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Single Ablative Intravesical Electromotive Mitomycin C Administration for Small Non-Muscle-Invasive Bladder Cancer: A Prospective Study

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Abstract

Aim: To explore the effect of Electromotive Drug Administration Of Mitomycin C (EMDA-MMC) using a single dose of intravesical mitomycin C (MMC) to avoid transurethral resection (TURBT) for small non-muscle-invasive bladder cancer.

Material and Methods: All patients presenting small papillary bladder tumors were proposed to undergo a single EMDA-MMC session with 60mg MMC before planning TURBT. The end point is complete disappearance of all papillary tumors at 2 to 4 weeks after EMDA-MMC.

Results: Thirty-six sessions were given to 32 patients. In general the treatment was well supported, except for two patients who had severe bladder spasms, resulting in early evacuation of the MMC. Complete response occurred in 28% (10/36 sessions). In 4 sessions with multiple tumors some tumors disappeared while others remained. In 61% (22/36) the tumors remained unchanged.

Conclusion: A single EMDA-MMC in small papillary bladder tumors gives insufficient ablative effect.

Keywords: Electromotive drug administration; Mitomycin; Intravesical chemotherapy; Urothelial bladder cancer; Chemoresection; Superficialbladder tumors; Non-muscle-invasive-bladder cancer

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Introduction

The ablative effect of repeated intravesical chemotherapy on small papillary non-muscle-invasive bladder tumors has been used to avoid transurethral resection of bladder tumors (TURBT) in about half of the cases [1-3]. In 1999, Masters et al. [4] obtained similar results even with a single instillation of epirubicin. This amazing experience was never repeated or at least not published by others. The excellent results obtained in the prevention of recurrences with the use of electromotive drug administration (EMDA) [5-10] let us expect an even better response than with a chemotherapeutic drug alone. It was our intention to repeat the experience of Masters et al. [4] with the use of a single electromotive drug administration of mitomycin C (EMDA-MMC). We hypothesize to avoid TURBT and to postpone recurrence in the responders in at least half of the patients.

Methods

Between May 2012 and September 2015 all patients in the department of urology presenting with, primary or recurrent, small (≤2cm) papillary bladder tumors were proposed to undergo an EMDA-MMC session before planning TURBT. Tumor size was estimated on cystoscopy and ultrasound. Recurrent patients treated with intravesical MMC within the last year or patients with a history of Tis of the bladder were excluded. On the basis of earlier ablative studies with mitomycin [1-4], the patients were given a 50% probability to avoid anesthesia and TURBT. A control cystoscopy was performed 2 to 4 weeks after EMDA-MMC and TURBT scheduled only when the tumors were persistent. The primary end point of this study is complete response, defined as complete disappearance of all papillary tumors at cystoscopy at 2-4 weeks after the treatment, in order to avoid TURBT. The secondary end point is toxicity. To identify potential predictors for complete response, tumor characteristics (primary versus recurrent, previous instillations, number and size of tumors and positive versus negative urinary cytology) were assessed with chi-square statistics. Written informed consent was obtained from all patients and the study was approved by local ethics committee (UZG 2012/459).

Technique of EMDA-MMC

The technique as described in the review publication of Kalsi et al. [10]. Using intravesical EMDA, drug delivery through the bladder mucosa is accelerated by the application of an electric field across the bladder wall, which stimulates directional ionic and solute movement. A low electric current, controllable between 0-30mA and 0 to 55V, is passed between 2 electrodes connected with the battery powered generator Physionizer 30 manufactured by Physion® (Mirandola, Italy). The dispersive ground electrodes are placed on a cleaned and unblemished skin of the lower abdominal wall with a wide area of contact. The active intravesical electrode is incorporated in a specifically designed single use, 18 Fr urethral Foley catheter, with a 3ml balloon. The urethral catheter is inserted using the standard sterile technique and intraurethral local anesthetic lubricant gel. The bladder is carefully drained and washed with distillated water to clear all solutes which can alter the electromotive activity. MMC 60mg dissolved in 100ml bi-distillated water is injected in the bladder through the catheter. The catheter electrode and the abdominal electrodes are then connected to the generator and a 25mA current is applied during 25 min. At completion the generator switches off automatically.

Results

Thirty-six EMDA-MMC sessions were given to 32 patients, including 4 patients who received a second session at a new recurrence. Patient and tumor characteristics are given in Table 1. Complete responseoccurred in 25% (8/32) of the patients, in 28% (10/36) of all EMDA-MMC sessions, and in 50% (2/4) of the repeated sessions. In cases with multiple tumors (n=16), some tumorsdisappeared in 4 of them, while others remained unchanged (partial response). In 61% (22/36), the tumors remained unchanged. The results according to tumor characteristics are summarized in Table 1. None of the tumor characteristics could predict for complete response. In general the treatment was well supported. However, two patients suffered severe bladder spasms when the EMDA current was applicated. One urinated immediately upon and one 9 minutes after the start of EMDA-MMC. Both patients were failures. One patient refused TURBT and disappeared for further follow-up. In 2 others, the TURBT was not performed because of serious undercurrent disease that made this patients unfit for surgery. The pathology of the resected tumors (Table 2) was TaG1 in 10, papillary urothelial neoplasia of low malignant potential (PUNLMP) in 2,Ta G2 in 3, Ta G3 in 3 and adenocarcinoma of the bladder in 1 patient. In 4 the delivered specimen was insufficient for an adequate pathology report.

