Management of Patients with Bacilli Calmette-Guérin–Refractory Carcinoma in Situ of the Urinary Bladder: Cost Implications of a Clinical Trial for Valrubicin

Albert Marchetti, MD,[1] Liping Wang, MS,[1] Raf Magar,[1] H. Barton Grossman, MD,[2] Donald L. Lamm, MD,[3] Paul F. Schellhammer, MD,[4] and Paula Erwin-Toth, MSN, RN, CETN[5]

[1]Health Economics Research, Secaucus, New Jersey, [2]Department of Urology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, [3]Department of Urology, West Virginia University School of Medicine, Morgantown, West Virginia, [4]Department of Urology, Eastern Virginia Medical School, Sentara Cancer Institute, Norfolk, Virginia, and [5]Cleveland Clinic Foundation, Cleveland, Ohio

ABSTRACT

Objective: This study was undertaken to identify the expected first- and second-year clinical costs associated with intravesical valrubicin therapy, using a decision analytic model, for patients with Bacilli Calmette-Guérin (BCG)–refractory carcinoma in situ (CIS) of the urinary bladder.

Background: Cancer of the urinary bladder is the fourth most common malignancy in men and the sixth most common noncutaneous carcinoma overall. One histopathologic stage of bladder cancer is CIS, for which BCG intravesical immunotherapy is the first-line therapy. Radical cystectomy has been recommended for patients with CIS who do not respond to or become refractory to therapy with BCG. Surgery, however, may not be appropriate for all patients, especially those who are ineligible for the lengthy procedure because of advanced age or comorbidities and those who prefer alternative nonsurgical management. For these groups, intravesical valrubicin therapy is a plausible alternative.

Methods: Models were developed and populated with data from 1 open-label study of 90 patients, information from the medical literature, and input from clinical experts. The analysis was conducted from the payor perspective for direct costs only.

Results: Our data indicate that first- and second-year expected costs for valrubicin therapy are $19,912 and $23,496, respectively. Expected cost for radical cystectomy was also evaluated, since some patients may have no other option if drug therapy fails.

Conclusion: Our cost-consequence analysis and clinical data provide decision-makers with tools to aid in global budgetary projections of fractional and total expected health care

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costs associated with the management of BCG-refractory CIS of the urinary bladder.

Key words: radical cystectomy, valrubicin, intravesical therapy, carcinoma in situ, expected cost. (*Clin Ther.* 2000;22: 422–438)

INTRODUCTION

Carcinoma of the urinary bladder is the fourth most common cancer in men and the sixth most common noncutaneous malignancy among all Americans, accounting for 4% of all neoplasms and an estimated 12,100 deaths in 1999.[1] Bladder cancer exhibits a distinct male proclivity, with a male:female ratio of 2.6:1.[1] In addition to a possible hereditary predisposition,[2–4] advanced age is a pivotal nonmodifiable risk factor; indeed, bladder malignancies are considered diseases of the seventh decade.[5] Risks of bladder cancer increase among persons with certain environmental and occupational exposures.[2,4]

Of the >50,000 cases of bladder cancer diagnosed annually in the United States,[1,5,6] ~75% are confined to the mucosa, submucosa, or lamina propria at presentation.[5] According to the tumor-node-metastasis staging system,[5] superficial bladder malignancies include Ta (noninvasive papillary carcinoma), Tis (carcinoma in situ [CIS]), and T_1 (invasion of the lamina propria).

Characterized morphologically as a flat tumor, CIS consists of malignant cells that do not extend into the bladder lumen or permeate the basement membrane into the lamina propria.[7] Consequently, it may be more difficult to detect than papillary carcinoma.[8] In ~20% of patients,[5] CIS presents as a diffuse multifocal disease involving the ureters, prostatic urethra, and prostatic ducts.

CIS is an aggressive malignancy with a potential for swift progression and invasion. Clinical studies have demonstrated that ~40% of patients diagnosed with CIS have invasive disease at 5 years and 60% at 10 years.[5,9] Between 15 and 21 years after diagnosis, mortality is 40%.[5,9] The presence of or risk for invasive carcinoma occurs in up to 83% of papillary bladder tumors associated with CIS.[10–12]

Bacilli Calmette-Guérin (BCG) immunotherapy has been reported to be more effective than intravesical chemotherapy in the treatment of patients with superficial bladder cancer.[13,14] The complete response rates after initial BCG treatment averaged 70% in 18 studies.[15] A second durable response to a repeat course of BCG occurred in 50% of patients who experienced a durable complete response to the first induction course.[16–18] However, patients in whom 2 courses of BCG failed had low rates of response to a third course and carried higher risks for the development of invasive or metastatic disease.[16–18]

