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# Evaluation of multidisciplinary treatment of bladder cancer, especially in chemoimmunotherapy (ADM and OK-432) as a consolidation therapy

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***Summary.*** *The relapse rate of bladder cancer (transitional cell Ca) is said to be about 45%–80% even after tumor resection. Multidisciplinary treatment was designed and studied to prevent such recurrence. This treatment was designed to have three steps: induction, consolidation, and maintenance therapy. Following surgical tumor removal, OK-432 and Adriamycin (ADM) were administered as consolidation therapy, followed by administration of PSK and carboquone (CQ) in small amounts as maintenance therapy continuously for about 3 years, and the course was observed.*

*In both consolidation and maintenance groups various non-specific immunoparameters were superior in groups receiving combined immunotherapeutic agents. Thus, the use of immunotherapeutic agents in combination with chemotherapeutic agents was considered to be effective. The 3-year recurrence rate was only 8% in the multidisciplinary treatment group, while that in the non-multidisciplinary treatment group was 61%. This approach, especially with chemoimmunotherapy (ADM and OK-432) as a consolidation therapeutic mode, is therefore considered to be useful for the prevention of recurrence.*

## Introduction

It is commonly known that primary superficial bladder cancer (transitional cell carcinoma of the bladder) relapses in 45%–80% of cases even after surgical removal of the tumor(s) [3, 12, 13]. Such a high frequency of recurrence must be prevented.

We have designed for administration in primary superficial bladder cancer a multidisciplinary treatment modality to prevent postoperative relapse. Our protocol uses the chemotherapeutic agent Adriamycin (ADM) in combination with the immunopotentiator picibanil (OK-432) as consolidation therapy. Effectiveness was evaluated by a randomized controlled trial and the rate of recurrence at 3 years was determined by Student's *t*-test [2, 4].

## Materials and methods

The subjects of the present study consisted of patients with primary superficial bladder cancer, in whom histopathologic methods yielded a diagnosis of transitional cell carcinoma of the bladder who were found to be tumor-free after TUR-Bt, TUC, or open surgery, and for whom periodical evaluation of tumor recurrence by means of postoperative cystoscopy was possible.

Originally about 60 patients were included in the present study but some dropped out, so that 39 male and 12 female patients, totalling 51 cases, were studied (Table 1).

The multidisciplinary treatment procedure consisted of induction therapy, consolidation therapy, and maintenance therapy. After admission, surgery and immunotherapy were performed as induction therapy. Subsequently, consolidation therapy consisting of concomitant administration of an immunopotentiator, OK-432, and ADM 30 mg (≧ 70 years old) or 50 mg (< 70 years old) twice a week for 3 weeks to give a total of 180 or 300 mg [14, 16, 17] was given followed by a 3-year maintenance therapy program with 0.5 mg/day of the anticancer agent carboquone (CQ) and 3.0 g/day PO of the immunopotentiator PSK.

During this period, urological tests and measurement of non-specific immunologic parameters (peripheral lymphocyte count, PPD, PHA skin test, Tγ, reactive ratio of lymphocytoblastogenesis ConA/PHA, CEA, etc.) were repeated regularly. The results for the 3-year period were examined statistically to compare the recurrence rate of the non-multidisciplinary treatment group (patients treated by surgical operation alone) with that of the multidisciplinary treatment group.

In addition, the side-effects of ADM alone in the consolidation therapy were compared with those in the group receiving concomitant immunologic agents.

Stages were determined in accordance with the UICC pT classification. Patients in $T_a$ through $T_3$ whose tumors had been removed surgically were studied [6, 15].

