Communication

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Intravesical $MgSO_4$ for the treatment of BCG refractory T1 G3 bladder cancer: Preliminary results on efficacy and safety

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SUMMARY An urgent need of therapy exists for patients with high-risk non-muscle invasive bladder cancer (NMIBC) for whom Bacillus Calmette-Guérin (BCG) refractory treatment has failed. We investigated the role of intravesical magnesium sulfate ($MgSO_4$) therapy in the management of BCG refractory T1 high grade (G3) NMIBC. Between January 2018 and July 2021, we performed a prospective trial enrolling participants with T1 G3 NMIBC refractory in BCG therapy. All patients included were considered ineligible for or have refused to undergo radical cystectomy. Subjects are enrolled into a single treatment group of a fixed dose of intravesical $MgSO_4$. The intravesical solution was given for 3 h bi-weekly × 6 then once per week for 12 months. Cystoscopic surveillance was performed every 3 months. Endoscopic resection was performed if suspicious findings were identified on surveillance cystoscopy to establish pathologic diagnosis. Oncological outcomes and any side effects were reported during follow-up. A total of 8 patients who received intravesical $MgSO_4$ for refractory TG3 tumors were included in our study. The median follow-up time was 29 months (range from 23 to 36). 62.5% of the patients (5/8) achieved a complete response to intravesical $MgSO_4$, while 25% of the patients (2/8) had a partial response and 12.5% (1/8) had persistent disease. None of the patients had disease progression. None of the patients experienced hypermagnesemia. In patients with pTG3 tumors who were refractory to BCG therapy, intravesical $MgSO_4$ was a well-tolerated and potentially effective regimen.

Keywords magnesium sulfate, intravesical, bladder cancer, non-muscle invasive

1. Introduction

Non-muscle invasive bladder cancer (NMIBC) is a challenging disease, with a high risk of recurrence and even progression to muscle invasive disease (*1*). Bacillus Calmette-Guérin (BCG) is the only intravesical agent shown to reduce the risk of progression of NMIBC to muscle-invasive disease but it still fails in up to 40% of patients (*2*). Currently, the best option for these patients is radical cystectomy. Novel treatment modalities for BCG failure include intravesical chemotherapy, BCG re-challenge or combination of BCG with IFN-α2β, valrubicin, radiotherapy, electromotive drug administration, vicinium, chemohyperthermia, photodynamic therapy, gene therapy, vaccine therapy, and immunotherapy (*3*). An urgent need for therapy exists for patients with high-risk NMIBC for whom BCG has failed and who seek further bladder-sparing approaches.

2. The rationality to use magnesium sulfate to induce toxicity of cancer cells

In animal models magnesium sulfate ($MgSO_4$) can induce cytotoxicity of cancer cells and release pro-inflammatory cytokines (*4*). The objective of this pilot study was to test if intravesical $MgSO_4$ therapy can manage BCG refractory T1 high grade (G3) NMIBC in patients for whom cystectomy was not an option due to medical reasons, or was offered but refused.

3. Trial design

Between January 2018 and July 2021, we performed a prospective trial enrolling participants with T1 G3 NMIBC refractory in BCG therapy and who are considered ineligible for or have refused to undergo radical cystectomy. BCG refractory disease was defined as biopsy-proven recurrence T1 G3 tumor at 3 months of

receiving a 6-week induction course of BCG, or if a high-grade tumor is present after 3 months and/or at 6 months after either re-induction or first course of maintenance of BCG therapy, or if a high-grade tumor appears during BCG maintenance therapy. All patients with initial or subsequent pathology that revealed carcinoma in situ (CIS) are excluded. Fully resected disease at study entry is also required. Re-resection was performed for all patients. All patients included in the study had the same initial pathology on re-resection specimen. Patients who had any upgrading in the re-resection pathology were excluded. Information regarding patient demographics, time to recurrence, response to $MgSO_4$ therapy, and side effect profile was recorded.

Subjects are enrolled into a single treatment group of a fixed dose of intravesical $MgSO_4$. The intravesical solution was given for 3 h bi-weekly × 6 then once per week for 12 months. Magnesium sulfate heptahydrate 50% (2 mmol Mg^{2+} in 1 ml) was used. Two 10 ml ampoules containing 20 mmol Mg^{2+} were diluted in 30 cc of normal saline solution. Solution preparation was supervised by a clinical pharmacist. The reconstituted $MgSO_4$ solution is injected into the bladder by gravity flow *via* a Foley catheter. Before each injection, a urinalysis was performed to exclude urinary infection. Patients should empty their bladder before each $MgSO_4$ administration. The patient should be repositioned from left side to right side and also should lie upon the back and the abdomen, changing these positions every 15 minutes to maximize bladder surface exposure to the agent. It is important to note that at least 8 weeks should be the interval between intravesical therapy and last bladder resection.

