The Schedule and Duration of Intravesical Chemotherapy in Patients with Non–Muscle-Invasive Bladder Cancer: A Systematic Review of the Published Results of Randomized Clinical Trials

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Abstract

Objectives: Intravesical chemotherapy has been studied in randomized clinical trials for >30 yr; however, the optimal schedule and duration of treatment are unknown. The objective is to determine the effect of schedule and duration of intravesical chemotherapy on recurrence in patients with stage Ta T1 bladder cancer.

Methods: A systematic review was conducted of the published results of randomized clinical trials that compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity.

Results: One immediate instillation after transurethral resection (TUR) is recommended in all patients. In low-risk patients, no further treatment is recommended before recurrence. In patients with multiple tumors, one immediate instillation is insufficient treatment. Additional instillations may further reduce the recurrence rate; however, no recommendations can be made concerning their optimal duration. A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer-term treatment schedules (grade C). Instillations during ≥1 yr in intermediate-risk patients seem advisable only when an immediate instillation has not been given (grade C). Higher drug concentrations and optimization of the drug’s concentration in the bladder may provide better results (grade C).

Conclusions: The optimal schedule and duration of intravesical chemotherapy after an immediate instillation remain unknown. Future studies should focus on the eradication of residual disease after TUR and the prevention of late recurrences.

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1. Introduction

Guidelines of the European Association of Urology for the treatment of stage Ta–T1 (non–muscle-invasive) bladder cancer recommend that all patients receive one immediate instillation of chemotherapy after transurethral resection (TUR) [1]. Further treatment depends on the patient’s risk of recurrence and progression to muscle-invasive disease [2]. In patients at low risk of recurrence and progression, no further treatment is recommended prior to a subsequent recurrence. In patients at high risk of progression, that is, those with high-grade tumors or carcinoma in situ (CIS), 1–3 yr of maintenance bacillus Calmette-Guérin (BCG) is recommended.

The remaining patients have an intermediate risk of progression and an intermediate to high risk of recurrence, with the risk of recurrence depending, to a large extent, on the number of tumors [2]. One immediate instillation by itself has been shown to be insufficient treatment after TUR in patients with multiple tumors [3]; however, there is no consensus whether further intravesical chemotherapy or intravesical BCG should be given in these patients.

Meta-analyses have shown that intravesical chemotherapy reduces the recurrence rate as compared to TUR alone [4–6], with a decrease of 8% in the percentage of patients who have recurrence [4]. However, the optimal frequency and duration of treatment remain unknown. Although one meta-analysis suggested that longer instillation schedules may be associated with greater treatment benefit [5], another meta-analysis questioned whether there was a long-term benefit beyond one immediate instillation [7].

To determine the effect of schedule and duration of intravesical chemotherapy on recurrence in patients with non–muscle-invasive bladder cancer, a systematic review of the published results of randomized clinical trials has been carried out. Because of the heterogeneity of the various treatment schedules within some of the groups being compared, it was not always justified to pool together the results from the different studies to get an overall quantitative estimate of the size of the treatment effect. Hence, meta-analyses have been carried out for only a limited number of comparisons.

2. Methods

All randomized trials in patients with stage Ta–T1 bladder cancer that compared different schedules or durations of intravesical chemotherapy after TUR were considered. Trials published or accepted for publication before May 2007 that compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity were identified by searching MEDLINE, reference lists in trial publications and review articles, and annual meeting abstracts in the Journal of Urology and European Urology. Studies assessing device-assisted chemotherapy (electromotive drug administration [EMDA] or hyperthermia) and chemotherapy relative to or in combination with BCG were not included.

Because individual patient data were not available and most publications did not provide sufficient information to compare the time to first recurrence, the primary end point was the percent of patients with recurrence. When available, for each trial the percent of patients with recurrence in each treatment group was calculated and compared using a $x^2$ test unless the log-rank $p$ value for time to first recurrence was provided.

For comparisons where a meta-analysis was done, estimates from individual studies were combined together using a fixed effects model and differences were tested for significance using the Mantel-Haenszel test stratified by study.

3. Results

Results are presented as answers to different questions about the schedule and duration of intravesical chemotherapy taking into account whether or not an immediate instillation of chemotherapy was given after TUR.

