Valrubicin: An Alternative to Radical Cystectomy for Carcinoma In Situ of the Bladder

Susan Randall

In the United States, bladder cancer is the fourth most common neoplasm in males and the eighth most common in females (American Cancer Society, 2000). While bladder cancer rarely presents before age 40 (median age of 65 years), the number of new cases and the reported prevalence is disturbing. According to the American Cancer Society (2000), more than 53,000 new cases are expected each year and the prevalence exceeds 400,000 cases (Crawford, 1996). People at the highest risk include those living in urban areas and those working in the dye, rubber, leather, and chemical industries (Crawford, 1996; Scher, Shipley, & Herr, 1997). There is a definite link between smoking and the development of bladder cancer (Vineis, Marlone, & Radone, 1995; Vineis et al., 1998).

Approximately 95% of superficial bladder cancers are transitional cell carcinomas (TCCs) derived from the urothelium (Mostofi, Davis, & Sesterhenn, 1988; Scher et al., 1997). The remainder are mainly squamous cell carcinomas and adenocarcinomas (Mostofi et al., 1988; Scher et al., 1997). Morphologically, TCC tumors occur as papillary tumors, which are limited to the bladder mucosa (stage Ta) and lamina propria (stage T1). TCC may also appear as carcinoma in situ (CIS or Tis) with diffuse malignant cells confined to the epithelium. Cystoscopic resection, with or without intravesical therapy, is preferred for tumors that have not invaded the muscle wall (<T1). Thus, superficial bladder cancer refers to a broad range of pathological and clinical stages that extend from low-grade, noninvasive, papillary transitional cell neoplasms to high-grade tumors that have invaded the lamina propria (stage T1 or a). These are still grouped under the heading of “superficial” bladder cancer because they can usually be removed by transurethral resection of bladder tumor (TURBT) (Soloway, 1992).

Diagnosis and Staging

When a patient first presents, he or she may have a number of symptoms that do not definitively indicate a diagnosis of bladder cancer. For example, a patient may present with one or more of the following: painless hematuria, dysuria, frequency, nocturia, suprapubic fullness or pain, back or flank discomfort, lower abdominal pain, and pelvic/perineal pain (Hudson & Herr, 1995; Scher et al., 1997). These symptoms may mimic a variety of urologic conditions. There is also the likelihood for patients to be asymptomatic, particularly if the lesion is focal (Hudson & Herr, 1995; Lamm, Riggs, Traynelis, & Nseyo, 1995).

When bladder cancer is suspected, a cystoscopic examination should be performed to confirm the diagnosis. Cystoscopy identifies tumors, enables their removal, and allows biopsy of suspicious areas (Lamm et al., 1995; Scher et al., 1997). The American Joint Committee on Cancer (AJCC, 1997) Staging Manual states that upon visual inspection and biopsy of suspicious areas, detailed bladder mapping of the size, number, location, and growth pattern of all lesions should be recorded. The biopsied areas typically include the dome, posterior wall, right and left lateral walls, trigone, and prostatic urethra. Urinary cytology and flow cytometry DNA assays of urine samples are complementary techniques that aid in definitive diagnosis and monitoring of bladder cancer (Lamm et al., 1995).

Clinical staging is based upon the results of a cystoscopy and biopsy, and reflects the depth of bladder wall invasion by the tumor. Clinical staging follows the TNM system (tumor, nodes, and distant metastases) of the AJCC. Here, CIS of the bladder is synonymous with TIS. The utility of the TNM system for predicting bladder cancer progression is somewhat limited due to the sys-
tem of random biopsies used to assess disease status (Cancer-Net PDQ, 1998; Pagano et al., 1991). Another staging system commonly used is the Jewett-Strong-Marshall system. A comparison between the TNM and the Jewett-Strong-Marshall system is outlined in Table 1 (Brettschneider & Orihuela, 1990). Pathologic staging is based on disease progression after cystectomy, and is of greater prognostic value than clinical staging because, with removal of the bladder, the status of the whole organ is evaluated. Factors other than pathologic staging that affect survival include growth pattern, size, multiplicity, degree of vascular and lymphatic invasion, and basement membrane discontinuity (Lamm et al., 1995).

