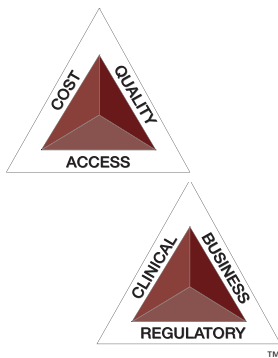


# AMERICAN HEALTH & DRUG BENEFITS®

## SUPPLEMENT



## Clinical and Cost Benefits of Abraxane for Breast Cancer Therapy

### EDITORIAL

#### Nab-Paclitaxel: Innovation and Value in the Golden Age of Cancer Care | *page 120*

Robert E. Henry

### CLINICAL

#### Metastatic Breast Cancer and the Use of Nab-Paclitaxel | *page 122*

### ROUNDTABLE DISCUSSION

#### Abraxane for Breast Cancer Therapy | *page 126*

George Dranitsaris, MPharm, FCSHP; William Gradishar, MD, FACP;  
Beth Overmoyer, MD

# Nab-Paclitaxel: Innovation and Value in the Golden Age of Cancer Care

Robert E. Henry, Editor-in-Chief, *American Health & Drug Benefits*

The revolution in cancer therapy over the past decade has shifted the use imperative for new drugs from quality to value. The current tug-of-war between cost, quality, and access demands earnest dialogue between all parties to the healthcare system: patients, providers, payers, purchasers, manufacturers, and government. In the “old” days—say, 10 years ago—providers prescribed everything at their disposal to prolong life. The treatment options were few, inexpensive, and did little to extend life expectancy. Baby boomers had not yet hit the epidemiologic hot spot for cancer, giving providers few reasons to factor economics into their clinical strategies. With the radical improvement in cancer drug quality and the cost increases during the past decade, payers are demanding changes to cancer drug coverage models. Cancer drugs consume significant healthcare resources today, and expectations are for a continued sharp growth as aging baby boomers increasingly require cancer care, causing payers to seek ways to manage overall resource allocation as innovative as the drugs they support. Now more than ever, novelty is not enough, and value must be considered.

This special supplement opens the door for a dialogue among patients, caregivers, providers, payers, purchasers, and manufacturers, by examining nab-paclitaxel (Abraxane) as the prototype of new drug therapies for metastatic breast cancer. This supplement defines the questions and criteria for resolution of the great debate over funding cancer care by identifying the key governing dynamics and the value propositions of different participants in the debate.

At stake is the preservation of the golden age of cancer care. Cancer drugs are so much better at prolonging life and reducing side effects than anything available even a decade ago, that no one was prepared for the sea change that this success would produce. Transforming many cancer disease states into chronic conditions has changed the fundamental economic burden of cancer. Here the tail begins to wag the dog, forcing clinical strategies to comply with the new economic realities of high-cost, long-term cancer treatment regimens. Meanwhile, old customs lag behind and oppose this

paradigm shift, among them the knee-jerk impulse to treat as hard and as long as possible. Patients and their advocacy groups pressure payers to continue the lax cost-control approach to cancer care, even as fiscal conservatism becomes essential to sustain the healthcare system.

Into this milieu steps nab-paclitaxel, a product with undoubted superiority to the generic drug it supercedes. The drug provides superior efficacy, improved patient acceptance by virtue of eliminating genuinely troubling side effects of the older formulation of paclitaxel, and the added advantage of eliminating the premedication required for standard paclitaxel, allowing patient throughput at clinics to be accelerated substantially. Therefore, this is not a “me-too” product; it offers genuine innovation with practical benefits.

However, payer satisfaction is as absent as the standards/metrics needed to gauge value for drugs that improve care and define patient selection for the higher-priced drugs, that is, how much should be paid for the advantage gained has not been established. This is incompatible with a value-based healthcare system and sets the stage for inter-stakeholder conflict. If payers try to limit drug coverage, providers decry that the kind of improvement to their drug armamentarium they have been seeking has been snatched away from them. Payers say exactly the opposite: just when the standard of care has gone generic, manufacturers come along with an improvement, snatching away the desired generic pricing structure. Patients, lacking an understanding of the costs of new drug development, feel caught in the middle, asking why they are being denied any advance in care. And why would they feel otherwise, when the entire history of healthcare has been an unrelenting pursuit of clinical progress against cancer?

For years the mantra has been cancer research, not fiscal restraint. Patient advocacy groups, focused on getting their constituency improved quality care, can be expected to insist on coverage of all new drugs that provide clinical advantages and not only survival but also time to progression, convenience, and maintenance of quality of life. Payers want to know where are

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the funds to pay for these innovative products and accuse manufacturers of overcharging. In contrast, manufacturers see 8 of 10 drugs failing to reach the market and wonder how anyone can blame them for aggressive pricing, when a drug does succeed. Purchasers worry how to pay for innovation without putting premiums out of reach of employees. Government demands an end to me-too drug development, yet the laws of economics cause truly unique products to merit monopoly status and therefore higher prices. As each stakeholder continues to regard the desired drug from its separate standpoint, without conferring with its fellow colleagues, the golden age of cancer care veers out of orbit, resentment replacing celebration.

This situation underscores the need for dialogue, to get the discussion of cost versus quality versus access out on the table in a collegial fashion. Manufacturers can no longer identify, develop, and price drugs in a vacuum. Payers can no longer deny or limit coverage of drugs based solely on a cost-minimization strategy. Drug research and development is as vital to healthcare as any resource, providing that it produces drugs of value. A healthcare system that fails to reward innovation is in the first stage of decay.

In this supplement we have engaged payers and researchers in a dialogue concerning their ways of assigning value to nab-paclitaxel; how they pursue the cost-management aspect of patient selection for the improved product; the missing element, a definitive formula for assigning value to a drug; and why quality-adjusted life-years has been rejected by the American healthcare system as the venue to striking balance between cost, quality, and access. They also discuss the fundamental strategic forces in play at the provider and the payer levels, and what nab-paclitaxel does clinically, as well as the reasons experts prefer it to standard paclitaxel.

This supplement addresses concerns of payers, providers, and manufacturers in the attempt to align their needs: payers will see why providers do not prescribe nab-paclitaxel indiscriminately; providers will understand why payers are not unreasonable in trying to establish cost-management controls in the face of rising cancer drug costs; and perhaps both will see that manufacturers are not pricing new products with the intent to gouge but to survive, indeed prosper, a prosperity essential for the stability needed to innovate. The ability to treat cancer effectively is demonstrated in this relatively new cancer therapy. How to fund it, and other cancer drugs currently in the pipeline, remains to be resolved. ■

AHDB1008

# Metastatic Breast Cancer and the Use of Nab-Paclitaxel

Breast cancer remains the second leading cause of death from cancer among American women. Although treatment does not cure metastatic breast cancer, it can reduce symptoms and extend life beyond the median survival period. The majority of patients diagnosed with breast cancer today will survive 5 years or longer. Use of combination chemotherapy has become standard in the adjuvant treatment of early and metastatic breast cancer. The anthracyclines and the taxanes are 2 important classes that have been added to chemotherapy regimens for breast cancer. The taxanes often cause severe side effects, which limit the dose that can be used safely. A novel, biologically interactive, albumin-bound paclitaxel was developed to avoid these toxicities associated with polyethoxylated castor oil-based paclitaxel. Data show that the albumin-bound compound is superior to the solvent-based paclitaxel in many ways, such as it does not require premedication with corticosteroids or antihistamines; it is infused over 30 minutes only compared with 3 hours for the other taxane; and it provided superior overall tumor response rate and time to tumor progression in a phase 3 study. [AHDB. 2009;2(suppl 4):S122-S125.]

**B**reast cancer remains the second leading cause of death from cancer, after lung cancer, among women in the United States. It is estimated that 182,460 women with breast cancer were diagnosed in 2008, and nearly 40,480 died from the disease.<sup>1</sup> Men, too, are affected by breast cancer. The National Comprehensive Cancer Network (NCCN) estimates that 1990 men were diagnosed with breast cancer in 2008, and that 450 died from the disease.<sup>1</sup>

Although treatment does not cure metastatic breast cancer, it can sometimes reduce symptoms and extend life beyond the median survival time of 18 to 24 months.<sup>2</sup> Depending on the patient's disease characteristics, chemotherapy is often recommended as a way to control and slow the cancer's spread, and to relieve other symptoms.

