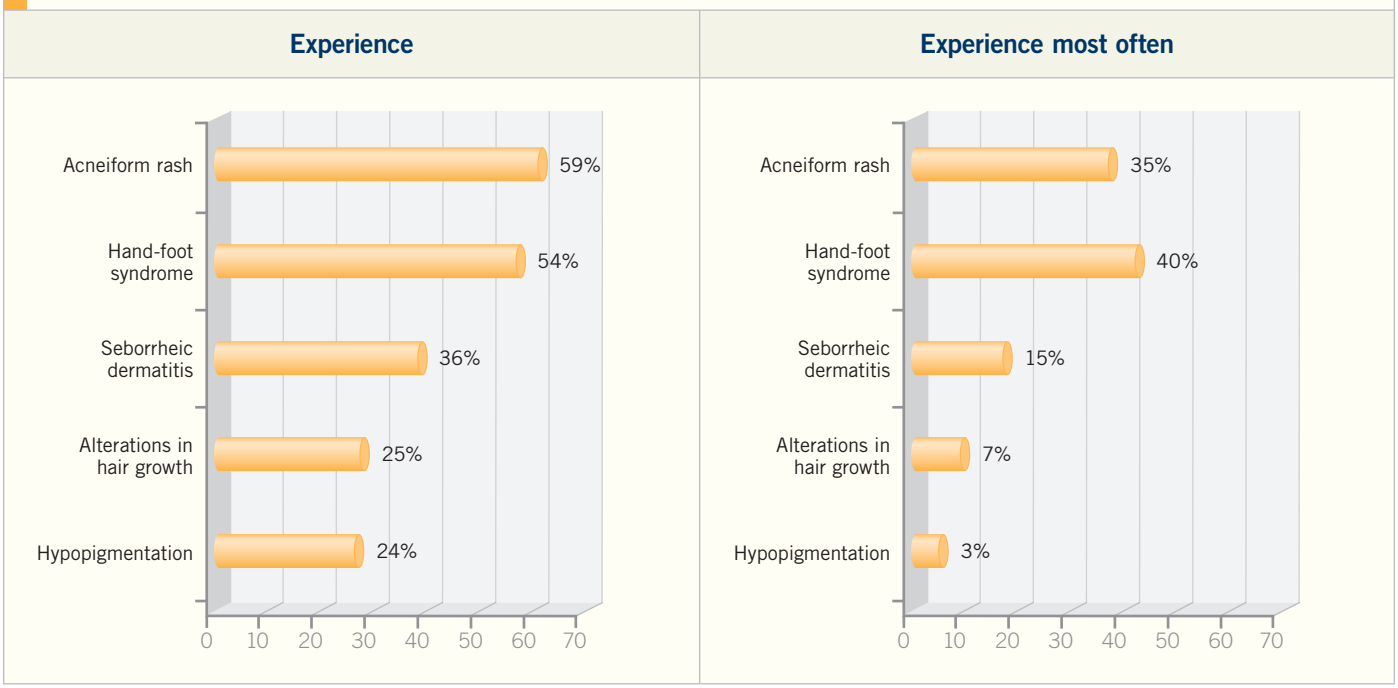
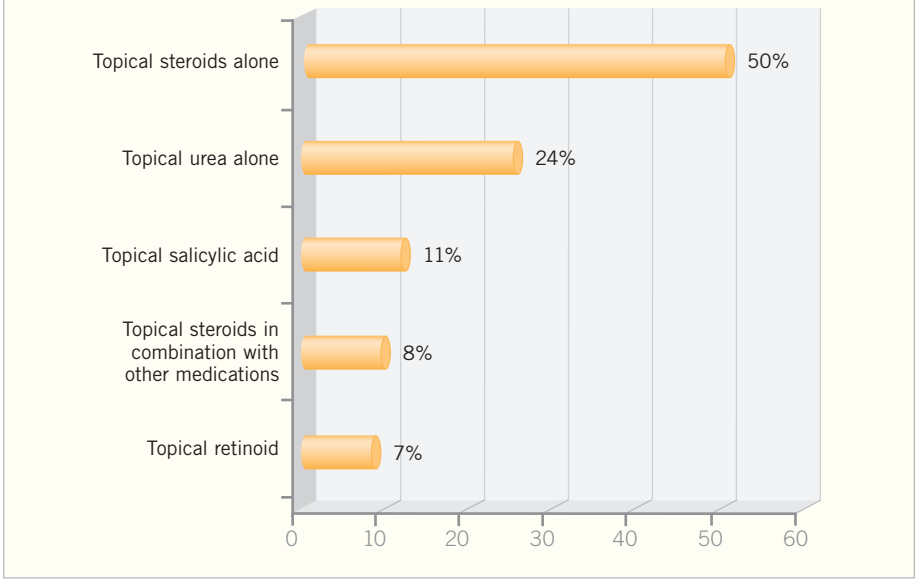


FIGURE 23

For a patient with hand-foot syndrome due to treatment with sorafenib or sunitinib, which of the following medications would you most likely recommend to manage this side effect?



sides and the skin rash improves. A minority will need a dose reduction or will not be able to tolerate the drug.

RTP Satellite Symposium: Molecular Oncology 101 2008

DR VENOOK: There's an adjuvant study (NCCTG-N0147) evaluating FOLFOX with or without cetuximab for patients with Stage III colon cancer. That is a tough sell. These patients believe they are cured. They're hedging their bets by taking more therapy, and we have trouble accruing patients and many drop out because they don't want a rash. I believe their perception of the gain and what's at stake is, as with most decisions by patients, the important factor.

However, in the advanced disease setting, patients tend to be much more forgiving of these kinds of toxicities. The perversion, of course, is the correlation with the degree of skin toxicity and efficacy of the agent. That may be favorable from a prognosis perspective, so in the waiting room, patients actually compare

rashes and they are pleased when they have a bad rash.

DR LACOUTURE: With regard to the dermatologic problems that patients who are receiving cetuximab may encounter, I believe that by instituting early intervention and frequent follow-up, we can maintain the majority of patients on therapy, and that is associated with their overall sense of well-being and quality of life.

The two randomized trials in which the administration of tetracycline antibiotics was administered prophylactically showed a significant benefit. In one study, tetracycline at 500 milligrams twice daily showed a significant reduction in Grade II or worse rash.

A second trial evaluating oral minocycline at 100 milligrams twice daily for cetuximab-associated rash, published in the *Journal of Clinical Oncology* in December 2007, showed treatment reduced the number of lesions.

Renal Cell Cancer Update Issue 2, 2008

ROBERT A FIGLIN, MD: We participated in the study that evaluated sorafenib in older patients with advanced renal cell carcinoma and found no apparent difficulty administering sorafenib to patients older than age 65 compared to younger patients.

In my experience, older patients tolerate sorafenib better than sunitinib. We see less fatigue, hand-foot syndrome and hypertension with sorafenib.

I believe that some of the problem with the hand-foot syndrome that's seen, specifically with the tyrosine kinase inhibitors, is that we don't realize how much we traumatize our hands and feet every day through our normal activities and that angiogenesis is part of wound healing.

When we inhibit angiogenesis and inhibit wound healing, we also inhibit the ability of these hands and feet to get better. That's why, when you stop these drugs for a period, the hands and feet get better quickly.

The single most important management strategy that my nurse tells me about all the time is anticipating the toxicities before they occur. We need to let patients know what they may experience, when to call and then what to do. They should not wait until the toxicity is so robust that the only alternative is to stop the drug.

Once the patient is experiencing them, the easiest way to manage toxicities such as hand-foot syndrome is to stop the drug, restart at a lower dose and recognize that we may be able to escalate the dose later. However, the further the toxicity has developed, the longer the patient will be off of treatment before it reverses.

