GENITOURINARY CANCER IN FOCUS

Current Developments in the Management of Genitourinary Cancer

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New Treatments for Bladder Cancer

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H&O How common is bladder cancer?

NH Bladder cancer is very common in the United States; it is the fifth most common cancer diagnosed in this country. Each year, approximately 76,000 patients are diagnosed with the disease and approximately 16,000 patients die of it. I think that a lot of oncologists are surprised to realize just how common it is.

H&O What treatments are available for patients with early bladder cancer?

NH In approximately three-fourths of cases, bladder cancer is detected when it is still clinically located in the bladder. If the disease has not invaded the muscle, the urologist usually will perform a procedure called transurethral resection of bladder tumor (TURBT). Subsequent therapy depends on the risk category the patient falls into. Patients with low-risk cancer often can be managed by resection alone. Those who have intermediate- or high-risk cancer generally receive intravesical therapy using bacillus Calmette-Guérin (BCG), an attenuated strain of mycobacterium. BCG therapy has clearly been shown to decrease recurrences in patients with non–muscle invasive bladder cancer. It also has been shown to decrease the risk of progression to muscle invasion. BCG is typically administered once weekly for 6 weeks, after which patients receive maintenance therapy over the course of the next 2 years. A number of different schedules are used for maintenance therapy, but the most commonly used schedule in the United States is the one used in the SWOG 8507 trial.

For patients with non–muscle invasive bladder cancer who receive BCG and then develop recurrent non–muscle invasive disease, additional BCG or other intravesical-administered agents such as mitomycin C, valrubicin, gemcitabine, docetaxel, interferon gamma (IFN-γ), or interferon alpha (IFN-α) can be used.

Patients who experience a recurrence while receiving BCG maintenance therapy, after 2 prior exposures to BCG, or within 6 months of the last BCG treatment generally are deemed unresponsive to BCG. These patients are at very high risk for muscle invasive disease and even metastatic disease, so cystectomy—removal of the entire bladder—typically is performed in patients who are fit enough for surgery.

H&O What treatments are used in patients with early bladder cancer that has invaded the muscle?

NH Patients who are diagnosed with bladder cancer that has invaded the muscle—the muscularis propria level of the bladder—typically require more definitive local therapy than TURBT and BCG. The options for these patients include cystectomy and—in carefully selected patients—chemotherapy and radiation with bladder-sparing intent. Patients who are unfit for cystectomy or chemoradiation because of age or poor health may be able to receive aggressive TURBT in some cases.

Randomized clinical trials and meta-analyses support the use of cisplatin-based chemotherapy prior to cystectomy in patients who are eligible. In order to be eligible, patients need to have good functional status and

renal function, among other requirements. Dr Matthew Galsky and colleagues have spelled out the eligibility requirements for cisplatin use in these patients in recent publications.

H&O What reconstructive options are available to patients who have had cystectomy?

NH There are 3 generally accepted urinary reconstructive options. The simplest is a urostomy, in which the ureters are reconnected to a portion of the small bowel. The small bowel is brought up under the skin, and a stoma is created that drains into an adherent urostomy bag that the patient empties several times per day.

The second option is the creation of a continent urinary reservoir. In this option, the surgeon isolates a portion of the small bowel and separates it from the remaining small bowel, which is then reconnected. The isolated portion of the small bowel forms an internal reservoir. The ureters are connected to that reservoir, which is brought up underneath the abdominal wall. A small communicating stoma is created that the patient catheterizes several times per day.

The third option is the creation of a neobladder, in which the reservoir that has been created from the small intestine is moved down into the pelvis and the urethra is connected from below. With appropriate training and exercise in the postoperative setting, patients are able to maintain urinary continence.

The choice among these forms of urinary reconstruction is highly dependent on the size and location of the bladder tumor, so the urologist has to first determine which operation provides the best opportunity for complete removal of the patient's cancer and then consider which operation maximizes the patient's quality of life. If all 3 options are on the table, the urologist will discuss the pros and cons of each with the patient before creating a surgical plan.

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H&O What treatments are available for patients with advanced bladder cancer?

NH For many years, the mainstay of initial treatment for metastatic bladder cancer has been chemotherapy. This is based on studies from the early 1990s in which combination cisplatin-based chemotherapy was shown to be more effective than single-agent cisplatin therapy. One of these trials, which was published by Loehrer and colleagues in the *Journal of Clinical Oncology* in 1992, found that a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) improved overall survival compared with cisplatin alone. In another trial, published by Logothetis and colleagues in the *Journal of Clinical Oncology* in 1990, M-VAC treatment improved survival over treatment with cisplatin, cyclophosphamide, and doxorubicin.

Although M-VAC was highly effective, it also was quite toxic. This was especially problematic when we did not have granulocyte-macrophage colony stimulating factor (GM-CSF) to reduce the risk of infection. I also think that the level of skilled nursing for these urologic cancers was not where it is today.

In 2000, a study by von der Maase and colleagues was published that compared cisplatin/gemcitabine with M-VAC. Although the trial did not find the 2-drug combination to be superior to the 4-drug combination, the toxicity profile was preferable, and it became a commonly used regimen. Two of the most common side effects with M-VAC are mucositis and neutropenic sepsis, whereas the cisplatin/gemcitabine regimen tends to produce thrombocytopenia.

At this time, no other chemotherapy regimens, targeted therapies, or immunotherapies have demonstrated superiority to M-VAC or cisplatin/gemcitabine as frontline treatments. A phase 3 trial of cisplatin/gemcitabine/bevacizumab vs cisplatin/gemcitabine alone in patients with advanced urinary tract cancer finished accrual about a year and a half ago, so we will see what those results show (NCT00942331).

