A Randomized Trial Comparing Intravesical Instillations of Mitoxantrone and Doxorubicin in Patients with Superficial Bladder Cancer

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Background: This randomized trial was conducted to compare the efficacy and side effects of intravesical mitoxantrone instillation with those of doxorubicin in superficial bladder cancer following transurethral resection.

Methods: Sixty-three patients were randomized into mitoxantrone and doxorubicin groups. Most of the patients enrolled were elderly people (mean age, 71 years). The instilled doses of doxorubicin and mitoxantrone were 30 and 14 mg, respectively. Disease recurrence and side effects were compared using Fisher's exact test. The interval to recurrence was shown by Kaplan-Meier survivorship curves, and the log-rank test was used to compare the time to recurrence.

Results: The median follow-up period was 36 months. Thirty-three patients received mitoxantrone, whereas 30 patients used doxorubicin. The recurrence rate in the doxorubicin group was 30% (95% CI: 19.8%-38.8%), while it was 27.3% (95% CI: 17.5%-36.8%) in the mitoxantrone group. The median recurrence-free survival in the mitoxantrone group and in the doxorubicin group was 22 and 20 months, respectively ($p = 0.580$). Higher recurrence rates were found for Grade III and multiple primary tumors. There was no significant difference in response rates ($p = 0.784$). The incidence of side effects was 20% in the doxorubicin group and 21.2% in the mitoxantrone group. However, the difference was not significant ($p > 0.99$).

Conclusions: The results revealed that the efficacy and side effects of mitoxantrone were similar to those of doxorubicin. Especially for patients with pulmonary tuberculosis or aged patients with primary bladder tumors, mitoxantrone and doxorubicin may be the tolerable and effective intravesical agents.

(Chang Gung Med J 2003;26:91-7)

Key words: **bladder cancer, intravesical chemotherapy, mitoxantrone, doxorubicin.**

According to the cancer registry annual report in Taiwan (1999), cancer of the urinary bladder accounted for 1.9% of all cancer-related deaths (550 deaths/year).[1] The incidence is similar to that

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Received: May 29, 2002; Accepted: Nov. 7, 2002
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reported for Western countries.[2] More than 2/3 of bladder cancers present as superficial (pTa or pTl) transitional cell carcinomas, which means tumors confined to the epithelium or lamina propria. Tumor grading and staging are the most important factors indicating recurrence and progression of superficial bladder cancer.[3-5]

The mainstay of treatment is transurethral resection (TUR) of the tumor, however recurrence rates still remain high. Recurrence was reported to be between 50% and 80% within the first year.[6,7] Therefore, adjuvant intravesical therapy after TUR has been used for prophylaxis against recurrence. Tumor recurrence rates were reduced by 15%-18% after adjuvant treatment in an early report.[8] Recently, better results showed that tumor recurrence rates may be reduced by as much as 30%-44%.[9] Randomized studies also showed that adjuvant intravesical treatment presented lower recurrence rates than TUR alone.[10,11]

Among the effective intravesically instilled agents, doxorubicin, epirubicin, mitomycin, mitoxantrone, thiotepa, and bacillus Calmette-Guerin (BCG) are the most commonly used drugs.[12-16] Due to the high prevalence of pulmonary tuberculosis in the Keelung area of northern Taiwan,[17] we did not select BCG for intravesical instillation in our hospital. Doxorubicin is an anthracycline antitumor antibiotic that interferes with DNA synthesis especially in S-phase cell division.[18] Mitoxantrone is a high-molecular-weight anthracenedione derivative which intercalates with DNA and inhibits topoisomerase II; it also exhibits steep dose-response relationships against bladder cancer cells grown in tissue culture.[19] Both agents have relatively low systemic absorption and show response rates of around 70%.[11,12]

Doxorubicin has been used as an intravesical agent for more than 20 years; it has also been used as a comparative agent in many clinical trials treating superficial bladder cancer.[8,11,12,18,20] There are no previous reports of randomized studies comparing doxorubicin and mitoxantrone. Therefore, we randomized and compared both the efficacy and safety between doxorubicin and mitoxantrone as an adjuvant intravesical treatment of pTa and pTl transitional cell carcinomas of the urinary bladder in this study.

