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# SEQUENTIAL INTRAVESICAL IMMUNOCHEMOTHERAPY FOR STAGES Ta AND T1 TRANSITIONAL CELL CARCINOMA OF THE BLADDER: AN UPDATE

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**Objectives:** To present an update of our experience with sequential immunochemotherapy using bacillus Calmette-Guerin (BCG) and epirubicin in superficial bladder tumors. In addition, the question of whether to start with BCG or epirubicin is answered.

**Patients and Methods:** Between January 1993 and December 2001, 156 patients with histologically proven Ta and T1 bladder transitional cell carcinoma were included in a prospective randomized study. Following transurethral resection of the bladder tumor (TURBT), the patients were randomly assigned to one of two groups. The patients in Group I received weekly doses of 150 mg BCG alternating with 50 mg epirubicin for 6 weeks. Maintenance was carried out by monthly doses of BCG alternating with epirubicin, to complete one year of treatment. The patients in Group II received the same protocol, but in a reversed order with epirubicin being used initially.

**Results:** 149 patients, 114 males and 35 females with a mean age of 55 years, were evaluable. Seven patients were excluded due to severe side effects. Mean and median follow up was 42.8 and 43 months, respectively. In the whole series, the recurrence rate was 18.1%, the recurrence rate per year was 0.06, the mean interval to first recurrence was 29 months and the progression rate was 12%. Side effects developed in 40 patients (25.6%) and were mostly in the form of mild cystitis (26 patients). The two groups were comparable regarding recurrence rate, recurrence rate per year, progression rate and side effects.

**Conclusion:** The sequential therapy is effective in recurrence prophylaxis of superficial bladder tumors. The side effects were less frequent than in our historical controls treated with BCG alone. It does not make any difference, if treatment is started with epirubicin or BCG in this regimen.

**Key Words:** bladder, transitional cell carcinoma, immunotherapy, epirubicin, sequential therapy.

## INTRODUCTION

Bacillus Calmette-Guerin (BCG) is the best adjuvant treatment, yet known, for the prophylaxis against recurrence of superficial bladder tumors. However, toxicity of intravesical BCG is an important consideration before taking the decision to use this drug. Local and systemic side effects have been reported secondary to intravesical BCG instillation[1-3] and many other intravesical chemotherapeutic agents have been reported to be less toxic than BCG.[4,5] To decrease the frequency and magnitude of these side effects, some authors have advised the use of a reduced dose of BCG.[6]

A new therapeutic regimen, the sequential immunochemotherapy, was first reported by Ali-El-Dein et al. in 1999.[7] The preliminary results of this regimen proved that it had the same efficacy and a lower toxicity than BCG alone.

Herein, an update of our experience with this new regimen, including a larger number of patients and a relatively longer follow-up is presented.

In addition, the question of whether to start the treatment with BCG or epirubicin is answered.

**Table 1:** Tumor Characteristics

| Variable | No. Patients | % |
|---|---|---|
| Stage: | | |
| pTa | 13 | 8.7 % |
| pT1 | 136 | 91.3 % |
| Associated CIS: | | |
| Yes | 15 | 10.1 |
| No. | 134 | 89.9% |
| Grade: | | |
| G1 | 16 | 10.7% |
| G2 | 81 | 54.4% |
| G3 | 52 | 34.9% |
| DNA ploidy: | | |
| Diploid/tetraploid | 106 | 71.1% |
| Aneuploid | 43 | 28.9% |
| Multiplicity: | | |
| Single | 61 | 40.9 |
| Multiple | 88 | 59.1% |
| Tumor size: | | |
| Less than 3 cm | 93 | 62.4% |
| 3 cm or greater | 56 | 37.6% |
| Tumor configuration: | | |
| Papillary | 139 | 93.3% |
| Solid | 10 | 6.7% |
| Recurrence history: | | |
| Primary | 89 | 59.7 |
| Recurrent | 60 | 40.3% |
| Therapeutic arm: | | |
| BCG and Epirubicin | 79 | 53.0% |
| Epirubicin and BCG | 70 | 47.0% |
| Recurrence at 3 months: | | |
| No | 140 | 94.0% |
| Yes | 9 | 6.0% |