These numbers appear to make for a grim statistical portrait, but within the past few decades significant improvements have been made in reducing mortality and overall better response to treatment among women with breast cancer. Some 35 years ago, approximately 75% of women diagnosed with breast cancer survived at least 5 years; clinical investigations of combination therapy and of hormonal therapy for neoadjuvant (presurgical) treatment were in their earliest stages; genes associated with increased risk of breast cancer had not been identified; and hormonal treatment of metastatic breast cancer with tamoxifen was being investigated but had not yet been approved by the US Food and Drug Administration. Besides tamoxifen, another agent in use at that time was the nitrogen mustard cyclophosphamide, which had undergone clinical

trials as far back as the 1950s; it is still being used in combination therapy.<sup>3</sup>

Today, by contrast, nearly 90% of women diagnosed with breast cancer will survive at least 5 years, and combination chemotherapy, although not entirely supplanting single-agent chemotherapy, has become standard in the adjuvant treatment of early and metastatic breast cancer.<sup>4</sup> In some circumstances, such as patients who are in their second or early third trimester of pregnancy or who have human epidermal growth factor 2 (HER2)-positive tumors, neoadjuvant therapy may be given before surgery or radiotherapy to reduce the size of large tumors before surgical intervention and to increase the likelihood of preserving as much of the breast as possible.

Genetic research has revealed several breast cancer susceptibility genes. The most important are believed to be *BRCA1* and *BRCA2*, which account for between 80% and 90% of hereditary breast cancers; women with these mutations are 10 times more likely to develop breast cancer than the general population.<sup>3</sup>

To the drugs introduced 35 years ago, many new drugs have been added, including aromatase inhibitors, which block the body's production of estrogen; the monoclonal antibody trastuzumab, which is used to treat breast cancers that overproduce HER2 (a protein implicated in approximately 20% of breast cancers); capecitabine, which inhibits DNA synthesis and slows growth of tumor tissue; and gemcitabine, which interferes with DNA replication and causes apoptosis (death of tumor cells).<sup>5</sup>

Probably the most important drug classes to be incorporated into chemotherapy for breast cancer are

the anthracyclines and the taxanes.<sup>6</sup> These 2 classes are used either in single-drug or in combination chemotherapy. Anthracyclines have 3 mechanisms of action: they interfere with DNA synthesis by inserting extra molecules into the base pairs; inhibit the topoisomerase II enzyme, blocking DNA transcription; and create free oxygen radicals that damage DNA and cell membranes.<sup>7</sup> Taxanes disrupt the action of microtubules, which are important components of the cellular cytoskeleton that are contained in the cytoplasm.<sup>8</sup>

### **Anthracyclines and Taxanes in Chemotherapy**

Before the 1990s, most metastatic breast cancer chemotherapy in the United States included drugs from the anthracycline family, usually doxorubicin and epirubicin. During the 1990s, taxanes were shown to be effective as first-line treatment for advanced breast cancer, as well as for the treatment of women who had developed resistance to anthracyclines.

The taxanes used in the United States are docetaxel and paclitaxel, including albumin-bound paclitaxel. Along with doxorubicin, epirubicin, docetaxel, and paclitaxel, the NCCN lists several other drugs among the preferred single agents in its guidelines for treating metastatic breast cancer—pegylated liposomal doxorubicin, capecitabine, and gemcitabine. Most of these drugs also are listed in the NCCN's preferred chemotherapy combinations.<sup>5</sup>

Both single-drug and combination chemotherapy have been shown to offer a survival advantage in large, randomized trials. For combination chemotherapy to treat metastatic breast cancer, the chemotherapeutic agents most often used in the United States are doxorubicin, cyclophosphamide, fluorouracil, epirubicin, docetaxel, and paclitaxel.<sup>5</sup> Piccart-Gebhart and colleagues conducted a meta-analysis (published in 2008) to evaluate the benefit of the taxanes paclitaxel and docetaxel—sequenced or combined with the anthracyclines doxorubicin or epirubicin—as first-line treatment for metastatic breast cancer. Results showed that in single-agent trials, response rate (RR) was similar with taxanes and with anthracyclines: 38% and 33%, respectively ( $P = .08$ ).<sup>4</sup> In trials evaluating combination chemotherapy, tumor RR was significantly better with taxane-based combinations compared with the control arms (57% versus 46%, respectively;  $P < .001$ ). The authors concluded that progression-free survival in patients administered taxanes was significantly worse than in those receiving single-agent anthracyclines; however, tumor response or patient survival rate in those taking taxanes was higher. Tumor response and

progression-free survival rates were significantly better with taxane-based combinations than with anthracycline-based combinations; the difference in survival was not significant.<sup>4</sup>

Although anthracyclines are efficacious, they are potent drugs that can be accompanied by cardiotoxicities, ranging from benign forms of arrhythmias to potentially fatal conditions, such as myocardial ischemia/infarction and heart failure.<sup>9</sup> For example, when the cumulative dose of doxorubicin reaches 550 mg/m<sup>2</sup>, the risks of developing cardiac side effects, including congestive heart failure, dilated cardiomyopathy, and death, dramatically increase.<sup>10</sup> Other acute side effects of doxorubicin can include nausea, vomiting, neutropenia, and complete alopecia. In addition, some patients may develop skin eruptions on the palms of their hands or soles of their feet (hand-foot syndrome). Patients may find the swelling, pain, and erythema so intolerable that they refuse chemotherapy.<sup>10</sup> Other chemotherapeutic agents, such as fluorouracil, cyclophosphamide, and trastuzumab have also been linked to cardiotoxicities.<sup>9</sup>

The taxanes frequently cause severe side effects, which may include a low white blood-cell count, weakness, infection, and muscle pain, as well as numbness, tingling, and burning sensations in the arms and legs (neuropathy). These side effects limit the dose of the drug that can safely be given to patients. Because taxanes are insoluble in aqueous solutions, they must be formulated with surfactants to facilitate drug delivery. But all too often, it is the solvent that causes the unwanted toxicities.<sup>11</sup> Moreover, the solvents may compromise efficacy by impeding drug delivery to the tumor. For example, Cremophor EL, the castor oil-based solvent used to make paclitaxel soluble, changes the clinical pharmacokinetic profile of paclitaxel by forming micelles, polymeric molecules that entrap the active paclitaxel in the plasma compartment and prevent some of it from reaching the tumor.<sup>12</sup> Higher doses of paclitaxel may be required to ensure that a sufficient quantity of the drug reaches the tumor, but this in turn increases the potential of toxicity in normal tissue, leading to dose reduction, delay, or cessation of treatment. Drug researchers concluded, therefore, that taxanes carried by delivery vehicles free of conventional solvents might improve side-effect profiles and increase the amount of paclitaxel delivered to the tumor.<sup>11</sup>

### **Nanoparticle Albumin-Bound Paclitaxel**

Trial data indicated that the solvents polyethoxylated castor oil and polysorbate 80 were probably linked to

the severe toxicities observed in patients being treated with paclitaxel and docetaxel. In addition, hypersensitivity reactions were definitely known to be associated with solvents. In some cases, hypersensitivity reactions were fatal, even though the patients had been premedicated with corticosteroids, and there were cases of prolonged peripheral neuropathy associated with demyelination and axonal degeneration.<sup>13</sup> To counteract the problem, drug researchers would have to find carriers that would be benignly interactive and yet ensure delivery of the active drug to the tumor.

Nanoparticle albumin-bound (nab)-paclitaxel, a novel, biologically interactive, 130-nm, albumin-bound paclitaxel particle, was developed to avoid the toxicities associated with polyethoxylated castor oil. The formulation takes advantage of the properties of albumin, which is a natural carrier of lipophilic molecules.<sup>13</sup> After injection, the albumin-bound nanoparticles disintegrate into 10-nm albumin-bound particles. The formulation allows for the safe infusion of significantly higher doses of paclitaxel than with the castor oil-based drug, and with shorter infusion times (30 minutes compared with 3 hours for the solvent-based paclitaxel). Furthermore, no premedication is necessary to prevent the hypersensitivity reactions associated with the castor oil-based solvent.<sup>13</sup> The albumin-bound formulation delivers more paclitaxel to the tumor by biologically interacting with the albumin receptors that mediate drug transport; *in vitro* studies show a 4.5-fold increase in the transport of paclitaxel across endothelial cells compared with castor oil-bound paclitaxel.<sup>14</sup>

Gradishar and colleagues conducted the pivotal phase 3 trial of nab-paclitaxel (published in 2005).<sup>13</sup> Eligible patients were randomly assigned to receive treatment with nab-paclitaxel, administered intravenously for 30 minutes and no corticosteroid or antihistamine premedication, or to treatment with castor oil-based paclitaxel, administered for 3 hours and with premedication and special infusion sets, as indicated by the prescribing information. Study participants received 260 mg/m<sup>2</sup> of nab-paclitaxel or 175 mg/m<sup>2</sup> of castor oil-based paclitaxel every 3 weeks.<sup>13</sup> Up to 2 dose reductions were allowed from the initial dose of nab-paclitaxel, and reductions in castor oil-based paclitaxel were allowed as well, based on the package inserts used in each country where the study was conducted. The primary measure of efficacy was overall RR; secondary efficacy measures were time to tumor progression (TTP) and overall survival.

