Prostatepedia[1]

[1]expert insight + advice

Chemotherapy

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In this issue....

Many patients fear chemotherapy not only because of its side effects but also because of what the need for chemotherapy implies about their prognosis. Fortunately, each physician we spoke with this month addresses both issues.

Taxotere (docetaxel), the chemotherapy drug most commonly used to treat prostate cancer, is usually used to treat patients with an aggressive form of this disease. However, multiple randomized trials have shown that this drug prolongs survival. We see the most dramatic impact in patients who have extensive metastatic disease at the time of diagnosis. The CHAARTED trial showed that initial treatment with Lupron (leuprolide) plus Taxotere (docetaxel) was markedly more effective than Lupron (leuprolide) alone in prolonging survival. There is a definite benefit to receiving the drug, if you need it.

The most common side effect of Taxotere (docetaxel) is fatigue, which is usually mild after the first dose, but worsens with each subsequent dose. Sometimes, this limits the total number of doses administered. Usually, this side effect disappears over time. Exercise lessens its potency, and each physician in this issue recommends exercise.

Taxotere (docetaxel) damages the nerves in the hands and feet. This leads to a feeling of numbness and tingling in the fingers and toes called neuropathy. This grows in severity with each dose of the drug, but when stopped in a timely fashion, the side effect is reversible.

In 2003, Gedlicka et al. reported that alpha lipoic acid minimized nerve damage (https://academic.oup.com/annonc/article/14/2/339/153613). Since the publication of this paper, we recommended two 300 mg tablets of time-release alpha lipoic acid twice a day during Taxotere (docetaxel) treatment in my practice. It appears to have a marked impact on the severity of this side effect.

Taxotere (docetaxel) damages the production of hair and nails. Hair loss can be prevented by chilling the scalp as the drug is administered. Chilling the hands and feet also seems to lessen the nail damage.

Prolonged Taxotere (docetaxel) treatment can also damage and block the tear ducts, causing tears to flow. Some physicians recommend inserting silicon rubber tubes in the tear ducts when the symptoms first appear. Once the tear ducts have closed, repair is much more difficult.

Many chemotherapy drugs cause a drop in hemoglobin, white cells, and platelets. While these can be a problem with Taxotere (docetaxel), it is milder than in the multidrug combinations used for other common cancers, such as breast cancer. Transfusions can be used if the drop in hemoglobin becomes clinically significant. Low white cell count can be managed with granulocyte stimulating factor (G-CSF). While a low platelet count can be managed by platelet transfusions, these lose their effectiveness over time. This can be a major problem in a few patients.

Patients on Taxotere (docetaxel) often experience inability to taste food. Patients have often reported that bland creamy foods are easier to eat.

Overall, the side effects of Taxotere (docetaxel) develop gradually as the number of cycles on the drug accumulates. If treatment is limited to six cycles, these side effects are usually mild and reversible. Most patients have nearly complete recovery within 6 months. If the cancer is still sensitive to the drug, a second round can be effective and well tolerated.

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Chemotherapy

Dr. Tanya Dorff is a medical oncologist who serves as associate clinical professor in the Department of Medical Oncology & Therapeutics Research and the Head of the Genitourinary Cancers Program at City of Hope, a research and treatment center for cancer based in Duarte, California.

Dr. Dorff's research interests in prostate cancer range from clinical trials in PSA-recurrent prostate cancer to the role of fasting in chemotherapy tolerability to CAR T cells that are primed to target prostate cancer tissue.

She leads one of the largest clinical trial portfolios in genitourinary cancers.

Dr. Dorff spoke with *Prostatepedia* about chemotherapy for prostate cancer.

Why did you become a doctor?

Dr. Tanya Dorff: When I was around three years old, I decided that what I wanted to do with my life was help people. And being a concrete thinker as a three-year-old, I felt like being a doctor was the only way to do that.

Have you had any patients over the years who have changed how you view the art of medicine or how you view your own role?

Dr. Dorff: There are so many who have influenced me. My mom had a rare form of leukemia when I was in college. It was uniformly fatal. But they had recently developed a new treatment with the discovery of a specific translocation of the retinoic acid receptor for acute promyelocytic leukemia (APL). All-trans retinoic acid was developed, and she received it as experimental (at the time) through compassionate access. She was cured, and she's still alive today. That influences how I feel about clinical trials and translational science. If we hadn't understood that biology, we couldn't have designed the overwhelmingly effective treatment.

How is chemotherapy used today for men with prostate cancer?

Dr. Dorff: When I started treating prostate cancer, chemo was pretty much our only tool besides standard hormone therapy. It worked, but it was sort of end-of-the-line. People didn't tolerate it very well, in part, because we used it in really advanced cases. Then, the drugs like Zytiga (abiraterone) and Xtandi (enzalutamide) came out, dramatically improved the situation for prostate cancer patients, and chemotherapy got pushed later and later.

The CHAARTED study was presented five years ago. That study showed that using chemotherapy early with the initiation of hormone therapy dramatically improved survival, above and beyond using it later. About 75% of the patients on the control arm got the chemo when they became resistant, so it was a pretty good experiment of now versus later, and not now versus never. To see that just using it early added an extra year or more of life for these men was really profound. That reinforced the strong role chemotherapy has in this disease.

With which other kinds of agents is chemotherapy frequently combined?

Dr. Dorff: Combinations with Taxotere (docetaxel) have never yet been successful in prostate cancer. There was Taxotere (docetaxel) with a high-dose Vitamin D, which was not only negative in that it failed to improve outcomes, but patients who received the combination actually fared worse. There was Taxotere (docetaxel) with Revlimid (lenalidomide), Taxotere (docetaxel) with atrasentan, Taxotere (docetaxel) with GVAX… All of these combinations have failed.

One of the ASCO presentations that prostate cancer physicians might remember most vividly is a slide presented by David Quinn in his presentation of the negative results of the SWOG S0421, the study of Taxotere (docetaxel) alone or with atrasentan. He showed a slide of a graveyard, implying that any drug tried in combination with Taxotere (docetaxel) is doomed to fail.

Why do you think that is? Is it just that the combination is too toxic?

Dr. Dorff: I don't know. I don't think it's too toxic. All of these combinations go through safety before they go into Phase III, and you can combine them safely. I do not understand why combinations fail. Maybe it goes back to biology. Why would the combination succeed? You want something that makes the chemo work better, or you want the chemo to make the drug work better. That's where we should probably start when planning combination studies. Even then, things that look good in early testing can fail in Phase III, so in some cases it may be that we need to sub-classify patients in order to design more successful trials.

Maybe a more interesting question when we're talking about combinations is: how do we get the best use of the chemo and do the least damage to the patients?

At University of Southern California, we started a study looking at a fasting-mimic diet to make the Taxotere (docetaxel) better. We found preliminary evidence that fasting prior to chemotherapy reduced toxicity, and I envision that could have two specific benefits in men with prostate cancer who might get Taxotere (docetaxel).

One might be that if we could mitigate toxicity, more men would actually receive it. There was a lot of therapeutic nihilism out in the community about how chemotherapy doesn't work so well for prostate cancer, or that these older patients can't handle it. If we could ratchet down the toxicity, maybe more prostate cancer patients would actually get chemo.

The second benefit might be that if we could reduce toxicity to normal host cells, we would be more likely to get in full doses on time, which might make it work better against the cancer versus what happens now, which is that we frequently dose-reduce and dose-delay because of toxicities. The fasting-mimic diet study is still ongoing but these are the outcomes I was hoping for when designing it.

"We found preliminary evidence that fasting prior to chemotherapy reduced toxicity."

How long are they fasting before they start the chemo? What does that look like?

Dr. Dorff: They fast for 48 hours on a fasting mimic diet, which means they get vegetable broth and an energy drink. So, it's a liquid, low calorie diet. It's hard, so that's part of why the study is still ongoing.

In our earlier trial, in which we did fasting with platinum chemo for up to 72 hours (48 before and 24 after the chemo dose), people really swore by it. They really felt like they had so much less toxicity compared to chemo cycles in which they didn't fast.

With the fasting mimic diet (created by L-Nutra), because it's not pure fasting, we extended it to three days before chemo. The first day is a fairly robust number of calories, just plant based and with specific amino acids left out, which is felt to be part of the effect. Then there's the two days before chemo with lower calories, and one day after. After fasting or the fasting-mimic diet the body needs a bridging diet for the first meal, and the L-Nutra regimen also included supplements to replenish the body.

If someone reading this is interested in participating, can they contact you directly or should they contact someone else?

Dr. Dorff: Sure, they can contact me directly at tdorff@coh.org. But the trial is going on only at USC, so they may wish to contact the clinical trials office at USC or the medical oncology group at USC.

Are you combining diet with chemo instead of another agent?

Dr. Dorff: Yes.

What kinds of side effects can patients expect from chemotherapy? What are you hoping to reduce?

Dr. Dorff: One of the most concerning side effects is the peripheral neuropathy, which can become permanent, but I don't want to scare any readers.

Can you explain what that is?

Dr. Dorff: It's damage to the small nerves out in the fingers and toes that can manifest as numbness or pins and needles, burning kinds of discomfort. That can be permanent.

Is there anything patients can do before or during getting chemo to reduce the likelihood of that happening?

Dr. Dorff: Not that we know of.

There's no way to predict who might suffer from that or not?

Dr. Dorff: It's not a complete no. We know patients who already have some preexisting neuropathy, whose nerves are already damaged, are more susceptible, for instance patients with diabetic nerve damage. That's one reason we might try to get them Jevtana (cabazitaxel) instead of Taxotere (docetaxel) because Jevtana (cabazitaxel) doesn't impact the nerves in the same way. I'm not sure if that's what patients worry about, but that's one of my number one concerns because I've seen patients a few years after chemo who are still vexed by the neuropathy.

If Jevtana (cabazitaxel) doesn't result in neuropathy, why wouldn't you use that agent over Taxotere (docetaxel)?

Dr. Dorff: Because insurance typically won't cover it. Head-to-head, they were compared in the FIRSTANA trial, and they were equally effective; one wasn't much better than the other. So, insurance companies can say that Jevtana (cabazitaxel) is not more effective; it's equally effective. Taxotere (docetaxel) is a fraction of the price because it's off-patent, and Jevtana (cabazitaxel) is actually approved specifically in post-Taxotere

"The ongoing combinations that I think people are still interested in are platinum with taxane and carboplatin with Jevtana (cabazitaxel)."

(docetaxel) patients, so it's off-label to use it first-line. You can make a case when you have a guy with neuropathy, but even if you have a guy without neuropathy, you sure would like to leave him without neuropathy at the end of his treatment.

