

Editorial on the value of an immediate intravesical instillation of mitomycin C in patients with non-muscle-invasive bladder cancer

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Provenance: This is a Guest Editorial commissioned by Editorial Board Member Dr. Xiongbing Zu, MD, PhD (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).

Comment on: Bosschieter J, Nieuwenhuijzen JA, van Ginkel T, *et al.* Value of an Immediate Intravesical Instillation of Mitomycin C in Patients with Non-muscle-invasive Bladder Cancer: A Prospective Multicentre Randomised Study in 2243 patients. *Eur Urol* 2018;73:226-32.

Submitted Sep 22, 2017. Accepted for publication Sep 26, 2017.

doi: 10.21037/tau.2017.09.20

View this article at: <http://dx.doi.org/10.21037/tau.2017.09.20>

Recently the largest study ever on immediate intravesical instillation of mitomycin C (MMC) in non-muscle-invasive bladder cancer (NMIBC) was published (1). It reports on the recurrence rate at 3 and 5 years in of 2,243 patients, divided in 3 risk groups for recurrence, randomized to an immediate versus delayed MMC intravesical instillations after transurethral resection of the bladder tumor (TURB). Because of the magnitude of this well-designed trial, this certainly is a key publication in the field of recurrence prevention in NMIBC. Until now, the evidence behind the European Association of Urology (EAU) guidelines (2) came from a systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy versus TURB alone (3), including 2,278 patients from 13 trials. Does the latest publication change this evidence or does it confirm the previous insights?

A significant reduction of the recurrence rate is confirmed

In the current study, at 3 years, an overall relative reduction in the recurrence rate of 34% (absolute reduction of 9%: from 36% to 27%) was obtained in the immediate over the delayed instillation group. This figure is remarkably similar to the 35% relative reduction at 5 years from the meta-analysis (3) and thus confirms the efficacy of the immediate instillation, whether adjuvant instillations of MMC or given or not. The absolute reduction in recurrence rate

in the meta-analysis was 14% (from 58.8% to 44.8%). The important differences in absolute recurrence rates can be explained partly by the difference in reported time to recurrence (3 and 5 years), but also by the fact that in the meta-analysis TURB alone was compared with an early instillation without further intravesical treatment in both groups. In the current study, the higher risks groups received additional 9 to 15 MMC instillations. With a relative reduction of 34%, not any later instillation is as efficient as the immediate one!

Timing of the instillation

The instillation was given “within 24 hours after TURB” in 90% of the patients. A non-randomized comparison suggested that the instillations are more effective when given within 2 hours after TURB (3,4). When the instillation was not strictly given on the same day as the TURB, a subgroup analysis of the Finnish study (4) showed a twofold increase of the relative risk of recurrence and another trial (5) even did not find an advantage of post-op instillation anymore when the instillation was not given strictly on the same day as TURB. Although all this delivers only level 2 evidence, it makes sense to perform the instillation as early as possible, this means in the recovery room or even the operating theatre. The current study does not give exact information on that topic and therefore is unable to deliver further evidence on optimal timing of the instillation.

Which patients do not have advantage of the early instillation?

The meta-analysis defined a group of patients in which the early instillation was not effective: patients with a recurrence rate in the past of >1/year and those with EORTC score >5 (3,6). This group consisted for 70% of tumors bigger than 3cm in which the TURB often ends with extended bladder wounds with fear of bladder wall perforation and extravasation of the chemotherapy. This is also the group in which BCG often will be used afterwards. Consequently, the European guidelines (2) do not advocate the use of the early instillation in these patients.

The current study found efficacy of the immediate instillation in all 3 defined risk groups and could not define a subgroup in which there was no advantage. However, as the protocol has been written 20 years ago, the risk groups are different from those currently used. For example, information on the diameter of the biggest tumor was not available. It could be useful to try to review their data according to the current EORTC risk group classification.

Early instillation before BCG?

If the early instillation is useful in patients who receive adjuvant BCG, remains unanswered. However, it is often unknown at the end of the TURB whether BCG will be given or not, as it depends, at least partially, from pathological report (T stage, grade or presence of concomitant Tis). Therefore, patients who could be candidates for adjuvant BCG, can still be candidates for the early instillation, based on the parameters available at TURB. This leaves the question whether the early instillation is useful in those who receive adjuvant BCG, a theoretical one with little practical consequences.