The overall tumor RR was significantly better with nab-paclitaxel than with castor oil-based paclitaxel (33% versus 19%, respectively;  $P = .001$ ). Patients who

received nab-paclitaxel as first-line therapy had an overall tumor RR of 42%, and those who received it as second-line therapy had an overall RR of 27%. Patients who received castor oil-based paclitaxel for first-line therapy had an overall RR of 27% ( $P = .029$ ), and those who received it as second-line therapy had an overall RR of 13% ( $P = .006$ ). Tumor RR was also higher in patients receiving nab-paclitaxel than in those receiving castor oil-based paclitaxel—34% versus 19%, respectively ( $P = .002$ ) for patients with visceral dominant lesions, and 34% versus 19%, respectively ( $P < .001$ ) for patients younger than 65 years.<sup>13</sup>

Median TTP was significantly longer for patients receiving nab-paclitaxel than for those receiving castor oil-based paclitaxel (23.0 versus 16.9 weeks, respectively;  $P = .006$ ). TTP was also longer for patients receiving nab-paclitaxel as first-line therapy compared with other patients (24.0 versus 19.7 weeks, respectively). For patients receiving nab-paclitaxel as second-line therapy compared with castor oil-based paclitaxel, TTP was 20.9 weeks versus 16.1 weeks, respectively ( $P = .020$ ). In addition, there was a trend for greater median survival among all patients treated with nab-paclitaxel than those treated with castor oil-based paclitaxel (65.0 versus 55.7 weeks, respectively;  $P = .374$ ).<sup>13</sup>

No grade 3 or grade 4 hypersensitivity reactions occurred among patient receiving nab-paclitaxel. By contrast, grade 3 hypersensitivity reactions occurred in patients receiving castor oil-based paclitaxel, despite being premedicated with corticosteroids or with antihistamines; 2 patients had chest pains, and 3 patients had allergic reactions. In all, 224 of 225 patients in the castor oil-based group received premedication during 95% of the treatment cycles.<sup>13</sup> The incidence of grade 4 neutropenia was significantly lower in the nab-paclitaxel arm than in the castor oil-based paclitaxel arm (9% versus 22%, respectively;  $P < .001$ ), despite a 49% higher paclitaxel dose in the former arm. Grade 3 sensory neuropathy was more common with the nab-paclitaxel therapy than with the castor oil-based paclitaxel (10% versus 2%, respectively;  $P < .001$ ), but this was easily managed and improved rapidly (median, 22 days).<sup>13</sup>

The investigators concluded that nab-paclitaxel demonstrated greater efficacy and a more favorable safety profile than castor oil-based paclitaxel, and that the new formulation was “an important advance in the treatment of metastatic breast cancer.”<sup>13</sup> Recognizing the favorable profile of nab-paclitaxel, the NCCN now includes, in its preferred single-agent guidelines, nab-paclitaxel 100 mg/m<sup>2</sup> or 150 mg/m<sup>2</sup> in weekly doses, or 260 mg/m<sup>2</sup> every 3 weeks.<sup>5</sup>

### A Superior Value-Based Proposition?

To provide health economic data for the Canadian healthcare system, Canadian researchers Dranitsaris and colleagues recently performed an economic analysis—using Canadian dollars and Canadian-based drug formularies, as well as incremental cost-effectiveness—to compare nab-paclitaxel and docetaxel for the treatment of metastatic breast cancer.<sup>15</sup> The researchers used data from a meta-analysis of randomized trials comparing either nab-paclitaxel (260 mg/m<sup>2</sup> every 3 weeks) or docetaxel (100 mg/m<sup>2</sup> every 3 weeks) with solvent (castor oil)-based paclitaxel (175 mg/m<sup>2</sup> every 3 weeks).<sup>15</sup>

Their analysis showed that nab-paclitaxel had the lowest incidence of grade 3 or grade 4 toxicity, resulting in lower overall costs for nab-paclitaxel in the management of grade 3 or grade 4 toxicity compared with docetaxel or solvent-based paclitaxel (\$597 versus \$2626 versus \$1227, respectively). Using the median number of cycles administered and the cost impact of grade 3 or 4 toxicity, the overall cost for nab-paclitaxel was calculated as \$15,105 compared with \$15,268 for docetaxel and \$3557 for generic paclitaxel<sup>15</sup> (using the generic paclitaxel partially explains the much lower dollar amount for that treatment).

When treatment preferences were assessed, 20 of 24 (83.3%) Canadian nurses and pharmacists who administered the drugs selected nab-paclitaxel as their preferred choice; the other 4 respondents selected docetaxel. These corresponded to a gain of 0.203 and 0.016 quality-adjusted life-year for nab-paclitaxel and docetaxel, respectively.<sup>15</sup>

The Canadian study clearly demonstrates a superior value-based proposition when nab-paclitaxel is compared with docetaxel. Although the analysis showed that castor oil-based paclitaxel is less expensive than nab-paclitaxel on a simple cost basis, other factors discussed earlier could do much to offset the apparent cost advantage. Furthermore, their reference trials were limited to clinical trials that restricted use of supportive care, most notable white blood-cell growth factors. (Use was limited to a documented neutropenic event.) Therefore, the use of white blood-cell growth factors may be less than that used in actual clinical practice, where preventive use has become more common. This distinction between use in actual practice versus a clinical trial could result in higher costs for drugs associated with a greater rate of neutropenic events, such as docetaxel.

Nab-paclitaxel is superior to castor oil-based paclitaxel in the following ways:

- It has a higher therapeutic index
- It can be infused in doses that are at least 1.5 times higher
- It requires no premedication with corticosteroids or antihistamines
- It is far less likely to cause grade 4 neutropenia
- It is not associated with grade 3 or grade 4 hypersensitivity reactions
- It requires only 30 minutes to infuse compared with 3 hours for castor oil-based paclitaxel
- It provided superior overall tumor RR and TTP results in a phase 3 study.

As more oncologists become familiar with nab-paclitaxel, it is likely to be recognized as an important advance in the treatment of metastatic breast cancer. ■

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# Abraxane for Breast Cancer Therapy

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This roundtable discussion was convened in February 2009 to deal with the current approach to the treatment of breast cancer, with an emphasis on the taxane-based nanoparticle albumin-bound (nab)-paclitaxel (Abraxane). Drs Dranitsaris, Gradishar, and Overmoyer offered professional clinical expertise on new cancer therapies and discussed the value proposition for these beneficial but expensive therapies. Robert Henry moderated the discussion. [AHDB. 2009;2(suppl 4):S126-S137.]

**Robert Henry:** Today, payers are trying to find answers to how to stretch healthcare resources at a time of economic downturn. This is especially true in cancer therapy, and the need for cancer drug utilization requires solutions on different levels to develop cures for cancer and define the value proposition for them. Let us begin by establishing “points of consensus”—the editorial premise of this journal—for finding consensus between the 3 aspects of the healthcare triangle—the clinical, the business, and the regulatory. To that end, we ask you to focus on the clinical advances that the newer treatment for breast cancer, nanoparticle albumin-bound (nab)-paclitaxel, brings to the table. Please consider it as a prototype of all new drugs used in cancer therapy, to understand the value that these drugs are offering patients. We have put together several questions about the clinical, strategic, and tactical considerations of these therapies. The first question relates to anthracyclines, which are considered the standard first-line chemotherapy for metastatic breast cancer. Is that still the case at leading institutions, such as Northwestern or Dana-Farber, or have other treatments supplanted anthracyclines as first-line therapy?

**William Gradishar:** I don’t think there is anything special about Northwestern with regard to anthracyclines. Generally, although they are still considered standard first-line therapy, the reality is that this has historical interest only, because anthracyclines are such a part of adjuvant therapy that by the time somebody has metastatic disease, these drugs are almost never the first choice. Of course, there are patients who present with de novo metastatic disease, but frequently in those cases other therapies may be used in preference to an anthracycline, because we are limited in how much drug we can give a patient, because of the potential cardiotoxicity associated with it. Anthracyclines are still very active agents. If somebody has metastatic disease and has not received an anthracycline, at some point that patient would probably get one. But these drugs don’t cure patients with metastatic disease, and generally they have been positioned elsewhere in the adjuvant setting. So we don’t use them very frequently anymore.

