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## Intravesical Instillation Treatment of Non-muscle-invasive Bladder Cancer

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### Abstract

Bacillus Calmette-Guérin (BCG) is a proven and valuable adjunct to transurethral resection (TUR) for decreasing recurrence and progression of non-muscle-invasive bladder cancer (NMIBC). The European Association of Urology (EAU) and American Urological Association (AUA) have similar recommendations for induction and maintenance treatment in patients based on clinical and pathologic risk factors. To most effectively treat this disease, clinicians must be aware of the risk factors for treatment failure, strategies to deal with failures and BCG intolerance, and the appropriate threshold to proceed with radical cystectomy (RC). Combination, alternative, and multimodal intravesical treatments for patients with BCG failure have arisen in recent years, and the outcomes data are reviewed here.

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### 1. Introduction

Various forms of non-muscle-invasive bladder cancer (NMIBC) comprise >70% of all new bladder cancer (BC) diagnoses [1]. About half of these are low-grade, Ta tumors with low risk (<5%) of progression. The others represent more worrisome lesions with higher risk of progression [2].

Standard treatment consists of transurethral resection of bladder tumors (TURBT), with the addition of intravesical adjuvant therapy when indicated. The most widely used agents include the immunotherapy drugs bacillus Calmette-Guérin (BCG), interferon- $\alpha$  (IFN- $\alpha$ ), and the chemotherapy agent mitomycin C (MMC), among others. BCG represents the only agent known to reduce progression into muscle-invasive bladder cancer (MIBC) [2].

### 2. Recommendations for treatment-naïve patients

In patients who have not previously been treated with intravesical agents, induction therapy should be preceded

by adequate and safe transurethral resection (TUR) of all visible tumors. Intravesical therapy should never be considered an alternative to satisfactory extirpation. In cases of high-grade T1 disease, it is strongly advised that repeat TURBT be considered 4–6 wk after the original resection, primarily because of frequent clinical understaging and the presence of unresected residual disease. Muscle invasion has been found on re-resection in up to 49% of cases when no muscularis propria was present and in up to 14% of cases when muscle was present in an original T1 tumor [3]. Residual disease has been found in 20–40% of cases [4]. The European Association of Urology (EAU) has recommended re-resection for all TaT1, high-grade tumors [5].

The optimal schedule for BCG remains unknown. Typical induction treatment for BCG-naïve patients begins 2–4 wk after TURBT and consists of six weekly instillations of a full vial of BCG suspension. Using a linear regression model, a dose-response relationship was found wherein at least 12 BCG doses were needed to show superiority over MMC in

preventing recurrence [6]. Currently, the general consensus calls for at least 1 yr [5] and even up to 3 yr of maintenance therapy [4], if tolerated.

The 2007 update to the American Urological Association (AUA) BC guidelines [4] and the 2008 EAU guidelines on NMIBC [5] generally agree on the recommendations for adjuvant immunotherapy in low-, intermediate-, and high-risk NMIBC. A summary of the general recommendations is provided below.

### 2.1. Low-risk disease (small volume, primary, low grade, stage Ta)

Neither the AUA nor the EAU have made BCG therapy a practice standard for this category, which generally includes patients with low to moderate risk of recurrence ( $\leq 15\%$ ) and very low risk of progression ( $\leq 0.2\%$ ) at 1 yr [5]. Surgical eradication of all visible tumors is a standard. The EAU advocates a single dose of intravesical chemotherapy (primarily MMC) postoperatively, but the AUA considers this optional.

### 2.2. Intermediate-risk disease (multifocal, large volume or recurrent, low grade Ta or T1)

There is a heterogeneous group of patients who fall in the intermediate-risk category as defined by the EAU guidelines, with low to moderate risk of progression ( $\leq 1\%$  at 1 yr,  $\leq 6\%$  at 5 yr), and recurrence risk of 46–62% at 5 yr [5]. In general, this would include patients with multifocal, recurrent, and/or large-volume, low-grade Ta (and sometimes T1) disease without carcinoma in situ (CIS) in both the EAU and AUA risk-stratification schemes.