We start to see the neuropathy around dose five. If you stop, it's more reversible, but if you keep going, that's where it can become permanent, and so again, when we're getting to how we can enhance the efficacy, if we could get more doses in without being limited by neuropathy, maybe we would do better with the drug, or maybe we just avoid the neuropathy, have equal efficacy and patients suffer less. There's two ways we can win.

Equal efficacy and side effects are a huge issue for men.

Dr. Dorff: Patients really worry about hair loss. I don't think we're impacting that with the diet, unfortunately. That is reversible. They also complain about the taste changes and mouth sensitivity because that really impacts eating.

Does that go away once chemotherapy is finished, or does that linger after?

Dr. Dorff: That goes away.

It's just while they're getting chemo that they lose sense of taste?

Dr. Dorff: Yes, but it's a long time to not be able to taste.

And the hair loss only happens while they're getting chemo, too? It comes back?

Dr. Dorff: Yes, it grows back.

What combinations with Taxotere (docetaxel) do you think will work best?

Dr. Dorff: The ongoing combinations that I think people are still interested in are platinum with taxane and carboplatin with Jevtana (cabazitaxel). That's an important combination for the more aggressive variants.

Part of how we think Taxotere (docetaxel) chemotherapy works is that it interferes with antigen receptor (AR) translocation in the cell to the nucleus, because the microtubules are needed for that. It still may be more for patients whose cancer is using a lot of AR signaling whereas platinum is more for cancer that might not be as dependent on that mechanism. That combination is pretty important.

There are some other biologics being studied together with Taxotere (docetaxel), but I'm not sure that those will be successful. There's Taxotere (docetaxel) with immunotherapy, but we have the negative GVAX trial that tried combining vaccines with Taxotere (docetaxel). We are also combining it with Xofigo (radium-223), which is a little interesting, but I don't know why those agents would necessarily help each other. Again, when you're looking at a combination, it'd be nice if there were a reason to expect synergy.

What about favorite sequences?

Dr. Dorff: We know that after you've had Zytiga (abiraterone) or Xtandi (enzalutamide), you can induce the androgen receptor splice variants such as AR-V7. These are associated with less responsiveness to Zytiga (abiraterone) or Xtandi (enzalutamide). Patients might want to go from Zytiga (abiraterone) straight to Xtandi (enzalutamide), but we know there's a lower likelihood of success, and we know AR-V7 is a big part of that. If we sequence in chemo, since they've shown that AR-V7 positive patients still benefit from chemo, I view the optimal sequence as Zytiga (abiraterone) or Xtandi (enzalutamide), followed by wiping out the AR-V7 population with a chemo drug, and then going to Zytiga (abiraterone) or Xtandi (enzalutamide) next. We don't know for sure if that's what happens when we use that type of sandwich approach, but it has theoretical appeal, and that's how I talk to patients about it. The other way to go is a clinical trial, especially for combination with Zytiga (abiraterone) or Xtandi (enzalutamide).

What about the side effects profile when you do those kinds of sequencing?

Dr. Dorff: Hormone drugs like Zytiga (abiraterone) and Xtandi (enzalutamide) have much better side effect profiles, generally speaking, but the chemo side effects are largely reversible, and we tell patients that it's not forever. There are good days and bad days, so it's important to note that most people are not feeling bad every single day that they're on the chemo. I don't think the side effects vary based on sequence.

Some of my colleagues feel that when they use chemotherapy up front like in the CHAARTED study, they see more side effects if they start the chemo right away, but they see fewer side effects if they wait a month or two into the hormone therapy to add the chemo.

Is that because the patients become used to the side effects and learn how to manage them before you add something else?

Dr. Dorff: No, because the side effects are totally different between the two treatments. This is speculative, but I think you debulk. I think that part of the reason people get a lot of chemo side effects is that when we're killing a lot of cancer there's a big inflammatory reaction. You can feel sick from it, and we see that anecdotally in certain patients. If you can debulk the cancer a little bit with a couple months of hormone therapy, and then give the chemo, it might be better tolerated.

That's interesting. So as the cancer's dying, it throws off some kind of signal?

Dr. Dorff: It does. There's a lot of dead stuff that has to be cleared by the body, and maybe that means it doesn't have as much attention to do the healing that it needs to do with the chemo. I don't know; that's purely speculation.

Is there anything else you think men should know about chemotherapy for prostate cancer?

Dr. Dorff: First and foremost, chemo is effective. People downplay the role but CHAARTED really showed us that this is a good tool. We are working on tools that have fewer side effects. I'm working on whether diet can help mitigate side effects, and other people are looking at things like exercise, but the bottom line is that chemo is a good tool.

But still some patients draw a line in the sand and say they'll never receive chemo because they've seen other patients getting chemo for other cancers. The chemo we use for other cancers is different than what we use for prostate, and every person's reaction to chemo is different. Of course, you can't erase that impression that's made on you when you see someone who you care about struggling through chemo, but it doesn't mean that's what your experience is going to be.

Your doctor's job, and your oncologist's job, is to make it livable, to allow you to still do the things you want to do and to keep you safe and healthy through your chemo. There are tricks up our sleeves that we use to make that happen.

Sometimes patients are surprised to hear that they can actually feel better on chemo.

Why would that be?

Dr. Dorff: Because sometimes the cancer's driving their side effects. It's a catch-22. There are patients who might want to wait until they're feeling better to get chemo, but if they're feeling bad from the cancer, it's really the chemo that's going to make them feel better.

I have patients who've been unable to eat, in too much pain to really get out and do anything, and when they start chemo, they feel better, they eat better, they have more energy, and they can do more. If you take someone with no cancer symptoms, sure, the chemo's going to make them feel worse. But if you take somebody with cancer symptoms, they may actually feel better.

That's interesting because there's this whole cultural perception of chemo as being catastrophic. The idea that chemo would make you feel better seems bizarre, but it makes sense the way you explain it.

Dr. Dorff: Yes, I think a lot of patients are shocked to hear it, and I think that's a good thing to put out there.

Do you have any suggestions for men as to how to handle side effects before going into it?

Dr. Dorff: Communication with your doctor is the way to be successful in your chemo. A lot of people don't want to bother the doctor, or they want to tough it out, but the earlier they tell the doctor that there's a side effect, the easier it is for the doctor to intervene and reverse it. There's no medal at the end of chemo for not having had to take a treatment for a side effect or not having called the doctor. Just pick up the phone and call. That's how your doctor can do their best by you, and how you can be most successful with your treatment.

Aside from that, staying active is really important. Getting out and walking, even if you're not *exercising* per se, but just moving around and not being sedentary is important for circulating the blood. We don't want you to get a blood clot during chemotherapy because you're not moving. It helps you expand your lungs, so maybe it can help keep your respiratory tract and heart healthier. Go into chemo as fit as possible, and try to maintain activity and mobility during treatment.

Alicia Morgans, MD
Putting Chemo in Perspective

Dr. Alicia Morgans is a medical oncologist at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago. She specializes in treating advanced prostate cancer and is particularly interested in addressing treatment side effects.

Prostatepedia spoke with her about chemotherapy for prostate cancer.

Why did you become a doctor?

Dr. Alicia Morgans: I've known since junior high school that I wanted to not only become a doctor but an oncologist. I knew I wanted to do something in science that engaged people on a personal level, and I had always admired the way physicians could do that. When visiting my grandmother during summers, I often went to her doctor appointments. I loved trying to understand things on a biologic level, and seeing the way the physicians she had listened and tried to help her. Even when they didn't have a fix to a problem, they could at least serve as a witness to validate her experience and lend support in any way they were able. Oncology specifically has always been a really challenging puzzle to understand, and the best opportunity to form long-term relationships with patients.

Medicine is an amazing way for individuals to engage at a very deep level, not only with intricate and exciting science but also with really rewarding human interaction. I'm glad I made the decision.

"Sometimes the people who feel the worst at the start feel much better with chemotherapy."

Have you had any patients over the years who have changed how you view the art of medicine or how you view your own personal role?

Dr. Alicia Morgans: There are always patients who change how we move forward with the practice, art, and science of medicine. As it comes to chemotherapy, in particular, there are a number of men that come to mind who, when offered chemotherapy, said there was no way they could do it.

These statements come probably from their prior experience with family members or loved ones who have had bad experiences with chemotherapy. These are real experiences that certainly need to be acknowledged, but I haven't met a person who we can't get through at least one cycle of chemotherapy to see if they truly can't manage it.

Most everyone can get through chemotherapy for prostate cancer because it's different than chemotherapy for things like breast cancer or leukemia, where we use many drugs in combination that can be intense. This is typically one chemotherapy drug at a time, unless we're specifically studying more intense combinations in clinical trials.

Most men do pretty well. There are several men who have been so sick from their cancer that, when I've given them chemotherapy, they actually feel a lot better, and that is really rewarding. It's an experience that I use to guide conversations with patients who are frightened of chemotherapy. Sometimes the people who feel the worst at the start feel much better with chemotherapy.

Because the chemo's killing their cancer?

Dr. Morgans: Exactly.

That's a really important point you're making. Just because, say, your neighbor had chemo for breast cancer and had a terrible time, that doesn't necessarily mean that you will have a terrible time with chemo for prostate cancer.

Dr. Morgans: Absolutely, and there are a number of men who I've taken care of through chemotherapy for prostate cancer, men in their 60s and 70s, who have continued to work. Sometimes, men who are in that phase of their career have a little more flexibility with their job, and they can do half days or relax in the afternoon for a half hour and go back to work. Sometimes these are men with relatively physical jobs, and they're still able to work, other than the day when they're actually getting treatment, when they're not able to be physically at work because they're getting chemotherapy.

It is different than the treatments that we give to young women with breast cancer or people who are getting treatment in the hospital. This is an outpatient treatment. It typically takes about an hour to an hour-and-a-half to infuse. It's something that we are sure to monitor very closely because we want to be safe, and we want to support people as they develop symptoms. For the most part, people do much better with this type of chemotherapy than they would expect.

At which points are men likely to encounter chemotherapy for prostate cancer?

Dr. Morgans: There are various points at which men can encounter chemotherapy in their prostate cancer journey. This has changed over the last few years. When men have metastatic disease today, whether that's hormone sensitive or castrate-resistant, we recommend chemotherapy. As of yet, we do not routinely recommend chemotherapy for men who are having radiation for localized disease or for men with biochemical recurrent disease (though both of those populations have been studied in clinical trials, and there appears to be, at least in some of these patients, potential benefits related to that).

There have also been studies looking at neoadjuvant chemotherapy, which is chemo before prostatectomy. There appears to be a potential benefit to that, particularly in high-risk patient populations. But again, that's not routinely recommended.

