Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy after Transurethral Resection to Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?

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Abstract

Context

EAU Non Muscle Invasive Bladder Cancer (NMIBC) Guidelines recommend all low and intermediate risk patients receive a single immediate instillation of chemotherapy after TURB, but its use remains controversial.

Objective

Identify which NMIBC patients benefit from a single immediate instillation.

Evidence Acquisition

A systematic review and individual patient data (IPD) meta-analysis of randomized trials comparing the efficacy of a single instillation after TURB to TURB alone in NMIBC patients was carried out.

Evidence Synthesis

13 eligible studies were identified. IPD were obtained for 11 studies randomizing 2278 eligible patients, 1161 to TURB and 1117 to a single instillation of epirubicin, mitomycin C, pirarubicin or thiotepa.

1128 recurrences, 108 progressions and 460 deaths, 59 due to bladder cancer, occurred. A single instillation reduced the risk of recurrence by 35%, HR = 0.65, 95% CI: 0.58-0.74, $p < 0.001$ and the 5 year recurrence rate from 58.8% to 44.8%. The instillation did not reduce recurrences in patients with a prior recurrence rate > 1 recurrence/year or in patients with an EORTC recurrence score ≥ 5.

The instillation did not prolong either the time to progression or death from bladder cancer, but resulted in an increase in the overall risk of death (HR = 1.26, 95% CI: 1.05 – 1.51, p = 0.015, 5 year death rates 12.0% versus 11.2%), with the difference appearing in patients with an EORTC recurrence score ≥ 5.

Conclusions

A single immediate instillation reduced the risk of recurrence, except in patients with a prior recurrence rate > 1 recurrence/year or an EORTC recurrence score ≥ 5. It does not prolong either time to progression or death from bladder cancer. The instillation may be associated with an increase in the risk of death in patients at high risk of recurrence in whom the instillation is not effective or recommended.

Patient Summary

A single instillation of chemotherapy immediately after resection reduces the risk of recurrence in non-muscle invasive bladder cancer, however it should not be given to patients at high risk of recurrence due to its lack of efficacy in this subgroup.

1. Introduction

In low and intermediate risk patients with non-muscle invasive bladder cancer (NMIBC), the EAU NMIBC Guidelines Panel recommends a single immediate instillation of chemotherapy after complete transurethral resection (TURB) [1]. This recommendation stems from a June 2004 literature based meta-analysis of a single immediate postoperative instillation of chemotherapy. Analyzing data extracted from publications of 7 randomized controlled trials (RCTs), the meta-analysis concluded that a single instillation significantly reduced the risk of recurrence after TURB, odds ratio = 0.61, 95% CI: 0.49-0.75, $p < 0.0001$, number needed to treat = 8.5 [2]. The AUA also supports use of an immediate postoperative instillation in patients with small volume, low grade Ta tumors [3]. Despite these recommendations, an immediate instillation of chemotherapy is not universally used in day to day clinical practice [4-7].

Several RCTs assessing the efficacy of an immediate instillation have been published since the meta-analysis, some of which questioned its efficacy, especially in intermediate risk patients [8]. One review called for it to be abandoned [9].

One limitation of the meta-analysis was that it was not based on individual patient data so time to recurrence, prognostic factor and subgroup analyses could not be carried out to identify which patients benefit from the instillation. Likewise, two recent literature based meta-analyses could not adequately answer this question [10 – 11].

To identify which patients benefit from an immediate instillation, a new systematic review and meta-analysis using individual patient data has been undertaken.

This project was prospectively defined in a protocol at https://db.tt/Q87Yvkk7.

2. Evidence Acquisition

2.1 Trial Eligibility Criteria

All RCTs comparing a single immediate instillation of chemotherapy after TURB to TURB alone in patients with single or multiple, primary or recurrent stage pTaT1 urothelial carcinoma of the bladder were eligible. Carcinoma in situ and/or postoperative irrigation were not exclusion criteria. Trials allowing additional treatment prior to first recurrence were not eligible.