Both organizations recommend an induction course of either BCG or intravesical cytotoxic chemotherapy (usually MMC), as there is a paucity of data to confirm a distinct advantage of BCG over chemotherapy for this cohort. In addition, the EAU more confidently recommends 1 yr of BCG maintenance or 6–12 mo of maintenance chemotherapy. The AUA considers maintenance therapy with either agent optional but acknowledges the superiority of maintenance over non-maintenance for MMC.

### 2.3. High-risk disease (high-grade Ta or T1 and/or carcinoma in situ)

Little controversy exists about the adequate treatment of high risk tumors, which generally include high-grade T1 tumors, CIS, or a combination of high-grade Ta disease and CIS. In general, this group has a  $\leq 17\%$  risk of progression to MIBC at 1 yr and 45% risk at 5 yr [5]. Both the EAU and the AUA recommend TURBT (with possible re-resection), followed by induction BCG, and then at least 1 yr of maintenance intravesical therapy. If cytotoxic chemotherapy is chosen instead, induction treatment should be followed by at least 6–12 mo of maintenance therapy. The AUA, although falling short of declaring BCG maintenance the standard of care, emphasizes that there is still a lack of data showing a clear progression advantage over

MMC, with maintenance, potential side effects of treatment, and financial burdens that may outweigh the benefits in some patients.

It is also important to consider the risks and benefits of early radical cystectomy (RC) in this patient cohort. This decision weighs heavily on issues of BCG failure risk and treatment side effects in high-risk patients. These are perhaps the most difficult and disputed treatment dilemmas regarding immunotherapy.

## 3. Effectiveness of intravesical treatment in preventing recurrence and progression

### 3.1. Papillary (Ta, T1) disease

The odds ratio for recurrence is 0.39 with the use of postsurgical BCG versus TURBT alone [7]. Several meta-analyses have shown the superiority of BCG over intravesical cytotoxic chemotherapy (primarily MMC) in preventing tumor recurrence and progression. However, it is essential to institute regular maintenance therapy in order to achieve a significant advantage with BCG therapy [2,5]. In a meta-analysis of more than 2700 patients with a median follow-up of 26 mo, the relative risk of recurrence was 0.75 with BCG compared to MMC, which decreased further to 0.64 in subgroups treated with BCG maintenance therapy [6].

### 3.2. Carcinoma in situ

A similar treatment effect is seen in patients with CIS, where BCG remains the treatment of choice. Approximately 5–10% of all NMIBC patients harbor this high-grade and often multifocal form of urothelial carcinoma (UC) [7]. A meta-analysis of more than 700 patients showed complete response (CR) rates of 68% and 52% and disease-free rates (at 3.6 yr) of 47% and 26% for BCG versus chemotherapy, respectively [8].

Justification for BCG maintenance treatment can reasonably be extrapolated from papillary carcinoma data. However, it was demonstrated in the Southwest Oncology Group (SWOG) 8507 study that the addition of even one 3-wk maintenance cycle could improve the 6-mo CR rate from 68% to 84% [9].

## 4. BCG failure

The decision to employ intravesical immunotherapy, or alternatively, when to abandon treatment, is typically more complex than simply inserting an index patient into the EAU or AUA guidelines. Many patients bring an array of other comorbidities and treatment obstacles to the table. Also, each risk group is heterogeneous and assumes other variables (eg, recurrence patterns, histologic variants, and molecular characteristics) that cannot easily be applied to straightforward algorithms. To fully understand and manage this complex issue, one must be versed on the types of BCG failure and strategies to manage BCG intolerance.

#### 4.1. Types of bacillus Calmette-Guérin failure

Traditionally, the term *BCG failure* has been applied generically in the literature, usually referring to patients who have recurrent disease any time after initiation of therapy. In fact, failure patients can roughly be divided into the categories of *BCG intolerant*, *refractory*, *resistant*, and *relapsing disease*.

*BCG intolerance* is defined as recurrence after an inadequate treatment course, halted prematurely because of symptomatic intolerance or serious adverse events. In contrast, *BCG-refractory* patients fail to achieve disease-free status by 6 mo after induction with either maintenance or re-induction at 3 mo. This group also includes patients with progression in grade or stage by 3 mo after the first induction cycle. *BCG-resistant* patients have recurrent or persistent disease (of lesser degree, stage, or grade) after initial induction but then have complete response at 6 mo after TURBT. In essence, the disease initially improves, and then resolves with BCG. In contrast, *BCG relapsing* patients achieve disease-free status before 6 mo post-TURBT but then have early (within 12 mo), intermediate (12–24 mo), or late (>24 mo) recurrence [10].

