



## Understanding Systemic Chemotherapy Options in Bladder Cancer

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### Part II: Chemotherapy Candidacy & Side Effects

#### Presented by



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What is the definition in terms of who is a good candidate for chemotherapy and who isn't? So, there really isn't a strict definition of it, but some of our colleagues in the BCAN think tank put this paper together a couple of years ago, which is at least a guidance document for clinicians both at academic centers and in the communities to think about who may be the best suited for cisplatin-based chemotherapy and who may not, just based on some of their medical problems. Again, these are not absolutes, but these are really guidance documents.

#### Neoadjuvant (preoperative) chemotherapy

Can it cure bladder cancer?  
At what point is chemotherapy started- (Best before or after bladder removal surgery?)  
Is chemotherapy preventative?

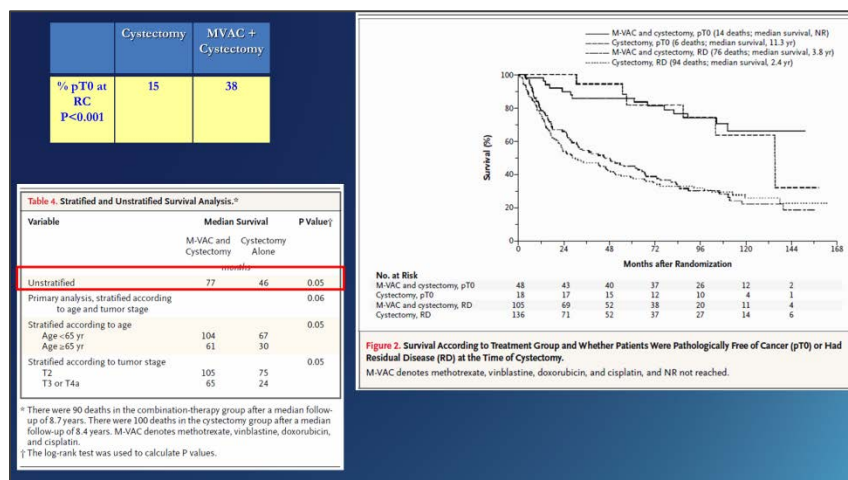


The next question to be answered is, when should chemotherapy be given? Should chemotherapy be preoperative or postoperative? And the absolute answer to this really is, it's best to be given preoperative. So, if we have the choice and if we have the proper information ahead of time, we do feel that it is best given prior to a radical cystectomy. So, it can cure bladder cancer and at what point is it started, and is

it preventative? And the reason that I have this picture up is because radical cystectomy is a tough surgery. So, many people do just fine after surgery, but it's many hours of surgery and it's associated with a very high rate of complication where patients may need to come back into the hospital within 30 days after surgery. Some patients will stay in the hospital for up to 10 days or sometimes even longer, or they need to go to rehab.

So, how fit someone is prior to the surgery does not equal necessarily how fit they may be after surgery, and we think that this may compromise how people are able to tolerate chemotherapy. And so, when we can we like to give the chemotherapy before the surgery. This is one of the more definitive articles that we have on bladder cancer. This was published in the New England Journal quite a few years ago, back in 2003, but it's essentially showing that a chemotherapy cocktail regimen with a chemotherapy group called the MVAC, methotrexate, vinblastine, adriamycin, and cisplatin, when given prior to a radical cystectomy, patients did better, they lived longer than patients that just underwent cystectomy alone. And that's this graph here, which shows that this was a benefit in terms of overall survival. That's the Level 1 Evidence that we talk about when one chemotherapy ... One treatment shows a statistically significant benefit in terms of overall survival.

The other thing that we saw in the study was something called a pathologic downstaging rate. So, those that had what's called pathologic T-zero at the time of radical cystectomy, meaning that the surgeon took the bladder out, the pathologist looked at it under the microscope, and the tumor had melted away with the combination of the transurethral resection and the chemotherapy. If patients only had the transurethral resection and then went on to the cystectomy, they had a 15% rate of pathologic complete response. But with the chemotherapy ahead of time, that rate was more than doubled at 38%. And bladder cancer, like other cancers, those that have a pathologic complete response to chemotherapy, those that go on this line, did better and lived longer than those that had tumor that was still present despite getting that very aggressive preoperative chemotherapy, those patients did not do as well.



