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Results from HIVEC-II for Intermediate-risk Non–muscle-invasive Bladder Cancer: Is This a Dead End for Mitomycin C Hyperthermia?

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Non–muscle-invasive bladder cancer (NMIBC) is a very heterogeneous disease with a limited number of effective treatment options. Consensus among different societies regarding risk stratification is still lacking. For intermediate-risk (IR)-NMIBC, a recent consensus document aimed to shed some light on this grey zone [1]. Treatment protocols for IR-NMIBC recommend adjuvant instillation of a chemotherapy agent (mitomycin C [MMC] or gemcitabine) after transurethral resection of bladder tumor (TURBT). The introduction of new technologies over the past 5 yr has exponentially increased the number of options for delivering chemotherapy into the bladder via external devices or intravesical slow-release mechanisms. Chemohyperthermia (CHT) was initially described in the 1990s. Two CHT approaches have been used in clinical trials so far: intravesical microwave-induced heating and conductive-based heating. The first system is based on controlled radiofrequency (RF) radiation (915 MHz) of the bladder tissue during chemotherapy instillations [2]. The RF applicator is a disposable, dedicated catheter equipped with a miniaturized RF antenna that heats the bladder wall to 42 ± 2°C, with multiple miniature thermometers used to monitor the temperature [2]. RF allows efficient homogeneous heating of bladder wall, which facilitates diffusion of drug molecules via Foucault currents and micropore permeation into cancer cells. Chemotherapy is introduced via the same catheter and each treatment session lasts for 60 min. The second approach involves a recirculation system with a conductive aluminum heat exchanger that heats MMC solution to 43 °C; the solution is then recirculated through the bladder at a constant flow rate via a three-way catheter [2].

In this issue of *European Urology*, Tan and colleagues [3] report on a randomized controlled trial (RCT) comparing adjuvant hyperthermic intravesical chemotherapy (HIVEC) to passive or standard room-temperature chemotherapy (MMC) in patients with IR-NMIBC. At median follow-up of 2 yr, there were no significant differences between the groups in disease-free survival (hazard ratio [HR] 0.98; p = 0.8), progression-free survival (HR 2.87; p = 0.06), and overall survival (HR 2.55; p = 0.09). Patients in the HIVEC group were less likely to complete their treatment (59% vs 89%) and more likely to experience adverse events, but the differences were not significant. In view of these results, the authors suggest that HIVEC cannot be recommended over MMC alone for IR-NMIBC [3].

Intravesical CHT delivered via conductive hyperthermia using the alternative RF-induced thermotherapy effect (RITE) approach and HIVEC have pros and cons in terms of oncologic outcomes, adverse events, logistics, and cost effectiveness. RCTs have compared RITE to bacillus Calmette-Guérin (BCG) maintenance therapy and other passive MMC instillations, demonstrating that RITE might achieve higher recurrence-free survival in comparison to BCG (p = 0.02), superior 10-yr disease-free survival in comparison to MMC (p < 0.001), and oncologic equipoise to maintenance BCG for IR-NMIBC [1,4,5].

In some studies, there was a lower level of association between CHT and urinary frequency, nocturia, incontinence, hematuria, fever, fatigue, or arthralgia, but catheterization

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difficulties, urethral stricture, bladder tissue reaction, bladder spasms or pain, and allergies were significantly more prevalent [4]. Other retrospective analyses suggest that CHT and other instillation therapies share similar safety profiles [1,5].

For MMC-RITE versus MMC alone in patients with IR-NMIBC or high-risk (HiR)-NMIBC without carcinoma in situ (CIS) and for whom BCG is unavailable or unsuitable, a cost-benefit analysis demonstrated considerable cost savings per patient over a lifetime horizon. However, in the same analysis and for the same patient population, MMC-RITE was associated with higher costs in comparison to BCG as a second-line treatment or to cystectomy [6]. Other studies suggested that CHT could have different costs according to tumor grade: in comparison to standard instillations, costs were significantly higher when CHT was used for low-grade NMIBC ($p < 0.001$), and significantly lower when used for high-grade (HG) NMIBC ($p < 0.001$) [7]. This is in line with prior evidence showing better survival outcomes for patients with IR-NMIBC or HG-non-CIS NMIBC when treated with CHT [1,4,5].

Better oncologic outcomes over standard instillations has been demonstrated for RITE, even in the setting of BCG-refractory NMIBC. However, studies demonstrating the efficacy of such therapy were conducted in a broad population, comprising patients with IR-NMIBC, HR-NMIBC with or without CIS, any pT1 or grade 3 urothelial carcinoma, or multifocal pTa (≥6 foci), with or without multiple recurrences of pTa lesions in the previous 24 mo [4]. A pilot phase 2 RCT in HR-NMIBC excluding CIS demonstrated comparable safety and efficacy between HIVEC and BCG, and progression-free survival was higher with HIVEC [8]. It has been shown that HIVEC is effective even for BCG-unresponsive cases, including BCG-refractory and BCG-relapsing disease [9]. Even if these results provide only low-level evidence, it seems somewhat controversial that HIVEC could play a role as a competitive strategy for BCG-refractory disease in HiR-NMIBC but not IR-NMIBC. Recent US Food and Drug Administration approval of new drugs (intravesical/intravenous) for this disease spectrum highlights the lack of advances for CHT.