### 5. BCG intolerance

Serious side effects occur in <5% of all patients undergoing BCG treatment, and a vast majority of these can be effectively treated [5]. Although a slightly higher rate of side effects has been associated with BCG over MMC, it is estimated that only 5–10% of patients fail to complete induction treatment, and about 5–11% have interruption but eventual completion [6,16]. However, 84% of patients on full-dose BCG using the rigorous SWOG 3-yr maintenance plan did not receive all of their planned doses [9].

BCG toxicity can be divided into local and systemic side effects. Local toxicities are generally more frequent and less severe than systemic toxicity, but they are more often the cause of treatment stoppage [11]. However, most local side effects are brief [10,12]. The incidence of local side effects is similar with or without maintenance therapy. For patients who receive or do not receive maintenance therapy, respectively, these include lower urinary tract symptoms (57–71%, 38–59%), hematuria (20%, 29%), and bladder contracture (3%, 1%) [4].

Similarly, others have found no difference in systemic side effects between maintenance and non-maintenance groups [6] and even reduced toxicity in the period after the first 6 mo of treatment [11]. Systemic side effects can be divided into infectious (bacterial cystitis, epididymitis/prostatitis/urethral infections, systemic infection) and non-infectious types (arthralgias, skin reactions, anaphylaxis). The most common systemic toxicities reported in the 2007 AUA guidelines update [4] include fevers, chills, and flu symptoms (22–30%, 19–26%); epididymitis, prostatitis, and urethral infections (4%, 4%); and systemic infection (7%, 1%) for patients treated with maintenance versus no maintenance, respectively. Less severe systemic toxicities such as fever (>39.5 °C), skin rash, arthralgias, and *BCGitis*

(established BCG infection with organ manifestation [epididymal-orchitis, pneumonitis, hepatitis]) occur at a rate of 2–6% [10,13].

### 6. Treatment strategies for bacillus Calmette-Guérin intolerance

#### 6.1. Dose adjustment

Dose adjustment remains one of the most common methods to manage BCG intolerance and is frequently employed to reduce dropout during maintenance treatments. A one-third dose of BCG showed similar efficacy in preventing recurrence and progression with significantly less toxicity, but there has been some concern about applying this strategy routinely in multifocal and high-risk tumors [14,15]. In one randomized, prospective trial, a one-third dose of BCG was more effective than MMC in preventing recurrence in intermediate-risk disease. However, a 1/6 dose of BCG was less effective without the benefit of decreased toxicity in these patients [16]. Further dose reduction (1/10, 1/30, and even 1/100 of BCG) in combination with IFN- $\alpha$  in patients with severe toxicity may also be efficacious for cancer control, but there is a paucity of published data at this time.

#### 6.2. Treatment schedule

One potential strategy to decrease side effects and improve tolerance is increasing the instillation interval during induction or maintenance (eg, doubling from 1 to 2 wk). Unfortunately, there is little data on the efficacy of this tactic. One small phase 2 trial showed decreased rates of mild to moderate side effects in the slow-rate group compared to standard rate. Twenty-five percent of patients in the standard rate cohort experienced severe side effects requiring delay of instillation, and 6% required treatment interruption, but no patient required delay or interruption in the slow-rate cohort [17].

#### 6.3. Dwell time

In patients with significant side effects, Andius et al showed improvement in fevers, chills, dysuria, and overall time to recovery by reducing BCG dwell time from 2 hr to  $\leq 30$  min [18]. Compared to a control group with normal dwell time, these patients had similar tumor-free results. Although this may represent a treatment alternative for patients with BCG intolerance, long-term efficacy data are currently lacking.

#### 6.4. Pharmacologic

Most BCG-associated cystitis symptoms can be effectively managed with aspirin, nonsteroidal anti-inflammatory drugs, urinary analgesics, and antispasmodics [10]. In addition, 200 mg ofloxacin given 6 and 18 hr after treatment has shown promise in a prospective, placebo-controlled, randomized, controlled trial [19]. There was a significant reduction in moderate to severe adverse events during the

second half of the BCG induction cycle and severe events throughout the induction and maintenance periods. Despite being tuberculostatic, more patients in the ofloxacin group completed all treatments without an obvious detriment to BCG efficacy. A newer fluoroquinolone antibiotic—prulifloxacin—significantly decreased moderate to severe adverse events and treatment interruption without affecting 6-mo recurrence rates in a prospective, randomized, controlled trial [20]. Here again, long-term data are lacking.