H&O Could you discuss the recent approval of immunotherapy for bladder cancer?

NH The US Food and Drug Administration (FDA) recently approved the anti–programmed death ligand 1 (PD-L1) monoclonal antibody atezolizumab (Tecentriq, Genentech) for patients with metastatic urothelial carcinoma that has progressed on a platinum-containing chemotherapy regimen.

Approval was based on the large, single-arm, phase 2 IMVigor 210 trial (A Study of Atezolizumab in Patients

With Locally Advanced or Metastatic Urothelial Bladder Cancer). The results appeared in the *Lancet* in March 2016, with Dr Jonathan Rosenberg as the first author. The objective response rate to atezolizumab was 15% for all 310 patients, and 26% among those with high PD-L1 expression. The side effect profile was very favorable, with grade 3 or 4 treatment-related adverse events—the most common being fatigue—affecting just 16% of patients. This is much lower than with chemotherapy. Grade 3 and 4 immune-mediated adverse events occurred in 5% of patients and included pneumonitis, increased aspartate aminotransferase, increased alanine aminotransferase, rash, and dyspnea.

> The fact that we saw so few advances in the treatment of bladder cancer over the past 20 to 30 years has made it an area rich for opportunity in drug development.

Other ongoing randomized phase 3 trials are looking at atezolizumab and other immunotherapy agents vs traditional chemotherapy following the use of platinum agents. We eagerly await the results of these trials over the next 1 to 2 years. The availability of immunotherapy has been the biggest change in the treatment of bladder cancer over the past few years.

H&O To what do you attribute the recent advances in bladder cancer?

NH A few things are happening right now. First, our understanding of the drivers of tumor biology has improved significantly over the last couple of years. The Cancer Genome Atlas (TCGA) results, which were published in *Nature* in 2014, gave us a roadmap for invasive bladder cancer in terms of genetic mutations and the molecular subsets of bladder cancer. This led to our ability to classify bladder cancer molecularly as either basal or luminal, so now we can design therapies and trials to address specific groups of patients with bladder cancer.

The second thing we have been seeing is encouraging results with immunotherapy across a number of different malignancies, including urothelial cancer. This advance has accelerated drug development across the board, and urothelial cancer has benefitted. Thanks to the use of BCG for non–muscle invasive bladder cancer, we already know a lot about the tumor immunology of bladder cancer—which is helpful as we develop the use of checkpoint inhibitors in bladder cancer.

Finally, the fact that we saw so few advances in the treatment of bladder cancer over the past 20 to 30 years has made it an area rich for opportunity in drug development.

H&O Are any drugs being developed specifically for nonurothelial carcinoma?

NH Although a couple of clinical trials are starting to look at nonurothelial histologies, there are not any drugs right now that have an indication for nonurothelial disease. Nonurothelial carcinoma is rare; approximately 85% to 90% of bladder tumors contain a component of urothelial carcinoma.

H&O What ongoing studies in bladder cancer would you like to call attention to?

NH Regarding advanced disease, we are beginning to see more trials of combination therapy: everything from combination immunotherapy to immunotherapy plus chemotherapy to immunotherapy plus targeted therapy.

For example, the BISCAY trial (Open-Label, Randomised, Multi-Drug, Biomarker-Directed, Phase 1b Study in Patients With Muscle Invasive Bladder Cancer) will be looking at the PD-L1 inhibitor durvalumab plus a fibroblast growth factor receptor (FGFR) inhibitor or poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor in metastatic urothelial cancer (NCT02546661). The study is designed to match tumor biology with appropriate targets in this immunotherapy era. Although accrual will take a couple of years, we stand to learn a lot from this trial.

In the setting of muscle invasive disease, which provides a good opportunity to learn about the ability of biomarkers to predict response or resistance, a couple of adjuvant clinical trials are enrolling patients who have had a cystectomy. In particular, a trial being led by Dr Andrea Apolo called the AMBASSADOR trial is looking at the use of adjuvant pembrolizumab (Keytruda, Merck) in patients with high-risk resected urothelial carcinoma. This will be an important trial because it is looking at patients who have already had definitive surgery to see whether we can push the cure rates higher.

Here at Johns Hopkins, we are about to launch an innovative trial in the neoadjuvant setting in which we will be giving immunotherapy alone to patients who are

ineligible for cisplatin-based chemotherapy. We will be randomly assigning patients to receive the programmed death 1 (PD-1) inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) alone or in combination with urelumab, an experimental monoclonal antibody that targets 4-1BB.

Finally, a number of trials are now being launched in the setting of non–muscle invasive bladder cancer that are looking at the use of checkpoint inhibitors in patients whose disease does not respond to BCG treatment. A SWOG trial that will be led by Dr Peter Black will be looking at atezolizumab in that setting (NCT02844816), and another trial will be looking at pembrolizumab in the same setting.

Another group of trials that hinge on the TCGA data are being carried out in the metastatic setting. Several trials are looking at FGFR inhibitors in patients with urothelial cancer who have genetic alterations in fibroblast growth factor receptor 3 (FGFR3). One of these trials is looking at the Novartis drug BGJ398 (NCT02160041), and another is looking at the Janssen drug JNJ-42756493 (NCT02365597). These trials are unique because they require up-front sequencing of the patient's tumors in order to determine eligibility. We have seen some initial results from phase 1 trials with these agents, so we know that they are active. Now they are working to recruit a much larger patient population to determine whether they might be eligible for FDA approval.

Disclosures

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Suggested Readings

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