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Drug therapy of bacillus Calmette-Guérin sepsis

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Abstract Intravesical bacillus Calmette-Guérin (BCG) is widely used for the treatment of transitional cell carcinoma of the bladder. Although it is usually well tolerated, sepsis can occur, which has resulted in at least eight deaths [3]. The survival of Connaught BCG-infected mice treated with single and combination antibiotic and steroid therapy was evaluated. Triple-drug therapy with isoniazid, rifampin, and prednisolone resulted in 53% survival compared with 25% survival in the control group (P=0.0209). A survival of only 10.5% was observed with treatment using prednisolone alone. This survival was worse than that of the control group (25%), and approached statistical significance (P=0.0669). Our data suggest that BCG sepsis probably has components of both a hypersensitivity reaction and bacterial sepsis; they support the current use of combination antibiotic and steroid therapy for treatment of BCG sepsis in humans, but argue *against* treatment with steroids alone.

Key words Bacillus Calmette-Guérin · Septic shock
Drug therapy · Bladder neoplasm

Intravesical BCG is well tolerated by 95% of patients. Mild side effects commonly seen include irritable voiding symptoms (91%), flu-like symptoms (60%), hematuria (43%), fever < 39 °C (28%), and nausea (8%) [4]. Five percent of patients experience more serious side effects, including fever >39 °C, prostatitis, hepatitis, pneumonitis, arthritis, and a septic reaction. Lamm et al. [3] found the incidence of sepsis to be 0.4% in a review of 2602 patients receiving BCG immunotherapy. This is always a serious reaction, and has been associated with death in at least eight patients [3].

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BCG sepsis may be defined as a life-threatening condition in a patient receiving intravesical BCG treatment which cannot be attributed to any source other than the BCG treatment. Symptoms of fever and malaise progressing to cardiovascular instability or collapse are most commonly seen. The exact etiology is not known, but it has been thought to be secondary to overwhelming mycobacterial sepsis; however, blood cultures almost never grow any mycobacteria. The fact that treatment with steroids seems to improve survival suggests that there may be a component of a hypersensitivity reaction or adrenal insufficiency also playing a role. A hypersensitivity reaction theory has also been proposed by others [2, 5].

Treatment of BCG sepsis has been variable in the past, but has primarily utilized antituberculous antibiotics and, more recently, steroids. Treatment regimens have been developed empirically; currently there are no Center for Disease Control guidelines for treatment of BCG sepsis. Rawls [6] reported that two patients with BCG sepsis survived after treatment with isoniazid and rifampin when combined with cycloserine for the first 72 h. Steg [7] reported survival in five out of five patients with BCG sepsis treated with isoniazid, rifampin, and prednisolone. DeHaven [1] recently reported the success of isoniazid, rifampin, and prednisolone in the treatment of BCG sepsis induced in mice using Tice BCG. Using a similar mouse model, we report the treatment of BCG sepsis induced by Connaught BCG with standard antituberculous antibiotics and prednisolone. To determine whether BCG sepsis was due to a hypersensitivity reaction alone, one of the treatment groups was treated with steroids alone. Standard treatment regimens were used in the other groups.

Materials and methods

Mouse model

During preliminary experiments, we learned that few or no deaths resulted from the acute toxicity of up to 50 mg intraperitoneal (i.p.)

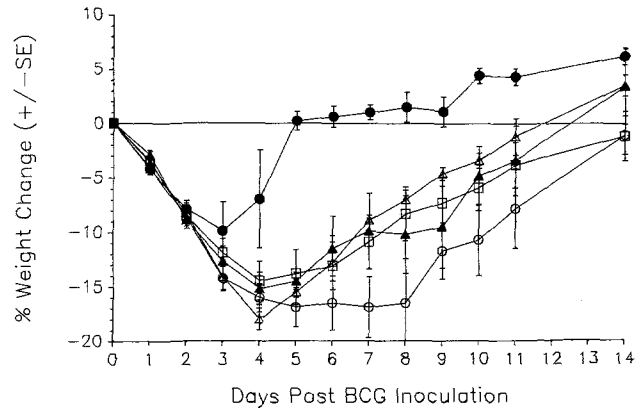

Fig. 1 Mean daily weight change per group after BCG rechallenge given on day 0. Drug therapy was given on days 0–5. The slope of the prednisolone treatment group is skewed due to only 10% survival in the group. ○—○ D5W; ●—● PRED; △—△ I+R; ▲—▲ I+R+C; □—□ I+R+P

Table 1 Peak weight loss (*P*, *Pred*, prednisolone; *I*, isoniazid; *R*, rifampin; *C*, cycloserine; *NS*, not statistically significant)

Group	Treatment	Peak weight loss (%)	Date
1	D5W	16.91	7
2	Pred	9.93	3
3	I,R	18.01	4
4	I,R,C	15.23	4
5	I,R,P	14.48	4

