



An immediate intravesical instillation of mitomycin C is of benefit in all prognostic risk groups with non-muscle-invasive bladder cancers

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A year ago, the largest and latest randomized clinical trial on immediate intravesical instillation with mitomycin C (MMC) in patients with non-muscle-invasive bladder cancer (NMIBC) was published (1) and was subject of an editorial in this journal (2). As suggested in that editorial, the trial has been reanalyzed to identify subgroups of NMIBC in which the treatment was not effective in prevention of recurrence (3). From the original study, it could be concluded that an immediate single MMC instillation was effective in all patients. However, the 3 risk groups used in the trial, were not in accordance with the contemporary, internationally accepted risk groups such as the European Association of Urology (EAU) risk groups or the European Organization for Research on Treatment of Cancer (EORTC) recurrence score (4). This is important as current EAU guidelines (5) do not recommend an early MMC instillation in NMIBC with a prior recurrence rate $\geq 1/\text{year}$ nor in EORTC recurrence score ≥ 5 . This recommendation was based on a large meta-analysis, using the original patient data of 11 clinical trials on this subject (6). Using the same statistical methods and reclassifying patients using contemporary EAU risk groups and calculated EORTC recurrence scores, the current study (3) could not identify any subgroup of patients with NMIBC who did not benefit from the immediate instillation with MMC after transurethral resection of the bladder (TURB). Should the EAU guidelines be rewritten and what are the practical consequences for daily urological practice?

Comparison of the results of the current study and the meta-analysis

In the EORTC recurrence score (4), the presence of 2–7 tumors count for 3 points, 8 or more tumors counts for 6 points. As such, multiplicity is the most important clinical prognostic factor. A previous recurrence rate of $< 1/\text{y}$ is responsible for 2 points and $\geq 1/\text{y}$ for 4 points. Tumour diameter ≥ 3 cm counts for 3 points. All these prognostic factors were evaluated in the current study.

In the current study, EORTC score ≥ 5 was present in 225 patients in the immediate group of which 57 (25.3%) recurred and in 280 of the delayed group of which 96 (34.3%) recurred, showing a clear benefit for the early instillation [HR 0.66 (0.64–0.93)]. Recurrence rate in the same score group in the meta-analysis was much higher: at 5 years 69.0% had recurred in the early instillation group (n=109) and 70.5% in the control group (n=113). Even if it is taken in account that additional MMC instillations were given to the patients at higher risk for recurrence and different follow-up times are considered, the huge difference in recurrence rate between the current study and the meta-analysis suggest that different risk groups are considered. In the meta-analysis the score was wide, ranging from 5–11. The grouping of patients in the meta-analysis was performed to have a sufficient number of patients to allow statistically significant conclusions and is as such

artificial. The current study includes more than twice the number of patients, but obviously with better outcome than those in the meta-analysis.

In the current study (3), prior recurrence rate of >1/year resulted in a recurrence rate of 31.7% (13/41) treated with an immediate instillation and in 45.3% (24/53) of the control group. This is less than half of the recurrence rate in the meta-analysis where 92.7% of the NMIBC recurred in 76 patients (38 in each group), with no difference between treated and untreated patients. Again, such mayor difference in recurrence rate between the current study and the meta-analysis cannot be explained only by the additional instillations given.

The diameter of the biggest tumor was unavailable in about half of the patients in the current study but in those with a known diameter of ≥ 3 cm (n=165), the immediate instillation with MMC was as effective in prevention of recurrence. Only 33 patients in the study had ≥ 8 tumors and 1,243 had 2–7 tumors. The immediate instillation was found to be effective in both.

Combining to mayor clinical prognostic factors, multiplicity and diameter of ≥ 3 cm, gives an EORTC score of 6 to 9. The analysis of the current study revealed 9 recurrences in 26.5% (9/34) in the immediate group and 44.2% (23/52) recurrences in the control group, demonstrating again the efficacy of an immediate instillation.

So, in contradiction to the meta-analysis not any subgroup of patients could be defined which did not benefit from an immediate instillation of MMC.

How to explain the differences between the current results and those of the meta-analysis?

The baseline characteristics of the patients included in the meta-analysis were more favorable than in the current study: 81% were primary versus 64% in the current study and respectively 77% were single tumors versus 43%. So obvious better clinical prognostic parameters were not available to explain the much lower recurrence rate than in the meta-analysis.