For the most part, men with metastatic disease are more routinely being offered chemotherapy, either in hormone-sensitive metastatic disease in the frontline setting or as one of the treatment options in metastatic castrate-resistant disease.

How is it usually sequenced? Or is there a usual sequence?

Dr. Morgans: There's not a usual sequence, and every individual who is being treated for advanced prostate cancer is probably aware that we don't have exact data to say which drug should be first, second, or third. These are conversations between men, their doctors, and their families to choose the treatment option that's best for them.

For men with brand new prostate cancer that is metastatic from the get-go, or for men who have had prostate cancer treatment in the past and now have recurrent disease that's metastatic but hasn't yet been treated, we often recommend chemotherapy, particularly for men who have a high volume or high burden of metastatic disease. In that setting, we use six cycles of chemotherapy, and we can help men live longer and feel better. We have data on both the efficacy for improving survival and on the quality of life that show benefits in that population.

It's important that we use it in that earliest stage of metastatic disease so that we only have to use six cycles of chemotherapy to get a pretty dramatic benefit whereas, if we use it in the later settings, we may use up to ten cycles of chemotherapy for lesser benefit. That's a consideration when I'm talking to men with high-volume, hormone-sensitive disease.

In the later stages of disease, if we've used androgen receptor or hormonal therapies first, then often we switch to chemotherapy after that hormonal approach because it's a novel mechanism of action and is expected to be more effective. Rather than continuing to hit on the same androgen receptor pathway, we're using a different way to approach the cancer and overcome resistance.

What are the side effects of chemo like on its own? What about when you're sequencing it either before or after hormonal therapy? Is there some sort of synergistic or cumulative effect to the side effects?

Dr. Morgans: Usually, we're using chemotherapy alone with a gonadotropin-releasing hormone (GnRH) agonist or antagonist therapy. That would include therapies like Lupron (leuprolide), Zoladex (goserelin),

and Firmagon (degarelix), medicines that act to stop the testes from making testosterone. Then we add on Taxotere (docetaxel) chemotherapy when we choose the first chemotherapy for men with prostate cancer. The side effects are generally similar whether you use it earlier or later if you're using it just in combination with that medicine.

With these injections, the most common side effect is fatigue. The next most common thing is neuropathy, which men would experience as a numbness or tingling in their fingertips or toes that, with repeated exposure, can go up into their hands or feet. It can become a more long-lasting issue, or eventually can lead to permanent numbness, especially as you get higher numbers of cycles. For example, if you use ten cycles in the metastatic castrate-resistant setting versus six cycles in the metastatic hormone-sensitive setting, you're going to have a higher risk of things like neuropathy.

At any point when we're using chemotherapy, we expect to cause blood counts to go down. Some men need a blood transfusion of either red cells for anemia or platelets for a low platelet count, though that's relatively uncommon. What's more common and possible is that the white count, the infection fighting cells, can go down with each dose of chemotherapy, and that count stays down until the bone marrow starts making more cells. We don't have a transfusion we can give people to make that improve more quickly. That puts men at risk of what's potentially a life-threatening infection when their blood counts are down, and the more cycles that they have of chemotherapy,

the longer it takes for their blood counts to recover. That's another reason to think about using it when you only have to do six cycles as compared to ten.

As men get older, sometimes the side effect burden can become a little more noticeable to them. If we have the opportunity to use chemotherapy in men in their 50s or 60s as opposed to their 70s, we may see that there are fewer side effects. If they're having a lot of side effects like loss of appetite and weight-loss, fatigue, and pain related directly to their cancer, the side effects of chemotherapy can actually be reduced fatigue, reduced pain, and improved quality of life between cycles.

"For the most part, people do much better with this type of chemotherapy than they would expect."

Because as we said, it's killing the cancer?

Dr. Morgans: Yes. There was a clinical trial that reported recently indicating that combined Xtandi (enzalutamide) and Taxotere (docetaxel) in addition to the GnRH agonist or antagonist therapy produced more side effects related to chemotherapy when we piled on an additional androgen receptor-directed therapy with the chemotherapy. Although the trial is done, and we see that people ultimately tolerated that more or less, because there was more toxicity and not a benefit to that triple-therapy approach, we're not recommending that we do anything more at this point than chemotherapy with a GnRH agonist or antagonist. We're not using a third androgen receptor-directed type medication in that cocktail, and that's just to say that the more treatments that you add together, the more toxicity related to chemotherapy.

Is there anything men can do before getting chemo to prevent some of these side effects?

Dr. Morgans: One side effect I didn't mention is that men can have some hair thinning. Usually, they don't go completely bald, but they can have some hair thinning and some hair loss. Men can use a cold cap during each cycle of chemotherapy, which can reduce hair loss during chemotherapy.

I've had a number of patients whose job requires that they put forth a healthy image. We all want a healthy image, but for some men who work in financial spheres, trying to get people to invest in their companies, or if they work in investing, they have expressed to me that they can't look sick, they can't have hair loss. They've used these cold caps and have not lost their hair. It's impressive and surprising to me how effective the caps were for them.

That is something that they can do to try to reduce hair loss. Cold caps are approved for women with breast cancer who are receiving chemotherapy, and they also seem to work in men. They're not always covered by insurance, but they can be really effective.

Cold caps were FDA-approved in 2017. You can read the FDA press release here: https://

www.fda.gov/news-events/press-announcements/fda-clears-expanded-use-cooling-cap-reduce-hair-loss-during-chemotherapy.] Other than that, it's important that men do their best to stay active. The more active they are before chemotherapy, the better able they'll be to stay active while they're getting chemotherapy and to make sure that their bowels are moving as regularly as possible. Some of the medicines that we use for even mild nausea associated with chemotherapy can cause constipation.

Are there any chemotherapy clinical trials that men should know about?

Dr. Morgans: There are a number of important clinical trials that are going to be reporting out in the next few years. STAMPEDE, out of the UK, has already reported out in terms of the benefit of Taxotere (docetaxel) for men with metastatic hormone-sensitive prostate cancer. We're expecting to see an update in an evaluation of that data-by-volume status, meaning high- versus low-volume of disease as defined by the CHAARTED trial, which was the Eastern Cooperative Oncology Group (ECOG) trial that led to the approval of Taxotere (docetaxel) for metastatic hormone-sensitive prostate cancer here in the United States.

The STAMPEDE trial is being reevaluated because they went back to the original records, counted up the metastatic sites for all of the patients, and then re-ran the analysis to see if men with high-volume disease versus low-volume disease both benefited from the addition of Taxotere (docetaxel) to traditional androgen deprivation therapy (ADT) or the GnRH agonist or antagonist.

We expect to potentially see that data this year at the European Society for Medical Oncology (ESMO) meeting.

The reason that's so important is that the CHAARTED trial found that there was a benefit to treating high-volume metastatic hormone-sensitive disease with chemotherapy but not a benefit necessarily in low-volume metastatic hormone-sensitive disease, and so if that's demonstrated again in the STAMPEDE trial, with over 1,000 men enrolled, that should solidify that volume status is important to consider for chemotherapy in metastatic hormone-sensitive disease. On the flipside, if there is no difference in benefit between men with high-volume disease and low-volume disease, then perhaps more men could benefit from treatment with Taxotere (docetaxel) with metastatic hormone-sensitive disease.

The PEACE-1 trial is going to be a really interesting trial that's combining Taxotere (docetaxel) and Zytiga (abiraterone) up front versus Taxotere (docetaxel) without Zytiga (abiraterone) to see if there's a benefit in a hormone-sensitive metastatic setting. They're also incorporating radiation to help us understand whether it's beneficial to radiate the prostate when we're doing really intensive systemic therapy. That's a four-arm trial. It's about twelve-hundred patients, and PEACE-1 is being run predominantly at sites in France and some in Europe.

The CASCARA trial is being run through the Prostate Cancer Clinical Trials Consortium (PCCTC), which is a group of high-accruing clinical trial sites across the country supported by the Department of Defense. This is looking at metastatic hormone-sensitive prostate cancer patients and trying to crank up the intensity of their therapy by giving them Jevtana (cabazitaxel) up front and Paraplatin (carboplatin) up front with traditional ADT to see if that is helpful. I think Zytiga (abiraterone) is included in that trial as well. We know that we can be helpful for high-volume patients with Taxotere (docetaxel) chemotherapy. If we have even more aggressive disease in certain patients, can we crank up the intensity, use more chemotherapy, try to do even better, and then combine it with Zytiga (abiraterone)?

The ARASENS trial is also in the metastatic hormone-sensitive setting. This is a trial in which all patients with metastatic hormone-sensitive prostate cancer were enrolled and received Taxotere (docetaxel) chemotherapy, and then they were randomized to receive Darolutamide, another androgen receptor-directed therapy, or a placebo to see if this combination would be synergistic, control disease, and help improve survival for more men versus just chemotherapy upfront. This is going to be important because the ENZAMET trial looking at patients receiving chemotherapy and Xtandi (enzalutamide) versus just chemotherapy and ADT did not necessarily appear to show a benefit to the triple-therapy of ADT plus Taxotere (docetaxel) plus Xtandi (enzalutamide), versus ADT plus docetaxel alone. That data is not mature yet, and it's very possible that the benefit we see to the triple-therapy may be seen after we follow for another year or two.

Is there anything else that you'd like men with prostate cancer to know about chemo that we haven't already covered?

Dr. Morgans: Chemotherapy sounds incredibly daunting, but men are a lot stronger than they give themselves credit, and the chemotherapy is not as terrifying as it seems on TV or when used in combinations that you see in friends who are treated for other cancers.

It's important for everyone to consider chemotherapy as one of the ways to control prostate cancer, help you live longer, and potentially feel better. It would be a shame to not even consider one of these tools when it may actually help make your life longer and better in the long run. Keeping an open mind about chemotherapy is really important and may end up making a huge difference in your day-to-day life.

There are ways to manage the side effects. As long as you're talking to your medical oncologist about what's happening, you can work out a plan for addressing them.

Dr. Morgans: Absolutely, it is not unusual for people to have a side effect or a symptom associated with chemotherapy, but these side effects and symptoms can be managed effectively with some communication and some simple support measures.

As you mentioned, you may not have those side effects, so you might as well try a round or two and see how it goes before you say you can't face it at all.

Dr. Morgans: Yes, a decision to move forward with chemotherapy is not a contract. You can decide to do one cycle. You can decide to do all of the cycles. It's a cycle-by-cycle decision, and you do not have to get all of the cycles just because you agreed to do one or two. Pp

Clinical Trial: Combining Taxotere + Xofigo

Dr. Michael J. Morris is a medical oncologist who specializes in prostate cancer at Memorial Sloan Kettering Cancer Center in New York City where he serves as the Prostate Cancer Section Head.