## 7. Refractory, resistant, and relapsing disease in bacillus Calmette-Guérin-naïve patients

High-risk NMIBC patients undergoing BCG treatment require diligent monitoring, as they face a rather grim fate with disease progression and fare as poorly as, or even worse than, patients who present with primary muscle-invasive disease. A clinician must be mindful of the risk categories for BCG failure when guiding intravesical treatment decisions.

### 7.1. Groups at highest risk for bacillus Calmette-Guérin failure

For patients in the highest risk group, it is suggested that a clinician more strongly consider radical therapy if a patient demonstrates significant BCG intolerance, resistance, or a concerning relapse pattern—particularly in patients with fewer comorbidities. The risk factors most clearly associated with recurrence and progression risk include tumor stage, grade, presence of CIS, recurrence pattern, multifocality, and high-risk histologic variants.

Large-scale, prospective studies have demonstrated that TNM stage can predict progression. The risk of progression is more than 2× greater for stage T1 versus Ta based on multivariate analysis [21]. There are less data to correlate TNM stage with recurrence, however. Similar to stage, tumor grade portends risk of tumor progression. Large-scale, prospective studies have demonstrated a hazard ratio (HR) for progression ranging from 2.7 to 5.8 for G3 disease compared to lower grades [14,22,23].

Recurrent tumors fare more poorly than grade- and stage-matched primary tumors, and early recurrence carries a worse prognosis than delayed recurrence. Recurrent tumors are about 1.5× more likely to progress to MIBC than primary tumors [12,22,23]. Multiply-recurrent tumors are an even worse prognostic indicator, carrying an HR of 2.3 for continued recurrence and 2.0 for progression to muscle-invasive disease [14]. Recurrence at the first post-treatment cystoscopy is one of the worst prognostic indicators for eventual T stage progression, particularly in the setting of other high-risk factors [21,37,24]. Large series have shown that 60–80% of patients with recurrence at first cystoscopy eventually have progression [24,39,25].

Despite the fact that CIS and high-grade papillary disease commonly coexist, CIS is clearly an independent prognostic factor. A large-scale meta-analysis of seven European Organization for Research and Treatment of Cancer (EORTC) trials showed progression rates of 10% at 1 yr and 29% at 5 yr in T1G3 tumors without CIS versus 29% and 74%,

respectively, with concomitant CIS. Here, multivariate analysis showed that the presence of CIS yielded a higher HR for tumor progression (HR: 3.41) than grade (2.67) and T category (2.19) [22].

Several studies have shown tumor multiplicity to be a significant predictor for recurrence in BCG-treated patients, with an HR of approximately 1.5 [14,22,23], but only one large-scale study has indicated an importance in progression [22]. The prognostic importance is also additive, wherein the risk of recurrence is proportional to the number of tumor foci [23].

There are aggressive histologic features and variants in which BCG treatment should be avoided in favor of early RC. These include lymphovascular invasion, which has been associated with overall decreased survival in cystoprostatectomy patients [26]. Furthermore, micropapillary variants of UC, squamous cell carcinoma, and adenocarcinoma of the bladder should not be approached like non-muscle-invasive UC and are clearly not appropriate for intravesical immunotherapy. In one series of patients treated with BCG for micropapillary variant, two-thirds progressed to MIBC and almost one-fourth to metastatic disease [27].

### 7.2. Other risk groups for bacillus Calmette-Guérin failure

There are an admixture of risk factors in which the clinician is urged to be more persistent for resistant/relapsing disease and more creative with adjusted treatment regimens in cases of BCG intolerance. Furthermore, the threshold to abandon immunotherapy for cystectomy may be somewhat higher. However, there is no substitute for cystectomy for refractory disease. The risk factors in this category include prostatic urethral involvement, large tumor size, advanced age, and urinary marker findings.

