Efficacy and Safety of Bacille Calmette-Guérin Immunotherapy in Superficial Bladder Cancer

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In the United States, bladder cancer is the fourth most common human malignancy. In the past decade, the incidence of bladder cancer has increased by 36%. However, mortality has declined by 8%. Intravesical chemotherapy was considered to be partially responsible for this improvement in survival, but a recent review of clinical studies shows no reduction in disease progression with intravesical chemotherapy. Fortunately, the results of immunotherapy with bacille Calmette-Guérin (BCG) are quite different, and it is expected that patients treated with optimal BCG treatment regimens will have a long-term reduction in tumor recurrence, tumor progression, and cancer mortality.

Most patients with bladder cancer will present with superficial disease that is amenable to surgical resection. However, these patients remain at risk for tumor recurrence for the rest of their lives. Approximately 88% of patients with a history of bladder cancer will develop tumor recurrence if they survive 15 years. In the past decade, the incidence of bladder cancer has increased by 36%, but mortality has declined by 8% [1]. Intravesical chemotherapy was considered to be partially responsible for this improvement in survival, but a recent review of clinical studies shows no reduction in disease progression with intravesical chemotherapy. On the other hand, recent clinical studies in papillary tumors show a 40% reduction in tumor recurrence in patients treated with BCG, compared with chemotherapy studies that show an average 14% reduction in tumor recurrence [2].

Immunotherapy with intravesical BCG provides an effective alternative approach to chemotherapy in the management of superficial bladder cancer. BCG has been shown to eradicate residual tumor in ⩾60% of patients with papillary disease and ⩾70% in patients with carcinoma in situ.

Controlled trials suggest that BCG immunotherapy reduces disease progression, decreases the need for cystectomy, and prolongs survival.

Intravesical Chemotherapy

In a review of 23 controlled chemotherapy studies involving 4013 patients, 10 of the 23 studies showed no statistically significant reduction in tumor recurrence after intravesical chemotherapy [2]. The overall average reduction in tumor recurrence at 1–3 years is only 14% [2]. Thiotepa (12%), doxorubicin (13%), mitomycin C (15%), and ethoglucid (31%) have been shown to reduce short-term recurrence by 12% to 31%, but long-term (⩾5 year) reduction of tumor recurrence has been difficult to confirm [3, 4]. The very modest 14% reduction in short-term recurrence would be worth the morbidity and expense of intravesical chemotherapy if it were accompanied by a commensurate reduction in disease progression or mortality. Unfortunately, data to suggest any reduction in progression or mortality are lacking. A further review of the 10 studies, involving 2011 patients, showed that incidence of disease progression overall in those treated with chemotherapy is 7.5%, compared with 6.9% in those treated with surgery alone [2]. Significant reduction in progression was not seen in any of the 10 studies reported, and no reports of improved survival are available.

BCG Immunotherapy

Multiple studies have established that BCG prophylaxis after complete transurethral resection (TUR) or fulguration of superficial disease significantly reduces recurrence and prolongs disease-free interval, compared with that of TUR alone [5]. A reduction in percentage of recurrence of 7%–65% is seen, and all of the studies [6] are highly significant. Cookson and Sarosdy [7] reviewed the San Antonio series of patients with T1 lesions treated with TUR and BCG and found 91% of patients to be free of tumor recurrence with a mean follow-up of 59 months. In this series, 69% remained free of disease after the initial therapy, and an additional 22% required an additional TUR and course of BCG before achieving a disease-free state.

Randomized controlled studies have failed to show that any of the newer, commonly used intravesical chemotherapies are superior to the first drug used, thiotepa [2]. In contrast, 3 comparisons of BCG with thiotepa and 3 comparisons of BCG with adriamycin found BCG to be significantly better. Only with mitomycin C has the advantage of BCG not been clearly apparent. Although the Finnish study headed by Alfthan [8] found Pasteur BCG to be superior to mitomycin C, 2 Dutch studies [9,10] failed to find RIVM or Tice BCG superior to mitomycin C. Rübben in [6] Germany found neither BCG nor mitomycin C to be superior to transurethral resection alone, with only a 7% reduction of recurrence with each treatment [1].