When BCG fails to control disease and the risk of progression increases, surgery is appropriate. Radical cystectomy is an effective surgical intervention for patients with CIS who are refractory to BCG therapy. Five- and 10-year cancer-specific survival rates of ≥90% have been documented.[19] The overall operative mortality rate is ~2.5%.[19,20] Long-term postoperative complications occurred in 30% of the patients in 1 retrospective clinical study.[20] After cystectomy, conduit diversions that require the use of external collecting appliances are commonly performed. These surgical procedures are associated with considerable physical and psychologic trauma that necessitate counseling and training predominantly related to enterostomal considerations.[21]

Although surgery is safe and effective after BCG failure, it may not be appropriate for some patients. For instance, the surgical mortality rate is higher in elderly patients (3% to 6%) than in younger patients (1% to 3%).[22] In addition, elderly patients are prone to a number of chronic conditions (eg, cardiovascular or cerebrovascular diseases, clotting disorders, hypertension, arrhythmias, and concurrent malignancy) that may complicate or contraindicate radical cystectomy.[23]

With the advent of valrubicin, a viable alternative to radical cystectomy has emerged for patients who are poor surgical candidates or who prefer medical rather than surgical management. Valrubicin is a cytotoxic anthracycline derivative that is structurally related to doxorubicin and has a similar mechanism of action. It exhibits high tumor-cell penetration and low absorption across the bladder wall.[24] In an open-label clinical trial, 90 patients with BCG-refractory CIS were treated with valrubicin at a dosage of 800 mg/wk for 6 weeks[25]; among patients who had undergone ≥2 courses of intravesical chemotherapy including ≥1 course of BCG therapy, disease-free response rates to valrubicin therapy were 44% at 3 months and 21% at 6 months.[25]

Valrubicin has been licensed as "intravesical therapy of BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality."[24] As with any newly licensed health care product, safety and efficacy are primary concerns, but they are not the only considerations that affect clinical decisions. The cost of care is also factored into the decision-making process. To identify the expected first- and second-year costs associated with intravesical valrubicin therapy for patients with BCG-refractory CIS of the urinary bladder, a cost-analysis was conducted from the payor perspective.

MATERIALS AND METHODS

Analytic Models

Based on the valrubicin clinical trial,[25] which was supplemented with information from the medical literature and expert opinion, a model was developed to depict management pathways for patients with BCG-refractory CIS of the urinary bladder who received valrubicin treatment. The 5 expert clinicians who contributed to this effort have extensive knowledge of bladder cancer and broad experience in the clinical management of patients; they were independent of the study grantor. For these reasons, they were asked to guide the clinical assessment and development of the model. No conflict of interest was identified before their participation. Advice was obtained in several ways without any weighting of geographic region for each advisor.

Initially, advisors were informed of the nature of the research and asked if they were interested in contributing. Next, each took part in a preliminary discussion to identify issues of clinical and economic importance. A survey was then created and sent to the advisors to capture relevant data and information based on their initial concerns. Finally, any discrepancies among the responses were resolved by telephone conversation. A final review was offered to each advisor.

Through the process, a simulation model was developed to depict management pathways for patients whose BCG treatment failed. Such models provide an analytic

framework from which to estimate clinical and economic consequences under uncertain conditions. Modeling and data analysis were facilitated with Microsoft Excel® 97 (Microsoft, Inc., Redmond, Washington) and Decision Analysis by TreeAge (DATA™) version 3.0.18 (TreeAge Software, Inc., Williamstown, Massachusetts).

After the models were constructed and reviewed by study advisors to assess face validity, economic and clinical data were collected and used to populate each treatment pathway. First, all medical and surgical resources dedicated to patient care were identified for each model branch, and then the resources were assigned a monetary value. These values included the cost of drugs and their administration, physician services, diagnostic and laboratory procedures, and hospitalization, plus the costs of management of adverse events and therapeutic complications. Clinical outcomes, such as disease-free survival, cancer recurrence, disease progression, mortality, adverse events, and complications, also were identified. The incidences of these clinical outcomes were used in the models as probabilities that weighted the costs associated with consumed resources to arrive at a total per-patient expected cost for patient management with valrubicin within the specific time frame. Figures 1 and 2 depict models for intravesical valrubicin therapy for a 1- and 2-year period, respectively.