Table 1: Patient, tumor characteristics and results.

Patient	N	M/F	Age (y), mean (range)	n sessions
	32	27/5	75(38-89)	36

Tumour		Patients	Sessions	CR	PR
Primary		12	12	2	1
Recurrent		20	24	8	3
Previous intravesical instillations	None	15	15	5	2
	Mitomycine	13	17	4	2
	BCG	4	4	1	0
Number	1		20	7	0
	2-7		12	2	3
	>7		4	1	1
Diameter	≤5mm		17	7	2
	6-10mm		15	2	2
	11-20mm		4	1	0
Cytology	Negative		20	8	1
	Positive		14	2	3
	Unknown		2	0	0

Table 2: Tumour Characteristics of 26 Non-Complete Responders (Pathology of TURBT).

Tumour stage and grade (WHO 1973)	Ta	G1	10
		G2	3
		G3	3
	PUNLMP		2
	adenocarcinoma		1
	unknown		7

Discussion

It has been well established that 4 intravesical instillations of MMC are able to completely destroy small papillary tumors and consequently have the possibility to avoid TURBT in about half of the patients [1-3]. Only one publication reports on the efficacy of a single chemotherapeutic intravesical instillation, comparing epirubicin 50mg and 100mg, before TURBT [4] in patients with small papillary lesions. In the 50mg epirubicin group, 24 out of 52 patients became tumor free and TURB could be avoided; in the 100mg dose group, 21 out of 50 patients responded. The authors concluded that doubling the concentration of the drug did not improve the efficacy. An overall "chemoresection" of 45 out of 102 patients with a single intravesical instillation is an amazing result. Repeating this experience with EMDA, which was considered as very promising by several authors [9,10], lets us expect that probably half of the patients can be spared a TURBT. Our previous experience showed that recurrent patients, previously treated with TURBT and intravesical instillations, largely prefer instillations over TURBT if they are given this opportunity [3]. The results of the present study are disappointing: only 10 complete responses in 36 sessions (28%). Therefore, we do not advocate the technique of a single EMDA-MMC session to avoid TURBT. In 11% (4/36) with multiple tumors, some tumors disappeared while others remained unchanged. One can call this a partial response, but of course the goal of the study, to avoid TURB, was not obtained. This 11% compares with the 13% partial response that we have seen in our previous study [3] with 4 MMC instillations. This supports the heterogeneous nature of TCC even within the same patient and therefore sensitivity to chemoresection may differ among tumors in the same patient. As we have also previously noted [3], bladder tumors can become resistant to intravesical chemotherapy over time, as we noticed that patients who completely respond to a first session, do only respond in half of the cases to a repeated session given for a recurrence. Previously MMC treated, larger tumors, multiple, primary or recurrent tumors, all had some CR. The best results were obtained in patients with small tumors (<5mm) and those with negative cytology however without reaching statistical significance. A study with a larger group of patients is needed whether this favorable trend could be confirmed.

We cannot explain the differences between our results and those obtained with a single instillation of epirubicin in the study of Masters [4]. Although the drug was different in both studies, major differences between the outcomes of MMC and epirubicin have not been

reported in the large number of publications on the intravesical use of both drugs in bladder tumors. On the contrary, given the theoretical advantages of EMDA in penetration of an intravesical delivered drug into the bladder wall, one would rather expect better results. It were the successful results of previous clinical investigations with 4 MMC instillations before TURBT [1-3], which incited us to the explore the effect of one single instillation, possibly improved by EMDA. It is possible that 2 or more instillation are more successful but this considerably diminishes cost effectiveness, exposes some patients to ineffective treatment and delays correct pathology with some weeks. Therefore we have not the intention to perform such studies.

The present study does not contradict the results obtained with EMDA-MMC in the prevention of recurrence and progression of bladder tumors the ablative effect of visible tumors is clearly different from the preventive setting.

Our study has some limitations. Our patient cohort is small and heterogeneous regarding primary or recurrent patients. However, all studies reporting on chemoresection have only between 25-102 patients and consistently report a 50% chance of complete remission, mainly in the recurrent setting [1-4]. As the number of complete remissions is low, only 10, it is impossible to find a relationship between response and urinary cytology, multifocality, primary or recurrent tumor, previous MMC use, volume of the tumors or final pathology of the resected tumors. We can only state that all types of tumors responded to a certain degree. The EMDA-MMC treatment also was started on the visual judgment of the tumor and it is nearly certain that some of the "tumors" were not urothelial neoplasms. When they disappear after intravesical chemotherapy it is most likely true, but when pathology in the non-responders could not demonstrate with certainty a tumor, as was the case in 7 treatments, the diagnosis remains uncertain. Excluding those 7 cases and the 2 cases which did not receive the full treatment because of intolerance to intravesical MMC, the CR would become 37% (10/27 EMDA-MMC sessions). But even such result remains below our expectations and in real life one would continue to propose EMDA-MMC after visual judgment of the tumor at diagnostic cystoscopy, including a few papillary formations which are not urothelial neoplasms.

Conclusion

A single EMDA-MMC in small papillary bladder tumors gives insufficient ablative effect to be advocated to avoid TURB. The best response occurred in single, small, recurrent papillary tumors with negative cytology but statistical significance was not reached. It was noticed that in the same patient some tumors disappeared by intravesical chemotherapy while others were resistant to the treatment. It was also observed that resistance to MMC developed over time.

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