**Table 1.** Multidisciplinary treatment of bladder cancer (background factors)

| | | | Controls | OK-432 | $X_0^2$ |
|---|---|---|---|---|---|
| 1. | Sex | Male | 13 | 26 | 0.279 (df = 1) |
| | | Female | 5 | 7 | (n.s.) |
| 2. | Stage | $T_1$ | 1 | 1 | 1.484 (df = 2) |
| | | $T_2$ | 5 | 8 | (n.s.) |
| | | $T_3$ | 12 | 24 | |
| 3. | Metastasis | (−) | 18 | 33 | (n.s.) |
| | | (+) | 0 | 0 | |
| 4. | Chemo-therapy | ADM | 15 | 33 | |
| | | Others | 3 | 0 | |

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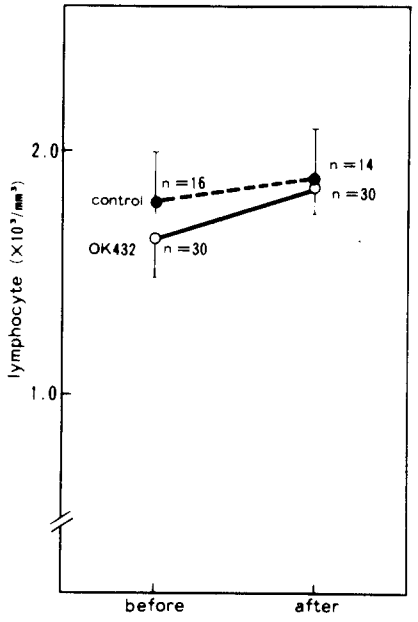


**Fig. 1.** Variations of lymphocyte counts after multidisciplinary treatment in bladder cancer

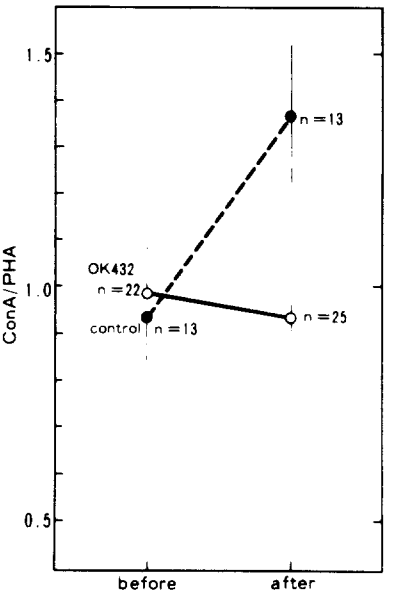


**Fig. 3.** Variations of reactive ratio mitogen Con A/PHA after multidisciplinary treatment of bladder cancer

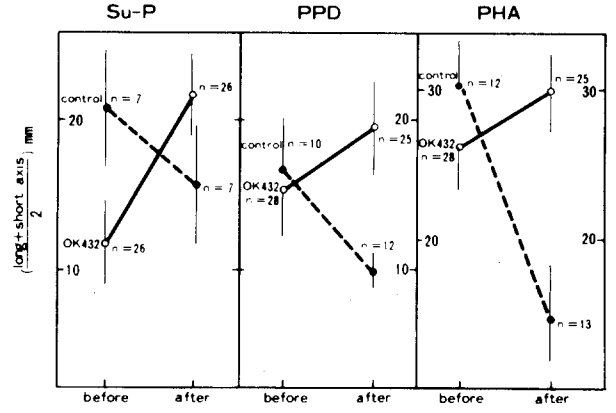


**Fig. 2.** Variations in PPD and PHA skin test and in Su-P skin test after multidisciplinary treatment of bladder cancer

## Results

*1. Variations in immunologic parameters during consolidation therapy*

Changes in immunologic parameters 1 week after consolidation therapy with ADM and OK-432 in comparison to baseline values were investigated.

*a) Peripheral lymphocyte count (Fig. 1).* Although no remarkable difference in the peripheral lymphocyte count was noted, a tendency for the lymphocytes to increase in number suggested the frequency of reaction of helper T cells and killer T cells in the cell-mediated immunity of the hosts.

*b) PPD and PHA skin tests, and Su-P skin test (Fig. 2).* A significant difference in PPD and PHA skin test was noted between the control and multidisciplinary groups.

*c) Reactive ratio of lymphocytoblastogenesis (ConA/PHA) (Fig. 3).* The reactive ratio of lymphocytoblastogenesis by mitogen ConA/PHA was determined. There was a significant difference between controls and the multidisciplinary group [19].

