Bladder cancer is more common than generally appreciated; 62,240 new cases and 12,710 deaths were expected in the United States in 2004 (Jemal et al., 2004). Patients typically present with either microscopic or gross hematuria. Bleeding from a bladder tumor is generally intermittent. Therefore resolution, either spontaneously or after antibiotic treatment for presumed bladder infection, does not reduce the need for urologic evaluation. Diagnostic studies most commonly used are intravenous urography, urine cytology, and cystoscopy. Fortunately, about 80% of patients present with superficial disease that can be successfully treated surgically (Lamm, Griffith, Pettit, & Nseyo, 1992). Effective treatment plans can lead to high survival rates. The goals of treatment are (a) reduce tumor recurrence, (b) lower the risk of disease progression, and (c) improve survival. Preventing progression to muscle-invasive disease is key, because only 50% of these patients will survive 5 years even with aggressive surgery (cystectomy) (Dalbagni et al., 2001). Prognosis, as noted later, is also highly dependent on grade.

Historically, two-thirds of patients have tumor recurrence within 5 years, and nearly 90% have recurrence by 15 years (Lamm & Griffith, 1992). Two factors best predict recurrence: (a) history of previous recurrence, particularly if within 3 months, and (b) the presence of multiple tumors. Solitary tumors recurred in 51% of patients, while those with recurrent tumors or multiple tumors had recurrence rates of 91% (Heney, 1992). As few as 20% of patients who are disease-free at 3 months will have tumor recurrence within 5 years. Invasion of the stroma (lamina propria) increases the risk of invasion into the bladder muscle from 4% to 30% (Vicente, Laguna, Duarte, Algaba, & Chechile, 1991). High-grade tumors have a significantly worse prognosis. In the National Bladder Cancer Group study, only 2% of patients with low-grade disease-free at 3 months will have tumor recurrence within 5 years.
grade (grade I Stage Ta) tumors had progression to muscle invasion, compared with 48% of patients with high-grade (grade III Stage T1) tumors. The presence of carcinoma in situ (CIS) signifi cantly worsens the prognosis of high-grade disease, increasing progression risk from 10% to 65% in one study (Bostwick, 1992). The best predictor of death from superficial bladder cancer is the presence of high-grade disease. Mortality for low-grade tumors was 6% compared with 21% for high-grade tumors (Heney, 1992).

The European Organization for Research and Treatment of Cancer (EORTC) divided superficial bladder cancer patients into low, intermediate, and high-risk groups based on their experience with thousands of patients enrolled in prospective studies. The authors’ experience corroborates that — low-risk patients are those with solitary grade I Stage Ta tumors; intermediate-risk patients are those with multiple or recurrent grade I Stage Ta tumors, or grade II Ta tumor(s) (single or multiple); high-risk patients are those with one or more of the following: grade III disease (high-grade, in the new terminology), lamina propria (T1) invasive disease, CIS, or recurrence at 3 months.

DIET, LIFESTYLE, GENETIC, AND ENVIRONMENTAL RISK FACTORS

Smoking has long been recognized as an important risk factor for bladder cancer, but only recently has the importance of smoking cessation been demonstrated. One study reviewed 286 patients, including ex-smokers, patients who quit smoking at the time of diagnosis, and patients who continued to smoke. Ex-smokers presented at a later age, had an improved recurrence-free survival compared to quitters and current smokers (p<0.03), and most importantly, had a higher progression-free survival (p<0.01) (Flesher et al., 1999). Therefore, early smoking cessation is not only effective at preventing recurrence of superficial bladder cancer, it is also the least toxic and most cost effective option (Chen, Su, Guo, Houseman, & Christiani, 2005).

Genetic predisposition is clearly a factor in the development of bladder cancer, but familial occurrence is rare. Environmental factors impact DNA to modify tumor suppressor genes (p53), genes controlling cell proliferation (Rb), growth factor genes (erbB-2), and others (p15, p16). Chemical carcinogens are thought to account for 20% of bladder cancers in the United States.

Dietary factors are also potentially important in bladder cancer. Diets low in vitamin A and low serum carotene levels are associated with increased risk of bladder cancer. Multiple animal studies and two clinical trials demonstrated that vitamin A derivatives reduce the development and recurrence of bladder cancer. Pyridoxine (vitamin B6) is reported to enhance tumor immunity in animals. B6 was as effective as thiotepa (discussed later) in reducing bladder cancer recurrence after 1 year, but subsequent studies failed to confirm its benefit (Byar & Blackard, 1977). Vitamins C and E may reduce patient’s risk of developing bladder cancer but studies are inconsistent. Evidence for anti-tumor activity also exists for folic acid and vitamin D (Kamat & Lamm, 1999). Finally, a vitamin preparation containing high doses of vitamins A, B6, C, and E demonstrated in a randomized clinical trial to reduce tumor recurrence significantly, and is commercially available as Oncovite® from Mission Pharmacal (Lamm et al., 1994).

