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CAN WE AMELIORATE THE COMPLIANCE TO INTRAVESICAL BCG MAINTENANCE? ANALYSIS OF THE CAUSES OF TREATMENT INTERRUPTION IN 160 CONSECUTIVE PATIENTS.

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Aim of the study
BCG maintenance for at least one year is advocated by Urological Guidelines as the best intravesical regimen in high risk non muscle invasive bladder cancer (NMI-BC), conservatively treated. Noteworthy, a relevant number of patients does not complete the planned treatment,although a small percentage of them suffers of moderate to severe toxicity. The causes of BCG interruption remain unclear. The aim of our study was to identify the reasons for treatment interruption to ameliorate patients' compliance.

Materials and methods
A homogenous population of patients affected by T1G3 NMIBC undergoing BCG maintenance for one year according to the SWOG schedule were considered. BCG (Connaught 81mg/50ml) was administered intravesically, 14-30 days after TUR, and maintained for 2 hours. If toxicity occurred treatment was postponed up to 2 weeks. No dose reduction was proposed. In case of recurrence maintenance regimen was continued after TUR. The causes of treatment interruption were registered.

Results
Out of 160 patients, 148 (92,5%) completed the induction cycle. Fifteen (9,4%) patients refused the maintenance. In 10 (6,3%) more patients an early recurrence was detected. In 123 patients (76,8%) maintenance for one year was planned. Eight patients never started and only 67 (54,4%) completed one year. Adherence to treatment decreased from 84,5% at 3 months to 57,7% at 12 months, 56 (45,6%) patients not completing one year. Only 9 patients (7,3%) interrupted the maintenance regimen due to recurrence. Toxicity requiring treatment interruption was recorded in 6 (4,8%) patients only. Analyzing the causes of patients' discomfort and treatment interruption, grade-I local toxicity, not requiring therapy interruption on urologists' opinion, was lamented by 91 out of 123 (74%) patients. In the last 2 years in our experience the introduction of programmed patients' counseling reduced the drop-out rates due to "low compliance" from 36,7% to 16.6%

Discussion
In EORTC protocol 30911 and 30962, only 25% and 62% of the patients completed 3-year and 1-year maintenance, respectively. Neither reducing the dose nor shortening the duration from 3 to 1 year decreased the percentage of patients who discontinued the treatment. Noteworthy, toxicity was reported in only 7.8% of cases while 26% and 17% of patients interrupted the treatment due to recurrence or other reasons, respectively. In our experience only 67 patients only (54%) completed one-year maintenance even if toxicity requiring treatment interruption was evident in 6 patients. An adequate patients' information is essential to increase adherence to protocol scheme, and drop-out rate was reduced by 20% introducing periodic patients counselling.

Conclusions
In our experience, moderate to severe toxicity caused the interruption of BCG maintenance in only 5% of cases. A timely recognition and therapy of the symptoms and a planned counseling with the patients undergoing BCG maintenance, significantly ameliorates the adherence to BCG regimen for one year.

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PROGNOSTIC FACTORS AND RISK GROUPS IN T1G3 PATIENTS INITIALLY TREATED WITH BCG: RESULTS OF A MULTICENTER RETROSPECTIVE SERIES IN 2530 PATIENTS

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Aim of the study
The impact of prognostic factors in T1G3 patients (pts) is critical for proper treatment decision making, however most available data are from small series of pts. The aim of the current study is to assess prognostic factors in a large group of pts who received BCG as initial treatment of T1G3 tumours and identify a subgroup of high risk pts who should be considered for early cystectomy.

Materials and methods
Individual pt data were collected for 2530 pts from 23 centers who received induction or maintenance BCG between 1990 and 2008. Using Cox regression analysis, the prognostic importance of the following variables were assessed for time to recurrence, progression to muscle invasive disease and overall survival: age (< 70 vs > 70 yrs), gender, primary T1G3 vs recurrent T1G3 after previous non T1G3 tumour, tumour size (< 3 vs > 3 cm), multiplicity (single vs multiple), concomitant CIS (no/yes), and maintenance BCG (no/yes).

Results
Median age was 68 yrs, 82% were male, 89% were primary T1G3, 58% had multifocal disease, 67% had tumours less than 3 cm, 25% had concomitant CIS, 42% had a restaging TUR, 37% received some sort of maintenance BCG. With a follow up out to 15 years, 1300 pts (51%) recurred, 480 (19%) progressed, 523 underwent cystectomy (21%) and 623 (25%) died, 230 (9%) due to bladder cancer. In multivariate analyses, the most important prognostic factors ($p < 0.01$) for recurrence were: tumour size and multiplicity; for progression: age, size and concomitant CIS; for overall survival: age and size. Maintenance BCG had a positive impact on recurrence ($p < 0.001$), progression ($p = 0.007$) and survival ($p = .002$). Patients were divided into 4 risk groups according to the number of bad factors for progression among age > 70, size > 3 cm and presence of CIS. Progression free rates at 10 yrs were 82%, 73%, 67% and 42% for patients with 0, 1, 2 and 3 bad factors while the corresponding overall survival rates were 78%, 53%, 46% and 16%, respectively.

Discussion
BCG therapy prevents, or at least delays, the risk of tumors progression. Even if most of the data available demonstrate the importance of a maintenance schedule BCG to improve outcomes, as compared to induction alone, fit pts over 70 yrs of age with tumours greater than 3 cm and concomitant CIS should be considered for an early cystectomy.

Conclusions
T1G3 patients treated with BCG have a heterogeneous prognosis, with overall survival at 10 yrs ranging from 78% to 16%.