### Nursing Assessment and Education

Nurses are in a prime position to advocate and educate the patient presenting with possible bladder cancer. Starting with the initial assessment, obtaining a thorough history is mandatory to assess for risk factors and current health status. If the patient currently has a risk factor like smoking, he or she should be encouraged to quit. Take this opportunity to counsel the patient and, if possible, prescribe nicotine patches or gum, or provide information about local cessation programs. Knowing a patient’s medical history can be as important as knowing his type of health insurance, so that in case of reimbursement issues, a patient is not lost to proper disease assessment and followup.

The role of the nurse in counseling a patient about disease management assumes a heightened importance once a definitive diagnosis and course of therapy have been established. At this time, the patient, and perhaps his or her spouse, will need to know that there is access to a broad support system that may include nurses, medical and surgical physicians, social workers, psychologists, and religious or spiritual counselors. While it is important that a patient takes an active role in therapy, it is equally important that treatment decisions are not based solely on consumer information. A knowledgeable nurse can assist the patient in obtaining additional sources of reputable information.

The post-surgical home environment also should be evaluated prior to surgery, particularly for those patients living alone. If the environment is not adequately supportive, home-care or assisted-care alternatives will need to be anticipated.

### The Natural History of CIS in the Bladder

CIS is aggressive and has significant potential to spread intravesically and extravesically (Cancer-Net PDQ, 1998). The likelihood of muscle-invasive disease when CIS is associated with papillary tumors of the bladder ranges from 42% to 83% (Hudson & Herr, 1995). Patients with diffuse disease are reported to have a 78% risk of subsequent invasion (Lamm et al., 1995). This high rate of progression mandates aggressive therapy.

### Current Standards of Care

The standard approach for treating superficial tumors is complete cystoscopic resection, but virtually all patients develop new tumors, 30% of which progress to a higher stage. Transurethral resection and fulguration of visible lesions and associated papillary tumors are the initial treatment for CIS. However, CIS may not be visible cystoscopically, may be too extensive to resect, and because the lesions may have ill-defined margins, TURBT is rarely definitive therapy for this disease (Hudson & Herr, 1995).

Therefore, vigilant followup with cystoscopy, urine cytology, and repeat TURBTs, as needed, are performed every 3 months. TURBT is by itself generally sufficient for tumors that are confined to the mucosa with an exophytic component (papilloma or T.) Because CIS has a high recurrence rate (63% to 92%), it is generally treated by a combination of cystoscopic resection followed by bacillus Calmette-Guérin (BCG) (Crawford, 1996; Scher et al., 1997). Until the advent of BCG intravesical immunotherapy, radical cystectomy was the first-line treat-

---

**Table 1. Comparison of TNM and Jewett-Marshall-Strong Systems for Staging of Bladder Cancer**

<table>
<thead>
<tr>
<th>Jewett-Marshall-Strong</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T0</td>
</tr>
<tr>
<td></td>
<td>T1S</td>
</tr>
<tr>
<td>Stage A</td>
<td>T1</td>
</tr>
<tr>
<td>Stage B1</td>
<td>T2</td>
</tr>
<tr>
<td>Stage B2</td>
<td>T3A</td>
</tr>
<tr>
<td>Stage C</td>
<td>T3B</td>
</tr>
<tr>
<td>Stage D</td>
<td>T4A, N1-3</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage D2</td>
<td>M1, N4</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

*continued on page 34*
Advanced Clinical Practice
continued from page 31

ment of choice for superficial disease. When introduced in the mid-1970s, BCG was hailed as the “most successful of all immunotherapies in man and the major step...toward the control of superficial bladder tumors” (Martinez-Piñeiro & Martinez-Piñeiro, 1997). A number of controlled clinical trials and long-term studies established BCG as the standard of care and first-line therapy for CIS (Hudson & Herr, 1995).

Recurrent or Persistent Disease

Despite the well-established efficacy of BCG in a majority of patients, approximately 30% of newly diagnosed patients do not respond and another 30% relapse after initially responding (Martinez-Piñeiro & Martinez-Piñeiro, 1997).