Intravesical Chemotherapy

Four intravesical drugs are available and commonly used as chemotherapy in the United States with one more that has been studied and used, but is currently not available. Randomized trials have failed to demonstrate that any of the chemotherapies — thiotepa, doxorubicin, mitomycin C, epirubicin, or the previously available valrubicin — is superior to the others. Randomized trials also failed to show that chemotherapy reduces progression or reduces mortality. The EORTC/MRC meta analysis showed a long-term reduction in tumor recurrence of 6%, but no reduction in disease progression or mortality (Pawinski et al., 1996).

Since the side effects of chemotherapy are generally less than bacillus Calmette-Guerin (BCG) immunotherapy, chemotherapy is the treatment of choice for low-risk patients (see Table 1). Patients who fail to respond to alkylating agents (thiotepa or mitomycin C) may be best treated with an intercalating agent (doxorubicin, epirubicin, or valrubicin) and vice versa.

Data now clearly show that...
and proportional to drug chemotherapy, response is proportional to drug concentration and duration of exposure. Since duration of exposure is limited by bladder capacity, and increased urine output reduces drug concentration, overnight dehydration is recommended prior to drug instillation. Patients are generally asked to retain the instilled drug for 2 hours. Care must be taken to completely empty the bladder prior to instilling chemotherapy. An ultrasound of the bladder after insertion of a catheter is useful in confirming complete emptying, since, surprisingly, catheterization does not reliably empty. This was objectively determined by Au et al. (2001). It resulted in a protocol that required confirmation of bladder emptying with a bladder scan prior to intravesical mitomycin instillation into the bladder for all patients. We recommend that patients lie prone for 15 minutes to displace the air bubble introduced with the catheter, thereby ensuring contact at the bladder dome.

**Available intravesical chemotherapies: Thiotepa.** The standard dosage of thiotepa is 30 mg in 15 cc sterile water. When given as a single instillation at the time of tumor resection, an exposure of 30 minutes is used. When not given in conjunction with tumor resection, doses of 30 mg to 60 mg are used in 15 cc to 30 cc of sterile water and held for 2 hours. Treatment is given weekly for 4 to 8 weeks, depending on volume of residual disease. When repeated treatments are used, blood counts should be obtained, since thiotepa has a molecular weight of 188 and drugs with molecular weight less than 300 are more readily absorbed from the bladder. Liver function studies are not required, since the primary toxicity of thiotepa is due to myelosuppression. The intravenous dose of thiotepa is 0.5 mg/kg, so a single treatment is safe even if, as is common with large tumors and recent resection, 100% absorption occurs.

Thiotepa has been used in many body cavities, including the peritoneum. Unlike most other chemotherapies, which are caustic, thiotepa can be instilled safely in the bladder even if perforation has occurred. Thiotepa can also be instilled in the bladder in patients who are undergoing cystectomy or partial cystectomy to reduce the risk of wound seeding. Thiotepa generally causes little or no symptoms of cystitis. For these reasons, this is the chemotherapy of choice at the authors’ facility. Studies suggest that a single instillation reduces the risk of tumor recurrence by about 20%.

**Doxorubicin.** The standard dosage of doxorubicin is 50 mg in 25 cc of sterile water. As with other chemotherapies, optimal response occurs when given as a single instillation at the time of tumor resection. An exposure of 30 minutes is used when given at the time of surgery. When given to treat existing disease rather than prevent recurrence, treatment is held for 2 hours, and given weekly for 4 to 8 weeks, depending on volume of residual disease. Side effects include irritative bladder symptoms and,

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**Table 1. Efficacy and Toxicity Comparisons of Intravesical Therapy in Bladder Cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>CR CIS *</th>
<th>Recurrence Reduction</th>
<th>Toxicity and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>72%-84%</td>
<td>40%</td>
<td>Cystitis: 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fever/chills: 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BCG infection: 1%</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>52%</td>
<td>14%</td>
<td>Myelosuppression: 0-10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cystitis: 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rash: 6%</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>48%</td>
<td>16%</td>
<td>Cystitis: 26%</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>73%</td>
<td>20%</td>
<td>Decreased capacity: 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anaphylaxis: Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cystitis: 10%-37%</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>28%</td>
<td>17%</td>
<td>Myelosuppression: 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cystitis: 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Azoospermia: Rare</td>
</tr>
</tbody>
</table>

*Carcinoma in situ
very infrequently, decreased bladder capacity.

Mitomycin C. The standard dosage of mitomycin C is 40 mg in 20 cc sterile water. Contra-indications include hypersensitivity, bladder perforation, myelosuppression, and thrombocytopenia. The main side effects are skin rash, irritative bladder symptoms, bladder calcifications, and myelosuppression.