Renal Cell Cancer Update Issue 2, 2007

DR LACOUTURE: For patients who are receiving sorafenib and sunitinib, the hand-foot skin reaction tends to develop after the first month of therapy. With sorafenib, for which an administration of 400 milligrams twice daily is uninterrupted, you tend to see it earlier than with sunitinib, as the sunitinib regimen allows for a two-week drug holiday. Patients are able to recover from the tenderness and pain during that two-week drug holiday.

Flushing — the red face and the seborrheic dermatitis-like reaction — occurs within the first two to four weeks. Hand-foot skin reactions usually occur later, and they tend to become worse over time if the symptoms are not managed. For management, we have used high-concentration urea-containing preparations, such as urea 40 percent creams.

These are keratolytics, so they disrupt the outer layer of the skin, the stratum corneum. They seem to thin out that thickened skin layer that may be responsible for the increased pressure leading to the pain.

We also prescribe high-potency topical steroids, such as clobetasol ointment, as this will minimize the proliferation or the division of those skin cells. It will also decrease the underlying inflammation.

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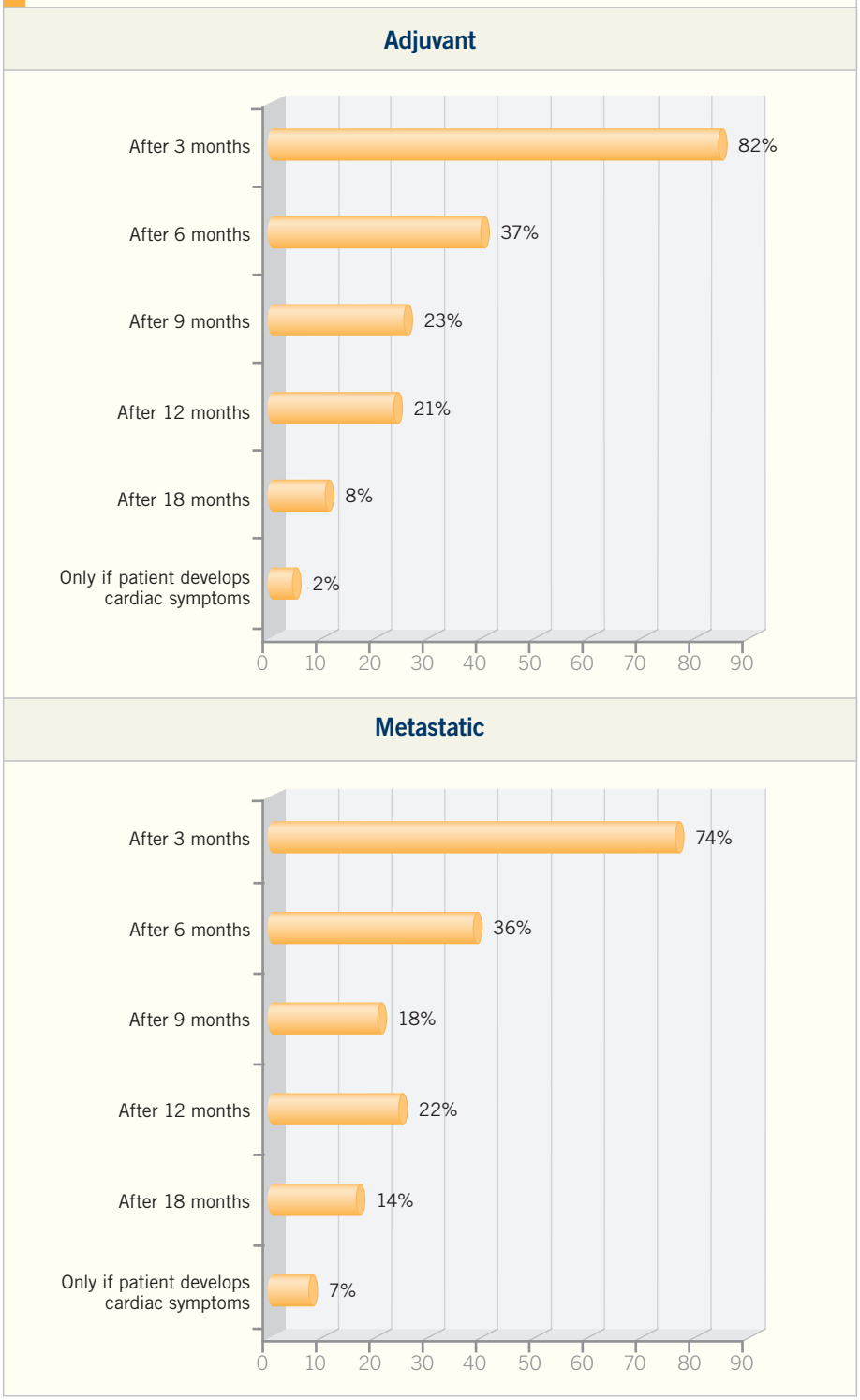
FIGURE 24

In addition to baseline evaluation, at which of the following points do you generally assess cardiac function in patients receiving trastuzumab in the following settings? (Check all that apply)



Special Edition Breast Cancer Update: Cardiologic Issues in Breast Cancer Management 2008

JEAN-BERNARD DURAND, MD: Symptoms of heart failure and the side effects of cancer treatment can be similar. As a result, physicians may be missing signs of cardiotoxicity with only history and physical examination.

In 2004, an interesting study was published in the *Journal of Clinical Oncology* that examined patients who had a constellation of eight symptoms and their physicians' ability to recognize these adverse events. It showed that 75 percent of the time, physicians did not pick up on what the patient was feeling. We might, therefore, have to rely on studies such as biomarkers, echocardiograms and MUGAs to better detect these symptoms.

The recommendations from a number of societies for patients receiving cardiotoxic drugs include an echocardiogram at baseline and when a change in symptoms occurs, such as lower extremity edema.

On physical exam, physicians should watch out for elevated neck veins, lower extremity edema, an S_3 on exam or bilateral rales. The problem is that the sensitivity of these physical exam findings is low. The accuracy of diagnosing heart failure based on something as simple as bilateral lower extremity swelling is approximately 35 percent.

The best clinical predictor we have found has to do with weight gain. We teach patients about the "rule of twos," which is if while on therapy they put on more than two pounds within two days, to contact us. We're watching for an early sign of fluid retention, and we treat that aggressively. Ultimately, that keeps patients on track so that they do not have to discontinue their cancer therapy.

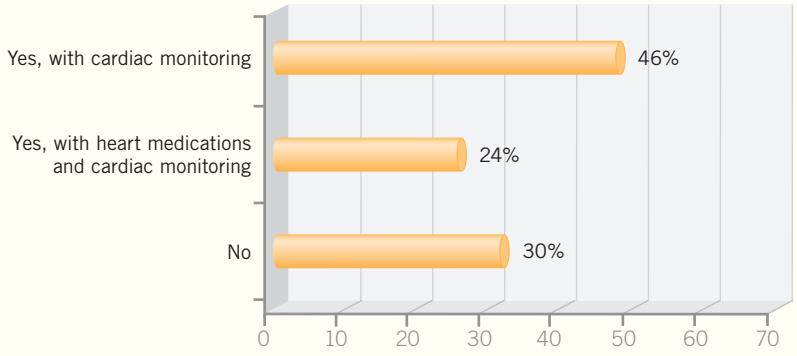
Special Edition Breast Cancer Update: Cardiologic Issues in Breast Cancer Management 2007

DENNIS J SLAMON, MD, PHD: In the adjuvant trastuzumab trials, we frequently saw patients with HER2-