3.1. After one immediate instillation, can additional intravesical chemotherapy reduce the recurrence rate in patients with multiple tumors?

A total of 879 patients were entered in three trials comparing one immediate instillation to one immediate instillation plus additional instillations (Table 1). In two Medical Research Council (MRC) trials, which were each published twice [8–11], four additional 3 monthly instillations were given during 1 yr. In the thiotepa study [8,9], there was no reduction in the percentage of patients who had recurrence, 41.9% versus 37.5%; however, this trial has been criticized because of the low drug concentration used, 30 mg/50 ml. In the mitomycin C (MMC) trial [10,11], based on updated summary data, there was a reduction in the percentage with recurrence from 48.3% to 36.3% overall ($p = 0.04$) and from 70% to 50% in patients with multiple tumors ($p = 0.09$). However, in both of these studies, patients who recurred at 3 mo prior to starting their additional instillations were already counted as having their first recurrence, potentially diluting the size of any treatment effect. The benefit of
additional instillations in patients still free of disease at 3 mo was not reported and may be underestimated by the overall results.

In a third trial, which assessed 4 weekly instillations of epirubicin starting within 24 h of TUR followed by monthly instillations to month 12 (15 instillations), there was a small nonsignificant reduction in the percent of patients with recurrence, from 31.8% to 24.0% \( (p = 0.11) \) [12].

There is thus a suggestion that additional instillations may reduce the recurrence rate, but no definitive conclusions can be drawn. Approximately 70% of the patients had a single tumor and only one study provided separate results for single and multiple tumors.

3.2. If further intravesical chemotherapy is given after one immediate instillation, how long should it continue?

Although there is no conclusive proof that additional chemotherapy after one immediate instillation is of benefit, three trials including a total of 598 patients compared 12 mo of treatment to either 6, 3, or 1 mo of treatment (Table 2).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TUR + 1 instillation</td>
<td>TUR + 1 instillation + maintenance</td>
</tr>
<tr>
<td>MRC [8,9]</td>
<td>1985</td>
<td>Thiotepa</td>
<td>69%</td>
<td>52/124 (41.9%)</td>
<td>45/120 (37.5%)</td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>30 mg/50 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolley [10,11]</td>
<td>1988</td>
<td>MMC</td>
<td>Single</td>
<td>51/119 (42.9%)</td>
<td>33/104 (30.8%)</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>40 mg/40 ml</td>
<td>Multiple</td>
<td>21/30 (70.0%)</td>
<td>21/42 (50.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75%</td>
<td>72/149 (48.3%)</td>
<td>53/146 (36.3%)</td>
</tr>
<tr>
<td>Selvaggi [12]</td>
<td>1990</td>
<td>Epirubicin</td>
<td>69%</td>
<td>55/173 (31.8%)</td>
<td>40/167 (24.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg/50 ml</td>
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</tr>
</tbody>
</table>

Maintenance treatment: References 8–11: 4 additional 3 monthly instillations during 12 mo starting at month 3 (total 5 instillations); for reference 12: 3 additional instillations during the first 4 wk followed by 11 monthly instillations to month 12 (total 15 instillations).

TUR = transurethral resection; MRC = Medical Research Council; MMC = mitomycin C.

* Log-rank test.

Comparing nine instillations of MMC or Adriamycin given during 6 mo to 15 instillations given during 12 mo, there was no difference in the percentage of patients with recurrence [13]; however, no results were presented taking 6 mo as time zero. In another study, no difference was found when comparing six instillations of epirubicin during 1 mo to 17 instillations in 12 mo [14]. A third study comparing nine instillations of epirubicin given during 3 mo to 19 instillations in 12 mo found that fewer patients had recurrence with 12 mo of treatment, 13% versus 31.5% \( (p = 0.005) \) [15].

The results are thus contradictory concerning whether 12 mo of treatment is more effective than a shorter duration of treatment after an immediate instillation.

3.3. In low-risk patients, can the same or better results be obtained with one immediate instillation as compared to multiple delayed instillations after TUR?

Three epirubicin trials including a total of 512 patients compared one immediate instillation to delayed instillations during 12 mo (Table 3).