Any side effects were reported. Even though systemic side effects were not expected, all patients using bladder instillation of $MgSO_4$ were tested for magnesium level three times (before, 4 hrs, and 12 h after therapy). Serum magnesium concentration > 2.6 mg/dL indicates hypermagnesemia. Urological follow-up was done by the same urologist who was blinded to the treatment solution.

Cystoscopic surveillance was performed every 3 months. Endoscopic resection was performed if suspicious findings were identified on surveillance cystoscopy to establish pathologic diagnosis. All specimens were examined by a single, experienced pathologist blinded to the treatment protocol. Complete response is considered if no tumor was identified during follow-up; partial response if lower grade and/or stage tumor was identified compared to before $MgSO_4$ therapy; persistent disease if the same grade and stage tumor was identified; or disease progression if higher grade and/or stage tumor was identified.

Adverse events observed after the administration of $MgSO_4$ for the follow-up period were recorded at regular visits by the same urologist who was blinded to the study protocol and intervention.

Table 1. Patient baseline characteristics

Patient number	Age (years)	Gender	Time since last BCG instillation
1	56	Male	6 months
2	62	Male	9 months
3	63	Male	10 months
4	64	Female	5 months
5	71	Female	4 months
6	66	Male	3 months
7	69	Female	3 months
8	59	Female	2 months

BCG: Bacillus Calmette-Guérin.

The study was done at Al Zahraa Hospital in Beirut. It was approved by its IRB (approval No. 2018.2). Informed signed consent was obtained from all patients and confirmed by the IRB. The authors confirm the availability of, and access to, all original data reported in this study.

4. Main findings

A total of 8 patients who received intravesical $MgSO_4$ for refractory TG3 tumors were included in our study. Baseline characteristics are summarized in Table 1. The median age of the patient was 66 years, the male: female ratio was 1. The median time since last BCG instillation was 4.5 months.

The median follow-up time was 29 months (range 23 to 36). 62.5% of the patients (5/8) achieved a complete response to intravesical $MgSO_4$, while 12.5% of the patients (1/8) had persistent disease. 25 % of the patients (2/8) had a partial response while on therapy. None of the patients experienced disease progression. The time since the last BCG instillation for patients who had persistent disease was 3 months (patient 6), whereas the time since the last BCG instillation for patients who had a partial response (patient 7 and 8) was 3 and 2 months respectively. Oncologic outcomes after intravesical $MgSO_4$ therapy are summarized in Table 2.

There were no serious adverse events reported in the treatment group. None of the patients experienced hypermagnesemia and the serum magnesium level did not change after therapy in all patients.

5. The effect of $MgSO_4$ on cancer cells

$MgSO_4$ can induce cytotoxicity of cancer cells. Zhang *et al*. conducted a study to assess the possible cytotoxicity of $MgSO_4$ on human gastric adenocarcinoma cells (AGS) and gastric mucosa in mice. $MgSO_4$ treatment decreased the viability of AGS cells in a concentration-dependent manner and showed a significant decrease in viability. $MgSO_4$ influences cytokine secretion. In AGS cells, the secretion of IL-1β and IL-8 decreased, and that of TNF-α increased with increasing concentrations

Table 2. Oncologic outcomes after intravesical $MgSO_4$ therapy

Patient number	Complete response	Partial response	Persistent disease	Disease progression	Follow-up time (months)	Pathology identified in patients who had a partial response to therapy
1	Yes	No	No	No	23	N/A
2	Yes	No	No	No	29	N/A
3	Yes	No	No	No	25	N/A
4	Yes	No	No	No	26	N/A
5	Yes	No	No	No	30	N/A
6	No	No	Yes	No	36	N/A
7	No	Yes	No	No	32	pTaHG
8	No	Yes	No	No	31	pTaHG

N/A: not applicable; HG: high grade; $MgSO_4$: Magnesium sulfate.

of $MgSO_4$ (*4*). In another study, $MgSO_4$ caused oxidative stress by generating reactive oxygen species (ROS) which caused DNA damage in testicular cells (*5*). $MgSO_4$ could also affect apoptosis of cancer cells by inducing a change in expression of Fas ligand (FasL) and Fas receptor (FasR) (*6*).

6. Important oncological outcomes in this trial

In our trial, none of the patients had disease progression, while 1 patient had persistent disease and 2 others had a partial response to therapy. Down-staging was observed in patients who had a partial response. We noted that the last time of BCG exposure for patients who had a persistent or partial response to $MgSO_4$ was shorter than that of other patients included in the trial (2 and 3 months).

Previously published results indicated that $MgSO_4$ reduced cancer cell viability. In this paper, we used $MgSO_4$ to study its effect on bladder tumor cells. Oncological outcomes and results of recurrence and progression, indicate that $MgSO_4$ could affect the viability of tumor cells within the bladder. Therefore, further research will be required to determine how $MgSO_4$ could induce apoptosis of urothelial tumor cells and to investigate the molecular mechanisms involved.

In conclusion, in patients with pTG3 tumors who were refractory to BCG therapy, intravesical $MgSO_4$ was a well-tolerated and potentially effective regimen.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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