METHODS

From January 1994 to August 2001, we conducted a randomized trial comparing doxorubicin and mitoxantrone as an adjuvant intravesical treatment for bladder cancer at Keelung Chang-Gung Memorial Hospital. Sixty-three patients with superficial bladder tumors who had received TUR were enrolled in the study. Among the enrolled patients, there were 53 with primary tumors and 10 with recurrent tumors. Among the 10 recurrent tumors, 7 patients had received no adjuvant intravesical therapy, whereas 3 patients had previously received mitomycin adjuvant intravesical therapy. Twenty-seven primary tumors and 6 recurrent tumors were categorized into the mitoxantrone group, whereas 26 primary tumors and 4 recurrent tumors were in the doxorubicin group. All patients must have received TUR with histopathologically proven transitional cell carcinoma (stages pTa and pT1, grades I-III).

In this study, 7 patients were found to have multicentric tumors; 4 patients were categorized into the mitoxantrone arm and 3 patients into the doxorubicin arm. The other inclusion criteria included: no evidence of active urinary tract infection; no distant metastasis; no other malignancy except basal cell carcinoma of the skin; no previous irradiation of the bladder; no intravesical chemotherapy during the last 3 months; white blood cell count higher than 3500/mm^3 and platelet count greater than 100,000/mm^3; performance status ≤2; normal cardiac, liver, and renal function; and informed consent.

Two weeks after TUR, all patients were randomized and received either doxorubicin (30 mg diluted in 50 ml normal saline) or mitoxantrone (14 mg diluted in 50 ml normal saline) via a urethral catheter into the bladder, which was retained for 2 h. The instillation was performed every week during the first month and once a month during the following 11 months. Adjuvant intravesical therapy was continued for 1 year unless recurrence was noted. Urinary cytology was performed every month during the first year and every 3 months thereafter. Cystoscopy was conducted every 3 months during the first year and every 6 months thereafter. If urinary cytology showed abnormal findings, cystoscopy was immediately performed to evaluate the possibility of recurrence. In case of abnormal lesions found

in the cystoscopic examination, a biopsy was done, and the histopathology was reviewed. Recurrence was established only by histologic examination of the biopsied lesion. Side effects were recorded at every drug administration. Failure of adjuvant treatment was defined as tumor recurrence, further TUR having to be repeated, and intravesical agents being changed. All patients were followed up at least for 2 years.

Proportions of patients in each group with recurrence or side effects were compared using Fisher's exact test. The interval to recurrence was shown by the Kaplan-Meier survivorship curves, and the log-rank test was used to compare the time to recurrence between these 2 groups.

RESULTS

Sixty-three patients were randomized into the mitoxantrone and doxorubicin groups. Two patients were unable to retain the intravesical agents in the bladder due to urinary incontinence after TUR, and another did not receive regular intravesical therapy because of painful chemical cystitis induced by mitoxantrone. According to the intent-to-treat population principle, these 3 patients were also included in the data analysis. Two patients were randomized into the mitoxantrone group, and the other was in the doxorubicin group.

This randomized study included 52 male patients and 11 female patients with a mean age of 71 (range, 56-81) years. There were 12 patients with a past history of pulmonary tuberculosis and 4 patients with pneumoconiosis. The clinical and pathologic characteristics of both the mitoxantrone and doxorubicin groups are shown in Table 1. The median follow-up period was 36 (range, 24-64) months. Nine patients developed recurrence in the doxorubicin arm with a recurrence rate of around 30% (95% CI: 19.8%-38.8%). Nine patients showed recurrence in the mitoxantrone arm, and the recurrence rate was 27.3% (95% CI: 17.5%-36.8%). Among the 10 recurrent tumors, 2 of 6 patients in the mitoxantrone group and 1 of 4 patients in the doxorubicin group developed recurrence. As for the 7 multicentrical lesions, 2 of 4 patients in the mitoxantrone arm showed recurrence, while the other 3 patients in the doxorubicin arm all developed recurrence. There was no significant difference in the response rates between the mitoxantrone and doxorubicin groups ($p = 0.784$; Fisher's exact test).

