



Understanding Systemic Chemotherapy Options in Bladder Cancer

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Part III: Chemoradiotherapy

Presented by



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Bladder Preservation - Chemoradiotherapy



I'm going to switch gears a little bit and talk about chemoradiotherapy or bladder preservation, so again thinking back to this slide, now moving on to this part of the talk. So, for bladder preservation probes, it's very important that the primary goal of preserving a bladder, to keep a bladder, the primary goal of the treatments that we do is really survival. It's living despite having the diagnosis

of bladder cancer, being a bladder cancer survivor. So, sparing the bladder is really only justified when there is a very high likelihood that we can eradicate the tumor within the bladder, that the risk of the recurrence is low, and that the bladder that someone is left with is one that they actually want to keep, that's not causing them a lot of tension, that the quality of life is not impaired by having that bladder.

Multimodality Therapy in Bladder Cancer

- For patients with muscle-invasive disease, the local control provided by single modality bladder-sparing approaches is unacceptably low.
- TURBT alone can be expected to achieve only a 20 % likelihood of local disease control.
- External beam radiation monotherapy associated with approximately 50 % likelihood disease control within the bladder, with 20-40% long term survival.

Rationale for multimodality therapy

1. Complete TURBT for local gross tumor eradication
2. Synergism of RT and chemo for locoregional disease
3. Ability of chemotherapy to treat micrometastatic disease

So, for patients with muscle-invasive disease, the local control provided by a stable modality therapy, meaning just scraping the tumor out, is very, very low. So, just going back to the urologist and getting tumor-scraping, that tumor, if it's a muscle-invasive tumor it has a very high likelihood of progressing. Transurethral section alone can achieve only a 20% likelihood of local disease control.

Radiation alone, a 50% likelihood of controlling the disease in their bladder but long-term survival is not really as good. To the rationale to put chemotherapy, and transurethral resection, and radiation together is, number one, completely scrape out the tumor that can be seen, so that the surgeon does really good local growth tumor eradication. Number two is to synergize radiation therapy with chemotherapy, at typically lower doses different than we would give prior to surgery, for local regional disease.

And then for some selected patients we do give chemotherapy at higher doses either before the radiation therapy or after the radiation therapy, with the goal of treating that micrometastatic disease, a disease that may have cells that may have moved outside of the bladder that we can't see, so that they die off and don't take up residence in the liver, lungs, or other parts of the body. Sorry, I think that's them. All right. So, again, careful patient selection. So, number one, they have to have that complete resection. Number two, no evidence of hydronephrosis or that kind of stepping on the garden hose where the tube between the bladder and the urethra gets blocked by the kidney. A functional bladder. Optimally, patients that have tumor, just one tumor and not multiple tumors throughout the bladder, and confined within the bladder itself and not poking outside. And again, that's a transitional cell or the more common histology, because we just have very limited data and wouldn't do it otherwise.

Your Questions - Chemotherapy and radiotherapy:

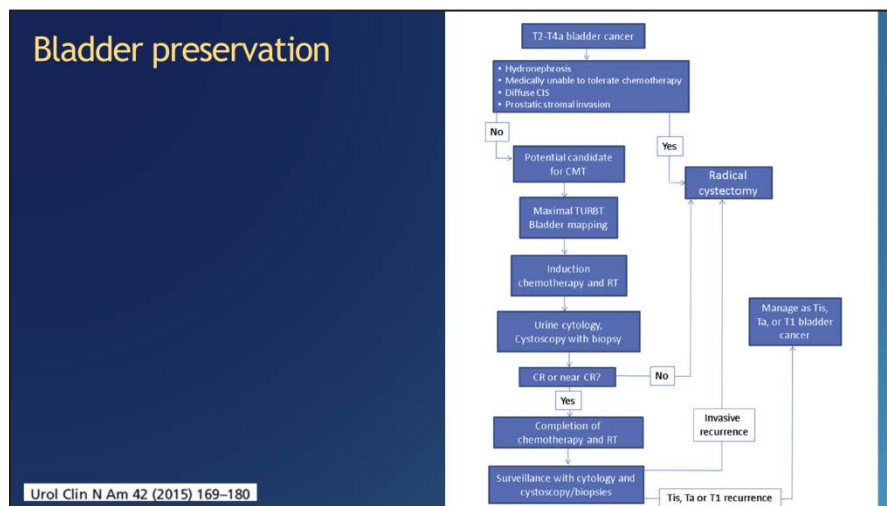


- How well does the bladder tolerate chemoradiotherapy?
- How well does the patient tolerate chemoradiotherapy?
- In tri-modality therapy, which drugs are used for radiosensitization, rather than to primarily kill the cancer?
- What is the schedule?
- Is there a place that summarizes the current success/ mortality rates for the various chemo and immunotherapy treatments?