## PATIENTS AND METHODS

Between January 1993 and December 2001, 156 patients with histologically proven bladder transitional cell carcinoma (stages Ta and T1) were included into a prospective randomized study. The eligibility criteria for inclusion in this study were one or more of the following criteria: grade 2 or 3, stage T1 disease, rapid disease recurrence within 6 months of initial resection, multicentricity, aneuploid deoxyribonucleic acid (DNA) pattern, tumor size equal to or more than 3 cm in greatest diameter, associated carcinoma *in situ* and/or positive postoperative urinary cytology. Initially urinalysis, urine culture, serum creatinine, fasting blood glucose level, complete blood count, chest X-ray, excretory urography, bladder wash for cytology and DNA flow cytometry were done. Complete transurethral resection of the bladder tumor (TURBT) was conducted in all patients. After TURBT patients were randomly assigned to two groups. Group I patients (79) received weekly doses of 150 mg BCG (Pasteur strain) alternating with 50 mg epirubicin for 6 weeks. Maintenance was carried out by a monthly course of the same dose of BCG alternating with epirubicin in order to complete one year of treatment. Group II patients (70) received the same protocol, but in a reversed order with epirubicin being used initially. Each dose of BCG or epirubicin was diluted in 50 ml normal saline and introduced into the bladder using a 12 Fr. Nelaton catheter under complete aseptic precautions, and therapy was retained for two hours. Instillation was initiated one to three weeks after TURBT.

The patients were evaluated every three months during the first two years and every six months thereafter. Clinical examination was performed regularly to detect evidence of disease recurrence and/or progression. Symptoms and signs of relevant complications and side effects of therapy were noted. Evaluation at each visit included urinalysis, urine culture, serum creatinine, complete blood count, cystourethroscopy, urine cytology and DNA flow cytometry. Excretory urography or magnetic resonance urography (MRU) was performed annually. Abdominal ultrasonography, liver function tests and chest X-ray were done when necessary.

The recurrence rate was defined as the number of patients per group in whom recurrence occurred during follow-up. It is expressed as a percentage of the total patient number in the group in question. The progression rate was defined as the number of patients per group in whom the disease progressed to muscle invasion during follow-up. It is expressed as a percentage of the total number of patients in the group in question. The period of recurrence or progression-free survival was defined as the time between the last

**Table 2:** Recurrence and Progression Rates in Both Study Groups

| Parameter | BCG + Epirubicin (Group I) | Epirubicin + BCG (Group II) | P-Value |
|---|---|---|---|
| Recurrence rate [No./total (%)] | 15/79 (19%) | 12/70 (17.1%) | 0.72 |
| Recurrence rate per year | 0.06 | 0.05 | 0.2 |
| Progression rate [No./total (%)] | 8/79 (10.1%) | 10/70 (14.3%) | 0.49 |

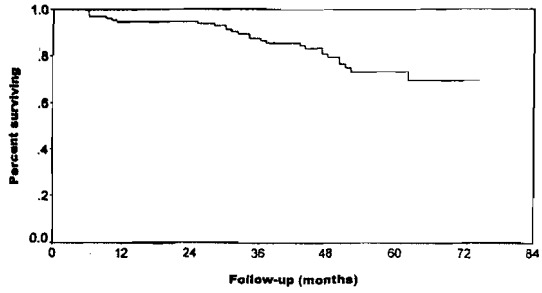


**Fig. 1:** Kaplan-Meier curve showing the recurrence-free survival of the whole series

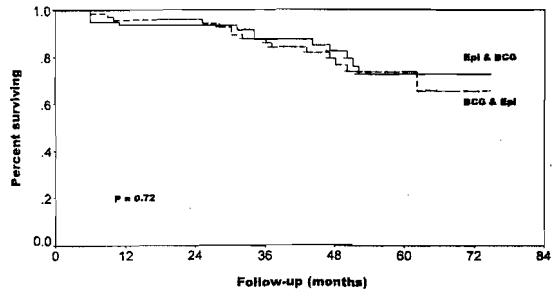


**Fig. 2:** Kaplan-Meier curves showing recurrence-free survival in both study groups.

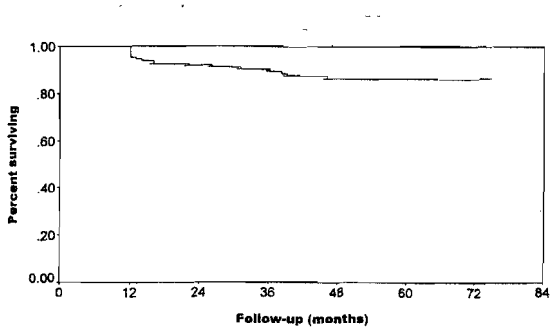


**Fig. 3:** Kaplan-Meier curve showing progression-free survival of the whole series

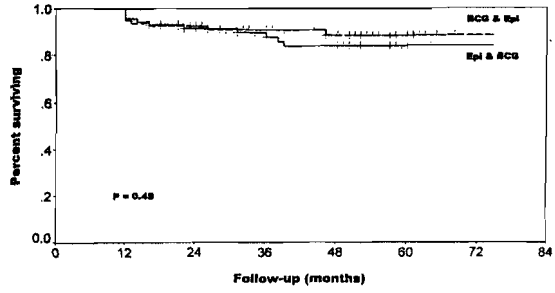


**Fig. 4:** Kaplan-Meier curves showing progression-free survival in both study groups

TURBT before inclusion into the study and the development of recurrence or muscle-invasive progression.