Table 1. Clinical and Pathologic Characteristics

	Doxorubicin	Mitoxantrone
No. of patients	30	33
Gender		
Male	25	27
Female	5	6
Mean age (year)	72	70
Range (year)	56-75	62-81
History of pulmonary tuberculosis	6 (20%)	6 (18%)
History of pneumoconiosis	1 (3%)	3 (9%)
Primary tumor	26 (87%)	27 (82%)
Recurrent tumor	4 (13%)	6 (18%)
Number of tumors		
Solitary	27 (90%)	29 (88%)
Multiple	3 (10%)	4 (12%)
Stage		
pTa	8 (27%)	9 (27%)
pTl	22 (73%)	24 (73%)
Grade		
G1	4 (13%)	5 (15%)
G2	17 (57%)	19 (58%)
G3	9 (30%)	9 (27%)

The median recurrence-free survival was 22 (range, 14-42) months in the mitoxantrone group and 20 (range, 9-40) months in the doxorubicin group ($p = 0.580$; by log-rank test). The interval to first recurrence is shown by the Kaplan-Meier survivorship curve (Fig. 1). Tumor recurrence in relation to stage and grade is shown in Table 2. Although adjuvant intravesical treatment with mitoxantron or doxorubicin was given, 11 of 18 patients with grade III tumors developed recurrence. Higher recurrence rates were noted especially for grade III and multiple primary tumors in both groups. Three patients (10%) in the doxorubicin arm showed progression to muscle invasive disease after 36, 38, and 42 months, respectively. Two patient (6.1%) in the mitoxantrone arm developed progressive disease after 32 and 39 months, respectively. These 5 patients all had stage pT1 or grade III tumors. In addition, there was no statistically significant difference found in disease progression between the doxorubicin and mitoxantrone groups. The results of urinary cytology were all negative during the follow-up period.

The main side effects included dysuria, urinary frequency, hematuria, urinary tract infection, and

bladder spasms. The incidences of side effects are shown in Table 3 (WHO criteria). Frequencies of symptoms were 21.2% in the mitoxantrone arm and 20% in the doxorubicin arm. One patient was unable to tolerate the dysuria induced by mitoxantrone, and was therefore excluded from the efficacy analysis. There was no significant difference in the frequency of side effects between the mitoxantrone and doxorubicin groups ($p > 0.99$; Fisher's exact test). In this study, there was no recurrence of pulmonary tuberculosis or aggravation of pneumoconiosis during the period of intravesical treatment.

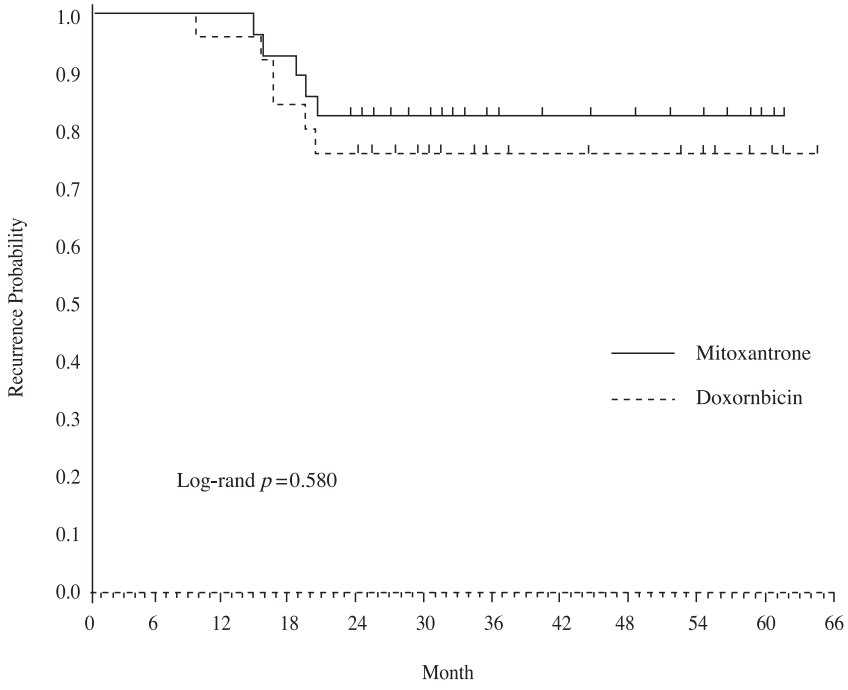

Fig. 1 Kaplan-Meir curves for interval to recurrence.