Is early instillation useful if additional instillations follow?

The current study differs from the data of the meta-analysis by including 9 additional MMC instillations (3 weekly and 6 monthly) in their intermediate risk group and 15 (3 weekly and 12 monthly) in patients at high risk for recurrence. At 3 years, the recurrence rates in their low risk group was 31% versus 41% in favor of the early instillation; no additional instillations were given in this group. In the intermediate group, the recurrence rate was 20% versus 32% and in the high-risk group it was 28% versus 35% in

favor of the early instillation. This means that the advantage of the early instillation remained even if further intravesical treatment is given up to 1 year monthly. This brings light to the somewhat conflicting results and conclusion from a previous systematic review (7) which suggested that one immediate instillation may still be necessary if further chemotherapy is given during only 6 months, but not if chemotherapy is given during 12 months. The current and largest study brings new evidence and shows that the advantage of the early instillation remains when the MMC instillations are continued, even monthly up to a year.

Post-TURB irrigation

A non-randomized comparison of 1,591 patients in the meta-analysis (3), showed a 21% relative reduction of recurrence by post-TURB bladder irrigation with saline or distilled water. However, immediate instillation still reduced the risk of recurrence in the irrigation group. Therefore, irrigation may be considered as the second best choice, when early instillation is not possible. The current study gives no data on post-TURB irrigation and therefore does not add to the evidence regarding this treatment.

Adverse events

Like in previous clinical trials, the adverse events were about 5% exanthema and 5% bladder irritation, similar in the immediate and delayed instillation groups. Also, extravasation of MMC was suspected in 6 patients only, but did not provoke serious trouble. Safety of the procedure was not a problem. Nevertheless, extravasation remains a possible serious, even life-threatening, complication (8). Therefore, it seems wise not to give an immediate instillation after TURB of tumors >3 cm, a group in which immediate instillation has not been proven to be efficacious (see above).

If it would be possible to replace MMC by an equally active chemotherapeutic drug with less toxic effects at extravasation, this could take away the restraints of some colleagues and increase the use of the early instillation.

The visual judgment at cystoscopy is trustable

The decision to give an early instillation after TURB is based on the visual judgment of the urologist, without pathological examination of the resected material. One can expect that some patients thereby receive a useless instillation because it

does not concern urothelial cancer or is muscle invasive.

Besides the above-mentioned conclusions, which can also be drawn from existing literature, the current study offers interesting information on the accuracy of the visual judgment at cystoscopy by the urologist. In Figure 1 in their publication, one can read that 1.9% (54/2,844) of the “bladder tumors” were benign. In 2.7% (79) the tumors were muscle-invasive. The number of missed muscle-invasive tumors was highest in the presence of multiple tumors and in the high-grade tumors. It was minimal (n=3/584) in the solitary, low grade tumors. This corresponds with previous studies. Thus, the number of patients to which the early instillation is given in vain is low.

Office fulguration at recurrence

Office fulguration of small recurrences without TURB was admitted in the protocol of the current study, but the frequency of this procedure, unfortunately, is not documented in their publication. In view of the above mentioned accuracy of the cystoscopy and as long as recurrences of low grade tumors are involved, this seems a safe procedure (9). The authors are invited to look if interesting conclusions on this subject can be deduced from their data.

Conclusions

The most recent and largest trial ever on the immediate instillation for the prevention of recurrence in NMIBC considerably supports the conclusions of the previous meta-analysis on which EAU guidelines are based. In general, immediate instillation gives about 35% relative reduction of the recurrence rate. If highly recurrent, large (>3 cm) or EORTC-score >5 tumors should be excluded for this treatment could not be confirmed or contradicted. The advantage of the early instillation stays when additional instillations of chemotherapy are given, even if monthly up to a year, and this is new evidence. Last, it was confirmed to be a safe procedure.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Oosterlinck W, Decaestecker K. Editorial on the value of an immediate intravesical instillation of mitomycin C in patients with non-muscle-invasive bladder cancer. *Transl Androl Urol* 2018;7(Suppl 1):S135-S137. doi: 10.21037/tau.2017.09.20