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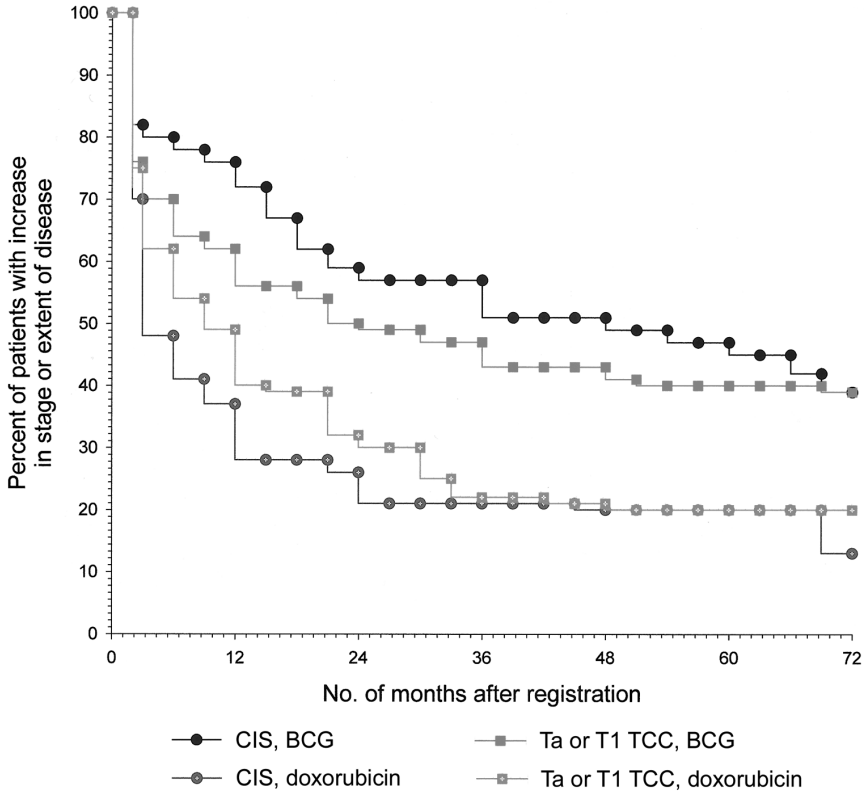

Figure 1. Southwest Oncology Group Study 8216. Kaplan-Meier plots of time to treatment failure [13]

These negative comparisons may relate to the preparation of BCG used, the schedule of treatment, or the high percentage of low-risk patients studied. It is clear, however, that when patients at high risk for tumor recurrence are studied using an appropriate BCG treatment schedule, BCG is far superior to mitomycin C. The Southwest Oncology Group (SWOG) study [2] that compared BCG with 20-mg mitomycin C, using the same 6 weekly and then monthly treatment schedule, had to be terminated at the first interim analysis because of the highly significant ($P < 0.006$) advantage of BCG. Overall recurrence was reduced from 32.6% with mitomycin C to 19.5% with BCG, and the median time to recurrence was prolonged from 20 to >36 months.

Encouraging data suggest that BCG immunotherapy, unlike chemotherapy, reduces long-term tumor recurrence, tumor progression, and mortality. Five- and 10-year follow-up on controlled and chemotherapy comparison studies show continued reduction in tumor recurrence. Herr [11] evaluated 86 patients and found the time to progression to muscle invasion or metastasis was prolonged significantly after BCG treatment. In this study, stage progression occurred in 35% of control subjects and 28% of patients treated with BCG. The mortality rate was reduced from 32% to 14% with BCG use, and cystectomy was required in 42% of control subjects, compared with 26% of patients treated with BCG. In a subsequent report [12], with 3 years additional follow-up, cancer deaths were reduced from 37% to 12% ($P < 0.01$). Figure 1 shows the SWOG's comparison of Connaught BCG with doxorubicin. This SWOG study found that an increase in stage or extent of disease occurred in 37% of patients receiving doxorubicin, compared with 15% of those receiving BCG [13]. Pagano et al. [14] studied 133 randomized patients and found progression to stage T2 or higher in 17% of control patients versus 4% of those treated with BCG.