In the pivotal valrubicin clinical trial, 40 of 90 patients (44%) and 19 of 90 patients (21%) exhibited a disease-free re-

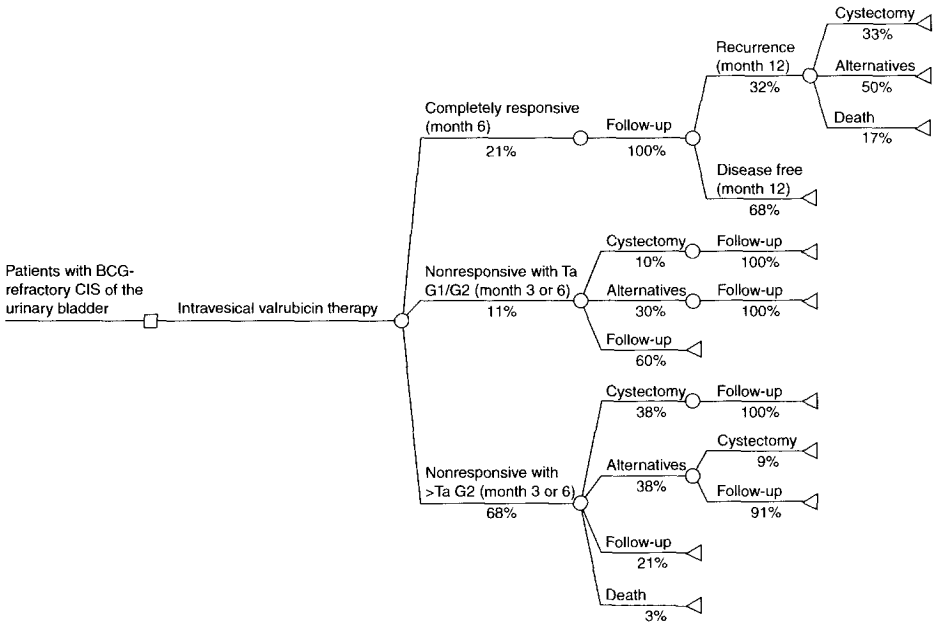

Figure 1. Simulation model for intravesical valrubicin therapy within a 1-year period. The algorithm depicts all outcomes, probabilities, and interventions assessed in the model over 1 year. BCG = Bacilli Calmette-Guérin; CIS = carcinoma in situ; Ta = noninvasive papillary carcinoma.