Within 5 yr of diagnosis, the prostatic urethra and ducts are secondarily involved in 10–15% of men with high-risk NMIBC [28]. Moreover, on careful pathologic analysis, it can be observed in more than 40% of cystoprostatectomy specimens. When CIS or multifocal BC is present, the risk for prostatic urethral involvement is increased more than 12-fold. Tumors involving the prostatic urethra have been associated with clinical understaging and shorter survival [29,30]. However, patients with CIS of the prostatic urethra alone enjoy a >70% CR rate and a 47–72% CR rate with both bladder and prostate involvement [28]. Thus, there is clearly a role for BCG treatment with superficial involvement of the prostate. In one prospective study, there was a 55% recurrence rate after CR from BCG therapy, but only 28% continued to fail local therapy, and disease-specific survival (DSS) was nearly 90% at 7.5 yr median follow-up [31]. It is important to liberally employ TUR of the prostate during restaging procedures in order to assess for prostatic duct and stromal invasion, which are indications for cystectomy.

Tumor size >3 cm predicted recurrence and progression (HR: 1.54 and 1.89, respectively) in the 2500-patient EORTC study by Sylvester et al. [22]. Based on a small, prospective study, there appears to be an independent risk associated with tumor size in high-risk (T1G3) tumors [32].

Like many other cancers (breast, ovarian, thyroid), BC is largely a disease of the elderly. BCG relies heavily on cell-mediated immunity, putting immune-suppressed individuals at higher risk for failure. With BCG monotherapy, Fernandez-Gomez et al showed a negative impact of age on progression to muscle-invasive disease by multivariate analysis (age >60 yr, HR: 1.57; age >70 yr, HR: 1.74) [23]. In a large, multicenter, phase 2 trial using combination intravesical BCG plus IFN- $\alpha$ , patients over 80 yr of age had statistically lower cancer-free survival at 24-mo follow-up [33]. However, no specific treatment strategies or surveillance protocols have been advised by the AUA or the EAU that differ from those for younger patients.

Fluorescent in situ hybridization (FISH) is widely available and may be helpful for predicting relapse and progression. One study showed 100% relapse in patients with positive FISH shortly after BCG induction compared to 50% relapse with negative FISH (HR: 4.6) [34]. Over half of the patients with positive FISH had muscle-invasive disease at relapse. However, another study showed that although the recurrence rate was clearly increased (~3-fold) by a post-TURBT positive FISH result, the progression rate was not affected [35]. Further studies in this area are needed.

## 8. Treatment of bacillus Calmette-Guérin–failure patients

Approximately 30–50% of patients will not respond to BCG treatment or have recurrence within 5 yr, and up to 90% will relapse by 15 yr [36]. Treatment strategies will depend heavily on the recurrence interval and other risk factors, as previously discussed. The following section is meant to guide the clinician through further treatment options after BCG failure—in particular, when to use and when not to use alternative immunotherapy regimens and intravesical chemotherapy.

### 8.1. Radical therapy

Foremost, the clinician must realize when to abandon immunotherapy in high-risk patients. The decision to proceed with RC for BCG failure is sometimes straightforward, such as in the case of dysfunctional bladder, progression in grade or stage, early recurrence pattern, or when it becomes impossible to cystoscopically control the tumor. At other times, the decision is not so clear, particularly when caring for suboptimal surgical candidates.

According to the EAU [5] and AUA guidelines [4], cystectomy can be offered to all high-risk patients at initial diagnosis but must be emphasized for BCG-refractory patients. There does not appear to be an overall survival or DSS advantage for early cystectomy over BCG therapy for primary NMIBC, even for high-risk (T1G3) disease [37], though this has not been formally tested in randomized clinical trials. In other words, careful and appropriate use of BCG can always be considered a first-line treatment for

primary NMIBC when confirmed by re-TUR and no residual T1 disease.

### 8.2. Second induction bacillus Calmette-Guérin

Patients who recur with the same or lower T stage and grade at 3 mo after induction are not considered treatment failures, as 35% will respond to a second 6-wk BCG induction. Treatment beyond two courses is not recommended and is associated with <20% success and increased chance of disease progression [10]. The appearance of higher grade or stage or new diagnosis of CIS during therapy is considered a treatment failure and should prompt discussion about cystectomy [5]. However, when recurrence is late (>2 yr after CR), these patients fare nearly as well with re-treatment as with initial BCG [38].