**Beth Overmoyer:** I agree entirely. What is interesting—and I’m interested in what Bill has to say about

this—is that with all the targeted therapies being evaluated, a lot of individuals are using bevacizumab with paclitaxel as front-line therapy. We are finding that often people with metastatic disease never have anthracycline exposure if they present with stage IV disease, because physicians forget about that drug.

**George Dranitsaris:** Bevacizumab will very likely never be used in Canada for initial treatment of metastatic disease. In the next 2 to 3 years, unless there are compelling survival data, we will never touch it.

**Gradishar:** I agree with Beth. It depends where certain new drugs are available. Bevacizumab has gotten some traction in the United States. I think it is a standard—likely not the standard, some would argue—but we are going to see more drugs like that, and how they are used will probably depend on cost. As George suggested, at the end of the day somebody is going to want to see a way of judging the efficacy of different therapies, and that surely will involve what things get paid for.

**Henry:** *This takes us to the next question, about combination therapies. What combinations are most efficacious, and when do you continue to rely on monotherapy?*

**Overmoyer:** This is a very good lead-in, because if the acceptance of these therapies is based upon improvement of overall survival, there have only been 2 studies that show increased overall survival with combination chemotherapy in metastatic disease—capecitabine/docetaxel and gemcitabine/paclitaxel. Another combination that is becoming more accepted is ixabepilone/capecitabine for heavily pretreated patients with metastatic disease. And then again, there's the combination of the angiogenesis inhibitors and chemotherapy. I'm not sure where you want to put them in terms of the discussion. We still have to raise the issue of combination targeted therapies and chemotherapies, especially if we are dealing with cost and efficacy, because the targeted therapies add a small amount. They are not the home runs we thought they would be.

**Dranitsaris:** Let me ask a general question. What is the intent of chemotherapy in the metastatic setting? Why do we give it?

**Overmoyer:** It's palliation, to help control symptoms associated with the disease. The goal is to prolong survival, but the overall goal is not cure.

**Dranitsaris:** So to live longer or better are the 2 objectives. If both are met, that's great. But at least 1 objective should be met. That said, most of the anti-neoplastic regimens we use don't do that in the metastatic setting.

**Overmoyer:** Indeed.

**Gradishar:** That's correct. To go back to what Beth was saying before, the combination regimens gemcitabine/paclitaxel, capecitabine/docetaxel, and ixabepilone/capecitabine may or may not lead to improved survival, but there is some suggestion that maybe they confer an incremental improvement in progression-free survival and possibly overall survival. Not all trials measure quality of life, but they should. The goal in any therapy should be to obtain responses that also translate into making the patient feel better. Some of these therapies, for instance ixabepilone/capecitabine, are based on pragmatism, even though there are preclinical data to support the combination. So what do you do? If capecitabine works, why not combine it with ixabepilone?

**Dranitsaris:** In most cases, won't a doublet be better than a single?

**Gradishar:** It depends how you define better, of course. Most data, whether from randomized trials or otherwise, would suggest that cocktails of drugs may result in a higher response rate. And most of the cocktails are associated with a greater risk of toxicity. Relatively few regimens or trials have demonstrated that the doublet translates into improved, progression-free survival, or overall survival. But that's true about the response rate.

**Dranitsaris:** I'm a big fan of single-agent therapy. There's nothing wrong with multiple lines of single agents. Nothing says that doublets are better than singles.

**Gradishar:** That's a favorite topic in any meeting on breast cancer. There is the inevitable discussion or debate—Are monotherapy approaches better than combination therapy? If we look around the United States, most oncologists give sequential single-agent therapy, and I'm among them. Usually, doublet therapy will produce more side effects in patients who have metastatic disease.

**Dranitsaris:** That's why I think taking a drug like nab-paclitaxel fits very nicely with that paradigm.

**Gradishar:** Right.

**Henry:** *Have any of your patients with breast cancer been administered paclitaxel plus trastuzumab, and has that combination been more effective than other combinations?*

**Gradishar:** Anything combined with trastuzumab in HER2-positive patients is better than chemotherapy alone. I'm not sure; you could run the list of chemotherapy drugs against single-agent chemotherapy versus single-agent chemotherapy plus trastuzumab in HER2-positive patients. It is going to be better, which is defined as a greater response rate. A number of randomized trials actually show survival benefits. There are few randomized trials, but every single trial, whether phase 2 or 3, strongly suggests that trastuzumab added onto chemotherapy is better.

**Henry:** *Let's move to pharmacology. How does the solvent used in standard paclitaxel differ from that in nab-paclitaxel? And does the difference in solvents affect the pharmacodynamics of active paclitaxel?*

**Overmoyer:** Because paclitaxel is hydrophobic, it has to be combined with some kind of a vehicle. What we call standard paclitaxel is combined with Cremophor EL, a polyethoxylated castor oil vehicle, and ethanol. Cremophor EL in standard paclitaxel, when given in the doses that we administer, can affect the pharmacokinetics of paclitaxel by forming micelles around the drug. It remains in the bloodstream and interferes with the pharmacokinetics of paclitaxel. It looks as if it has nonlinear pharmacokinetics, but it actually is quite linear.

By contrast, nab-paclitaxel is formulated with paclitaxel bound in nanometer-sized albumin particles. Albumin is a natural product. This is a genius approach for 2 reasons. First, it does not affect the pharmacokinetics of the drug, so it has linear pharmacokinetics. Second, the body already has mechanisms for transporting albumin across the endothelial cells into the tumor interstitium, through structures called calveoli. The albumin binds to glycoprotein 90 and then activates another protein, and the calveoli transport the albumin/paclitaxel molecules into the intertumoral space. So when you look at the drug concentration in the tumor, it is higher with nab-paclitaxel than with standard paclitaxel, because of the vehicle.

Do you want to go into the other mechanisms? I think it is more theory than actuality, but it may be proved in mouse models. SPARC (secreted protein,

acidic and rich in cysteine) is a natural protein that binds albumin. SPARC is overproduced in lung and breast cancers, and consequently it is also associated with a poor prognosis in those diseases. So in addition to the natural transport of the drug through the calveoli, we also have sequestration of albumin binding to SPARC in a tumor, which also improves the concentration of drug in the tumor. I think the vehicle in nab-paclitaxel improves efficacy of the active drug, whereas Cremophor EL potentially can interfere with the efficacy of the drug.

**Gradishar:** That's a nice summary. As Beth mentioned, Cremophor EL diminishes the efficacy of the chemotherapy drug. Of course, we also associate Cremophor EL, the solvent used as the vehicle for standard paclitaxel, with the side effects that some people naively attribute solely to the chemotherapy drug. But Cremophor EL does have an effect on neurotoxicity, bone marrow suppression, and demyelination. So rather than simply always looking at the chemotherapy drug as the sole mechanism for these toxicities, we must look at the solvent as well. Add to this the catastrophic thing we always worry about in the clinic— anaphylactic or hypersensitivity reactions. Hypersensitivity reactions have been associated more with the solvent than with the chemotherapy drug. By discarding the solvent, we can diminish some of the side effects and all the added adjunctive medications, such as corticosteroids, that we administer with solvent-based paclitaxel therapy.

**Henry:** *How important is it that clinicians understand the pharmacologic basis for drug performance?*

**Gradishar:** It's important to have a broader understanding of how these drugs work. Let me use an example not about the taxanes. We are now increasing our understanding of pharmacogenomics—the influence of genetic variation on a patient's response to drugs. Through the use of pharmacogenomics, we are trying to determine which patients are good, intermediate, or poor metabolizers of even oral medications like tamoxifen. So a broader understanding of pharmacologic mechanisms by which drugs work may allow us to more wisely use these drugs in patients. Getting back to the taxanes, the hope would be that by modifying the platform for how the drug is delivered, you may get greater efficacy, and that would be an argument in favor of using one drug over another. We're trying to improve efficacy and diminish side effects.

**Henry:** *Is there any way of gauging the extent to which oncologists understand these dynamics?*

**Gradishar:** This is something many of us talk about. If you were to quiz oncologists, my guess is that most don't have a clear understanding of what Beth just talked about. They may have some sense that there is some difference between albumin and Cremophor EL, but I'm willing to bet that there is not a deep understanding.

