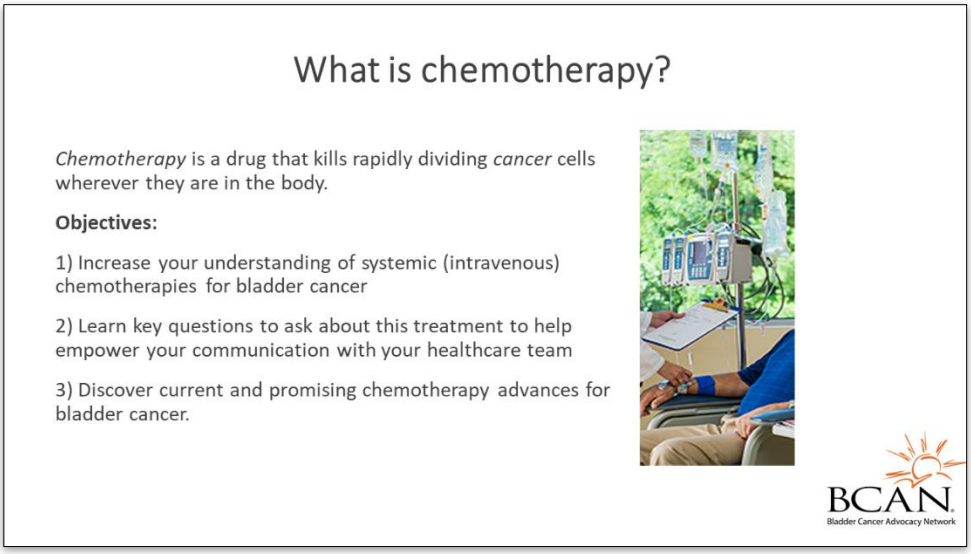
Introduction

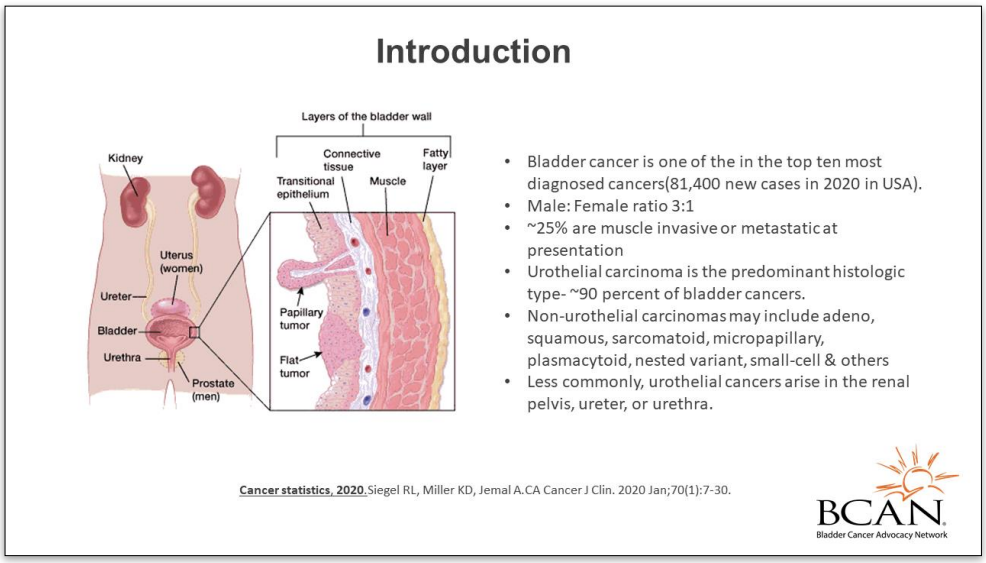
Stephanie Chisolm: My name is Stephanie Chisholm and I'm the Director of Education and Research at the Bladder Cancer Advocacy Network. Chemotherapy has long been used to treat most types of cancers, and I know you probably heard about it. It's a drug or combination of drugs that really are designed to kill cancer cells, wherever they are in the body, and you could receive chemotherapy before, known as neoadjuvant, or after surgery, known as adjuvant therapy, to increase the chance of finding a cure. If you have bladder cancers that spread, you might receive chemotherapy as your main type of treatment, and you would go to a medical oncologist, like Dr. Guru Sonpavde,

Meet the Expert: Dr. Guru Sonpavde, who is the Bladder Cancer Director at Dana Farber Cancer Institute, where he leads multiple cutting-edge clinical trials that study novel immunotherapies and targeted drugs to cure bladder cancer. Dr. Sonpavde completed his medical oncology fellowship at Indiana University, and his primary focus is on clinical trials to develop new drugs and combinations to treat urologic cancers, with a focus specifically on bladder cancer. So Dr. Sonpavde, welcome.

Dr. Sonpavde: Thank you, Stephanie. I really appreciate this opportunity to talk about bladder cancer chemotherapy and inform our patients.We are here to talk about chemotherapy. So what is chemotherapy? Chemotherapy is a drug that kills rapidly dividing cancer cells wherever they are in the body. So the objectives of this talk are to increase your understanding of intravenous chemotherapies for bladder cancer and learn



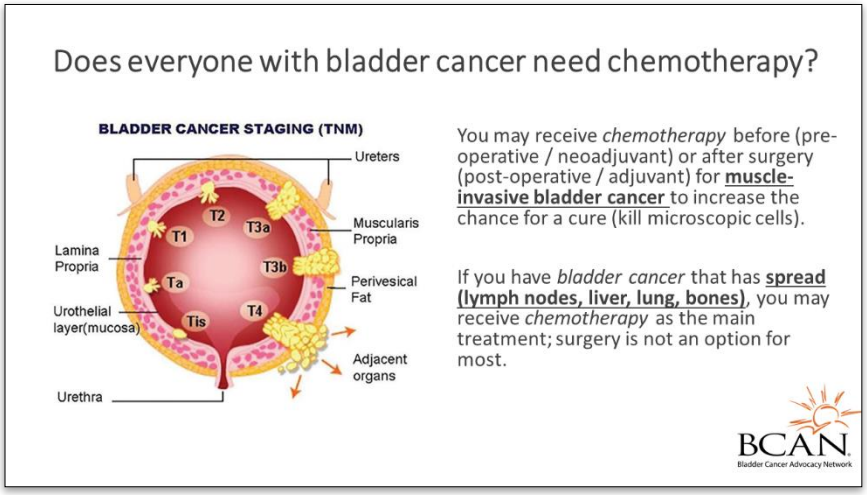
key questions to ask about this treatment, to help empower your communication with your healthcare team. And also to discover the current and promising chemotherapy advances for bladder cancer.