2.2 Literature Search

Medline, Embase, and Cochrane controlled trials databases and clinicaltrials.gov were searched for relevant studies. No time limitations were applied. The search was supplemented by hand searching EAU and AUA meetings abstracts from 2005 to 2013, reference lists, searches in Google and discussions with clinical experts. The literature search strategy was developed starting in July 2013 with the final search in November 2013 using the strategy in Online Appendix 1.

2.3 Review of Studies Identified by the Literature Search

Each abstract was reviewed by at least 2 independent reviewers (see Acknowledgements). A Study Eligibility Form was filled out for studies identified as potentially eligible or where eligibility was unclear. These studies were entered in an Excel database to keep track of their status and final disposition. Full publications were requested to allow a more detailed assessment by the reviewer. For AUA and EAU abstracts, a similar procedure was followed.

Studies proposed as being eligible or where eligibility was unclear or there was disagreement between reviewers were reviewed by at least one member of the Steering Committee to reach a decision.

2.4 Data Collection and Quality Control

Individual patient data on baseline characteristics, treatment, and outcome were requested for eligible studies using a pre-defined format (Online Appendix 2).

Data of each study were analyzed separately and compared to those in the publication. Results were sent to the principal investigator for approval along with any discrepancies noted.

2.5 Data Synthesis and Statistical Evaluation

2.5.1 Outcome Measures

The efficacy of a single immediate instillation of chemotherapy after TURB was compared to TURB alone with respect to:

Primary outcome: time to first recurrence, histologically confirmed.

Secondary outcomes: time to progression to muscle invasive disease, overall duration of survival, time to death due to bladder cancer

2.5.2 Statistical Evaluation

The primary analysis was carried out in all eligible patients with pTa or pT1 tumors. Confirmatory analyses in all randomized patients could not be done due to missing data for ineligible patients.

Ignoring recurrences after the first, the number needed to treat (NNT) to prevent one recurrence within 5 years was calculated in eligible patients and in all randomized patients assuming ineligible patients recurred within 5 years.

For time to event comparisons, starting point was date of randomization. For patients who died prior to an event of interest, death from a cause other than bladder cancer was a competing risk and date of death was the date of the competing risk event. Patients without an event were censored at last date of follow up.

Times to recurrence, progression and death due to bladder cancer were estimated by cumulative incidence functions taking death prior to an event as competing risk.

Overall duration of survival was estimated by the Kaplan-Meier technique. Median duration of follow up was calculated in all patients based on censoring at time of event.

Time to event distributions were compared using a Cox proportional hazards model stratified by study. The Fine-Gray test for competing risks was calculated as a sensitivity analysis. All tests were two sided using 0.05 significance level.

Fixed effect meta-analysis Forest plots were used to visually assess heterogeneity along with Cochran's Q chi-square test for heterogeneity and Higgins I^2. Heterogeneity of treatment effect was tested in a Cox proportional hazards model using treatment by covariate interactions for variables in Figure 3. This included the 2006 EORTC risk scores for recurrence and progression [12] and the 2013 EAU risk group classification [1]. Subgroup analyses were carried out for factors where the interaction was significant at 0.05.

Exploratory non-randomized comparisons were carried out according to the chemotherapy, delay between TURB and immediate instillation, and use of post-operative irrigation.

No studies or patients were excluded for quality reasons.

3. Evidence Synthesis

3.1 Literature Search Results

2365 abstracts were identified by the literature search (Online Appendix 1). After deletion of duplicates, 1559 abstracts remained and divided among 6 reviewers so that each abstract was reviewed by two reviewers. They identified 171 abstracts for which the full text was reviewed.