**Table 2 – TUR plus one immediate instillation followed by short-term versus long-term instillations during 12 mo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short-term instillations</td>
<td>Long-term instillations (12 mo)</td>
</tr>
<tr>
<td>Bouffioux [13]</td>
<td>1995</td>
<td>MMC 30 mg/50 ml</td>
<td>62%</td>
<td>70/160 (43.8%)</td>
<td>67/150 (44.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADM 50 mg/50 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okamura [14]</td>
<td>1995</td>
<td>Epirubicin 40 mg/40 ml</td>
<td>67%</td>
<td>NA/69 (22.8%)</td>
<td>NA/69 (24.9%)</td>
</tr>
<tr>
<td></td>
<td>2 yr</td>
<td>2 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koga [15]</td>
<td>2004</td>
<td>Epirubicin 30 mg/50 ml</td>
<td>61%</td>
<td>23/73 (31.5%)</td>
<td>10/77 (13.0%)</td>
</tr>
<tr>
<td></td>
<td>2 yr</td>
<td>2 yr</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>

Treatment schedules: Reference 13: 9 instillations during 6 mo vs. 15 instillations during 12 mo; reference 14: 6 instillations during 1 mo vs. 17 instillations during 12 mo; reference 15: 9 instillations during 3 mo vs. 19 instillations during 12 mo.TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available.

* Log-rank test.
No differences were found in trials comparing one immediate instillation to either 8 weekly instillations starting 1–2 wk after TUR followed by monthly instillations to 1 yr (18 instillations) [16] or to weekly instillations for 6–8 wk followed by monthly instillations to 1 yr (16–18 instillations) [17]. In another trial comparing one immediate instillation to 4 weekly instillations starting 2 wk after TUR followed by monthly instillations to 1 yr (15 instillations), fewer patients had recurrences in the delayed multiple instillation group, 24.8% versus 30.2% ($p = 0.05$) [12]. These results suggest that one immediate instillation of epirubicin might not be less effective than a delayed course of multiple epirubicin instillations in patients at low to intermediate risk.

### 3.4. Is an immediate instillation still important if it is planned to give long-term chemotherapy?

#### 3.4.1. Six months of chemotherapy

Two trials assessed the benefit of an immediate instillation when chemotherapy was given during 6 mo (Table 4). In the first trial in which patients were randomized to start immediately or start 1–2 wk after TUR (9 instillations of MMC or Adriamycin during 6 mo), fewer patients receiving immediate chemotherapy had recurrence, 43.8% versus 55.8% ($p = 0.03$) [13]. However, in the second trial in which patients received 4 weekly instillations of epirubicin followed by 5 monthly instillations (9 instillations in 6 mo) preceded or not by one “immediate” instillation within 48 h, no significant difference was found [18]. This last study has been criticized because the first instillation was not given on the same day as the TUR; however, there was no difference according to whether or not the immediate instillation was given within 24 h.

#### 3.4.2. Twelve months of chemotherapy

Three trials with 784 patients compared 4 weekly instillations starting within 24 h to 4 weekly instillations starting within 1–2 wk, followed in both arms by 11 monthly instillations to month 12 (Table 5). In the first two studies, the percentage with recurrence in the two treatment groups was similar [12,13]. In the

### Table 3 – TUR plus one immediate instillation versus TUR plus delayed instillations to month 12

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TUR + 1 instillation</td>
<td>TUR + delayed instillations (12 mo)</td>
<td></td>
</tr>
<tr>
<td>Ali-el-Dein [16]</td>
<td>1997</td>
<td>Epirubicin 50 mg/50 ml</td>
<td>Single 8/34 (23.5%)</td>
<td>5/33 (15.2%)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple 5/21 (23.8%)</td>
<td>10/26 (38.5%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Liu [17]</td>
<td>2006</td>
<td>Epirubicin 80 mg/40 ml</td>
<td>13/55 (23.6%)</td>
<td>15/59 (25.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>68% 5/14 (35.7%)</td>
<td>11/30 (36.7%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Selvaggi [12]</td>
<td>1990</td>
<td>Epirubicin 50 mg/50 ml</td>
<td>55/173 (31.8%)</td>
<td>41/181 (22.7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>69% 73/242 (30.2%)</td>
<td>67/270 (24.8%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Delayed instillations: Reference 16: 8 weekly instillations starting 1–2 wk after TUR followed by monthly instillations to month 12 (18 instillations); reference 17: 6–8 weekly instillations followed by monthly instillations to month 12 (16–18 instillations); reference 12: 4 weekly instillations starting 2 wk after TUR followed by monthly instillations to month 15 (15 instillations).