So just to introduce you to bladder cancer a little bit, bladder cancer is one of the top 10 most diagnosed cancers in the US. We saw around 81,000 cases last year in the US. There is a male to female predominance, which we don't fully understand. And out of all of these bladder cancer diagnoses, around a quarter of patients have muscle-invasive disease. If you see the figure here, the cancer arises in the lining of cells of the urinary bladder, and once you get deeper into the muscle layer, that's what's called muscle-invasive bladder cancer, and that's what's the dangerous form of bladder cancer, which can spread out and become metastatic.

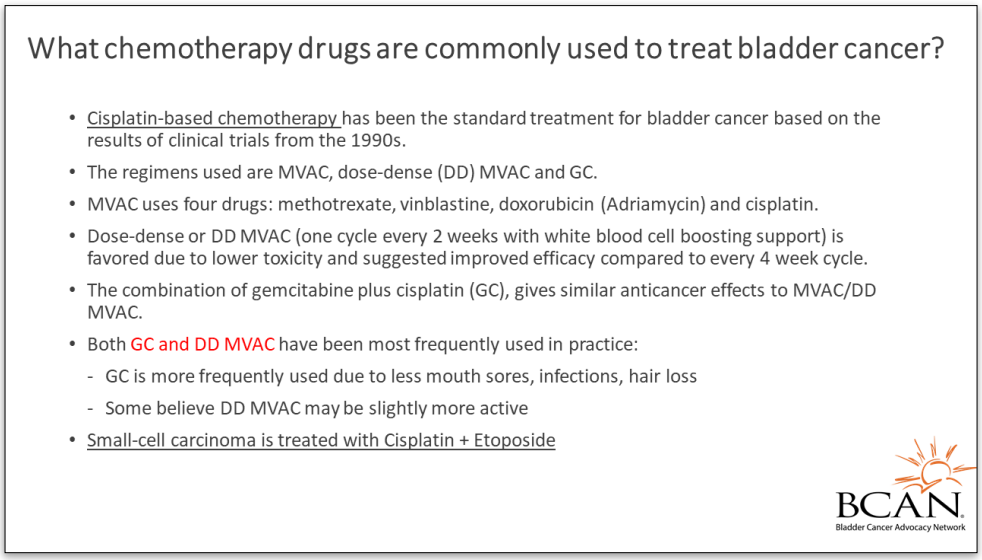
Dr. Sonpavde: So again, the predominant cell type is urothelial carcinoma. There are many cell types of cancer that can arise in the bladder, and urothelial is the most common cell type. You may have heard this name before. But there are other non-urothelial cell types, including adenocarcinoma, squamous cell carcinoma, sarcomatoid, and many other cell types that I mention here. And also, I would mention that it's not just the bladder where these urothelial carcinomas can arise. They can also arise in the upper urinary tract, which is the tract that leads from the kidney down to the bladder; that is the ureter.

Dr. Sonpavde: So one of the questions I frequently get asked is: does everyone with bladder cancer need chemotherapy? So first of all, what are the settings of chemotherapy? How do we define these various chemotherapy settings? One is chemotherapy given before surgery, or before radical cystectomy to remove the bladder. We also call it neoadjuvant chemotherapy, so that is chemotherapy before we remove the cancer by removing the entire bladder. And also there is adjuvant or postoperative chemotherapy, which is chemotherapy given after we remove the bladder, and this is, of course, only for muscle-invasive bladder cancer. And the reason we do this chemotherapy before or after removing the bladder is to kill microscopic cells that are hiding somewhere else in the body outside the bladder. So we want to kill these cells before they grow and cause metastatic disease.



Now, the second type of chemotherapy would be chemotherapy for metastatic disease, which is also a type of systemic or intravenous chemotherapy which would be done if patients have metastases seen on the scan and this could be spread; metastases implies spread to other areas of the body, like lymph nodes, liver, lung, bone, and even other areas. So when the cancer has spread out and is visible on the scan, that is not a stage at which you can cure by removing the bladder or performing a radical cystectomy, as we call it, removing the bladder. So in that case we have to consider systemic intravenous chemotherapy.

Now what are the common chemotherapy drugs used to treat bladder cancer? So cisplatin-based chemotherapy is commonly used, and you may have heard the name cisplatin. Cisplatin is a component of all of the chemotherapy regimens used to treat bladder cancer, and I list them here: the MVAC, dose-dense MVAC, or the Gemcitabine-Cisplatin (GC) regimen. The MVAC regimen consists of these four chemotherapy drugs I mention here: methotrexate, vinblastine, Adriamycin, and cisplatin. And the MVAC can also be given in a dense fashion, so that's called dose-dense MVAC, given every two week cycles rather than every four week cycles. The GC regimen consists of two chemotherapy drugs, gemcitabine and cisplatin.