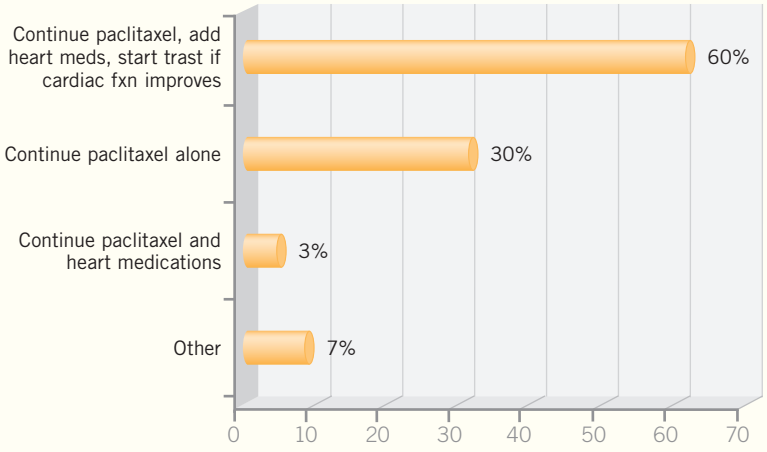
FIGURE 25

A 63-year-old woman with hypertension and ER/PR-negative, HER2-positive, node-positive breast cancer is treated with dose-dense AC for 4 cycles, with plans to follow this with concurrent weekly paclitaxel and trastuzumab for 12 weeks followed by trastuzumab alone to 1 year. Baseline MUGA prior to initiation of chemotherapy showed a left ventricular ejection fraction (LVEF) of 66%, and repeat MUGA after the 4 cycles of AC shows an LVEF of 50% (lower limit of institutional normal).

Would you recommend initiating paclitaxel/trastuzumab?



If "no," which of the following would you most likely recommend?



positive disease who were treated with AC but never received the taxane/trastuzumab therapy because they had declines in their LVEFs, yet those are not scored as toxicities.

It's a greater negative when that happens than when other things happen because now you're denying a potentially active drug to a woman who might benefit from it because you forced the agenda with the anthracycline. That happened between three and five percent of the time in all the studies that were examined, and it's more frequent among older patients. The problem is that once physicians see the LVEF drop, they're reluctant to take the risk.

I believe that oncologists are becoming increasingly aware that the cardiac toxicities might continue for longer than previously believed. The assumption had been that once we stopped trastuzumab, the cardiac problems reversed in a matter of a couple of weeks or months. However, the data — at least the BCIRG 006 data — show that they are longer lasting. We now know that a year and a half later, those subclinical LVEF declines seem to be maintained at some level.

We previously thought that the patients with clinical congestive heart failure improved with treatment. However, at least two thirds of them require continued treatment. That means that you can treat their congestive heart failure, but it doesn't mean that you've made the heart better. I believe that these definitions must be more carefully stated when some of the data are presented.

Special Edition Breast Cancer Update: Cardiologic Issues in Breast Cancer Management 2008

HAROLD J BURSTEIN, MD, PHD: Monitoring ejection fractions in patients on adjuvant trastuzumab and deciding when to stop and start the agent is a difficult situation because we have a black-box warning about cardiotoxicity with the use of trastuzumab.

Clearly, these patients merit cardiac surveillance. It seems as if borderline ejection fraction at baseline, age and perhaps preexisting hypertension stand out as predictors of trastuzumab-related cardiomyopathy.

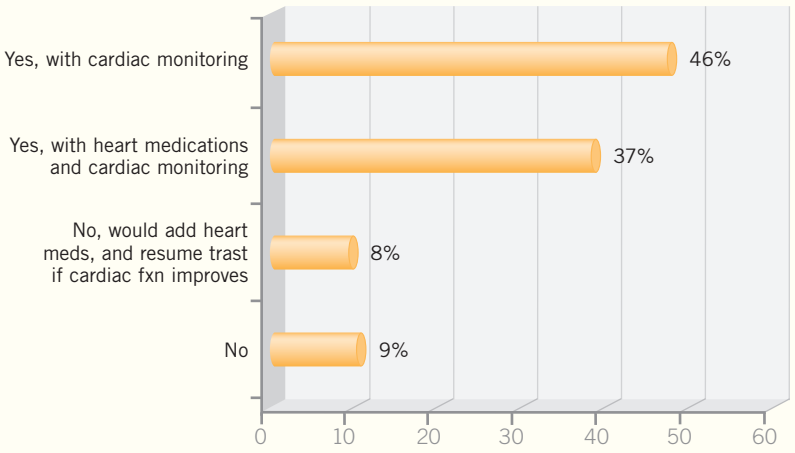
The patients still require surveillance, irrespective of those risk factors. My practicing algorithm is to check cardiac function at baseline, after the anthracycline-based chemotherapy, after three to four months of the taxane/trastuzumab combination and at some point again. It must be said that these safeguards were put in place when we did not know the clinical efficacy of trastuzumab.

The challenge arises in cases with high-risk breast tumors in which you are trying to bring important therapy to bear on the patient's disease. When you are trying to combat these reductions in ejection fraction of unknown clinical significance, it's tough to be a clinician because we have no hard and fast rules.

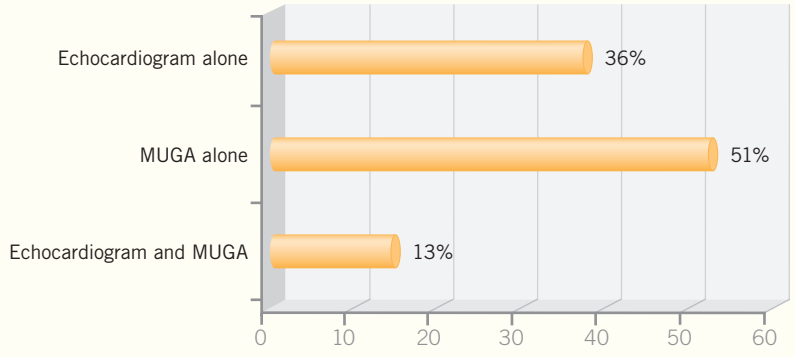
FIGURE 26

A 43-year-old woman with ER/PR-negative, HER2-positive, node-positive breast cancer is treated with dose-dense AC, followed by concurrent weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab every 3 weeks. The patient has an EF of 60% prior to initiation of trastuzumab, which decreases to 45% after 6 months of trastuzumab. The patient is asymptomatic. Trastuzumab is discontinued for 4 weeks, and without any other interventions, the patient's EF increases to 50%.

Would you recommend resuming treatment with trastuzumab at this time?



Which of the following tests do you use most often to assess LVEF prior to cardiotoxic anticancer therapy?



The rules in the trials were based on not knowing that trastuzumab would be a lifesaving drug for women.

Special Edition Breast Cancer Update: Cardiologic Issues in Breast Cancer Management 2008

DR DURAND: The use of trastuzumab has shifted to earlier and earlier and despite that, the safety data remain good. The data from the clinical trials show the incidence of heart failure is low — two to four percent — and we saw few deaths. The morbidity was higher than anticipated, but at the time these trials were conducted, we weren't administering ACE inhibitors and beta blockers or trying to track these events as secondary endpoints. I believe that with medical intervention, the incidence of heart failure would probably be even lower.

In addition, we know that the reversibility of the trastuzumab-induced cardiac damage is excellent. At our institution, we have seen clinically that when we put these patients on beta-blockers and ACE inhibitors, they have an excellent ability to completely recover their normal heart function.

We presented a paper at the Heart Failure Society of America in 2002 on young women who were asymptomatic but developed small drops in heart function. Their heart function was in the range of 40 to 50 percent.

The patients wanted to remain on the trastuzumab because they knew it reduced their rate of disease progression by 50 percent, so we spoke with their oncologists and we put them on both an ACE inhibitor and a beta-blocker without stopping the trastuzumab. We never stopped the trastuzumab, their heart function went back to completely normal and our longest follow-up is now five years.

Breast Cancer Update Issue 6, 2008

DR PICCART-GEBHART: The issue of an anthracycline- versus a nonanthracycline-containing chemotherapy for a patient with HER2-positive, node-positive disease is a hot topic. In Europe, we are selecting the type of chemotherapy based on risk factors for cardiotoxicity, including age, obesity, poorly controlled hypertension and a left ventricular ejection fraction that is on the low end of the normal range prior to initiating therapy.