**Overmoyer:** I agree. And what Bill said about pharmacogenomics is also very important. I agree with Bill that we're headed in the direction of individualizing disease treatment based on the patient's own mechanisms of metabolism. I think that part of the resistance of the oncologic community toward some of these data stem from lack of understanding.

**Henry:** *This is the reason we convened this panel, to begin the debate about the value of nab-paclitaxel based on its scientific and clinical contribution. Is the therapeutic index of nab-paclitaxel higher than that of standard paclitaxel, and how does a higher therapeutic index affect the treatment of patients with breast cancer?*

**Gradishar:** If I'm interpreting the question correctly, one of the things that oncologists like to do, historically, is dial up the dose of whatever drugs they're giving, and see what happens, always with the idea that more is better. And in many, maybe even most, situations we found that this strategy, although working in some diseases, has not been particularly effective in breast cancer.

With respect to taxane therapy, solvent-based paclitaxel has been looked at historically in trials at a range of doses and schedules and infusion times. The trial that everybody focuses on when trying to discuss this particular point is the Cancer and Leukemia Group B study, that assessed solvent-based paclitaxel administered as a 3-hour infusion every 3 weeks. The amounts administered were 175 mg/mm<sup>2</sup>, 210 mg/mm<sup>2</sup>, or 250 mg/mm<sup>2</sup>. There was no clear demonstration of an improvement in outcome as judged by response rate or time to disease progression. Higher-dose therapy was accompanied by greater toxicity. Thus it was concluded that 175 mg/mm<sup>2</sup> should be the optimal dose. And, of course, there's been subsequent work looking at weekly schedules and different doses. It was concluded that simply increasing the dose, particularly with solvent-based paclitaxel, was not going to get us anywhere.

We've come to appreciate that we probably can give

more drug with nab-paclitaxel. As Beth said, when we increase the dose of solvent-based paclitaxel, we are also increasing the amount of Cremophor EL. As a consequence, efficacy of the active drug probably diminishes, because it's entrapped in micelles formed in the plasma compartment, and toxicity increases, because there is more Cremophor EL. But in the absence of that solvent, as we increase the dose of nab-paclitaxel, we actually see what we call dose-response, which is different from what we see with solvent-based paclitaxel. Dose-response means we improve the clinical outcome as we increase the dose.

**Overmoyer:** Not only is there the anticancer effect of the drug itself but also, when speaking of taxanes, an effect on angiogenesis. When we expose cancer cells to the taxanes over a longer period of time, we not only have the direct anticancer effect but also the antiangiogenic effect, which Cremophor EL sometimes can interfere with. We need to understand more about the other effects of these drugs that support a global antitumor effect, and how these vehicles interfere with it.

**Henry:** *The next question is how nab-paclitaxel compares with the anthracyclines. In what ways is standard paclitaxel superior to anthracyclines for treating breast cancer, and in what ways are anthracyclines superior to standard paclitaxel?*

**Overmoyer:** Has nab-paclitaxel ever been compared to anthracyclines, Bill?

**Gradishar:** I don't know of any such data.

**Overmoyer:** Right. The classic head-to-head comparison was the E1193 Intergroup trial, which compared paclitaxel single agent, doxorubicin single agent, and then a combination of the 2 drugs. There wasn't a big difference between the 2 drugs, although a European trial did show that doxorubicin was superior to paclitaxel. Not seen is whether docetaxel is superior to doxorubicin. But again, I don't think we'll see much clinical research comparing the taxanes with the anthracyclines as single agents, because it's just not important in terms of our clinical care.

**Gradishar:** I suppose the only way we can approach the question is indirectly, which is probably not a valid way of doing it. There have been meta-analyses looking at taxane-based therapy—not nab-paclitaxel, but taxanes versus anthracyclines—and individual trials.

Probably some of those trials would suggest that taxanes are better. Then we look at nab-paclitaxel versus the solvent-based taxanes, and maybe they're better. So we get this indirect sequence of logic, which probably is not the right way to do it. But as Beth said, this is a question that we've moved beyond; we are not going to be comparing anything with anthracyclines at this point.

**Henry:** *In the phase 3 trial comparing standard paclitaxel with nab-paclitaxel, what was the overall response rate, time to tumor progression, and overall survival? Were there differences in quality-of-life data?*

**Gradishar:** In the pivotal phase 3 trial, patients were randomly assigned to 3-week cycles of either nab-paclitaxel 260 mg/mm<sup>2</sup>, without corticosteroid or antihistamine premedication, or solvent-based paclitaxel 175 mg/mm<sup>2</sup> with premedication. There was almost a doubling of the response rate favoring nab-paclitaxel. And you can look at the population subsets—whether they were getting treatment as first line, whether they had anthracycline exposure. The individuals who received nab-paclitaxel had a better overall response rate, and it was consistent across all the subsets of patients. In terms of time to tumor progression, there was an advantage for patients receiving nab-paclitaxel compared with those receiving solvent-based paclitaxel. Among the entire intent-to-treat population, there was not an overall survival benefit, or alternatively, there was no decrement in outcome, but no survival benefit was observed. Quality-of-life data instruments were not used universally throughout the pivotal trial. We should look at toxicity data as a way of maybe getting at some of those issues. Feel free to chime in, Beth, because I don't have the manuscript in front of me to give the exact details.

**Overmoyer:** I think that's fine. Later on, when we talk about weekly nab-paclitaxel, we can touch upon the comparison of the 3-week nab-paclitaxel to the 3-week docetaxel, and then to weekly nab-paclitaxel. I think one of the concerns of the pivotal trial was that we no longer believe that the 3-week standard paclitaxel is the optimal way of utilizing that drug.

**Henry:** *Let's move on to the next question. Grade 3 sensory neuropathy reportedly occurs more frequently with nab-paclitaxel than with standard paclitaxel. How do you manage these episodes of neuropathy in your patients?*

**Gradishar:** That was one of the observations that came out of the pivotal trial. And at first blush, after all

the discussion about how getting rid of the Cremophor EL would be sort of a panacea in every respect, we are left with the data suggesting a higher frequency of sensory neuropathy in the patients who got nab-paclitaxel. But we have to look a little bit deeper, because there's a consistent finding—not only across the pivotal trial but in the individual phase 2 pilot studies and the randomized phase 2 trial—that among the patients in the nab-paclitaxel arm who developed neuropathy, there was a different time course for improvement than what we would see with solvent-based paclitaxel.

Although admittedly the numbers of patients we're talking about are not large, we observed that among the patients taking nab-paclitaxel, these episodes of grade 3 neuropathy improved—after interruption of treatment—to grade 2 or 1 in a median of 22 days. Improvement meant that we could rechallenge the patient with the drug. Of course, it doesn't mean that neuropathy goes away completely, but it diminishes to a point where we feel comfortable re-treating the patient. And that's very different when you look at the time course of severe neuropathy with solvent-based paclitaxel. So again, the number of patients who take nab-paclitaxel and who experience neuropathy may be a bit higher, but the time course and the behavior of the neuropathy are very different. And it may again reflect what Beth was talking about a few questions earlier, that is, Cremophor EL may have a more irreversible effect on the nerves compared with what we see with nab-paclitaxel.

**Overmoyer:** I have nothing to add. That's perfect.

**Gradishar:** The only thing I would add to that answer is related to how we manage these patients. Obviously, if they have severe neuropathy, we delay and probably reduce the dose of the drug. And if it's prohibitive, then obviously we have to think of an alternative, as we do with any drug.

**Henry:** *What drugs do you use to premedicate patients being infused with standard paclitaxel, and how often is the premedication not effective enough, which may result in adverse events? Does nab-paclitaxel offer a superior value compared with standard paclitaxel?*

**Overmoyer:** When standard paclitaxel is administered every 3 weeks, the recommendations are to use dexamethasone 20 mg, 12 hours and 6 hours before the infusion, and then to give some type of an H<sub>2</sub> blocker, such as ranitidine or cimetidine and diphenhydramine,

about 30 minutes before the infusion. Can we avoid premedicating people when the drug is given weekly? I think we may be able to avoid the dexamethasone 20 mg, given 12 and 6 hours prior, but I believe the practice is still to give the H<sub>2</sub> blocker and diphenhydramine, as well as a smaller amount of steroid 30 minutes before infusion when standard paclitaxel is administered weekly.

