for whom maintaining fertility potential is a critical factor in determining an appropriate treatment plan [5].

Taken together, these data highlight that AAS abuse is risky behavior. The manuscript by Horwitz and colleagues provides a critical resource in counseling men who are considering or currently using AAS to improve their muscular potential. However, TRT in an appropriate clinical setting remains an important therapeutic option for men with symptomatic hypogonadism. While AAS abuse probably has significant health consequences, results from the TRAVERSE study will be critical to determine how this translates to therapeutic TRT use.

Conflicts of interest: The authors have nothing to disclose.

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Re: Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial

Tan WS, Panchal A, Buckley L, et al

Eur Urol 2019;75:63–71

Experts' summary:
This multicentre prospective study recruited patients with recurrent non-muscle-invasive bladder cancer (NMIBC) previously treated with bacillus Calmette-Guérin (BCG) to receive second-line treatment in the form of radiofrequency-induced thermochemotherapy (RITE) with mitomycin (MMC) or the institutional standard of care (BCG rechallenge in most cases). The trial closed prematurely after 104 patients were randomised because of the shorter disease-free survival noted among patients with carcinoma in situ (Cis) in the experimental arm (24-mo disease-free survival [DFS] 24% vs 47%). Apart from this finding, the study showed no DFS differences between the study arms in general or among non-Cis patients, and there was no difference in the rate of complete responses at 3 mo among Cis patients. Moreover, a safety analysis did not indicate any difference in the risk of treatment-related toxicity between the study arms. The authors concluded that RITE with MMC can be considered as a second-line treatment for BCG-treated patients with recurrent papillary NMIBC with no concomitant Cis foci [1].

Experts' comments:
Patients who do not tolerate or respond to BCG therapy and for whom radical cystectomy is not an option are always problematic. In this scenario, there is no standard treatment and no standard follow-up schemes, and the risk of disease progression is high, especially in cases defined as BCG failure. The HYMN trail raised hopes for identification of an effective treatment modality, but failed to meet these expectations. The patient heterogeneity at baseline (intermediate- and high-risk cases, BCG failure and no failure, papillary and flat lesions), treatment diversity in the control group (BCG rechallenge, conventional intravesical MMC, intravesical MMC with an electromotive drug administration [EMDA] system), a low number of randomised patients, and underpowered results (especially in subgroup analyses) make unambiguous conclusions on the value of RITE in this clinical situation difficult. Nevertheless, after the study by Arends et al. [2], the HYMN trial is the second published randomised controlled trial comparing RITE with BCG showing no progression-free survival benefit with RITE. In our opinion, this is the most important clinical endpoint with a probable effect on overall survival. As long as BCG therapy—a gold standard—is available, except for BCG failure cases, it offers at least comparable efficacy and safety, and is much less expensive and time-consuming for high-risk NMIBC patients. Another option for high-risk NMINBC patients is a combined treatment. The combination of BCG therapy and intravesical chemotherapy is associated with an unacceptable rate of adverse events [3]. However, the different toxicity profile of immune checkpoint inhibitors potentially offers an alternative regimen for combination with BCG, which is currently under investigation (NCT03519256, NCT02792192, NCT03711032, NCT03528694).

The HYMN trail results also prompt reflection on achievements for high-risk NMIBC in the last few decades.

Since the study by Morales et al. on BCG therapy in 1976 [4], numerous diagnostic (narrow-band imaging, photodynamic diagnosis, and others) and medical (RITE, EMDA, alternative intravesical chemotherapy regimens, and others) modalities have been developed and accepted [5]. However, none of them appears to have a clear positive impact on progression-free, cystectomy-free, or overall survival. We are now awaiting data on the efficacy of immune checkpoint inhibitors in NMIBC. Although there is hope that these will become a new treatment option, one cannot forget that until now they have only partly met needs in the field of muscle-invasive disease [6]. In summary, we need to reinforce research in the field of high-risk NMIBC, which remains a highly aggressive disease with very limited and morbid treatment options.

Conflict of interest: The authors have nothing to disclose.

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