He spoke with *Prostatepedia* about a clinical he's running that looks at combining Taxotere (docetazel) and Xofigo (radium-223).

What attracted you to medicine in the first place? Why did you become a doctor?

Dr. Michael Morris: I came to medicine from a somewhat different background than many physicians. I grew up in a family that's heavily focused on the humanities—history, culture, and literature. I inherited those genes from my family, but I also had a real scientific interest that I found to be equally compelling.

In college, I divided my time between literature and science. What attracted me to medicine was that it perfectly merged humanism and science – both patient care and research require an understanding of the history of a patient, his disease, and his treatments. The challenge of medicine is to creatively conceive how biology can be brought to bear to alter these for an individual and the field.

Have you ever had any patients over the years whose stories have changed how you view either the art of medicine or your own role?

Dr. Morris: Many people feel absolutely devastated when they get prostate cancer, which for many people can be a chronic disease. The anxiety provoked by a cancer diagnosis, and even by a detectable or rising PSA can be existential. One of my patients was a Vietnam War veteran. He had been through his share of battles before, and saw more than a few of his closest friends not live past early adulthood. For him, prostate cancer was a reminder to him of what he had survived already. He felt that he was lucky to have lived long enough to face prostate cancer as the primary threat to his life. He took his prostate cancer journey as the next opportunity to lead, to teach, and to be in charge of and help so many people through their disease. Even in our waiting room, he was guiding people and keeping everybody's anxiety in line. That made a huge impression. People who have faced risks before can be incredibly helpful to those who are not experienced with the helplessness and fear that a cancer diagnosis provokes. We have a lot of first responders in our practice, and their experience managing risk and anxiety can be very helpful to those without those skills. They can help the care providers as much as the patients, too.

From a clinical trial standpoint, I'm struck by the selflessness of so many of our patients. They understand that their treatments are the result of the efforts of patients on studies who have preceded them, and they're willing to volunteer so that we can learn how to best treat those patients who will follow them. They're saying, "I'm going to give my body to a clinical trial so that the next generation of prostate cancer patients can learn from my experience." That's inspiring.

Talk to us about your Phase III trial combining Xofigo (radium-223) and Taxotere (docetaxel). Why this particular trial? Why now?

Dr. Morris: In general, my research focus is where nuclear medicine and medical oncology intersect. That is, looking at drugs that you can deliver systemically, that are targeted to either the prostate cancer cell itself or to the host organ of most metastatic disease, which is bone. And that also means looking at combining those drugs with other drugs that can help patients either feel better or survive longer.

This trial comes out of a long history of work, trying to combine radioligand therapy, which are essentially liquid systemic radioactive drugs, with other systemic treatments, to target both the cancer cell itself and bone, which is the host organ to most metastatic disease.

Xofigo (radium-223) is a known, life-prolonging radioactive agent that targets metastatic disease to bone. Since most metastatic disease in prostate cancer is in the bones, you can really encompass most of the disease by targeting that one bony compartment. Within the bone is the cancer itself, and the chemotherapy is used to target the prostate cancer cell. It's a concept of dual targeting, both the environment that the cancer is hosted in and the cancer itself. That's why we're using these two agents, one of which targets bone and the other cancer, and both of which prolong survival independently, to see if those effects can be amplified by giving them together.

What will you be doing step by step?

Dr. Morris: The first thing is, a man has got to qualify for the trial, which means that he has to have predominantly bone metastases because that is the target for the Xofigo (radium-223).

The second thing is that he can't have a significant amount of soft tissue disease in either the lungs or the liver. He has to have progressed through standard testosterone-lowering agents, such as Zytiga (abiraterone) or Xtandi (enzalutamide). If that patient is otherwise a chemotherapy candidate, then the treatment involves giving chemotherapy once every three weeks and then the Xofigo (radium-223) once every other chemotherapy dose, so every six weeks. They're both IV agents. That's the essence of the treatment of the study.

Xofigo (radium-223) is a unique radioactive drug. It emits an alpha particle, which releases a lot of energy in a very tiny distance, only a few cell-lengths deep. It has virtually no side effects, so it's a well-tolerated, life-prolonging treatment.

Chemotherapy is standard first-line chemotherapy in the form of Taxotere (docetaxel). It's given every three weeks. It's life-prolonging as well, and is a member of a class of taxane-based chemotherapy.

What are the side effects like for that?

Dr. Morris: Primarily fatigue, but some patients can have tingling in their fingers and toes as well, and sometimes changes in taste. A very small number of patients can have their white blood cell counts suppressed.

How long are you going to be following these men while they're on these two agents?

Dr. Morris: Patients receive a total of six doses of Xofigo (radium-223) and no more than ten doses of chemotherapy. After that, they've completed the treatment portion of the protocol, and they could go on, if they needed, to any other treatments. But we follow them for the rest of their lives.

Are there any fees associated with the trial? I'm assuming the Xofigo (radium-223) and the Taxotere (docetaxel) are provided.

Dr. Morris: The Xofigo (radium-223) is provided by the study, and the patient is responsible for the docetaxel, which is standard chemotherapy.

What else do you hope to learn from this study?

Dr. Morris: There are a whole host of innovative biomarkers and science that is built into this trial, so we learn as much as we can about each patient as they're treated.

We're looking at circulating tumor cells and cell-free DNA. We're looking at the impact of the treatment using novel imaging techniques. We're looking at quality of life. There's a whole component of the study that will allow us to learn as much about the prostate cancer and the efficacy of the drugs as well.

Those will be covered under the trial as well, right?

Dr. Morris: Absolutely. Those are all covered by the study.

Is that information shared with the patient?

Dr. Morris: Any information we gather in real-time can be shared with the patient. Some of the scientific aspects of the trial will only be performed after the trial is done, so results from those will be delayed until after the study. But as we learn new information, we pass it on to our patients. Pp1

For more information …

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Julie Graff, MD
Chemotherapy, Xtandi, and Zytiga

Dr. Julie Graff is a medical oncologist at Oregon Health & Sciences University.

Prostatepedia spoke with her recently about chemotherapy, Xtandi (enzalutamide), and Zytiga (abiraterone) for prostate cancer.

Why did you become a doctor?

Dr. Graff: Even as a child, I wanted to become a doctor, so my whole life I thought about it. Then I went to college, I fell in love with science, and I thought I would get a job somewhere working in a lab.

During college, I volunteered for a hospice, and I realized how much I love patients, how special people are, and how people with cancer are among the strongest people. I was drawn to work with them, and also, my scientific side could still be engaged in research.

Have you had any patients over the years who stand out in your mind as having either changed how you see your own role as a doctor or how you view the art of medicine in general?

Dr. Graff: I've had multiple patients who've meant a lot to me over the years. Someone I met in hospice stands out. The first time I met him, he said, "I know that I'm 80. You look at me, and what you don't realize is that I want to live just as much as you do." He had emphysema and was dying, but the drive to live can stay so strong, even at 80. Your body's not even working that well anymore, and you're suffering. Still, just this drive to stay alive is important. I've kept that in mind since then.

On the other hand, I've had some patients who say that years don't matter—it's quality of life. I can appreciate both sides. When I talk to patients, even those who say they want to live forever, I tell them that what we want to do is help them live as long as possible while maintaining a quality of life that they can enjoy.

I guess each person falls somewhere along that spectrum.

Dr. Graff: Exactly. As a doctor, you really just have to educate people, and tell them, "I know you want to live and that you think it's a good idea to get surgery, even though there's a 50% chance you could die during surgery or whatnot. But what are your real goals, and how can we help you reach them?" We want to move the focus of the conversation a little bit.

Can you give us a brief overview of how and when chemo is used for prostate cancer. I know it's different from how and when chemo is used in other cancers.

Dr. Graff: In prostate cancer, there are a couple of settings where chemotherapy is used. We've been using the drug Taxotere (docetaxel) for 15 years now. It used to be something we gave at the very end of the disease course, when the hormone shots stopped working, but as of 2015, we use it early in the disease also.

"He had emphysema and was dying, but the drive to live can stay so strong, even at 80."

Chemo has a bad rap in some ways. It's thought to be something you should avoid at all costs, but what people don't realize is that, when symptoms of the cancer (such as bone pain) get bad, chemo can help.

The type of chemo we use in prostate cancer is not as toxic as we do for other cancers. We just use one drug. It doesn't cause a lot of nausea and vomiting, which is a lot of patients' worst nightmare. We use it in early and late settings, and I don't think anything's going to replace it. Even though we have other drugs now, we run out of hormonal options, and chemo's a decent option.

When and how are Zytiga (abiraterone) and Xtandi (enzalutamide) used in prostate cancer?

Dr. Graff: Zytiga (abiraterone) and Xtandi (enzalutamide) are similar to chemo in that, initially, they were used at the very end of the disease. Now they can be used up front when people are diagnosed with metastatic prostate cancer, so it depends.

Most people get some mileage out of one or the other, but there is a large degree of cross-resistance between the two. It's not likely that people would get good cancer response out of both of them. It's going to be interesting to see what happens to Xtandi (enzalutamide) now that there are other drugs that target the same pathway.

What is androgen-receptor splice variant 7 messenger RNA (AR-V7), and what is its role in resistance to Zytiga (abiraterone) and/or Xtandi (enzalutamide)?

Dr. Graff: The androgen receptor has several domains, and one of them is the ligand-binding domain, which is very important. As this androgen receptor floats around in the cell, the androgens (male hormones) bind to that ligand-binding domain, and so does Xtandi (enzalutamide) for that matter. Cancer cells can lose that part of the androgen receptor, then lose their dependence on the androgens that are circulating and lose the target for Xtandi (enzalutamide). The AR-V7 splice variant can predict resistance to both Zytiga (abiraterone) and Xtandi (enzalutamide), and it might be a reason why there's cross-resistance between them.

What role does chemotherapy play in this resistance to Zytiga (abiraterone) and/or Xtandi (enzalutamide) that we see?

Dr. Graff: Fortunately, chemotherapy is still active in people whose cancers are resistant to Zytiga (abiraterone) and Xtandi (enzalutamide), so it still plays an important role. It can be very useful when people have prostate cancer-related symptoms.

"The type of chemo we use in prostate cancer is not as toxic as we do for other cancers. We just use one drug."

We use chemo early on in metastatic disease, right after diagnosis. There are three studies presented in the past year in which they use chemo followed by Xtandi (enzalutamide) or a drug like it. It might be more effective in combination with those other drugs. We're trying to learn still.

Can chemo reverse resistance to Zytiga (abiraterone) and/or Xtandi (enzalutamide), or does it play any role in that scenario?