Table 2 Survival according to treatment (*P*, *Pred*, prednisolone; *I*, isoniazid; *R*, rifampin; *C*, cycloserine)

Group	Treatment	Survival (%)	*P* vs. 5	*P* vs. 1
1	D5W	25	0.0209	–
2	Pred	10.5	0.0006	NS
3	I,R	15.8	0.0038	NS
4	I,R,C	20	0.0228	NS
5	I,R,P	53	–	0.0209

BCG (first exposure), but death was predictable after rechallenge with the same dose (second exposure). An approximate LD_{50} rechallenge dose was determined, in order to measure the differential abilities of test substances to prevent death due to BCG sepsis. A group of ten mice were given an acute dose of 20 mg Connaught BCG (i.p.), allowed to recover for 2 months, and then given a rechallenge dose of 20 mg BCG (i.p.). This group had an overall survival of 40%. Based on these data, we used an acute and rechallenge dose of 20 mg in our experiment.

Treatment

One hundred C3H/HeN mice received an acute dose of 20 mg Connaught BCG ($0.2–3.4\times10^8$ CFUs) (i.p.) without treatment. After a 2-month recovery period, they were randomized into 5 treatment groups (20/group), anesthetized, and given a rechallenge dose of 20 mg Connaught BCG (i.p.) along with 0.5 ml of the appropriate drug therapy given by oral gavage. The rechallenge of BCG and first treatment were given at the same time to avoid the need for an additional anesthetic. Anesthesia and treatment were repeated daily for a total of 5 days (five doses). Change in weight from baseline (the day of rechallenge) and survival were recorded daily for 14 days (Fig. 1). Five deaths due to aspiration during oral gavage were excluded from the final survival analysis.

Five drug therapies and dosages were administered as follows in a volume of 0.1 ml/drug, with final volume adjusted to 0.5 ml using 5% dextrose (D5W). Dosages were: isoniazid (INH), 0.283 mg/0.1 ml, 700 mg/70 kg per day; rifampin (R), 0.566 mg/0.1 ml, 1400 mg/70 kg per day; cycloserine (C), 0.804 mg/0.1 ml, 2000 mg/70 kg per day; prednisolone (Pred), 0.033 mg/0.1 ml, 80 mg/70 kg per day. The five groups were as follows: group 1 (control)=D5W; group 2 (Pred)=prednisolone; group 3 (I,R)=isoniazid (INH)+rifampin; group 4 (I,R,C)=INH+rifampin+cycloserine; group 5 (I,R,P)= INH+rifampin+prednisolone.

Statistics

The statistical significance of differences between the experimental groups was determined using the Generalized Savage (Mantel Cox) test (one-tailed, BMDP). The Mann-Whitney Rank Sums test was used to determine the statistical significance of mean weight changes between the experimental groups.

Results

Weight change

The percentage change in weight from baseline paralleled the results in the pilot experiments, and suggested that the model of sepsis was reproducible. Peak weight loss data are found in Table 1. No significant differences were observed between treatment and control groups in peak weight loss or rate of weight regained. This parameter was, therefore, not considered to be of value in determining efficacy of therapy. Percentage weight change per group is shown in Fig. 1. Baseline weight was used as the zero reference. The average percentage weight loss for the group was then calculated and plotted on a time graph. All groups except group 2 had similar patterns of weight loss and regain. Weight data were only recorded for live mice. Because the mice in group 2 died earlier than those in other groups and there were only two survivors after day 3, it only appears that their performance was superior, whereas they had the worst survival of all.

Survival (Fig. 2)

Five (25%) of the control group survived the rechallenge dose, while only 2/19 (10.5%) in group 2 (Pred) and 3/19 (15.8%) in Group 3 (I,R) survived (Table 2). Therapy with isoniazid, rifampin, and cycloserine (group 4) resulted in a 20% survival. Therapy with isoniazid, rifampin, and prednisolone resulted in significant improvement in survival (53%, group 5 vs. control, P=0.0209). Groups 2 (Pred), 3 (I,R), and 4 (I,R,C) had no significant survival advantage when compared with any of the other groups. The lowest survival (10.5%) occurred in mice treated with prednisolone alone. Comparison of our control group (D5W)

