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Oncology Practice™ UPDATE

An Audio Review Journal for Nurse Practitioners and Physician Assistants Specializing in Oncology

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Physician Assistant Review Panel PA Approved Category 1 CME

CNE for RNs and NPs

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents, changes in the indications for existing treatments and unique symptomatologies associated with those advances. In order to offer optimal patient care — including the option of clinical trial participation — the nurse practitioner, physician assistant and registered nurse specializing in oncology care must be well informed of these advances. To bridge the gap between research and patient care, *Oncology Practice Update (OPU)* will communicate the perspectives of leading oncology investigators and simultaneously balance those perspectives with those of practicing clinicians. By providing access to the latest research developments and expert perspectives as well as case-based discussions between researchers and practicing clinicians, *OPU* will assist nurse practitioners and physician assistants in the formulation of up-to-date clinical management strategies.

PURPOSE STATEMENT

To present the most current research developments in breast cancer and to provide the perspectives of medical oncologists, oncology nurses and physician assistants on the diagnosis and treatment of breast cancer.

LEARNING OBJECTIVES

- Describe the computerized risk models and genetic markers available to determine a patient's quantitative risk of breast cancer relapse including how to use these to guide adjuvant therapy decisions.
- Describe the absolute risks, benefits and toxicities of various adjuvant systemic therapy approaches, including supportive care strategies available to manage these toxicities.
- Discuss selection and sequencing of endocrine therapy and chemotherapy for metastatic disease including the risks, benefits and toxicities of these therapies.
- Describe management strategies for primary prevention and treatment of treatment-related hematologic toxicities, including individual patients' risks of developing these toxicities.
- Discuss how to incorporate the individual patient psychosocial situation, needs and values into discussions of systemic therapy options.

HOW TO USE THIS ACTIVITY

This activity contains both audio and print components. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **OncologyPracticeUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in blue underlined text. There are no fees for participating and receiving credit for this activity. To receive credit during the period of April 2006 through April 2007, participants should read the learning objectives and faculty disclosures, listen to the CDs, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on the website.

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AANP

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CME-PA INFORMATION

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This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

STATEMENT OF CREDIT

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 70% or better. Your statement of credit will be mailed to you within four to six weeks.

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Note: Cases from the practices of Maureen Major, RN, MS and J Michael Glendening Jr, MMSc, PA-C and interviews with Gary H Lyman, MD, MPH and Charles L Vogel, MD are not included in the print monograph but are discussed on the audio program.

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EDITOR'S NOTE

Neil Love, MD

The best of both worlds

Our cancer education group in Miami is thrilled to launch this series targeting nurse practitioners and physician assistants specializing in oncology. We've been producing physician education programs for more than 20 years and stuff every piece with *p*-values and survival curves in an attempt to satisfy that audience's insatiable interest in numbers and data. Our oncology nurse education programs are also rewarding to produce because these professionals are deeply interested in the complex and fascinating psychosocial issues of cancer practice.

We figured that ARNPs and PAs would combine the best of both education components, and when we invited a handful of these oncology professionals to present cases to medical oncologists Gary Lyman and Chuck Vogel, they did not disappoint.

Enza Luke started things off with a fascinating clinical dilemma: A 61-year-old woman with node-positive breast cancer clearly requiring adjuvant chemotherapy. Initially, the patient absolutely refused this treatment because of a prior devastating life experience — assisting her 38-year-old daughter through adjuvant chemotherapy three years previously. Eventually, the patient changed her mind, largely due to the encouragement of her daughter, who pleaded with her mom to fight for every possible chance for cure.

Maureen Major then presented another compelling and insightful case to the group — a 70-year-old woman with a node-positive, HER2-positive tumor and a prior history of diabetes and peripheral neuropathy. This situation raised the challenging issue of whether to use taxane-based chemotherapy with trastuzumab.

Clinical trials first reported a year ago proved that this clinical approach reduces the risk of relapse by about 50 percent above and beyond the benefits of endocrine therapy and nontrastuzumab-based chemotherapy.

The question looming before the treatment team was whether a taxane would worsen the patient's neuropathy and how much this might affect her quality of life. To hear equally compelling cases presented by Desiree Grogan and James Glendening, pop the enclosed CDs into your car stereo or listen to them while you work out to learn what happened.

The discussion during this tumor panel recording session was so lively and intense that we never got around to Julie Plantamura's patient, a 49-year-old woman with metastatic breast cancer treated in her practice for four and a half years. The patient, who died last October, was a teacher who at age 18 was cured of an osteosarcoma by a right leg amputation. The patient's husband was also a teacher and also an amputee.

Like our other roundtable participants, Ms Plantamura has a unique insight into oncology practice that is evident from her comments about this case during our planning conference for this meeting:

Both the patient and her husband were always very optimistic and hopeful, and even in the few days before she passed away, the patient never thought she would die from breast cancer. She understood how serious her disease was but just had such a will to fight and such support from her family that she did not think that she would die from breast cancer.

We're always honest with our patients and help them hope for the best, but we also let them know from the beginning that when breast cancer is metastatic, although it's often controllable, it is generally not curable.

This patient's tumor responded well to both endocrine treatment and chemotherapy, and her quality of life was excellent for most of the years we treated her. She went on a number of vacations to a home her family rented every summer in New Jersey. She was also able to get her son packed up and off to college, which was important as part of her need to keep normalcy at home.

This woman had prolonged periods of being asymptomatic during the years we treated her. She was very active, worked full time and volunteered in the community. She was also very involved with breast cancer support groups.

The patient was very nervous when we first started chemotherapy, but she was one of those patients who accepts whatever is put in front of them. She would do anything to beat breast cancer. One year we were able to give her a three-month chemo holiday, during which she helped plan her daughter's wedding.

Last summer, after more than four years of therapy, the disease finally started to progress rapidly while she was vacationing in New Jersey. She was terrified and called me, but I was away on vacation. Our office tracked me down and I coordinated a last-ditch effort, arranging for her transfer by ambulance to our hospital, where she received services not only from us but from the pulmonology, cardiology, nephrology and infectious disease services for a variety of complications. She insisted on pursuing every possible therapy and, in fact, received chemotherapy on the day she died.

She was a wonderful human being, as is her husband. They kept meticulous notes about every blood count, every treatment, every office visit and every scan. They came to each appointment with a list of questions and were very appreciative of all the time that we spent with them. They were a truly wonderful and amazing family. Occasionally, her husband still visits our practice.

— Julie Plantamura, RN, MSN, FNPc

We have focused most of our continuing education efforts on audio because it allows multitasking while learning, but I wish you could have seen Ms Plantamura's facial expressions as she told this fascinating story. It is obvious that her patients receive the best of both oncology worlds: scientific advances that can provide precious years of life and the empathy, love and hope that patients need and deserve.

It's a pleasure to bring professionals like Ms Plantamura and her colleagues to you. Let us know your thoughts on this program — what you like, what could be improved and what other education needs you have in both worlds.

