Highlighting Clinical Trials | Muscle Invasive Bladder Cancer

Part I: The Basics of MIBC Clinical Trials

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BCAN Patient WEBINAR SERIES

Presented by:

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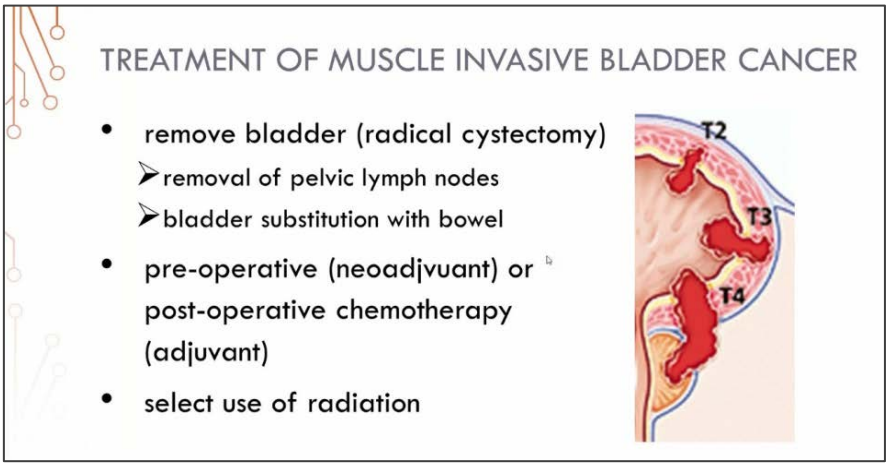
Dr. Black: The topic today is muscle invasive bladder cancer. We want to focus on what's going on in the field of clinical trials. I'm going to start with a bit of background just on how we treat muscle invasive bladder cancer. When we're talking about muscle invasive bladder cancer, of course, we're distinguishing that from non-muscle invasive bladder cancer, which was addressed in the last webinar in this clinical trial series.



Here, as the diagram shows, these are tumors that are going into the muscle or beyond. These are tumors that we typically treat with removal of the bladder. That's the mainstay of treatment. That's the radical cystectomy.

At the time of cystectomy, we will also remove lymph nodes, the pelvic lymph node dissection. Of course, we have to replace the bladder with a segment of bowel, whether it's a neobladder, an ileal conduit, or something else, like an Indiana pouch. It's really a three-part surgery.

This is sometimes preceded by chemotherapy, cisplatin-based chemotherapy, which we call neoadjuvant chemotherapy, or it can be followed by chemotherapy. If a patient goes straight to surgery and has a significant cancer at the time of surgery, we'll sometimes give chemotherapy afterwards.

Some patients, we will treat primarily with radiation, usually in combination with chemotherapy, if the patient's eligible to get chemotherapy. We sometimes refer to this as trimodal therapy because it

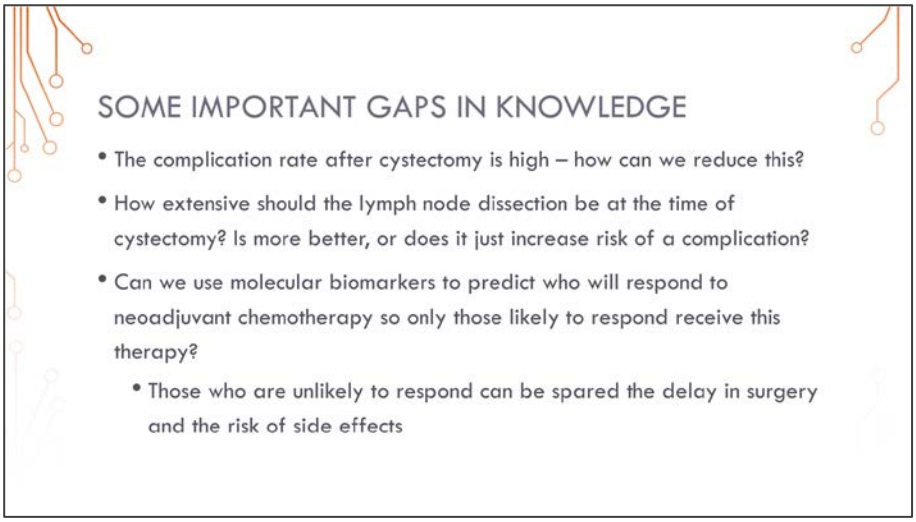
includes a transurethral resection, which is the initial biopsy of the tumor, followed by the radiation given together with chemotherapy. This is something that Parminder is going to focus on later.