These 3 controlled studies show significant reduction in disease progression with the use of intravesical BCG. Overall, the mean rate of progression is reduced from 28% in control subjects to 14% in those receiving BCG. BCG immunotherapy reduced tumor recurrence by an average of 40%, compared with the 14% average reduction with chemotherapy. The benefit of immunotherapy lasts long term and includes reduction in disease progression. Importantly, direct randomized comparison have demonstrated BCG prophylaxis to be superior to thiotepa, doxorubicin, and mitomycin C.

BCG Treatment Schedules

The optimum dose and treatment schedule for intravesical BCG remains under investigation. The original treatment schedule of 6 weekly instillations completed by Morales [15] in 1976 has been the gold standard and it has been difficult to prove that

any other schedule is superior. Care must be taken not to administer excessive BCG immunotherapy. Unlike chemotherapy, where increased dose results in increased tumor cell kill, the dose response curve of BCG is bell-shaped. Excess BCG can reduce antitumor activity and even produce enhanced tumor growth. Care should therefore be taken in extending treatment beyond the 6-week induction phase, where studies of immune response demonstrate optimal stimulation. The antitumor effect of BCG is not immediate but is the consequence of prior immune stimulation. Herr reports 32% of patients showing the presence of disease at 3 months after a 6-week course of BCG proceed to a disease-free state by 6 months [16]. Catalona et al. [17] found 44% of 100 patients responded completely to a 6-week course of BCG, whereas the cumulative complete response was improved to 63% if nonresponders were treated with a second 6-week course of BCG. Haaff et al. [18] treated patients who did not respond to an initial 6-week course of BCG with an additional 6-week course of BCG and found 43%–67% of these patients to become tumor-free after the additional therapy.

In patients originally enrolled in our controlled BCG trial initiated in 1978, we observed that quarterly maintenance BCG immunotherapy, using a single instillation, reduced the rate of tumor recurrence 4-fold, from 1.9 to 0.49 tumors per 100 patient months [19]. Using the murine bladder cancer model, we confirmed that BCG treatment without maintenance provides long-term (9-month) protection from subsequent tumor challenge, but further BCG treatments significantly reduced tumor growth in animals challenged at 15 months [20]. Subsequent clinical trials, however, were unable to demonstrate any benefit of maintenance BCG immunotherapy over a single 6-week induction course [21, 22].

To evaluate maintenance therapy, 660 SWOG patients with rapidly recurring stage Ta or T1 lesions or CIS received the standard 6-week induction using 120 mg of Connaught BCG. Patients were then stratified by prior therapy, disease type (papillary vs. CIS), and PPD skin test and were randomized to observation versus 3 weekly BCG instillations at 3 months, 6 months, and every 6 months to 3 years. After an average follow-up of 3.2 year, the time to biopsy-confirmed recurrence revealed a dramatic and highly significant advantage of maintenance therapy [23]. In patients with CIS, additional 3 weekly treatments at 3 months increased the complete response rate at 6 months from 73% to 87% ($P < 0.04$). Considering only those patients who had complete response and were disease-free at 3 months after induction therapy, maintenance BCG resulted in an increase in long-term disease-free status—from 65% in the observation group to 83% in the maintenance group. In 270 evaluable patients with rapidly recurring Ta and T1 disease, the advantage of BCG was even more dramatic. Long-term disease-free status was increased from 50% in the induction only group to 83% for those in the maintenance therapy group. This 33% improvement in long-term disease-free status is statistically significant at $P < 0.000001$ and therefore leaves no remaining question about the superiority of continued maintenance treatment in patients with bladder cancer rendered disease-free after induction therapy. More importantly, this maintenance therapy has resulted in statistically significant improvement of patients' survival compared with that of induction only. In 391 randomized patients, the excellent 86% survival at 4 years observed with induction therapy was improved to 92% in patients receiving maintenance BCG [23].