— Neil Love, MD
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SELECT EXCERPTS

CASE 1: From the practice of Enza Esposito Luke, RN, MSN, ONP, Orange, California

A 61-year-old woman with a 1.9-centimeter, poorly differentiated, ER/PR-positive, HER2-negative invasive ductal carcinoma with one positive node

MS LUKE: This 61-year-old woman was diagnosed during a routine screening mammogram with a 1.9-centimeter, poorly differentiated invasive ductal carcinoma with involved margins and one positive lymph node. The tumor was ER/PR-positive and HER2-negative. A second surgical intervention was done to clear the margins, and this was followed by local radiation therapy.

The patient has a family history of breast cancer, with a 38-year-old daughter diagnosed a few years ago and a paternal aunt also with a history of breast cancer. She is an independent, headstrong woman who made it clear during our first meeting that she did not want chemotherapy.

DR LOVE: What was that based on?

MS LUKE: She saw her daughter and aunt go through chemotherapy, and those were vivid memories for her. Her daughter is still NED and received AC for four cycles.

DR LOVE: What specifically happened with her daughter, and what problems occurred with the chemotherapy?

MS LUKE: Nausea, vomiting, hair loss, fatigue, a change in her body image and disassociation from family involvement. The daughter, at the time, had a two-year-old little girl at home.

DR LOVE: Can you tell us more about the patient?

MS LUKE: She is married and recently retired. Her husband was trying to be as supportive of his wife as he could, while also expressing the fact that it was difficult for both of them to have seen their daughter go through diagnosis and treatment.

DR LOVE: In your practice in these kinds of situations, do you offer patients specific numbers about their risk of recurrence and how that's affected by therapy? A lot of people use Peter Ravdin's Adjuvant! Online model (Olivotto 2005). Do you generally use that?

MS LUKE: My colleague and I use Adjuvant! Online, and we went through that process with this patient.

DR LOVE: Gary, globally, for a patient with one positive node and ER/PR-positive, HER2-negative disease, what would you roughly calculate the risk for recurrence to be, and how might that be affected by chemotherapy and hormonal therapy?

DR LYMAN: Although it's just barely a T1 tumor, there is a positive node, and she is clearly at risk, and we would want to offer her adjuvant options.

In this setting, particularly with strong reluctance to consider chemotherapy, we do believe we have a fallback position with adjuvant hormonal therapy, but I would present to the patient the real risk of recurrence.

We give a range of numbers that would probably incorporate about 20 to 30 percent risk of recurrence over a five- to 10-year period, even with hormonal therapy.

I think you have to be honest with patients. Each one belongs to one of the following groups: Those who aren't going to experience recurrence even if they don't take chemotherapy, those who are going to experience recurrence even if they do take it, and those who will avoid recurrence by receiving chemotherapy. We cannot tell her

which of these groups she falls into; therefore, you have to offer treatment for the possibility that she is in the third group.

DR LOVE: What if the patient tried to pin you down and said, "Okay, you're saying it's a 20 to 30 percent chance of recurrence, but what will it be if I take chemotherapy?"

DR LYMAN: That cuts right to the chase and assumes she will receive hormone therapy. Generally, the benefit of chemotherapy in this situation is small. Depending on the circumstances, it may be as little as two to three or four percent.

Is it worth going through four, six, eight cycles of adjuvant chemotherapy, losing your hair and going through the various toxicities for that gain?

Patient surveys suggest that many patients are willing — in fact, anxious — to be offered any possibility of preventing recurrent disease, even down to a one percent margin, despite the toxicities. Some patients feel that their quality of life will be too adversely affected and will choose not to do it.

It sounds as if she may be one of those patients and has already thought through some of those issues. You still need to present a range of numbers and your recommendation, and then, of course, she makes the choice.

DR LOVE: Chuck, what kind of numbers would you present to her in terms of risk of recurrence, despite hormonal therapy, and how might that be affected by chemotherapy?

DR VOGEL: I have an advantage here because yesterday I saw a virtually identical patient for a consultation. She was a 66-year-old woman and had a poorly differentiated tumor. I ran Adjuvant! Online, and I know the numbers.

DR LOVE: What are they?

DR VOGEL: The numbers are a 57 percent likelihood of being alive and free of disease at 10 years with no therapy, so a 43 percent chance of relapse. We presuppose, of course, that she will need radiation therapy. I bypass the tamoxifen part of Adjuvant! Online because I use up-front aromatase inhibitors (AIs). The AI would give her 17 percent absolute benefit, which would bring her up to 74 percent chance of being alive and free of disease.

DR LOVE: Or a 26 percent recurrence rate even with an AI.

DR VOGEL: Correct. And if you were to give her AC times four or CMF times six, you would increase that by two percent. If you were to give her third-generation chemotherapy, you would increase it by seven percent.

DR LOVE: So the numbers are similar to what Gary pulled off the top of his head.

DR VOGEL: Correct.

DR LOVE: We're going to stay focused on the issue of chemotherapy, but as a footnote, Gary, has it also been your practice to switch from using tamoxifen, as a routine, to aromatase inhibitors in postmenopausal women receiving adjuvant therapy?

DR LYMAN: Yes, it has. Some low-risk situations may occur in which we'll continue to use tamoxifen, particularly if evidence of bone loss or osteopenia or actual osteoporosis is documented.

In the usual setting for a postmenopausal woman with one or more significant risk factors, we do encourage use of an aromatase inhibitor. With proper monitoring, our experience with the aromatase inhibitors is favorable.

DR LOVE: Ms Luke, can you talk a little bit more about how she reacted to some of these numbers?

MS LUKE: At first, she was shocked when we reviewed the numbers from the Adjuvant! Online website (**adjuvantonline.com**). The interesting twist on the discussion with this patient was that her husband insisted she go back and talk to her daughter and that the three of them discuss the situation at more length before the patient made a decision.

DR LOVE: One node doesn't sound too bad, but the numbers — a 50-50 chance of

recurrence without treatment — suggest a high-risk situation.

MS LUKE: Right, and I think she thought, "Well, with local radiation therapy, that should be sufficient."

About a week or so later we got a phone call from the patient, who said she wanted to come in with her daughter. In the course of the discussion with her family, she had changed her mind.

I think the daughter — having gone through that experience and now being on the other side — was able to make the patient see a different point of view. The patient is still a young 61-year-old woman with no comorbid complications, and she could possibly have another 20 to 30 years of life.

DR LOVE: So now the patient is open to receiving chemotherapy, and the question is, what type? Chuck, what are some of the options you think would be reasonable in this situation?

DR VOGEL: Four options are most supportable by studies with Level 1 evidence (1.1). One is the dose-dense AC followed by paclitaxel regimen (Citron 2003; Hudis 2005). Second would be TAC, including docetaxel (Martin 2005a). A third option would be that of the PACS-01 study from France, FEC times three followed by docetaxel times three (Roche 2004). The fourth option is a newcomer to the field, and that's the GEICAM study from Spain. Miguel Martin presented it at San Antonio, using FEC followed by weekly paclitaxel (Martin 2005b).

