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European Association of Urology

Clinical Controversies

How to Treat Multifocal Ta High-grade Disease if Bacillus Calmette-Guérin Is Unavailable

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Article info

Article history:
Accepted June 14, 2019

Associate Editor:
Gianluca Giannarini

Keywords:
pTa
Low grade
High grade
Multiple lesions
Cystectomy
Epirubicin
Gemcitabine
Chemohyperthermia

Abstract

A 71-yr-old man was transferred to our institution with multiple and recurrent high-grade pTa bladder cancer 26 mo after an initial presentation of multiple and large pTa low-grade tumors and concomitant carcinoma in situ, treated with transurethral resection plus 6-mo postoperative mitomycin C. This case discusses several treatment options in the absence of bacillus Calmette-Guérin (BCG). Immediate radical cystectomy is an option with excellent survival, since there is a substantial risk of understaging and disease progression; however, this results in overtreatment in ~50% of these patients. Therefore, a conservative approach could be intravesical combination therapy such as gemcitabine/docetaxel or epirubicin/interferon. In addition, device-assisted intravesical therapy is becoming an option to consider. Finally, patients could be included in trials such as immunotherapy trials.

Patient summary: This 71-yr-old patient was diagnosed with recurrent, moderately severe noninvasive bladder tumors, which were removed. The recommended additional therapy, intravesical bacillus Calmette-Guérin (BCG) instillations, was not available. Both the pros and the cons of radical surgery (bladder removal) and a more conservative approach (other intravesical treatments) are discussed.

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1. Case presentation

The patient was a 71-yr-old man with a primary presentation of microhematuria. He was a retired pulmonologist but a current smoker, with a history of 50 pack-years. His cytology was normal, but cystoscopy revealed multiple lesions. At the original hospital, a transurethral resection of the bladder (TURB) without a photodynamic diagnosis (PDD) revealed pTa low-grade tumors; because there were multiple lesions, this was a case of intermediate-risk category.

He was given one instillation of mitomycin C (MMC), followed with 6 mo of MMC maintenance. However, this regimen caused urgency, with voiding every 20–30 min, up to 10 times per night, necessitating stopping of further

https://doi.org/10.1016/j.euo.2019.06.011

intravesical instillations. Cystoscopy at 3 mo after stopping MMC was normal, but at 6 mo he had two small recurrences, which were treated with outpatient coagulation. At 20 mo after his initial presentation, he had another recurrence. Although cytology was still normal, the tumor appeared more aggressive on cystoscopy than it had been initially. Another TURB revealed multiple small pTa lesions, but now of high grade. The detrusor was free of disease. Owing to his urgency complaints, no additional intravesical therapy was given. At 26 mo, he had a fourth recurrence and was referred to Nijmegen.

An outpatient cystoscopy revealed multiple small, aggressive-looking tumors. TURB confirmed that his tumors were pTa high grade and more numerous than was noted on the cystoscopy the month before. His voiding complaints had essentially resolved, with a capacity of about 300 ml, and his nocturia decreased to two times per night. For the sake of this discussion, we will suppose that bacillus Calmette-Guérin (BCG) is unavailable (as has happened in recent BCG shortages).

At this point, it is important to consider whether this represents disease progression. His status has moved from low grade to high grade, still pTa, but this indeed can be considered progression based on the definition of the International Bladder Cancer Group [1]. Since no PDD was used, random biopsies could have been taken, but since cytology was normal, not taking biopsies can be defended.

The question is, what should be the next steps regarding additional therapy? The patient has already had 6 mo of MMC, so what is next—one instillation of chemotherapy? Continue with chemotherapy? Start with BCG? What do you do if no BCG is available?

2. Option A: if BCG is unavailable, radical cystectomy should be recommended

2.1. Evidence

The first diagnostic question is: what is the risk level of this patient—high risk or very high risk? Ta high-grade disease represents 7% of all Ta confined disease [2]. However, the pathologic diagnosis of Ta or T1 is difficult, and the likelihood of a diagnostic concordance between the local and the central pathologists within European Organisation for Research and Treatment of Cancer (EORTC) studies was only 23%, which is very low. Ta of high grade is found to be understaged at cystectomy in one-third of cases [3]; concomitant carcinoma in situ (CIS) is undetected in >30% of the cases, and of patients with multifocal Ta high-grade disease, about 8% already have micrometastatic disease in the lymph nodes at the time of the first diagnosis.

