Editorial

A single immediate instillation of chemotherapy for non-muscle invasive bladder cancer: in all patients?

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In order to determine the most appropriate schedule of adjuvant intravesical treatment after transurethral resection (TURBT) in patients with non-muscle invasive (Ta, T1, CIS) urothelial carcinoma of the bladder (NMIBC), the European Association of Urology (EAU) guidelines divide patients into three risk groups: low, intermediate and high risk (1).

Low risk includes those patients with tumors that are primary, solitary, Ta, low grade (LG)/G1, <3 cm in diameter, and without CIS. All these conditions must be satisfied.

High risk patients have tumors with any of the following characteristics: T1, high grade (HG)/G3, or CIS. In addition, this category also includes patients with multiple and recurrent and large (>3 cm) Ta LG/G1G2 tumors.

Intermediate risk patients are those with tumors falling between the low and high-risk categories.

These risk groups have been derived from the EORTC risk tables which provide probabilities of recurrence and progression to muscle invasive disease for NMIBC patients who have not been treated with maintenance BCG (2). More recently, risk groups have also been provided for patients treated with BCG beyond the standard 6 induction instillations (3,4).

At 5 years, low risk patients have a probability of recurrence of 30% and a probability of progression to muscle invasive disease of less than 1%. At the other extreme, high risk patients have a probability of recurrence of about 80% and a probability of progression of approximately 45% (2).

In low risk patients, a single immediate instillation of intravesical chemotherapy is recommended as the complete and only treatment after TURBT prior to an eventual recurrence (1,5). In high risk patients, where intravesical chemotherapy has no effect on tumor progression, full-dose BCG instillations for 1 to 3 years are the recommended treatment, with cystectomy being an option in the subgroup of the very highest risk patients. A single immediate instillation of chemotherapy is not recommended in patients receiving BCG as there are very little data to support its use in this setting (6).

The subgroup of intermediate risk patients is quite heterogeneous as far as prognosis is concerned (7). These patients should receive either 1 year of full-dose BCG treatment (induction plus weekly instillations for 3 weeks at 3, 6, and 12 months) or instillations of chemotherapy during a maximum of 1 year (1). The optimal schedule of chemotherapy is not known (8).

In the subgroup of "lower risk" intermediate risk patients with a previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score <5, a single immediate instillation of intravesical chemotherapy after TURBT is also recommended (1,5).

The current recommendations for the use of a single immediate instillation of chemotherapy are based on an individual patient data meta-analysis of 2,278 patients, none of whom received additional instillations prior to recurrence (5). There is some evidence that the instillation may also be effective in intermediate risk patients who

receive further adjuvant instillations of chemotherapy, however the evidence is scarce and the studies do not take into account the EORTC recurrence score (8).

The results of a large randomized study have recently been published that suggest that a single instillation may be effective in all patients who receive further instillations of chemotherapy (9). A total of 2,243 patients were randomized to receive either an immediate instillation of mitomycin C (MMC) within 24 hours of TURBT or to an MMC instillation two weeks after TURBT. The single instillation was the only treatment in the low risk patients whereas the immediate and high-risk patients received a further 8 and 14 instillations of MMC, during 6 and 12 months, respectively.

The median follow-up in patients without a recurrence was 32 months. Globally, the immediate instillation reduced the risk of recurrence as compared to the delayed instillation by 27%, HR 0.73, 95% CI: 0.63–0.85, P<0.001. The test for interaction between risk group and treatment was not statistically significant so the authors concluded that the immediate instillation of chemotherapy reduced the risk of recurrence as compared to the delayed instillation in all 3 risk groups, i.e., independent of the number of additional instillations that were received. However, based on all available follow up, the difference was not statistically significant in the low risk group as the time to recurrence curves for the two treatment schedules in this group were identical beginning at 5 years.

So should the single instillation be given to all patients who go on to receive further instillations of chemotherapy?

The results of this new paper are limited by the fact that the study recruited patients from 1998 to 2003 and the definitions of their low, intermediate and high-risk groups are different from the current risk groups which were published several years after the study completed patient entry. In the current study, the following definitions were used:

- Low risk: primary, solitary, pTa/pT1, grade 1–2 tumor;
- Immediate risk: primary, solitary pTa/pT1 grade 3 tumor or recurrent, solitary pTa/pT1 grade 1–3 tumor;
- High risk: all multiple tumors and/or carcinoma *in situ*, independent of stage or grade.

These risk groups reflect the probability of recurrence whereas the current EAU risk groups and their accompanying treatment recommendations reflect more the probability of progression. For example, the low and intermediate risk groups in this study could include patients with pT1 tumors whereas patients with pT1 tumors are classified as high risk in the EAU guidelines due to their increased risk of progression. Multiple tumors, which have a high risk of recurrence, are classified as high risk in this study whereas they could be classified as intermediate risk or high risk in the EAU guidelines.

As such, the risk group analyses in the current study are not as helpful as they might be in current day clinical practice since some of the low risk patients in this study would be classified as high-risk patients according to the EAU guidelines and thus receive BCG. Likewise, an unknown proportion of the intermediate risk patients would have also received BCG according to current recommendations. The carcinoma *in situ* patients in this study received MMC, and were thus under treated according to today's standards. Of note, higher recurrence rates were found in the low risk group, but this was attributed to the fact that the patients in the intermediate and high-risk groups received additional instillations of MMC.

Coming back to our question, should the single instillation be given to all patients who go on to receive further instillations of chemotherapy?

While the author's conclusions would seem to suggest that the answer is yes, the current study unfortunately cannot adequately answer this question due to the non-standard definition of their risk groups and the fact that an unknown number of patients in all 3 risk groups would have received BCG according today's guidelines. In addition, current guidelines recommend a re-TUR in high risk patients and blue light cystoscopy wasn't available yet at the start of this study in 1998.

To answer this question, a new appropriately powered clinical trial is required whereby all intermediate risk patients who are scheduled to receive a series of intravesical instillations of chemotherapy are randomized to receive or not to receive an immediate instillation of chemotherapy post TURBT. And at the same time, patients could be randomized to two different maintenance schedules of chemotherapy in order to better determine the optimal duration of treatment.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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