DR LOVE: Gary, all four of those regimens have in common a taxane and an anthracycline. We know from our Patterns of Care studies that patients with node-positive disease are receiving these kinds of therapies. Is that your practice also?

DR LYMAN: Absolutely. In some low-risk, node-negative settings, we may just administer four cycles of AC, but for patients with node-positive disease, we always add a taxane to the regimen and discuss the various regimens, all of which are supported by good evidence that they affect disease-free survival.

DR LOVE: If this woman asks you, "Which one of the available regimens is the most likely to prevent me from having a recurrence?" how do you answer?

DR LYMAN: Head-to-head comparison of these regimens is limited. They're all active and they're all toxic and will need aggressive supportive care to accompany them. If she leaves it to our recommendation, we will go with the ones with which we have the most familiarity and, therefore, the greatest comfort.

That's usually dose-dense ACT or TAC. Those regimens are being used at my institution at probably a two-to-one ratio, and both are accompanied by growth factor support.

DR LOVE: Again from Patterns of Care studies, we know that, at least right now, dose-dense AC → paclitaxel administered every two weeks with growth factors is the most common regimen used for patients with node-positive disease in the United States.

Chuck, what's your usual, preferred regimen in this situation?

DR VOGEL: We published on TAC and have extensive experience with that regimen and feel comfortable with it. Some patients have a hard time with TAC, but in our hands, those are the minority.

Larry Norton frequently speaks about considering dose-dense AC followed by paclitaxel not as dose-dense but as "toxicity-reducing" therapy. However, there is a concern about the dose-dense regimen in this situation, although it's based on unplanned, retrospective subset analyses.

This patient has ER-positive disease, and a diminishing rate of effectiveness seems to occur with the dose-dense regimen in ER-positive patients, with all of the caveats about retrospective and subset analyses.

DR LOVE: The ER-positive status of this patient's tumor is one of the interesting issues with this case and one of the biggest

1.1

Clinical Trials of Adjuvant Chemotherapy

Trial	Chemotherapy regimens	DFS	*p*-value	OS	*p*-value
Hudis 2005	AC/paclitaxel q3wk AC/paclitaxel q2wk	71.7% 76.7%	0.012	79.5% 83.0%	0.049
Martin 2005a	FAC TAC	68% 75%	0.001	81.0% 87.0%	NR
Roche 2004	FEC 100 x 6 FEC 100 x 3 → docetaxel x 3	73.2% 78.3%	0.014	86.7% 90.7%	0.017
Martin 2005b	$FE_{90}C$ x 6 $FE_{90}C$ x 4 → paclitaxel qwk x 8	79.2% 86.9%	0.0009	91.8% 94.5%	0.1375

DFS = disease-free survival; OS = overall survival; NR = not reported

SOURCES: Hudis C et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 41**; Martin M et al. *N Engl J Med* 2005a;352(22):2302-13. **Abstract**; Roche H et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 27**; Martin M et al. San Antonio Breast Cancer Symposium 2005b;**Abstract 39**.

controversies going on right now in adjuvant chemotherapy. Gary, we're hearing more and more about this issue of trying to evaluate the effect of chemotherapy based on estrogen receptor status. What's your take on that at this point?

DR LYMAN: I agree with Chuck and think it is a reason for continued follow-up of these patients. We still recommend dose-dense treatment in this setting. It does have some advantages, particularly the low rates of toxicity, so that's still one of our main front-line regimens, even in the ER-positive group of patients.

DR LOVE: What about the use of growth factors with TAC? How do you approach that, Chuck?

DR VOGEL: I've never used TAC without growth factor support. From the beginning, when we first presented our data, a 24 percent rate of febrile neutropenia was just not acceptable, so I've always used growth factor support.

With the current availability of pegfilgrastim, it's a "no-brainer" to prescribe it. We now know from Miguel Martin's analysis of a node-negative TAC versus FAC study that by giving prophylactic white-cell growth factor support, the febrile neutropenia rate can be reduced from 24 percent to, in his study, 3.5 percent.

DR LYMAN: I wanted to make an additional point about TAC and growth factor support. We've been following — through our national prospective registry that was instituted in 2002 — the use of supportive therapies on various adjuvant regimens.

A comparative group in Europe has been running the same registry across six major countries, and use of growth factor support with TAC there is in the range of 80 to 90 percent. We don't find those numbers in the United States. When we began our registry, only about 25 percent of patients receiving TAC were reported to receive growth factor support.

Now that has increased to the range of 40 to 50 percent, but it's certainly not 80 to 100 percent, as you'd think would be the case given the high level of toxicity with that regimen. Obviously, emphasis on growth factor support is increasing, but many patients appear to be receiving TAC adjuvantly without growth factor support in the United States.

DR LOVE: Chuck mentioned the issue of the cost of using growth factors. What do we know about the financial "play-out" of using growth factors? For example, with TAC, obviously, you're preventing febrile neutropenia hospitalizations. Has that been evaluated?

DR LYMAN: We've done a number of economic analyses, most recently focusing on pegfilgrastim (Cosler 2005). Our earlier analyses go back almost a decade.

Our more recent analysis in the adjuvant setting demonstrates a break-even cost threshold — at which you begin to save money with growth factor support — with a febrile neutropenia risk in the area of 20 percent. Reducing hospitalizations counterbalances the cost of the growth factors.

These data, of course, were fed into the National Comprehensive Cancer Network (NCCN) guidelines process (NCCN Practice Guidelines in Oncology Version 2.2005).

A year ago, when we generated the NCCN myeloid growth factor guidelines (1.2), the group decided that the economic data were supportive, but they felt the main reason they needed to define a threshold was based on evidence of clinical benefit.

Chuck's study of primary pegfilgrastim prophylaxis in patients with breast cancer demonstrated that with a regimen with a risk around 20 percent — I think the actual risk was about 17 percent — the risk of febrile neutropenia was dramatically reduced if patients received primary prophylaxis with growth factors. So it's clinically effective in that range.

Our economic numbers just provide a little "icing on the cake" that you're not spending too much when you do that because you are preventing a costly, life-threatening toxicity with these growth factors. I should mention that ASCO is still going through revisions of their guidelines, which have been in place for about a decade.

So, in terms of up-to-date guidelines, we have the NCCN guidelines (Lyman 2005a). The EORTC will be coming out with guidelines early this year that will probably be similar to the NCCN, which says that higher than 20 percent consider primary prophylaxis routinely (1.2).

In the 10 to 20 percent range, the intermediate-risk range, the NCCN guidelines emphasize how important it is to evaluate and assess risk factors for these complications in individual patients. Usually, the thresholds are determined by the published risk in a given regimen, but we know that TAC and other regimens behave differently in different patients.