Regarding prognosis, multifocality together with size is a prognostic factor, and this patient has multifocal disease. Patients with multifocal Ta high-grade lesions have the third highest risk of both recurrence (40% in 1 yr) and progression (5% at 1 yr, but 17% at 5 yr), and the EORTC risk table shows a concordance with these statistics [3].

According to the European Association for Urology (EAU) 2016 guideline update for non-muscle-invasive bladder cancer (NMIBC) [4], Ta high-grade disease with multiple lesions falls into the high-risk category. Primary multifocal Ta high-grade lesions are at a high risk, but *recurrent* multifocal lesions plus CIS are at a higher risk, and the higher-risk patients are eligible for radical cystectomy, since the presence of CIS with Ta high-grade lesions will increase the risk of progression to 17% at 1 yr and 45% at 5 yr. In this patient, CIS was not looked for, nor were biopsies taken. Therefore, a good investigation and a correct diagnosis are imperative. TURB must be complete and adequate, and the use of PDD or narrow-band imaging is suggested, to improve the diagnosis of CIS. Metastases can occur prior to muscle invasion through lymphovascular invasive spread in these patients.

2.1.1. Recommendation

The evidence favors radical cystectomy for this patient in the absence of BCG, and removal of the lymph nodes at this stage may be curative. Indeed, radical cystectomy is the best option for recurrent multifocal Ta high-grade disease after MMC alone or MMC via electromotive drug administration (EMDA) or radiofrequency-induced chemohyperthermia (rf-CHT). In fact, about 20–30% of patients treated with MMC or EMDA recur after 1 or 3 yr, respectively [5]. A Cochrane review concluded that EMDA may delay time to recurrence, but the impact on other endpoints was uncertain due to study limitations [6]. However, a potential role was suggested in settings where BCG was not available (for example).

Disease-specific survival with cystectomy for Ta high-grade disease ranges from 85% to 90%, and delaying cystectomy is associated with reduced cancer-specific survival in these patients. The Denzinger et al's [7] series reported that with early cystectomy there is 78% cancer-specific survival at 10 yr, whereas with delayed cystectomy there is 51% survival. Oddens et al. [8] reported that at least one-third of patients receiving doxorubicin, epirubicin, or MMC have disease recurrence by 1 yr, and the probability of disease progression is high.

2.2. Conclusion

The argument is for immediate cystectomy for a young patient with more than five tumors, diameter >3.0 cm, and concomitant diffuse CIS in the absence of BCG immunotherapy. For these patients, an acceptable approach may be orthotopic neobladder with prostate and seminal sparing, preserving continence, potency, and probably fertility. For a recurrent tumor after chemo- or device-assisted therapy, cystectomy is adequate. Although radical cystectomy is an overtreatment in 50% of these patients, any initial informed discussion about treatment of multifocal Ta high-grade disease in fit patients should include the possibility of radical cystectomy.

3. Option B: alternative intravesical therapy can be considered

The question is how to treat a 71-yr-old male, heavy smoker, with multifocal Ta high-grade disease if BCG is unavailable.

3.1. Evidence

According to the EORTC risk tables [1], this patient is at an especially high risk of disease progression, but the recurrence rate is about the same as for low-grade disease. This contrasts with the results in the registry at my institution (Akademiska sjukhuset), where out of 581 of such patients, the mean recurrence rate was 41%, but occurrence of progression was 9%. However, this patient has already had recurrences, so the progression risk will probably be higher in him.

The patient has already received a course of chemotherapy with MMC. In our study almost 20 yr ago [9], we found that BCG was better than MMC for treating CIS, but for papillary tumors, as in this patient, there was no significant difference. Therefore, MMC was a good choice for initial treatment in this patient, but in this case it failed.

Since BCG is not available for this case, we have to look at other drugs. In a systematic review of six trials with 704 patients [10], three of the trials compared gemcitabine versus BCG. The efficacy for gemcitabine and BCG in intermediate-risk patients was similar, but this patient is at a high risk and gemcitabine was found to be less effective than BCG in high-risk patients. However, in the absence of BCG, gemcitabine is at least a promising option, although more prospective, controlled trials are needed to assess its efficacy and dosage.