Typically, we would reserve this for tumors that are maybe a little bit smaller and the patient has good bladder function. It's just a solitary tumor. There are some specific criteria we use to select these patients.

If we look at this general treatment domains for muscle invasive bladder cancer, it can highlight where the unmet needs are. We try to design trials, clinical trials, to address unmet needs.

With radical cystectomy, one of the big things is that it is associated with a lot of complications. It's major surgery. We would like to do what we can to reduce complications, to enhance recovery, and improve outcomes. I'll come back to a trial that is going on that addresses this issue.

Another important surgical question is how extensive should the lymph node dissection be at the time of radical cystectomy? Do we just remove a little bit of tissue or do we remove a lot of tissue? There's a feeling in the field that more is better and that we should do an extensive node dissection, more up to a point, of course. But there's a risk that it could just increase complications without being beneficial. In other cancer sites, trials have shown that it's not necessarily beneficial. This is another important question that we can ask with a clinical trial.

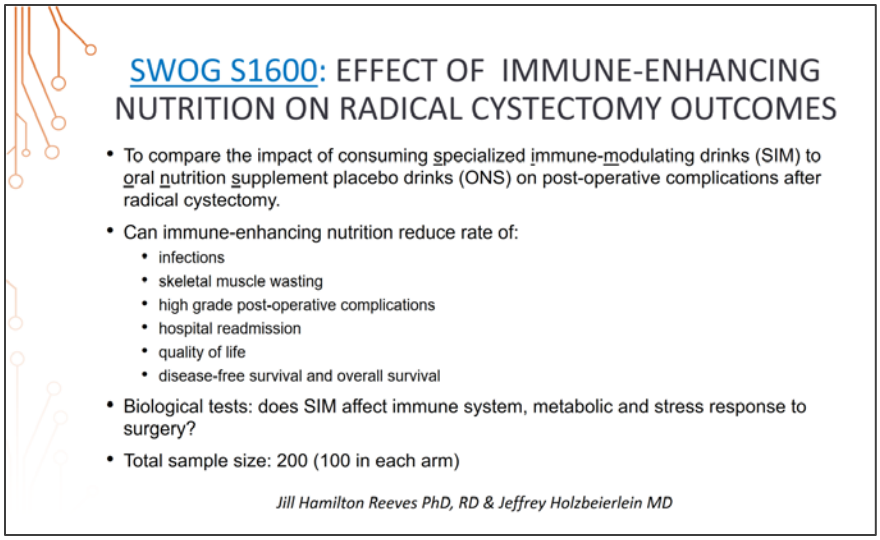


With respect to chemotherapy, we know that chemotherapy causes side effects. We know that patients generally aren't excited about receiving chemotherapy. We'd really only like to give it to patients who we expect will have a good response to chemotherapy. The best way to potentially identify patients who will benefit is with biomarkers, especially molecular biomarkers.

There's a lot of work ongoing right now to develop biomarkers that will answer these important questions. If we can identify who's likely to respond, we would give those patients chemotherapy. Other patients would go straight on to surgery or radiation and would be spared both the side effects of the chemo and the potential delay in the surgery.

The first trial I would like to highlight fits in that first question of how can we improve outcomes and reduce complications and ultimately improve quality of life around the time of radical cystectomy. This is a SWOG trial, so it's a corporate group trial. All these trials have numbers. This is 1600.

This is a trial that's looking at a special nutritional shake that's to be taken before surgery for several days and after surgery. It has a special content, so special fatty acids and amino acids and other trace elements that are thought to enhance immune function and decrease the stress of surgery and improve outcomes would be the hope.