Abstracts of two potentially eligible but unpublished studies were identified [13,14]. Attempts to contact the authors of these studies were unsuccessful. One study was ineligible due to use of fulguration instead of TURBT [15]. In another, a subgroup of 19 patients was potentially eligible. Since there were no recurrences in these patients, they would have not contributed to the treatment comparisons and were not included [16]. Three other potentially eligible unpublished studies without abstracts identified in clinicaltrials.gov were reviewed: NCT01475266, NCT00003725 and NCT00445601.

After review of 171 full texts, 13 RCTs published between 1985 and 2011 were eligible for inclusion [8, 17–31].

44 studies identified from EAU and AUA meeting abstracts did not provide additional eligible studies.

Further details are provided in the PRISMA flow diagram (Online Figure 1).

3.2 Eligible Studies

Table 1 lists the 13 eligible studies. For 2 studies with 106 (4.4%) of the 2384 eligible patients, it was not possible to obtain individual patient data [30-31]. In these two studies and the two unpublished studies with abstracts [13-14], a single instillation reduced the recurrence rate as compared to TURB alone.

3.3 Eligible Studies with Individual Patient Data

Individual patient data were obtained for all 2278 eligible patients entered [8, 17-29].

Four were single center [22,23,28,29] and seven were multicenter (1 multi-national), three with a central randomization [21,25,26] and four with envelopes or local randomization lists [8,18,20,27]. No studies were double blind.

3.3.1 Study Characteristics

As found in the original publications, 2278 (84.2%) of 2705 randomized patients were eligible: 86% on control (TURB only) and 83% on a single instillation. The main reason of ineligibility was an inappropriate histology as patients were randomized and treated prior to pathological confirmation. 1161 (51.0%) were randomized to control and 1117 (49.0%) to a single instillation. In three studies, patients in the control group received an immediate instillation of sterile water or saline after TURB [21,27,28].

Median follow up was 6.0 years for recurrence and 9.0 years for survival (Table 1).

3.3.2 Baseline characteristics

Table 2 provides the distribution of baseline characteristics. Median age was 64.0 years, 73.3% were male, 81.4% had primary tumors and 77.3% a single tumor. The median tumor size was 2 cm and 18.2% had a tumor $\geq$ 3 cm. 74.3% were pTa, 52.8% G1/LG, 6.6% G3/HG and 1 patient had CIS. Among the 1620 patients for whom the EORTC recurrence score could be calculated, 609 (37.6%) had a score of 0, 789 (48.7%) a score of 1-4 and 222 (13.7%) a score of 5-11. In the 1865 patients for whom the EORTC progression score could be calculated, 879 (47.1%) had a score of 0, 699 (37.5%) a score of 2-6 and 287 (15.3%) a score of 7-17.

Baseline characteristics are well balanced in the treatment groups, except there are slightly more T1 patients, 24.7% versus 21.8%, and HG/G3 patients, 8.0% versus 5.3%, on immediate instillation. There are thus more patients at high risk of progression on a single instillation.

Epirubicin was used in 5 studies, mitomycin C in 4, pirarubicin in 1 and thiotepa in 1. Time of instillation was available in 837 patients: 335 (40.0%) received the instillation within 2 hours, 467 (55.8%) between 3 to 12 hours and 35 (4.2%) after 12 hours (Table 3).

Post-operative irrigation (non-randomized) was used in 898 (56.4%) patients while 694 (43.6%) patients did not receive irrigation. (Online Table 1).

3.3.3 Time to First Recurrence

1128 (49.5%) of 2278 patients recurred: 475 (42.5%) allocated to a single instillation and 653 (56.2%) to TURB (Table 4). Median tumor diameter at first recurrence was 3 mm in both groups (Online Table 2).

The difference in time to first recurrence between treatments is statistically significant in favor of immediate instillation, with a reduction of 35% in the relative risk of recurrence: HR = 0.65, 95% CI: 0.58 – 0.74, $p < 0.001$. 5 year recurrence rates were 44.8% (95% CI: 41.6% – 48.0%) on a single instillation and 58.8% (95% CI: 55.7% – 61.9%) on TURB. Median times to first recurrence were 12 and 3 years, respectively (Figure 1).