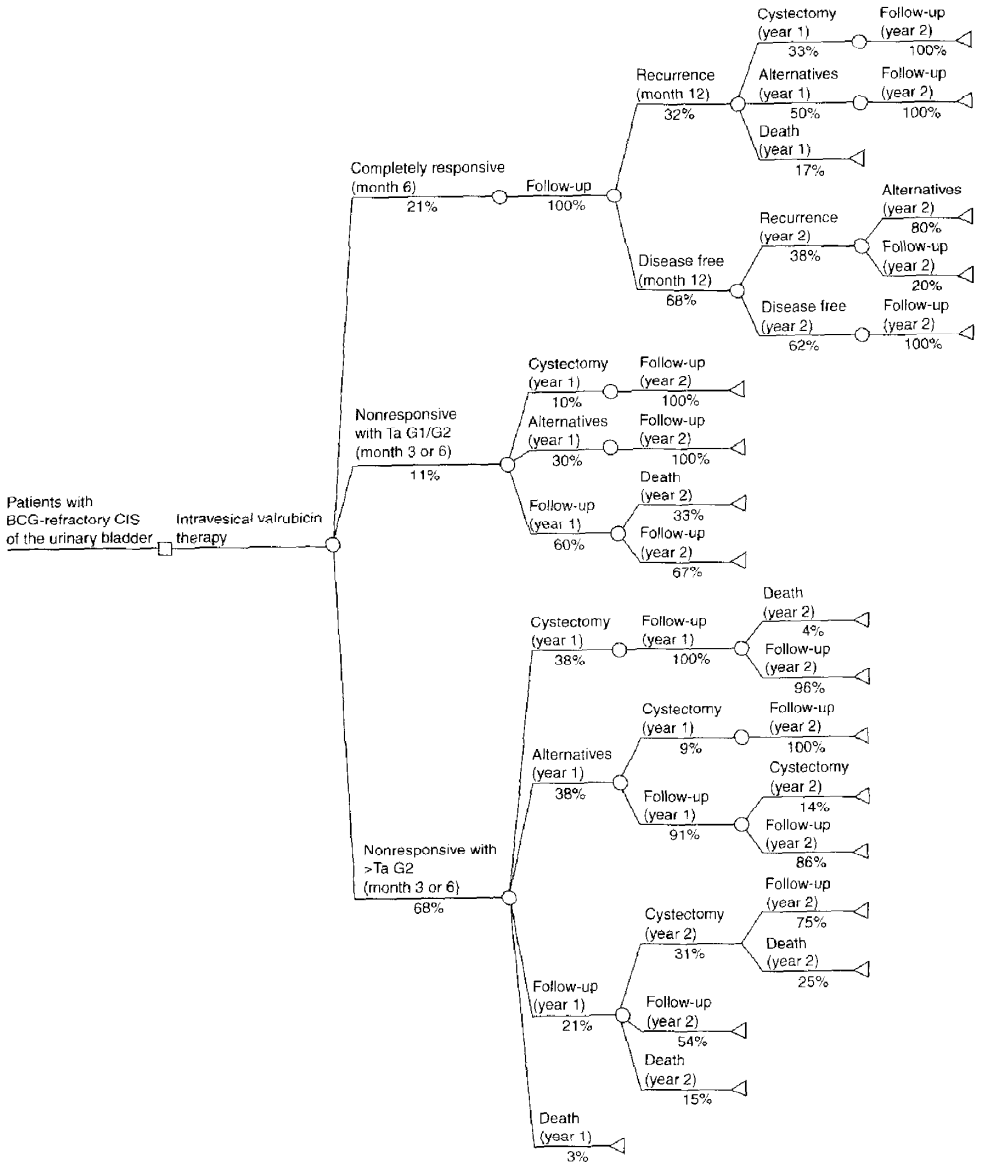

Figure 2. Simulation model for intravesical valrubicin therapy within a 2-year period. The algorithm depicts all outcomes, probabilities, and interventions assessed in the model over 2 years. BCG = Bacilli Calmette-Guérin; CIS = carcinoma in situ; Ta = noninvasive papillary carcinoma.

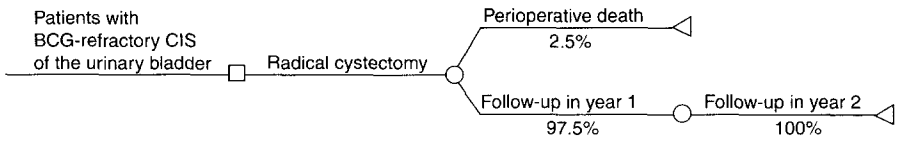

Figure 3. Simulation model for radical cystectomy within a 2-year period. The algorithm depicts outcomes and probabilities associated with cystectomy for 1 and 2 years of follow-up. BCG = Bacilli Calmette-Guérin; CIS = carcinoma in situ.

sponse at 3 and 6 months, respectively, after initial instillation; 10 patients (11%) were nonresponsive with low-grade papillary tumors only (Ta G1/G2); and 61 patients (68%) were nonresponsive with >Ta G2 disease.[25] (These numbers are not additive, since some patients were referenced more than once during the course of treatment.) Radical cystectomy or alternative intravesical therapies were provided to some nonresponders and some responders with recurrence. Other patients were assessed at 3-month intervals until subsequent treatments were needed or death occurred. For instance, among 10 nonresponders with Ta G1/G2 malignancies, 1 patient (10%) underwent radical cystectomy in the first year, 3 patients (30%) were treated with alternative intravesical therapies, and 6 patients (60%) had follow-up only.[26]

For all patients treated with valrubicin, costs were assumed to be incurred with pretreatment assessment and management, drug acquisition and intravesical administration, primary disease assessment at month 3, follow-up assessments, management of adverse events, and treatment after valrubicin failure, which included alternative intravesical therapies and radical cystectomy. At the end of 2 years, 63 of 82 patients (77%) whose valrubicin therapy failed had received some form of additional therapy.[26]

For patients undergoing surgery, a similar approach was used to estimate per-patient expected costs (Figure 3 illustrates the related 2-year simulation model). A 2.5% perioperative mortality was assumed based on previously published data.[20] Likewise, late surgical complications were assumed based on published rates of occurrence. Moreover, in the model, follow-up assessments for surgery survivors continued for 2 years. Resources consumed before, during, and after surgery along with their costs were identified, including management of late complications and urostomal care.