It's in this trial that the special immune modulating drink is going to be compared to a placebo drink. The main outcome that's going to be measured in the trial is the rate of postoperative complications after cystectomy. Also, the investigators were listed at the bottom there. Jill Hamilton Reeves and Jeff Holzbeierlein are the two principal investigators.

They will also be testing whether the immune modulating drink can reduce the rate of infections after surgery, muscle wasting. A lot of patients will experience not only weight loss but actual muscle wasting after surgery. The rate of high-grade complications, so not just minor complications but the more significant ones, the rate of readmission to the hospital. There'll be quality of life questionnaires. They'll even look at survival. Does something as simple as a special nutritional shake around the time of surgery actually enhance survival outcomes?

There'll also be some interesting biological tests that'll be done with blood, urine, and tissue in patients on this trial, where the investigators will look at actually how the immune system is responding to the drink versus the placebo, also the metabolic response and the overall stress response to surgery.

This is going to be a trial of 200 patients. Patients are going to be randomly assigned to one of two arms. There's a slide missing. It's a very simple trial design where one arm will get the shake, the other arm will get the placebo drink. It starts five days before surgery, it continues for five days after surgery. All these different endpoints are captured. Blood, urine, and tissue, as I mentioned, is investigated. I think there's also a bone density study after 30 days. This is a trial that is launching anytime now and will accrue across the US and Canada.

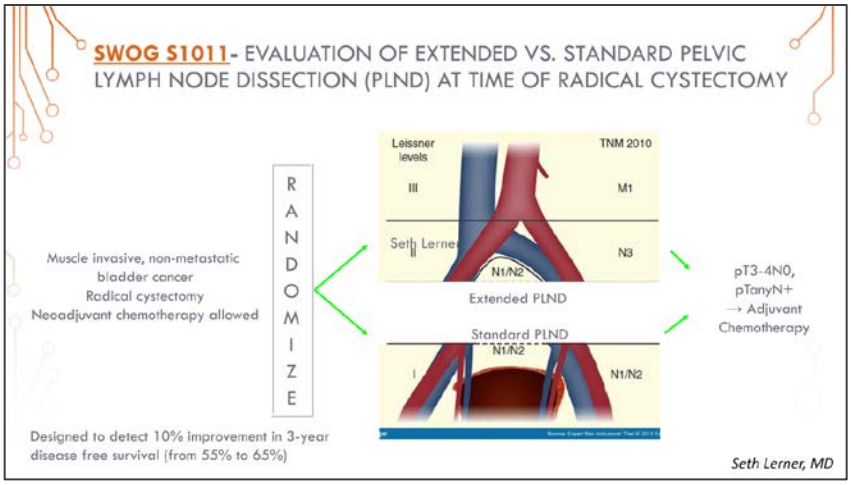
This slide here is SWOG S1011. This is a trial that has actually completed accrual. It's no longer open, but we're waiting for the results as more follow up information is gathered on the patients.

This is a trial that is looking at the extent of lymph node dissection, trying to determine what is optimal at the time of radical prostatectomy. We think if bladder cancer is spread to the lymph nodes that it's beneficial to remove it, and we can still cure patients with node dissection. If we remove more, we might be able to cure more is the basic idea.

This is a trial that includes any patient with non-metastatic muscle invasive bladder cancer, who was fit for radical cystectomy. They can or cannot have neoadjuvant chemotherapy, whatever the treating physician is able or wants to do. Then the randomized to either an extended or a standard node dissection.

You can see based on the anatomy here that the standard is just down in the pelvis. We talked about where the artery splits. This would be the split of the iliac artery into an external and an internal. We would define the standards that lymph node dissection is something below that towards the bladder. The extended dissection then goes all the way up to the ... This is the aorta here where it splits.

A lymph node dissection is really just a removal of fatty tissue around the blood vessels. The pathologist subsequently actually sifts through the tissue and identifies the lymph nodes. If we go a little bit higher, remove a little bit more, it could have a positive impact or it could have no impact and increased risk of complications, as I mentioned.