The NNT to prevent 1 recurrence within 5 years is 7 eligible patients, 95% CI: 5.5 – 10, and 10 randomized patients, 95% CI: 7 - 15.

Figure 2 shows the Forest Plot of time to first recurrence stratified by chemotherapy and study. There was significant heterogeneity between studies, $p < 0.0001$, $I^2 = 73.8$. Immediate instillation was not effective in the thiotepa study, interaction test $p = 0.002$. Reductions in relative risks of recurrence were similar for the other 3 chemotherapies. Non randomized comparisons suggest better efficacy when the instillation is given within two hours after TURB.

3.3.3.1 Effect of an Immediate Instillation according to Patient Characteristics

In Figure 3, the test for interaction is significant only for the prior recurrence rate and EORTC Recurrence Risk Score. Recurrent patients with a prior recurrence rate > 1 recurrence per year (Online Figure 2) and patients with a recurrence score $\geq$ 5 (Online Figure 3) did not benefit from the instillation.

3.3.3.2 Post-Operative Irrigation

In a non-randomized comparison of 1592 patients, post-operative irrigation reduced the risk of recurrence, both overall (HR = 0.69, 95% CI: 0.59, 0.88, $p < 0.001$) and in the two treatment

groups. Adjusting for the randomized treatment and EORTC Recurrence Risk Score, post-operative irrigation reduced the relative risk of recurrence by 21%, HR = 0.79, 95% CI: 0.67 – 0.93, p = 0.004. A single instillation reduced the risk of recurrence, both in patients receiving and not receiving post-operative irrigation.

3.3.4 Time to Progression

Time to progression data were available in 8 studies with 1765 patients. 108 patients (6.1%) progressed, 57 (6.6%) of 866 patients receiving a single instillation and 51 (5.7%) of 899 patients on TURB alone (Table 4).

Figure 4 presents the time to progression by treatment. The difference was not statistically significant: HR = 1.21, 95% CI: 0.83 – 1.78, p = 0.32. Five year progression rates were 5.6% (95% CI: 3.8% – 7.4%) on a single instillation and 4.8% (95% CI: 3.2% – 6.5%) on TURB alone.

Time to progression stratified by chemotherapy and study is provided in Online Figure 4, with no significant heterogeneity between studies, $I^2 = 13.7$. Stratification by the EORTC Progression Risk Score yielded similar results: HR = 1.09, 95% CI: 0.74 – 1.60, p = 0.68, as did stratification by stage and grade.

3.3.4.1 Effect of an Immediate Instillation according to Patient Characteristics

No interactions were statistically significant for progression, although the same trends as for recurrence were seen. There was a suggestion of a higher risk of progression (HR = 1.60) on an immediate instillation in the 220 patients with an EORTC Recurrence Risk Score $\geq$ 5 (Online

Figure 5), however instillation patients in this subgroup had a higher baseline EORTC Progression Score, 8.2 versus 7.8.

3.3.5 Overall Duration of Survival

Survival data were available in 7 studies with 1509 patients. The duration of follow up was similar in the two treatment groups with median of 9.0 years on a single instillation and 8.9 years on TURB. 460 (30.5%) deaths were reported, in 242 (32.8%) of 737 patients receiving a single instillation and 218 (28.2%) of 772 patients with TURB alone. 59 (3.9%) died due to bladder cancer, 75 (5.0%) due to another malignant disease, and 282 (18.7%) due to associated chronic disease (Table 4).

The difference in survival is statistically significant in favor of no instillation with a relative increase of 26% in the risk of death on an immediate instillation: HR = 1.26, 95% CI: 1.05 – 1.51, p = 0.015 (Figure 5). 5 year survival rates were 88.0% (95% CI: 85.3% – 90.3%) with a single instillation and 88.8% (95% CI: 86.1% – 91.0%) on TURB, with the curves separating after 6 years. Median survivals were 13.1 years and 14.9 years, respectively.