*d) IgGFcR⁺ T cell (Tγ) in T cell subsets (Fig. 4).* When the control group was compared with that receiving the ADM and OK-432 combination, the Tγ of the controls showed an increase, which suggested stimulation of the function of suppressor T cells, while the recovery of cell-mediated immunity in the combination group was possible.

*e) Blood CEA (Fig. 5).* Controls showed a tendency toward some increase in blood CEA, while the ADM plus OK-432 combination group showed a marked decrease in this parameter from abnormally high levels down to normal levels.

From this it was postulated that when ADM is administered in large doses in consolidation therapy, the non-specific immunity of the host is increased by the concomitant use of adjuvant immunotherapy in spite of the strong immunosuppressive action of ADM, which in turn permits administration of large doses to provide increased effectiveness.

*2. Side-effects of ADM*

It is well known that ADM has severe side-effects, such as leukopenia, alopecia, gastrointestinal disturbances, and myocardial disorders [1, 18].

In our study, gastrointestinal disorders generally continued for 2–3 days in the ADM plus OK-432 combination group, but these were relatively moderate in degree, and in most cases leukopenia abated within 2 weeks, although it was severe in a couple of cases.

Nearly all patients treated with ADM alone showed alopecia; however, in the combination group it was limited to 10%–30% of their hair, and none showed myocardial disorders. This shows that the addition of the immunopotentiator OK-432 to ADM therapy was useful in the prevention of drug side-effects.

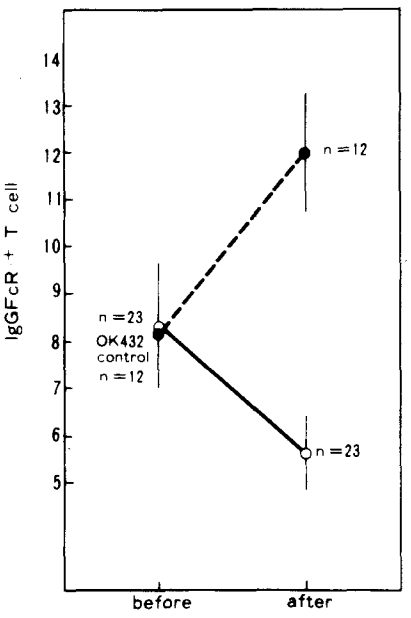


**Fig. 4.** Variations in lgGFcR$^+$ T cell after multidisciplinary treatment of bladder cancer

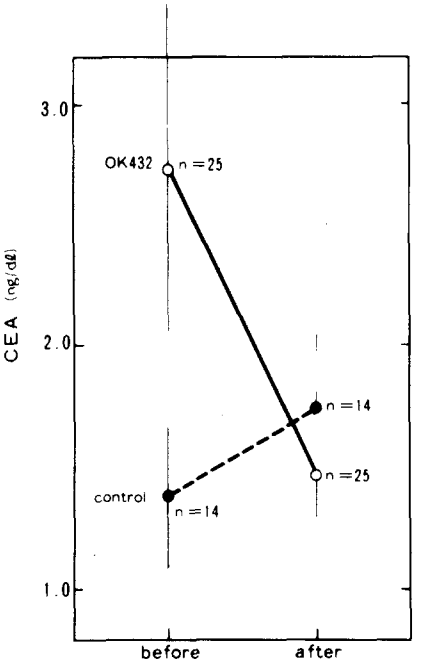


**Fig. 5.** Variations in CEA after multidisciplinary treatment of bladder cancer

*3. Maintenance therapy*

Following consolidation therapy, the subjects received maintenance therapy at outpatient clinics. Maintenance therapy consisted of 0.5 mg/day of CQ and 3.0 g/day of the immunopotentiator PSK for 3 years. During this period, the patients were followed-up with periodical measurements of immunologic parameters and other examinations including cystoscopy to check for relapse.

*4. Recurrence rate (Table 2)*

The recurrence during the 3-year period was studied statistically to determine the usefulness of the multidisciplinary treatment for prevention of recurrence.