The subgroup of EORTC score ≥ 5 in the meta-analysis was mainly composed of patients with multiple tumors (50.9%), tumors ≥ 3 cm (69.8%) and T1 tumours (75.7%) or highly recurrent tumors (>1/year) which correspond with score 6 at least. The composition of the EORTC score ≥ 5 in the current study is not documented and this makes direct comparison impossible.

The most important factor for the therapeutic response to MMC is the chemo-sensitivity of the tumor. Based on marker lesion studies (7), one can expect that about 45% of NMIBC are sensitive to the drug which means that more than half of the NMIBC receive the drug without benefit. This was and could not be tested nor in the current study nor in the meta-analysis. An imbalance of this factor in both studies cannot be excluded.

An important difference between both publications is the period during which the trials have been conducted. The current study was started in 1998 when most of the trials of the meta-analysis were finished. Better visualization of the tumors and better TURB techniques can be responsible for a better outcome. The current study was conducted in one region, The Netherlands, while the other studies are distributed internationally. Diet, smoking habits, drinking water, environment are factors that can influence tumor behavior. The EORTC score system is also based on older studies and its current accuracy using all the new improvements in the treatment of NMIBC has not been proven. But all the above considerations remain hypothetically and cannot be proven with the data of the current study and the meta-analysis.

There were important differences in treatment schedule after the initial treatment. Eight additional MMC instillations were given up to 6 months for grade 3 or recurrent tumors in the current study. All multiple tumors or carcinoma *in situ* received further 14 instillations during a year. Based on the literature one can expect a further 12% objective reduction of the recurrence rate.

Office fulguration for small recurrences was allowed in the current study. The number of cases in which this was performed was not mentioned. There are arguments to expect that this is responsible for fewer recurrences because it avoids implantation sites at the wounds by the TURB. Bladder irrigation after TURB is also not documented but may be responsible for less recurrence.

MMC was used in the current study while several drugs have been tested in the meta-analysis. However, differences between drugs have never been demonstrated. So, it is unlikely that this may explain the difference in recurrence rate.

Finally, there may be a difference in the duration of follow-up. In the current study this was a mean of 32 months, while this is not specified in the meta-analysis.

Should the guidelines be modified and how?

One cannot neglect the results of the largest clinical trial

ever, nor those of a large meta-analysis when writing guidelines. At first glance the results seem contradictory but this is only partially true. The recurrence rate in subgroups of patients in whom the immediate instillation is not advocated in the meta-analysis (EORTC score ≥ 5 but especially in the group with >1 recurrence/year) is very high. In spite of a similar recurrence risk score, the recurrence in the current study is much lower. Obviously other, largely unknown, factors are playing an important role. The conclusion of both mayor studies together is that patients with a very high risk for recurrence did not benefit of an immediate MMC but currently this subgroup of patients is not yet defined. Currently EORTC score ≥ 5 and >1 recurrence/year are insufficient parameters to withhold the immediate instillation with MMC.

Rare but serious adverse events play a role in the application of the immediate MMC

An important reason for not giving an early instillation was the fear for extravasation of the drug. In none of the reported clinical trials safety was a problem, but very serious complications have been described in case reports. Rare devastating complications can occur when bladder perforation is present at the end of the TURB. It is reasonable to accept that many complications were never reported, as is the case with our own experience of 5 severe complications during about 30 years use of early instillations. One should be aware of this problem whenever early instillation is given. For many urologists this may be the reason for not giving this treatment in a disease which is not life threatening (8). It is indeed often difficult to judge whether bladder perforation is present or not. Anyhow, there is a strong relation between the extent of the TURB and the chance of perforation. The higher the number and diameter of the tumors, the more extensive the TURB and the higher the chance for perforation.

The EORTC recurrence score for ≥ 8 tumors is 6 and for tumors with a diameter of ≥ 3 centimeters is 3. When both are present it means a score of 9. Many of the large and multiple tumors belong to the category in which extravasation can be feared and therefore, in daily practice, will not be treated with immediate MMC after TURB. Further investigations should be directed to drugs which are harmless at extravasation such as apaziquone and taxanes (9). Also, bladder irrigation post-TURB should be better explored.

Conclusions

The current study adds considerably to the evidence that an immediate MMC instillation after TURB for NMIBC is an effective treatment in the vast majority of the patients, also when other chemo-instillations are given afterwards. With a relative reduction in the risk of recurrence of 34%, it is the most effective single instillation. Based on the meta-analysis, there probably is a small group of highly recurrent tumors that do not benefit, but their clinical prognostic factors are not yet well defined. They probably are among the multiple and large tumors of >3 cm. In daily practice, this group is often excluded from early instillation anyway because of fear for extravasation after TURB.

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Footnote

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

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