Dr. Graff: I don't know if it can reverse it. I have seen data showing that, if you're on Xtandi (enzalutamide) and the cancer cells become resistant to that, then if you put a patient on chemo, some of those cells that aren't resistant to Xtandi (enzalutamide) might come back, and it might be reasonable to re-treat it then. That's not carved in stone.

Is it being explored in any clinical trials that you know?

Dr. Graff: I hope so. I don't know which trials those would be.

What about the side effects of these various agents?

Dr. Graff: It's complicated. Chemotherapy can cause some low blood counts and a risk of neutropenic fever, but then it has other side effects, like neuropathy in the hands and feet, that don't just reverse automatically. There is also some tear-duct scarring and watery eyes. These might get a little better off the chemo, but they could be permanent side effects for the patients.

This type of chemo doesn't hurt the kidneys, you need good liver function to get it, and it doesn't seem to cause hypertension. In those ways, chemo is a good option for elderly men with prostate cancer.

Zytiga (abiraterone) can cause mineralocorticoid excess, which means the adrenal glands aren't functioning normally. You could get too many of one type of hormone that causes high sodium and low potassium. Zytiga (abiraterone) can also irritate the liver, so we're careful to watch for the liver function. It can also exacerbate the hormonal side effects of castration.

Xtandi (enzalutamide) is known to cause profound fatigue, which was

its dose-limiting toxicity. Of course, it's linked to seizures, but in people without a history of seizures, that's pretty unusual. And just like Zytiga (abiraterone), it can cause hypertension. Management of blood pressure and cognitive decline is critical. People have reported that they feel a bit foggier on Xtandi (enzalutamide), and they have also reported increased falls, especially in the elderly. Once you're off Xtandi (enzalutamide), some of those things will reverse, but it's possible that being on Zytiga (abiraterone) and Xtandi (enzalutamide) could result in muscle mass loss or other things that won't recover off those treatments.

> *"Exercise is critical for any prostate cancer patient."*

What would you suggest to manage those side effects?

Dr. Graff: Exercise is critical for any prostate cancer patient. The drugs we use—even just the initial hormone therapy of turning off the testicles—lead to so many side effects like thin bones, muscle loss, weight gain, and all those things can be mitigated with some exercise. They won't be taken away, but they could at least be improved. That exercise should continue on the other drugs.

It's really hard to exercise when you're on these drugs because you've got more fatigue. A lot of patients with prostate cancer have arthritis or some barrier to exercise that makes it difficult for them, but as much exercise as possible is important.

I guess any exercise is better than none, right?

Dr. Graff: Exactly.

Do you have any further thoughts about chemo, Zytiga (abiraterone), or Xtandi (enzalutamide) that you think patients should know about or might not be aware of?

Dr. Graff: They've been out for a while now. Any prostate cancer patient starts with a blank slate and has to learn all this stuff with the help of the provider. Think about your goals in life and if these drugs are going to interfere with those. If your goal is to continue working as an architect or something that requires a lot of thought and careful planning, maybe Xtandi (enzalutamide) is not the best choice, and maybe Zytiga (abiraterone) is a better choice.

Some of these drugs are contraindicated in certain patients. A patient with bad heart function, like congestive heart failure or something, should not be on Zytiga (abiraterone), and a patient with a history of seizures should not be on Xtandi (enzalutamide). A lot of thought should go into picking these. The first drug you use is likely to be the most effective, and then as you go down the line, they become less effective.

As a prostate cancer patient, you have several options now; it's not just chemo or nothing once the prostate cancer becomes resistant to the androgen blockade. Consider lifestyle when making a choice. Pp

Benjamin Gerendash, MSN, RN, NP Chemo: A Nurse's Perspective

Mr. Benjamin Gerendash is an Oncology Nurse Practitioner who works with prostate cancer patients at City of Hope, a comprehensive cancer research and treatment center in Duarte, California.

He spoke with *Prostatepedia.*

Why did you become an oncology nurse; how did that happen?

Mr. Ben Gerendash: I started out in a Master's program to become a nurse practitioner; I worked as an oncology nurse at that time. It comes down to how I view nursing. Nursing is about helping people become healthier. If they're sick, it's about helping them along their journey in their illness or disease, helping them improve their health and providing knowledge, information, and assistance in helping them get better.

There's a real need for that in the oncology population because there are so many different things that happen when a patient is faced with the challenges of battling cancer. The role of a nurse in that setting, providing information and guiding them along that journey, is really important. That's what drives me in oncology nursing.

Have you had any patients over the years who have changed either how you view your own role or how you view the art of nursing in general?

Mr. Gerendash: I've definitely had patients who have taught me the importance of what oncology nurses do. I have one patient who was having a lot of gastrointestinal (GI) symptoms with their therapies, and I was able to give some advice on how to manage that. They went from where they weren't able to leave the house to having good control. They got their life outside the house back.

Small things like that, where you see how the small time investment that you can make during a clinic visit can have huge impacts on people outside of the clinic on a day-to-day basis throughout the rest of their lives. That's something that I wouldn't have understood until I'd experienced it.

Speaking with patients and understanding from a nursing perspective that the role of the provider is not just ordering tests and medications or seeing patients in a clinic visit but connecting on a human level and understanding what challenges they're facing. We help with the stresses they're facing, and we help them face those challenges in a constructive way, helping them overcome those challenges. When you address those challenges, and you help them overcome it, that's also very powerful.

Even when the clinical environment is busy, and you only have 20 minutes to see a patient, sometimes you have to take that time to address those issues. People don't have anybody else to take those questions to. They don't have any other way to address them, and those are things that need to be addressed.

As you say, you can have a profound impact on someone's quality of life.

Mr. Gerendash: Oh, for sure! People recognize that, and they know the difference that it's making for them. I often hear someone say that they didn't feel like it was appropriate to ask the question. But they feel comfortable when you take the time to address their concerns. The relief they feel from that, their feeling of well-being is improved. That appreciation tells you what a difference it made to them.

What might patients experience in the process of getting chemotherapy for prostate cancer?

Mr. Gerendash: A lot of patients come in to us when they've been diagnosed with metastatic prostate cancer. They're concerned because they've had friends or family members who have had other cancers, and they have fears about getting chemotherapy.

One of the first things that we explain is that, in the current state of practice, chemotherapy agents are usually used in later stages of prostate cancer. That's something that is actually different from other cancers. Once chemotherapy is necessary, that'll usually be after a patient has failed hormonal therapies. A patient will have PSA progression to a certain point, or they'll have changes on scans that show progression. We'll go over that with them and explain that they are having progression of the cancer, and that the next step in treating it is chemotherapy.

We go over the agents that we like to use for chemotherapy. For prostate cancer, it is commonly a single agent, a taxane. We'll go over the infusion schedule and what kind of benefits we're expecting to see from getting the chemotherapy. We'll also review the expected side effects, toxicities, and things to watch out for. At City of Hope, we'll also order some medications that they can pick up from their pharmacy in case they have side effects like nausea, even though that tends to be on the rare side for the agents that we use for prostate cancer.

We schedule them to visit with a nurse for a teaching session regarding chemotherapy to reinforce what we've discussed in the clinic visit. When they're getting news that they've had progression, and that they're going to need chemotherapy, it's a stressful time for patients. We found that many times, patients don't necessarily absorb all the information the first time around, and so reinforcing that with a teaching visit with a nurse is very helpful. That teaching is also reinforced when they go for infusion by the infusion nurse.

Walk me through the infusion process. Is it one visit or multiple? How long does it last?

Mr. Gerendash: It's multiple visits. Typically, the agents that we use, Taxotere (docetaxel) and Jevtana (cabazitaxel), are given intravenously every three weeks. The infusions usually take place over about two hours, and an infusion visit often takes around three. That depends on how it's ordered, and in which facility it's given.

There are medications that can be taken before infusions, either orally or intravenously, that help prevent reaction to the infusion. That includes steroids and antihistamines.

They take that before the infusion or at the visit?

Mr. Gerendash: Both. If they're given medication to take home, it's taken typically the day before, the day of, and the day after. If it's given intravenously, it's given the day of the infusion, just before.

Is the infusion process painful?

Mr. Gerendash: The infusion itself is not, but it does require intravenous access. If a patient has access already in place, like with an implanted port or a peripherally inserted central catheter (PICC line), it can be hooked up directly to that. If they actually require intravenous access to be established at the time of the infusion, then it's the nurse placing an IV line. That can be a little painful for a minute, but the infusion itself is not painful.

What do men do during this two-hour period while they're getting the infusion? Do they just sit there? Do they read? Do nurses come in and talk to them?

Mr. Gerendash: Any of those things can definitely happen. If all is going well, the infusion is not exciting. We encourage people to bring a book, and at our infusion centers, people can watch a movie on a tablet device or television. I was talking with a patient yesterday who was at one of our new infusion centers, and they hooked up their iPad to the TV over Airplay and watched Netflix on it.

So bring something to do.

Mr. Gerendash: That's a good idea. After the first time, once people know what to expect, then they know what to do. They know if they have a family member with them, if they want to spend time and talk, bring a deck of cards, a novel, or an electronic device. Any of those things are good ways of passing the time.

When the infusion is done, can they just get up and leave? Do they need to have someone drive them?

Mr. Gerendash: We recommend that they have somebody available to drive them because, if they're taking pre-medications like Benadryl, it can make them sleepy, so it's definitely a good idea for somebody to drive them after that. Typically, there are not any side effects immediately after therapy. The side effects that people get from chemotherapy, like fatigue, usually happen a couple of days later. We definitely recommend that people not drive themselves, just in case they react to some of the medication. It's just a safety issue. Physically, people probably could drive, but it's just not a good idea.

You mentioned two side effects: fatigue and nausea. Are there any other common side effects that men deal with?

Mr. Gerendash: For the most part, with the chemotherapies that we use, nausea is minimal. Around three to five days after infusions, people have some profound fatigue. We have to watch out for white blood cell counts dropping, which is called neutropenia. That's usually about a week to nine days after the infusion.

Depending on the drug, we might give colony stimulating factors, which help boost the white count. That's very typical with Jevtana (cabazitaxel). It's almost always given with Jevtana (cabazitaxel) and sometimes given with Taxotere (docetaxel) depending on provider preference. But colony stimulating factors can cause bone pain because that's where those cells are produced. Sometimes, Claritin (loratadine) helps with the bone pain, but we don't really understand why.

What about the nausea and fatigue? Is there anything that people can do to prevent those?