So, in terms of, can chemotherapy cure bladder cancer? Can it do it by itself? I don't think we have the answer to that question yet, and certainly in modern paradigms of how we treat this disease, if we believe that the best rates of cure would include chemotherapy followed by either surgery or radiation in carefully selected patients, but

hopefully that answers at least some of the questions. And then this was the overall survival benefit, in that chemotherapy with cystectomy, overall survival is 77 versus 46 months, this P value of .05 or less is a statistically significant benefit, and that was what raises it to the Level 1 Evidence. So, the MVAC chemotherapy back in the 10 years prior to 2003 when that study was being conducted, we did not have

the modern supportive care that we have now, and that chemotherapy was associated with a lot of side effects.

And so, this study was done looking at a combination of gemcitabine and cisplatin versus the MVAC chemotherapy in patients with locally advanced or metastatic disease. The kind of take-home from the study was that most people felt that those two chemotherapies were working at about the same pace, and therefore this is how gemcitabine and cisplatin in part became one of the other standard cocktails that we give for preoperative chemotherapy. There have been multiple other studies done, as well as combinations called meta-analysis, looking at smaller studies in groups of patients that are really pretty large, putting a bunch of studies together, 11 smaller studies leading up to 3,000 patients, all of which have really supported this overall survival benefit in giving preoperative cisplatin-based chemotherapy prior to radical cystectomy.

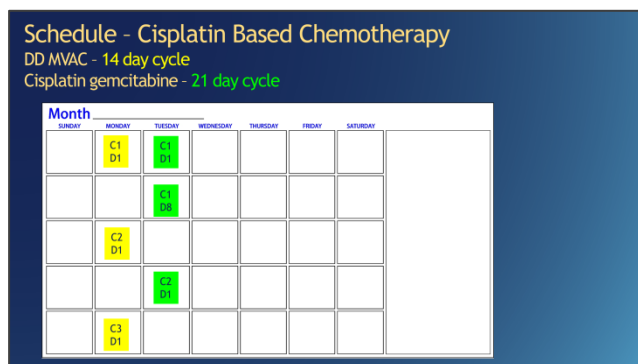
Another regimen that came about was using the MVAC regimen in a slightly different way, and this is based on this here. So, again, in the metastatic setting doing something called dose-dense MVAC, so taking the MVAC chemotherapy regimen that was a multiple-day regimen, and shortening it into a one-day regimen, speeding it up, giving prophylactic ... what's called Growth Factor Support with it, and doing it once every 14 days, and those who got the high doses of dose-dense MVAC did better compared to those that got the standard dose MVAC. They also had a higher amount of chemotherapy that they were able to tolerate, and the overall disease control rates, complete response as well as partial response, was higher at 72% in the MVAC arm. So, the multi-day regimen of chemotherapy has fallen out of favor, and that's how all of these studies were done, with something called dose-dense MVAC.

Summary of Neoadjuvant DD- MVAC Studies				
Studies	N	Cycles	Path response	Toxicity
Plimack et al JCO June 2014 cT2-T4a, N0/N1	44 60% stage III or IV  Median 64 yrs	3	40 evaluable 38% pT0 14% <pT2	Grade 3/4 Anemia, fatigue, neutropenia 1 pt PD on therapy  Median time from start chemotherapy to cystectomy 9.7 weeks
Choueri et al JCO June 2014 cT2-T4a, N0/N1	39 43% cN1	4	47% downstaged to <pT1  28% pT0	1 pt PD on therapy >grade 3 mucositis, HFS, low K, neutropenia, no NF
McConkey, D et al Eur Urol May 2016	60 44 Bladder 16 UTUC  cT3b disease on EUA LVI Hydro Micropap features Tumor in diverticula	4 with bevacizumab	pT0 39% in bladder	Most common grade ≥3 neutropenia in 27% One patient experienced cardiac ischemia.

So, really dose-dense MVAC and gemcitabine and cisplatin are the two chemotherapy cocktails that we use predominantly in patients with bladder cancer that are pending to go to surgery. And based on these three clinical trials, one that we did with Betsy Plimack at Fox Chase and here at Jefferson, with the [inaudible] Group in

Boston, and then David McConkey, who was at MD Anderson but now in Hopkins, three separate groups of physicians looked at this really efficient chemotherapy regimen of dose-dense MVAC, and this is now a regimen that's much more commonly used prior to surgery. So, what about the question of, can you use the chemotherapy after surgery? So, there has been no study like the ones that I showed you beforehand, no study that has shown an overall survival benefit if we give [inaudible 00:29:44] or MVAC after surgery.