### 8.3. Combination bacillus Calmette-Guérin–interferon

Other intravesical agents, particularly combination BCG–IFN- $\alpha$  or sequential chemotherapy regimens, have arisen as viable treatment options for BCG-resistant and relapsing disease, principally in high-risk cystectomy patients who fail primary therapy. However, they cannot be advocated for true BCG-refractory disease. Noting that BCG owes part of its activity to a T-helper type 1 (TH1) immune response in the bladder, in vitro studies have shown that IFN- $\alpha$  potentiates the TH1 response by inhibiting interleukin-10 (IL-10: a TH1 inhibitory cytokine) [39]. IFN- $\alpha$  monotherapy has a favorable toxicity profile, but the high cost and reduced efficacy compared to BCG make it an inferior choice for monotherapy [40].

Combination BCG plus IFN- $\alpha$  has shown promise for treatment of recurrent UC in BCG-resistant and BCG-relapsing patients. A large, multicenter, phase 2 trial demonstrated that 45% of BCG-failure patients were disease free at a median 24-mo follow-up after combination low-dose BCG plus IFN- $\alpha$  (50 million units [MU]) [33]. This compared favorably to the response rate in BCG-naïve patients, where 59% were disease free at 24 mo. Several other studies have shown a 50–60% disease-free rate (12–30-mo follow-up) for BCG plus IFN- $\alpha$  after BCG failure, even in recurrent T1 disease [41–43]. For patients with CIS, the 24-mo disease-free rate after BCG plus IFN- $\alpha$  compared favorably between patients failing one previous course of BCG (57%) and BCG-naïve patients (60%) [44].

The early reports from a large, multicenter, randomized, controlled trial do not find a clear advantage for combination BCG plus IFN- $\alpha$  therapy in treatment of NMIBC in BCG-naïve patients. The unpublished results were presented at the 2008 AUA National Meeting [45]. The study randomized more than 600 individuals to recommended daily allowance or high-dose antioxidant vitamins and also to induction plus 3 yr of maintenance using either BCG monotherapy or BCG plus IFN- $\alpha$  (50 MU). The results showed no significant difference in tumor recurrence with the addition of IFN- $\alpha$  versus supplementation with high-dose antioxidant vitamins for BCG monotherapy patients. Further investigation in this area is needed.

BCG plus IFN- $\alpha$  therapy is well tolerated and compares favorably to BCG monotherapy. In one study, serious side effects were reported in 6.2% and 4.8% of BCG-naïve and BCG-failure patients, respectively [46]. Severe symptoms occurred in <2% of patients during maintenance therapy in both groups. In all,  $\leq$ 10% patients reported moderate to severe symptoms, and  $\leq$ 36% reported moderate symptoms, even through the duration of three maintenance cycles. Less than 5% of BCG-failure patients had permanent termination of therapy resulting from toxicity, and <5% required dose reduction.

#### 8.4. Intravesical chemotherapy

Several chemotherapeutic agents (MMC, valrubicin, gemcitabine) have shown durable response rates of  $\leq$ 21% when used as monotherapy after BCG failure [47–49]. Better results have been observed with sequential gemcitabine-MMC regimens [50] but have not been substantiated by large prospective trials. In addition, a recent prospective trial using docetaxel induction along with nine monthly maintenance treatments in BCG-failure patients showed a 46% disease-free rate at 13 mo follow-up [51]. Again, large-scale and long-term studies on treatment durability are needed. Finally, device-assisted therapies such as thermochemotherapy, electromotive drug administration, and photodynamic therapy have shown promise but await randomized, controlled trials before they will be used large scale [51].

### 9. Conclusions

NMIBC is a heterogeneous disease encompassing a number of treatment variables. In the case of intermediate- and high-risk cases, the current standard of care is adjuvant BCG after adequate TUR. However, this treatment carries an inherent toxicity profile that limits the ability to deliver the necessary treatment to some individuals. In addition, there are certain risk factors for tumor progression and recurrence despite therapy. It is important for practitioners to grasp alternative treatment strategies to circumvent side effects and to firmly understand risk categories for treatment failure.

#### Conflicts of interest

The authors have nothing to disclose.

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