While mitomycin C is highly effective, like doxorubicin it should never be given if bladder perforation is suspected. In a randomized study, recurrence was nearly cut in half by using an optimized schedule: 40 mg/20 cc (compared with 20 mg/20 cc), overnight dehydration, ultrasound-confirmed complete bladder emptying, alkalinization using 1.3 g of sodium bicarbonate the night before, morning of, and 30 minutes prior to treatment. Mitomycin C is inactivated by acid urine (Au et al. 2001).

Recent studies also suggest that local hyperthermia, which can be obtained with a microwave applicator inserted into the bladder with a special catheter (not available in the United States), can also enhance the efficacy of mitomycin C, albeit with a significant increase in systemic absorption. Myelosuppression is the primary systemic toxicity of mitomycin.

Epirubicin. Epirubicin is a very popular intravesical drug in Europe. Standard dosage is 80 mg in 40 cc sterile water. The main side effects are irritative bladder symptoms. Systemic absorption is minimal, but systemic administration is associated with myelosuppression, cardiomyopathy, congestive heart failure, and arrhythmias. Like doxorubicin, mitomycin C, and valrubcin, epirubicin is a vesicant and will result in necrosis with extravasation. Best results occur with immediate postoperative instillation, but instillation should not be done if bladder perforation or any risk for extravasation is present, since this would put the patient at risk for peritonitis.

Valrubcin. Valrubcin was specifically approved for BCG-refractory carcinoma in situ of the bladder, where it is effective in about 20% of patients. The standard dose is 800 mg in 75 mL normal saline weekly for 6 weeks. However, valrubcin is currently not available in the United States.

Intravesical Immunotherapy

Like chemotherapy, immunotherapy for superficial bladder cancer is instilled in the bladder with the goal of eradicating existing disease, reducing disease recurrence and progression, and improving patient survival. Immunotherapy has very little else in common with chemotherapy. It is important, therefore, to keep the anticipated treatment schedules, side effects, and results separate (see Table 1). Cytotoxic chemotherapy directly kills cancer cells, while immunotherapy generally stimulates the patient’s immune response. Increasing the dose of chemotherapy results in increased cancer cell killing. However, increasing immunotherapy beyond the effective dose will begin to suppress the patient’s immune response.

Chemotherapy penetrates the bladder by diffusion down a concentration gradient, while BCG immunotherapy attaches by means of specific receptors. Such differences have important clinical consequences. While chemotherapy is best given immediately at the time of tumor resection, immediate immunotherapy does not reduce tumor recurrence, and in the case of BCG, can result in life-threatening toxicity. Maintenance chemotherapy has not improved results, but maintenance BCG immunotherapy not only reduces recurrence, but also appears to be required to reduce disease progression. Surprisingly, low-grade urothelial carcinoma is relatively more responsive to chemotherapy than high-grade carcinoma. In contrast, with BCG immunotherapy, low-grade tumors appear to be relatively less responsive. Therefore, chemotherapy is used initially in low-grade disease, where the risk of progression is very low and the side effects and cost of a single postoperative treatment are also appropriately low.

Available intravesical immunotherapies: BCG immunotherapy, BCG, or bacillus Calmette-Guerin, is an attenuated form of the bacterium Mycobacterium tuberculosi, used to prevent tuberculosis. It is a potent immune stimulant. The standard dose of BCG is 81 mg for TheraCys® and 55 mg for TICE®, both in 50 cc physiologic saline. Treatment should be postponed for at least 1 to 2 weeks following tumor resection or bladder biopsy. A purified protein derivative (PPD) test may be performed as the response and side effects vary according to PPD status. Those with a positive PPD will have a more vigorous and accelerated response, with more hypersensitivity. Treatments are repeated weekly for 6 weeks, with dose reductions to 1/3, 1/10, 1/30, or 1/100 as needed to prevent increasing or severe symptoms of bladder irritation. Three additional instillations, given at 3 months (6 weeks after completion of the initial 6-week course) increase the complete response in CIS from 56% to 84%. Maintenance BCG, using up to 3 weekly instillations in disease-free patients given at 3, 6, 12, 18, 24, 30, and 36 months, decreased 7-year recurrence in high-risk patients from 52% to 25% and significantly reduced disease worsening. However, since only 16% of patients received treatment at each scheduled interval, it is clear that a reduced treatment regimen may be appropriate, and in
our hands, the 30-month maintenance dose is now omitted in many patients. It is also clear that the risk for recurrence and progression lasts for decades. Therefore, based on what is known of the long-term risk of disease progression with CIS or high-grade disease, we continue 3-week maintenance at years (counting from the start of treatment) 4, 5, 6, 8, 10, and 12 for patients with CIS or high-grade disease.

