Health-related quality of life after BCG or MMC induction for non-muscle invasive bladder cancer

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Introduction: To evaluate health-related quality of life (HRQoL) in patients with non-muscle invasive bladder cancer (NMIBC) during the induction phase of intravesical instillations with BCG or MMC.
Materials and methods: HRQoL was measured by two questionnaires from EORTC (QLQ-C30 and QLQ-BLS24), stratifying results by gender, age and therapy at the start of the therapy (T0), at last instillation (T1) and at 3 months after T1 (T2). The persistence of QoL-related side effects after 3 months from the end of the induction cycle was evaluated.

Results: We enrolled 108 naïve patients and 103 patients self-completed the questionnaires. Treatment was well tolerated in both groups. Side effects were reported by 46.6% of patients at T1 and 47.5% of patients at T2. QoL dropped at T1, returning to the baseline at T2. Drop of QoL was greater in the physical, role, emotional and social functioning domains and in some clinical domains as pain, fatigue and insomnia. Our stratified analysis showed that patients > 70 years have a worsening of QoL, a higher incidence of patient-reported side effects or symptoms in the BCG arm as compared to MMC arm.
Conclusions: Our study shows that intravesical instillations of BCG or MMC during the induction phase might have a relevant effect on HRQoL.

Key Words: intravesical instillation, NMIBC, HRQoL, MMC, BCG

Introduction

Bladder cancer is the most frequent cancer of the genitourinary tract[1] and one of most costly tumors due to disease surveillance and treatment.[2-4] Non-muscle invasive bladder cancer (NMIBC) is similar to a chronic disease and its burden is high in all phases of treatment and surveillance owing to the frequent tumor recurrence and progression of disease, with an impact on patients' quality of life.[5] In this context health-related quality of life (HRQoL) evaluation is crucial because patients with bladder cancer continue experiencing treatment-related concern over a long follow up period.[6-8]

However, literature on HRQoL in bladder cancer is limited and most studies regard patients with muscle invasive bladder cancer (MIBC) who underwent radical cystectomy, and focus on the effect of different urinary diversion techniques.

The aim of this study is to verify HRQoL in patients during Bacillus Calmette-Guérin (BCG) or Mitomycin C (MMC) induction for NMIBC.

Materials and methods

We evaluated the HRQoL of naïve patients who underwent BCG or MMC induction for NMIBC as reported by EAU guidelines.[9] The primary outcome was to evaluate HRQoL during BCG and MMC treatment, stratifying patients by gender and age while secondary outcome was to verify the persistence of QoL-related side effects after 3 months from the end

of last instillation (T2). HRQoL was measured during the induction period of MMC or BCG by two cancer-specific questionnaires from European Organization for Research and Treatment of Cancer (EORTC): the QLQ-C30[10] and the QLQ-BLS24.[11]

From December 2011 to December 2014 we enrolled 108 consecutive patients affected by NMIBC in a single academic center. The study was approved by our internal board and verbal informed consent was obtained from all individual participants enrolled in the study.

The inclusion criteria were as follows: pathological confirmation of a first-time diagnosis of urothelial carcinoma with intermediate or high risk; patients not previously treated by transurethral resection (TUR) and/or intravesical instillation; patients with no contraindications for intravesical instillations of BCG or MMC. Exclusion criteria were: performance status 2 or more according to the WHO performance status criteria; history of genitourinary tuberculosis; inadequate bone marrow reserve (white blood cells less than $3x10^9$/L, platelets less than $100x10^9$/L); presence of uncontrolled or untreated urinary infections and/or with multi-drug-resistant pathogens.[12]

Data collection

Within 20 days after TUR patients with an intermediate and/or high risk NMIBC underwent the adjuvant cycle of intravesical instillations of BCG or MMC according to EAU guidelines risk classes.[13]

The cohort of patients was divided into two groups. In the first group patients received an induction cycle of 6 weekly instillations, according to Morales schedule,[14] of TICE strain BCG - OncoTICE 2 mL (Organon Teknika, Boxtel, The Netherlands) containing $2-8x10^8$ Colony Forming Units (CFU) diluted in 50 cc of saline. In the second group patients received an induction cycle of 8 weekly instillations of 40 mg of Mitomycin-C (Kyoma Italiana Farmaceutici S.r.l.) diluted in 50 cc of saline. Tumors were staged according to the 2009 TNM classification and the 1973 WHO grading system. Treatment was discontinued in case of severe side effects and adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[15]

HRQoL was assessed at three different times: the first (T0) immediately before the start of induction cycle of intravesical instillations; the second (T1) coinciding with the last instillations (6 or 8 weeks after the first instillations); finally the third (T2) during the follow up (cystoscopy) at 3 months after the cycle. Interviews including sociodemographic characteristics were conducted, and patients self-completed HRQoL questionnaires at the outpatient visits.