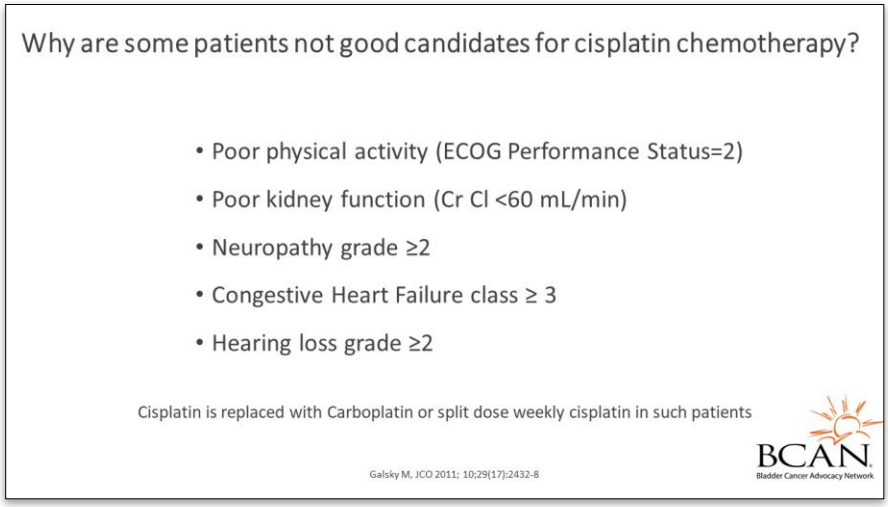


Dr. Sonpavde:

So both GC and dose-dense MVAC have been more frequently used in practice, but the GC regimen is more frequently used because it is less toxic, less side effects, less chances of side effects like mouth sores, infections, hair loss. But some investigators believe, based on some data, that the dose-dense MVAC might be slightly more active. So they prefer the dose-dense MVAC, but most of us, most investigators and oncologists, have resorted to the GC regimen.

Now small-cell carcinoma is a slightly different cell type of cancer that arises in the bladder, one of the ovarian cell types that I touched upon before. And for this there is a slightly different chemotherapy regimen consisting of cisplatin. Again, cisplatin is part of all of these regimens, but combined this time with etoposide, so that is a slightly different regimen for small-cell cancer.

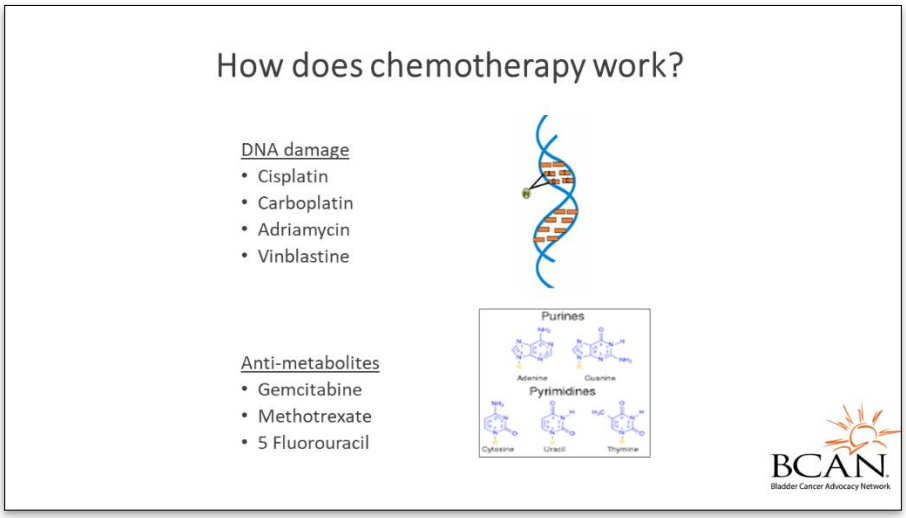
Now there are some patients who are not candidates for cisplatin chemotherapy, unfortunately. Why does that happen? Why are some patients not candidates for this cisplatin that we want to give so badly for improving outcomes? So that is because the patients may have what we call poor performance status, which basically is another technical medical word for poor physical activity.



And secondly, if you have poor kidney function, which we can measure with a blood test. We measure something called the creatinine clearance, and if that's less than 60, and some consider less than 50 as a threshold, then you cannot really do cisplatin safely because cisplatin has some toxicities and side effects of reducing kidney function.

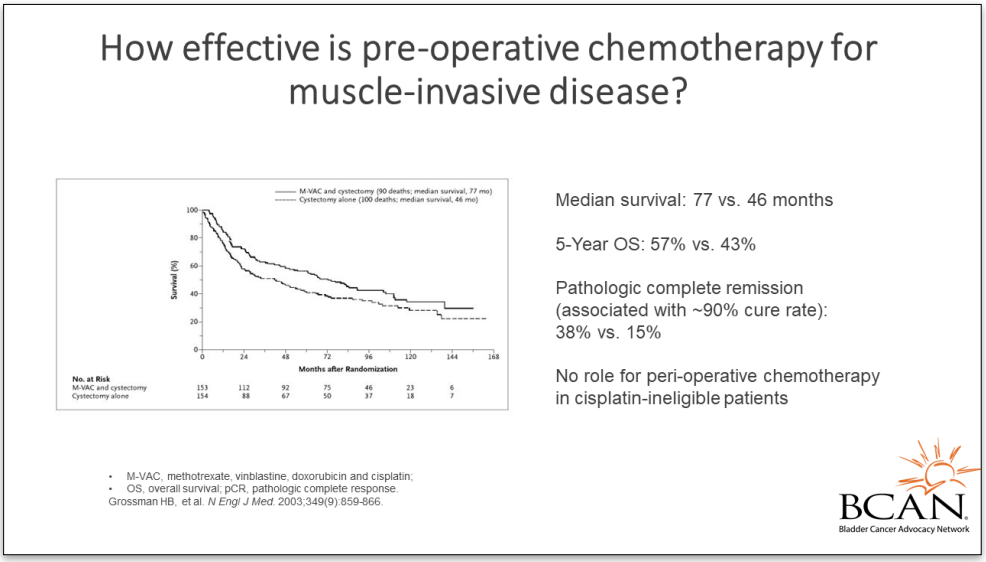
And then, some patients have neuropathy, and that's tingling and numbness in the hands and feet. Usually, this can happen from things like diabetes can do that. Heart failure, if your heart muscle is weak because of heart or cardiac disease, then it's a problem giving cisplatin because cisplatin needs to go in with lots of fluids to hydrate the patient while it's going in to prevent kidney damage. And then you may also be unable to give cisplatin if the patient has a hearing loss, because cisplatin does have toxicities on the ear and does affect hearing, and so that is a problem if someone has a hearing loss.