If you have a regimen with which you're in that intermediate-risk area, it is impor-

1.2

NCCN Recommendations for the Use of Myeloid Growth Factors (CSF) for Prophylaxis of Febrile Neutropenia and Dose Schedule Maintenance during Adjuvant Chemotherapy

Clinical factors to consider in the determination of patient risk category	Risk of febrile neutropenia	Prophylaxis for febrile neutropenia
• Chemotherapy regimen • Individual patient risk • Neutropenic complication in the immediate previous cycle	High (>20%)	CSF recommended
• Chemotherapy regimen • Individual patient risk	Intermediate (10%-20%)	Consider CSF
• Chemotherapy regimen • Individual patient risk	Low (<10%)	No CSF. Only if patient is at significant risk for serious medical consequences of febrile neutropenia, including death, is CSF to be considered.

SOURCE: NCCN Clinical Practice Guidelines in Oncology — Myeloid Growth Factors in Cancer Treatment Version 2.2005.

tant to consider the individual patient. If the patient is elderly, is frail and has various comorbidities, she is not likely to do well with febrile neutropenia, and you may want to use growth factor prophylaxis in regimens with published risk in the 10 to 20 percent range.

At less than 10 percent, which we considered low risk, these growth factors play no routine role, but in the 10 to 20 percent range, the primary emphasis is on individualization of care. We hope in the future to base these assessments on objective models that we're working on and attempting to validate (Lyman 2005b; Wolff 2005).

As with Adjuvant! Online, you can plug in the patient's characteristics and come out with an individualization of risk and an objective quantification of that risk.

DR LOVE: Putting aside the cost and the social implications of the cost, how would you respond to a healthy, younger person who is about to receive AC and asks you about the chance of developing febrile neutropenia if she receives growth factors?

DR LYMAN: We don't know. At ASCO, we presented an updated meta-analysis of all the prophylactic growth factor trials — approximately 17 trials — and we don't see a bottom risk below which growth factors don't work (Kuderer 2005; [1.3]). Historically, filgrastim risk reduction has been around 50 percent, but Chuck's data with pegfilgrastim demonstrated more than a 90 percent relative risk reduction. It may be that the longer-acting growth factors are somewhat more potent.

I'm sure risk is reduced, whether it's from 10 percent to five percent or three percent or two percent. But the counterargument is that 90 percent of those patients are receiving growth factor support, and they wouldn't develop febrile neutropenia anyway.

DR LOVE: Chuck, can you talk about your study? It has certainly changed the way people view chemotherapy in the adjuvant setting.

DR VOGEL: The study involved first-cycle use of docetaxel and open-label pegfilgrastim (Vogel 2005; [1.4]). The results were striking. They showed a 17 percent risk of febrile neutropenia if you didn't receive pegfilgrastim and a one percent risk if you did receive it, and they showed a 14 percent versus a one percent risk of hospitalization. It was a gratifying result.

DR LOVE: What percentage of those patients received therapy for metastatic disease versus adjuvantly?

DR VOGEL: It was 30 percent adjuvant, 70 percent metastatic.

DR LOVE: For AC followed by docetaxel, when docetaxel is used in the adjuvant setting, it is generally dosed at 100 mg/m^2. In that situation, do you think that growth factor support should be used during the docetaxel?

DR VOGEL: Definitely.

DR LOVE: What about growth factors with AC?

DR VOGEL: We haven't had much of a problem with febrile neutropenia during AC. A tendency has emerged, based on the dose-dense experience, to say, "Well, if we're going to administer AC, we can dose densify it, add a dose of pegfilgrastim and administer it every two weeks."

For those people who are using AC followed by docetaxel — which, incidentally, has no Level 1 evidence behind it at the moment — you could use it that way. The BCIRG 005 trial, randomizing between TAC and AC followed by docetaxel, should provide an answer (Eiermann 2005).

DR LOVE: Do you offer growth factors to your patients who receive AC?

DR VOGEL: I do because I usually dose densify AC.

DR LOVE: Let's hear some more about what happened with this patient.

MS LUKE: After the discussion with her daughter and husband and our going over, again, the choices that she had for treatment, she chose to go with TAC for six cycles. I believe her daughter helped her

with that decision.

DR LOVE: What was her greatest concern about the chemotherapy?

MS LUKE: Loss of her hair, nausea and vomiting. This is a woman who comes into the office well dressed and well put together. She values her self-image. I counseled her right away to get fitted for a wig, so we could match her hair color and texture before we started the chemotherapy. Through the American Cancer Society, I set her up with a support group, and they have some self-image classes that she also attended.

DR LOVE: So she got started on the TAC; then what happened?

MS LUKE: She got started on the TAC and had some nausea and mild vomiting. She felt a little tired, but overall, she felt fairly well. On day eight of the first cycle she came into the office for an issue not related to chemotherapy. My oncologist colleague decided to do a CBC on her that day, and we found her to be neutropenic, with an ANC count of 400/mm^3, despite receiving growth factor support.

DR LOVE: Chuck, what would you have done?

DR VOGEL: I would put her on prophylactic antibiotics. I know that's a "no-no" in a lot of practices, but I would do that. The question is, should you expect this neutropenia? Pegfilgrastim will not absolutely abrogate the nadir. It decreases the length of the nadir.

1.3

Meta-Analysis of Randomized Controlled Trials of Prophylactic G-CSF in Patients Receiving Chemotherapy (N = 3,091)

Outcome*	Control	G-CSF†	RR [95% CI]
Febrile neutropenia	37.3%, range 7-77%	20.4%, range 0-63%	0.54 [.43, .69]; $p < 0.0001$
Infection-related mortality	4.4%, range 0-14%	2.4%, range 0-7%	0.55 [.36, .84]; $p = 0.005$
Dose intensity	88.1% [85.6, 90.2]	94.5% [92.6, 95.9]	$p < 0.001$

* Fourteen randomized controlled trials from 13 reports were included (3,091 patients). Febrile neutropenia was assessed in all reports. Infection-related mortality was reported in 10 studies (2,483 patients). Dose intensity was reported in 8 trials (1,574 patients).

† G-CSF consisted of filgrastim, lenograstim or pegfilgrastim

SOURCE: Kuderer NM et al. *Proc ASCO* 2005;**Abstract 8117**.

1.4

Efficacy of Pegfilgrastim versus Placebo in Reduction of Febrile Neutropenia among Patients Receiving Docetaxel Chemotherapy

Event	Placebo (n = 465)	Pegfilgrastim (n = 463)	OR [95% CI]
Febrile neutropenia	17%	1%	15.02 [6.51-34.6]
Hospitalization	14%	1%	11.99 [5.17-27.78]
Anti-infective use	10%	2%	7.47 [3.35-16.67]

OR = odds ratio

SOURCE: Vogel CL et al. *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

So I would expect her to have virtually no white cells on day eight; it's just that the duration is short. However, as long as I knew this lab result, I probably would have put her on prophylactic antibiotics to try to keep her out of the hospital.

DR LOVE: How low would the count have to be for you to use antibiotics in an asymptomatic patient?

DR VOGEL: Less than 500/mm^3.

DR LOVE: Gary?