HRQoL measures instruments

QoL was measured by two cancer specific questionnaires, namely the EORTC QLQ-C30 and the EORTC QLQ-BLS24. The QLQ-C30 is an integrated and validated system used to measure cancer related QoL. It incorporates five functional scales, three symptom scales, a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by patients with cancer and perceived impact of the disease. In detail, it consists of 30 items that are scored on 4-point Likert scales ranging from 1 (not at all) to 4 (very much). Two items in the global health and quality of life subscale are scored on a 7-point linear analog scale. All functional scales and individual item scores are transformed to a 0 to 100 scale. Higher scores in the five functional scales and global health status scale represent better functioning, whereas higher scores in symptom scales reflect a greater extent of symptom distress.

The QLQ-BLS24, a specific bladder cancer module, was used to measure bladder cancer specific QoL. This questionnaire covers the domains of urinary symptoms, intravesical treatment problems, future perspective, abdominal bloating and flatulence, and sexual functioning. Both questionnaires were administered at T0, T1, T2.

Statistical analysis

Statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Inc., NC, USA). Mean values with standard deviations ($\pm$ SD) were computed and reported for all functional scales and individual items scale of HRQoL. Paired t-test was used to verify differences in means of HRQoL according to time of follow up (at T0 versus at T1, and at T0 versus at T2). In addition, HRQoL were stratified for gender (male and female), age ($\leq$ 70 and > 70 years), instillation therapy (TUR-BCG and TUR-MMC), and degrees of risk (low-intermediate and high risk) to verify differences in each strata by time of follow up. Statistical significance was achieved if p value was $\leq$ 0.05 (two-sides).[16]

Results

We enrolled 108 patients. Five of these patients dropped out of the study: 3 left the follow up after the instillations and 2 experienced BCG side effects of the second and third degree of CTCAE 3.0 grading criteria. The therapy was conducted following recommendations for the treatment of BCG-related complications and instillations were definitively stopped for both patients. Therefore we analyzed and followed 103 patients. These patients self-completed

the QLQ-C30 and QLQ-BLS24 questionnaires as established by the study protocol. Treatment was well tolerated in both groups of patients. Grade I and grade II side effects were reported by 46.6% of patients at T1 and 47.5% at T2 respectively.

Table 1 shows selected descriptive and sociodemographic characteristics. Seventy-nine patients (76.7%) were male and 24 were female (23.3%) with a median age of 73 years (range: 38-94). Twenty-nine patients (28.2%) were at high risk neoplasm and 74 patients (71.8%) were at low/intermediate risk neoplasm. Fifty-seven patients (55.3%) underwent treatment with intravesical BCG and 46 patients (44.7%) with MMC.

Table 2 shows mean and standard deviation (± SD) of HRQoL according to time of follow up. At T1 the QLQ-C30 showed a significant decline in QoL in comparison with baseline (T0), in the physical, role, emotional and social functioning domains, p values were p = 0.008, p = 0.001, p < 0.0001, p = 0.002 respectively. In domains corresponding to clinical symptoms patients showed a worsening of the same items resulting in a decline of QoL. Fatigue, pain, dyspnea, insomnia, p values were p = 0.004, p < 0.0001, p = 0.02, p = 0.0005 respectively. At T2 patients showed a return to the initial score prior to intravesical therapy, with a return to baseline QoL for major parts of domains. By contrast, we found a significant worsening of social functioning (p = 0.05), and significant improvement of pain symptoms (p = 0.0008).

At T1 the QLQ-BLS24 domains showed a significant decline in QoL in comparison with baseline (T0), in particular for urinary symptoms (p < 0.0001), worry about future disease (p = 0.04), erection problem (p = 0.008), and sexual intercourse to feel uneasy (p < 0.0001). At T2 patients showed a progressive return to the initial score prior to intravesical therapy, with a gradual return to baseline QoL for sexual functioning, erection problems, and vaginal problems. For the other domains we found a significant improvement of urinary symptoms (p < 0.0001), problems about cystoscopy exam (p = 0.008), worry about future disease (p = 0.02), and abdominal bloating flatulence (p = 0.0009).