Dr. Sonpavde: Now how does chemotherapy work? So chemotherapy works generally, as I show on top there, by causing DNA damage, so that's the DNA which codes for everything in the cell, including the cancer cell. If you damage their DNA and prevent the DNA from dividing you can kill these rapidly dividing cancer cells. That's how cisplatin, Adriamycin, vinblastine-based chemotherapy drugs. I also mention a drug there called carboplatin that is a cousin of cisplatin. We like to give it in patients who are not fit for cisplatin because of those reasons I just showed you: poor kidney function, poor physical fitness. We have done carboplatin in those patients instead of cisplatin.



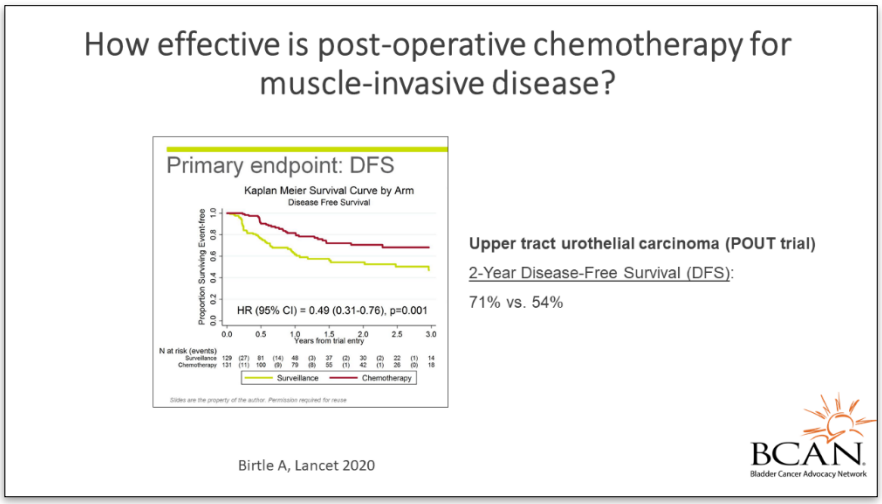
And then the second class of drugs we have used is the antimetabolites. So these antimetabolites don't directly attack DNA division, but they attack the metabolites that are necessary for the manufacture of their DNA. So that is these other drugs I mention here again: gemcitabine, methotrexate, 5-fluorouracil.

Now one question patients can be expected to ask is how effective is preoperative chemotherapy, that's neoadjuvant or chemotherapy done before removing the bladder, when someone has muscle-invasive bladder cancer; how effective is chemotherapy? So this is a big study that actually established the role of this preoperative cisplatin-based combination chemotherapy. As you can see, it improved the survival of patients compared to patients who went for cystectomy alone; giving three months of preoperative MVAC chemotherapy improved survival, the median survival actually, by two and a half years, which is a very robust improvement. It also caused pathologic complete remission in about a third of patients. Pathologic complete remission is when you remove the bladder and you look under the microscope and you see no cancer at all, suggesting that the chemotherapy knocked out all the cancer cells, which is a very good sign. That happens in approximately a third of patients.

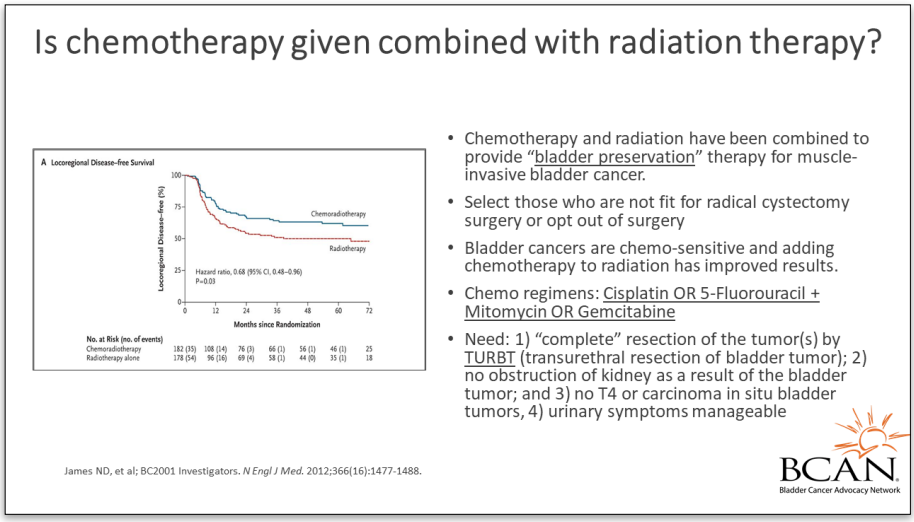


Dr. Sonpavde: Now some patients who are not cisplatin-eligible because of the poor kidney function or poor physical fitness, those patients, unfortunately, we do not give any other chemotherapy because there is no data to show that carboplatin or some other chemotherapy is also effective in this situation.