Several studies have evaluated and questioned the efficacy of repeated courses of BCG in patients who failed initially (Bretton et al., 1990; Bui & Schellhammer, 1997; Catalona, Hudson, Gillen, Andriole, & Ratliff, 1987). A review of the literature reveals that the rates of progression and metastasis in patients who received three or more courses of BCG are high (Bretton et al., 1990; Catalona et al., 1987). Catalona and colleagues (1987) found that among patients who had failed two or more courses of BCG, the risk of invasive (30%) or metastatic (50%) cancer developing exceeded the prospects for eradicating the superficial tumor present (20%) with further BCG therapy. The clinical trial data suggest that patients who fail two courses of BCG should consider alternate treatment (Bui & Schellhammer, 1997; Coplen, Marcus, Myers, Ratliff, & Catalona, 1990).

Treatment Options After BCG Failure

The treatment options for a patient who fails BCG therapy are limited. Neither radiation nor additional doses of BCG have proven effective. Experimental intravesical agents such as alfa-2b interferon and mitomycin C have been used; however, data supporting their long-term efficacy and safety are still preliminary (Lundholm et al., 1996; Stricker et al., 1996; Williams et al., 1996).

With a lack of proven therapeutic alternatives, many physicians turn to cystectomy. Because of the curative potential of cystectomy, it is the standard by which other therapies are often measured (Amling et al., 1994). Certain situations — poor overall health, fragile psychological status, and even patient and physician preference — may compel one to consider the use of chemotherapeutic therapy.

Bladder cancer patients may present with concomitant conditions including a history of cardiovascular disease, renal or kidney dysfunction, or poor physical health that may preclude them from safely undergoing surgery and radical resection. While age is not a contraindication to cystectomy, older patients may have a greater potential for negative consequences (Skinner, Raghavan, Kim, & Skinner, 1997).

There may be psychological considerations that exclude patients from undergoing cystectomy. Approximately 20% of patients undergoing stoma procedures may be unable to adjust psychologically to the physical alteration, and may experience postoperative depression, anxiety, and sexual dysfunction (White, 1997). Regardless, patients and their caretakers contemplating radical surgery should be cognizant of the life-extending potential of bladder removal as well as the quality-of-life benefits offered with therapeutic management of recurrent disease.

For patients in whom a bladder-sparing alternative may be more appropriate, the semisynthetic analog of doxobucin, called valrubucin (Valstar™), represents a new, second-line intravesical therapeutic option. This agent was approved by the Food and Drug Administration September 1998 as an intravesical treatment for patients with BCG-refractory CIS of the bladder in whom immediate cystectomy would be unacceptable.

Clinical Experience with Valrubucin

Valrubucin has been studied in over 230 patients in clinical trials. In a multicenter, pivotal study, 18% of patients had a complete response to treatment at 6 months as documented by negative biopsies and cytologies. Median duration of response was 13.5 months when measured to the last bladder biopsy without tumor, and 21 months as measured until time of documented recurrence. A retrospective analysis of the 16 patients who experienced a complete response demonstrated that time to recurrence of their disease after treatment was longer than time to recurrence of their disease after previous courses of intravesical therapy. Approximately 88% of patients in the clinical trials experienced local adverse events; 50% of these were reported as irritable bladder symptoms prior to treatment. The local adverse reactions usually occurred during or shortly after instillation and resolved within 1 to 7 days (Steinberg et al., 2000).

Patients who are candidates for valrubucin will have already failed prior therapies, including BCG. These patients, having already experienced failure with intravesical therapy, will need realistic expectations of what therapy can and cannot achieve for them. While valrubucin represents a major milestone in bladder-sparing treatment options, its use induces a complete response in only about 1 in 5 patients. While delaying cystectomy could potentially lead to the development of metastatic bladder cancer, clinical studies with valrubucin have not shown undue risk of recurrence and/or progression. However, if there is not a complete response of CIS to valrubucin treatment after 3 months or if CIS recurs, cystectomy should be reconsidered.
Table 2.
Procedure for Administering Valrubin at the Urology Health Center in New Port Richey, Florida

- Insert a urethral catheter into the patient’s bladder under aseptic conditions.
- Drain the bladder slowly.
- Instill the solution via gravity flow.
- Hang the instillation bag and tubing 12-24 inches above the bladder level.
- Do not clamp the catheter, as this can cause bladder spasm or perforation.
- Instill valrubin over a period of several minutes.
- Withdraw catheter. Some centers may send patients home with the catheter still in place if they are evaluated to be competent to remove the catheter. If a patient has received BCG or valrubin, caution should be taken to change the tubing and drainage bag before the patient is sent home. The patient should also be instructed as to the proper procedures for removing the catheter and disposing of the biohazardous agent.
- Retain the agent for approximately 2 hours before voiding.
- Turn the patient every 30 minutes during the retention phase.