Mr. Gerendash: I'm not aware of anything that can be done about the fatigue right after the chemotherapy. It's good for patients to just rest throughout that period but still try to be as active as they feel comfortable, especially for older patients. If they're less active, it can be a kind of *use it or lose it* situation. For people beyond a certain age, and we give chemotherapy to some patients in their 80s, if they're lying in bed for three days, when they get up, they're not as strong as when they laid down. The chemotherapy itself causes that fatigue and some weakness, but if the person is not active and they're not moving around, they can get deconditioned from that as well. It's important to stay as active as you are comfortable doing.

Appetite and taste changes are other side effects. People need to eat to keep up their strength, and they need good nutrition, but if food is not tasting good to them, then a lot of people eat less. It's important to find food that is appealing, or to eat, even if they don't find it appealing. When you're getting medications that can weaken you, food is medicine, and you've got to keep your strength up.

Taxotere (docetaxel) can cause some hair loss, banding of the nails, some swelling of the extremities, and tearing of the eyes. Jevtana (cabazitaxel) often has those, except less hair loss and the banding on the fingernails is less common. The side effects generally seem to be a little bit better on Jevtana (cabazitaxel), just from experience.

Most of these side effects seem relatively manageable, are they not?

Mr. Gerendash: Yes, compared to some of the other medications for other cancers. For a lot of other cancers, where they're doing multiple agents, each medication has its own toxicities and side effects. When you combine them together, then you have the combination of all those side effects that can affect a person at the same time. If a person is on a five-medication regimen, they'll often have more severe side effects than they would, say, on a single agent regimen. Mostly in prostate cancer, we're using single-agent regimens. There are some dual-agent regimens that are used in very specific cases.

Are there any other diet recommendations during chemo? Anything that they should avoid or that they should eat in particular?

Mr. Gerendash: Not specifically with regards to food. We typically recommend a heart-healthy diet. A lot of people look for nutritional supplements, antioxidants, and things of that nature, and we recommend people avoid that during chemotherapy.

Why? Are the antioxidants protecting the cells from the very agents that you're using?

Mr. Gerendash: Right. We're giving a chemotherapy agent that's toxic to cells, and we don't want anything to get in the way of the action of the drug.

How long before someone gets chemo should they stop taking these supplements?

Mr. Gerendash: I don't have the data proving what the exact time period is, but I think a week is a good amount of time, just to get it out of your system.

Is there anything you'd like patients to know about the experience of chemo for prostate cancer?

Mr. Gerendash: It's true that prostate cancer is mostly a slow moving disease, and you can watch it, and you don't have to worry about it. But that's by no means all of the cases. There has been a move to withhold PSA testing for cost reasons, and while that is valid from a population standpoint, epidemiologically, each person has to care for themselves, especially if they have a family history of prostate cancer or any kind of warning sign.

Most of the time, prostate cancer doesn't have any warning signs, but if you develop urinary symptoms and have a slow stream or difficulty starting to urinate, those are all signs of an enlarged prostate. You shouldn't hesitate to see a urologist and be evaluated. Definitely after 50, you should be getting your PSA checked because a sudden PSA rise triggers you to get further evaluation for prostate cancer.

The key with prostate cancer is early detection and early treatment; that's when it's curable. If you wait until after the prostate cancer has already advanced, and if the disease has moved outside of the prostate, then it's still treatable but not necessarily curable.

Surviving prostate cancer is very much a question of getting the right treatments at the right time, and then changing treatments at the correct time when the current treatment is no longer effective. It's very important to get the right care from the right provider. If you feel like you're not getting that care, then get a second or third opinion.

At the end of the day, each patient is really responsible for looking after themselves and making sure they're getting the proper care. The proper care is out there. Patients need to look out for themselves and advocate for themselves because their life is at stake. We've definitely seen patients who were told by another provider that they have less than six months to live. They came to City of Hope, we treated them, and we're still seeing them two years later.

Be proactive, right?

Mr. Gerendash: Definitely be proactive! Pp

Catherine E. Guider, RN
An Infusion Nurse's Perspective

Catherine Guider is an infusion nurse with Kaiser Permanente in Sacramento, CA.

She offers *Prostatepedia* her perspective on chemotherapy for prostate cancer.

Why did you become an oncology nurse?

Ms. Catherine Guider: I was interested in oncology even back in nursing school. I had a grandfather who had cancer and was given a very short timeline of survival, and he was one of those that beat the odds and made it to 93. I got to see a side to cancer that some people don't get to see.

In nursing school, I did some time on an oncology inpatient floor and found it challenging and rewarding when it came to the personal relationships that I got to build with patients and their families.

When I came to Kaiser, I didn't start in that department, but after a couple of years, I took an opportunity to move to the floor that does inpatient chemotherapy. A short time later, I was certified with chemotherapy and biotherapy, and I stayed there for many years. Now, I'm in the outpatient infusion oncology clinic.

Have you had any patients over the years who changed how you see your own role or how you see nursing in general?

Ms. Guider: Because I was in the inpatient side where sometimes people stayed for longer than a day or two, I saw the impact that we can have on their lives. I would spend my lunchbreak with some of our oncology patients, sharing lunches and time together, and I noticed that sitting with them would help them eat more and make them feel lighter. It's gone both ways; they have enriched my life also.

There are definitely some who have impacted me. Being on the infusion oncology team, I'm part of a patient's cheer group and their support group. When they cry, sometimes I cry, and sometimes that's difficult. It's definitely made nursing more personal for me.

What's the process like for getting chemo for men with prostate cancer?

Ms. Guider: We have a good process here when it comes to onboarding new chemotherapy patients. Our doctors work with our nurse navigators, who then work with our triage on our medical assistance to get the patient scheduled for their chemo class and their first chemo treatment. All these people make sure that labs, pre-med home medications, and post-treatment meds are ordered with support. Overall, there are a lot of people involved to make sure that the patient and their family are well-informed. When they come in, they already have an idea of what that day and treatments are going to be like.

When they arrive, we make sure that a patient is up to chemotherapy. We make sure that they are physically and mentally well, and then we notify our pharmacy to make the medication. We have our own pharmacy within our department. If there is anything questionable, we get in contact with the patient's oncologist, and they're directly across the hall from us, so it's very easy to do. All of that is addressed right then and there.

What is the infusion like? Is it painful?

Ms. Guider: No. You have to start an IV or access a port, which could be painful. But the majority of people don't feel the chemotherapy. There's always a potential reaction to certain medications, but we are good about how we handle those. We already have medications ordered that we can administer if someone has a side effect on the premises, and we can get that side effect reversed.

How long does the actual infusion last?

Ms. Guider: It all depends on the regimen. With prostate cancer, that's normally Taxotere (docetaxel), and that is an hour infusion.

I have only given Jevtana (cabazitaxel) once or twice before, but I believe that's an hour also. Taxotere (docetaxel) is still the first choice IV treatment.

What kinds of side effects have you seen patients deal with after chemo?

Ms. Guider: The normal: nausea. We send patients home with a list of medications to use for the nausea, and we recommend smaller meals throughout the day to stay ahead of it. There's the hair loss, nailbed changes. You can have peripheral neuropathy with the chemotherapy. There's fatigue, of course, and the impact on white blood cells, red blood cells, and platelets that we're watching for as well.

Do you have any tips or advice for men to make the whole process of getting chemo easier?

Ms. Guider: Somebody's mindset has a lot to do with how they come into it and how they handle it.

Somebody who's active, eating a well-balanced meal, and good on their hydration normally does better than someone who isn't. Some people don't like to take additional medication, and so there is not that adherence there.

We give patients a list of antiemetics to use if they become nauseated. Sometimes, they take them that first or second day, just as a safety measure to keep the nausea away. Some people don't like to do that. But it's always better to stay ahead of the nausea than let the nausea set in because it's hard to play catch-up and get it to go away once it's there. Nausea doesn't only make patients feel unwell, but they're not going to drink the amount of fluids that they need or eat the meals that they need if they're nauseated. Coming in with all of that already in place, makes somebody tend to do better.

"Being on the infusion oncology team, I'm part of a patient's cheer group and their support group."

What role do you see the caregivers playing in the whole chemo process?

Ms. Guider: We invite caregivers to the chemo class. It's always up to the patient if they want their caregiver to come to join them. Sometimes people and their family members come for the first appointment, and then after a while, the patients come by themselves. We have other people whose family members come every time. It all depends on the role that they already have in the relationship.

Sometimes caregivers are more of the voice for the patient. Sometimes they speak up and say that the patient is having a difficult time getting their food in, or they're having this nausea afterwards, but the patient is not telling us.

Other times, caregivers are the cheerleaders who will bring a sandwich, and when the patient eats half, they're the cheerleader saying "why don't you take just one more bite? Don't quit yet." They all have different roles.

We also have caregivers who take an unproductive role, and that's probably been in the relationship. Encouraging people to do better or take that next bite is very different than a person saying: "you need to eat that."

Presentation can be huge, and if that avenue isn't already developed between them, then sometimes we'll see people bicker over how much they drank the day before.

I guess any conflicts that are already in the relationship will be highlighted by a situation like this, right?

Ms. Guider: Yes, along with the stressors of all of it.

Any other tips you have for men who are about to get chemo or maybe have already had chemo and are struggling with side effects?

Ms. Guider: When it comes to the side effects, you don't have to struggle through them. Your team is there for you if you speak up. We can change pre-medications around. We can change medications at home. We can try completely different meds. We also have a social worker. We have nutrition. We have mental health. We have various support groups. Be open to reaching out.

Be open to asking questions, getting things clarified, and

gathering more information, especially if it's researched-based. There's a lot of misinformation on Google that can backfire. You need to make sure that your information is based on research.

"Overall, there are a lot of people involved to make sure that the patient and their family are well-informed."

We all come in with a different knowledge base, so when it comes to what's on the internet, sometimes it's written for a certain group only, and at times there's not even anything factual.

It's great to talk to other people who have gone through cancer and treatment, but always keep in mind that every body is different. You could have the same people going through the same exact treatment, and for whatever reason, their side effects will be different, and how they handle them will be different. It's not a cookie cutter.

Just like everybody comes in with a different level of fitness and a different mindset, right?

Ms. Guider: Yes, and it's the history of how they took care of their bodies. The other comorbidities that they might have will factor in how they're going to physically handle the chemotherapy. There's the whole emotional side of handling the cancer itself. Just the word brings so much with it. Pp

Patients Speak
Gerald Stern:
Getting Chemo: My Story

Mr. Gerald Stern talked to *Prostatepedia* about his experience in getting chemotherapy for prostate cancer.

What was your life like before you had prostate cancer?

Mr. Gerald Stern: I was jogging at that point, and I felt great mentally and physically. I always watched my weight and intake of food. My father died when he was 49, so that made me very sensitive to cholesterol. I married someone who was very concerned about that, so she did the cooking in the house. I was a picture of health.

How did you find out you had prostate cancer?