The primary side effects of BCG are increased urinary frequency, dysuria, hematuria, and flu-like symptoms. Systemic symptoms can include arthralgia/arthritis, rash, fatigue, fever, and systemic BCG infection, which can present as pneumonia, hepatitis, epididymitis, prostatitis, renal abscess, or sepsis. BCG is sensitive to ciprofloxacin and other fluoroquinolones as well as most antitubercular antibiotics, such as isoniazid, ethambutol, etc. Septic reactions should be treated with combination antibiotics including isoniazid and rifampicin as well as steroids. Steroids should be tapered gradually to prevent relapse.

BCG induces an anti-tumor response in bladder cancer by drawing lymphocytes and macrophages to the bladder and stimulating a cellular (TH1) immune response. Cytokines associated with this response result in symptoms of bladder inflammation and even flu-like symptoms. Patients who have a fever associated with BCG have a lower risk of tumor recurrence, but fever and increasing local symptoms can also herald a severe BCG reaction. Therefore, we have adopted the policy of reducing the dose of BCG in patients with increasing side effects.

The primary effect of BCG is local, at the site of administration. Patients with high-grade bladder cancer or CIS are at risk of developing malignancy within the prostatic urethra and upper urinary tracts. These patients require long-term followup with prostatic urethral biopsies and upper-tract ureteral washes, imaging studies, or ureteroscopy to prevent silent progression from disease in those sites.

**Interferon Alfa 2b.** Though not specifically approved for superficial bladder cancer, interferon alfa 2b has a response rate of 47% in CIS and 25% in papillary tumors. These results compare favorably with those of intravesical chemotherapy. The results in prophylaxis have been less favorable, but a recent study reported a reduction in recurrence from 68% to 28% (Papatsoris, Deliveliotis, Gianopoulos, & Dimopoulos, 2004). The primary advantage of interferon treatment is the absence of significant side effects. Doses as high as 1 billion units have been given intravesically without dose-limiting side effects (Turti et al., 1988). The standard dose is 50 to 100 million units weekly for 6 weeks. Additional maintenance treatments may be beneficial, but the ideal regimen is unknown. Based on the favorable experience with 3-week maintenance BCG, we have used this regimen for patients treated with interferon as well.

Interferon is remarkably non-toxic. Many patients who have major BCG reactions have long-term persistence of the organism within their systems. Interferon in combination with BCG appears to potentiate the effect of BCG. Therefore later use of interferon as a single agent may be very useful in potentiating these residual levels in BCG-intolerant patients.

**Combination Intravesical Therapy**

BCG immunotherapy has been combined with chemotherapy, primarily mitomycin C. These studies demonstrate no improvement in efficacy compared with BCG alone. Combination chemotherapy is now standard for patients with metastatic transitional cell carcinoma but has not been adequately studied in patients with superficial disease. Combination immunotherapy, specifically the use of BCG plus interferon alfa 2b, is highly effective. About 60% of patients who fail to respond to BCG can be rescued with BCG plus interferon (O’Donnell, Krohn, & DeWolf, 2001). The standard dose is 50 mg to 81 mg of BCG plus 50 million units of interferon alfa 2b. Treatments are given weekly for 6 weeks, with maintenance using up to 3 weekly instillations at 3 or 6 months, and then every 6 to 12 months. The dose of BCG is reduced to 1/3, 1/10, 1/100 as needed to prevent increased side effects. While we try to avoid giving a second 6-week course of BCG to patients who have previously received BCG because they are at risk of immunosuppression, the addition of interferon appears to reduce this risk.

**NURSING IMPLICATIONS**

Nurses are key to vital patient communication for optimal intravesical therapy. This is particularly critical with BCG where increasing symptoms need to be noted so that dosage can be reduced before major side effects occur. Patients need to know that BCG requires special antibiotic treatment, and symptoms such as night sweats, fever, and chills can present months and even years after BCG administration. This information should be communicated directly to the urologist, since physicians in other specialties, even infectious disease, may not be aware of this
consideration. A nurse should be able to explain the procedure selected by the physician, understand, discuss, and interview for possible complications, and be able to assist as directed in the administration of intravesical treatment.

Conclusions

Superficial bladder cancer is a heterogeneous disease that requires a variety of treatments. Low-risk patients typically have a benign course and can be effectively treated with transurethral resection followed by a single instillation of cytotoxic chemotherapy. Intermediate and high-risk patients require, in general, the addition of BCG immunotherapy due to the risk of disease progression. BCG, and presumably BCG plus interferon-alfa, can significantly reduce the risk of progression when used in a maintenance schedule. Nurses provide a vital role in patient communication, and can help reduce potential complications. Cystectomy is used when topical therapies fail, and is associated with an excellent survival rate with local disease.

References