Table 3.
Occurrence of Local Adverse Reactions Before and During Valrubin Treatment
(n=170)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Before Treatment (percent)</th>
<th>During 6-Week Treatment (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any local bladder symptom</td>
<td>45</td>
<td>88</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>Dysuria</td>
<td>11</td>
<td>56</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>27</td>
<td>57</td>
</tr>
<tr>
<td>Bladder spasm</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Hematuria</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Bladder pain</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Cystitis</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Nocturia</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Local burning symptoms — procedure related</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Urethral pain</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria (gross)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients received multiple-cycle treatment regimens of 800 mg dose. Based on data from multiple clinical trials.

Administering Valrubin

Unlike BCG, an attenuated mycobacteria, valrubin does not need to be handled as infectious material or biohazardous waste. This simplifies the delivery of drug for the nurse and the patient’s home care following therapy.

One course of valrubin consists of 800 mg administered intravesically once a week for 6 weeks. Valrubin administration is not significantly different from administering BCG. However, to assure optimal outcome, one should take additional time to acquaint themselves with the specific steps involved in safely and effectively administering valrubin (per pharmaceutical manufacturer’s recommendation). Table 2 presents the procedure for administering valrubin at the Urology Health Center in New Port Richey, Florida.

Nursing Interventions

During the instillation and retention phases, patients may be scared and tense. There are several simple ways that nurses can help to make patients feel more comfortable, including:

- Play music in the treatment room.
- Provide blankets and/or dim the lights.
- Allow patient to have a companion sit with them through the procedure, or check on them frequently if no one is available.
- Allow patients to have reading materials.
- Allow patients as much privacy as possible.

Once home, it is important for patients to consume a minimum of six 8 ounce glasses of water and fluids within 24 hours, and urinate as often as possible. Patients should avoid caffeine and caramel-colored fluids (coffee, tea, or soda), as they are irritants to the bladder.

Prior to each treatment, it is recommended to review a checklist of side effects with patients. If reactions are severe and warrant treatment, valrubin administration may need to be rescheduled. As a precautionary measure, the nurse will conduct a urinalysis before each instillation. If the urinalysis is positive, a culture will be performed to confirm the presence of an infection and therapy will be delayed until it is resolved.

When scheduling patients for this procedure, it is important to consider their lifestyles and work schedules. It may be difficult for some patients to take off a few hours during the day, have the
procedure, and then return to work to complete their workday. Some patients may require more recuperation time because of symptoms associated with valrubicin, but cannot take time away from work. In such cases, try to accommodate their needs, as this will ultimately improve compliance. If possible, schedule the procedure for a Friday afternoon, thereby providing a full weekend for recovery. The goal here is to ensure adherence to the instillation schedule without making “being sick” the patient’s entire focus. Remember, an integral part of treatment is preserving and maintaining as much of the patient’s normal, active lifestyle as possible.

Side Effects

A patient’s bladder may be irritated from previous procedures and, therefore, may be more vulnerable to subsequent irritation. Like most other medications used, valrubicin is associated with adverse reactions, particularly by the fifth or sixth dose. Let patients know that side effects are usually an unavoidable component of treatment and should not deter them from continuing with the prescribed treatment plan. With valrubicin, the most common local side effects include frequency, urgency, dysuria, and bladder spasm, which typically resolve within 1 week. Systemic side effects (for example, abdominal pain, asthenia, and urinary tract infection) appear to be mild and self-limiting. If the patient experiences side effects beyond 24 hours following treatment, instruct them to call the doctor’s office (see Table 3).

Conclusions

Nurses play a key role in managing a patient’s treatment, counseling them about procedures, and educating them to ensure the best outcomes. Now, with the availability of valrubicin, there is a bladder-sparing treatment option for patients who have failed BCG and who are not appropriate candidates for cystectomy.

References