Table 3 shows mean and standard deviation (± SD) of parameters of QoL statistically significant in terms of change (i.e., worsening or improvement) at time T2 in comparison with T0 (baseline). In addition, the table shows whether these changes in QoL are homogeneous between each strata of gender (male versus female), Age (≤ 70 versus > 70 years), and type of therapy (BCG versus MMC). We found that social functioning had significant worsening for males but not for females who had a progressive return to the initial score (T0), while age (≤ 70 versus > 70 years) and type of therapy (BCG versus MMC) kept the same significant worsening among each strata.

Looking further into these aspects, in the analysis stratified by age (≤ 70 years and > 70 years) at T1 in the QLQ-C30 we detected different results. In particular the emotional functioning domains revealed a significant decrease in scores major in patients > 70 years: 75.3 ± 18.2 compared 80.3 ± 17.9 before treatment in patients > 70 years and 72.7 ± 22.4 compared to 77.3 ± 22.0 before treatment in patients ≤ 70 years (p = 0.0003 and p = 0.05 respectively). Social functioning domains instead showed a worsening slightly major in patients ≤ 70 years compared to patients > 70 years (p = 0.05 and p = 0.02 respectively). Fatigue and pain clinical domains showed an important increase in symptoms in patients > 70 years compared to patients ≤ 70 years. In particular regarding pain we observed in patients > 70 years 32.2 ± 26.0 compared 20.0 ± 23.9 before treatment and in patients ≤ 70 years 21.7 ± 25.1 compared to 14.0 ± 19.6 before treatment (p = 0.01 and p < 0.0001 respectively). By QLQ-BLS24 we detected statistically significant differences between two groups in the urinary bladder symptoms and sexual sphere domains. In particular we found an increase in urinary symptoms greater in patients > 70 years (23.4 ± 15.7 versus 16.3 ± 13.0) than in patients ≤ 70 years (19.5 ± 16.5 versus 12.2 ± 12.3), p = 0.0002 and p = 0.0004 respectively. Then as regards the sexual intercourse domains there were more trouble related to older patients (p = 0.0008 and p < 0.0001 respectively).

TABLE 1. **Characteristics of population**

Characteristics	n (%)
Gender	
Male	79 (76.7)
Female	24 (23.3)
Age (years)	
≤ 70	43 (41.7)
> 70	60 (58.3)
Median (range)	73 (38-94)
Degrees risk	
Low	9 (8.7)
Intermediate	65 (63.1)
High	29 (28.2)
Type of therapy	
TUR-BCG	57 (55.3)
TUR-MMC	46 (44.7)

TUR-BCG = transurethral resection and instillation with Bacillus Calmette-Guérin; TUR-MMC = transurethral resection and instillation with Mitomycin C

At T2 we found in each the questionnaires a globally return to baseline values with a significant improvement only in clinical domains such as urinary symptoms, pain and abdominal flatulence, greater in patients ≤70 years compared to patients > 70 years (p = 0.002, p = 0.02 and p = 0.006 respectively).

In the analysis stratified by intravesical therapy (BCG and MMC) at T1, QLQ-C30 showed a worsening of QoL which was greater for BCG compared to MMC in emotional functioning domains (p = 0.05 and p = 0.002 respectively) and in some clinical domains (pain and insomnia with p < 0.0001 compared p = 0.03 and p = 0.01 compared p = 0.02 respectively). The Global Quality of Life Score (item 30) revealed a decrease in QoL greater for BCG arm than MMC arm: 63.7 ± 16.0 in BCG arm and 69.9 ± 13.4 in MMC arm (p = 0.002 and p = 0.003 respectively). In the QLQ-BLS24 we detected statistically significant differences between two groups only in sexual intercourse domains urinary bladder symptoms with an increase in symptoms greater in men than in women: 51.9 ± 34.4 in BCG arm and 48.1 ± 27.9 in MMC arm (p < 0.0001 and p = 0.0002 respectively). Instead as regards the urinary bladder symptoms there were not significant differences between both group