So, it's the same chemotherapy, it's the same population of patients, but when we give the chemotherapy after surgery we're not getting those same numbers. And a lot of us really I do think it's in part based on the ability of patients to tolerate this chemotherapy after surgery. A lot of people don't even get to a medical oncologist after surgery because they may have a long-lasting side effect from the surgery. Does that mean that we don't offer it if someone comes to our office and didn't get preoperative chemotherapy? I think the answer to that is no. But if we have our ability to choose, we definitely will choose to give chemotherapy before surgery. This is, I think, one of the better studies and really informative studies that are of looking at a population of patients who did not get preoperative chemotherapy.



So, patients who had a cystectomy, have locally advanced bladder cancer, and whether or not they may have had a positive lymph node, and there is no evidence of metastatic disease, these patients signed on for this clinical trial, and within 90 days of radical cystectomy, were randomized to get either four cycles of immediate postoperative chemotherapy, either gemcitabine and cisplatin, high-dose MVAC, or

standard MVAC. Or the chemotherapy was deferred, they got follow-up imaging done every three months, and if they had metastatic disease then they went on and got standard chemotherapy. Like almost every postoperative study that has been started in bladder cancer, this one had to be stopped early because the enrollment was so slow, and this does cloud how we're able to interpret the data.

So, they weren't able to get to their primary end point showing that immediate chemotherapy was better in terms of overall survival, but I think the study is still very informative. So, the median in five-year overall survivals were different between giving the chemotherapy upfront, and doing it in a deferred fashion if someone had evidence of metastatic disease. Immediate adjuvant chemotherapy led to a significant improvement in what's called the secondary end-point of progression-free survival and a non-significant decrease in the risk of death. So, essentially what these data tell me is that if someone either wasn't offered or wasn't able to get chemotherapy prior to surgery, I think that this is still beneficial but may not give the same benefit as if the chemotherapy was prior.

So, what does the schedule look like if these chemotherapies and ... let's talk a little bit about the side effects. So, if someone was going to get dose-dense MVAC at the 14-day cycle, so if they were going to start on a Monday, they would get their first cycle on this Monday. He would get the rest of the week off, the rest of this week off, and then would start their cycle two here and their cycle three here. So, gemcitabine and cisplatin is a little bit of a different schedule, so this is once every 14 days. The optimum number of cycles I think it still a little bit unclear, between three and four cycles, depending on how people tolerate the chemotherapy prior to surgery. For gemcitabine and cisplatin it's a 21-day cycle. So, cycle one, day one would fall on the first day. That would be two drugs together. This is gemcitabine and cisplatin on day one. And then day eight it's just gemcitabine alone. Day 15 would be

off, and then cycle two would start again on Day 21.

So, as you can see, it takes a little bit longer to get through the chemotherapy cycle if gemcitabine and cisplatin is chosen, versus MVAC, which is pretty efficient and we can get people through chemotherapy and then off to surgery pretty quickly. So, what are the side effects of cisplatin-based chemotherapy? There are a lot of side effects when we are consenting patients for chemotherapy. The things that we can almost guarantee are fatigue, hair loss, and nausea. Can we mitigate those toxicities? We can, but those are the things that are typically expected. Other things that can happen but aren't as common, but I think are also very important are the ringing in the ears. Sores inside the mouth are changing the taste of food. We want to make sure that someone can still eat and drink even if they have sores inside their mouth. If they can't do this then we have to support them with IV fluids. And the numbness and tingling can sometimes limit the number of cycles that somebody is able to tolerate.

#### Side Effects of Cisplatin Based Chemotherapy

- Fatigue, hair loss, nausea
- Ringing in ears, mouth sores, numbness and tingling
- Vomiting, diarrhea, constipation, liver function changes
- Vascular side effects
- Decline in kidney function
- Decreased blood counts with increased infection risk

Vomiting and diarrhea are definitely things that we don't like during chemotherapy, because people can get dehydrated leading to more increased risks of toxicity in the kidneys. Constipation and liver function changes are typically self-limited. Vascular side effects. So, anyone with bladder cancer is at high risk of blood clots, blood clots typically in the legs and the lungs, but chemotherapy can potentially increase

the risk of those as well as increase risks of things like heart attack and stroke during the time of chemo. Declining kidney function we talked about, and then finally decrease in blood counts, which can put patients at risk of [inaudible] or life-threatening infection. So, we tell people to be very mindful of any signs of symptoms of infection. And then, infection may not manifest the same way off chemotherapy than on.