Data Extraction

At the commencement of the study, a literature search was conducted through EMBASE, MEDLINE®, and DIALOG™ to retrieve information on the treatment of patients with BCG-refractory CIS of the urinary bladder. Then, the 5-member expert advisory panel (4 urologists and 1 enterostomal nurse) was surveyed to identify components of oncologic care and the resources used during patient management. Safety and efficacy data for valrubicin were obtained from a pivotal open-label clinical study of 90 patients.[25] Clinical consequences for patients receiving valrubicin were based on follow-up data collected in the first 2 years of the

clinical study.[26] Clinical consequences of radical cystectomy were based on information from the medical literature as well as the opinion of the advisors.

Cost data were extracted from various sources.[27–30] The drug-acquisition costs of valrubicin and other drugs, including alternative intravesical antineoplastic agents and drugs administered in the management of adverse events or complications, were based on average wholesale prices listed in the *1998 Drug Topics® Red Book®*.[30]

Current procedural terminology codes[31] were identified for each diagnostic and therapeutic procedure. Based on these codes, costs related to consumed resources were culled from Medicare reimbursement data, including the 1998 National Physician Fee Schedule[27] and the 1998 Clinical Diagnostic Laboratory Fee Schedule.[28] National average values were used consistently throughout the analysis.

Diagnostic-related group codes[32] also were identified for inpatient surgical procedures, such as radical cystectomy, and for management options of late surgical complications. Costs of hospitalization were assessed using the 1998 Prospective Payment System[29] for Medicare reimbursement. National average values for hospitals in large urban areas were used consistently throughout the assessment. The cost of urostomy supplies was determined from information provided by the expert panel.

RESULTS

Cost of Valrubicin Therapy

Table I displays the clinical components of routine medical care related to valrubicin therapy and their related resource costs, based on the previously expressed assumptions and model designs. The drug-acquisition cost, which was $9360 for 6 weekly instillations, contributed most substantially to the total financial outlay for valrubicin therapy. In addition, intravesical administration during the treatment course ($506) and pretreatment assessment ($760), which included the costs of physical examination, cystoscopy with biopsy, transurethral resection (TUR), and other diagnostic and laboratory procedures, contributed to the overall cost of care. Additional expenses incurred were $292 for the first posttreatment assessment performed at month 3 and $277 for each additional 3-month follow-up assessment, which consisted of a physical examination, cystoscopy with biopsy, urine cytology, and urinalysis.

The expected cost of managing adverse events (eg, urinary frequency, 61% incidence; dysuria, 56%; and urinary urgency, 57%)[24] associated with valrubicin was $149 (Table II). The major factor contributing to this cost was a physician fee for physical examination. Because drug-related systemic adverse events were infrequent (incidence <1%), mild, and self limited,[24] they were not assessed in the current study.

In addition to routine medical costs directly associated with valrubicin, other expenses were incurred with the pharmacologic or surgical management of patients with nonresponsive or recurrent disease. In the valrubicin clinical trial, 29 patients—3 complete responders with recurrence, 3 nonresponders with Ta G1/G2 disease, and 23 nonresponders with Ta G2 carcinomas—received alternative drug therapies in the first year after initial valrubicin therapy.[26] In the second year, 4 more complete responders received alternative drug therapies for disease recurrence.[26] Several intravesical agents, including BCG, mitomycin, inter-

Table I. Per-patient cost of routine medical care related to intravesical valrubicin therapy.

Clinical Component (frequency)	Cost ($)
Pretreatment assessment	760
Physical examination (1)	94*
Urine cytology (1)	36*
Cystoscopy with biopsy (1)	176*
Transurethral resection (1)	345*
Intravenous pyelography, upper tract (1)	88*
Complete blood count (1)	15†
Urinalysis (1)	6†
During treatment	9866
Drug acquisition (6)	9360‡
Intravesical administration (6)	506*
Primary disease assessment at month 3	292
Physical examination (1)	59*
Cystoscopy with biopsy (1)	176*
Urine cytology (1)	36*
Complete blood count (1)	15†
Urinalysis (1)	6†
Follow-up assessment every 3 months	277
Physical examination (1)	59*
Cystoscopy with biopsy (1)	176*
Urine cytology (1)	36*
Urinalysis (1)	6†
Cost of dying	3000

*Data based on 1998 Medicare National Physician Fee Schedule.[27]
†Data based on 1998 Medicare Clinical Diagnostic Laboratory Fee Schedule.[28]
‡Data from *1998 Drug Topics® Red Book®*.[30]

feron, and thiotepa, were administered to these patients. Drug-acquisition and administration costs were identified for each agent, then weighted by frequency of use to obtain the expected cost per patient, which was $5374 (Table III).[33,34]

Cost of Radical Cystectomy

Radical cystectomy was performed on 28 patients (31%) in whom valrubicin therapy failed in the first year. Twenty-three of these patients were nonresponders with >Ta G2 disease at month 3 or 6. In the second year, 7 more patients underwent surgery. For all these patients, the cost of radical cystectomy contributed to the total cost of care with valrubicin and was included in the analysis.