This is a key trial that has already enrolled approximately 650 patients. The outcome of the trial it's measuring is patient survival, disease-free survival after several years. The diagram indicates there that patients can also have adjuvant chemotherapy after surgery if they need to.

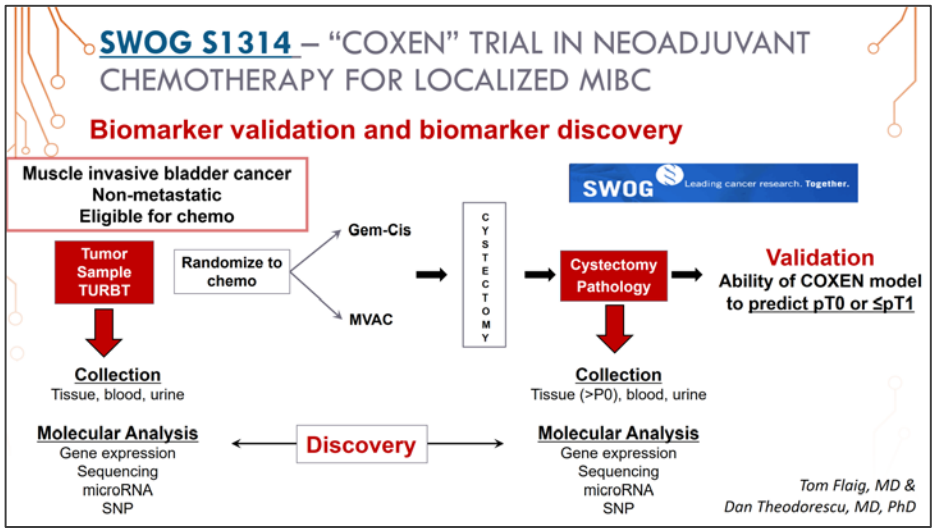
Since it's looking at a five-year endpoint, it takes several years of follow up before the trial's actually reported back to the scientific community and as well as back to patients. Sorry, it's a three-year disease-free survival.

Then another trial in the area of biomarkers is this trial that looks a little bit complicated. This is one that Tom Flaig in Colorado and Dan Theodorescu, who was also in Colorado, he's now at Cedar Sinai, they've led this trial. This is a trial where patients are really being treated according to the standard of care. They have a TURBT to remove bladder tumor. They are found to have muscle invasive bladder cancer, no metastasis. They have to be eligible for chemotherapy.

Then they're randomized to two different chemotherapies; although the trial is really not to compare the different chemotherapies, they just want to include both of them. I'll come back to that.

The patient then has surgery to remove the bladder. There's tissue available from that. There's tissue available from the original TURBT and, again, at the time of the cystectomy. We can measure the response to the chemotherapy. Is the tumor completely gone or is there still tumor left?

This response is going to be correlated to a biomarker that's called the COXEN biomarker, which is based on RNA expression in the tumor prior to chemotherapy. It's a special algorithm that uses this RNA data to predict whether the patient is likely to respond or not. That has been tested in other small series of patients, but this is now the prospective randomized trial to see if we can validate it in this trial.



At all-time points, so before chemo and after chemo, we'll have tissue, blood, and urine collected. We'll do all sorts of different tests, not just the COXEN mode. But, primarily, the trial is designed to validate the COXEN model to see if it really does predict pathologic stage. Then there's also this discovery component where new markers can be tested as well and not just the COXEN model.

Since the endpoint of this trial is the response to chemotherapy, which we really know at the time of cystectomy, this is not going to require long-term follow up. This trial also just finished accrual earlier this year, and the molecular analysis is ongoing. We may have initial results before the end of this year, where we'll see if the COXEN model adequately predicts outcome.

Again, as I highlighted earlier, if it did predict outcome efficiently, then we could spare chemotherapy in the patients who were predicted not to respond and we would prioritize chemo in those predicted to respond. Another very important trial.