TUR = transurethral resection.

### Table 4 – TUR plus one immediate instillation plus additional instillations during 6 mo versus TUR plus delayed instillations during 6 mo

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TUR + immediate instillation</td>
<td>TUR + delayed instillation</td>
<td></td>
</tr>
<tr>
<td>Bouffioux [13]</td>
<td>1995</td>
<td>MMC 30 mg/50 ml</td>
<td>62% 70/160 (43.8%)</td>
<td>86/154 (55.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADM 50 mg/50 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hendricksen [18]</td>
<td>2007</td>
<td>Epirubicin 50 mg/50 ml</td>
<td>20% 109/238 (45.8%)</td>
<td>117/239 (49.0%)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Treatment schedule: reference 13: 4 weekly instillations starting immediately or 1–2 wk after TUR followed by 5 monthly instillations to month 6 (9 instillations); reference 18: 4 weekly instillations followed by 5 monthly instillations to month 6 (9 instillations) preceded or not by an “immediate” instillation within 48 h.

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin.
third study, more patients had recurrences on the delayed treatment \((p = 0.04)\); however, patients on delayed treatment tended to have a worse prognosis [19]. Combining these three studies, the percentage with recurrence on the immediate and delayed arms was similar. In a fourth study, there were no significant differences in the 3-yr recurrence rates [20].

These results suggest that one immediate instillation may still be necessary if further chemotherapy is given during only 6 mo; however, it might not be necessary if chemotherapy is given during 12 mo.

### 3.5. If one immediate instillation is not given, how long should further chemotherapy be continued?

Table 6 summarizes nine trials comparing delayed short-term instillations to delayed long-term instillations.

#### 3.5.1. One year of chemotherapy

Three trials using various drugs compared short-term instillations of 5–6 mo to instillations during 1 yr [13,18,21]. In one study, fewer patients had recurrence with 12 mo of MMC or Adriamycin (15 instillations) as compared to 6 mo of treatment (9 instillations), 41.2% versus 55.8\% \((p = 0.01)\) [13]. However, in another study comparing 11 instillations of epirubicin during 12 mo to 9 instillations during 6 mo, no difference was found [18]. Likewise, no difference was found in a study comparing 19 instillations of epirubicin during 12 mo to 12 instillations during 5 mo [21]. In all three of these trials there is a possible dilution of the size of the treatment effect due to recurrences in the long-term treatment arm prior to starting the long-term instillations at 5 or 6 mo.

In another study comparing 12 instillations of Adriamycin during 6 wk to an additional 15 instillations to 1 yr, no difference was found [22]. A further study comparing 4 mo (40 mg/40 ml) to 7 mo (30 mg/40 ml) to 12 mo (20 mg/40 ml) of epirubicin found a higher percentage of patients with recurrence on the 12-mo arm, but treatment duration is confounded with drug concentration so no conclusions can be drawn from this study concerning the optimal duration of treatment [23].

Although some evidence suggests that 1 yr of chemotherapy may be better than shorter durations, the study results are inconsistent.

#### 3.5.2. Two years of chemotherapy

Two trials compared weekly instillations of Epodyl or Adriamycin during 6 wk to 6 weekly instillations followed by monthly instillations during 2 yr (30 instillations) [24,25]. There was no difference in the percentage of patients who had recurrences in the two treatment groups in either study.

#### 3.5.3. Three years of chemotherapy

Weekly instillations of MMC for 20 wk were compared to either weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) or to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations) [26,27]. There was no difference in the percentage who had a recurrence on 20 wk or 3 yr of treatment; however, the
comparisons are confounded by different treatment intensities during the initial 20 wk.

In a recent study comparing 6 weekly instillations of MMC to 6 weekly instillations followed by monthly instillations during 3 yr (42 instillations), there was a large decrease in the percentage of patients with recurrence in the group receiving 3 yr of MMC, 25.7% versus 10.5% (p = 0.0006) [28]. Based on these contradictory results, no clear conclusions can be drawn concerning the optimal duration of chemotherapy when one immediate instillation is not given. One year and 2 yr of treatment do not appear to be superior to 6 wk, and 3 yr of treatment was not found to superior to 20 wk, so it was unexpected when 3 yr was recently reported to be more effective than 6 wk [28].

