PhD Thesis

Abstract

ADJUVANT ENDOCAVITAR TREATMENT WITH BCG AND CHEMOTHERAPICS IN SUPERFICIAL BLADDER TUMORS

Phd Candidate: Dr. SORIN LUPU
Scientific Supervisor: Prof. Dr. RADU MIHAIL BOJA

General considerations

PhD thesis is structured in two parts: general (contains 46 pages consisting of 5 chapters) and the personal contributions part (contains 114 pages). There are 220 references in this thesis.

In the general part we present the principals anatopathology dates of the bladder tumors, about epidemiology and etiopathogeny, genetics aspects, the diagnosis and the treatment of the non-muscle invasive bladder tumors. In the context in wich the incidence of bladder tumors is growing, with two possibilities of evolution (reccurrence and progression), the adjuvant endocavitar treatment get more importance in the treatment of this neoplasia.

Introduction

Transurethral resection of bladder tumors (TURv) is the gold standard for diagnosis and initial treatment of bladder tumors. However, transurethral resection as a single treatment is ineffective long term. This finding has led to instillational adjuvant therapy. The role of therapeutic drug is instilled (destruction of remaining tumor cells), adjuvant (prevention of implantation of tumor cells after resection) and prophylactic (prevention of recurrence and tumor progression). The current trend is to consider appropriate instillational adjuvant treatment for all the patients with non-muscle invasive bladder tumors.

Study Objectives

The main purpose of this study was to evaluate the effectiveness of adjuvant treatment with chemotherapy and BCG instillations in non-muscle invasive bladder cancer, in order to
prevent or to reduce recurrence rate and tumoral progression. The secondary objectives we proposed was to evaluate the epidemiology, the etiopathogeny and diagnosis of non-muscle invasive bladder tumors, the evolution of patients treated just by TURv or with adjuvant instillational chemotherapy or BCG and to evaluate de side effects of this treatments.

**Material and Methods**

We conducted a study during 2006–2010 in the Clinic of Urology Brasov, where we seized a total of 103 patients diagnosed with non-muscle invasive bladder cancer, aged between 42 and 74 years with highest frequency in the 7th decade. Distribution of patients according to sex showed a predominance of men, in a ratio of 2.2/1. Of the total patients, 71 have undergone single bladder resection and 32 for multiple bladder tumors. Of the 103 patients studied, 80 (77.66%) received instillational treatment postoperative (adjuvant) with chemotherapy or BCG. Patients were divided into three groups: a control group (23 patients) who have not benefited from any form of adjuvant therapy for various reasons, a group who received adjuvant instillational chemotherapy treatment (27 patients) and a group that has received instillational treatment with BCG (53 patients). Chemotherapy used was 50 mg epirubicin hydrochloride. Treatment was started at 14-21 days post TURv, after histopathological result. Therapeutic protocol consisted of four weekly epirubicin instilations (loading dose) and a monthly instillation for 12 months. BCG strains used were different: strain of the Romanian Institute „Cantacuzino”, Calgevax (SL 222 Bulgarian sub-strain Sofia), Medac BCG (RIVM substrain) and ImmuCyst (Connaught substrain). Instillational treatment was started at 14-21 days post TURv. Therapeutic protocol consisted of 6 weekly BCG instillations (loading dose) and a monthly instillation for 12 months.

**Results**

Tumor recurrences were statistically significant reduced (p<0.05) with adjuvant instillational treatment with epirubicin and also with BCG, this being valid for 2 years and 5 years of follow up. In the first 2 years after surgery the decrease of the recurrence rate is approximately equal for both groups of patients who received one or the other adjuvant treatments; once passed, immunotherapy appears to be superior to chemotherapy in terms of recurrence rate reduction.

Local progression in the control group is close to 40%, being reduced greatly by one of the adjuvant treatments. The group that received epirubicin intravesical the tumor progression
rate at 5 years was 18.51%; the reduction is important for our group but not statistically significant (p>0.05). Group that received intravesical immunotherapy was also a clear reduction in tumor progression up to 15.68%, but statistically significant (p<0.05).

Metastatic rate for the group of patients who has not received adjuvant therapy was 13.04%. There is a reduction in the rate of metastases in patients who received adjuvant treatment with epirubicin or BCG, the reduction being approximately equal, but statistically insignificant (p> 0.05). Regarding specific mortality rate (from cancer), for the control group was approximately 8.7%. Instillational treatment seems to influence the specific mortality, but not extensively and, especially, statistically insignificant. Also, there is a slight reduction in overall mortality in patients who have received adjuvant instillational treatment.

Patients who were treated only by TURv recurred on average at 24 months. There is a clear extension of the average time of occurrence of relapse in patients who received instillational treatment, especially in the group treated with epirubicin (up to approximately 39 months).

In the group of patients who received treatment with instillational chemotherapy, side effects were minor: frequency (33.33%), dysuria (25.92%), suprapubic pain without other symptoms (14.81%), macroscopic haematuria of low intensity (22.22%).

The most common side effects reported in the group of patients treated with BCG were: fever between 38 and 38.5°C (under 48 hours) and chills (43.39%), frequency (79.24%), dysuria (73.58%), minimal mictional imperiosity (33.96%), macroscopic haematuria of low intensity (77.35%), minimal myalgia (15.09%), acute epididymitis (3.77%) histopathologically confirmed granulomatous prostatitis (1.88%), cutaneous erythema (1.88%). Side effects were easily managed. In the case of two patients BCG treatment was discontinued because of side effects and was used tuberculostatic medication.

Conclusions

Our study shows a net favorable evolution of patients who received adjuvant instillational chemotherapy or BCG, with the evolution being better as they comply with treatment recommendations depending on the degree of risk of the tumor. Instillational treatment benefits are obvious both in reducing recurrences and also the progression of the tumor. Appearance of this treatments was radical changed the prognosis of the superficial baldder tumors, with improve the patient's quality of life.