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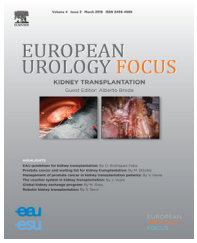

Guidelines

Indication for a Single Postoperative Instillation of Chemotherapy in Non–muscle-invasive Bladder Cancer: What Factors Should Be Considered?

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Abstract

An early single instillation of intravesical chemotherapy (SICI) used immediately after transurethral resection of the bladder (TURB) can significantly reduce the recurrence rate in selected patients with non–muscle-invasive bladder cancer (NMIBC). SICI should be used in patients with low-risk and with selected intermediate-risk tumours, in particular for multiple primary small papillary tumours, single primary papillary tumours >3 cm, and single recurrent papillary tumours recurring >1 yr after the previous resection. The available data do not support any recommendation to reduce the role of SICI in patients after fluorescence cystoscopy–guided TURB or en bloc TURB. SICI can even provide some benefit in patients with intermediate-risk tumours subsequently treated with further instillations. During instillation, contraindications should be taken into account and safety measures should be applied.

Patient summary: An early single instillation of intravesical chemotherapy immediately after transurethral resection of the bladder can significantly reduce the recurrence rate in selected patients with non–muscle-invasive bladder cancer. It should be used in patients with low-risk and selected intermediate-risk tumours.

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1. Introduction

All published meta-analyses of prospective randomised trials have confirmed that an early single instillation of intravesical chemotherapy (SICI) used immediately after transurethral resection of the bladder (TURB) can significantly reduce the recurrence rate in selected patients with non–muscle-invasive bladder cancer (NMIBC) [1–4]. The most robust meta-analysis, based on individual patient data (IPD) for 2278 eligible patients, demonstrated that SICI reduced the risk of recurrence by 35%, with 5-yr recurrence rates of 44.8% and 58.8% in the instillation and control groups, respectively [4]. These observations formed the basis for the European Association of Urology (EAU) guideline recommendation on NMIBC, which supports SICI in all patients with low-risk NMIBC and in selected patients with intermediate-risk NMIBC [5].

In spite of the clearly demonstrated benefit of SICI, its role in the NMIBC treatment algorithm has been questioned by some authors [6]. More importantly, the relevant guideline recommendation is insufficiently followed in daily practice [7,8].

We must therefore ask whether the indications for SICI are clearly and accurately specified and whether the therapeutic benefit cannot be achieved by other methods during diagnosis and therapy.

To clarify and support the criteria for the indication for SICI, the members of the EAU guidelines panel on NMIBC summarize their opinion here.

2. What tumour characteristics support an indication for SICI?

The scientific rationale for the efficacy of SICI is its antitumour effect on tumour cells in the irrigation fluid and urine after TURB and its ablative effect on residual tumour cells at the site of the resection and on small overlooked tumours [9,10]. The highest SICI efficacy is observed if it is given within few hours, preferably within 2 h, after TURB [4]. For this reason, the decision does not depend on definitive pathology, but must be based on factors known immediately after surgery, such as the frequency of previous recurrences, positive cytology, and the size, number, and appearance of resected tumours.

The IPD meta-analysis demonstrated that SICI was not effective in patients with highly recurrent tumours, that is, tumours with a previous history of more than one recurrence per year. It was also not effective in patients with a higher risk of tumour recurrence, as represented by a European Organization for Research and Treatment of Cancer recurrence risk score of $\geq$5 [4].

2.1. Panel opinion

According to the IPD meta-analysis and the weight of each parameter in calculating the risk of recurrence [11], early SICI should be used in patients with low-risk tumours (primary, single, papillary tumours smaller than 3 cm without carcinoma in situ) and selected intermediate-risk tumours, in particular for multiple (up to 7 lesions) primary papillary tumours smaller than 3 cm, single primary papillary tumours >3 cm, and single recurrent papillary tumours recurring >1 yr after the previous resection.

3. Should the decision be influenced by methods used for previous therapy (eg, imaging methods such as fluorescence cystoscopy), TURB technique, or methods potentially available for further treatment (later instillations or outpatient fulguration of small recurrences)?

Theoretically, failure to use SICI could be compensated by other methods that might achieve a reduction in the recurrence rate. To challenge this approach, we must consider each individual situation and discuss its principles and potential benefits.