For patients who are at a higher risk for cardiotoxicity, it is reasonable to choose a nonanthracycline-based chemotherapy. I prefer TCH, the regimen that has been piloted in the BCIRG 006 study. It is important to be able to clearly explain to patients the side effects they can expect with this regimen.

For a 38-year-old woman who has five positive nodes but is in otherwise perfect health, we have two options. The five positive nodes are worrisome and indicate a higher risk for an early relapse. You do not want to give a six-month chemotherapy

FIGURE 27

For a woman in average health with a 1.2-cm, Grade II, ER-positive/PR-positive, HER2-positive tumor with 3 positive nodes, how would you compare TCH to your preferred anthracycline/taxane/trastuzumab regimen?

Safety and tolerability

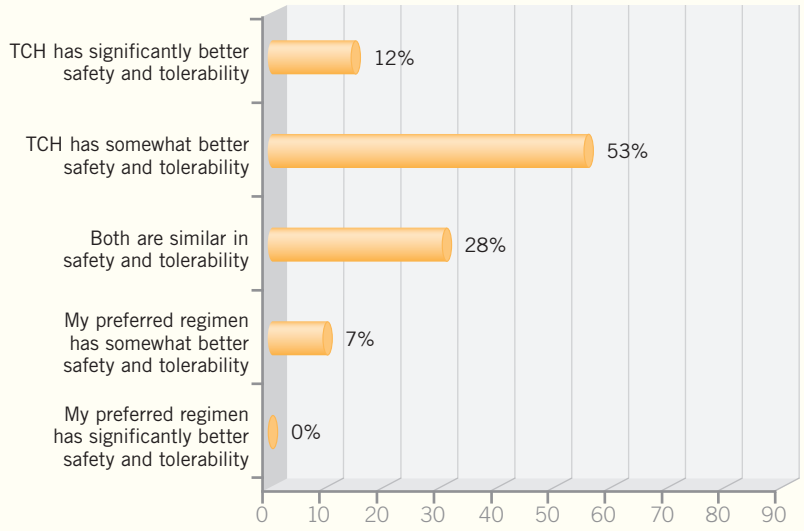
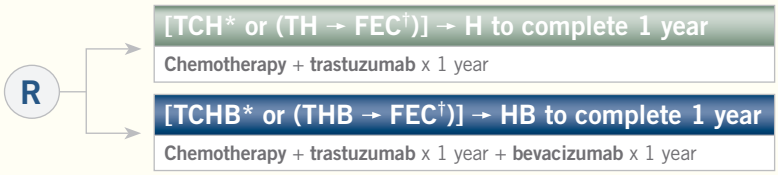


FIGURE 28

BETH: NSABP/CIRG trial of chemotherapy and trastuzumab with or without bevacizumab in patients with HER2-positive early breast cancer

Protocol IDs: NSABP-B-44-1, CIRG (TRIO) 011, BETH, NCT00625898
Target Accrual: 3,500



Eligibility

- Node-positive or high-risk, node-negative early breast cancer
- HER2-positive by central FISH testing

Stratification

- Nodal status
- Hormone receptor status

T = docetaxel; C = carboplatin; H = trastuzumab; FEC = 5-FU, epirubicin, cyclophosphamide; B = bevacizumab

* Chemotherapy used by NSABP/CIRG investigators (Cohort 1)
† Chemotherapy used by independent investigators (Cohort 2)

SOURCE: NCI Physician Data Query, October 2008.

regimen and then start trastuzumab. It makes sense for such a woman to go with TCH or what we like to do in Europe, which is three cycles of FEC — this is anthracycline-based but only three cycles — and then move on to a taxane, which can be docetaxel or paclitaxel, administered concomitantly with trastuzumab.

Breast Cancer Update Issue 5, 2008

DR WOLMARK: The BETH study — the adjuvant trial being conducted by the NSABP and CIRG evaluating trastuzumab with or without bevacizumab — opened recently (Figure 26). I believe we need to know what the addition of bevacizumab to trastuzumab will yield in the adjuvant setting, based on some interesting preclinical work and early clinical findings. Cardiovascular concerns exist with both agents, so the NSABP and the CIRG are offering TCH as the template.

We made the decision not to use an anthracycline template to test the combination of trastuzumab and bevacizumab, with one of the rationales being the potential toxicity of using both agents on an anthracycline template.

However, some participating physicians, particularly those in Europe, will administer an anthracycline template along with bevacizumab and trastuzumab, so I believe we will receive an answer rapidly as to whether that regimen is tolerable.

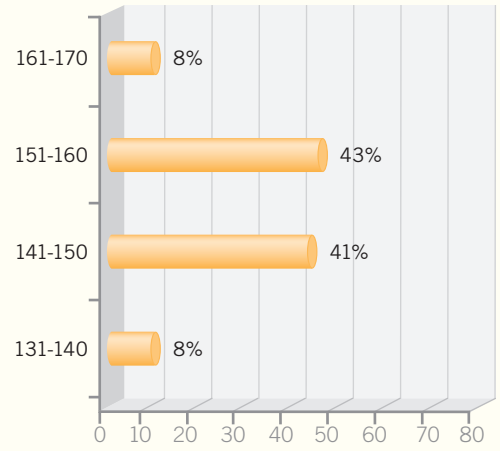
Special Edition Breast Cancer Update: Cardiologic Issues in Breast Cancer Management 2008

DR DURAND: At our institution, with bevacizumab we have a recommendation that the patient's blood pressure must be less than 140/90 for treatment, and that is incorporated into all our clinical trials. We have follow-up data that show our incidence of heart failure is actually quite low, less than two percent, if we control the patient's blood pressure more aggressively. We are finding that we are able to keep women involved in these newer trials that include trastuzumab and bevacizumab on therapy much longer if we just do a better job of internal medicine.

FIGURE 29

At what persistent blood pressure do you generally initiate antihypertensive therapy for a patient without cardiac risk factors who is receiving bevacizumab for metastatic disease?

Systolic



Diastolic

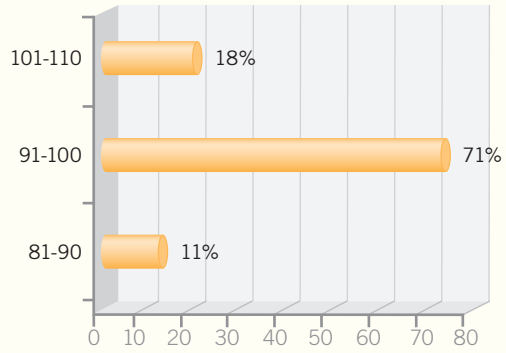
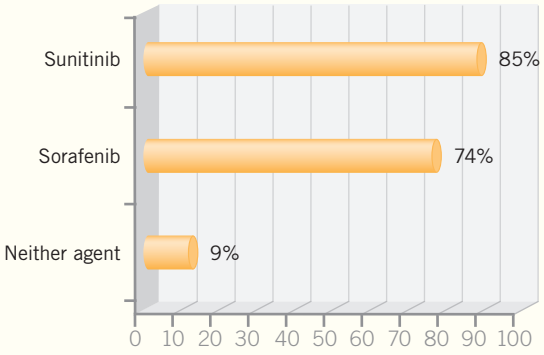
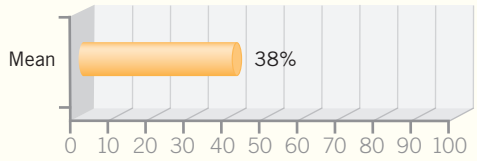


FIGURE 30

Which of the following tyrosine kinase inhibitors (TKIs) have you used?



If sorafenib or sunitinib is used in your practice, what percent of the patients who receive sorafenib or sunitinib develop hypertension?