### 3.6. Does dose intensity or frequency of instillation influence the recurrence rate?

#### 3.6.1. Total dose and dose concentration

Five trials, as summarized in Table 7, compared different total doses or drug concentrations.

Comparing 180 mg of epirubicin instilled within 6–11 wk (6 instillations) to 360 mg instilled within 10–12 wk (12 instillations), fewer patients had recurrences on the higher total dose, 31.8% versus 70.2% (p = 0.012) [29].

One study showed that the efficacy of MMC can be improved by increasing the drug’s concentration in the bladder. A dose of 20 mg/20 ml was compared to an optimized dose with 40 mg/20 ml and pharmacokinetic manipulations to maintain a high drug
concentration in the bladder, with fasting to decrease the urine volume and urine alkalinization to stabilize the drug [30]. It is not known which, if any, of these three factors was the most important.

Other studies did not, however, find a difference in efficacy between different drug concentrations [31–34]. Two concentrations of Adriamycin, 20 mg/40 ml and 30 mg/30 ml, were compared using two different treatment schedules: 8 instillations within 4 wk (160 mg vs. 240 mg) or 21 instillations within 2 yr (420 mg vs. 630 mg) [31,32]. No difference in efficacy was found between the two doses for either 4 wk or 2 yr of treatment. When 18 instillations of epirubicin were given within 1 yr, there was no difference between 50 mg/50 ml (900 mg) and 80 mg/50 ml (1440 mg) in the percentage who had recurrence, 25.0% versus 17.6%, respectively [33]. Likewise, there was no difference in efficacy in a trial comparing

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TUR + less intense or frequent schedule</td>
<td>TUR + more intense or frequent schedule</td>
</tr>
<tr>
<td>Mitsumori [29]</td>
<td>2004</td>
<td>Epirubicin</td>
<td>33/47 (70.2%)</td>
<td>7/22 (31.8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Au [30]</td>
<td>2001</td>
<td>MMC</td>
<td>73/111 (65.8%)</td>
<td>61/119 (51.3%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Akaza [31a]</td>
<td>1987</td>
<td>ADM</td>
<td>64%</td>
<td>NA/148 (48.0%)</td>
<td>1.5 yr</td>
</tr>
<tr>
<td>Niijima [32]</td>
<td>1987</td>
<td>ADM</td>
<td>60%</td>
<td>NA/158 (40.9%)</td>
<td>2 yr</td>
</tr>
<tr>
<td>Akaza [31b]</td>
<td>1987</td>
<td>Epirubicin</td>
<td>38%</td>
<td>16/64 (25.0%)</td>
<td>12/68 (17.6%)</td>
</tr>
<tr>
<td>Ali-el-Dein [33]</td>
<td>1997</td>
<td>Thiotepa</td>
<td>71%</td>
<td>NA/23 (37%)</td>
<td>1 yr</td>
</tr>
<tr>
<td>Koontz [34]</td>
<td>1981</td>
<td></td>
<td></td>
<td>NA/23/31 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7 – Dose intensity and frequency of instillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>% single tumors</th>
<th>Recurrence/total no. of patients</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
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<td>2004</td>
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<td>0.012</td>
</tr>
<tr>
<td>Au [30]</td>
<td>2001</td>
<td>MMC</td>
<td>73/111 (65.8%)</td>
<td>61/119 (51.3%)</td>
<td>0.005</td>
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<td>Niijima [32]</td>
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<td>ADM</td>
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<td>1997</td>
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</tbody>
</table>

