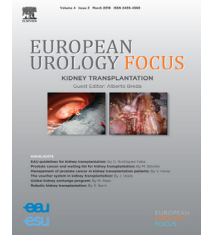


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Clinical Studies Update

Overview of Taris GemRIS, a Novel Drug Delivery System for Bladder Cancer

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1. Introduction

Intravesical delivery of drugs to treat bladder cancer has many potential advantages over systemic drug delivery including lower toxicity and better local drug delivery. While traditionally reserved for reducing the recurrence of non-muscle-invasive bladder cancer (NMIBC) [1], intravesical delivery could potentially also be used for muscle-invasive bladder cancer (MIBC).

2. The TAR-200/GemRIS device

The GemRIS device, developed by Taris Biomedical, is a drug delivery system designed for prolonged intravesical drug delivery. The device consists of a 5-cm semipermeable silicone tube that functions as an osmotic pump and slowly releases dissolving gemcitabine tablets (Fig. 1) [2]. Pharmacokinetically, 60–70% of the drug load is delivered over 2 wk, compared to the 2-h conventional dwell time for intravesical drugs [3].

The GemRIS device is inserted via an 18 F urethral catheter and self-coils into a pretzel shape intravesically (Fig. 1) [4]. In a phase 1 safety assessment among ten patients the empty device was very well tolerated, although all patients reported mild symptoms that returned to near baseline by day 3 [3,5].

3. Trials in NMIBC

A phase 1 marker lesion trial among 12 NMIBC patients was recently conducted in the Netherlands. In one of two arms, patients received the device on day 0 for 7 d, a second device on day 21 for 7 d, followed by transurethral resection of

bladder tumor (TURBT) on day 28. The second arm investigated two 21-d courses of the device without a holiday between treatment courses and TURBT on day 42 (Table 1). Patients were followed for 2 yr for recurrence-free survival, although the primary outcome was device safety and tolerability. Secondary outcomes evaluated drug concentrations over time in blood and urine and preliminary antitumor effects via histologic evidence of drug-induced cell death [6]. Results from this trial have not yet been reported.

4. Trials in MIBC

4.1. Neoadjuvant treatment in cisplatin-ineligible patients

4.1.1. Single-agent GemRIS

A multicenter phase 1b study is under way using GemRIS in the neoadjuvant setting before cystectomy for cisplatin-ineligible MIBC. The study is designed with two treatment arms on the basis of the presence of residual visual tumor following TURBT. Patients in arm 1 ($n = 10$) had visible tumor and received two 7-d deployments of the GemRIS device separated by a 2-wk holiday and cystectomy on day 28. Patients in arm 2 ($n = 10$) did not have visible tumor and received the same two GemRIS doses (days 0 and 21). According to preliminary data from arm 1, five subjects had cT2 and five had cT3 disease, and all had tumors >3 cm at enrollment. At cystectomy, 80% (8/10) had a complete or partial response (Supplementary Table 1). One patient (10%) achieved pT0 and another seven (70%) had a partial response with significant shrinkage of or no residual visual tumor. Only two patients (20%) had no shrinkage of visual tumor; both had clinical stage cT3 tumors and had persistent pT3 disease at surgery. This study

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TAR-200 (GemRIS™)

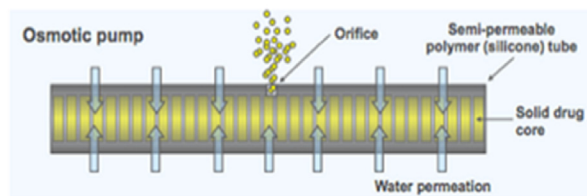
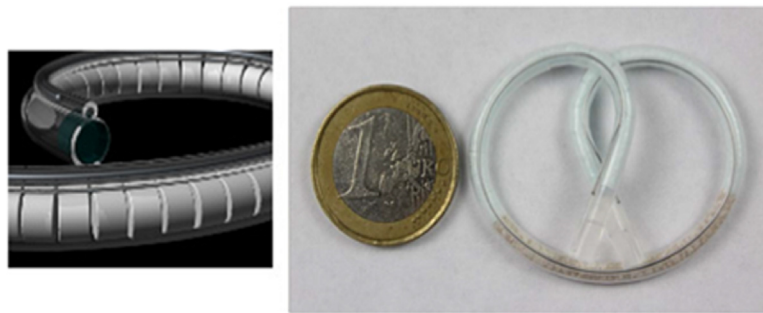


