CONSIDERATIONS FOR THE OFF-LABEL USE OF MEDICATIONS IN ONCOLOGY

Sarah L. Scarpace

I'd like to thank you for inviting me to speak today. This is definitely a very timely and relevant topic. It's something that we deal with every day in oncology practice and especially as an oncology pharmacist.

Practicing at the VA, one of our roles there is to really assess for the off-label use of medications whether or not there is enough evidence to support allowing a prescription to go through and reach a patient. And so we're often in that situation where we're trying to make a decision about a physician who would like to treat a patient with a medication that's not indicated and we're kind of the barrier. We're one of the final people who are able to review that before allowing it to go through the system. So it's definitely an issue that we deal with on a regular basis.

I'd like to describe a little bit for you, as the first speaker, some of the incidence of the use of off-label medications in oncology practice. I'll describe a little bit for you and you guys probably know this already about the FDA's role and their role in the approval process for medications in general. I'd also like to talk about compendia. There are certain compendia that actually list medications as being appropriate for non-FDA approved uses of drugs, and that's something that we rely on in terms of determining whether or not it's acceptable to use a product off-label. And in fact, the Centers for Medicare and Medicaid Services use some of these compendia in terms of allowing off-label uses of medications. So even the government will rely on these compendia for regulating these products.

Certainly there are ethical questions and I'm sure every speaker will address some of these issues and we'll probably get into that a little bit in the discussion time. I'd like to review some of the professional society position papers on the use of these medications. A lot of the professional societies will, at a minimum, outline a process for trying to determine whether a

medication that is being used off-label is appropriate. And then I'll just give you some of my viewpoints as a practicing oncology pharmacist.

Depending on the literature that you read, the incidence of off-label use of medications in oncology can be quite high. Anywhere from 7 to 33%, and in some cases it can be as high as 75%, of any particular drug may be used for off-label indications. And there are a lot of reasons for that. Some of it is just with the rapidity of the way that information becomes available to us in practice that we have access to information much more quickly than the approval process can take and we want to use these products in patients who may not have other options. We use this a lot in the palliative setting in patients who may not have any other alternatives, they've tried every approved product that's on the market and there's no other options, they may not qualify for clinical trials. It's often very difficult to qualify for trials when you're heavily pre-treated. That's a very difficult situation when a patient still wants to fight or their family still wants to fight and we believe that a product may work for them. So that's really where a lot of the usage comes into place.

Some of the reasons why drugs are used outside of their labeled indication by the FDA include other indications, so often a product is approved for a specific disease state. And even more so in oncology there are not only a specific disease state, but also a certain stage or only after a certain line after treatment has failed in a patient. So it's a very, very specific group of patients that these products are approved for and so we may end up using it for a somewhat different population because, you know, we might believe that it works even though it's specifically indicated in that group.

Sometimes we use alternative dosing regimens. A lot of this has to do with ensuring that the patient can tolerate a regimen or as new studies become available that they may be more convenient for patients. So if a drug is approved for a weekly administration, sometimes new schedules are looked at clinically to see if maybe we can extend that interval at different doses and difference frequency to assist the patient in terms of making it more convenient for them.

One of the other age groups that often receive drugs off-label is pediatric patients. As we know most of these trials for drug therapies that are new to the market are done only on adult patients, that leaves this whole group of children who may have

similar diseases as what we see in adults and so we may want to try these drugs on pediatric patients because those trials are very difficult to do. To consent there are a lot of ethical issues with getting children involved in clinical trials, consenting the patient, or their parents, for trial can be very difficult.

As I mentioned before, some of these drugs have very narrow labels, so it's not a matter of it's just approved for breast cancer it's approved for a particular stage after certain therapies have already been tried and that really restricts its use. And because of that restricted use we may want to use it in other types of breast cancer patients. Sometimes there are diseases that have very few actually approved drugs for their disease state. Prostate cancer is one of these diseases that before 2004 there were only two drugs that were available on the market that were actually approved to treat prostate cancer. And so because we knew that there were other drugs on the market that seemed to be effective in a variety of solid tumors we started using this drug in prostate cancer before it was officially approved with good results. But this was a disease where there were no other options for the patient and there are only a couple of drugs that were approved, neither of which, I might add, extended survival. These drugs actually only seem to improve the use of pain medications. So we really were limited in terms of the effectiveness of some of these drugs.

This product ixabepilone—IXEMPRA is the brand name—is just one example of a drug that has a very restricted label was just recently approved last summer with very specific uses. As you can see in the way that this label is written, you have to have failed certain therapies; it has to be used in combination with another product; it has to be a specific stage of the disease. So you're talking about a very narrow group of patients when you may think it has activity in the disease and it may be reasonable to use it in the disease outside of this specific labeling.

In terms of the FDA, the FDA doesn't really regulate practice, they approve a label for marketing. They're not even really approving a drug, but I think sometimes in the clinical world we get caught up in that a little. Some practitioners think the FDA's the only one who can kind of make these decisions about how to prescribe drugs. And it's really just that they are approving a label for marketing to make sure that it's accurate and not misleading.