Table 2. Tumor Recurrence in Relation to Stage and Grade

	Doxorubicin	Mitoxantrone
Recurrence no. (%)	9 (30%)	9 (27.3%)
Follow-up period (median) (month)	25-64 (36)	24-61 (36)
Recurrence-free survival (month) (median)	9-40 (20)	14-42 (22)
Recurrence related to stage	3 (37%)	3 (33%)
pTa		
pTl	6 (27%)	6 (25%)
Recurrence related to grade		
G1	0 (0%)	0 (0%)
G2	3 (18%)	4 (21%)
G3	6 (67%)	5 (56%)

Table 3. Side Effects of Intravesical Doxorubicin and Mitoxantrone Instillation

	Doxorubicin	Mitoxantrone
No. of patients enrolled for evaluation	30	33
No. of patients with complications (%)	6 (20 %)	7 (21.2%)
Dysuria	4 (13.3%)	5 (15.1%)
Urinary frequency	5 (16.7%)	6 (18.1%)
Hematuria	4 (13.3%)	5 (15.2%)
Urinary infection	3 (10%)	4 (12.1%)
Bladder spasm	2 (6.7%)	3 (9.1%)

DISCUSSION

Nowadays, TUR is known as the most effective and standard treatment for superficial bladder tumors. However, nearly 50%-70% of patients develop recurrence following TUR, and progression was found in approximately 15% of these patients.[20] Adjuvant intravesical chemotherapy is able to decrease recurrence rates by 15%-18% during the first 2 years after TUR.[8] In several reports of adjuvant intravesical instillations of BCG, the recurrence rates even decreased by 20%-30%.[21-23] Despite BCG having been the most effective intravesical agent in recent years, the side effects are still prominent; complications include granulomatous and ulcerative cystitis, hepatitis, and lung infections.[24]

According to the annual report on public health in Taiwan, coal miners, and those with pneumoconiosis and lung cancers are all high-risk groups for pulmonary tuberculosis infection.[17] This study was performed after 1994, and BCG instillations were not popular at that time. As there are many coal miners, and pneumoconiosis and pulmonary tuberculosis patients in our hospital, we were not certain of the influence of BCG instillations on pulmonary tuberculosis patients. This was why we selected doxorubicin and mitoxantrone as adjuvant intravesical agents in this study. In a subsequent study, we will compare the efficacy of mitoxantrone against BCG instillations. In the meantime, we hope to evaluate the influence of BCG instillations on pulmonary tuberculosis patients.

The recurrence rates after adjuvant doxorubicin instillation have been reported to be 30%-38% in earlier studies.[25] In this study, the recurrence rate (30%) of doxorubicin instillation was lower than those of several previous reports. This might be a result of a relatively smaller population and larger percentage of grade II disease in this study. Although mitoxantrone installation showed a slightly lower recurrence rate (27.3%) than doxorubicin treatment (30%) in this randomized study, there was no significant difference in the efficacy between these 2 groups.

Both mitoxantrone and doxorubicin are anthraquinone derivatives. The major difference between them is that mitoxantrone has more-intense and broader antitumor activity according to an in vitro study, and it also has high molecular weight with extensive binding to tissue.[26] Before this study, we tried to use 16 mg/ml of mitoxantrone as an intravesical dosage for patients. Unfortunately, several episodes of urinary irritation developed, which made patients intolerant of further treatment. That is why we selected 14 mg of mitoxantrone as the intravesical dosage. In this study, higher recurrence rates were noted especially for grade III tumors. A poor response rate was also found in the group of multicentrical lesions despite adjuvant intravesical treatments being given. These results are comparable with those of other previous reports.[8,19,20] Yet, there was only a small number of recurrent cases or multicentrical lesions enrolled in this study; thus, we recommend that these results should be confirmed using a larger population.

As for side effects, the incidence in the doxorubicin arm and that in the mitoxantrone arm were 20% and 21.2%, respectively. The severity of the side effects was mostly within grade II (WHO criteria). However, there was also no significant difference between these 2 groups. There was no recurrence of pulmonary tuberculosis or episodes of myelosuppression during the follow-up period, implying that these 2 intravesical agents can be used safely.