Mr. Stern: I was going for regular, annual examinations with my internist, and I was taking the PSA test. The next time I saw him, I asked him whether my PSA, which had jumped from 2.6 to 3.7, was significant. He told me it was not. I later learned that it was, but in any event, he told me not to worry as long as it's below 4.0. The next time I saw him, it was 4.0, and he said it was time to see a urologist. I felt I had time because he was not concerned.

"I hate to break the news to you, but you probably have cancer for the third time."

I waited six months before I saw a urologist. That was early- to mid-2002. On the first meeting, he did a biopsy in his office and took 12 samples, 95% of which showed prostate cancer. I didn't even have my clothes on yet, and he broke the news to me. I was in shock and very sad. He said, "We'll have to follow up on this. It looks like it's substantial." I had a Gleason score of 7-8 (two hospitals disagreed as the same slide).

I spoke to my urologist a couple of times. He recommended a partner of his who was a local surgeon. I'm 25 miles or so from Memorial Sloan Kettering Cancer Center and Columbia Presbyterian, and I had no intentions of having surgery based on the urologist's recommendation.

I called both Memorial Sloan Kettering and Columbia Presbyterian. It was the summertime, so the medical director of Memorial Sloan Kettering was traveling. I spoke to a friend who is in the medical malpractice field as a lawyer, and I asked him if he knew anyone at Columbia Presbyterian. He did, and arranged the meeting with a top surgeon there, whom I saw right away.

Based upon the tests and the other records from the urologist, he said, "You know, it's fairly substantial. There may have been some escape from the prostate, and I am not going to remove the prostate surgically. There are reasons that you should have radiology. You should see a radiologist in our radiation department." When I called for an appointment, they scheduled one for six months later. I decided that I couldn't wait. I was very nervous at that point.

I was able to see Dr. Peter Scardino at Memorial Sloan Kettering. He studied my medical records and scans, and said also he would not do surgery. He recommended a radiologist who was in charge of prostate cancer intensity-modulated radiation therapy (IMRT).

I met with another radiologist-oncologist at the hospital and he arranged the plan for the IMRT, and I went through that for 45 treatments. That was known as an aggressive dosage. As I recall, it was 48 Gray. That was towards the end of 2002, and we finished in January 2003. I listened and did whatever they wanted, and the results were great, but only for five years. When my PSA increased again in 2008, I was concerned, and the doctor was concerned. A biopsy showed prostate cancer. The radiologist recommended a new treatment at Memorial Sloan Kettering, which had been done in California: High Dose Rate (HDR) brachytherapy. My doctor was doing a study of 200 patients, and he could fit me in. I agreed and went through two or three days of the HDR brachytherapy, and the results were good for a few years.

"In December 2017, I started chemo treatments, and I had side effects."

At the Prostate Cancer Research Institute (PCRI) Patient Conference in 2011, I heard Dr. Snuffy Myers speak about the statistical evidence of PSA doubling within a few months. My PSA had nearly tripled within three months, so I waited to talk to him. I asked if my PSA went from 0.2 to 0.6, would he suspect cancer again. He said, "Yes."

He asked about my numbers, and I told him that I went from 0.5 to 1.3 in three months. He said, "I hate to break the news to you, but you probably have cancer for the third time." I thanked him profusely for the information.

I went back to New York and spoke to my doctor who said that it could be scar tissue from the previous treatment of HDR brachytherapy and that we should watch it. That was in October 2011. Three or four months later, I learned that I had metastatic cancer that had spread to my lungs. I was hysterical at that time.

My doctor at Memorial Sloan Kettering referred me to another doctor at the same hospital and I was happy to stay there. He was calming, and he said that all of his patients suffer from advanced metastatic cancer. Based on the MRI, CAT, and bone scans I had taken shortly before, I did not have it in my bones. He thought that was unusual, but I had it in both my left and right lungs. He gave me Lupron (leuprolide) to see how it worked, and it did work for a while, but I still had metastatic cancer. I understood, at that point, that there was no cure. At some point, he and I did not agree, and I decided to switch oncologists at Memorial Sloan Kettering.

I have had my current oncologist since 2013, and we have a great relationship. He listens to me; I listen to him. We negotiate, and I have had no treatment other than drugs. I had Zometa (zoledronic acid), Firmagon (degarelix), and Lupron (leuprolide), and none of them have stopped the progression of the cancer.

In my left lung, I developed a nodule that was measured at 1.5. He thought that it would be wise to take that out surgically, and he referred me to a surgeon at Memorial Sloan Kettering who removed it in July 2015. He did the analysis of the nodule that he extracted, and it was prostate cancer that had metastasized to the lung. I also have had a biopsy in the right lung that confirmed that it was prostate cancer.

In 2017, my oncologist told me I would need chemo. Based upon the growth of the cancerous nodules,

In December 2017, I started chemo treatments, and I had side effects. I had dizziness for between four and seven days after each chemo treatment. I was dizzy, and sometimes around the clock for two or three days. Sometimes, I'd get up at 2:00 a.m. to urinate, and I had to hold on to the walls in my apartment to make it to the bathroom. But I did not want to stay in bed for the full week that I felt weak or dizzy. I went out, probably foolishly on one occasion, and I fainted when I got back to my building. I was found in the elevator. They called EMS. In any event, I came to, and my blood pressure and the color in my face came back after about an hour. I was more careful after that. I also developed neuropathy of my toes, feet, ankles, and felt pain up to my knees. That has been an ongoing problem. I also developed edema of my legs, which is swelling because of fluid retention.

About a month later, after about the sixth chemo treatment in 2018, I was expecting a call from my wife and I jumped up from the couch when the phone rang in the kitchen. I felt very dizzy. I staggered into the kitchen, and down I went. I hit my head on the kitchen marble counter. I was laying on the kitchen floor and could not get up easily. I rolled over, and I didn't realize I was bleeding on my forearm as well. I fell on my ribs, and that took a couple of months to heal. That was the second fainting and falling.

During the first series of chemo treatments, I fell two more times without fainting, walking too quickly and, on one occasion, tripping over a bump in the sidewalk. I had some negative experiences, and I was not careful enough. I would recommend to anyone else that if you're dizzy during that first week, stay home and stay in bed. I was lethargic, tired, and nauseated during that week, but I never threw up. I was not myself.

Even during that period, though not in that week after infusion, I would be in a gym working out, walking, or on the stationary bicycle in the morning, which I do now every day. I believe I have helped myself through physical exercise. I do physical therapy (PT) at Memorial Sloan Kettering, where I've been given homework to stabilize myself. I do specific exercises on stabilizing so that I don't fall.

"I believe I have helped myself through physical exercise."

From late December 2017 to June 2018, I had nine treatments of the Taxotere (docetaxel), which was successful for a while, but then my nodules in the left lobe went back to where they were. My oncologist said that we ought to start Jevtana (cabazitaxel) about nine months after I finished Taxotere (docetaxel).

In the meantime, I digested every word of the four oncologists who discussed Jevtana (cabazitaxel) in your August 2018 issue of *Prostatepedia*. My luck! I developed confidence in the treatment I was having based upon my relationship with my oncologist, and with those articles. I really appreciated reading the experience of the two patients who were interviewed. And based on the entire article, including the experiences of the patients and the oncologists, I learned a lot about the expected side effects of Jevtana (cabazitaxel).

Thank you for saying that. I appreciate that. What was the experience of getting the Jevtana (cabazitaxel) like for you?

Mr. Stern: Jevtana (cabazitaxel) has been far less of a concern to me in terms of side effects. I don't get dizzy at all, and that's why I was optimistic, from reading that article in your August 2018 issue. I haven't lost my hair this time, so far. I've had four treatments, and not a bit of hair has come out of my head. With Taxotere (docetaxel), I lost my hair after the second treatment. My face blew up from the steroids. I was not happy with myself, and it's understandable that it affects your mental well-being. For those who would take Taxotere (docetaxel) as prescribed, it's necessary, and I would say, go for it.

Jevtana (cabazitaxel) has been wonderful for me. I get a bit tired. With Taxotere (docetaxel), my white blood count went below the level that I could safely take the next chemo treatment. My oncologist reduced the Taxotere (docetaxel) and extended the time from two weeks to three weeks. I take Neulasta (pegfilgrastim) the day after the chemo treatment; I have an injection. It keeps my white blood counts up and helps other readings that I need to keep up in order to have chemo. I have had no problems with neutropenia in that regard.

You're tolerating it, and you're four doses in?

Mr. Stern: Four chemos in. The oncologist mentioned that he would like me to take nine treatments, but I suggested that I would take six. He said we'll have scans after the six and see the results. We'll then discuss the chemo schedule.

That sounds reasonable. Are you comfortable with that?

Mr. Stern: Yes, but I'm pretty sure I'm going to stick to six. Even if I take four months' break and use the seventh, eighth, and ninth months as the first, second, and third treatments of the third series of chemo. That's my fallback position with him. I will ask him whether there's anything wrong with that logic. That's how we talk to each other. He compliments me on my logic and reasonableness.

I have two cancerous nodules in my right lung that have reacted extremely well to Lupron (leuprolide), and they have not changed in size since 2015. My left lung is a problem; that's not responding to Lupron (leuprolide). That's primarily why we did the chemo. The oncologist would like to rule out lung cancer in the top rear of the lung. He sent me to a pulmonologist at Memorial Sloan Kettering, and he and I had a wonderful conversation. I thought he was persuaded by my indication that it was prostate cancer and not lung cancer. And he conceded that the nodule would not have reacted well to Taxotere (docetaxel) if it were a lung cancer.

My oncologist and I agreed to hold off on doing a biopsy. My oncologist had sent me to another surgeon. He's called a radiation specialist who does the biopsies. He said to me that it was a risky situation, based upon the placement of that nodule.

I told my oncologist I appreciate his scientific background, and that he wants to know for sure whether that one nodule is lung cancer, but I don't. He agreed not to pursue the point based upon my strong feelings.

That particular nodule was reduced to 50% by the Taxotere (docetaxel). The pulmonologist at Memorial Sloan Kettering said to me that it wouldn't have reduced it if it were lung cancer. That's a strong indication that it is not lung cancer. I've had biopsies in my right and left lungs, and they all turn out to be prostate cancer.

The plan is to finish up the chemo, do the scans after six infusions, and then decide on the three more? Then just monitor?

Mr. Stern: We haven't met yet. We're going to talk in late August, after I have the six treatments, the PET scan, and the CAT scan. We'll see what the results were from the Jevtana (cabazitaxel). My fallback logic is that we should wait a few months. I need to wait for a few months because I fear that my worst side effects with Taxotere (docetaxel) had occurred during the seventh, eighth, and ninth treatments. I would just as soon skip the cumulative effect of the chemo and the more serious side effects.