DR LYMAN: I would have examined her and, if there were no sign of infection, I would have told her to go home and to call me if she develops a fever and wasn't feeling well. I wouldn't have used prophylactic antibiotics, but some of my colleagues do.

More often, we consider that if they fall below 200/mm^3 of absolute neutrophils. Even there, I think a real concern remains about emerging fluoroquinolone resistance.

A recent Italian study published in *The New England Journal of Medicine*, albeit with more patients with leukemia, lymphoma and transplants, saw significant increases in both gram-positive and gram-negative fluoroquinolone resistance among those receiving prophylaxis for infection going through chemotherapy with a fluoroquinolone (Bucaneve 2005). So we would often wait until the ANC fell lower.

I agree with Chuck. This decrease is to be expected. Patients' counts fall, and some become neutropenic. You shouldn't panic. You shouldn't add filgrastim to the regimen at that point because the pegfilgrastim is still in the serum. It's still working, and hopefully, the duration of neutropenia will be short.

DR LOVE: Ms Luke, what did you do?

MS LUKE: The patient was examined and did not have any signs or symptoms of an infectious process at the time, but we did treat her prophylactically with antibiotics. By the time she came back for cycle number two, her neutrophil count had completely recovered.

DR LOVE: Chuck, at that point, what would you do in terms of chemotherapy dosing?

DR VOGEL: I'd readminister at the same dose level.

DR LOVE: Would you tell her not to get a white count on day eight?

DR VOGEL: I don't do interim counts if I'm giving pegfilgrastim.

DR LOVE: Gary, same question: Would you continue at the same chemotherapy dose?

DR LYMAN: I would continue at the same dose, along with pegfilgrastim, and I don't check the counts. I do reiterate to the patient, "Call me if you develop a fever or if you feel chilled or if you feel ill, but otherwise, go about your business."

DR LOVE: We've had this concept, Gary, of the importance of delivering the planned dose of chemotherapy on time. In the adjuvant setting, we're going for cure. How much data do we have supporting the idea that dose delivered makes a difference?

DR LYMAN: Unfortunately, evidence is sparse, and I think everybody would agree with that. Most oncologists believe in the concept of delivering the planned dose on time. Even in the metastatic disease setting, a dose-response relationship exists.

Obviously, in the adjuvant setting, at some level of dose reduction you lose the benefit completely. We know adjuvant therapy works, but we don't know where the break point is at which you lose the benefit.

DR LOVE: Ms Luke, can you follow up on what happened?

MS LUKE: She has now gone through four cycles of TAC and she's having a lot of problems with dry eyes and skin rash. She continues to receive growth factor support, as she did on cycle one.

DR LOVE: What's her state of mind?

MS LUKE: She often calls with many questions and complaints. She requires a lot of psychosocial support by the staff.

DR LOVE: Do you think that she regrets

taking chemotherapy or is thinking about wanting to stop it?

MS LUKE: I know for a fact she's thinking about stopping the chemotherapy. I don't think she'll go through all six cycles. She finished cycle four about a week ago, and she's almost ready to come in and receive cycle number five.

I know quality of life is important to her, so I think we'll probably end up splitting the difference at five. ■

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SELECT EXCERPTS

CASE 2: From the practice of Desiree Grogan, RPA-C, Great Neck, New York

A 50-year-old premenopausal woman who presented with a fungating, ulcerated breast mass. Breast biopsy revealed a poorly differentiated, ER/PR-positive, HER2-negative infiltrating ductal carcinoma, and staging workup revealed diffuse metastatic disease to the bones, lung and liver

MS GROGAN: This was a 50-year-old premenopausal woman who is a wife and mother of four. She initially presented to our office in July 2004 with an eight-month history of a fungating, ulcerated breast mass. The mass had almost completely replaced the entire left breast and had a purulent discharge. The patient was admitted to the hospital for debridement of the mass and a biopsy.

To no one's surprise, the biopsy revealed extensive, poorly differentiated, infiltrating ductal carcinoma, which was noted to be ER- and PR-positive but HER2-negative.

An extent-of-disease workup revealed, unfortunately, widely metastatic disease to the bones, liver and lungs. At the time of presentation, the patient also complained of right-sided hip pain and had difficulty ambulating without assistance.

DR LOVE: This is a dramatic, unusual presentation. Women presenting with metastases constitute five percent or less of breast cancer cases. Would you talk more about the woman, her lifestyle and her thoughts as she saw this disease developing in her breast?

MS GROGAN: We call this woman the "Martha Stewart" of our practice. She is your average suburban, stay-at-home mom. She loves being a mother, being a wife and taking care of her house. She excels in crafts and is very creative.

Her mother and maternal aunt both had breast cancer. I don't know the details of their treatment, but I believe her mother passed away from the disease when she was in her sixties.

It was hard to imagine a 50-year-old woman presenting like this. Her husband was with her at presentation. He is active in her care and supportive.

You wonder how neither of them sought medical attention. If she was in denial, how did her husband not notice something? Unfortunately, by the time they presented, she already had Stage IV disease.

DR LOVE: This is a tricky situation. Were you able to tease out a little bit more about what she was thinking?

MS GROGAN: In retrospect, she clearly knew what was going on. She was just afraid to find out, which I think is true for a lot of patients, although it's hard to imagine ignoring this evidence.

This isn't just a lump under your breast that, if you don't touch it, is not there. This was objective, visible evidence, but she said she was fearful. She knew, with her family history and the symptoms, what she was dealing with and she was just trying to avoid dealing with it for as long as possible.

DR LOVE: Did she keep up with her other healthcare?

MS GROGAN: Yes. She had mild hypertension that was controlled with antihypertensive medication.

DR VOGEL: Did she have a previous mammogram?

MS GROGAN: No, she had not had a mammogram.

DR LOVE: Chuck, this situation in which

you have someone who's taking care of a family, accepting all kinds of responsibility and has this isolated denial in the breast, how often do you see patients present like this, and what do you think is going on?

DR VOGEL: We probably see two or three women a year in our practice, which is limited to breast cancer, with about 400 new breast cancer consults a year. Every year, we see a few patients like this, and you just sit back and wonder how on Earth they could do this. I have no explanation. There's just a lot of denial, and there's nothing one can say about it.

DR LOVE: Gary, what's your experience been with this? Is there a lot of self-recrimination?

DR LYMAN: It's hard for us to put ourselves in their situation, particularly as male oncologists. Chuck and I have been around long enough, and we both used to see this a bit more frequently in the past, but we still do see it.

I often feel that I'm able to distinguish two categories here. One is a slow-growing tumor that was just ignored, often in a postmenopausal woman with a lot of denial who doesn't want to bother the family or be a burden and is ignoring the fact that eventually she will be a burden, maybe even more so than if the condition was addressed early.

The other category, which I believe does happen, is an inflammatory-type tumor that has grown rapidly. This patient doesn't seem to fall into that category, or maybe she's somewhere in between. Obviously, this tumor was present for some time and should have been noticed by the husband and the wife.