Treatment schedules: reference 29: 180 mg within 6–11 wk (6 instillations) vs. 360 mg within 10–12 wk (12 instillations); reference 30: MMC 20 mg/20 ml vs. 40 mg/20 ml with dose optimization (6 instillations); references 31a, 32: 8 instillations within 4 wk: 20 mg/40 ml vs. 30 mg/30 ml (160 mg vs. 240 mg); reference 31b: 21 instillations within 2 yr: 20 mg/40 ml vs. 30 mg/30 ml (420 mg vs. 630 mg); reference 33: 18 instillations within 1 yr: 50 mg/50 ml vs. 80 mg/50 ml (900 mg vs. 1440 mg); reference 34: instillations every 4 wk for a maximum of 2 yr: 30 mg/30 ml vs. 60 mg/60 ml; references 26a, 27a: weekly instillations for 20 wk vs. weekly instillations for 8 wk followed by monthly instillations to 3 yr (20 or 42 instillations); references 26b, 27b: weekly instillations for 20 wk vs. instillations every 2 wk during 1 yr, then every 4 wk during year 2, then every 3 mo during year 3 (20 or 42 instillations); references 26c, 27c: weekly instillations for 8 wk followed by monthly instillations to 3 yr vs. instillations every 2 wk during 1 yr, then every 4 wk during year 2, then every 3 mo during year 3 (42 instillations); reference 23: weekly for 2 wk and every 2 wk to month 4 followed or not by monthly instillations for 3 mo followed or not by monthly instillations to month 12 (9 [40 mg/40 ml], 12 [30 mg/40 ml], or 17 [20 mg/40 ml] instillations).

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available; NS = not significant.

* Log-rank test.

1 Log-rank test for trend.
30 mg/30 ml to 60 mg/60 ml of thiotepa where instillations were given every 4 wk for a maximum of 2 yr [34]. Once again the results of the different trials are inconsistent and no definitive conclusions can be drawn.

3.6.2. More intense or frequent short-term instillations compared to less intense long-term instillations

3.6.2.1. Frequent short-term instillations versus less frequent early instillations followed by long-term instillations (different total dose). Weekly instillations of MMC 20 mg/20 ml for 20 wk were compared to weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) and to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations). There was no difference in efficacy between the frequent short-term instillations and either of the less intense long-term instillations [26,27].

3.6.2.2. Intense short-term instillations versus less intense long-term instillations (same total dose). Comparing 20 mg/40 ml of epirubicin (17 instillations in 12 mo) to 30 mg/40 ml (12 instillations in 7 mo) to 40 mg/40 ml (9 instillations in 4 mo), the percentage of patients with recurrence decreased as the drug concentration increased despite the decrease in the duration of treatment [23].

3.6.2.3. Frequent early instillations versus less frequent early instillations followed by long-term instillations in both arms (same total dose). Weekly MMC instillations for 8 wk followed by monthly instillations to 3 yr were compared to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations). There was a small nonsignificant decrease in the percentage of patients with recurrence in the group receiving 8 weekly instillations, 17.7% versus 24.4% [26,27].

Thus, evidence indicates that frequent, dose intense, short-term instillations may provide results that are at least as good as less intense instillations given over a longer period of time.

4. Discussion

Although the schedule and duration of intravesical chemotherapy have been the subjects of many studies, the optimal instillation scheme remains unknown. Controversy exists because underpowered trials have produced inconsistent results. Comparisons of different treatment durations have been diluted because patients have had recurrences and gone off the study before the time when additional long-term instillations should have started. The benefit of continuing treatment in patients who were free of disease at the end of the short-term treatment period was not assessed. In addition, trials have included varying proportions of good- and intermediate-risk patients, making it difficult to draw conclusions according to risk of recurrence. Different chemotherapeutic agents and different doses have also been used and the quality of TUR may differ among studies. Although there are no concrete data proving that one drug is more effective than another, one cannot rule out differences in efficacy according to the regimen used. For all these reasons, firm conclusions based on a high level of evidence cannot be drawn for most comparisons.

One immediate instillation reduces the recurrence rate, not only in good-risk patients with single tumors but also in patients with multiple tumors for whom one instillation is an incomplete treatment [3]. Beyond this, the results of this systematic review are disappointing and only limited conclusions can be drawn concerning the value of further treatment.

This review suggests that after one immediate instillation, additional instillations may further reduce the recurrence rate, especially in patients with multiple tumors, but no definitive conclusions can be drawn (Table 1). Likewise, if further treatment is given, no recommendations can be given concerning its optimum duration (Table 2).

If one immediate instillation is not given, a minimum of 12 mo of treatment appears to be necessary to achieve the same prophylactic effect on recurrence as compared to one immediate instillation, either without (Table 3) or with additional instillations (Tables 4 and 5).