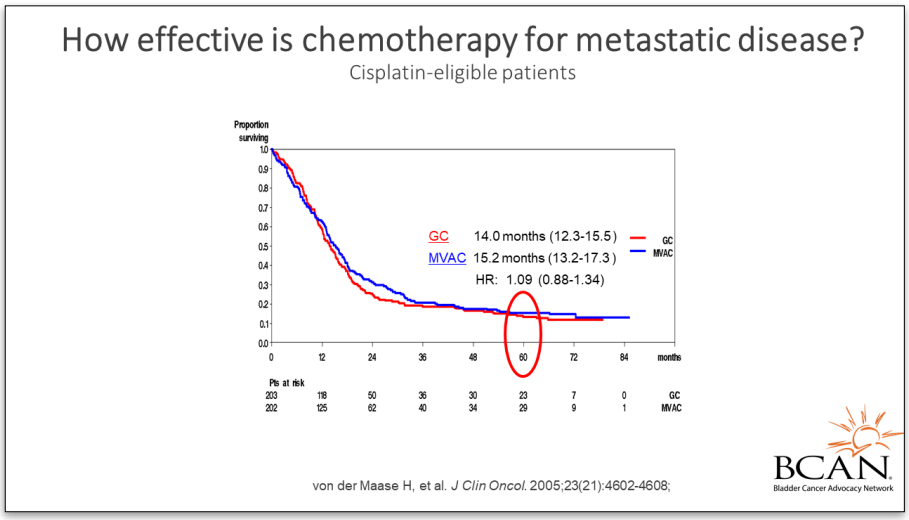
What about postoperative chemotherapies? So can you do a radical cystectomy first for cancer invading the muscle and give chemotherapy after radical cystectomy? Actually, we don't have great data for bladder cancer in this situation, but we do have good data for upper tract urothelial carcinoma. So this is essentially the same type of carcinoma, but it arises in the upper tract, that's the ureter, the tube that leads down from the kidney to the bladder. When it arises there it's called upper tract urothelial carcinoma, and in that situation, we do have a good study here called the POUT study, which showed that there was an improvement in disease-free survival, as we call it: time to recurrence of disease. It prevented disease from coming back in significantly more patients.



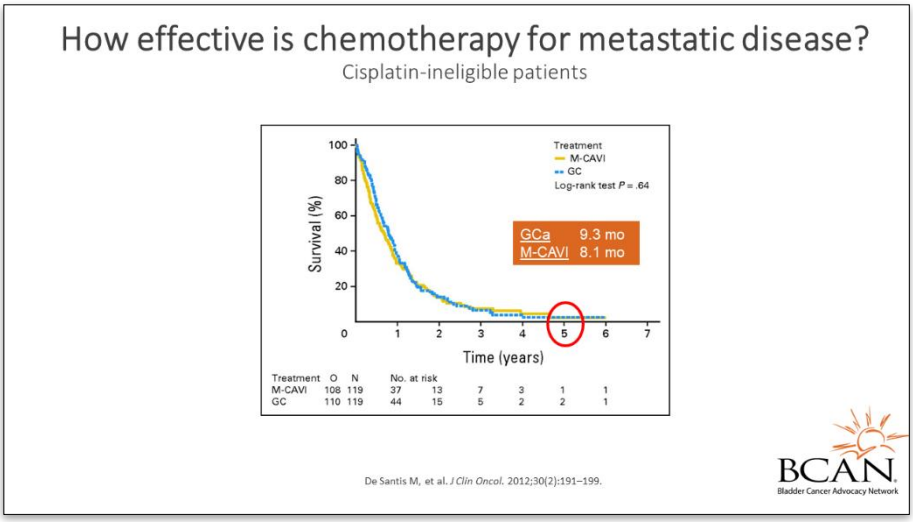
Now do we sometimes combine chemotherapy with radiation therapy? That is a question I get asked a lot. Patients have heard about radiation therapy. So the answer to that is we prefer neoadjuvant chemotherapy, so preoperative chemotherapy first, followed by radical cystectomy, remove the bladder, as the preferred standard of care in patients with bladder cancer invading the muscle. But in some patients who are not fit for surgery, which could be for a number of reasons ... other diseases, other problems that make it difficult to undergo radical cystectomy, which is a fairly major surgery ... in those situations we have then a combination of chemotherapy and radiation therapy in patients like that, and in fact we have evidence to show that combination of chemotherapy and radiation therapy is better than radiation therapy alone to prevent recurrence of the disease. But there are few patients who may not qualify for this, based on the large size of the tumor, so generally you need a smaller-sized tumor to unable chemotherapy and radiation therapy combination to be effective.



Dr. Sonpavde: Now what about metastatic disease? So this is disease where the cancer has spread out on the scan, so it's well beyond just invading into the muscle layer of the bladder. So in this situation, again we have used the same regimens I mentioned before. They all contain cisplatin, the C there stands for cisplatin. GC or MVAC, and as you can see here, both of these regimens look very similar. These curves are showing the survival of patients with time. As you can see, these two regimens look fairly similar and have a similar survival when you look over six or seven years.