3.1. Should SICI be used after TURB with fluorescence cystoscopy?

A multicentre prospective randomised trial demonstrated a 16% relative reduction in the recurrence rate using hexaminolevulinate fluorescence cystoscopy to guide TURB [12]. Recently, a four-arm prospective randomised trial showed that fluorescence cystoscopy was more effective in reducing the recurrence rate than SICI with doxorubicin. Unfortunately, there were several limitations in the methodology for that study, such as missing information on the true interval between TURB and SICI, and nonstandardised further management (re-TURB, bacillus Calmette–Guérin [BCG] instillations), which may have biased the outcomes. In addition, the statistical power of the study was not sufficient to demonstrate the real role of SICI [13]. By contrast, fluorescence-guided TURB provided no additional benefit over white-light TURB in another prospective randomised trial with SICI used in both arms [14].

3.1.1. Panel opinion

The available data do not support any recommendation to reduce the role of SICI after fluorescence-guided TURB compared to the standard white-light procedure.

3.2. Can en bloc TURB reduce the necessity for SICI?

Theoretically, reduced manipulation of the tumour via en bloc TURB may translate into a lower risk of tumour seeding and a lower early recurrence rate. However, this must be confirmed by future prospective trials.

3.2.1. Panel opinion

En bloc TURB techniques do not change the criteria for the indication of SI at present.

3.3. Does early SICI benefit patients even when further multiple chemotherapy instillations are used?

From a clinical point of view, we must ask whether early SICI has benefit in patients with intermediate-risk tumours who

will in any case receive further intravesical treatment. A prospective randomised trial showed that further instillations after early SICI can improve recurrence-free survival in patients with intermediate-risk tumours [15]. There is evidence from several studies in patients with intermediate-risk tumours showing that SICI might have an impact on recurrence even when further adjuvant instillations are given [16,17]. This specific question was asked by a recently published randomised controlled trial evaluating 2243 NMIBC patients. The authors compared SICI with mitomycin C (MMC) to an instillation of MMC delayed until 2 wk after TURB, followed by further repeat instillations in both treatment arms. The results showed a significant reduction of 9% (from 36% to 27%) in the risk of recurrence at 3 yr in favour of SICI. The effect was significant in patients with intermediate- and high-risk tumours receiving additional adjuvant MMC instillations. Unfortunately, the authors' definition of risk groups differed significantly from those currently recommended [16]. As a consequence, some patients did not receive adequate therapy and the study conclusions must be considered with caution.

3.3.1. Panel opinion

Although not fully proven, SICI can provide some benefit even in patients with intermediate-risk tumours subsequently treated with further chemotherapy or BCG. Therefore, its application following TURB is possible and should not be considered a mistake.

3.4. What strategy is less burdensome for the patient, SICI or a greater number of further endoscopic surgeries?

A prospective randomised trial showed that early SICI was only able to reduce recurrences smaller than 5 mm [18]. Theoretically, these small recurrences can be better managed via office fulguration without a significant burden to the patient [19]. Therefore, it is justifiable to address what strategy is less dangerous and burdensome for the patient: an approach using SICI with a lower number of small recurrences or an approach without SI with a greater number of small recurrences that will require further endoscopic management.

While office fulguration of small recurrences is advocated by some authors [6,19], its oncological safety is relatively low and its indication and performance strongly depend on the experience of the urologist. Moreover, management of NMIBC recurrences invariably depends on the health care system in individual countries, which in many cases does not include office endoscopic treatment.

3.4.1. Panel opinion

To draw a final conclusion, we will need prospective analyses of the oncological safety of both approaches and of the risk and severity of complications, as well cost-benefit analyses based on individual situations in each country. Until we have these data, we strongly believe that SICI should be used in all patients for whom the oncological criteria are met.

4. What is the risk of SICI-related complications? Should this risk influence the indication?

There is no doubt that SICI is not without danger and can be associated with serious complications, as evidenced in some case reports [20]. Although the evidence is limited, their frequency seems to be very low. The latest prospective trials reported higher numbers of local side effects related to SICI, but no severe complications [16,21].

4.1. Panel opinion

As the risk of complications is low, this should not influence the indication for SICI. It is of the utmost importance, however, to respect contraindications. SICI should be omitted in all cases of overt or suspect bladder perforation and bleeding requiring bladder irrigation. During instillation, safety measures should be applied [5].

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Study concept and design: Babjuk.
Acquisition of data: Babjuk, Burger.
Analysis and interpretation of data: Babjuk, Burger, Compérat, Gontero, Mostafid, Palou, van Rhijn, Rouprêt, Shariat, Sylvester, Zigeuner, Capoun, Cohen, Dominguez-Escrig, Hernández, Peyronnet, Seisen, Soukup.
Drafting of the manuscript: Babjuk.
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