Online Figure 6 shows the duration of survival stratified by study and chemotherapy, with no evidence of heterogeneity between studies, $I^2 = 0$. Stratification by the EORTC Progression Risk Score yielded similar results: HR = 1.24, 95% CI: 1.02 – 1.50, p = 0.03, as did stratification by stage and grade.

3.3.5.1 Effect of an Immediate Instillation according to Patient Characteristics

There was a suggestion of a shorter survival on an immediate instillation in recurrent patients, patients with an EORTC Recurrence Risk Score $\geq$ 5 and EAU high risk patients. (Online Figure 7)

3.3.6 Time to Death Due to Bladder Cancer

59 (3.9%) patients died due to bladder cancer, 32 (4.3%) of 737 patients receiving a single instillation and 27 (3.5%) of 772 patients on TURB (Table 4).

Figure 6 presents the time to death due to bladder cancer by treatment group. The difference was not statistically significant: HR = 1.31, 95% CI: 0.78 – 2.19, p = 0.31. 5 year bladder cancer death rates were 2.1% (95% CI: 1.0% – 3.3%) in patients receiving a single instillation and 2.0% (95% CI: 0.9% – 3.1%) on TURB. Online Figure 8 presents time to death due to bladder cancer stratified by chemotherapy and study, with medium heterogeneity between studies, I^2 = 47.3. Stratification by EORTC Progression Risk Score yielded a slightly reduced hazard ratio: HR = 1.13, 95% CI: 0.67 – 1.91, p = 0.65, as did stratification by stage and grade.

3.3.6.1 Effect of an Immediate Instillation according to Patient Characteristics

The number of deaths due to bladder cancer is small and no interactions in Online Figure 9 were statistically significant, but similar trends were seen as for overall survival, with a suggestion of a shorter disease specific survival on a single instillation in patients with recurrence risk score $\geq$ 5.

3.3.7 Relationship between Cause of Death and EORTC Recurrence Risk Score

Table 5 lists the cause of death by treatment group according to EORTC Recurrence Risk Score. In patients with Scores 0 and 1 – 4, the duration of survival and the distribution of the causes of

death were similar in the two treatment groups. Despite adjustment for an imbalance in tumor stage and grade, this exploratory analysis suggests that in patients with Recurrence Risk Score $\geq$ 5, more patients may have died on a single instillation, 65/106 (61.3%), than on TURB alone, 44/102 (43.1%), with a higher percent of patients dying from malignant disease (bladder cancer or other) compared to patients not receiving an instillation, 35 (33.0%) versus 20 (19.6%). This was not a planned subgroup analysis and these differences could have occurred by chance.

4. Conclusions

The results of our IPD meta-analysis have clearly confirmed the efficacy of a single immediate instillation of chemotherapy. The scientific rationale and explanation for its efficacy is based on its anti-tumor effect in destroying tumors cells floating in the irrigation fluid and urine after TURB and on its ablative effect on residual tumor cells at the site of the resection and on small overlooked tumors [32,33].

A single immediate instillation was not effective in patients with a prior recurrence rate > 1 recurrence per year and in patients with EORTC recurrence score $\geq$ 5. This last subgroup was mainly composed of patients with multiple tumors (50.9%), tumors $\geq$ 3 cm (69.8%) and T1 tumors (75.7%).

These results can help us make more precise recommendations for clinical practice. The decision to give an early instillation should be based on information available at time of TURB: the previous recurrence rate and the size and number of tumors. The definitive stage and grade is unknown at this time. From the weight of these parameters in the EORTC Recurrence Score [12], an early instillation is recommended in patients with:

1) single or multiple (up to 7 lesions) primary papillary tumor(s) smaller than 3 cm

2) single primary papillary tumors larger than 3 cm

3) single small recurrent papillary tumor with an interval of more than 1 year since the previous recurrence

Patients with multiple tumors, at least one of which is $\geq$ 3 cm, will have an EORTC Recurrence Score $\geq$ 6. An immediate instillation is not recommended in these patients.