The findings reported by Tan et al. [3] suggesting a lack of benefit from hyperthermia bring into discussion the real mechanism underlying the effect of hyperthermia on IR-NMIBC. The first studies conducted on HIVEC therapy on mixed groups, which included IR-NMIBC, HiR-NMIBC, and MMC- or BCG-recurrent disease, showed that HIVEC was a safe and effective treatment with high efficacy in both the neoadjuvant and adjuvant settings [10]. Taking the next studies, which involved subgroup analyses, it seems that only some groups of patients with NMIBC may benefit from HIVEC. This may be because of different issues. First, we should better address which patients are included in the "IR-NMIBC" group. There are variations among current guidelines regarding the definition of IR-NMIBC, which seems to be more a diagnosis of exclusion. The International Bladder Cancer Group synthesized available guideline suggestions for this heterogeneous disease, since a standardized definition is crucial for titration of treatment [1]. Second, the majority of dropouts in the study were associated with equipment issues, followed by irritative symptoms and allergic reactions. Standardized administration and revision of the device seem to be crucial for reducing the number of dropouts. Third, the main factors affecting intravesical MMC pharmacokinetics are the low absorption rate, effects of dilution due to urine production, viscosity, urinary pH, and exposure time [10]. Keeping the temperature constant is therefore crucial for treatment outcomes, but HIVEC achieves a lower depth of heat penetration in comparison to RITE, and does not directly act on the bladder wall, which is itself a good insulator. Fourth, studies have demonstrated the effectiveness of CHT in different populations, including patients with recurrent disease or IR-NMIBC and/or HiR-NMIBC. In the study by Tan et al. [3], 95% of patients had pTa disease and 46% had experienced a prior intravesical treatment failure, in comparison to 35% and 60%, respectively, in a similar study with Synergo. Could patient selection play a role in the efficacy of CHT? Or could the intrinsic nature of HG tumors play a role, since they are characterized by a higher level of DNA instability and are perhaps more susceptible to heat effects? To date, prospective RCTs comparing the systems are lacking, but head-to-head comparisons could shed light on the effects of the two systems in the same population. In fact, the simplest approach would be to deliver neoadjuvant chemotherapy intravesically before TURBT, avoiding the potential for extravasation and trying to downsize the bladder tumor via chemoablation.

In conclusion, the main question remains whether the advantages of HIVEC treatment outweigh its disadvantages in some subgroups of patients with NMIBC. Further research could possibly identify the optimal candidates for bladder hyperthermia.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Tan WS, Steinberg G, Witjes JA, et al. Intermediate-risk non–muscle-invasive bladder cancer: updated consensus definition and management recommendations from the International Bladder Cancer Group. Eur Urol Oncol 2022;5:505–16. https://doi.org/10.1016/j.euo.2022.05.005.

[2] Liem EIML, Crezee H, de la Rosette JJ, de Reijke TM. Chemohyperthermia in non-muscle-invasive bladder cancer: an overview of the literature and recommendations. Int J Hyperthermia 2016;32:363–73. https://doi.org/10.3109/02656736.2016.1155760.

[3] Tan WS, Prendergast A, Ackerman C, et al. Adjuvant intravesical chemohyperthermia versus passive chemotherapy in patients with intermediate-risk non–muscle-invasive bladder cancer (HIVEC-II): a phase 2, open-label, randomised controlled trial. Eur Urol. 2023;83:497–504.

[4] Arends TJH, Nativ O, Maffezzini M, et al. Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C versus bacillus Calmette-Guérin for adjuvant treatment of patients with intermediate- and high-risk non-muscle-invasive bladder cancer. Eur Urol 2016;69:1046–52. https://doi.org/10.1016/j.eururo.2016.01.006.

[5] Zhao H, Chan VWS, Castellani D, et al. Intravesical chemohyperthermia vs. bacillus Calmette-Guerin instillation for intermediate- and high-risk non-muscle invasive bladder cancer: a systematic review and meta-analysis. Front Surg 2021;8:775527. https://doi.org/10.3389/fsurg.2021.775527.

[6] National Institute for Health and Care Excellence. Synergo for non-muscle-invasive bladder cancer. Medical technologies guidance

MTG61. London, UK: NICE; 2021. https://www.nice.org.uk/guidance/mtg61.
[7] Wang S, Yu Z, Du P, et al. Combination of hyperthermia and intravesical chemotherapy for the treatment of pT1 stage bladder cancer: a retrospectively clinical study. Asia Pac J Clin Oncol. In press. https://doi.org/10.1111/ajco.13931.
[8] Guerrero-Ramos F, González-Padilla DA, González-Díaz A, et al. Recirculating hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) versus BCG in high-risk non-muscle-invasive bladder cancer: results of the HIVEC-HR randomized clinical trial. World J Urol 2022;40:999–1004. https://doi.org/10.1007/s00345-022-03928-1.
[9] Pijpers OM, Hendricksen K, Mostafid H, et al. Long-term efficacy of hyperthermic intravesical chemotherapy for BCG-unresponsive non-muscle invasive bladder cancer. Urol Oncol 2022;40:62.e13–. https://doi.org/10.1016/j.urolonc.2021.07.019.
[10] Sousa A, Piñeiro I, Rodríguez S, et al. Recirculant hyperthermic intravesical chemotherapy (HIVEC) in intermediate–high-risk non-muscle-invasive bladder cancer. Int J Hyperthermia 2016;32:374–80. https://doi.org/10.3109/02656736.2016.1142618.