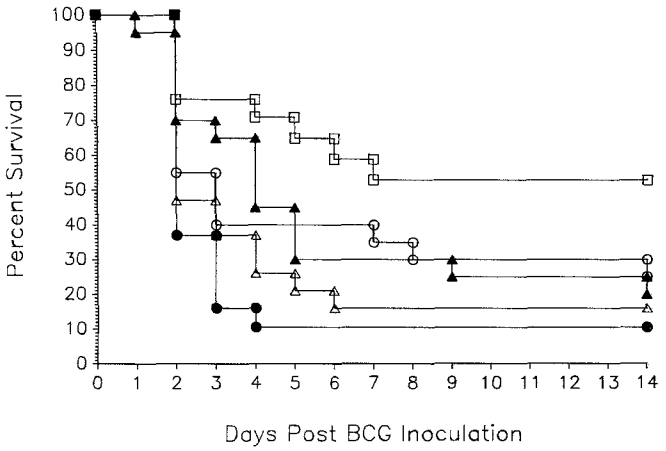

Fig. 2 Survival according to treatment after BCG rechallenge on day 0. ○—○ D5W; ●—● PRED; △—△ I+R; ▲—▲ I+R+C; □—□ I+R+P

with prednisolone alone [3] approached statistical significance (P=0.0669), suggesting that prednisolone alone could have a negative effect. Although our control group had better survival than group 2 (Pred), group 3 (I,R), or group 4 (I,R,C), this difference was not statistically significant.

Discussion

BCG is widely accepted as the treatment of choice for carcinoma in situ and has become one of the standard therapies for recurrent superficial transitional cell cancer (TCC) of the bladder. Serious side effects occur in 5% of patients and sepsis occurs in up to 0.4% [4]. We must be knowledgeable of the potential side effects; more importantly, we must know how to prevent and manage any serious side effects.

BCG is a live, attenuated organism, provided in a lyophilized form for intravesical instillation. Efficacy has been related to vaccine viability, but this viability can result in local or systemic infections after primary treatment, especially after traumatic catheterization on retreatment. The improvement in the survival of septic mice (DeHaven) [1] and patients (Steg) [7] when prednisolone was added to treatment with antituberculous antibiotics suggests that a hypersensitivity reaction may be a major contributing factor responsible for the septic reaction.

BCG sepsis is more commonly seen in situations where there is inflamed or disrupted urothelium allowing for i.v. absorption. It is recommended that treatment be withheld for several days after traumatic catheterization or biopsy, or until active infection (cystitis) has cleared [6]. The symptoms of continued fever and cystitis suggest the persistent presence of living organisms, and these patients are at increased risk of developing BCG sepsis. They should be treated with isoniazid, and BCG treatments should be withheld until the symptoms have resolved. Prophylactic treatment with isoniazid for 3 days beginning the morning before treatment can help prevent the fever and cystitis. These patients can still develop a septic reaction, despite prophylaxis, but this has occurred to our knowledge in only two patients [4].

Patients who develop sepsis may or may not be purified protein derivative (PPD) positive. PPD reactivity should not be taken as an indicator that the patient is safe to treat despite the presence of continued fever and/or cystitis [8]. All of the BCG strains available commercially appear to have similar incidences of sepsis.

Antituberculous antibiotics have been the primary treatment for BCG sepsis. BCG retains susceptibility to isoniazid, *para*-aminosalicyclic acid, streptomycin, ethambutol, rifampin, pyrazinamide, and, in most instances, cycloserine. The bacteriostatic effects of all antituberculous agents (except cycloserine) are not seen until after 3 days of treatment. Cycloserine is active within the first 24 h, but its benefit is controversial. The addition of steroids to the treatment regimen has proven of critical benefit to survival. Steg [7] first reported successful management of BCG sepsis in five of five patients using INH, rifampin, and prednisolone in 1989. Three of these patients developed sepsis after traumatic catheterization. Therapy was continued for 3 months. This is the treatment regimen currently recommended by Lamm. Our previous study of BCG sepsis using Tice BCG further supports combination therapy for BCG sepsis [1].

Our results in this animal model support the use of combination therapy with steroids and antituberculous antibiotics to treat BCG sepsis. Treatment with this regimen (group 5) resulted in a significant survival benefit compared with all other treatments and the control group. A survival rate of 53% in this group demonstrates the seriousness of BCG sepsis despite the aggressive treatment. Although our model showed no survival advantage for isoniazid and rifampin, or isoniazid, rifampin, and cycloserine, clinical experience has shown better survival than no treatment at all [6].

An important finding was the apparent reduction in survival in the group receiving only prednisolone. Immunosuppressed patients are more susceptible to overwhelming mycobacterial infections, and it follows that mice treated with steroids alone would be less capable of surviving an episode of BCG sepsis. A poor response to steroids also indicates that BCG sepsis is probably not due to a hypersensitivity reaction alone.

In summary, BCG is an excellent agent in our armamentarium against superficial TCC of the bladder. Although usually well tolerated, there are serious and life-threatening complications which must be recognized and treated when they occur. It is also important to use preventive measures when possible to avoid a septic reaction. Survival in BCG sepsis in humans is improved with combination therapy of antituberculous antibiotics and steroids, and our data show similar results in our mouse model. We also provide evidence that suggests treatment with steroids alone will result in worse overall survival.

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