So, some of the questions you asked is, "How well does the bladder tolerate this treatment?" "How well does the patient tolerate this treatment?" "Which drugs are used for radiosensitization?" "What's the schedule?" And, "Is there a place that summarizes the current success rates for some of the treatments that we have?" I think this is a great question, and Stephanie, I don't know if you might

have the answer to this. We'll talk a little bit about review articles, but I don't think that there is a great summary that goes over all these different things, although there may be that resource on the BCAN

website that I'm not aware of. So, again, kind of thinking about treating patients as a map in our mind. Those with localized bladder cancer, no evidence of any lymph nodes on a scan, and if they have any of these high-risk features we really don't think that they're a good candidate for chemoradiotherapy ... If they don't have any of these then we need to talk about, "Okay, you're a good candidate for chemoradiotherapy."



Induction therapy and radiation would be chemotherapy before if the patient is suitable for that. And then the other thing is that once we go down the path of doing radiation and chemotherapy, at least in some centers and for selected patients, there is a stop in the middle where urologists will go back inside the bladder to make

sure that the intent that we have, which is eradicating the tumor, is happening. If halfway or three-quarters of the way through treatment it doesn't look like the tumor is shrinking down, or worse, if the tumor looks like it's growing despite the treatment that we're doing, then we think it doesn't make sense to complete this therapy to try and save the bladder because that tumor is going to grow through the bladder. And so, if there really is no evidence that the tumor is melting away, then we would leave this path of trying to save the bladder and go on to cystectomy.

So, there have been a couple of studies. So, most of the studies in looking at radiation with bladder cancer are a little bit smaller and at smaller sites. But this is a nice article, published back in 2014, looking at a bunch of sites kind of put together. So, looking at multiple prospective studies altogether, you pull the data to see if we can get additional information. So, multiple different clinical trials with a total of 468 patients, all using cisplatin-based chemotherapy as a radiosensitizer, and all patients have this muscle-invasive disease, because some selected patients with T1 or non-muscle invasive disease will sometimes get radiation. And looking at different endpoints, this is just summarizing the different chemotherapies that people got, sometimes getting treatments twice a day with radiation therapy, different chemotherapy regimens that were really mixed in there.

I think one of the important things to look at when we're looking at ... And I think it's challenging to compare radiation series with chemotherapy series, but I think one of the important things to look at is, sometimes the age of patients, if they're a little bit older those patients sometimes will have more medical problems. But the other thing is, the majority of the patients in this study really had just this muscle-invasive disease and not more locally advanced disease. And then the number of patients that had that hydronephrosis was small. So, these are really not patients that had this no high-risk features. Those patients that had T2 disease in the blue versus T4 disease, T3 and T4 disease, tended to do better

longterm in terms of overall survival and then what's called disease-specific survival, people who lived but had their bladder cancer come back.

Outcome	No. of Patients	5 Years			10 Years		
		Estimate (%)	95% CI (%)	No. of Patients at Risk	Estimate (%)	95% CI (%)	No. of Patients at Risk
Local failure, any	212	43	39 to 48	146	46	43 to 53	39
Local failure, muscle invasive	86	13	10 to 17	191	14	10 to 17	52
Local failure, non-muscle invasive	156	31	27 to 36	162	36	32 to 41	44
Nodal recurrence	66	13	10 to 16	199	16	12 to 19	54
Distant metastases	153	31	27 to 36	186	36	30 to 39	53
Disease-specific survival	150	71	67 to 75	205	65	61 to 70	57
Bladder-intact disease-free survival	282	56	51 to 61	173	55	50 to 60	45
Overall survival	282	57	52 to 61	205	36	31 to 42	57

- 5yr OS 57%, 10yr OS 36% (similar to cystectomy series) though these are highly selected populations
- Bladder preservation rate of 80% at 5 years in highly selected population

And those that completely had the tumor melt away was the multimodality treatment, of course, did better than those that had a tumor that was refractory to that treatment. And then, in terms of the five-year overall survival, 57% arrived at five years. The 10-year overall survival was a little bit lower, but again, we're talking

about patients who were older even at the time of entry into the study, and broader preservation rate at 80%, meaning that 20% of the patients still had to have their bladder removed at the end of surgery, again, in this very highly selective group of patients. So, I think really that there are studies definitely supporting trimodality therapy, and that in selected patients who are motivated it definitely can be the right choice.

This is a more modern study published in The New England Journal in 2012, looking at radiation therapy with a different combination of chemotherapy. This is looking at 5-fluorouracil mitomycin versus chemotherapy alone. In the interest of time I will show you the overall results. So, the two-year recurrence-free survival, getting chemotherapy was 67%, versus 54% just getting radiation therapy alone. The local control rate was higher and a trend to reduction and cystectomy, meaning that the patients who didn't have to have a salvage cystectomy was much lower getting chemotherapy. Overall survival was 48% versus 35%. So, this combination of 5-fluorouracil and mitomycin can be given in a little bit of a frailer population of patients, so that's another option that's been afforded to us based on that clinical trial.