I've had four treatments, and I feel pretty good after a few days. I get three or four days of slight nausea and tiredness, but again, no dizziness whatsoever. I'm active. I'm in the gym every single morning. If the nodules get bigger again after a while, I would be open to another round of Jevtana (cabazitaxel).

Do you have any advice for other men? You mentioned taking it a little bit easier after Taxotere (docetaxel), but any other advice for men who have been prescribed either of these agents or who are already going through chemo?

Mr. Stern: With Taxotere (docetaxel), I believe I had substantial side effects. A patient need not have the same side effects I have or as serious. It may be that it is much better for them than it was for me. Just endure. Regardless, when chemo is called for, I'd strongly recommend doing it. The side effects may be as severe as mine were, but really it's very tolerable.

I am happy that I went through the first nine treatments of chemo with Taxotere (docetaxel). For about six months, I saw the reduced size of the cancerous nodules, and I was very pleased. I regained my strength and felt great during those nine months before I started Jevtana (cabazitaxel).

With four treatments of Jevtana (cabazitaxel) so far, I've had mild side effects. I'm pleased with the side effects so far. I'm pleased with the total treatment plan at Memorial Sloan Kettering, including the first nine treatments in 2017-18.

A patient should carefully choose a cancer center. I was fortunate to have some major cancer centers 25 miles from my home. I feel very lucky. I'm 84, I try to walk at least a mile every day, I'm on the stationary bike in the mornings, and I do weights. I do my exercises that are prescribed by my PT. I'm getting more and more stable on my legs. I don't need a cane, and I'm feeling very good. After all these chemo treatments, I feel that I'm doing well. Pp

JEVTANA® (cabazitaxel) injection

Combat advanced prostate cancer after treatment with docetaxel.

An option today for TOMORROW'S OPPORTUNITIES

***In the clinical study, among 378 men who received JEVTANA, median overall survival[1] was 15.1 months, versus 12.7 months among 377 men who received mitoxantrone.**

[1]The median overall survival is the time, when 50% of the patients who receive a certain treatment are still alive.

Talk to your doctor and visit JEVTANA.com/info

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. **Please see Important Safety Information on next page.**

Talk to your doctor and visit JEVTANA.com/info

Who is JEVTANA for?

JEVTANA is a prescription anti-cancer medicine used with the steroid medicine prednisone. JEVTANA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has worsened (progressed) after treatment with other medicines, including docetaxel.

Important Safety Information

JEVTANA may cause serious side effects, including:

Low white blood cells, which can cause you to get serious infections, and may lead to death. Men who are 65 years or older may be more likely to have these problems. Your healthcare provider (HCP):

- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your HCP decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

What is most important to know about JEVTANA?

Tell your HCP right away if you have any of these symptoms of infection during treatment with JEVTANA: fever (take your temperature often during treatment with JEVTANA), cough, burning during urination, or muscle aches.

Also, tell your HCP if you have any diarrhea during the time that your white blood cell count is low. Your HCP may prescribe treatment for you as needed.

Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your HCP should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your HCP right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA: rash or itching, skin redness, feeling dizzy or faint, breathing problems, chest or throat tightness, or swelling of face.

JEVTANA can cause severe stomach and intestine problems, which may lead to death. You may need to go to the hospital for treatment.

Vomiting and diarrhea can happen when you receive JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Your HCP will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA.

Tell your HCP if: you have vomiting or diarrhea, or if your symptoms get worse or do not get better. JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine. This can lead to death. **Tell your HCP if you get any of these symptoms:** severe stomach-area (abdomen) pain, constipation, fever, blood in your stool, or changes in the color of your stool.

Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your HCP will check you for this problem and treat you if needed.

Tell your HCP if you develop these signs or symptoms: swelling of your face or body, or decrease in the amount of urine that your body makes each day or blood in your urine.

Lung or breathing problems may happen with JEVTANA and may lead to death. Men who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your HCP will check you for this problem and treat you if needed.

Tell your HCP right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough or fever.

Please see additional Important Safety Information and the Brief Summary on the following pages.

SANOFI GENZYME

 SAUS.CAB.18.06.3538(1) 07/19

JEVTANA® (cabazitaxel) injection

Important Safety Information– *continued*

Who should not receive JEVTANA?

Do not receive JEVTANA if: your white blood cell (neutrophil count) is too low, you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80 (ask your HCP if you are not sure), you have severe liver problems or you are pregnant. JEVTANA can harm your unborn baby or possibly cause loss of pregnancy.

What should I tell my HCP before receiving JEVTANA?

Before receiving JEVTANA, tell your HCP if you:

- had allergic reactions in the past
- are age 65 or older
- have kidney or liver problems
- have lung problems
- are a male with a female partner who is able to become pregnant. Males should use effective birth control (contraception) during treatment with JEVTANA and for 3 months after your final dose of JEVTANA.

JEVTANA may cause fertility problems in males. This may affect your ability to father a child. Talk to your HCP if you have concerns about fertility.

Tell your HCP about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your HCP first. Your HCP will tell you if it is safe to take the new medicine with JEVTANA.

What are the possible side effects of JEVTANA?

Common side effects of JEVTANA include:

- low red blood cell count (anemia) is common with JEVTANA, but can sometimes also be serious. Your HCP will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- low blood platelet count is common with JEVTANA, but can sometimes also be serious. Tell your HCP if you have any unusual bruising or bleeding.
- numbness, tingling, burning or decreased sensation in your hands or feet
- blood in your urine. Tell your HCP if you see blood in your urine
- fever
- diarrhea
- tiredness
- nausea
- vomiting
- constipation
- weakness
- stomach pain
- back pain
- change in your sense of taste
- shortness of breath
- cough
- joint pain
- hair loss
- decreased appetite

Tell your HCP if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of JEVTANA. For more information, ask your HCP or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see the Brief Summary on the next two pages.

SANOFI GENZYME

Summary of Information about JEVTANA® (cabazitaxel) Injection
(JEV-ta-na)

Rx Only

What is the most important information I should know about JEVTANA?

JEVTANA may cause serious side effects including:

Low white blood cells. Low white blood cells can cause you to get serious infections, and may lead to death. Men who are 65 years or older may be more likely to have these problems. Your healthcare provider:

- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your healthcare provider decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

Tell your healthcare provider right away if you have any of these symptoms of infection during treatment with JEVTANA:

- fever. Take your temperature often during treatment with JEVTANA.
- cough
- burning on urination
- muscle aches

Also, tell your healthcare provider if you have any diarrhea during the time that your white blood cell count is low. Your healthcare provider may prescribe treatment for you as needed.

Severe allergic reactions. Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your healthcare provider should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your healthcare provider or nurse right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA:

- rash or itching
- skin redness
- feeling dizzy or faint
- breathing problems
- chest or throat tightness
- swelling of your face

Severe stomach and intestine (gastrointestinal) problems. JEVTANA can cause severe stomach and intestine problems, which may lead to death. You may need to go to a hospital for treatment.

- Vomiting and diarrhea can happen when you receive JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Your healthcare provider will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA.

Tell your healthcare provider if:

- you have vomiting or diarrhea
- your symptoms get worse or do not get better

JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine. This can lead to death. **Tell your healthcare provider if you get any of these symptoms:**

- severe stomach-area (abdomen) pain
- constipation
- fever
- blood in your stool, or changes in the color of your stool

Kidney failure. Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider if you develop these signs or symptoms:

- swelling of your face or body
- decrease in the amount of urine that your body makes each day
- blood in your urine

Lung or breathing problems. Lung or breathing problems may happen with JEVTANA and may lead to death. Men who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough or fever.

What is JEVTANA?

JEVTANA is a prescription anti-cancer medicine used with the steroid medicine prednisone. JEVTANA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has worsened (progressed) after treatment with other medicines that included docetaxel.

JEVTANA is not for use in females.

It is not known if JEVTANA is safe and effective in children.

Who should not receive JEVTANA?

Do not receive JEVTANA if:

- your white blood cell (neutrophil count) is too low
- you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80. Ask your healthcare provider if you are not sure.
- you have severe liver problems
- you are pregnant. JEVTANA can harm your unborn baby or possibly cause loss of pregnancy.

Before receiving JEVTANA, tell your healthcare provider about all your medical conditions, including if you:

- had allergic reactions in the past
- are over the age of 65
- have kidney or liver problems
- have lung problems
- are a male with a female partner who is able to become pregnant. Males should use effective birth control (contraception) during treatment with JEVTANA and for 3 months after your final dose of JEVTANA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your healthcare provider first. Your healthcare provider will tell you if it is safe to take the new medicine with JEVTANA.

How will I receive JEVTANA?

- JEVTANA will be given to you by an intravenous (IV) infusion into your vein.
- Your treatment will take about 1 hour.
- JEVTANA is usually given every 3 weeks. Your healthcare provider will decide how often you will receive JEVTANA.
- Your healthcare provider will also prescribe another medicine called prednisone for you to take by mouth every day during treatment with JEVTANA. Your healthcare provider will tell you how and when to take your prednisone.

It is important that you take prednisone exactly as prescribed by your healthcare provider. If you forget to take your prednisone, or do not take it on schedule, make sure to tell your healthcare provider or nurse. Before each infusion of JEVTANA, you may receive other medicines to prevent or treat side effects.

What are the possible side effects of JEVTANA?

JEVTANA may cause serious side effects including:

- **See "What is the most important information I should know about JEVTANA?"**

Common side effects of JEVTANA include:

- Low red blood cell count (anemia). Low red blood cell count is common with JEVTANA, but can sometimes also be serious. Your healthcare provider will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- Low blood platelet count. Low platelet count is common with JEVTANA, but can sometimes also be serious. Tell your healthcare provider if you have any unusual bruising or bleeding.
- diarrhea
- tiredness
- nausea
- vomiting
- constipation
- inflammation of the bladder has happened in men who have previously received pelvic radiation therapy. Tell your healthcare provider if you have blood in your urine, burning sensation during urination, or frequent or urgent need to urinate.
- weakness
- stomach (abdominal) pain
- blood in your urine. Tell your healthcare provider or nurse if you see blood in your urine.
- back pain
- decreased appetite
- shortness of breath
- hair loss
- cough

JEVTANA may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of JEVTANA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of JEVTANA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about JEVTANA that is written for health professionals.

What are the ingredients in JEVTANA?

Active ingredient: cabazitaxel

Inactive ingredient: polysorbate 80

Manufactured by: sanofi-aventis U.S. LLC,
Bridgewater, NJ 08807 A SANOFI COMPANY

For more information, go to www.sanofi-aventis.us or call 1-800-633-1610.

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