Expenditures for the management of patients who underwent radical cystectomy are presented in Table IV. Costs related to hospitalization and physician fees (2 urologists and 1 anesthesiologist) constituted nearly 80% of the total expense of routine surgical management. The hos-

Table II. Expected per-patient cost of the management of adverse events associated with valrubicin therapy.

Local Bladder Symptom (% incidence)[24]	Clinical Component (frequency)	Cost ($)
Urinary frequency (61)	Physical examination (1)	39*
	Tolterodine (QD, 5 days)	12†
	Expected subtotal cost	32
Dysuria (56)	Physical examination (1)	39*
	Oxybutynin (QD, 5 days)	6†
	Expected subtotal cost	25
Urinary urgency (57)	Physical examination (1)	39*
	Tolterodine (QD, 5 days)	12†
	Expected subtotal cost	30
Bladder spasm (31)	Physical examination (1)	39*
	Hyoscyamine sulfate (QD, 5 days)	4†
	Expected subtotal cost	13
Hematuria (29)	Physical examination (1)	39*
	Expected subtotal cost	12
Bladder pain (28)	Physical examination (1)	39*
	Hyoscyamine sulfate (QD, 5 days)	4†
	Expected subtotal cost	12
Urinary incontinence (22)	Physical examination (1)	39*
	Tolterodine (QD, 5 days)	12†
	Expected subtotal cost	11
Cystitis (15)	Physical examination (1)	39*
	Kanamycin sulfate (1 day)	3†
	Expected subtotal cost	7
Nocturia (7)	Physical examination (1)	39*
	Tolterodine (QD, 5 days)	12†
	Expected subtotal cost	3
Local burning (5)	Physical examination (1)	39*
	Expected subtotal cost	2
Urethral pain (3)	Physical examination (1)	39*
	Expected subtotal cost	1
Pelvic pain (1)	Physical examination (1)	39*
	Expected subtotal cost	0.5
Total expected cost of the management of adverse events		149

*Data based on 1998 Medicare National Physician Fee Schedule.[27]
†Data from *1998 Drug Topics® Red Book®*.[30]

Table III. Expected per-patient cost of alternative intravesical therapies after valrubicin failure.

Intravesical Agent	Regimen (wk) (dosage/length of treatment)	Drug Acquisition Cost ($)[30]	Intravesical Administration Cost ($)[27]	Total Cost ($)	Incidence (%)[26]
Bacilli Calmette-Guérin	120 mg/6[33]	1021	506	1527	52.5
Mitomycin	40 mg/8[33]	7321	674	7995	27.5
Interferon	100 MU/12[34]	13,565	1011	14,576	15.0
Thiotepa	60 mg/6[33]	3248	506	3754	5.0
Expected cost of alternative therapies				5374	

MU = million units.

pitalization cost was $11,686 based on Medicare payment data.[29] Fees for urology services were $2736 for continent urinary diversion and $2092 for incontinent urinary diversion. Weighted by the frequency of selection of these 2 types of urinary diversion (40% continent, 60% incontinent according to the expert panel), the average urology cost was $4700.

A preoperative expense of $1768 (Table IV) was incurred predominantly (63%) through the use of TUR and pelvic/abdominal computed tomography. Other routine costs resulted from laboratory testing and 2 preoperative physical examinations, assuming no other assessments were required to investigate comorbidities.

The total annual postoperative cost not including urostomy supplies was $1890 (Table IV). This included a physical examination and enterostomal assessment every 3 months postoperatively for patients in our model. In addition, diagnostic and laboratory tests were ordered twice yearly.

Urostomy supplies for patients with incontinent diversion cost $1026 annually, assuming two 1-piece pouches were used every week. Because 60% of the patients underwent incontinent diversion, the expected cost of urostomy supplies was $615 per patient per year. Considering the increasing national rate of continent diversions, the expected cost would decrease proportionally.