Renal Cell Cancer Update Think Tank Issue 1, 2008

WALTER STADLER, MD: I want to emphasize that we cannot minimize some of the cardiovascular toxicities of the multikinase inhibitors, sunitinib and sorafenib, in renal cell carcinoma. The rate of hypertension in the clinical trials is approximately 20 percent, and increases in blood pressure occur in probably two thirds to three fourths of patients. We're talking about chronic treatment with these agents — perhaps years of treatment when we use these agents sequentially — and we're talking about an elderly population, which may have multiple comorbidities, including cardiovascular disease.

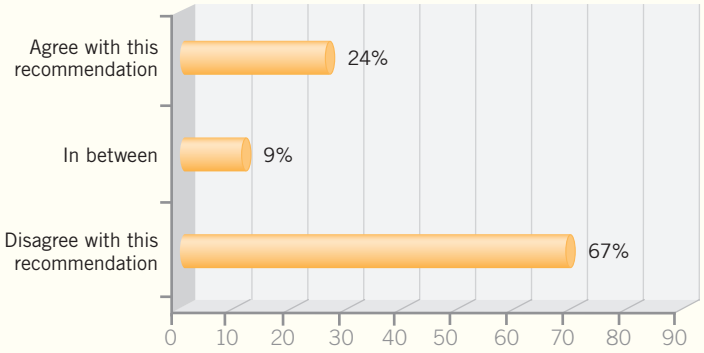
We observe cardiovascular events, even with short follow-up, in the current Phase III trials — an increased risk of cardiovascular and cerebrovascular events. Attending to the cardiac toxicities from these agents will be an increasingly important issue in terms of patient care.

I tell patients that a risk of a cardiovascular or cerebrovascular event exists on the order of about three percent, in comparison to one percent in controls in the randomized trials.

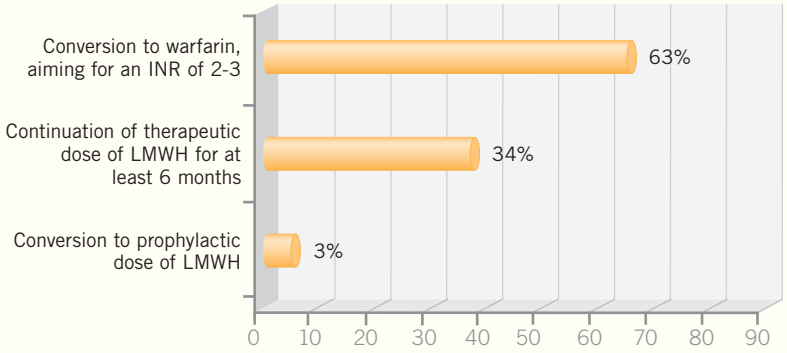
FIGURE 31

A 53-year-old man with metastatic colon cancer is receiving treatment with FOLFOX/bevacizumab and presents with DVT/PE. He is treated acutely with LMWH at a therapeutic (full) dose for 5 days and has an uncomplicated course. You expect to continue the same chemotherapy regimen after the patient's condition becomes stable.

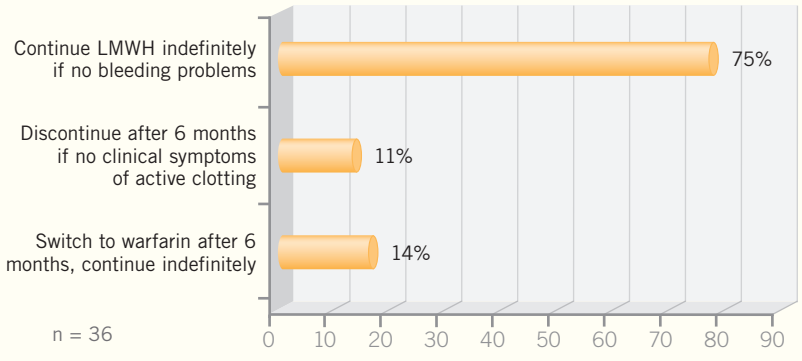
Placement of an inferior vena cava (IVC) filter is recommended.



Your most common systemic anticoagulation recommendation, if any, for this patient assuming an IVC filter is not in place:



This patient is maintained on LMWH for his DVT/PE. What would be your recommendation for the duration of his anticoagulation therapy?



Lung Cancer Update Issue 3, 2008

DR LYNCH: It appears that anticoagulation therapy can be part of the approach to lung cancer in patients who are receiving bevacizumab. It's more difficult to come by data on patients who are receiving anticoagulants prior to therapy. I have been hesitant to use bevacizumab in that setting. I'm not simply concerned about the anticoagulants — I'm concerned about why they were receiving these agents.

Most of my patients who are anticoagulated have experienced an acute thrombotic event. I've been hesitant to use bevacizumab for the patient with a pulmonary embolism discovered at diagnosis, who has an acute need for heparin, whereas for the patient who has been receiving warfarin for a long time for atrial fibrillation, I suspect it's fine to use bevacizumab. The concern is more for the patient who's been acutely anticoagulated for a clotting event such as a deep vein thrombosis, pulmonary embolus or a myocardial infarction.

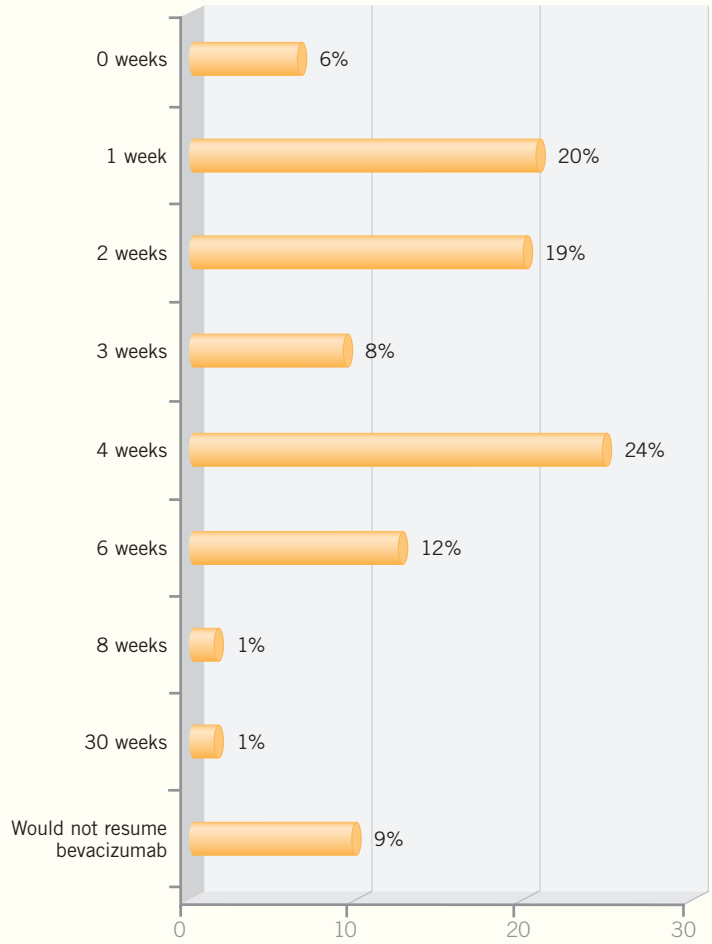
Colorectal Cancer Update for Nurses Issue 1, 2007

DR HALLER: The issue of wound healing in patients receiving bevacizumab is subjective. Surgeons evaluate wound healing every day, and I suspect if they knew their patient was on bevacizumab, they might say the healing was slower than usual. No huge difference exists in operative complications in patients receiving bevacizumab. The agent has a long half-life of more than 21 days, so even when the patients are six weeks out, they still have enough bevacizumab in their system to inhibit anything. The truth is that sometimes people need to go to surgery and don't delay surgery just because they received a dose of bevacizumab two weeks ago.