They're really regulating more the manufacturers; they're not

really regulating physicians or other health care professionals. An FDA-approved drug is just one that is approved for marketing in the United States and they're really looking at the label, the actual label that goes on the container, the wording that's in the package insert that we use to look up information or perhaps give information to patients as well as some of the advertising. And that's really it. They don't really try to regulate what you determine its role in therapy is. That's a clinical, professional judgment on behalf of the healthcare professional.

Unlabeled uses. There are a variety of ways that a drug can be used off-label and that includes things like using it for a different indication or at a different dose or in a different population than what's in that label. The American Hospital Formulary Service is one of the relevant compendia that the Center for Medicare Services actually relies on for determining reimbursement of off-label drugs. This is one of those compendia that has been around a long time, it's been around for over fifty years, it was actually written into law that this is one of the compendia that clinicians can use to, you know, feel comfortable that their products are going to be reimbursed.

A lot of third-party payers also will follow in the footsteps of the Medicare and Medicaid system in terms of determining reimbursement. And certainly reimbursement plays into all of this usage of off-label medications, because if insurance carriers are not paying for drugs, it's much less likely that patients are going to be able to afford them and then they may not have access to these drugs. That alone can introduce other ethical dilemma in terms of practice.

The AHFS are actual professional staff, they are not consultants. They don't have drug company influence, they're not consultants from the outside, which can happen with other types of services. They're drug information analysts with strong scientific and therapeutic backgrounds. They really review the literature with an emphasis on those trials that are very well designed and controlled. They look at meta-analysis and systematic reviews. They also take into consideration cost effectiveness, which we never really thought about a lot until recently in practice, and do now that we have more drugs available. Where some of these drugs may have equivalent outcomes and we may be able to treat oncology like we do other diseases, where we can kind of look at if the outcome is the same what's the most cost effective way to get to that end result.

They also use clinical practice guidelines in making their decisions. So they look at these clinical studies, they look at the peer reviewed literature, they also try to take into consideration the severity of the disease, how rare the disease is, if there're other options that are available on the market. These are all things that the FDA does not consider in their decisions. So this is one of the reasons why this process is very important because it's all relevant to patients and to clinical practice. So—and I mentioned this already—they take into consideration the importance and severity of the disease. They look at what the alternatives are and their toxicities compared to the drug they're evaluating. They look at the strength of the evidence and in their review they will actually rate how good the evidence is in terms of the types of studies that were done so that you can make a decision about how good that evidence is.

Then they also consider new information. This is really supposed to be one of the reasons why these compendia are so important to practice: because they're supposed to look at information that's hot off the press. They're supposed to make faster decisions in terms of whether or not these drugs are appropriate much more quickly than the FDA would. But there have been some questions about that. Recently there's been some criticism of these compendia in terms of how quickly they are making these decisions. There have also been some questions in terms of how reliable these compendia are in adhering to their own practices and their own processes.

The agency for Health Care Research and Quality actually supported a study that looked at an evaluation of several different compendia. Each of these compendia are actually supported by CMS. AHFS is the one that we sort of traditionally rely on, but there are other compendia that we can use. They looked at this group of compendia and they really looked at a few different factors. They wanted to evaluate their methods. They wanted to look at, well, how good their methods are and how well they stick to their own described processes.

They selected four different off-label indications in 2006 in oncology. They also looked at one update in 2008 for the use of Gemcitabine in bladder cancer. There's been data on the use of that drug with that disease for a long time so they were thinking it gave plenty of time for these compendia to make a determination about using this off-label because it's not actually indicated in bladder cancer.

Then they actually looked at each compendium's content and their citations, again against their own methods, and then compared them to what these investigators used to determine whether or not the drug should be used off-label. This slide is just a schematic in terms of the end results of that trial. What you can see is the take-home message. There're a lot of yes's and no's in the column, which shows that there is a lot of variability in terms of the way that these compendia adhere to their own practices and the differences between compendia in terms of whether or not they made the same recommendations. You would think if they had similar processes and they were looking at the same type of information they should have the same end results or end recommendation. But they did not. So this is very important.

The other issue that is shown in this graph, that you may not see very well here, is that they did not necessarily have very readily-available, the hot off the presses, information. When they looked at that 2008 update that had information available for several years, many of them did not include that information in their compendia listing or evaluate it, they had made no determination about it. They may not be as quick to evaluate the literature as we had all hoped. There was certainly a lack of transparency in the way that these compendia operated. They seemed to cite little current evidence at least the way that the investigators felt should have been cited in terms of their own reviews. And they seemed to lack adherence to their own systematic methods, which is really one of the biggest concerns.

This is important because we want to make sure that there is a strict process in place. If we just allow all drugs that become available to be used without any regulation there's certainly very serious dangers that can happen. Before there were strict regulations in the way that drugs were available, heroin used to be sold without regulation. We all know the story of Thalidomide, that people were using this off-label with very tragic results. And the same is true for all of these other drugs that I have listed up here.