It is remarkable that the efficacy of BCG has been confirmed with multiple different BCG preparations, doses and treatment schedules. Dosage employed in the studies mentioned in this review include 81 mg of dry weight Connaught BCG ($2–19 \times 10^8$ cfu), 50 mg of TICE BCG ($3–8 \times 10^8$ cfu), and 10^9 cfu of RIVM BCG. Authors have primarily used the original schedule of Morales—that is, diluting BCG in 50 cc of normal saline of irrigation and instilling it within the bladder to be held for 2 h weekly for 6 weeks. Evidence suggests that a single 6-week course of BCG is suboptimal. Response to BCG was increased from 38% to 60% with the addition of a 6-week course [24]. The current gold standard schedule is the 3 weekly maintenance regimen given every 6 months. This schedule has markedly increased and extended the benefit of BCG.

Carcinoma In Situ

The malignancy most susceptible to BCG immunotherapy is carcinoma in situ. More than 700 patients with CIS around the world have been treated with BCG, and the average complete response rate is over 70%. In the first comparative SWOG study, 70% of CIS patients treated with BCG had complete response, and 65% maintained complete response for at least 5 years [13]. In the second SWOG study [23], the overall complete response rate was increased to 87% when patients received an additional 3-week course of BCG at 3 months and 3 weekly maintenance treatments at 6 month intervals for 3 years. This study has yielded an estimated 4-year disease-free rate of 83%. This remarkable long-term success with BCG in the treatment of CIS exceeds that reported in early cystectomy series; therefore, BCG has replaced cystectomy as the initial treatment of choice for CIS.

Complications of BCG

The complications of BCG are illustrated in table 1. It should be emphasized that >95% of patients tolerated BCG without significant morbidity. Most of the symptoms associated with BCG immunotherapy are a result of the immune stimulation that is required to effectively eradicate cancer cells. These symptoms include urinary frequency and burning, mild malaise, and low-grade fever. Fever has been associated with improved response to BCG immunotherapy.

For patients with increased symptoms, the dose of BCG can be reduced to one-half or one-third, and isoniazid 300 mg daily

Table 1. Complications in 2602 patients with superficial bladder cancer who were treated with different BCG substrains.

Complication	No. (%) of patients with complication	Armand Frappier (n = 718)	Tice (n = 726)	Connaught (n = 353)	Pasteur (n = 325)	RIVM (n = 129)
Fever	75 (2.9)	3.8	4.7	4.7	0.6	2.1
Granulomatous prostatitis	23 (0.9)	1.8	1.0	0.2	0.6	—
Pneumonitis and/or hepatitis	18 (0.7)	0.4	0.8	0.6	1.2	0.8
Arthralgia	12 (0.5)	0.7	0.1	0.6	1.8	—
Hematuria	24 (1.0)	0.3	0.6	2.4	1.0	0.4
Rash	8 (0.3)	0.4	—	0.9	—	—
Ureteral obstruction	8 (0.3)	0.6	0.4	0.2	—	—
Epididymitis	10 (0.4)	0.4	—	0.2	1.2	0.8
Contracted bladder	6 (0.2)	—	0.3	0.2	0.6	—
Renal abscess	2 (0.1)	—	—	0.4	—	—
Sepsis	10 (0.4)	0.1	0.4	0.9	0.2	—
Cytopenia	2 (0.1)	—	0.3	—	—	—

NOTE. Data are percentage of patients with complication per BCG substrain unless otherwise indicated.

can be given. Patients with evidence of BCG infection, such as epididymitis, hepatitis, or symptomatic prostatitis, are treated with isonazid plus rifampin 600 mg daily.