Doxorubicin has been used as an intravesical agent with positive results for more than 20 years,[20] however there have only been a few previous studies on mitoxantrone intravesical treatment.[14,20,27] In this randomized study, mitoxantrone instillation revealed a comparable result to doxorubicin treatment. Even though the mean age (71 years) of the enrolled patients in this study was older than that of other reports, most were able to tolerate the dosage of mitoxantrone instillation.

For elderly patients and those with a history of pulmonary tuberculosis, mitoxantrone or doxorubicin may be the drug of choice for adjuvant intravesical treatment. The recurrence rate with mitoxantrone intravesical adjuvant treatment in this study was 27.3%, whereas that of BCG installations was around 15%-25%.[21-23] To date, there are no clinical trials being conducted comparing the efficacy of mitoxantrone against BCG instillation. Therefore, we will perform further randomized studies comparing these 2 adjuvant intravesical agents.

REFERENCES

1. Cancer registry annual report 1999. Department of Health in Taiwan.
2. Silverbery E, Boring CC, Squires TS. Cancer statistics, 1990. CAT Cancer J Clin 1990;40:9-26.
3. Torti FM, Astan D, Bert L, Aston D, Mackenzie N, Farysel M, Freiha F. Superficial bladder cancer: the primary grade in the development of invasive bladder disease. J Clin Oncol 1987;5:125-30.
4. Henri T, Pham HT, Mark S, Soloway MS. High risk superficial bladder cancer: Intravesical therapy for T1G3 transitional cell carcinoma of the urinary bladder. Semin in Urol Oncol 1997;15:147-53.
5. Sidramsky D, Frost P, Eschenback AV, Oyasu R, Antonette C, Preisinger RA, Vogelstein B. Clonal origin of bladder cancer. N Engl J Med 1992;326:737-40.
6. Haaff EO, Dresner SM, Ratliff TL, Catalona WJ. Two courses of intravesical bacillus Calmette-Guerin for transitional cell carcinoma of the bladder. J Urol 1986;136: 820-4.
7. Altay B, Girgin C, Kefi A, Cikili N. The best management of superficial bladder tumors: comparing TUR alone versus TUR combined with intravesical chemotherapy modalities? Int Urol Nephrol 2000;32:53-8.
8. Kurth KH, Bouffioux C, Sylvester R, Vander Meijdan AP, Oosterlinck W, Brausi M. Adjuvant chemotherapy of superficial transitional cell bladder carcinoma: preliminary results of a European Organization for Research in treatment of Cancer randomized trial comparing doxorubicin and transurethral resection only. J Urol 1984;132: 288-90.
9. Kurth KH, Bouffioux C, Sylvester R, Vander Meijden AP, Oosterlinck W, Brausi M. Treatment of Superficial bladder tumors: achievements and needs. The EORTC Genitourinary Group. Eur Urol 2000; 37 suppl 3:1-9.
10. Krege S, Giani G, Meyer R, Otto T, Rubben H. A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transitional resection only versus transurethral resection plus mitomycin C versus transurethral resection plus bacillus Calmette-Guerin. J Urol 1996;156:962-6.
11. Ali-el-Dein B, el-Baz M, Aly AN, Shamaa S, Ashamallah A. Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stage pTa and pT1): a randomized prospective study. J Urol 1997;158:68-74.
12. Sengor F, Beysel M, Erdogan K, Erol A, Tuzluoglu D. Intravesical epirubicin in the prophylaxis of superficial bladder cancer. Int Urol Nephrol 1996;28:201-6.
13. Boccardro F, Cannata D, Rubagotti A, Guarneri D, Gurotto A, Martorana G, Pegorari C, Salvaggi F, Salvia G, Gomeri G, Bvno A, Borella T, Gialiami L. Prophylaxis of superficial bladder cancer with mitomycin or Interferon alfa-2b: results of multicenter Italian study. J Clin Oncol 1994;12:7-13.
14. Latif Y, TalatY, Zissis NP, Arihan N, Yasar B. Intravesical mitoxantrone for superficial bladder tumors. Anti-cancer Drug 1994;5:95-8.
15. Heney NM, Barton B, Kovntz WW, Soloway M, Trump DL, Hazra T, Weinstein RS. Intravesical thiotepa versus mitomycin C in patients with Ta, T1 and TIS transitional cell carcinoma of the bladder: a phase III prospective randomized study. J Urol 1988;140:1390-3.
16. Pansadoro V, Emiliozzi P, Defidro L, Donadio D, Florio A, Maurelli S, Lauretti S, Sternberg CN. Bacillus Calmette-Guerin in the treatment of stageT1 grade3 transitional cell carcinoma of the bladder; Long-term results. J Urol 1995;154:2054-8.
17. Annual report of Department of Health in Taiwan. 1996
18. Chai M, Wientjes MG, Badalament RA, Burgers JK, Au JL. Pharmacokinetics of intravesical doxorubicin in superficial bladder cancer patients. J Urol 1994;152:374.
19. Huncharek M, Geschwind JF, Witterspoon B, Mcgarry R, Adecok D. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trial. J Clin Epidemiol 2000; 53:676-80.
20. Vander Meijdan AP, Kurth KH, Oosterlinck W, Debruyne FM. Intravesical therapy with adriamycin and 4-epirubicin for superficial bladder tumors. The experience of the EORTC group. Cancer Chemother. Pharmacol 1992; supp1:95-8.
21. Herr HW. Transurethral resection and intravesical therapy of superficial bladder tumors. Urol Clin N Am 1991;18: 525.
22. Brake M, Loertzer H, Horseh R, Kellar M. Long-term results of intravesical bacillus Calmette-Guerin therapy for stage Tl superficial bladder cancer. Urology 2000;55: 673-8.
23. Cookson MS, Sarosdy MF. Management of stage T1 superficial bladder cancer with intravesical bacillus Calmette-Guerin therapy. J Urol 1992;148:797-801.
24. Habscheid W, Feire F, Dahm HH. Miliary pneumonia after the intravesical BCG therapy of a superficial urothelail carcinoma of the bladder. Dtsch Med Wochenschr 1999;124:993-7.
25. Zincke H, Utz DC, Taylor WF, Myers RP, Leary FJ. Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: a prospective randomized, double blind, controlled trial. J Urol 1983;129:505-9.
26. Hepburn PJ, Oliver RT, Riley PA, Hill BT, Masters JR. Comparison of the cytotoxic activities of chemotherapeutic drugs using a human bladder cancer cell line. Urol Res 1985;13:27-34.
27. Chiang PH, Chiang CP. Intravesical mitoxantrane in superficial bladder cancer. Kaohsiung J Med Sci 2000: 16:91-4.