In terms of side effects of radiation combined with chemotherapy, this is just looking at one series from Massachusetts General Hospital. Patients who've had treatment with broader preservation followed up for over six years. Most of them were thought to have bladders that had normal capacity, normal flow. Most of the patients in this series didn't really feel like they had urgency or if they had it was very manageable. 25% had occasional to moderate bowel control symptoms, so one of the side effects of diarrhea that can be long-lasting, and 50% of men had some degree of erectile dysfunction. This is also something that's seen with radical cystectomy patients, so I think that's just really just to compare here.

In terms of the person who asked about summaries, one place to look for summaries if you're savvy with either looking on the internet or the Google Scholar, getting into PubMed, is really looking at review articles that do things like this, which is put all the studies together. Not compare them head to head, but just give you a sense of the stage of tumor that was looked at, the number of patients that were in

the trial, the dose of radiation, which is going to be slightly different. Did they get chemotherapy? Big doses of chemotherapy before they had treatment and some that did and some that didn't. What was the radiosensitizing drug? Did they get chemotherapy afterwards? So, I think this is one of these nice summaries that just helps us all better understand the landscape of the data studies that have been done in this space.

Your Questions - Chemotherapy for cystectomy :



- When will systemic chemo be applied in micrometastasis (the finding of circulating tumor cells while still classified as NMIBC)?
- When is chemotherapy used? Is Keytruda an allowed drug as with some others for chemo mix? Can a patient ask for specific chemo drugs?
- If you have tolerated second line chemo well, how long can you keep taking it? What about long term low-dose chemo?

I'm going to move on to recurrent and metastatic bladder cancer, the disease that's gone to the outside of the bladder into other parts of the body. So, one question is, "When will systemic chemotherapy be applied in micrometastasis or circulating tumor cells?" I think this is a good question as of right now. Circulating tumor cells for

bladder cancer as far as I know are really a research-based study and not part of a standard of care. Again, will that change in the future? It potentially could, but as of right now that's not a part of a standard of care. "When is chemotherapy used in this study, and is Keytruda, which is pembrolizumab, one of the checkpoint inhibitor therapies, an allowed drug, as with some others, and can you mix that with chemotherapy? And can a patient ask for a specific chemotherapy?"

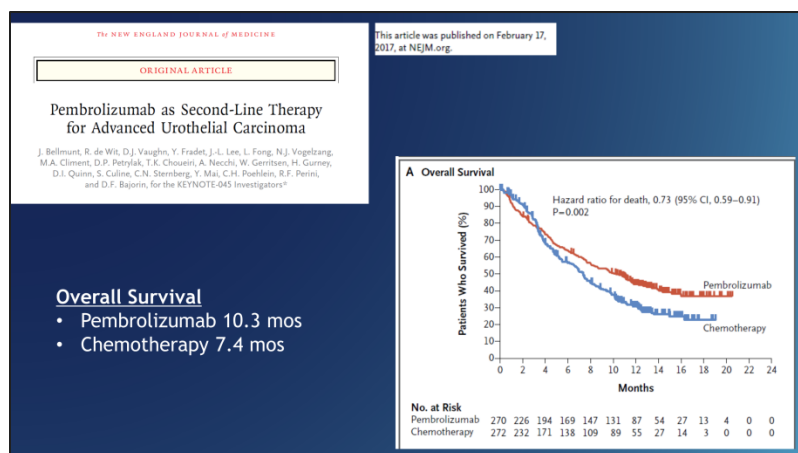
I think the answer is yes. All the things that we do are shared decision-making, but as a doctor we have to present ... If there are options, why are there ... What's the information behind the option, and based on getting to know a patient, what is going to be the best treatment for them. And someone else asked, if you can tolerate a second line of therapy, well, how long can you keep taking it? And then what about long-term low-dose chemotherapy? And I think that this question, the answer to this question can change depending on the mode of therapy. Chemotherapy drugs, like paclitaxel and docetaxel that were previously given in the second line and beyond setting, those drugs really had a ceiling in terms of how much a person could tolerate.

Over time, you'd see a decrease in blood counts, peripheral neuropathy would build and become cumulative and it just didn't make sense to keep on chemotherapy anymore. Immunotherapies, as of now, when patients go on immunotherapies, they go on cycle treatments and tend to not stop unless they have progression or intolerable side effects. I guess the answer to this question is really, in evolution. Patients with metastatic disease are not all alike, and I think that tumors that are involved just in the lymph nodes, sometimes we tend to find that based on how somebody feels with metastatic disease in addition to where the disease is in the body, can change the outcomes, so that it's not a one-size-fits-all approach.