This is sort of the extreme of what can happen if there's not good regulation and if we don't have some type of system in place to oversee this process. This is Wall Street Money Market. Some of the ethical considerations when health care professionals use a drug off-label in practice pertain to the one who takes responsibility for it. If you're using a drug on its label according

to the package insert, you can go back to the manufacturer if something goes wrong because you followed the instructions. But when a practitioner does it kind of off-label, using their own judgment, we assume some of that responsibility. Physicians can make a decision not to use it. Pharmacists can decide not to fill the medication. And this is something that in part of our review process in the VA system, if we get a request for using a drug off-label we can evaluate the evidence and if we feel that there's not strong enough evidence, it may not be safe. Perhaps a physician wants to use this based only on a phase I/II study that's been reported in abstract form at some meeting. That may not be enough information for us to really say, "Okay, go ahead and use this."

Other countries have some regulations in place in terms of how they make decisions. They're all different than what we do here in the United States. The U.K. will actually deny drugs based on whether or not they can prove it is cost effective. In Europe, there are some countries that actually will not allow some of the supportive care medications to be prescribed. Aprepitant, or Emend, is a new drug that's used to treat nausea and vomiting or prevent nausea and vomiting from very highly emetogenic chemotherapy regimens. They feel it's not cost effective, so in some countries it's not available.

France actually has a little bit more liberal approach. They have a list of therapeutic protocols that are sort of available to you to be used on a temporary basis. It's sort of similar to these off-label indications that might be appropriate. In Japan, they are further along the spectrum. In pediatric patients they will allow approval of drugs in pediatrics even without very rigorous clinical trials. There's really this whole spectrum of the way the rest of the world deals with off-label medications.

One of the other questions is, really, how do we know what a contraindication is really contraindicated? We use carboplatin in children, but in the package insert says it is contraindicated. So if we become desensitized to some of these very important safety warnings, how do we know when to pay attention? That's why we have to be very careful when using some of these drugs off-label. We use them based on limited evidence. Continued use of off-label medications further limits knowledge because you're not allowing rigorous collection of data that we can rely on later on.

We have to consider the role of patients. These days, patients come to you with all kinds of testimonials about this drug might

work or this crazy treatment in Mexico is something he wants to do. And we have to sort of deal with that. And that also will influence your decision in terms of whether or not you want to proceed with an off-label use of a medication.

In terms of some of the professional societies, the American Society of Health System Pharmacists has a position. This is an old position paper of 1992, it has not been updated, so this is the most recent update that there is. They advocate that the pharmacist is a patient advocate and a drug information specialist, and that our role is really to develop standard operating procedures for the evaluation of drug orders and dispensing of drugs, and that we can develop proactive approaches to engage third-party payers. So again, part of what we do at the VA is just kind of trying to look at the literature to make these types of decisions.

The Europeans also have a concern, they state that off-label use is an urgent concern when it's supported by evidence or accepted practice. They want the regulatory bodies to take more responsibility so that the health care professional is not the only one assuming liability. They think that some of these agencies know the information is out there, they just want the money to be paid to them to actually go through that review process. So they want to see the regulatory bodies taking more information, and they also suggest having this list available of sort of approved/unapproved indications.

Australia also makes recommendations to practitioners. The key message here, and the one that I feel is really one of the most critical pieces of the use of off-label medications, is making sure that the patients give informed consent. That to the best of your ability, in an unbiased way, you present what you know and what you don't know and let the patient decide and get it documented. You all know that. Document everything that you've told them, didn't tell them, and what the final decision was. And really the patient has to be the biggest part of making these decisions about using drugs off-label.

ASCO is the American Society of Clinical Oncology; they feel that medications for off-label uses should be reimbursed. Again, if there is evidence to support it from peer review journals. They don't like the fact that CMS only relies on some of these compendia listings, they feel that this is an outdated method. That we're not getting really quick information made available to practitioners. They want to see certain peer review journals also

take into consideration when making those CMS reimbursement decisions. In terms of practical applications, we have to balance those known, as well as unknown, risks and benefits, and describe them to the patient. A critical evaluation of the literature is very important. At the VA they're all into rules and regulations.

Recently, physicians had to go through this training process for sensitivity training to make sure they don't badger other health care professionals, and they don't really. I work with great practitioners across the street so it was very funny that they had to do that. But, in some settings, the nurse, the pharmacist, other supportive health care professionals can feel very pressured just to do what the doctor says and it's very important that we take that step out and look at ourselves as an independent safety process, review process, and make a collaborative decision, make sure that there is informed consent.

I think it is important to consider the costs of therapy these days. Some drugs are upwards of $10,000 a month. And even when you look at the literature, there was a drug that was approved a couple of years ago with statistically significant improvements in progression-free survival in colorectal cancer. When you look at the actual data, it was a difference of five days. This is one of the drugs that costs $10,000 a month. That is a very important critical review of the literature in making your decisions.

Recommend that patients do clinical trials whenever appropriate. This is really key to practice in the future of practice so that we get good information to make decisions later on and then document everything that you tell your patients. I think just ran out of time, but I really appreciate the opportunity to speak today and I look forward to our discussions later on.