隨機研究Mitoxantrone及Doxorubicin治療表淺性膀胱癌

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背 景： 這是個隨機研究比較Mitoxantrone及Doxorubicin兩種藥物在膀胱灌注的效果及副作用。

方 法： 63位表淺性膀胱癌病患手術後，隨機分配接受Mitoxantrone 14mg或Doxorubicin 30mg作膀胱灌注。大多數的病人均爲老年人(平均年齡71歲)。我們用Fisher's exact test比較兩種藥物的效果及副作用，用log-rank test比較二者發生復發的時間，並用Kaplan-Meir的圖形表示。

結 果： 追蹤期的中位數爲36個月，其中33位接受Mitoxantrone，其復發率爲27.3% (95% C.I.: 17.5-36.8%)，無疾病復發存活期的中位數爲22個月，其他30位接受Doxorubicin，其復發率爲30% (95% C.I.: 19.8-38.8%)，無疾病復發存活期的中位數爲20個月。雖然Mitoxantrone之復發率較低($p=0.784$)及發生復發時間較長($p=0.580$)，但二者之差別並沒有達到統計意義。而分化度爲Grade III或多發性原發位腫瘤較容易復發。膀胱灌注的副作用包括血尿、頻尿、解尿疼痛及泌尿道感染，其中Mitoxantrone副作用的發生率爲21.2%，而Doxorubicin則爲20%，但二者之差別也無統計意義($p>0.99$)。

結 論： 膀胱化療灌注的確可降低復發率，而Mitoxantrone及Doxorubicin二者在治療效果及副作用都差不多。對於肺結核好發區或不適合BCG膀胱灌注的病人，這二項藥物可考慮選擇。

(長庚醫誌 2003;26:91-7)

關鍵字：膀胱癌，膀胱化療灌注，Mitoxantrone，Doxorubicin。

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