A paper was published on patients who underwent liver resection after receiving six cycles of chemotherapy and bevacizumab, but the bevacizumab was held during the last cycle so that four weeks had elapsed between surgery and the last dose. The data revealed no obvious difference in regeneration of liver or bleeding,

FIGURE 32

A patient is receiving CAPOX in combination with bevacizumab as treatment for metastatic colon cancer and is responding well to treatment. However, after 2 months of treatment, he requires a Mediport® due to loss of all peripheral venous access. It is inserted without complications or wound-healing problems. How long after placement do you recommend waiting before resuming bevacizumab?



so while I believe that it's an issue theoretically, and probably somewhat real, in practice it doesn't seem to be a "deal breaker." Nor is it a major issue for minor but necessary surgical procedures, such as insertion of a port or dental surgery.

Lung Cancer Update Issue 3, 2008

F ANTHONY GRECO, MD: Most of our protocols require a week between putting a port in and using bevacizumab. Personally, I have done it the same day for several patients, and so far I've not seen a problem. That's not a huge incision and it doesn't go through viscera.

I certainly wouldn't use bevacizumab within a week after bowel resection. Sometimes patients who have received bevacizumab then have an emergency in which they need surgery and we don't have a choice. Interestingly enough, most of those patients fare well, but I don't tempt fate and undertake major surgery by design after proximate use of bevacizumab.

Lung Cancer Update Issue 2, 2008

JULIE R BRAHMER, MD: With regard to predictors of hemoptysis secondary to bevacizumab, there are many thoughts. Some believe the location of the tumor is important — central versus peripheral. Others believe a history of hemoptysis increases a patient's risk. Still others feel it is related to the presence of tumor cavitation, which is borne out in a small analysis by Dr Sandler. Therefore, if tumor cavitation is present initially, I generally avoid using bevacizumab.

If the tumor develops cavitation while responding to bevacizumab, some recommend stopping bevacizumab. Some recommend using radiation therapy in that local area to try to decrease the risk of bleeding with bevacizumab. If cavitation did occur with therapy, particularly in a central lesion, I would seriously talk with the patient about the increased risk.

I don't believe location is quite as important, because bevacizumab has been administered to patients with small cell lung cancer. Those tumors are all mainly central, and we've seen no increased risk of bleeding in that patient population.

Lung Cancer Update Issue 3, 2008

DR LYNCH: The eligibility criteria for the AVAiL trial and ECOG-E4599 did not restrict tumor location, and in subsequent reviews, central tumors didn't appear to be a problem. So in my practice, having a tumor that's central or abutting the pulmonary artery or aorta, in and of itself, doesn't mean that patient can't receive bevacizumab.

However, I believe we are learning that pretherapy cavitation may be significant. One of the big challenges now is how to manage tumor cavitation that develops in response to therapy. In a way, that's what you're hoping for because those cavitary responses are some of the best responses we see. However, they are associated with an increased rate of hemoptysis, which is of concern.

In my practice, when a patient's tumor has an enormous cavitary response, I generally stop the chemotherapy and bevacizumab and observe that patient. That is completely unevidence based — I'm

FIGURE 33

A 52-year-old man with Stage IV nonsquamous non-small cell lung cancer (NSCLC) is undergoing treatment with paclitaxel/carboplatin/bevacizumab and is responding to treatment. Three months into treatment, the patient begins developing hemoptysis despite radiographic improvement. It is reasonable to continue with bevacizumab in this situation.

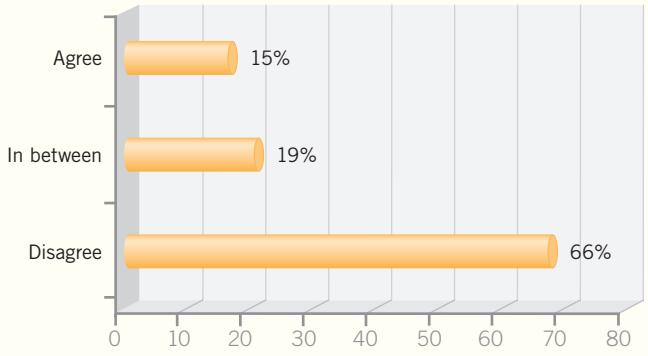
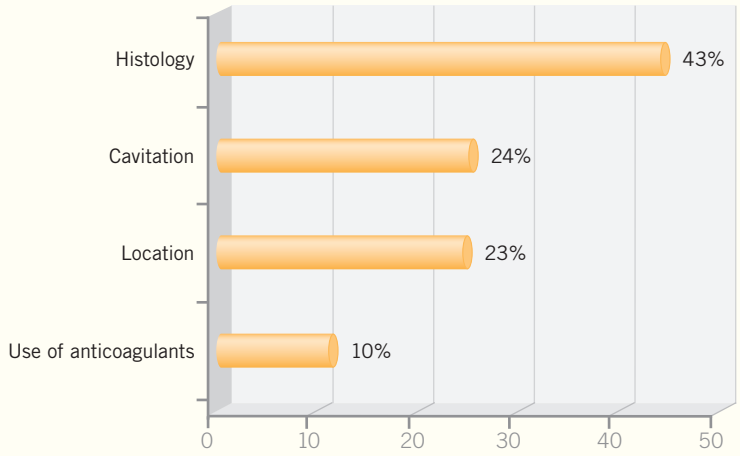


FIGURE 34

Which of the following tumor characteristics do you consider to be the most important predisposing risk factor for hemoptysis in patients with NSCLC receiving bevacizumab?



simply nervous in that setting. I believe we need to spend more time examining exactly how those patients fare.

SELECT PUBLICATIONS

Allegra CJ et al. **Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer.** *Proc ASCO* 2008;**Abstract 4006**.

Bria E et al. **Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: The dark side of the moon? A meta-analysis of the randomized trials.** *Breast Cancer Res Treat* 2008;109(2):231-9. **Abstract**

Chu DT et al. **Risk of thromboembolism associated with an angiogenesis inhibitor bevacizumab in cancer patients.** *Proc ASCO* 2008;**Abstract 14559**.

Dang C et al. **The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/amplified breast cancer.** *J Clin Oncol* 2008;26(8):1216-22. **Abstract**

Escudier B et al. **Sorafenib in advanced clear-cell renal-cell carcinoma.** *N Engl J Med* 2007;356(2):125-34. **Abstract**

Giantonio BJ et al. **Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200.** *J Clin Oncol* 2007;25(12):1539-44. **Abstract**

Hurwitz H, Saini S. **Bevacizumab in the treatment of metastatic colorectal cancer: Safety profile and management of adverse events.** *Semin Oncol* 2006;33(5 Suppl 10):26-34. **Abstract**

Llovet JM et al. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90. **Abstract**

Mackey JR et al. **Cardiac management during adjuvant trastuzumab therapy: Recommendations of the Canadian Trastuzumab Working Group.** *Curr Oncol* 2008;15(1):24-35. **Abstract**

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

Motzer RJ et al. **Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.** *N Engl J Med* 2007;356(2):115-24. **Abstract**

Perez EA et al. **Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial.** *J Clin Oncol* 2008;26(8):1231-8. **Abstract**

Purdie DM et al. **The safety of long-term bevacizumab use: Results from the BRiTE observational cohort study (OCS).** *Proc ASCO* 2008;**Abstract 4103**.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

FIGURE 35

What is your management approach for patients who are depressed because of cancer diagnosis or cancer-related treatment?