The most dangerous complication of BCG is systemic septic and/or hypersensitivity reaction that is characterized by chills, fever, hypotension, and progressive multisystem organ failure. The incidence of this reaction was initially reported to be 0.4%. More recent estimates are that the septic reaction occurs in about 1 of 15,000 patients treated with intravesical BCG. A limited clinical experience, as well as our controlled murine study, suggests that optimal survival in these patients occurs with the addition of prednisone 40 mg daily to the standard treatment of isoniazid plus rifampin. Steroid treatment is tapered gradually after patients have responded. Exacerbation of this hypersensitivity response has been seen in patients who have had prednisone discontinued abruptly. Antituberculous antibiotics are continued for 3–6 months.

Further Improvement of BCG Immunotherapy

Epidemiologic and laboratory studies suggest that vitamin supplements may be helpful for the prevention of some cancers, but clinical trials have failed to demonstrate protection with naturally occurring vitamins. Without substantiation of the highly touted benefits of vitamins, few physicians caring for cancer patients have recommended their use.

To evaluate the potential benefit of high-dose vitamins, 65 patients with biopsy-confirmed, resected stage Ta or T1 transitional cell carcinoma were enrolled in a randomized comparison of intravesical BCG with or without percutaneous administration [25]. These patients were also randomized by closed envelope to receive multiple vitamins in the recommended daily allowance (RDA) versus RDA multivitamins plus 40,000 units of vitamin A, 100-mg vitamin B6, 2000-mg vitamin C, 400 units of vitamin E, and 90-mg zinc (Oncovite).

The addition of percutaneous BCG did not significantly reduce tumor recurrence, but recurrence after 1 year was markedly reduced in patients receiving high-dose vitamins. Five-year estimates of tumor recurrence are 91% in the RDA group and 41% in the zinc arm ($P = 0.0014$, Mantel Cox). Overall recurrence was 24 (80%) of 30 in the RDA group and 14 (40%) of 35 in the high-dose group ($P = 0.0011$, Fisher's exact). High-dose vitamins A, B6, C, and E plus zinc reduce bladder tumor recurrence in patients receiving BCG immunotherapy. Although chemoprevention has been assumed to be the mechanism of action of these vitamins, immunotherapy has been reported to induce profound reductions in serum levels of vitamin A, beta-carotene, vitamin C, vitamin E, and folic acid. Preliminary studies have shown that this vitamin combination is associated with significantly increased cellular immunity, as measured by natural killer cell cytotoxicity in BCG-treated patients [26]. Further research will be required to identify which ingredient(s) provides this protection, but it appears clear that vitamin supplementation has the potential to significantly improve the results of intravesical treatment.

Safety of BCG

In a review of 2602 patients treated with intravesical BCG, <5% of patients had other than minor adverse reactions to treatment [27]. Severe complications, such as systemic BCG infection, are almost invariably associated with systemic absorption of BCG. By withholding BCG when patients have cystitis, previous high fever, or most importantly, traumatic catheterization, systemic BCG reactions can be nearly eliminated. Current evidence suggests that, when such reactions occur, optimal treatment consists of 300-mg isoniazid, 600-mg rifampicin, and 40-mg prednisone daily [28].

Conclusions

The traditional approach to adjuvant treatment in superficial bladder cancer using intravesical cytotoxic chemotherapy has now been demonstrated to have significant limitations. Immunotherapy with intravesical BCG provides superior reduction in short-term tumor recurrence and unlike chemotherapy provides a measure of long-term protection from recurrence, progression, and cancer death. Current optimal BCG regimens that use maintenance therapy significantly improve long-term results, and reduction in the dose of BCG administered may further improve the safety of intravesical BCG. The efficacy of BCG immunotherapy may be further enhanced by the addition of high doses of vitamins A, B6, C or E. These latter 2 proposals are the subject of further research.

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