Kaplan-Meier survival curves were used to estimate recurrence-free and progression-free survival.

## RESULTS

Seven patients were excluded from the study in view of severe side effects. Therefore, 149 patients, 114 men and 35 women, with a mean age of 55 ± 8 years (range 40 – 75 years) were evaluable. Follow-up ranged from 12 to 74 months with a mean ± SD of 42.8 ± 16.9.

Table 1 demonstrates the tumor characteristics in 149 eligible patients. During the follow-up period recurrence developed in 27 patients (18.1%) and the recurrence rate per year (12 patient-months) was 0.06 (Fig. 1). The mean interval to first recurrence was 29 ± 17.8 months. In both study groups, the recurrence

**Table 3:** Toxicity and Side Effects

| Parameter | No. Patients | % |
|---|---|---|
| Overall toxicity | 40 | 25.6% |
| Systemic toxicity: | | |
| Fever | 2 | 1.3% |
| Nausea/vomiting | 3 | 1.9% |
| Cystitis and haematuria: | | |
| Cystitis | 26 | 16.0% |
| Haematuria | 3 | 1.9% |
| Therapy discontinuation: | | |
| * Temporary | 5 | 3.2% |
| * Permanent | 7 | 4.5% |
| * severe cystitis | 3 | 1.9% |
| * epididymoorchitis | 1 | 0.6% |
| * tuberculous prostatitis | 1 | 0.6% |
| * toxic hepatitis | 1 | 0.6% |
| * BCG sepsis | 1 | 0.6% |

rate and the recurrence rate per year were comparable (Table 2, Fig. 2). Progression to muscle-invasive disease developed in 18 patients (Fig. 3). The mean interval to progression was 20.2 ± 11 months. Again both groups of therapy were comparable in terms of progression-free survival as documented in Fig. 4 and Table 2.

Side effects were noted in 40 out of 156 patients (25.6%), 22 patients in Group I and 18 in Group II. Systemic toxicity in the form of fever developed in two patients, nausea and/or vomiting in three, hepatitis in one and BCG sepsis in another (Table 3). Cystitis and haematuria developed in 26 and 3 patients, respectively. Temporary discontinuation of therapy was necessary in 5 patients (3.2%). Permanent discontinuation due to severe toxicity was required in 7 patients (4.5%), who were excluded from the study. These included four patients in Group I (2 with severe cystitis, one with epididymoorchitis and one with toxic hepatitis) and three in Group II (one with severe cystitis, one with tuberculous prostatitis and one with BCG sepsis).

## DISCUSSION

Combination chemoimmunotherapy has been investigated in many clinical trials dealing with prophylaxis against recurrence of superficial bladder tumors. This combination may produce a synergistic effect that can result in a superior therapeutic benefit.[8-11] Raitanen and Lukkarinen compared the efficacy of combination immunochemotherapy using epirubicin and interferon-alpha-2b versus epirubicin alone in 81 patients with superficial bladder tumors and demonstrated that the combination regimen was more effective.[9] Rintala and associates tried a combination of BCG and mitomycin C for prophylaxis against recurrence of stages Ta and T1 bladder cancer and the treatment of carcinoma in situ in188 and 68 patients, respectively.[10,11] They stated that this combination was superior to historical controls treated with BCG alone in terms of the frequency and severity of toxic effects.

Bono et al. used a sequential therapy of 8 weekly doses of 50 mg of epirubicin followed by 6 weekly doses of BCG for T1G3 bladder tumors with a mean follow-up of 48 months.[12] The recurrence and progression rate in this high-risk group of patients was 23.4% and 7.4%, respectively. Bono et al. concluded that this mode of therapy was efficacious and well tolerated in this group of patients. In accordance with the aforementioned results, we have proved in a previous report that the alternating combination of immunochemotherapy (BCG for one week and epirubicin during the following week) was as effective as and less toxic than BCG alone.[7]

In a small number of patients with a short follow-up (9 – 24 months) Bilen et al. reported on a prospective comparison of alternating BCG and epirubicin in one group and BCG alone in another.[13] They concluded that the recurrence rate was 15% and 19%, respectively, and the progression rate was 4.7% and 10%, respectively. The difference was in favour of the alternating therapy, but it did not reach statistical significance. Serious side effects developed in three patients in the alternating therapy group and therefore the authors did not advocate this mode of therapy. However, neither in our previous nor in other studies, the side effects of alternating sequential immunochemotherapy were more severe or more frequent than with BCG alone.[7,10-12]