The total expected cost of managing late postsurgical complications was $1048 (Table V). As before, total expected cost was calculated by multiplying resource cost by incidence of occurrence. Average incidence rates of late postsurgical complications were computed using data from 6 published clinical studies.[20,35–39] Only complications with a >1% average incidence rate were assessed. Management of these complications involved physical examination as well as laboratory and diagnostic testing. Medications were prescribed in some cases. Surgical procedures were anticipated for small bowel obstruction, ureteral obstruction, stomal stenosis, and incisional/parastomal hernia. Based on resource consumption before, during, and after surgery, the total expected cost of radical cystectomy was determined to be $22,288 and $24,730 at 1 and 2 years, respectively.

Table IV. Per-patient cost of routine medical care related to radical cystectomy.

Clinical Component (frequency)	Cost ($)
Preoperative assessment	1768
Physical examination (2)	187*
Enterostomal consultation (2)	110†
Urine cytology (1)	36*
Cystoscopy with biopsy (1)	176*
Transurethral resection (1)	345*
Computed tomography pelvis (1)	379*
Computed tomography abdomen (1)	389*
Urinalysis (1)	6‡
Laxative for bowel preparation	15§
Complete blood count (1)	15‡
Sequential multiple analysis–12 (1)	110‡
Intraoperative management	17,058
Hospitalization	11,686‖
Urologist surgical services (2)	4700*
Anesthesiologist surgical services (1)	672*
Postoperative assessment within 1 year	1890
Physical examination (4)	238*
Enterostomal consultation (4)	110†
Urine cytology (4)	146*
Computed tomography pelvis (2)	757*
Intravenous pyelography (2)	177*
Chest roentgenogram (2)	156*
Vitamin B_{12} level (2)	56*
Complete blood count (2)	29‡
Sequential multiple analysis–12 (2)	221‡
Urostomy supplies	615
Average annual cost of pouches for incontinent diversion (2 weekly)	1026‡
Estimated incidence (%)	60
Total	21,331

*Data based on 1998 Medicare National Physician Fee Schedule.[27]
†Data based on expert estimates (November 1998).
‡Data based on 1998 Medicare Clinical Diagnostic Laboratory Fee Schedule.[28]
§Data from *1998 Drug Topics*® *Red Book*®.[30]
‖Data based on 1998 Medicare Prospective Payment System.[29]

Table V. Expected per-patient cost of the management of late complications after radical cystectomy.

Major Late Complication (% incidence)[20,35–39]	Clinical Component (frequency)	Cost ($)
Small bowel obstruction (7.6)	Physical examination (1)	59*
	Abdominal x-ray (1)	45*
	Complete blood count (1)	15†
	Serum sodium (1)	9†
	Serum chloride (1)	9†
	Serum potassium (1)	9†
	Bicarbonate (1)	9†
	Serum creatinine (1)	10†
	Surgery (1)	5201‡
	Subtotal of procedure cost	5364
	Expected subtotal cost	405
Ureteral obstruction/ stenosis/stricture (6.2)	Physical examination (1)	59*
	Intravenous pyelography (1)	88*
	Abdominal ultrasonography (1)	116*
	Complete blood count (1)	15†
	Urinalysis (1)	6†
	Serum creatinine (1)	10†
	Surgery (1)	5229‡
	Subtotal of procedure cost	5523
	Expected subtotal cost	344
Incisional/parastomal hernia (4.1)	Physical examination (1)	59*
	Surgery (1)	3209‡
	Subtotal of procedure cost	3268
	Expected subtotal cost	134
Stomal stenosis (4.1)	Physical examination (1)	59*
	Complete blood count (1)	15†
	Computed tomography abdomen (1)	389*
	Surgery (1)	2804‡
	Subtotal of procedure cost	3267
	Expected subtotal cost	134

continued

Table V. (continued)

Major Late Complication (% incidence)[20,35–39]	Clinical Component (frequency)	Cost ($)
Renal calculi (2.5)	Physical examination (1)	59*
	Complete blood count (2)	29†
	Urinalysis (2)	12‡
	Urine calcium (2)	23†
	Uric acid (2)	17†
	Serum calcium (2)	19†
	Urine creatinine (2)	19†
	Urine pH (2)	13‡
	Oxalate (2)	48‡
	Citrate (2)	104‡
	Lithotripsy–extracorporeal shock wave (1)	708*
	Allopurinol (QD, 2 weeks)	9§
	Subtotal of procedure cost	1060
	Expected subtotal cost	26
Pyelonephritis (2.1)	Physical examination (1)	59*
	Urinalysis (1)	6†
	Complete blood count (1)	15†
	Urine culture (1)	15†
	Aztreonam (TID 2 days)	102§
	Trimethoprim (BID 2 weeks)	28§
	Subtotal of procedure cost	224
	Expected subtotal cost	5
Expected cost of managing late complications		1048