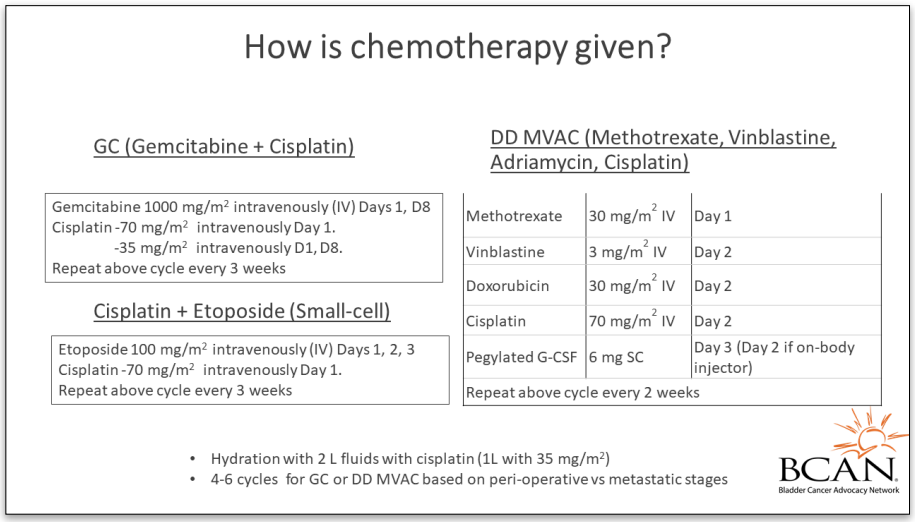


How effective is chemotherapy for metastatic disease on the scan if someone is not cisplatin-eligible? That is a little bit disappointing here, unfortunately as you can see here, we use carboplatin instead of cisplatin in patients like this who are not eligible for cisplatin. In this, the curves you see here, there is a difference, as you can see. You don't see patients alive unfortunately, that much when you go five, six years out. And also the median survival is less than a year in patients who get this chemotherapy. So we still have a long way to go to improve outcomes in these patients because if someone is not fit for cisplatin, this alternative chemotherapy regimen of carboplatin-based regimen is actually not as effective, unfortunately.



So how is chemotherapy given? Chemotherapy is given intravenously. As you can see here, the GC regimen, gemcitabine and cisplatin, gemcitabine is given intravenously. This is all done in the clinic. We don't admit people. It's done once a week, two weeks on, one week off, the gemcitabine. The cisplatin we like to give it all at once, slowly with lots of fluids. It takes five or six hours to get it in just on that first day after a three week cycle. So it's once a day, two weeks on, one week off. Keeps going like that. And sometimes we will split the cisplatin up between the first and the second week; if we think that someone's kidney function is not good enough for handling all of the cisplatin in one day, we split that up, and that's called split-dose cisplatin. And sometimes we have done the split-dose cisplatin instead of carboplatin in some patients.

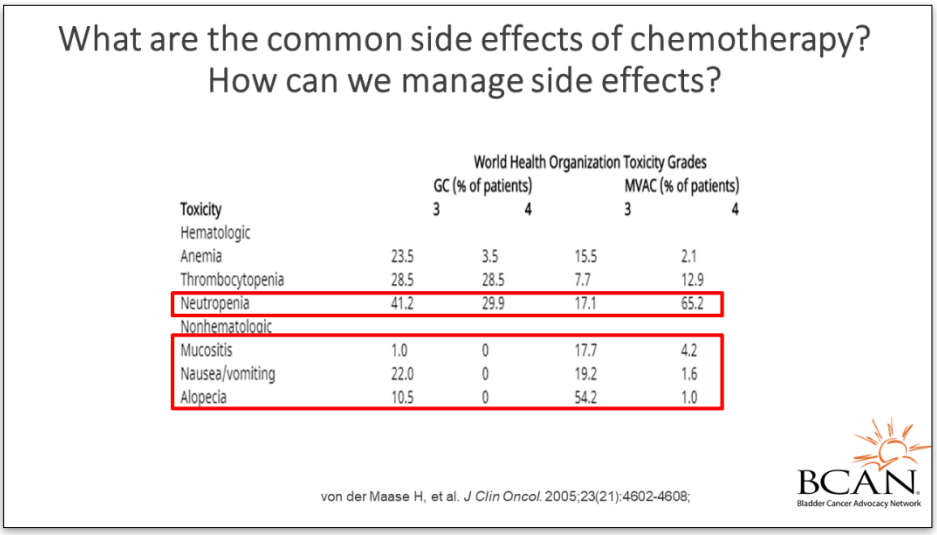
Dr. Sonpavde: Now in the small-cell type of bladder cancer, we have done the combination of cisplatin plus etoposide. That's a different chemotherapy regimen. Again, the small-cell type of cancer in the bladder is not that common, but when we see that, this is the regimen we use.



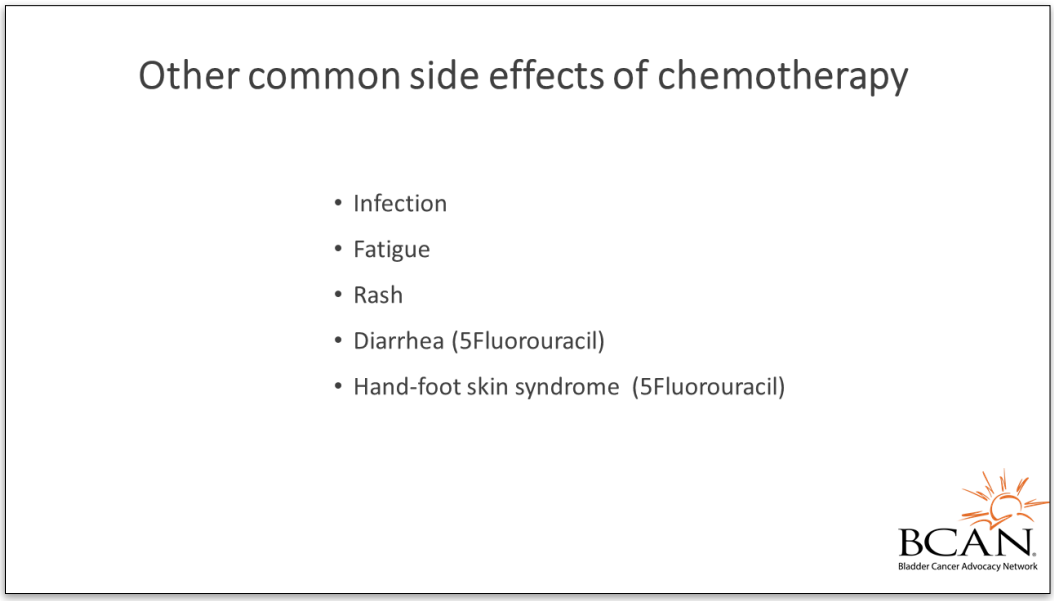
Now the dose-dense MVAC or the MVAC regimen uses these four chemotherapy drugs I mention here. The standard MVAC regimen is given over four week cycles and in general, we go up to six cycles of chemotherapy in patients with metastatic disease. That's how long we can give it when it's metastatic. In patients where we're giving it preoperatively or postoperatively to prevent it from coming back, in that situation we usually go three or four cycles.