The group in which multidisciplinary treatment was performed completely as planned was called group A, while another group of patients whose tumors were removed by surgery and who received no other adjuvant therapy were placed under observation and called group B. There were 24 patients in group A and 27 in group B. Recurrence was evaluated according to the pT classification.

In group A, no recurrence occurred among six cases in $T_a$ through $T_1$; among 10 of $T_2$ cases, recurrence occurred in one case (10%); in $T_3$ patients, one of eight cases, or 13%, had recurrence; thus a total of two cases of recurrence, or 8% of all 24 cases was seen.

In group B, there were 10 $T_a$–$T_1$ cases, with recurrence occurring in one case (10%); among $T_2$ patients tumor relapsed in eight of 10 cases, or 80%; in $T_3$ patients recurrence occurred in eight of eight patients (100%); thus in total, recurrence was seen in 17 of 28 patients, or in 61% of the total.

Comparison of the disease-free rates (%) for groups A and B also shows a significant difference between the two groups (Fig. 6).

**Table 2.** Recurrence rate (%) in bladder cancer

| Stage | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Cases | No. of recurrences | Recurrence rate (%) | Cases | No. of recurrences | Recurrence rate (%) |
| $T_a$~$T_1$ | 6 | 0 | 0 | 10 | 1 | 10 |
| $T_2$ | 10 | 1 | 10 | 10 | 8 | 80 |
| $T_3$ | 8 | 1 | 13 | 8 | 8 | 100 |
| Total | 24 | 2 | 8* | 28 | 17 | 61* |

* The difference between group A and group B is statistically significant ($P < 0.01$)

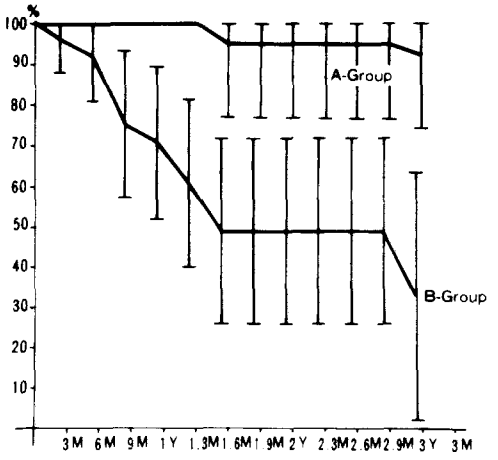


**Fig. 6.** Disease-free rate (%) in bladder cancer

## Discussion

Immunotherapy for cancer, which was first advocated by Mathé et al. [7] in 1969 and Morton et al. [8] in 1974, now requires review even though it is widely used. Nevertheless, it has been our contention that the combination of immunologic agents with chemotherapeutic agents such as ADM, which have strong immunosuppressive actions, is an effective means

of making the use of large doses of the chemotherapeutic agents possible while reducing their side-effects [9–11].

BCG and OK-432 are considered effective immunopotentiators for use in consolidation therapy, as they help to increase the immunity of the host above the normal level. Ideally they should be given intracutaneously to stimulate the immunologic system [5, 9–11].

Our protocol for prevention of the recurrence of bladder cancer is to remove the patients' tumors, after which consolidation and maintenance therapy are administered and the patients are followed-up for long periods of time. It is important to combine consolidation therapy with maintenance therapy in the treatment of patients once their tumors have been removed. This is where the significance of our multidisciplinary treatment lies.

Overall, in group A, in which the patients received our multidisciplinary treatment protocol for prevention of recurrence of bladder cancer, the recurrence rate was only 8%; while the rate was 61% in group B, in which multidisciplinary treatment was not given.

The most important element of this treatment is to persuade patients to agree to consolidation therapy with ADM and OK-432 even after their tumors have been removed.

The side-effects of ADM observed in our study were significantly lower than those reported by Carter et al. [1]. The difference in the rates of recurrence in the group receiving multidisciplinary treatment and the group not receiving multidisciplinary treatment is evidence that our multidisciplinary approach was useful in the prevention of recurrence of bladder cancer.

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