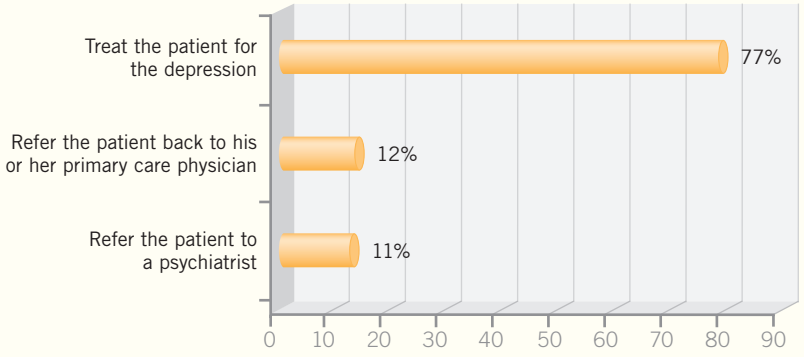
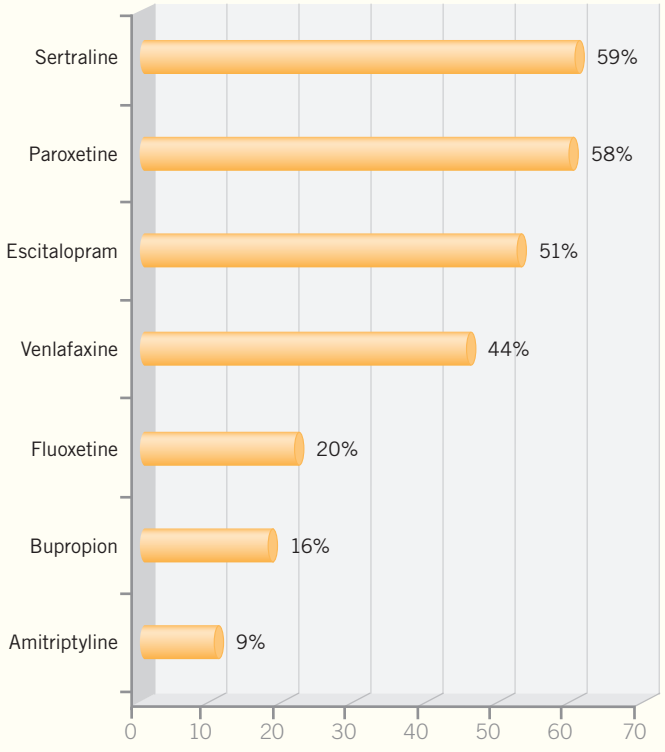


FIGURE 36

Which of the following do you generally prescribe for patients who are depressed because of cancer diagnosis or cancer-related treatment?



M Miovic, S Block. Psychiatric disorders in advanced cancer. Cancer 2007;110(8):1665-76.

Because of the low rate of complications from treatment of depression, experts recommend a strategy of "if in doubt, treat." A combination of antidepressant medication, supportive psychotherapy, and patient and family education are the gold standard of treatment for depression in advanced disease. Several randomized, controlled trials that compared antidepressants with a placebo for depression in cancer patients suggested a benefit from treatment...

Serotonin-specific reuptake inhibitors (SSRI) are the first-line agents when life expectancy is 2-3 weeks or more, and they are safe and well tolerated in cancer patients. They are especially useful for depression with irritability and/or comorbid anxiety.

To avoid initial side effects, oncologists should prescribe a starting dose for 4-7 days, then increase to the normal dose. Educate the patient that antidepressants take about 2 weeks for initial response and 4-6 weeks to reach peak effect at a given dose.

If the patient obtains a partial response after 1 month on a normal dose, increase to a higher dose to get a complete response. If the patient shows little or no response, switch to another agent.

Patients who fail 2 different SSRIs, or obtain only a partial response, should be referred to a psychiatrist for further evaluation and treatment.

JE Bower. Behavioral symptoms in patients with breast cancer and survivors. J Clin Oncol 2008;26(5):768-77.

The majority of studies find that 20% to 30% of women experience elevated depressive symptoms, although the prevalence of major depressive disorder may be considerably lower. Major depressive disorder is a clinical syndrome that lasts for at least 2 weeks and causes significant impairment in normal functioning.

FIGURE 37

If a patient's depression does not improve with the antidepressant you prescribe, which of the following best describes what you do?

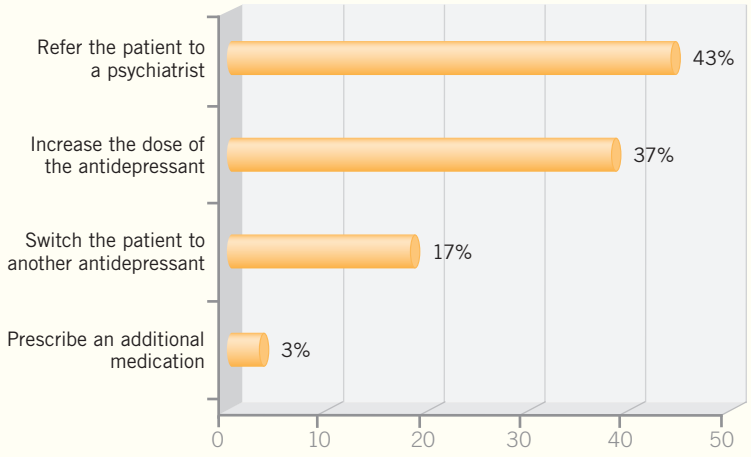
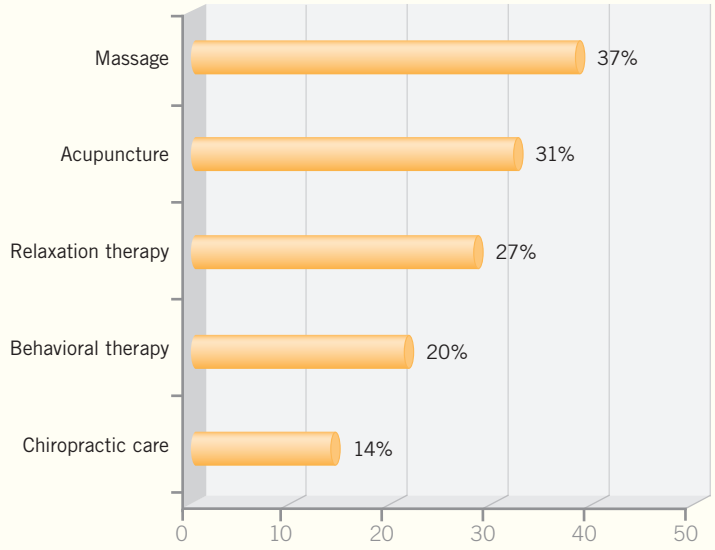


FIGURE 38

What are the top complementary and alternative practices you have recommended for your cancer patients receiving anticancer treatments?



n = 63 who have recommended holistic therapy

One recent study that used a structured clinical interview to diagnose depression found that 9% of ambulatory breast cancer patients met criteria for major depression. Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time as women adjust to the initial shock of diagnosis and acute effects of cancer treatment...

As might be expected, depression has a detrimental effect on all aspects of quality of life in cancer patients and is associated with poorer medical adherence and more barriers to cancer care, including lack of understanding of treatment recommendations and worries about treatment adverse effects.

There is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients. As such, depression represents an important target for timely identification and treatment.

L Corbin. Safety and efficacy of massage therapy for patients with cancer. Cancer Control 2005;12(3):158-64.

Conventional care for patients with cancer can safely incorporate massage therapy, although cancer patients may be at higher risk of rare adverse events. The strongest evidence for benefits of massage is for stress and anxiety reduction, although research for pain control and management of other symptoms common to patients with cancer, including pain, is promising.

The oncologist should feel comfortable discussing massage therapy with patients and be able to refer patients to a qualified massage therapist as appropriate.

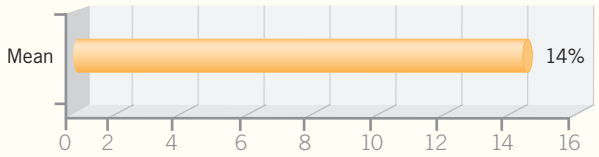
WA Mellink et al. Cancer patients seeking a second surgical opinion: Results of a study on motives, needs, and expectations. J Clin Oncol 2003;21(8):1492-7.

In 212 consecutive patients seeking a second opinion at the Surgical Oncology Outpatient Clinic, satisfaction with the first specialist, motivation for the second opinion, need for information, preference for decision participation, and hope for and expectation of a different second opinion were assessed with a questionnaire...