Now with dose-dense MVAC, we also give concurrently a drug called GCSF, or you may have heard the name, Neupogen or Neulasta. So this is a drug that boosts your neutrophils. It's a type of white blood cell that goes down with the chemotherapy, so this Neulasta or Neupogen might elevate this count and prevent the risk of infections. I should mention that along with the cisplatin, we give a lot of fluids, and that's why the cisplatin day is a long day, when we give cisplatin with these regimens.

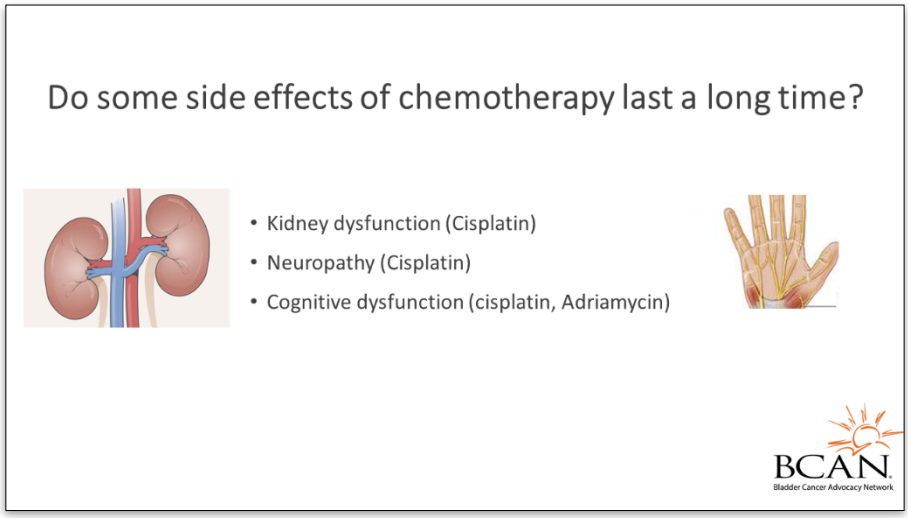
Now how common are the side effects? What are the side effects of chemotherapy, and how do we manage them? So the most important thing that we worry about is neutropenia, which is a technical term, I'm sorry about that, but what that means is a low neutrophil count in the blood. It's a white blood cell called neutrophil. When that count goes down, those are rapidly dividing cells, so chemotherapy attacks anything rapidly dividing so you get this low neutrophil count, and that's what causes a risk of infection, unfortunately. You can also get mucositis, that's inflammation in the lining of the mouth. You can get nausea and vomiting, and you can get alopecia, is hair loss, the technical term for hair loss. The hair loss is much more common with the MVAC regimen as you can see here, almost about half of all patients, as opposed to the GC regimen, where hair loss is much less common in the 10% range.



Dr. Sonpavde: So what are the other common side effects? The infection risk, because of the low neutrophil count. You do get fatigue, it's very variable. Some people feel a lot of fatigue, some people feel less fatigue. You might get a skin rash. It tends to be mild, and that's associated with gemcitabine. Diarrhea, that is seen sometimes with 5-fluorouracil. That is a chemotherapy drug given in combination with radiation. When we do the chemo and radiation together in patients who are not fit for radical cystectomy bladder removal surgery, that's when we do 5-FU that can cause diarrhea. And again, the same drug, the 5-fluorouracil or we call it 5-FU for short, can also cause hand-foot-skin syndrome, which is a skin rash in the hands and feet. So we watch for those side effects.

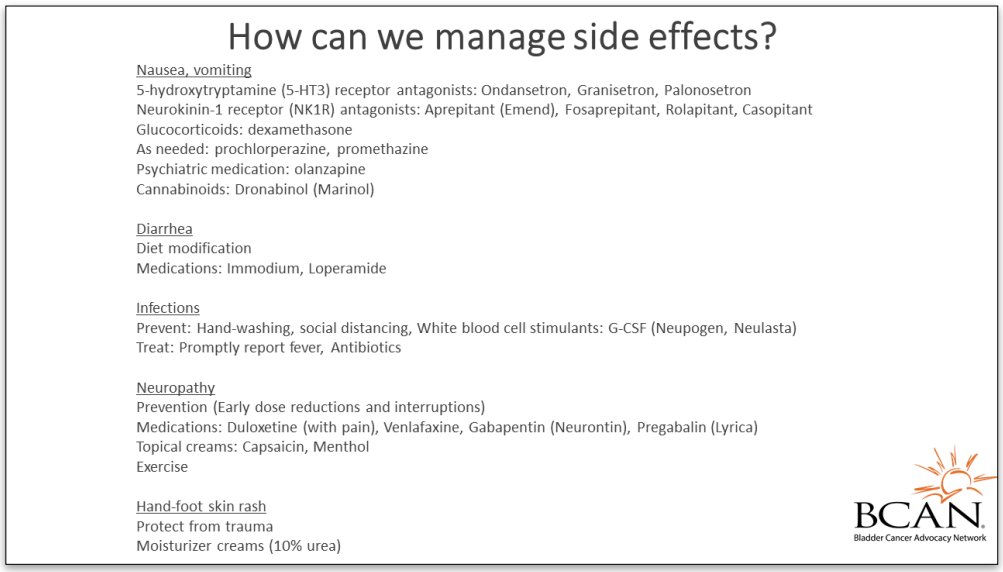


We also get this question commonly, which is: do some of these side effects last a long time? Do they all go away? When do they happen? So most of these side effects, like nausea and vomiting, the risk of infection, the mouth sores that can happen, they occur during chemotherapy or soon after. However, some side effects can last a long time, so one of them is kidney dysfunction from cisplatin, which can cause the creatinine number in the blood, which affects kidney function, to go up a little bit and kind of stay there for a while, and sometimes forever. So we do need to pay attention to hydration throughout the course of chemotherapy. Neuropathy is the other one, that is tingling in the hands and feet. Mostly it's called sensory neuropathy, and that's from the cisplatin affecting nerves. So that can sometimes hang around a long time, and this is why we like to jump on patients who are showing some early signs of neuropathy in order to make some changes and prevent it from getting worse.



