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Platinum Priority – Editorial

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Optimising Existing Therapeutic Strategies for the Treatment of Non-Muscle-Invasive Bladder Cancer: The Role of Intensive Neoadjuvant Intravesical Mitomycin C

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Urology seems to be entering an exciting era in non-muscle-invasive bladder cancer (NMIBC) research, with new momentum and new enthusiasm. NMIBC is now seen as a significant disease entity in its own right, distinct from muscle-invasive disease. This change may result from the following factors:

- The predicted increase in the global incidence of bladder cancer (BCa), of which 70–80% of cases will be NMIBC [1]
- The significant cost of managing BCa patients, the majority of which is due to the treatment and surveillance of NMIBC [2]
- The increasing age of the incident BCa population in developed countries [3]
- The previous poor spending on BCa research, resulting in a lack of scientific advancement [4]
- The realisation of the limitations of transurethral resection of bladder tumour (TURBT) and its “incise and scatter” nature [5]
- An understanding of the potential to improve patient outcomes and quality of life with technological innovations ranging from novel optical modalities (eg, photodynamic diagnosis and narrow band imaging [6]) to high-throughput platforms for biomarker discovery [7].

However, aside from these innovations, urologists already have the tools required to combat each of the four recognised mechanisms of NMIBC recurrence, described as incomplete tumour resection, tumour cell reimplantation, the growth of microscopic tumours present (but undetected) at initial TURBT, and “genuine” new tumour formation [8,9]. As recently highlighted by Brausi [10], optimising and

implementing all of our existing capabilities to abrogate each of these mechanisms would further improve our therapeutic impact on NMIBC and in doing so progress towards a paradigm shift, as has been observed in muscle-invasive disease with the advent of neoadjuvant chemotherapy and chemoradiotherapy [11,12].

In this issue of *European Urology*, Colombo et al. present their preliminary results of a randomised phase 2 study of neoadjuvant short-term intensive intravesical mitomycin C (MMC) compared with a weekly schedule of MMC for the treatment of low-grade recurrent NMIBC [13]. Their regimen of MMC administered three times per week for 2 wk in the intensive short-term schedule is based upon previous in vitro studies and thus takes into account the observed biology of bladder tumour growth, rather than the “empirical” nature of the authors’ alternative schedule of single weekly instillations for 6 wk, both schedules being administered before TURBT. In effect, this study represents a “window trial” with a primary end point of systemic toxicity; tumour response rate was the secondary end point. During an 18-mo period, 54 patients were randomised (27 patients per schedule); all patients were under follow-up after treatment of low-grade NMIBC and were subsequently diagnosed with single recurrent tumours ≤ 1.5 cm at 3 mo to 3 yr after TURBT. The MMC schedules commenced within 1 wk of the diagnosis of recurrence, and the subsequent TURBT was carried out within 2 wk of completing the schedules. Interestingly, this system creates a shorter time period between diagnosis and TURBT in the intensive schedule, potentially introducing heterogeneity between the treatment arms, although the two groups were otherwise well-matched for gender, tumour size, previous

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recurrences, and previous perioperative instillations. There were no significant differences in local or systemic toxicity between the groups, although two patients on the intensive schedule discontinued treatment after the fourth instillation because of severe cystitis symptoms and proceeded straight to TURBT. Accordingly, the authors considered the primary end point to have been achieved, and this paper represents a preliminary report of the secondary end point, tumour response.

The findings relating to the secondary end point are notable: At the post-MMC TURBT there was a pathologic complete response in 70.4% of patients on the intensive schedule (mean tumour diameter of 8.9 mm at diagnosis), including the two patients who could not complete treatment, compared with 44.4% of patients in the alternative schedule (mean tumour diameter of 9.5 mm at diagnosis), representing a borderline statistically significant difference ($p = 0.04$). Importantly, no patients experienced disease progression, and recruitment is ongoing to identify prognostic factors associated with tumour response.

The study is not without its limitations, some of which the authors refer to in the discussion section; principally, small patient numbers, short follow-up, and absence of blinding of those operators assessing tumour size and response. In addition, the details of the retention time of MMC in each arm of the trial have not been discussed. Despite these limitations, these results are interesting, although we should not be particularly surprised by such data. As the authors state, we have known for some time that MMC is an effective chemoablative agent for NMIBC, and in the setting of muscle-invasive disease, systemic MMC is effective when combined with fluorouracil and radiotherapy [11].

The authors conclude that the two schedules have a similar tolerability profile and that the intensive schedule “might be considered a safe alternative to TURBT in select low-grade bladder tumour patients”—potentially elderly patients or patients with comorbidities who experience a single low-grade recurrence of <1 cm.

We know that age is an increasingly important factor in the BCa setting, with a significant increase in the median age at presentation during the last 20 yr and a significant increase in the proportion of patients newly diagnosed at >80 yr [3,14]. Identifying less-invasive therapeutic strategies for NMIBC that avoid the need for frequent surgical procedures is therefore likely to be highly important in the near future, and this is where the utility of this intensive treatment regimen may lie. However, although these preliminary results are promising, this treatment would represent a significant change in practice, and more robust evidence is required before such a change can be recommended. It is important to realise, however, that small single-centre studies with innovative protocols, such as this study, become the basis for the larger studies that subsequently change practice. Such innovation should be commended and encouraged.

And so, where next for intensive neoadjuvant intravesical MMC? Appropriately for a phase 1/2 study of this

nature, the findings are directly relevant only to this select group of patients with small low-grade tumours. It remains to be seen whether this potential indication can be extended to a wider group of patients with more clinically significant disease (eg, larger tumours or multifocal tumours), and research should continue in this direction; the window trial design is an ideal way to achieve this goal, since definitive surgery (TURBT, in this case) is performed after trial treatment.

From a practical point of view, the logistics of administering an intensive regimen of intravesical chemotherapy also need to be considered, especially in terms of clinic, nursing, and pharmacy resources, because such resources are currently organised around weekly instillations of such agents. Delivering an intensive MMC schedule could result in a disproportionate cost elevation for these resources, which should be assessed in future studies incorporating measurements of cost effectiveness.

Traditionally, intravesical chemotherapy is instilled after TURBT to prevent tumour cell reimplantation, a premise originally established by Weldon and Soloway in the 1970s [15]. It is therefore tempting to consider that these results have some relevance to the adjuvant setting, but as the authors highlight, these results cannot be extrapolated in this way. However, trials of the intensive regimen (which is based upon the observed biology of bladder tumour growth *in vitro*) in the adjuvant setting are attractive, and we await such studies.

The European urologic community should maintain its renewed momentum and enthusiasm for NMIBC research and try to answer some of these questions in the near future so that we can continue to improve outcomes and health-related quality of life for these patients, as well as reduce the costs for health care providers.

Conflicts of interest: The author has worked as an unpaid advisor to Olympus Medical Systems in the setting of narrow band imaging cystoscopy.

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