*Data based on 1998 Medicare National Physician Fee Schedule.[27]
†Data based on 1998 Medicare Clinical Diagnostic Laboratory Fee Schedule.[28]
‡Data based on 1998 Medicare Prospective Payment System.[29]
§Data obtained from *1998 Drug Topics*® *Red Book*®.[30]

Total Expected Cost of Valrubicin Therapy Including Radical Cystectomy

As previously described, the costs of resources associated with valrubicin therapy were weighted by outcome probabilities to obtain total expected per-patient first- and second-year costs of $19,912 and $23,496, respectively. These expected costs include surgery, dying, and other pharmacotherapy after valrubicin therapy has failed.

Sensitivity Analysis

Sensitivity analysis was performed for the drug-acquisition cost of valrubicin in

Table VI. Sensitivity analyses for drug-acquisition cost of intravesical valrubicin.

% Change	Expected Cost ($)	
	1-Year	2-Year
+15	21,316*	24,900*
−15	18,508*	22,092*
+15	29,317†	34,863†
−15	26,509†	32,055†

*Data based on 1998 Medicare Prospective Payment System.[29]
†Data from the Healthcare Cost and Utilization Project 1988–1995.[40]

both the 1- and 2-year models to assess the impact of this variable on total expected cost.

Based on a ±15% change in drug-acquisition cost for valrubicin, expected costs ranged from $18,508 at a 15% discount using Medicare costs to $34,863 at a 15% premium using Healthcare Cost and Utilization Project 1988–1995 (HCUP-3) data[40] (Table VI).

Study results indicated that the cost of hospitalization associated with radical cystectomy was a major determinant for the total expected cost of care. When Medicare hospitalization reimbursement data was replaced with HCUP-3 data,[40] the average charge for hospitalization for radical cystectomy was $37,099. When this figure was used in the current analysis and other costs remained constant, the 1- and 2-year costs associated with radical cystectomy were higher ($47,701 and $50,143, respectively), as were the expected costs of valrubicin therapy ($27,818 and $33,169, respectively). The HCUP-3 data[40] provide another national source for payor-related expenditures and are presented here to broaden this analysis to include the perspective of commercial insurers.

DISCUSSION AND CONCLUSIONS

Radical cystectomy is considered the definitive form of therapy for patients with superficial bladder disease that is recalcitrant to TUR.[19] The surgical procedure is associated with low mortality and infrequent pelvic cancer recurrence; in patients with CIS, postoperative cancer-specific survival approaches 100% at 5 years.[19] In addition, oncologists who recommend such surgery feel a certain level of confidence. On the other hand, radical cystectomy entails substantial patient counseling and training for hygienic stoma maintenance and reliable identification of signs and symptoms of complications, which contribute to postoperative costs.[21]

Intravesical valrubicin therapy provides a clinical benefit for patients with BCG-refractory CIS of the urinary bladder who do not want or cannot tolerate radical cystectomy. In an open-label clinical trial of 90 patients with BCG-refractory CIS treated with valrubicin, disease-free response rates were 44% at 3 months and 21% at 6 months among patients who had undergone ≥2 courses of BCG therapy.[25]

The current cost-analysis demonstrated that first- and second-year expected costs

for valrubicin were $19,912 and $23,496, respectively, which include the cost of radical cystectomy for patients who did not respond to drug therapy. In addition, since at least some patients who do not respond to valrubicin will require surgery after the trial observation period, these costs must be added to the cost of valrubicin therapy. This also may be true for patients in whom surgery failed and who need chemotherapy.

Results of the present analysis are based on a simulation model and data from 1 open-label clinical trial of valrubicin in which 90 patients were evaluated for therapeutic response. Of these, 43% did not respond to valrubicin therapy and underwent radical cystectomy.[26] No other data on valrubicin were available during the course of the economic study, and study results depend largely on drug performance in a rigid controlled setting. Validation of these results with data from actual clinical practice and refreshed analysis is appropriate.

For decision-makers, the ability to provide adequate health care within budgetary constraints will always be difficult, because clinical intuition alone may not provide the desired information. These results provide additional information for the decision-making process. Although they are based on data from a controlled setting, they do reveal at least some budgetary considerations. Related decision-analytic software to customize results with site-specific data is currently available to help the decision-making process.

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Address correspondence to: Albert Marchetti, MD, Health Economics Research, 400 Plaza Drive, Secaucus, NJ 07094.

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