TABLE 2. **HRQoL before and after therapy**

Questionnaire	Before treatment (T0) Mean (± SD)	At the end of induction (T1) Mean (±SD)	p value[a]	After 3 months (T2) Mean (± SD)	p value[a]
EORTC QLQ-C30					
Physical functioning*	90.2 (± 9.8)	88.3 (± 11.9)	0.008	89.4 (± 10.0)	
Role functioning*	95.1 (± 11.8)	90.6 (± 15.9)	0.001	95.3 (± 9.5)	
Emotional functioning*	79.0 (± 19.7)	74.2 (± 20.0)	< 0.0001	80.7 (± 18.0)	
Cognitive functioning*	94.3 (± 9.2)	93.9 (± 10.2)		95.3 (± 8.9)	
Social functioning*	94.2 (± 12.7)	90.9 (± 15.1)	0.002	92.4 (± 13.8)	0.05
Fatigue§	16.0 (± 15.6)	19.2 (± 17.2)	0.004	16.5 (± 13.9)	
Nausea and vomiting§	0.8 (± 4.3)	1.3 (± 5.6)		0.6 (± 4.0)	
Pain§	17.5 (± 22.3)	27.8 (± 26.0)	< 0.0001	11.3 (± 16.5)	0.0008
Dyspnea§	7.4 (± 15.4)	9.7 (± 17.2)	0.02	9.1 (± 15.6)	
Insomnia§	13.3 (± 18.3)	19.4 (± 22.6)	0.0005	12.3 (± 17.5)	
Appetite loss§	3.9 (± 10.7)	4.5 (± 11.5)		2.6 (± 9.0)	
Constipation§	9.4 (± 16.4)	9.7 (± 17.2)		8.7 (± 16.8)	
Diarrhea§	2.9 (± 9.5)	3.2 (± 11.0)		3.6 (± 11.3)	
Financial difficulties§	2.3 (± 9.6)	2.3 (± 9.6)		0.6 (± 4.6)	
Global quality of life§	73.2 (± 14.7)	66.5 (± 15.2)	< 0.0001	75.2 (± 11.3)	
EORTC QLQ-BLS24					
Urinary symptom§	14.6 (± 12.8)	21.8 (± 16.1)	< 0.0001	9.5 (± 9.7)	< 0.0001
Problem about cystoscopy exam§	21.4 (± 17.1)	24.1 (± 18.5)		17.3 (± 14.7)	0.008
Worry about future disease§	39.3 (± 23.3)	42.9 (± 25.0)	0.04	34.3 (± 18.7)	0.02
Abdominal bloating flatulence§	10.0 (± 14.6)	12.3 (± 16.3)		6.5 (± 12.4)	0.0009
Sexual functioning§	23.3 (± 24.6)	21.0 (± 22.9)		21.0 (± 22.9)	
Erection problem (male)§	24.3 (± 26.1)	33.3 (± 30.3)	0.008	27.8 (± 27.5)	
Vaginal problem (female)§	7.7 (± 20.0)	8.3 (± 20.7)		11.1 (± 21.7)	
Feeling uneasy abouts exual intercourse§	21.1 (± 18.4)	50.4 (± 31.7)	< 0.0001	16.7 (± 12.2)	0.04

HRQoL = health-related quality of life; SD = standard deviation; *for the functional items, the higher score represents a higher level of functioning; §for the symptoms/single items, a higher score means a higher level of symptomatology/problems; apaired t-test, p value in comparison with before treatment.

TABLE 3. **HRQoL stratified**

Questionnaire	Before treatment (T0) Mean (± SD)	After 3 months (T2) Mean (± SD)	p-value[a]	Gender		Age (years)		Therapy	
				M	F	≤ 70	> 70	BCG	MMC
EORTC QLQ-C30									
Social functioning*	94.2 (± 12.7)	92.4 (± 13.8)	0.05	+	=	+	+	+	+
Pain§	17.5 (± 22.3)	11.3 (± 16.5)	0.0008	+	=	+	+	+	=
EORTC QLQ-BLS24									
Urinary symptom§	14.6 (± 12.8)	9.5 (± 9.7)	< 0.0001	+	+	+	+	+	+
Problem about cystoscopy exam§	21.4 (± 17.1)	17.3 (± 14.7)	0.008	=	+	=	+	=	+
Worry about future disease§	39.3 (± 23.3)	34.3 (± 18.7)	0.02	+	=	=	+	+	+
Abdominal bloating flatulence§	10.0 (± 14.6)	6.5 (± 12.4)	0.0009	+	=	+	+	+	+
Feeling uneasy about sexual intercourse§	21.1 (± 18.4)	16.7 (± 12.2)	0.04	+	+	+	+	+	+