Non-randomized comparisons suggest the instillation is more effective when given within two hours after TURB. Indirect comparisons could not detect any differences in efficacy between mitomycin C and epirubicin.

Once the stage and grade are available, further treatment can be planned according to the risk stratification [1].

The benefit of an early instillation was most pronounced in low risk patients in whom no further treatment before recurrence is recommended.

In intermediate risk patients, where the 5 year recurrence rate after a single instillation is nearly 40%, the results support EAU guideline recommendations that a single instillation alone is insufficient and should be followed by further instillations [1]. A systematic review demonstrated the best results for schedules where an early instillation preceded further instillations of chemotherapy [34]. In high risk patients receiving BCG, the only study assessing a single instillation was inconclusive [35].

Recurrences in low risk patients are usually low stage, low grade [36,37]. In this meta-analysis, recurrences were mostly small, median size 3 mm. Theoretically, small recurrences can be managed by office fulguration under local anesthesia without a significant burden to the patient [9,38,39]. There are, however, no prospective randomized comparisons of this procedure.

This meta-analysis provides non-randomized evidence that use of post-operative irrigation also reduces recurrences. It may act by helping prevent implantation of circulating tumor cells at the site of resection. This confirms the results of a previously published abstract [40], but should be considered with caution as details about duration of irrigation are lacking and the type of fluid was not available in all patients.

As can be expected from its mode of action, a single instillation did not have a positive effect on either the long-term progression or survival rates. It was surprising that a significant increase of 26% in the overall risk of death was found in patients with the instillation. Despite adjustment for imbalances in tumor stage and grade, exploratory analyses suggest a single instillation may be associated with a shorter survival in patients at high risk of recurrence, i.e. with an EORTC recurrence risk score $\geq$ 5. This subgroup, with only 222 (13.7%) of the 1620 patients for whom the score could be calculated, is precisely the subgroup of patients in which an immediate instillation is not effective or recommended. Patients with a high prior recurrence rate and risk of recurrence may be at higher risk of (unrecognized) perforation, which could contribute to their poor prognosis [41].

Lamm et al [42] found that intravesical chemotherapy did not influence the long-term course of the disease and raised concerns that repeated intravesical chemotherapy might be carcinogenic, however the EORTC found no evidence of carcinogenicity in 3 studies with more than 1200 patients [43,44].

This is the first meta-analysis to study this question which is based on individual patient data with a relatively long follow up and identify patients who benefit or not from an immediate instillation. Nevertheless, there are a number of limitations in the interpretation of the data, especially the long-term results. No information was collected on further treatment after recurrence or progression or on the occurrence of distant metastases. Only 7 studies contributed to progression comparisons and 5 studies to survival comparisons, 3 with a median follow up of more than 10 years. Survival was not a formal endpoint in these studies and it is unknown to what extent the cause of death was based on autopsy evidence.

Finally, no information on adverse events was collected. Although some severe complications after early instillation have been reported [45,46], their frequency is low if indications for their use are respected and proper safeguards followed.

In summary, although a single immediate instillation of chemotherapy reduced the relative risk of recurrence by 35% and 5 year recurrence rate by 14%, it is not effective in patients with a prior recurrence rate > 1 recurrence per year or in patients with EORTC Recurrence Risk Score $\geq$ 5. It does not prolong either the time to progression or the time to death due to bladder cancer. Exploratory analyses suggest that the instillation may be associated with an increase in the risk of death in patients at high risk of recurrence in whom the instillation is not effective

and thus not recommended. The long-term survival differences may be biased by the treatment received after recurrence and thus may be chance findings. Non-randomized evidence indicates the use of post-operative irrigation may also reduce recurrences.

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