This is looking at ... A little bit further up, is a chemotherapy study of gemcitabine and cisplatin versus

MVAC. The response rates in the MVAC arm of this are really impressive. The overall response rate is 54%, and that's really dramatically different than we're seeing in the front line in immunotherapy. So, even though we're quite excited about the use of immunotherapy and what all the different possibilities are, it's still very important to recognize that cisplatin-based chemotherapy, and I have shown these slides before, the outcomes that we get from this are very robust and in some patients it can be durable. What about those patients who progress after getting cisplatin-based chemotherapy? So, prior to immunotherapy coming on, getting FDA-approved, the only drug that was approved was this one called Vinflunine, approved in Europe.

It really didn't seem to be different than really just good medical care. There have been multiple different studies, and this not at all an exhaustive list of other kinds of chemotherapy given beyond platinum but none of which that have shown a really impressive overall response rate and overall survival on those drugs that's really different. And so, here is really where the game changer is, and again, another BCAN webinar covered this in much more detail, so that's why I'm going to go quickly through this looking at pembrolizumab, which is a checkpoint inhibitor therapy. It's a second-line therapy for advanced urothelial carcinoma testing chemotherapy.



So, all the patients on this trial had gotten either perioperative cisplatin-based chemotherapy or chemo for metastatic disease, and these patients were randomized to get either pembrolizumab once a week for three weeks, or paclitaxel, docetaxel, or vinflunine, and the patients that had the immunotherapy did better and lived longer than those who had

chemotherapy. And so, this is practice-changing. This drug improved overall survival. And the patients, this is called a swimmer's plot, so this is looking at times that patients stayed on the study, so those on the pembrolizumab group were able to stay on for a longer period of time, and these yellow dots are where they had their first radiographic assessment response. So, if people are going to respond they tend to do so fairly early.

Other drugs have been ... Five other drugs the FDA approved. For several checkpoint inhibitors the FDA approved, that all had done better than the historic 10% expected rate of control with chemotherapy and also have shown improvement in what would be expected in terms of overall survival. Just to finish up with our future direction, so you had questions about, "How does chemotherapy and radiotherapy work in conjunction with immunotherapy?" And, "Is systemic treatment ever done for preventative treatment?" Someone who was asking about their husband that had high-risk muscle invasive disease. So, hopefully in part that question was answered with the perioperative chemotherapy, but in terms of combinations, all the combinations that we have of combining immunotherapy with chemotherapy, or

combining immunotherapy with radiotherapy are in clinical trials.

Selected Post Consolidation Studies

- Phase Ib/II Study of Concurrent Durvalumab And Radiation Therapy (DUART) Followed by Adjuvant Durvalumab in Patients With Urothelial Cancer (T2-4 N0-2 M0) of the Bladder: Big Ten Cancer Research Consortium BTCRC-GU15-023
- A Phase II Open Label Single Arm Study of Adjuvant Nivolumab Following Chemo-Radiation in Localized Muscle-Invasive Bladder Cancer (NEXT)
- A Study of Atezolizumab Versus Observation as Adjuvant Therapy in Participants With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection [IMvigor010]

Will that be practice-changing and get out to the general population and become a standard of care, that question is still to be answered, but we are asking these questions all the time, and doing so quickly. So, just some selected preoperative combination trials to give you an idea of what's already out there, so there's a preoperative trial combining that pembrolizumab with gemcitabine and

cisplatin, or just gemcitabine alone if someone can't get cisplatin that's prior to cystectomy. There is also a study of pembrolizumab alone prior to cystectomy for patients with muscle-invasive disease. For patients with advanced bladder cancer, recurring or metastatic, there are multiple studies looking at the difference between either immunotherapy alone, or immunotherapy combined with chemotherapy.

I think the furthest alone is this one called the "DANUBE Study," looking a drug called durvalumab combined with an anti-CTLA-4 inhibitor, a different immunotherapy drug called tremelimumab, either alone or in combination versus chemotherapy, to see which one is better. We also want to look at toxicity profiles, so if one is not better than the other, well, is one more tolerable than the other? The same, looking at pembrolizumab combined with chemotherapy, pembrolizumab as well as durvalumab combined with chemotherapy. And then, finally, post-consolidation studies. So, postoperative or postradiation studies. There is a current study going on with durvalumab with radiation and then following radiation. And adjuvant or postoperative durvalumab following radiation as well as atezolizumab following bladder cancer surgery. This is not an exhaustive list, but it certainly gives you an idea of the clinical trials that are active that you may be interested in, and can potentially be involved in still.

BCAN would like to thank



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