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Platinum Priority – Editorial

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Radiofrequency-induced Thermochemotherapy for Recurrent Non–muscle-invasive Bladder Cancer: A New Treatment for an Unmet Need?

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In this issue of *European Urology*, Tan and colleagues [1] address an important unmet need for the treatment of patients with non–muscle-invasive bladder cancer (NMIBC) who fail on standard treatment with bacillus Calmette-Guérin (BCG) and who are unfit for or refuse cystectomy. The European Association of Urology guideline provides a strong recommendation that radical surgery should be performed in patients failing BCG, since treatment other than cystectomy, such as immunotherapy, intravesical chemotherapy, device-assisted therapy, or combinations thereof, must be considered oncologically inferior [2]. Radiofrequency-induced thermochemotherapy (RITE) in high-risk NMIBC is described as promising on the basis of a randomized controlled trial (RCT) [3].

The current phase 3 RCT (the HYMN trial) [1] compares disease-free survival (DFS) between RITE and an institutional standard second-line therapy in patients with recurring intermediate- or high-risk NMIBC after induction/maintenance BCG. RITE was carried out with 40 mg (20 + 20) mg of mitomycin C (MMC). The trial showed a nonsignificant difference in DFS for 33 patients without carcinoma in situ (CIS) (53% for RITE vs 24% for controls; $p = 0.11$). In addition, complete response (CR) at 3 mo did not differ significantly for the 71 CIS patients (30% for RITE vs 47% for controls; $p = 0.15$). However, among patients with CIS, DFS was significantly lower for RITE ($p = 0.01$), which can be attributed to results in the group with CIS and concurrent papillary tumors. For CIS-only patients, again DFS was similar. Progression and adverse events were comparable.

The authors should be commended for conducting a multicenter RCT with a new treatment regimen in this patient population. This is a longstanding unmet need and the study has certainly generated information for further research. However, this trial did not meet my personal expectations, having worked with this technique since 2001 [4], and is not in concordance with other previous reports [5,6].

The study was closed after 104 patients were randomized (planned sample size 242), which makes the study underpowered, as acknowledged by the authors. Moreover, the 104 patients were included over a period of more than 3 yr from 14 centers, meaning an average number of 2.5 per center per year. Having used RITE for 18 yr for hundreds of patients, we have learned that this treatment requires experience and proper patient information to achieve effective therapy (eg, sufficient heating). No data on the temperature achieved are presented, although the target was 42 ± 2 °C.

A second concern, noted by most reviewers, is the patient selection at entry. The patients included had different treatments, which is a confounding factor. Although this trial started before the recent US Food and Drug Administration definition of BCG-unresponsive disease [7], the patients selected for the HYMN trial had clearly differing risk profiles. Other missing information with regard to treatment was the use of enhanced imaging and the use of perioperative chemotherapy. Apart from treatment history, pretrial pathology also remains an issue: was pathology reviewed, especially CIS? For example, a post hoc analysis shows a higher number of concurrent papillary and

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CIS tumors in the RITE arm than in the control arm (25% vs 16%; $p = 0.38$), which is a small bias. For subgroup analyses, however, the trial is too small.

In addition, the treatment regimens deserve some attention. RITE was given with 40 mg of MMC, whereas, as again acknowledged by the authors, 40 + 40 mg is the standard for these patients. They apparently followed "the manufacturer's guidance", but the reference from 2004 ([15] in the manuscript) refers to preliminary results from a study in papillary tumors for which no guidance is mentioned. This dose is certainly one of the reasons for the lower results in this trial with RITE: the 24-mo DFS was 35% overall, and approximately 25% among CIS patients, versus results in the literature: 78.1% DFS in the RCT versus BCG in untreated patients [3], and 47% and 56% 2 year DFS in two large retrospective studies in patients also previously treated with BCG [4,5]. The 3-mo response rate of 30% in CIS is also lower than results from a recent large retrospective analysis for CIS patients, for which the 6-mo CR rate was 46.0% among BCG-unresponsive patients ($n = 50$), 71.7% among other patients previously treated with BCG ($n = 50$), and 83.0% among treatment-naïve patients [6]. Furthermore the endpoint for CIS was 3 mo, whereas 6 mo is usually considered a better endpoint. The control group was treated according to the institutional standard, which is heterogeneous (BCG, MMC, or electromotive drug administration [EMDA]). Again, the numbers are too small for a subanalysis of the different results for different control treatments (what was the impact of EMDA in the control group?).

There was also no pathology review after treatment, and no information on stage and grade for disease recurrence and progression was provided. Considering the visual appearance of hyperthermia necrosis after induction RITE (Fig. 1), I certainly hope that recurrence or progression was histologically proven. The use of cytology to define response, as well as the definition of response, remains unclear.

My conclusion is that treatment for BCG-unresponsive NMIBC is still an important unmet need, and in that sense I have to compliment the study group for conducting this trial with a new treatment regimen. However, the results should be interpreted with care. The patient selection, treatment regimens, and outcome measurement can be criticized. I have used RITE as a salvage treatment for similar patients for 18 yr now, and the results of the HYMN trial will not change my attitude after achieving successful results in many of my patients. How the current trials with other regimens such as cytokines, device-assisted strategies, new intravesical chemotherapy combinations, and PD(L)1 antagonists in BCG-unresponsive NMIBC will change the landscape will become clear in the coming few years. In particular, there is increasing interest in PL(L)1 antagonists in bladder cancer, and after decades we will hopefully be able to offer new nonradical treatments to these patients in the near future.

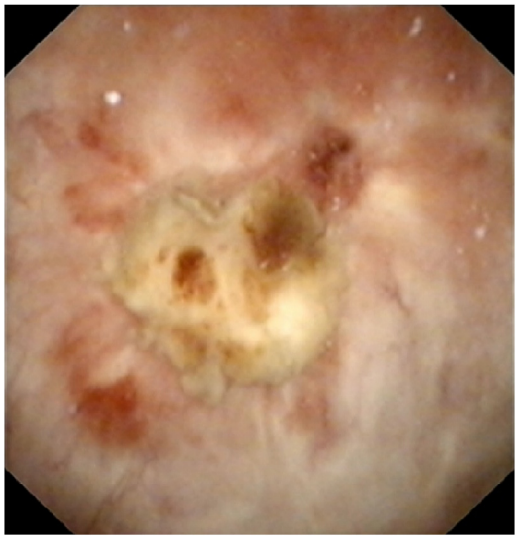

Fig. 1 – Cystoscopic image of bladder dome necrosis after induction radiofrequency-induced thermochemotherapy treatment.

Conflicts of interest: The author has acted as an advisor for MEL.

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