

Age does not matter: the relevance of immediate instillation therapy with Mitomycin C in non-muscle invasive bladder cancer

Frank Christoph, Martin Schostak

Universitätsklinik für Urologie und Kinderurologie, Otto-von-Guericke-Universität, Magdeburg, Germany

Correspondence to: Frank Christoph, MD, PhD, FEBU. Universitätsklinik für Urologie und Kinderurologie, Otto-von-Guericke-Universität, Leipziger Str. 44, 39120 Magdeburg, Germany. Email: praxis@urologie-christoph.de.

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Urothelial carcinoma is the second most common urological malignancy, and the majority of patients with this diagnosis are between the ages of 75 and 85. In most cases, patients initially present with non-muscle invasive bladder cancer (NMIBC), which accounts for about 70% of all diagnosed bladder carcinomas. However, about one third of these tumours will recur. Therefore, the natural history of bladder cancer and its need for post-treatment surveillance makes bladder cancer one of the most cost intensive tumour diseases, not to mention its additional costs to the patient including the burden of undergoing ongoing invasive procedures such as bladder cystoscopy or instillation treatment.

Instillation therapy is a well-implemented treatment, and findings from several meta-analyses have supported the safety and efficacy of chemo- or immunomodulatory instillation therapies using Mitomycin C (MMC) or Bacille Calmette-Guérin (BCG). Yet, studies have only recently determined which of these therapies is ideal for a given type of patient. For example, meta analyses have recently outlined which therapy is ideal for low-, intermediate- or high-risk bladder tumour patients. Risk status also determines the regimen of the specific therapy, the interval between each instillation cycle, and the optimal timing and duration of the complete instillation therapy cycle. Not only is the strategy of utmost importance, but the dose (20 or 40 mg MMC) and strain (BCG Tice or BCG Connaught) also have been the subjects of various debates (1).

Ultimately, the patient needs to receive the appropriate and best therapy. Therefore, many publications have dealt with risk stratification of the underlying tumour type with regard to its histopathology or multifocality. Recently, there has been a debate about the appearance of more aggressive NMIBC in the elderly, highlighting the need to understand how to perform bladder instillation therapy especially in this group of patients.

The European Association of Urology (EAU) guidelines advocate one immediate postoperative intravesical instillation of a chemotherapeutic drug which reduces the 5-year recurrence rate by 14 percentage points, from 59% to 45% (2). The immediate instillation should be administered within 24 hours after transurethral resection. However, it has not been proven as effective in patients with high risk of tumour recurrence and thus is not recommended in this subgroup. Another prospective study has shown that early instillation with 40 mg MMC is associated with a 31% risk reduction in patients with primary and low-risk bladder tumours (3).

Despite these recommendations and findings favouring the early instillation of MMC, it still seems to be underused in daily practice. A US-based national survey reported that only 17% of elderly patients with bladder cancer were treated with early instillation of MMC (4). In a recent study, Xylinas *et al.* have highlighted potential reasons for the low use of early instillation therapy (5). For example, various authors have reported that less aggressive use of

these therapies for bladder cancer in the elderly leads to more unfavourable outcomes. Also, a reduced response to intravesical BCG has been reported. The authors hypothesize a change in the biological behaviour of these tumours over time and suggest a decline in patients' baseline immune status especially in those older than 80 years, leading to a weaker response and worse outcome when BCG is administered (6). However, little is known about the effect of MMC in this group of elderly patients and data about the efficacy of early instillation in this subgroup are not currently available.

In their recent study, Xylinas *et al.* included a total of 4,258 patients with NMIBC that received single-dose MMC immediately after transurethral resection (5). Patients that received further adjuvant instillation therapy with either MMC or BCG were excluded from this study. The median age of these patients was 67 and 66 years and the median follow-up duration was 48 months. Interestingly, 61% of all participating patients had received early instillation, in contrast to the aforementioned 17% in the study published by Cookson *et al.* (4). Reluctance to early instillation is still a challenge but seems to be improving over the years. When patients were divided into two groups based on their receipt of MMC, recurrence rate after 1, 2 and 5 years was significantly lower in the early MMC instillation group, than in the group that did not receive MMC (i.e., 68% *vs.* 73%, 57% *vs.* 62% and 41% *vs.* 51% respectively). This translates to a relative risk reduction of recurrence of 38% (which is in line with previously published studies by DeNunzio *et al.* and Perlis *et al.* (3,7)). In a second step, the authors applied a Multivariable Cox proportional hazards regression model to estimate any potential influence of age on the effect of the early instillation therapy. It is noteworthy that MMC instillation therapy remained effective and recurrence risk was reduced regardless of the patient's age. By contrast, Noon *et al.* published a population-based study demonstrating higher cancer-specific mortality in elderly patients with low-risk NMIBC, increasing from 0.9% in patients in their 60 years old to 8.4% in patients 80 and older (8). The authors do not provide information about adherence to instillation therapy in the different subgroups, but note less frequent use of BCG instillation in high-risk NMIBC patients to less than 30% if patients were older than 80 years old. Thus, it is unclear whether age is a risk factor for more aggressive behaviour of the tumour itself or if it is simply associated with the administration of a less aggressive anti-tumour therapy.

Xylinas *et al.* do not mention several limitations of their study.

Toxicity data are not provided, and a central pathology review was not performed. The authors mention that, due to a low event number, it was impossible to stratify patients into those who benefit most by early instillation therapy. Furthermore, it is unclear why 39% of the patients in the instillation group were classified as having high-risk (G3) tumours but, yet, did not receive any adjuvant instillation therapy.

The rationale behind early instillation therapy has been the topic of various debates between urologists and oncologists (9). Even if early instillation therapy lowers risk of tumour recurrence, sparing subsequent invasive therapy in about one in eight patients, this is only a minor benefit if it does not contribute to a profound change in follow-up modalities. This affects first and foremost the physical burden of regular surveillance cystoscopies for the patient leading to an extension of the intervals between each cystoscopy. Second, the economic burden and expense of extensive follow-up care should then also be reduced.

The study by Xylinas *et al.* has shown that early instillation therapy seems to be feasible and effective in patients with NMIBC irrespective of their age. However, it does not address the question of which group of low- and intermediate-risk patients above the age of 80 years will potentially benefit most from a less aggressive treatment. Urologists that treat patients with NMIBC must balance the morbidity of each of these diagnostic and therapeutic options with cost and patient burden to create the least burdensome but most effective treatment strategy.

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Footnote

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

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