Dr. Sonpavde: Another one is cognitive dysfunction, which is changes in memory and mental functioning, which can sometimes occur in patients, and has been noted after a long period of time of chemotherapy. So that is mostly a problem in the minority, I would say, and mostly after a long period of time. So it's not something you would see acutely or during chemotherapy that much.

So how do we manage these side effects? Nausea and vomiting is the main thing we worry about acutely during the chemotherapy going in or for the first one or two days after chemotherapy, although sometimes it can be delayed. But we have good drugs now to prevent nausea and vomiting. I mention here the 5HT3 antagonists. You may have heard of Ondansetron, Zofran. There are other drugs called the neurokinin-1 receptor antagonists, and you may have heard of Emend. So we have some very good drugs, and we also give dexamethasone along with these drugs to prevent nausea and vomiting. And there are other drugs to prevent nausea and vomiting in really severe cases.



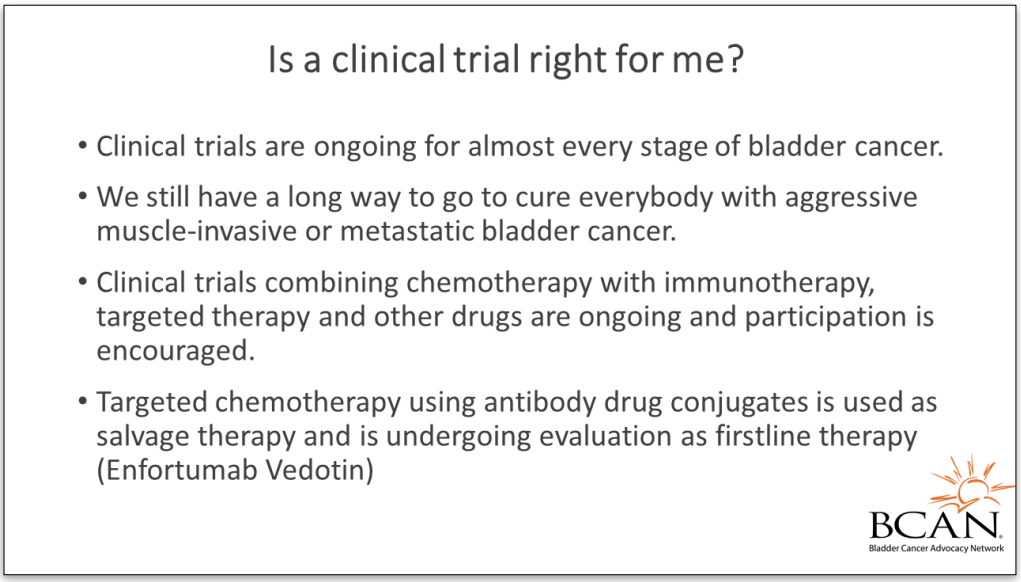
For diarrhea, diet modification. We have other drugs, Imodium, to control diarrhea from, for example, the 5-fluorouracil. Infections: prevention of infection is important, and during this COVID pandemic going on, we have all become attuned to how to prevent infection, so this is something that we advise patients during chemotherapy.

The neuropathy is mostly about prevention, so you really want to jump on neuropathy as soon as we see the symptoms. We want to give breaks to patients, we want to interrupt treatment or cut the dose early so we don't exacerbate the neuropathy, allow it to get worse. We have medications for neuropathy. You may have heard of duloxetine or Cymbalta, neurontin, gabapentin. So we have certain drugs that can help a little bit, but I think that the major intervention is to jump on the neuropathy early and make modifications in your treatment, or even whole treatment if it's bad enough.

Now for hand-foot-skin rash, again the protection from trauma in the hands and feet is important. Moisturizing creams is important to prevent microtrauma that is the cause of this hand-foot-skin rash that occurs sometimes with the 5-fluorouracil chemotherapy. And sometimes with the Adriamycin chemotherapy.

Dr. Sonpavde: One other question patients ask is: does everyone need something, which some of you may know, at least, is called a port-a-cath. A port-a-cath is a good basically intravenous access line, an IV line. And this is how it looks. I'll show you a figure here, it sticks under the skin here on the chest wall. There's nothing hanging out all day long, but when we need to do chemotherapy we put a needle through this port-a-cath to infuse the chemotherapy, and then the needle comes out when the patient walks out of the clinic. And we consider this in some patients who need long-term treatments for metastatic disease, but for neoadjuvant and adjuvant, which is a brief three months of chemotherapy, we usually can live without a port-a-cath, especially in patients with good veins.

You might also want to ask is a clinical trial right for me? So clinical trials are, I think, a necessary facet of treatment of every stage of bladder cancer. We don't cure everybody with bladder cancer. Neoadjuvant and adjuvant chemotherapy improves outcomes but does not cure everyone, so we really need to consider trials, research for patients whenever possible. There are exciting trials going on combining chemotherapy or sequencing chemotherapy with immunotherapy to boost the immune cells to fight the cancer. There are targeted chemotherapy drugs coming onboard. It's about antibody drug conjugates. You may have heard the name enfortumab. So there are numerous clinical trials coming that you should consider for every stage of the disease, whether it's neoadjuvant, preoperative, adjuvant, or for metastatic disease.



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