Clinical Trials: Non-Muscle Invasive Bladder Cancer

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Part II

Presented by

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Dr. Svatek talked to you a little bit about the layers of the bladder and the staging, and it’s important to note as you can see on this slide, that the stages of the bladder cancer depends on the depth of invasion. When we talk about recurrence and progression, the most important factors are the depth of invasion and the grade of the cancer. Bladder cancer is either low-grade or high-grade.
One of the most difficult aspects of bladder cancer is its high propensity for occurrence and progression. When we talk about recurrence, we mean the same cancer comes back at the same stage and grade. If you had a noninvasive high-grade cancer, the cancer can recur as a noninvasive high grade, and that would be termed a recurrent. A progression though, means the cancer got worse. It either went from low-grade to high-grade or from a noninvasive to an invasive tumor. Low-grade tumors are mostly considered nuisance tumors in the sense that mostly they recur, which is a good thing, they very rarely turn into high-grade cancers and they very rarely progress to invasive disease.

Once you get to high-grade cancers though, the risk of invasion increases significantly and a noninvasive tumor might become invasive into the lamina propria as high as 40% of the time, and invade the wall of the bladder as much as 25% of the time. If it's already invading the lamina propria, in which case it's a T1 tumor. About a quarter of patients have that diagnosis at that stage of diagnosis, but these tumors are much more likely to recur and progress in a relatively short timeframe. Carcinoma in situ is also a high-grade noninvasive tumor. It's usually a flat tumor and it most often happens with other tumors in the bladder, and is also associated with a very high rate of recurrence and progression.

There are different ways for us as clinicians to identify risk factors for patients, and predict the likelihood of recurrence. That's based on primarily the number of tumors that somebody has, the size of the tumor, whether or not they've had many tumors in the past or whether or not this is the first tumor. Then the stage, whether or not they have invasion of the lamina propria, carcinoma in situ, and then finally the grade. This is an older grading system, 1, 2, 3. 1 is low grade, 3 is high grade, and 2 falls in between.
This is a figure, and what this shows is that if you take the different risk factors and you add them up, you can get a recurrent score, what is basically shows is that obviously those with the highest numbers, highest score, are at a very high risk of recurrence. You can see at 2 years as many as 80% on the very top curve. Even the patients who are very low risk, the solid dark line, have a risk of recurrence as high as 20% to 30% over the first five years.

There is no group of patients with what I would consider safe bladder cancer. The good news is that progression to muscle invasion is very rare, at least in the very low risk group, where you see a nearly flat line down there by the zero risk, 0%. Unfortunately the risk rises pretty quickly and as you have more risk factors, the risk of progression rises fairly dramatically. There’s some patients who are quite higher risk for progression, which is concerning.
As was mentioned earlier, we use treatments in the bladder to try to reduce the chance for recurrence and progression, and we wait for the bladder to heal from the initial resection, about 2 to 6 weeks, and then we give treatment primarily to patients at higher risk for recurrence. Those patients with carcinoma in situ, and rarely those patients who we cannot completely resect their tumor. Mostly this means intermediate and high-risk patients. Those patients with solitary low-grade tumors are such a low risk for progression that we usually spare them the side effects of the treatments in the bladder. The main treatments that we give are BCG, which is a live and attenuated form of tuberculosis.

**Adjuvant Intravesical Therapy**
- Intravesical therapies can also be applied adjuvantly (usually started 2-6 weeks after TURBT) to prevent the recurrence and progression of bladder cancer.
- **Indications**
  - NMIBC with high risk of recurrence
  - NMIBC with high risk of progression
  - Carcinoma in situ
  - Residual tumor (rare indication for small volume tumors, TURBT almost always preferred).
- Adjuvant intravesical therapy is reserved for intermediate and high risk patients

We don't know exactly how it works, and we've been using it though for over 40 years. The main way we think it works is by stimulating the immune response to fight bladder cancer. The alternative to that is chemotherapy, which works to kill cells and keep them from dividing. Interestingly enough though, there are many studies that have shown that BCG is superior to chemotherapy, largely because the chemotherapy does not get absorbed by the bladder wall. Even so it's quite effective at killing cells, if it can't reach them because they're deep to the lining, then it can't work well. BCG works in about 60%, 65% of patients initially and the chemotherapy about 30% to 40% of the time.

We're talking about clinical trials, and these treatments, these intravesical therapies are an important area where clinical trials have been very beneficial to us. Certainly we've been very appreciative that patients have been willing to participate in these trials. As I mentioned, when people started using BCG about 40 years ago, and even today we don't know exactly how it works, but we wanted to find out whether or not it's more effective than chemotherapy or not.
There have been many studies comparing BCG to giving different types of chemotherapy and whether or not you should use maintenance therapy. The bottom line is that through these clinical trials, we've been able to find out that not only does BCG work better than the chemotherapy, but it's important to do maintenance treatment. In fact, for high-risk patients it's important to not only do maintenance, but 3 years of maintenance at a full dose compared to reduced doses, which we use sometimes in patients with lower-risk disease or patients who are having a lot of side effects. We also know that based on trials, BCG is a first-line therapy for carcinoma in situ because it works twice as good as chemotherapy in the blood.

Why do we still need to do trials? The problem is that BCG doesn't work in everybody. You can see here in this graph that the blue columns represent what happens after the first cycle of BCG.

In other words, patients who have never gotten BCG before, it worked in about 77% of patients. Only 7% of patients developed invasive disease or metastases. In people who had gotten previously gotten BCG who recurred, and now you give them another cycle of BCG, you see the response rate goes down and the risk of invasive disease and metastases goes up. Finally you see that if you failed after two cycles of BCG or more, I should say the BCG failed you, you'll find that it only works 20% of the time by the time you give a third cycle. The odds of metastases goes up to 50%.

- BCG induction with maintenance has been shown to be better than epirubicin and mitomycin C in high risk patients.
- For intermediate risk patients, BCG and chemotherapy are similar in efficacy.
- A large clinical trial recently demonstrated the superiority of 3 years of full dose BCG over reduced doses in high risk patients.
- BCG should be considered first line therapy for CIS since the response rate is double that of chemotherapy.
After two cycles of BCG, we don't think that giving more BCG is a good idea if the cancers didn't respond because of the high likelihood that it won't work and that metastases will occur. The guidelines for patients who have a recurrence after BCG basically say that if you need to resect all of it and if you have lamina propria invasion, you might need to re-resect and make sure you don't have additional tumor. This is the point where we have a problem is that we should consider removing the bladder, because of the fact that our alternative treatments are not very good and giving more BCG is not very good.

There are options, obviously to give other intravesical therapies. This is where clinical trials might play an important role because we're trying to find out if we have other treatments that are effective so that we can avoid having to take out the bladder.

This is a somewhat complex figure, but what it shows you is that these are the national guidelines for patients who don't have a complete response to BCG. What you can see again is cystectomy or bladder removal is one of the top options. Changing agents is an option in some patients, but it's important to note that the guidelines recommend clinical trials as an important consideration for patients because we know that what we're doing right now is not good enough for many patients.
We still prefer to avoid removing the bladder if we can to spare some patients the decrease in quality of life. Just to let you know, why we want to avoid cystectomy is because there are obviously side effects. On the other hand, removing the bladder when the cancer is still confined to the bladder, is the best chance of cure. It's definitive treatment. You don't have to worry about recurrence and progression as much, but we worry about quality of life implications. The benefit of intravesical therapy is that you preserve the bladder. On the other hand, there is a chance that the cancer will progress or spread while you're trying to keep your bladder and trying other treatments, and you might end up dying of bladder cancer which could have been preventable.