Fig. 1 – Schematic of the GemRIS device. Source: Witjes F. Activity four: how to treat bladder cancer when BCG is unavailable. Educational Centre: current clinical problems in bladder cancer.

www.webedcafe.com/extern/program_media/mededcafe.com/2017/bladder_cancer/activity4-Witjes/figure.php?present=Witjes&lang=EN&figure=57.

also showed that the device is safe, with no treatment-related severe adverse events, discontinuations, or events causing a delay in cystectomy [7,8]. Full results, including data for arm 2, are expected in late 2019 [9].

4.1.2. Combination with nivolumab

A multicenter phase 1b/2 study using GemRIS in combination with nivolumab is also under way. In this study, 25 cisplatin-ineligible patients will receive GemRIS and nivolumab, each dosed every 3 wk for four cycles, leading up to cystectomy. Phase 2 trials of nivolumab showed a response rate of ~20% in the metastatic setting, and neoadjuvant use is currently being investigated [10]. Combining local cytotoxic effects of GemRIS to drive tumor antigen release with immune stimulation by nivolumab offers enhanced

systemic antitumor immunity through the abscopal effect, as demonstrated in renal cell carcinoma, melanoma, and multiple other cancers [11–13]. Along with safety and tolerability, the aim of this study is to demonstrate a role for intravesical drug delivery in MIBC in the neoadjuvant setting [14].

4.2. Patients ineligible for cystectomy or chemoradiation

A final trial is investigating the palliative role of GemRIS in patients deemed unfit for cystectomy or chemoradiation with curative intent. Highly comorbid patients with organ-confined, nonmetastatic MIBC ($n=30$) will undergo a debulking maximal TURBT and then four 3-wk GemRIS instillations followed by up to three 3-wk maintenance

Table 1 – Summary of past and current clinical trials investigating GemRIS use in bladder cancer.

Study	Population	Intervention	Status
NMIBC			
NCT02720367	12 patients with low- or intermediate-risk NMIBC	Arm 1: two 7-d cycles separated by 14-d treatment holiday before TURBT Arm 2: two 21-d cycles without holiday before TURBT	Active, not recruiting
MIBC			
NCT02722538	20 patients with MIBC in neoadjuvant setting split into 2 arms on the basis of visible tumor after TURBT	Arm 1 (visible tumor): 2 cycles of GemRIS for 7 d separated by 14-d treatment holiday and cystectomy on day 28 Arm 2 (no tumor): 2 cycles for 7 d separated by 14-d treatment holiday and cystectomy on day 42	Active, not recruiting (estimated results late 2019)
NCT03518320	25 patients with MIBC in neoadjuvant setting	4 cycles of GemRIS + nivolumab every 21 d before cystectomy	Recruiting (estimated completion September 2020)
NCT03404791	30 patients with MIBC unfit for curative treatment	4 cycles of GemRIS every 21 d plus up to 3 maintenance cycles	Recruiting (estimated completion March 2020)

NMIBC = non-muscle-invasive bladder cancer; MIBC = muscle-invasive bladder cancer; TURBT = transurethral resection of bladder tumor.

cycles every 3 mo. Use in this setting may offer a better clinical response and symptom palliation in a population with limited treatment options [15].

5. Conclusions

GemRIS shows promise as a well-tolerated local drug delivery option for bladder cancer. While continuous dosing improves drug delivery to the bladder, it is unknown if this method of administration will improve outcomes. The ideal patient population and use for the technology remain to be determined, but are the subject of ongoing trials with neoadjuvant, palliative, and combination applications.

Conflicts of interest: Brant A. Inman serves as a clinical trial investigator for an ongoing Taris GemRIS trial. The remaining authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.euf.2019.09.006>.

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