ABSTRACT: Although superficial bladder cancer can be successfully treated by a transurethral resection (TUR), the high frequency of intravesical recurrence remains a concern. *Lactobacillus casei* (LC) preparation, a powdered preparation containing about $1 \times 10^{10}$ cells of LC strain Shirota per gram, has been safely used as a probiotic agent for more than 30 years in Japan. When orally administered, LC preparation has been reported to act as an immunomodulator and to potentiate antitumor responses in mice. Based on these reports, two randomized, controlled clinical trials have been conducted, and the oral administration of LC preparation has shown to be safe and effective not only as monotherapy, but also as a combination therapy with intravesical instillation chemotherapy, for preventing recurrence after TUR of superficial bladder cancer. Furthermore, a case-control study has also been conducted and the habitual intake of LC preparation was shown to reduce the risk of bladder cancer. Thus, LC preparation is considered to be effective for preventing not only the occurrence, but also recurrence after TUR of superficial bladder cancer.

KEY WORDS: Bladder Cancer, Probiotics, Transurethral resection

INTRODUCTION

Although superficial bladder cancer can be treated with transurethral resection (TUR), the high frequency of intravesical recurrence is a great concern to urologists. It has been reported that intravesical recurrence develops in 50-70% of patients within five years after TUR, and that the risk of progression to muscle invasive cancer is 5-20% (Jone and Campbell, 2007). Intravesical instillation of anticancer agents such as epirubicin (epi-ADM) has been reported to decrease the recurrence rate by about 20% (Nilsson et al., 2001).

The *Lactobacillus casei* (*LC*) preparation (Yakult Honsha, Co., Ltd., Tokyo) is a powdered preparation that contains about $1 \times 10^{10}$ cells of LC Shirota strain per gram. This preparation has been available as an agent for intestinal dysfunction for more than 30 years in Japan and has an established safety profile. Furthermore, this preparation has been widely taken as fermented milk products. When orally administered, *LC* preparation has been reported to act as an immunomodulator through the intestinal tract and to potentiate antitumor responses in mice (Kato et al., 1994).

We conducted a prospective, randomized controlled trials (Trial 1) (Aso et al., 1995) to investigate the safety of an oral administration of *LC* preparation and its preventive effect on the recurrence after TUR of superficial bladder cancer, and also conducted a prospective, randomized controlled trial (trial 2) (Naito et al., 2007) to evaluate whether it can enhance preventive effect of recurrence by intravesical instillation of epi-ADM after TUR of superficial bladder cancer. Furthermore, we conducted a case-control study to investigate the risk reduction of bladder cancer by habitual intake of *LC* preparation (Ohashi et al., 2002).

PATIENTS AND METHODS

Cases assigned to the *LC* preparation group received oral administration of *LC* preparation (3 g/day) for one year. Control cases received no medication. Patients were evaluated for intravesical recurrence and adverse drug reactions (ADRs).

1) Trial 1: Trial 1 was set as a placebo-controlled, double-blind study. 138 patients with superficial bladder cancer were enrolled from Sep. 1990 to Nov. 1991. Patients were stratified into the following 3 groups: (A) with primary multiple tumors, (B) with recurrent single tumor, and (C) with recurrent multiple tumors.

2) Trial 2: Between August 1999 and December 2002, 207 patients with superficial bladder cancer were registered as study candidates, and underwent TUR followed by intravesical instillation of epi-ADM (30 mg/30 mL saline) twice during one week. After histological confirmation of superficial bladder cancer, they were registered again as study participants and randomized to receive either treatment with 6 additional intravesical instillations...
of epi-ADM during the 3-month period after TUR (epi-ADM group; n=102) or intravesical chemotherapy on the same schedule as the epi-ADM group plus oral administration of LC preparation (3 g/day) for one year (epi-ADM+ LC group; n=100). Intravesical recurrence and ADRs were evaluated.

3) Case-control study: A total of 180 cases were selected from 7 hospitals, and 445 population-based controls matched by gender and age were also selected. Interviewers asked them 81 items. The conditional logistic regression was used to estimate adjusted odds ratios (OR).

RESULTS

1) Trial 1: LC preparation showed a better prophylactic effect than placebo in subgroup A and B, whereas no significant difference was observed in subgroup C. Slight ADRs by LC preparation were observed, but they were tolerable.

2) Trial 2: LC preparation significantly enhanced the prophylactic effect of epi-ADM. Incidence and severity of ADRs did not significantly differ between the groups.

3) Case-control study: The OR of smoking was 1.61 (95% confidence interval: 1.10-2.36). Those of previous (10-15 years ago) intake of fermented milk products were 0.46 (0.27-0.79) for 1-2 times/week and 0.61 (0.38-0.99) for 3-4 or more times/week, respectively.

DISCUSSION AND CONCLUSIONS

Oral administration of LC preparation is safe and effective for preventing recurrence after TUR of superficial bladder cancer. The habitual intake of LC preparation reduces the risk of bladder cancer. Oral administration of LC preparation can also enhance the preventive effect of intravesical epi-ADM on recurrence after TUR of superficial bladder cancer. Combination of Intravesical instillation of epi-ADM plus oral administration of LC preparation is a novel, promising treatment for prevention of recurrence after TUR of superficial bladder cancer.

REFERENCES