Nab-paclitaxel does not require any premedication. Clearly, that's helpful. How often do we have adverse events? Very severe adverse events such as anaphylaxis, hypotension, or angioedema are uncommon. I think it's 1% to 3% incidence with standard paclitaxel. But we can have less severe hypersensitivity reactions—flushing, abdominal pain, a little shortness of breath—that require the infusion to be halted and the patient to receive more diphenhydramine and more steroid. Then the patient can be rechallenged. I believe that severe hypersensitivity is even less common, if seen at all, with nab-paclitaxel.

**Gradishar:** I would add that the only thing that will really grind a clinic to a halt—and I say that obviously tongue and cheek, but seriously, too—is somebody having an anaphylactic reaction. Though not common, an anaphylactic reaction is life-threatening; when it happens, it can be catastrophic.

Also, whenever patients who get solvent-based paclitaxel have hypersensitivity reactions, it may affect future treatments. Not only will patients have to be premedicated, but may receive slower infusions. There are different tricks that nurses use to keep things moving along, but once the event has occurred, the clinic becomes a more labor-intensive enterprise. The economic impact is undeniable.

**Henry:** *To continue with the value proposition, the infusion time for standard paclitaxel takes approximately 3 hours. About how much time is spent premedicating the patient, and how much time infusing paclitaxel?*

**Overmoyer:** Premedications are normally given about 30 minutes before. It doesn't take long to premedicate, we just have to wait. Then we infuse the patient with paclitaxel. If it's given every 21 days, it takes maybe 3 to 4 hours, start to finish. If it's given weekly, the infusion time is still 1 to 2 hours. In contrast, nab-paclitaxel doesn't require premedication, and the infusion time is less than 1 hour.

**Dranitsaris:** We have our nab-paclitaxel infusion time

down to about 20 minutes. We can get it in pretty quick.

**Gradishar:** So there's a huge practical application there. I'm sure George can speak to that. Beth and I can echo the realities in the clinic. We all work in very congested double- or triple-booked areas. The nurses are always trying to get patients in and out, and it is not that we're trying to create an assembly line in an effort to crank out more patients. Although we have to take care of patients, when we tie up chairs for an extended period of time, it drives the whole place into chaos.

We can perhaps compare nab-paclitaxel with oral medications that in certain situations may be as efficacious as intravenous medications, and thereby have added value, because fewer resources, including time, are required to administer them. This touches on the issue of economic reimbursement. The same thing is true of nab-paclitaxel. Being able to move somebody in and out, getting their therapy effectively and safely in a fraction of the time that it would take to give them the alternative, is a huge bonus not only for the patient but for the office as well. Things can run so much more smoothly.

**Henry:** *George, do you have anything to say about this?*

**Dranitsaris:** With respect to infusion-related efficacy? For us, it's a double-edged sword. In Canada, the more efficient we get, the higher our patient volumes. Even if more patients come through, you don't get any more money from the government. Our clinics are given annual operating budgets. If they treat more patients, that's great. It means the cost per infusion is cheaper, but there is increased stress among the staff, because we have more patients being treated.

But, patients who take nab-paclitaxel are in and out of the clinic in half an hour. And they're not concerned about toxicity. If we compare them with somebody who has received standard paclitaxel, they don't look as though they've received chemotherapy.

**Henry:** *I wonder how that would compare with the experience in the United States. The situation would probably be different.*

**Dranitsaris:** You could probably bill more, if you have a clinic that's fee-for-service. So the more patients you can treat, the more revenue you have.

**Gradishar:** Yes. I think that's probably true in a private practice setting. I'd love to say that works in aca-

demetic medicine, but I haven't seen any evidence of that. Although more patients are pushed through, our compensation has not changed.

**Overmoyer:** I like the point that George made, which was that patients don't suffer the toxicity and side effects of the premedication—fatigue from the diphenhydramine and weight gain and hyperactivity from the steroids. I think that's a very good point.

**Henry:** *Next question involves a group at Memorial Sloan-Kettering that conducted a phase 1-2 trial of weekly nab-paclitaxel to treat patients with stage IV non-small-cell lung cancer. Do you know any oncologist treating breast cancer patients with weekly infusions? What are the probable benefits of weekly infusions versus every 3 weeks?*

**Gradishar:** Are you referring to patients with lung cancer?

**Henry:** *No, breast cancer.*

**Gradishar:** Yes, we do that as well. I think weekly therapy is a very common practice. It was adopted because it was demonstrated quite some time ago that there were advantages of giving weekly solvent-based paclitaxel in terms of efficacy. And when the pilot studies were done with weekly schedules of nab-paclitaxel, not only in taxane-pretreated or taxane-refractory patients, it was demonstrated that responses were seen. More recently, we conducted a randomized phase 2 trial of weekly schedules in previously untreated patients with metastatic disease. The trial showed that weekly dosing was highly effective, and one of the treatment arms was docetaxel given every 3 weeks, so in many people's minds the most active taxane has been or is docetaxel, and frequently that's given every 3 weeks as opposed to weekly.

The results of that phase 2 trial were reported at the recent American Society of Clinical Oncologists meeting in San Antonio, and will probably be published in the *Journal of Clinical Oncology* in the near future. The report will show that weekly dosing is very efficacious, compares favorably with the 3-week schedule, and was well tolerated. Based on these data, and doing what oncologists do, which is extrapolating from other experiences, a lot of oncologists probably prefer to use weekly schedules of nab-paclitaxel.

**Henry:** *Is it well established that oncologists are using weekly treatments of nab-paclitaxel for breast cancer?*

**Gradishar:** I don't know whether I can say it's well established, but I think a lot of oncologists are doing it. I can say that.

**Overmoyer:** I agree. The only issue is the optimal weekly dose. There seems to be a range of 100 mg/mm<sup>2</sup> to 150 mg/mm<sup>2</sup> weekly. But I agree with Bill, I think we all use it weekly.

**Henry:** *What dose are you using?*

**Overmoyer:** I base my recommendations on Bill's study. I believe that 150 mg/mm<sup>2</sup> was the most efficacious dose. In a patient who is robust, I certainly start with 150 mg/mm<sup>2</sup>. But based on toxicity, age, and other factors, I can always reduce the dose without feeling that I'm compromising the patient's treatment.

**Gradishar:** For the average patient, we probably give 100 mg/mm<sup>2</sup> to 125 mg/mm<sup>2</sup>, and that's not because I think 150 mg/mm<sup>2</sup> is wrong. It was the study we did. The one thing about 150 mg/mm<sup>2</sup>, and Beth can comment on this, is when you look at the data from the randomized phase 2 trials mentioned, it clearly showed the progression-free survival was best with 150 mg/mm<sup>2</sup>. If that's the sole end point we are looking at in an otherwise very healthy patient, we do give 150 mg/mm<sup>2</sup>. If it's somebody who has gotten other therapies, who is a little (for the lack of a better phrase) beat up from having gotten a lot or gone through a lot, we'd probably use a lower dose, because 150 mg/mm<sup>2</sup> has a higher risk of neurotoxicity and other side effects. So we always have to—we do this every day, we look at patients—balance side effects and efficacy in any given patient.

**Overmoyer:** Absolutely, especially when you treat metastatic disease.

**Henry:** *Do you anticipate that nab-paclitaxel will influence the National Comprehensive Cancer Network (NCCN) guidelines?*

**Gradishar:** It's already in the NCCN guidelines as one of the drugs for use in the metastatic disease setting. And since I sit on the NCCN Guideline Steering Committee, let me use the example of aromatase inhibitors, even though they have nothing to do with what we are talking about now. When the results of the adjuvant therapy trials of the aromatase inhibitors were initially available, oncologists asked, "Which one is better?" "How should we use it?" "Should we use it only

after the patient has received tamoxifen?” And so on. The oncologists who reviewed the guidelines were attempting to be very rigid and adhere to trial design. Then, after some time had passed, everybody just said, “This is crazy. Just say that aromatase inhibitors should be used, as opposed to trying to draw minor distinctions between them based on trial design.”

Why do I bring that up? When we look at the guidelines for metastatic disease and chemotherapy, and if you look at the tables, there’s essentially a list of acceptable drugs that could be used—either monotherapy or combination therapy drugs. My guess is that there won’t be huge efforts to dictate that we must use a particular dose or we must use it after a particular drug. I don’t think we’ll get into micromanaging how the drug is positioned. The key thing every company wants to do is be on the list. That said, nab-paclitaxel is on the list.

**Overmoyer:** I agree. How doctors use nab-paclitaxel in sequencing their single-agent regimens for the patient will be based on their own personal experience and their own comfort level with the drug. But in terms of someone dictating when they should use it, I don’t think that that will ever happen.