It has been shown that binding of mycobacteria (BCG) to the bladder wall is necessary for the production of an immune response and for anti-tumor activity.[14,15] One of the factors that may facilitate this binding is fibronectin, which

is present in large amounts following electrocoagulation of the bladder wall and chemical induction of cystitis after BCG instillation or any other therapy. Therefore, the prior administration of a cytotoxic therapy may be a significant factor in this binding. Some authors speculated that the adherence of BCG to the bladder wall and hence its efficacy would be stronger if a prior chemical cystitis had been induced by a chemotherapeutic agent.[16] The chemotherapeutic agent will produce inflammation and denudation of the bladder mucosa so that the immunotherapeutic agent will come into direct contact with the submucosa, which has now a large number of lymphocytes.[7]

In the current study, to test the validity of this hypothesis, we compared, in a prospective way, sequential intravesical BCG and epirubicin in one group versus epirubicin and BCG in the other group. There was no difference regarding efficacy or toxicity in the two study groups. The effectiveness of this mode of therapy was comparable to that of BCG in historical controls treated by BCG alone.[7] The mean interval to first recurrence was relatively long (29 months) and this confirms the results reported in our previous trial.[7] In addition, it our study showed that toxicity of the sequential therapy was less frequent and less severe than that reported for BCG alone in previous studies.[7,10,11]

It is worth noting that we did not include a control group treated by TURBT alone, since all cases in our study had a high risk for recurrence, which made the use of adjuvant intravesical therapy imperative. Furthermore, although many other studies compared sequential combination of chemoimmunotherapy versus cytotoxic chemotherapy alone[17], in our study epirubicin alone was not considered as a therapeutic arm so as not to deny these high-risk patients of any potential therapeutic benefit of BCG therapy.

In conclusion, evidence has been provided that sequential immunochemotherapy has a lower toxicity profile than BCG in historical controls treated with BCG alone. Sequential therapy was comparable in terms of efficacy to BCG alone in historical controls. In addition, sequential intravesical BCG and epirubicin was comparable to epirubicin and BCG in recurrence prophylaxis for superficial bladder tumor. Both treatment groups were similar in terms of toxicity. Furthermore, both groups had lower recurrence rates compared to historical controls treated with TURBT alone.

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## RESUME

### L' Immunochimiothérapie Intravésicale Séquentielle pour Carcinoma à Cellules Transitionnelles Stades Ta et T1 de la Vessie: Une Mise à Jour

**Objectifs**: Présenter une mise à jour de notre expérience en matière d'immuno-chimiothérapie séquentielle utilisant le bacille de Calmette-Guerin (BCG) et l'Epirubicin dans les tumeurs superficielles de vessie. En outre, la question de commencer par BCG ou epirubicin est traitée. **Méthodes**: Entre janvier 1993 et décembre 2001, 156 patients présentant un carcinome à cellules transitionnelles de la vessie au stade pTa et pT1 histologiquement prouvé ont été inclus dans une étude randomisée. Après la résection transurethrale de la tumeur de vessie (TURBT), des patients ont été aléatoirement affectés à 1 de 2 groupes. Les patients dans le groupe 1 ont reçu des doses hebdomadaires 150 mg de BCG alternant avec 50 mg d'epirubicin pendant 6 semaines. L'entretien a été effectué par des doses mensuelles de BCG alternant avec l'epirubicin, pendant 1 an de traitement. Les patients dans le groupe 2 ont reçu le même protocole, mais avec un ordre inversé avec l'epirubicin étant employé au début du traitement. **Résultats**: 149 patients, 114 hommes et 35 femmes présentant un âge moyen de 55 ans, étaient inclus dans l'étude. 7 patients étaient exclus à cause d'effets secondaires graves. Le suivi moyen et médian était de 42.8 et 43 mois, respectivement. Dans toute la série le taux de récidive était de 18.1%, le taux de récidive par an était de 0.06, l'intervalle moyen à la première récidive était de 29 mois et le taux de progression était de 12%. Les effets secondaires ont été constatés chez 40 patients (25.6%) dont la plupart étaient des cystites à minima (26 patients). Les 2 groupes étaient comparables concernant le taux de récidive, le taux de récidive par an, le taux de progression et les effets secondaires. **Conclusions**: La thérapie séquentielle est efficace dans la prophylaxie de récidive des tumeurs superficielles de vessie. Les effets secondaires étaient moins fréquents que dans nos précédentes séries traitées avec BCG seul. Il importe très peu de commencer par l'epirubicin ou le BCG dans ce protocole.

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