The denial must have been enormous, or maybe paralyzing fear prevented them from seeking treatment. They knew what the answer would be, but if they didn't go in, perhaps they could pretend it wasn't true.

It's hard, psychologically, to know what they've gone through, but if you think of yourself in paralyzingly fearful situations, you can get a little bit of a feel for what they've gone through. It doesn't change the situation, but it may allow you to empathize a bit more with what they're facing and what they've gone through over the last few months or even a year or more.

DR LOVE: Chuck, how would you think through management at this point?

DR VOGEL: A lot of what she has is probably reversible, and my gut feeling would be that she has a hormonally sensitive tumor, but she's gone beyond where you could just put her on a hormone and observe. You have to shrink the tumor. I think you have to quickly show her that you can make a tangible difference.

This would be one of those situations in which I would probably go with chemotherapy up front to get a maximum response and then switch over to a hormone and try to maintain that response.

DR LOVE: Was she having symptoms from the metastases?

MS GROGAN: She had right-sided hip pain and difficulty ambulating.

DR LOVE: How bad was it?

MS GROGAN: She was using a cane when I first saw her.

DR LOVE: What did her hip look like on x-ray? Did anything look as if it were ready to break?

MS GROGAN: A note of a possible impending fracture was made on the MRI.

DR LOVE: Gary, how would you think this through, both in terms of the question of radiation therapy or even prophylactic surgery in the hip, and what are your thoughts about Chuck's comments regarding chemotherapy?

DR LYMAN: I agree with him completely. When you have liver and pulmonary disease, you have to get this controlled in addition to local control. That will require an aggressive approach. I would also approach the hip aggressively because the last thing that you want is a clean-through fracture and to have this patient laid up and end up with PEs, DVTs and so forth.

So you want to address the hip quickly: If you don't see a pending fracture, just radiation therapy can be utilized, or if it looks as if it's about to break, surgical pinning along with some radiation therapy can be done, which will result in pain relief and prevent the dire consequences of a break. Then move on promptly with chemotherapy. I think hormonal therapy is also in her future, but it's not the first step.

DR LOVE: What was her state of mind at that point? Was she depressed? Did she feel guilty? I'm sure she was scared. How did she come across to you?

MS GROGAN: As Dr Lyman was saying, she was ready for treatment at that point. She was aware of the diagnosis, and we put the treatment plan out to her and said, "Look, this is advanced. However, we have effective treatments."

We tried to approach it as a chronic disease. We have a lot of treatments. We can go through them until we find something that is effective. It may be difficult in the beginning, because we're going to be a little more aggressive with our treatments, but hope remains for good quality of life and for extension of her survival.

DR LOVE: How do you approach the issue of the curability or lack of curability of metastatic breast cancer? Do you bring it up to the patient?

MS GROGAN: In general and in this situation, I usually wait to play off what patients ask. If they ask, "Is this curable?" I'm generally honest and blunt with them and say, "This is not curable, but it's treatable."

I try to avoid questions about life expectancy and things like that because I don't feel that any of us have the specific answer for each patient. For this patient, we were honest with her and said this is not curable.

DR LOVE: Chuck, if she wanted to pin you down in terms of what to expect for the next few years or five years, how would you have responded?

DR VOGEL: I would just say that nobody can predict what's going to happen. I would take the same approach that Ms Grogan took and say that this has now become a chronic disease process, like diabetes or congestive heart failure. There will be times when the disease will be in remission and times when it will come out of remission.

I'd give her anecdotes about patients who have had metastatic disease in our practice for 10, 12, 14 years, and I would try to avoid precise statistics unless she's one of those who's going to pin me to the wall. I would try to parry that off.

Even now, we do have one study from MD Anderson Cancer Center on survival from first relapse that has shown sequential improvements over time, up to a 40 percent five-year survival. We usually have quoted two years median survival from first relapse.

In the study that we did at the University of Miami when I was there, we saw a tremendous heterogeneity. Basically, if you were hormone receptor-positive, the median survival was four years, and if you were hormone receptor-negative, the median survival was less than two years. I try to avoid getting into those discouraging statistics and, instead, leave the patient with encouraging anecdotes.

DR LOVE: This woman presented in the summer of 2004, and now in 2006 we have an additional issue on the table in terms of chemotherapy for metastatic disease, which is bevacizumab (2.1). Gary, right now, how would you think through chemotherapy for this woman and, assuming it was reimbursed, would you include bevacizumab?

DR LYMAN: At our institution, bevacizumab is not front-line therapy for metastatic disease for the oncologists, but it sometimes is to the patients. They come in having read and heard about bevacizumab and wanting to know a lot more about it, and we have those discussions.

Generally, in a chemotherapy-naïve patient such as this, although our treatment intent or long-term goal is a bit different, we often will turn to an anthracycline-based

regimen to try to put the disease into remission. I think a taxane-based regimen and any of the regimens we've talked about in the adjuvant setting are equally viable options.

Again, the treatment intention's a bit different, so it's a little hard to talk about pushing the doses and forcing patients to experience a lot of toxicity. So you find the proper dose and schedule that they can tolerate but still try to get them into remission.

I agree with Chuck about proving to this woman that you can help her. The first thing you want to do is get her hip under control and then get this tumor regressed and show her that we can, in fact, relieve her symptoms and reduce her burden of disease. Then I think you'll have a buy-in from her to continue with therapy.

DR LOVE: This woman's tumor is ER/PR-positive, so you have hormonal therapy on the table. How would you integrate that into the initial plan?

DR LYMAN: I don't usually start hormones and chemotherapy together, but I have colleagues who do, saying, "What have you got to lose?" My thinking, which is entirely conjectural, is that, number one, if the patient responds, you don't know which agent is working. Number two, maybe you're putting some cells into G0 with the hormonal therapy, and maybe it won't be quite as responsive to chemotherapy. These are issues that have never been fully resolved.

Some of my colleagues just go ahead with combined-modality therapy, and data exist to support that. I generally would go with chemotherapy initially, get the patient through if she's responding, and exhaust the standard anthracycline cumulative dose.

If the patient were in a good remission at that point, I'd turn to hormonal therapy. If not, then I'd turn to one of the other agents, either a taxane or gemcitabine or some reasonably active second-phase agent.

DR LOVE: Can you bring us up to date with this woman's situation?

MS GROGAN: She initially received radiation therapy to the hip. She also received aggressive anti-infective therapy to the mass with home care from a nurse. We started her on chemotherapy with a combination of doxorubicin and docetaxel with pegfilgrastim support. The patient received a total of eight cycles of therapy to reach her maximum lifetime dose of doxorubicin.

During the course of treatment, the hip pain resolved. She began to ambulate without any assistance, and strikingly, the breast mass slowly began to shrink.