Although some evidence suggests that 1 yr may be better than 5–6 mo of treatment when one immediate instillation has not been given [13], results among the different studies were inconsistent (Table 6). There was no suggestion that 1 or 2 yr of treatment is more effective than 6 wk or that 3 yr is more effective than 5 mo; however, the number of patients studied is insufficient to draw definitive conclusions. On the other hand, a recent study showed a large decrease in the percent of patients recurring with 3 yr as compared to 6 wk of MMC [28]; it is unknown if this difference will lead to fewer cystectomies, progressions, and deaths due to bladder cancer. In an European Organization for Research and Treatment of Cancer (EORTC) study comparing 3 yr of epirubicin and BCG in intermediate- and high-risk patients, the results with epirubicin were
disappointing despite an immediate instillation having been given [35]. Based on these contradictory results, no clear conclusions can be drawn concerning the optimal duration of chemotherapy when an immediate instillation has not been given.

Two studies in Table 7 suggest that more intense treatment during the initial 3–4 mo, either with respect to number of instillations [29] or drug concentration [30], reduces the recurrence rate. Other studies did not find a difference in efficacy between different drug concentrations [31–34,36]. Weekly instillations during 5 mo appear to be as effective as long-term instillations during 3 yr, which were given less frequently during the initial 5-mo period [26,27]. Thus, some evidence indicates that an initial intense schedule of instillations is of benefit and may be as effective as less intense long-term treatment.

The schedule and duration of intravesical chemotherapy should be guided by recurrence rates observed over time. Several publications have focused on the high recurrence rate at the first follow-up cystoscopy after TUR due to an incomplete resection or residual tumor [37–39]. There is thus justification for giving an early schedule of instillations to eradicate residual tumor after TUR.

The effect of one immediate instillation occurs early on, mainly during the first 1–2 yr, and is not effective in preventing late recurrences [40]. One study found two patterns of recurrence after TUR alone, early and late, with multiple tumors showing a peak in recurrence at 4 mo and solitary tumors showing a peak in recurrence at 1 yr. The effect of intravesical epirubicin or Adriamycin continued for a maximum of 500 d after TUR [41]. Another study with epirubicin found peaks in the recurrence rate at 18 mo and 4 yr, but with an earlier and increased risk of recurrence on short-term treatment of 3 mo as compared to 12 mo treatment [15]. These results suggest that additional therapy should be given prior to or at 1 yr in an attempt to prevent late recurrences.

Although intravesical chemotherapy reduces the recurrence rate, there is no proof that long-term chemotherapy will lead to fewer cystectomies, fewer progressions, or fewer deaths due to bladder cancer. In addition, its impact on quality of life is unknown. Long-term chemotherapy has, however, certain drawbacks including its costs, inconvenience, toxicity, and possible carcinogenicity [7]. Thus, it should not be given for a longer period of time than is necessary. Restarting instillations only after recurrence in intermediate-risk patients might in the long-term be as effective as immediate treatment, thus sparing patients from needless instillations. Hence, the cost effectiveness of long-term chemotherapy needs to be considered.

One could hypothesize that the excellent results that were recently reported with 3 yr of chemotherapy [28] might also have been obtained with an immediate instillation followed by an early short intensive course of instillations and an additional course of maintenance instillations at approximately 1 yr. However, randomized trials are required to test this strategy.

5. Conclusions

One immediate instillation after TUR reduces the recurrence rate and is recommended in all patients with papillary tumors except in the case of a perforated bladder or extended TUR (grade A). In patients at low risk of recurrence, no further treatment is recommended prior to recurrence.

In patients with multiple tumors for whom one instillation is insufficient treatment, the results of this systematic review are inconclusive and firm recommendations cannot be provided. The effect of one immediate instillation lasts for approximately 1.5 yr (level of evidence 1B). Additional instillations may be able to further reduce the recurrence rate although no recommendations can be given concerning their optimal duration. A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer term treatment schedules (grade C).

Additional instillations at or after 1 yr may be useful in preventing late recurrences in intermediate-risk patients, but results of trials studying the benefit of 1, 2, and 3 yr of treatment are conflicting (grade C). Long-term instillations during >1 yr seem advisable only when an immediate instillation has not been given (grade C).

Higher drug concentrations and optimization of the drug’s concentration in the bladder by decreasing the urine volume and controlling urine pH may provide better results (grade C).

Conflicts of interest

The authors have nothing to disclose.

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