The mean age was 53 years. Most patients were women (82%), of whom 76% were diagnosed with breast cancer. Half of the patients (51%) had a low educational level. The majority of patients (62%) only had internal motives for second-opinion seeking associated

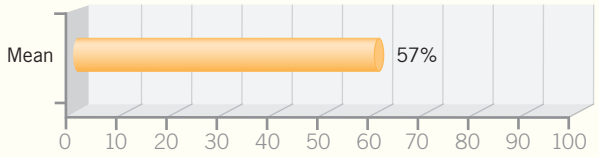
FIGURE 39

Approximately what percent of your patients consult another medical oncologist for a second opinion at any point during their illness?

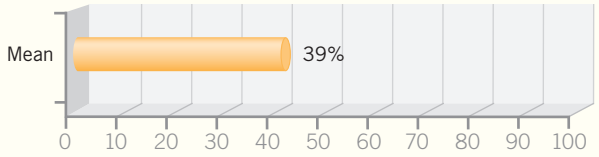


Of those patients who seek a second opinion, what percent seek it at each of the following time points?

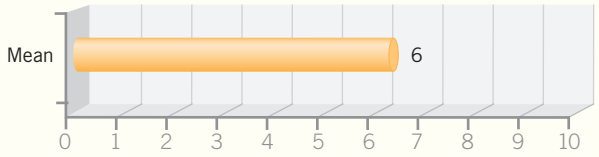
At the time of diagnosis



At disease progression when a change of treatment is required



On a scale of 0 to 10, how positive or helpful have second opinions been for your patients? (0 = not at all positive/helpful, 10 = very positive/helpful)



with the need for reassurance and more certainty, whereas a substantial minority of patients (38%) also had external motives related to negative experiences or unfulfilled needs.

The externally motivated patients had a higher anxiety disposition, were less satisfied with their first specialist, preferred a more active role in medical decision making, and more often hoped for and expected a different second opinion.

N Moumjid et al. Seeking a second opinion: Do patients need a3 second opinion when practice guidelines exist? Health Policy 2007;80(1):43-50.

Patients often search for a second opinion (ie, a search for additional information on the diagnosis and/or treatment options and the potential prognosis, which will help the patient decide what to do or not to do, where, with whom and how). The scope of this phenomenon is not well documented. Also it is not clear if this is warranted or not.

This paper aims to explore whether knowing that his clinician follows practice guidelines eliminates the need of a patient's to seek a second opinion. Given that practice guidelines should allow each patient to benefit from the best current clinical evidence, one might wonder if in such a context a second opinion is still necessary, and if so, for what reasons? ...

We conclude that the implementation of practice guidelines will not eliminate the need for a second opinion consultation. On the contrary, the use of guidelines can even stimulate a broader request for second opinions.

SELECT PUBLICATIONS

Bardia A et al. **Efficacy of complementary and alternative medicine therapies in relieving cancer pain: A systematic review.** *J Clin Oncol* 2006;24(34):5457-64. Abstract

Boon HS et al. **Trends in complementary/alternative medicine use by breast cancer survivors: Comparing survey data from 1998 and 2005.** *BMC Women's Health* 2007;7:4. Abstract

Corbin L. **Safety and efficacy of massage therapy for patients with cancer.** *Cancer Control* 2005;12(3):158-64. Abstract

Dy S et al. **Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea.** *J Clin Oncol* 2008;26(23):3886-95. Abstract

Matthews AK et al. **Complementary and alternative medicine use among breast cancer survivors.** *J Altern Complement Med* 2007;13(5):555-62. Abstract

Mellink WA et al. **Discrepancy between second and first opinion in surgical oncological patients.** *Eur J Surg Oncol* 2006;32(1):108-12. Abstract

Miovic M, Block S. **Psychiatric disorders in advanced cancer.** *Cancer* 2007;110(8):1665-76. Abstract

Moumjid N et al. **Seeking a second opinion: Do patients need a second opinion when practice guidelines exist?** *Health Policy* 2007;80(1):43-50. Abstract

Oskay-Ozcelik G et al. **Breast cancer patients' expectations in respect of the physician-patient relationship and treatment management results of a survey of 617 patients.** *Ann Oncol* 2007;18(3):479-84. Abstract

Rodin G. **The treatment of depression in cancer patients: A systematic review.** *Support Care Cancer* 2007;15(12):123-36. Abstract

Tascilar M et al. **Complementary and alternative medicine during cancer treatment: Beyond innocence.** *Oncologist* 2006;11(7):732-41. Abstract

Williams S, Dale J. **The effectiveness of treatment for depression/depressive symptoms in adults with cancer: A systematic review.** *Br J Cancer* 2006;94(3):372-90. Abstract

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Management of chemotherapy-induced emesis . . . 4 3 2 1
- Nonanthracycline chemotherapy regimens in HER2-positive and HER2-negative breast cancer . . . 4 3 2 1
- Side effects and toxicities of bevacizumab and other anti-angiogenic therapies . . . 4 3 2 1
- Management of bone loss secondary to aromatase inhibitors . . . 4 3 2 1
- Treatment of chemotherapy-associated neuropathy . . . 4 3 2 1
- Dermatologic toxicities associated with anticancer therapies . . . 4 3 2 1
- Cardiovascular events related to anti-angiogenic or anti-HER2 therapy . . . 4 3 2 1
- Management of depression secondary to cancer diagnosis or treatment . . . 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Management of chemotherapy-induced emesis . . . 4 3 2 1
- Nonanthracycline chemotherapy regimens in HER2-positive and HER2-negative breast cancer . . . 4 3 2 1
- Side effects and toxicities of bevacizumab and other anti-angiogenic therapies . . . 4 3 2 1
- Management of bone loss secondary to aromatase inhibitors . . . 4 3 2 1
- Treatment of chemotherapy-associated neuropathy . . . 4 3 2 1
- Dermatologic toxicities associated with anticancer therapies . . . 4 3 2 1
- Cardiovascular events related to anti-angiogenic or anti-HER2 therapy . . . 4 3 2 1
- Management of depression secondary to cancer diagnosis or treatment . . . 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:

- Compare and contrast self-reported supportive care management strategies utilized by community oncologists when addressing toxicities related to the endocrine treatment of breast cancer . . . 4 3 2 1 N/M N/A
- Maintain effective anticancer regimens by employing prophylactic and acute supportive care strategies that minimize the incidence and severity of aromatase inhibitor-associated joint discomfort and bone loss . . . 4 3 2 1 N/M N/A
- Identify premedication regimens to reduce the risk of hypersensitivity and emetogenic reactions among patients receiving systemic chemotherapy . . . 4 3 2 1 N/M N/A
- Recall the chemical entities that are associated with chemotherapy-induced peripheral neuropathy, and utilize practical interventions to abrogate this toxicity without compromising the efficacy of primary anticancer treatments . . . 4 3 2 1 N/M N/A
- Describe the incidence and clinical presentation of cutaneous side effects accompanying specific cytotoxic agents and EGFR and multitargeted tyrosine kinase inhibitors, and incorporate evidence-based management strategies into routine patient care . . . 4 3 2 1 N/M N/A
- Develop a cardiovascular risk-reduction strategy and monitoring plan to reduce the incidence of short- and long-term toxicity associated with anti-angiogenic and anti-HER2 therapies . . . 4 3 2 1 N/M N/A
- Recognize the signs of cancer-related depression and recommend medical and behavioral alternatives for affected patients . . . 4 3 2 1 N/M N/A
- Delineate the complementary and alternative practices employed by cancer specialists to support oncology patients undergoing conventional antineoplastic treatments . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

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To what extent do you feel the faculty members' comments were helpful or not helpful?
Please be as specific as possible about individual faculty.

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Please recommend additional faculty for future activities:

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Other comments about the faculty for this activity:

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