So, how do we manage these things? Particularly we definitely want to make sure that people stay hydrated, they have good nutrition, and really self-regulating, because the things that you could do a week ago may not be the same things that you can do today and you need to take it easy. So, the hair loss as far as I know we really don't have too much in terms of trying to prevent this, but I think really being upfront and honest with people that this is going to happen is, I think, very important. Nausea, vomiting, diarrhea, and constipation. So, we do give prophylactic medications during and with the chemotherapy that I think really significantly cut this down. I also make sure that our patients have medication on their medication shelf in case they need it in the middle of the night if they don't feel well.

So, for mouth sores we do have medicated mouth washes, and just recognition that the mouth sores can happen. Maybe change what someone is eating. The fizzy sodas, bubbly water, those kinds of things, spicy foods, can really aggravate it, so just being mindful of what you're eating. For numbness



and tingling, I want to let people ... to be aware of it, let us know if it starts to happen, and just be kind of cautious and follow up. The same thing with vascular side effects. The risk of DVT or blood clot in a leg is high, so any new swelling in the leg specifically, particularly if it's unilateral, one side versus another, or cast pain or redness is definitely something that is concerning to us, as well as new shortness of breath or chest pain. Declining kidney function we typically will see with laboratory studies, although it's not too common.

#### Side Effects of Cisplatin Based Chemotherapy - management

- Fatigue - hydration, nutrition, self regulation
- Hair loss - preparation
- Nausea, vomiting, diarrhea, constipation - prophylaxis and rx at home, hydration
- Mouth sores - medicated mouthwash, recognition
- Numbness and tingling -awareness and follow up
- Vascular side effects-awareness and follow up
- Decline in kidney function - hydration, "plumbing"
- Decreased blood counts with increased infection risk -growth factor support

And also the plumbing. So, bladder cancer can block the plumbing or the connection between the kidneys and the bladder, and that can happen during the chemotherapy.

Oftentimes urologists, if they're concerned about a blockage or if patients present with a blockage, we can put in stents to try and alleviate the blockage, but we still have to be concerned about that. And then, of

course, decrease in blood counts, which can put patients at risk for a series of life-threatening infections. So, with all these different side effects of chemotherapy, some people will respond to chemotherapy, some people are going to have a complete pathologic response and be on that high part of the curve and hopefully do well for a long period of time.

But some people will go through chemotherapy, unfortunately potentially if they have the side effects of chemotherapy they can be long-lasting, and at the time of surgery may still have residual tumor or node-positive disease, and those patients their prognosis isn't as good. So, are we able to tell upfront who is the best candidate for chemotherapy or whose tumor is most likely to respond to chemotherapy? Can we take those patients, put them through this and give them the chemo, and then the ones whose tumors are less likely to respond, maybe those patients should just go to surgery. I think that that is something that we're very hopeful for in the future, because we want to be able to make better choices about who is going to get the most benefit out of chemotherapy, but right now all we have is association.

So, currently we cannot make choices up front about who should or should not get chemotherapy based on molecular subtypes at least outside of the clinical trial, but this is at least some data that shows that patients whose tumors have defects in DNA-repair genes tend to be more sensitive to getting cisplatin-based chemotherapy, and that kind of makes sense after we talked about how that chemotherapy works. This is not at all the only predictor, but it's one that we worked on in our group with Fox Chase, and I think that understanding these patterns and looking for them is important, so these are some of the questions that we ask as we come to work every day. So, as a summary, preoperative cisplatin-based chemotherapy for pathologic T2 tumors or greater improves overall survival and decreases the risk of recurrence.

Careful selection of patients can improve the risk-to-benefit ratio. Chemo side effects are typically manageable. Some side effects can unfortunately be long-lasting. Postoperative chemo is generally endorsed for patients with high-risk tumors who did not receive preoperative chemotherapy. And the optimum number of cycles, some clinical trials we use three, some clinical trials we use four, it's not entirely clear. What I do tell patients is that, "I'll see you before every cycle of chemotherapy and we'll make a joint decision as to whether or not you're ready for the chemotherapy today, with the goal of getting in at least three, potentially four cycles of chemotherapy if we can." And we are developing studies to kind of predict which tumors may be the most sensitive.

BCAN would like to thank



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