**Henry:** *Is the issue of off-label drug use of concern here? Medicare has been rattling sabers about not paying for off-label use of drugs. Does this have the potential to affect off-label use of nab-paclitaxel?*

**Overmoyer:** It is a concern, especially for the smaller hospitals and the private practitioners. Thus far, large academic institutions have been able to get away with using drugs off-label. But—and we’re addressing that at Dana-Farber—even the larger institutions are going to become much more strict about using these drugs off-label. My experience with Medicare, even speaking with them personally, is that they will not permit off-label use. And I suspect that with the economy being the way it is, that effect will trickle down to the private insurers, and they will become more strict, too. They haven’t been thus far, but that’s my supposition.

**Dranitsaris:** Didn’t Medicare recently relax their off-label use criteria? And won’t they start paying for more off-label use?

**Overmoyer:** I just know from personal experience that I have had a very difficult time trying to get Medicare to pay for off-label use. I can’t say whether they’ll relent.

**Henry:** *It seems that off-label use of cancer drugs has been much more common than for other therapeutic areas?*

**Gradishar:** I can’t speak to other therapeutic areas, but that’s certainly true in oncology. Oncologists have always been fairly liberal in their creative use of drugs, even when they aren’t approved, and there have not been a lot of obstacles put in their way. Whether that will be true going forward, I don’t know.

**Henry:** *Has the arrival of biologics changed this, that is, what was okay for conventional drugs may not be so for the more complex pharmacologic drug profile?*

**Overmoyer:** Yes. I’m sure that the use of biologics has stimulated a reassessment of how often these drugs are used off-label, and it’s basically a cost issue. So, yes, this really does stimulate a reassessment. I think the tide is turning.

**Gradishar:** I agree with that. I see no way around it. I’m not a politician or a policy person, but just being aware of the things we do on a daily basis, we’re going to have no choice. We simply can’t pay for all these things.

**Overmoyer:** Right.

**Henry:** *That leads us to the next question. Under the new economic stimulus package, the federal government will spend \$1.1 billion on comparative effectiveness research over the next 18 months. Some people are worried that this initiative, coupled with tight budgets, will quickly devolve into more coverage discussions based narrowly on cost-effectiveness. Others see this as a positive move, with more resources going to the research community. How do you see this big, new push for comparative effectiveness research influencing clinical research and the discovery process?*

**Gradishar:** It is what I was alluding to earlier. Assessing comparative effectiveness is going to be a necessary step. Perhaps it may help us in clinical research. It may also help us recruit patients to trials if this is the way that they are going to get the drugs. I’m not sure I want to be the person whose name is associated with who gets and who doesn’t get therapy. That person is going to have a tough job, but this is inevitable. Many countries, including Canada, do this. It’s not a popular thing, but the pot is only so big, and there are a lot of people vying for a piece of the pie.

**Dranitsaris:** Well, if you look at the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, one immediate impact is price reductions. Recently, for some of the newer molecules, such as sunitinib, for example, NICE was able to negotiate a lower price with Pfizer. Similarly with erlotinib, they got a lower price. So lower prices will be one impact. But as Bill said, if you're saying, "No, you can't get this drug," there will be a lot of fighting. Once again, in the United Kingdom there are always lawsuits, people complain to the BBC about NICE's decisions. At the end of the day, it's not a nice way to treat patients with cancer.

**Overmoyer:** But if it has the benefit of lowering prices of these drugs, that is very positive. I hope, too, that we will see more research facilities, particularly research pharmaceutical companies that can develop novel agents that are substantially more effective. I'm not talking about modifying a drug to make it a little bit better. But it may embolden them to be more creative in terms of developing really new and effective drugs as a focus, rather than just trying to get into a competitive market.

**Henry:** *I'd like to share with you some comments from Dr Ken Schaefer, Medical Director at Select Health, about this question. The point of comparative effectiveness analysis isn't academic. The logical progression should be that it will impact coverage decisions. The whole point of comparative analysis is to help determine where limited economic resources can best be used. Anyone who is worried about this as an outcome likely has invested financial interest in a product that may have an inferior outcome and thus be disadvantaged. Obviously, different patients may benefit from different therapies. By doing comparative analyses, providers and payers, specialty societies, and others should be able to develop evidence-based algorithms that provide the most cost-effective strategy to manage specific conditions. This we hope will also stimulate investigation by manufacturers on new technologies that truly advance care rather than on 'me-too' drugs designed just to garner profit and add nothing to patient health outcomes.*

**Dranitsaris:** One of the biggest issues with cost-effectiveness is where do you draw the line of cost-effectiveness? What is your value threshold? In Canada, it's different by disease sites. Frankly, if you have lung cancer, it is very unlikely that the government will pay for the newer monoclonal antibodies. If you have breast cancer, you will likely get access to get

most drugs. That's kind of a moving end point with us here. But where do you draw the line?

**Henry:** *The following question was provided by Gary Owens, MD, who for 10 years had been chairman of the P&T Committee at Independence Blue Cross. "Not all patients have severe side effects from paclitaxel, although they are common. Is there a reliable way to determine in advance which patients will more likely have significant side effects from paclitaxel? In other words, can one come up with a risk model or marker that may allow advance selection of appropriate patients?"*

**Dranitsaris:** I think docetaxel should be the drug we're talking about, not paclitaxel. That's the one that can actually put a patient in the hospital.

**Overmoyer:** We look at patient selection intuitively—patients who are elderly, who are frail, as Bill said, who were highly pretreated, who have diabetes, who have a higher risk of having sustained toxicity from paclitaxel. Those are the patients who may benefit from drugs that are associated with less toxicity but have comparable, if not greater, efficacy. So we try to select our patients appropriately, which, of course, definitely goes against the concept of choosing one drug for everyone. Not everyone can get the same drug. We need some "me-too" drugs in that setting, because not everyone can tolerate these drugs.

**Henry:** *A point well taken. What are your thoughts, Dr Gradishar, about patient selection? This is such a key factor in establishing value-based care, personalized medicine as opposed to population-based medicine.*

**Gradishar:** As others have said, that's where we are evolving. I hope that the science we are all interested in is going to make us better clinicians by giving us the ability to use the right drugs in the right people. Until we have more information, until we have more targets, until we know, for example, who will benefit from bevacizumab, until we know more clearly what the genotype of a given patient is so we can use tamoxifen, we won't be nearly as effective as we would like. Those are the types of things that are going to allow us to use drugs in a more appropriate way and, as a consequence, cut down costs. If we are not just blindly treating patients—and that's not a criticism of me or the field—but applying what is the state of the art. We just don't have the nuanced knowledge yet to know where these drugs are optimally used. Until then, we rely on the

clinical impressions of patients: Can they tolerate this or that? What did they respond to in the past? What is their performance status? If we have some clues about the biology of their disease, we might want to exploit it. But we're still fairly primitive in terms of how we select drugs for patients.

**Henry:** *That's a good representation of how difficult it is to achieve truly value-based, patient-centered care. You don't have perfect information in advance as to which patients need which drug, and yet, as you are saying, this is the goal or should be the goal of future research. Would comparative effectiveness or improved personalized medicine techniques be serving the interests of breast cancer therapy to best advantage?*

**Gradishar:** Undoubtedly. Everybody wants to personalize the therapy we give to patients, which sounds like a nice phrase. It sounds like something a hospital marketing brochure would say, but the reality is that it's based on science. Until the science catches up, or we can apply it to individual patients, it's a phrase that's probably limited to those patients whose tumors have certain targetable characteristics. I think that knowledge will expand as we go forward.

**Dranitsaris:** Let me be the devil's advocate. I mean realistically, given the volumes we are seeing in the clinics these days, given the cost of these tests, given validation issues, is it ever going to happen? Because if you look at the history of oncology, the only 2 tests to date that are used in breast cancer are hormone positivity and HER2. These are the only validated tests that are currently in wide use, and its 2009.

**Overmoyer:** A good example is the utilization of the Oncotype DX screening test. Wouldn't you say, Bill, that now we can have a better tool to find patients who do not necessarily benefit from chemotherapy, which would have been offered to them based on standard prognostic indicators or standard recommendations?

**Gradishar:** Right, I think that's a good example because that indirectly, potentially can have an enormous cost-savings or redirect patients toward clinical trials if they are going to get treated. If you know they are not going to benefit from chemotherapy, they either get the standard hormonal therapy, or we may find as we go forward that the standard chemotherapies that we use in the adjuvant setting based on subgenomic tests are going to be ineffective. Those patients

who get what's not going to help them could be redirected toward novel trials.