By the time she completed the eight cycles of doxorubicin and docetaxel, approximately a 50 percent reduction had occurred in the breast mass and a 50 percent reduction in her hepatic and pulmonary metas-

2.1

ECOG-E2100: Paclitaxel with or without Bevacizumab as First-Line Therapy

Efficacy endpoints	Paclitaxel + bevacizumab (n = 341)	Paclitaxel (n = 339)	*p*-value
Response rate			
All patients	29.9%	13.8%	<0.0001
Measurable disease	37.7%	16.0%	<0.0001
Progression-free survival	11.4 months	6.11 months	
	Hazard ratio = 0.51 (CI: 0.43-0.62)		<0.0001
Overall survival	28.4 months	25.2 months	
	Hazard ratio = 0.84 (CI: 0.64-1.05)		0.12

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

tases, with stabilization of her bone metastases.

At this point, we felt she still needed to receive chemotherapy because she still had substantial disease. We changed her to a combination of gemcitabine and paclitaxel; she continued to show improvement and the mass completely resolved.

Currently, she's on single-agent gemcitabine. We stopped the paclitaxel because she started to develop some neuropathy and she was a seamstress, so it was beginning to affect her life. She has an active life with her children and is still ambulating without any trouble, and she just witnessed the birth of her first grandchild. She has a terrific attitude and realizes that we've come a long way, but there's still a way to go.

DR LOVE: How about hormonal therapy?

MS GROGAN: She was initially premenopausal. After about four months, she stopped having her periods, and about eight months after that we started her on anastrozole in combination with the chemotherapy.

DR LOVE: Chuck, what about the issue of using an aromatase inhibitor in patients who start out premenopausal and then stop having their periods with chemotherapy?

DR VOGEL: She's 50 years old, so the likelihood of her regaining menses is low, but you always have to be cautious, and we closely follow our patients who start out premenopausal and become postmenopausal. I've seen women who have been on an aromatase inhibitor regain menses after a year. I watch them closely with serum estradiol levels.

You can't use LH and FSH if the patient is on tamoxifen because the pituitary views tamoxifen as an estrogen. You have this strange situation in which the estradiol level is low and LH and FSH levels continue to be low on tamoxifen.

DR LOVE: How did she tolerate the initial chemotherapy with the doxorubicin and docetaxel?

MS GROGAN: She tolerated it very well. As I said, once she was diagnosed, she went in with a positive attitude. She had some mild fatigue and hair loss but did not have any problems with nausea or vomiting.

DR LOVE: You said you used growth factor support with pegfilgrastim?

MS GROGAN: Yes. Doxorubicin and docetaxel are highly myelosuppressive.

DR LOVE: Gary, can you talk about the issue of growth factors in metastatic disease and what you do in your own practice?

DR LYMAN: As I've mentioned, it's difficult to be too adamant about maintaining dose intensity when your treatment intention clearly is not cure. Nonetheless, as we discussed earlier, dose reductions and treatment delays will affect remission rates in the metastatic setting also.

You want to maintain some reasonable level of dose intensity, and for the more aggressive regimens, like this one, use of growth factor support is reasonable. It enables the patient to receive enough drug to have a reasonably high chance of remission.

In fact, the pivotal studies comparing pegfilgrastim to filgrastim that led to pegfilgrastim approval involved the use of doxorubicin and docetaxel (Holmes 2002a, 2002b). These were noninferiority studies, designed to evaluate the duration of severe neutropenia.

What's interesting, though, is that the pegfilgrastim arms of those studies showed a lower rate of febrile neutropenia than the filgrastim arms (Siena 2003).

This led to interest again in the issue of whether the pegfilgrastim was more active or more effective in preventing this particular outcome, although it was a secondary outcome in those studies. It clearly is the primary focus of concern about neutropenic complications. So growth factor support does work.

Pegfilgrastim may be more active. This regimen carries about a 40 percent risk of febrile neutropenia without growth factors and about a 20 percent risk of febrile neutropenia with filgrastim. In the pegfil-

grastim arms, it's down closer to a 10 to 12 percent risk. These clearly do work and enable delivery of most of the dose intensity, probably optimizing the chance for remission.

DR LOVE: What other regimens utilized in the metastatic setting do you consider for preventive growth factors in healthier patients?

DR LYMAN: Growth factors are used in the metastatic setting with the TAC regimen. I don't generally use dose-dense AC → T in that setting, but I think with any combination of an anthracycline and a taxane, I would bring growth factors to bear.

What we're seeing with agents such as gemcitabine — and some of those patients are receiving growth factor support — is more thrombocytopenia.

So alluding to comments that Chuck made earlier, as we minimize the major dose-limiting toxicity of many of the regimens, which is febrile neutropenia, we're seeing more anemia, thrombocytopenia or non-hematologic toxicities become the focus of concern.

DR LOVE: We talked about Peter Ravdin's Adjuvant! Online model that combines different factors. Do models or tools exist that will predict neutropenic fever?

DR LYMAN: They're under development. At the last ASCO meeting, we presented a model based on some 4,500 patients followed prospectively — a cohort of patients from 120 practices in the United States — and were able to identify significant independent risk factors in a multivariate model that accurately discriminated high- from low-risk patients from the start of therapy (Lyman 2005a).

The goal was to identify who should be considered for primary prophylaxis from the beginning of therapy. We presented the breast cancer component, but the whole study includes multiple major disease categories.

We modeled the breast cancer patients — approximately 1,200 — separately and presented at San Antonio in December, again showing that we could accurately discriminate high- from low-risk patients for first-cycle neutropenic complications (Lyman 2005b; [2.2]). We've submitted the validation in an independent group of patients for this year's ASCO meeting.

We're also working with a larger group to package this in a computer-based, maybe Palm-based, Adjuvant! Online-like program that could be used in the clinic at the bedside to predict who is likely to develop these complications.

Approximately one quarter of our patients in that trial are in the metastatic setting and three quarters are in the adjuvant setting, at least among the breast cancer patients.

These models, though, as of today, are not ready for prime-time use. Clinicians already know about an increasing list of risk factors, but the hope would be that once validated, these models will put this all on a much more objective plane.

DR LOVE: What are the key factors, and how are they weighted?

DR LYMAN: Most of them won't be any big surprise: First is the chemotherapy administered, particularly anthracycline-based therapies in breast cancer. Various comorbidities, including hyperglycemia and diabetes, increase risk.

Patients with low glomerular filtration rates bear increased risk, probably reflecting the impact on drug metabolism or drug excretion.

Prior chemotherapy is also a risk factor. Patients who receive primary prophylaxis with growth factors have a lower risk of febrile neutropenia.

DR LOVE: What about age?

DR LYMAN: When you adjust for other comorbid conditions, age is not a significant factor in the breast cancer data. It is still significant; that is, higher age equals higher risk in the risk model across disease categories, which includes lung, colon, ovarian, breast cancer and lymphoma.

DR LOVE: What's the age break at which the risk increases?

DR LYMAN: It's around age 70, although it is on a continuum. We don't see much of a break, or increase in risk, until you get up to age 70, but much of the information contained in age is absorbed into the comorbidities. Once you include those in the model, age becomes a much weaker predictor.

DR LOVE: The last thing I want to ask about is the local therapy for this woman's breast tumor. Currently, what does the breast look like, and is it causing symptoms?