HRQoL = health-related quality of life; SD = standard deviation; *for the functional items, the higher score represents a higher level of functioning; §for the symptoms/single items, a higher score means a higher level of symptomatology/problems; [a]paired T-test, p value in comparison with before treatment. The symbol "+" shows that there is a significant difference in QoL (p value ≤ 0.05, paired t-test compare T2 vs. T0); the symbol "=" shows that there is no significant difference in QoL (p value > 0.05) for the selected strata.

but we detected significant trouble in BCG arm at T1 compared to T0 (25.0 ± 16.5 of DS compared to 14.6 ± 12.6 ($p < 0.0001$). At T2 we detected a globally return to baseline values with a significant improvement only in abdominal bloating flatulence and in urinary bladder symptoms greater in MMC arm than in BCG arm (for the last 8.1 ± 7.1 in MMC arm compared to 10.7 ± 11.3 in BCG arm – $p = 0.001$ and $p = 0.01$ respectively).

Finally, pain, worry about future disease, abdominal bloating flatulence had significant improvement in males whereas females showed a progressive return to the initial score. Urinary symptom and feeling uneasy about sexual intercourse showed a significant improvement for both genders. Vice versa, only the problem about cystoscopy exam showed a return to the initial score for males and a significant improvement in females. For the other age groups and types of therapy we detected a globally significant improvement in the majority of parameters of QoL between each strata.

Discussion

NMIBC is considered a non-fatal disease, but patients with this condition feel that their health is very compromised.[17] At present there are few studies on HRQoL in patients with NMIBC[7,8] and based on maintenance therapy.[12] The literature offers little evidence about the impact that cancer has on the HRQoL during BCG or MMC induction.[18] The limited information on the HRQoL of NMIBC and its clinical management may be due to the lack of specific studies in a validated setting. Our study shows that bladder cancer and intravesical instillations might have a relevant effect on HRQoL. Patients after treatment often returned to the baseline QoL but some sequelae may persist and they could affect some components of QoL. Drop of QoL was greater in the physical, role, emotional and social functioning domains and in some clinical domains (pain, fatigue, insomnia). All these factors, according to Botteman,[8] may influence the QoL of patients in a strictly subjective way: QoL may change according to the clinical and pathological features of the disease and according to the subjective interpretation that each patient has of pain, surgical operations and prospect of life.[12]

Interestingly the analysis at 3 months revealed that in most patients there is a recovery of the principal domains. In particular, side effects (urinary bladder symptoms and abdominal symptoms domains) decreased or disappeared when therapy was finished. Patients' worries about their future decreased during follow up with an improvement compared to baseline values. Instead there is no further degree of improvement in the psycho-functional and overall domains. Indeed general status of fatigue with physical elements, such as fatigue and the difficulty performing heavy activities remained unchanged.

Nevertheless, the toxicity observed with topical intravesical therapy is sometimes very painful for the patient, annoying, and difficult to cure or palliate as reported by others.[19]

In 2016 Yokomizo published a randomized controlled study with, as a secondary end point, the QoL after induction therapy with standard dose or low dose of BCG: he identified a better QoL, after reducing the dose, only in certain aspects such as role function and global QoL, without testing at 3 months and without any stratification in terms of gender or age.[20] In this way our study showed that patients over 70 years old, who underwent BCG instillation, had a worsening of QoL, and a higher incidence of patient-reported side effects or symptoms, especially at the end of the induction cycle. This finding reflects and impacts negatively on the psychological domain and the perception of health status by patients. In this context the side effects degree of risk is closely related to the therapy used and the age of patients.

Therefore it is evident that age is an important factor that could affect the HRQoL. In fact, older patients are more affected by clinical symptoms such as pain, fatigue, insomnia and irritative urinary symptoms. This aspect may create a strong negative psychological impact as reported by Mack,[21] who described that patients > 70 years old had more trouble imagining their future.

Conclusions

This study shows several limits, the main one is the low number of female patients enrolled and a limited number of participants under 70 years old. Nevertheless we observed an almost complete recovery of HRQoL, with the exception for social functioning, pain, urinary symptoms, worry about cystoscopy exam and future disease, flatulence, sexual sphere, that need to be confirmed by further studies.

In particular in our series, the moderate improvement that occurs at 3 months after the end of intravesical cycle is at present unclear. Probably this is due to a progressive decrease of BCG and MMC side effects.

Finally, regarding the sexual sphere, we observed that patients often ask if they can have sexual intercourse during induction therapy and this question often causes troubles that are age-dependent. □

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