**Dranitsaris:** If we ever get there.

**Gradishar:** Right, I'm not saying we're there.

**Overmoyer:** But I think that we've actually made some inroads, and it's not only the laboratories and science that have to keep up; we also have to change the mindset of oncologists to accept these newer forms of diagnostic tests to find out which therapies patients should receive.

**Henry:** *That is an important point to payers. When I spoke recently to Dr Ken Schaefer, he expressed frustration, saying that he felt handcuffed in his ability to help marshal and manage the allocation of precious healthcare resources to all the treatments, and in particular breast cancer. He said that the ability of a payer to decline any form of new therapy, not singling out nab-paclitaxel in terms of breast cancer, he felt constrained by the litigious nature of American society, in terms of the strong likelihood that a healthcare plan would be sued for denial of coverage of anything for breast cancer. And it was his impression that it was a free-for-all when it came to clinicians making treatment decisions right now and the emphasis is right now. Payers can't really intervene without the patients coming back on them with the support of patient advocacy groups. I asked whether the pressure was coming from the political arena, the legal arena, the advocacy groups. He said, you name it, it's there. He felt that the dynamics are not aligned well for responsible cost management. I asked, are we talking about the distinction between population-based research versus personalized medicine? He said it's gone beyond that to the point of individual research. He was very down on the whole thing, saying that an N of one is enough to get any drug approved for, especially, patients with breast cancer. How do we address this? A dialogue is perhaps the best starting point for redressing this antagonism between the payers and the providers of breast cancer care.*

**Dranitsaris:** It's amazing. I was in South Africa over Christmas, visiting a cancer center there. The public system in South Africa only pays for adjuvant cyclophosphamide/methotrexate/fluorouracil. You cannot get an anthracycline. The disparities around the world are incredible.

**Gradishar:** I don't know the answer to this. We all bear some responsibility. Obviously there are many clinicians who treat creatively in the absence of data;

they treat continuously. The providers, just using one example, were probably influenced by the experience with bone marrow transplant when it was being done for breast cancer. There was a total absence of data from randomized trials, yet providers were being taken to court on a daily basis by plaintiffs who demanded this particular therapy. And on the clinical side during that time, there was a lot of pressure, as though that was the answer to the problem. But we didn't have the data, so you have this retrenching, with people probably being a little reluctant on the payers' side to just pay for anything. And on our side, there was the expectation that whatever we did was right, and that we should be reimbursed for it. And then, of course, in the interim, during the past 20 years, there has been enormous development and strengthening of advocacy for breast cancer. Breast cancer advocates are a very powerful and very vocal group. I'm not sure I said anything that is usable or sensible, but I said something.

**Overmoyer:** And you said it very well. I have very little to add to that.

**Henry:** *It is important to get providers and payers to bring ideas like this to the table. It's important for all stakeholders to realize that they don't have the answer themselves, that together all healthcare stakeholders—patients, providers, payers, manufacturers, government, academia—everyone involved is essential to providing answers. Dr Owens asked if there are good data on the ability to administer chemotherapy at the proper dose and at the proper timing of the cycle, comparing paclitaxel and nab-paclitaxel. In other words, do more patients get full benefit of the regimen, and more important, can this be translated into a clinical advantage?*

**Overmoyer:** Bill, do you know how many patients? I can't recall. In terms of the pivotal trial, was there a discrepancy between the median number of cycles with standard paclitaxel?

**Gradishar:** No. Actually, when you look at the data for dose intended and number of cycles administered, it's pretty close to the ideal, in terms of the optimal dose of paclitaxel and nab-paclitaxel. There was maybe one cycle less than the median administered for those getting solvent-based paclitaxel. The probable explanation is that more patients progressed, so they ended up getting less. But it was well-balanced.

**Overmoyer:** But that type of discrepancy has been

shown in other situations. M-VAC chemotherapy for bladder cancer is my favorite example, even though it's outside my norm. This is a regimen that is very effective, but very few people were able to receive the entire dose of the combination therapy, and very few people were able to receive more than, let's say, 2 or 3 cycles. I think it's a good point; I just don't see that happening with these 2 drugs.

**Henry:** *Finally, Dr Owens asked, "In the area of significant coinsurance on the part of patients, does the potential for increased out-of-pocket cost and the potential for some patients not to be able to afford the expensive treatment temper the use of nab-paclitaxel?"*

**Gradishar:** I think it will, and that will be true with other drugs as well. But then we get into this overall healthcare system with 2 tiers, and it's unethical that certain people cannot afford the copay of these expensive drugs, which may be an increasingly large number of people, whereas others can. I find that problematic and troubling.

**Overmoyer:** And on a more global level than just these 2 drugs.

**Henry:** *We looked at these drugs as a microcosm of a larger picture for cancer care overall. We're asking everyone to scratch their heads and say, "What about our healthcare system?" It's obvious that our ability to pay for advances is lagging behind our ability to invent good cures or good treatments for cancer. It's a very big challenge, and it always bespeaks the 1960s song of Joan Baez: "If life were a thing that money could buy/The rich would live and the poor would die." On a much less poetic stance, the question is if cost-sharing for biologics is all punitive, and if it's a barrier to a lot of patients seeking care. Systems changes are needed, and justification for value proposition, and as you pointed out, we don't have all the techniques to qualify patients in advance. We do know the things that you pointed out earlier—the scientific understanding of the disease process and the pharmacodynamics of nab-paclitaxel suggest reasons for the efficacy and reduced side effects associated with this taxane. I welcome any final thoughts or recommendations, things you recommend for the benefit of clinicians and payers alike, as well as the policy folks, about what advance nab-paclitaxel brings to the treatment of breast cancer patients.*

**Gradishar:** That's a heavy burden you have laid on us. I guess the only comment I would make, which is true

of any drug, not just this one, is that all the stakeholders have to have a so-called global perspective, not just one that's self-serving. When we look at using this drug as an example, we could start looking at the cost only, or we could focus instead only on toxicity or on efficacy. All those things have to be brought together, and then we have to reduce them to one question—Is there an advantage for patients? Can you tease out an advantage, thinking about the global cost of administering this kind of drug? I'm talking about a taxane. When you use one over the other, is there a net benefit to the patient and perhaps to the healthcare system? And if you can answer those questions in an affirmative way, then I think the equation suggests that it's an advance.

**Overmoyer:** That's beautifully stated, and the only issue is what is going to be the degree of that effect, based primarily upon our current healthcare problem, which is the 46 million uninsured people that we're starting to speak about. And then there are the insured to whom these drugs are being allocated, but their number is becoming less and less. So someone, or some group, like the one you mentioned, Bob, has to start some sort of dialogue so that we can quantify the efficacy of this combination that Bill had talked about in terms of cost and toxicity. And they should be able to design these therapies so that everyone has access to them, as Bill stated, on a global level.

**Henry:** *A couple of years ago at an Academy of Managed Care Pharmacy meeting, Dr Dan Malone from the University of Arizona gave a presentation on Lambda—meaning the amount of money that society decides it wants to allocate for an improvement in health-care. It's really up to each society to decide how much it wants to pay for an advance. George, do you have any final thoughts, notations, anything before we close?*

**Dranitsaris:** From a policy point of view, focusing on a drug like nab-paclitaxel, and other drugs like that,

should be less of a concern for payers, because for the most part they replace existing therapies, so it's kind of an offset. The therapies that they should be more concerned about are the incremental ones, the ones that are an add-on to existing therapies, like bevacizumab, for example. Those are the ones that have a bigger impact on the budget.

**Henry:** *That's a good point. It is worth starting a dialogue with the payers and trying to give some feeling that cost management is still a reality, still a possibility for them. I think it is the sense of having decisions taken away from them only in this area of medicine that has them worried.*

**Dranitsaris:** I have a question. Is anyone in your centers using sequential nab-paclitaxel after docetaxel?

**Gradishar:** We have done that. There are data to support doing that. If a patient progressed while using docetaxel, either on an adjuvant or a metastatic basis, although that patient may have used other drugs first, I think you would come back to a paclitaxel-like drug at some point. I think it's reasonable to give nab-paclitaxel.

**Dranitsaris:** So you are not finding a cross-resistance?

**Gradishar:** No, there are data that have been looked at, including the data in Joanne Blum's early trial. But this is not a huge response rate. I don't want to suggest that 50% of patients respond, but there are a fraction of patients who, after having received docetaxel, will respond to either solvent-based paclitaxel or to nab-paclitaxel.

**Overmoyer:** I agree.

**Dranitsaris:** We're seeing some of that right now, this sequential use. ■

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