MS GROGAN: It's not causing any symptoms. Some scar tissue is visible but no obvious disease. It is essentially in complete remission.

DR LOVE: Chuck, how do you approach the issue of the primary tumor in a woman with metastatic disease? In what situations will you attempt surgery or radiation therapy? This woman has never had local therapy to her breast.

DR VOGEL: I believe the tumor is likely to come back, and the key at this juncture will probably be the hormonal therapy. I have seen women come in essentially with breast autoamputation, by which the tumor has grown and just completely destroyed the breast so that there is nothing left.

You might want to consider local therapy to the breast. After performing imaging, we're doing mastectomies for people who have uncontrolled local problems, but this patient's breast tumor seems to be nicely controlled.

At this juncture, if you're down to a microscopic disease burden, you may be able to forestall that type of horrible complication by irradiating the breast.

MS GROGAN: That's a viable option we should look into at this point. On her CAT scan, tumor is still visible beneath the skin surface. She may benefit from radiation therapy.

2.2

Factors Associated with Increased Risk of First-Cycle Severe Neutropenia (SN) and Febrile Neutropenia (FN) Based on a Prospective Risk Model (N = 438)

Variable	Odds ratio	(95% CI)	*p*-value
Anthracycline-based chemotherapy	5.306	1.550-18.168	0.008
CAF	3.081	0.680-13.962	0.144
CEF	5.499	1.165-25.946	0.031
TAC	8.476	1.679-42.790	0.010
Docetaxel	8.979	2.666-30.241	0.000
Planned RDI > 85%	4.199	2.243-7.860	0.000

"The clinical risk model presented here has very promising test performance characteristics. It is of interest that the risk score generated exhibits a distinct bimodal distribution, consistent with two populations representing high-risk and low-risk patients. A cutpoint for individual patient risk based on NCCN criteria of 20% was associated with first-cycle SN or FN risks of 48% and 9% in high-risk and low-risk patients, respectively. A cutpoint risk based on the median of predicted risk of 35% was associated with first-cycle risks of 53% and 13% in high-risk and low-risk patients, respectively."

Citations omitted

RDI = relative dose intensity

SOURCE: Lyman GH et al. Poster. San Antonio Breast Cancer Symposium 2005b;**Abstract 3006**.

DR VOGEL: You might even want to remove the breast surgically. I don't know that I'd be too concerned about margins, but fungating, ulcerating lesions are difficult to contend with, and that is in her future, unless she is very lucky. ■

SELECT PUBLICATIONS

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Siena S et al. **A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily filgrastim in patients with stage II-IV breast cancer.** *Oncol Rep* 2003;10(3):715-24. **Abstract**

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Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status Report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patient surveys suggest that many patients are willing to take adjuvant therapy, despite toxicities, for as little as a one percent reduction in risk of recurrence.**
   a. True
   b. False

2. **In a study by Vogel et al, pegfilgrastim reduced the incidence of febrile neutropenia secondary to chemotherapy by approximately _____.**
   a. 30 percent
   b. 50 percent
   c. 70 percent
   d. 90 percent

3. **The ECOG-E2100 trial evaluated paclitaxel with or without _____.**
   a. Cetuximab
   b. Bevacizumab
   c. Erlotinib
   d. Trastuzumab

4. **Patients with node-negative, ER-positive tumors and a high recurrence score, according to the Onco*type* DX™ assay, have been shown to benefit from adjuvant _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Chemotherapy
   d. All of the above

5. **Aromatase inhibitors are efficacious in _____ patients with early, ER-positive breast cancer.**
   a. Premenopausal
   b. Postmenopausal
   c. Pre- or postmenopausal

6. **According to the NCCN guidelines, primary growth factor prophylaxis should be routinely considered if the patient's risk of febrile neutropenia is 20 percent or greater.**
   a. True
   b. False

7. **In the HERA study, in patients who received adjuvant trastuzumab after chemotherapy, there was a _____ reduction in the relapse rate.**
   a. Five percent
   b. 15 percent
   c. 30 percent
   d. 50 percent

8. **About five percent of breast cancer tumors with immunohistochemistry (IHC) of zero or 1+ for HER2 are positive by FISH.**
   a. True
   b. False

9. **Which of the following regimens has Phase III trial support as adjuvant chemotherapy for patients with node-positive breast cancers?**
   a. Dose-dense AC followed by paclitaxel
   b. AC + docetaxel
   c. FEC followed by docetaxel
   d. FEC followed by paclitaxel
   e. All of the above

10. **The risk of fluoroquinolone resistance is an emerging concern when treating patients with prophylactic antibiotics for asymptomatic neutropenia.**
    a. True
    b. False

EVALUATION FORM

Oncology Practice Update — Issue 1, 2006

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Please answer the following questions by circling the appropriate rating:

5 =	4 =	3 =	2 =	1 =
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LEARNING OBJECTIVES

To what extent does this issue of *OPU* address the following learning objectives?

- Describe the computerized risk models and genetic markers available to determine a patient's quantitative risk of breast cancer relapse, including how to use them to guide adjuvant therapy decisions. 5 4 3 2 1
- Describe the absolute risks, benefits and toxicities of various adjuvant systemic therapy approaches, including supportive care strategies available to manage these toxicities. 5 4 3 2 1
- Discuss selection and sequencing of endocrine therapy and chemotherapy for metastatic disease, including the risks, benefits and toxicities of these therapies. 5 4 3 2 1
- Describe management strategies for primary prevention and treatment of treatment-related hematologic toxicities, including individual patients' risks of developing these toxicities. 5 4 3 2 1
- Discuss how to incorporate the individual patient psychosocial situation, needs and values into discussions of systemic therapy options. 5 4 3 2 1

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Desiree Grogan, RPA-C	5 4 3 2 1	5 4 3 2 1
Enza Esposito Luke, RN, MSN, ONP	5 4 3 2 1	5 4 3 2 1
Gary H Lyman, MD, MPH	5 4 3 2 1	5 4 3 2 1
Maureen Major, RN, MS	5 4 3 2 1	5 4 3 2 1
Julie A Plantamura, RN, MSN, FNPc	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Will assist me in improving patient care. 5 4 3 2 1

Fulfilled my educational needs. 5 4 3 2 1

Avoided commercial bias or influence. 5 4 3 2 1

IMPACT OF THE ACTIVITY

The information presented (check all that apply):

☐ Reinforced my current practice/treatment habits. ☐ Enhanced my current knowledge base.

EVALUATION FORM

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IMPACT OF THE ACTIVITY (CONTINUED)

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

.....

How committed are you to making these changes?

(5 = very committed; 1 = not at all committed).....5 4 3 2 1

FUTURE ACTIVITIES

Do you feel future activities on this subject matter are necessary and/or important to your practice?

☐ Yes ☐ No

Please list any other topics that would be of interest to you for future educational activities:

.....

.....

Additional comments about this activity:

.....

.....

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UPDATE

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