The Finnish Multicentre Study Group [11] and the FinnBladder VI trial [12] used a combination of epirubicin and interferon in patients with low-grade Ta or T1 disease. The former group found a promising effect for the combination; the latter group found similar benefit for progression, but for recurrence BCG was significantly more effective. Likewise in the Nordic bT1 trial [13], randomizing epirubicin versus BCG, there were more recurrences in the epirubicin/interferon combination than in the BCG arm, but 30% of the BCG-resistant patients were recurrence free on the combination after 2 yr; therefore, this would also be an option, although there were no patients similar to the present one with Ta tumors in Nordic T1.

Another possibility in the absence of BCG could be a combination of gemcitabine and either MMC or docetaxel. This has been tried in a few small trials, with few patients, usually as salvage therapy after failure of BCG [14]. Little is known about the long-term efficacy of these combinations; about a third of the patients seem to be responding after 3 yr, and the toxicity seems acceptable. However, prospective controlled trials are needed for these combinations.

A Cochrane Database systematic review of EMDA [6] included only three trials because the quality of all the others was thought to be too low. The same principal investigator was a pioneer in this and conducted all three of the reviewed trials, but the conclusion was that there was uncertainty regarding serious adverse events and the quality of the evidence for efficacy could not be properly estimated. In other words, more rigorous trials are needed for proper assessment of this approach.

Chemohyperthermia is another device-assisted treatment application. The latest in a series of yearly systematic reviews looked at 15 publications [15], and found that while this method is promising, evidence is limited due to a lack of high-quality randomized trials. Thus, the value of both of these device-assisted MMC applications is hindered by poor supporting evidence

Finally, experimental drug delivery systems (eg, Taris, a device inserted into the bladder where it slowly secretes chemotherapy, or Urogel, where chemotherapy is released in a biogel) could be an option in the future, but for now they are available only for application in controlled trial settings.

3.2. Conclusion

In conclusion, treatment for this patient is a challenge in the absence of availability of BCG. Disease progression is a real problem because this patient has high-grade tumors. Chemotherapy combinations, such as gemcitabine and docetaxel, and epirubicin and interferon, have demonstrated possible efficacy in trials. Of course, these combinations have not really been shown to be better than BCG, but in its absence, they can and should be given careful consideration. Device-assisted intravesical therapy is becoming a commonly considered option, and quite a few large trials are ongoing, but more randomized trial results are needed. There are new immunotherapy options that have been proved to be successful for advanced bladder cancers, but trials are needed, and definitive results are still awaited.

4. Discussion of treatment options

Although Ta high-grade NMIBC is not very frequent and experience therefore is limited, both the EAU and the American Urological Association guidelines [4,16] provide clear therapeutic recommendations: this tumor is considered to be of high risk, and these patients should be treated with a re-TURB and maintenance BCG in case of an ongoing complete response. The only difference is that the additional benefit of the 2nd and 3rd years of BCG treatment should be weighed against added costs and inconveniences according to the EAU guideline.

This leaves a question of what to do if there is no BCG and there is recurrent high-grade Ta disease, as in this patient. A conservative approach would mean a high chance of additional recurrences. In the absence of progression, this approach is inconvenient for the patient; it will mean additional resections and more chance of bladder dysfunction, which although already present was somewhat improving. From an oncologic point of view, there is little risk; however, if there is progression, this worsens the prognosis. Especially if there is progression to muscle-invasive disease, cancer-specific survival falls dramatically from around 90% in NMIBC to around 35% after progression to muscle-invasive disease, and 35% is only half of that of patients with muscle-invasive disease and no history of NMIBC [17].

It is of utmost importance to discuss all these factors and risks with the patients and their families, and to

include a discussion about the option of radical surgery. If the conclusion is to proceed with conservative treatment, MMC remains a viable option. MMC, if used appropriately, remains an effective drug [18]. Newer and other chemotherapeutic drugs have been assessed in small series, such as gemcitabine and taxanes, and combination chemotherapies using these agents are under investigation, such as the new class of PD(L)-1 checkpoint inhibitors. Device-assisted therapies (EMDA and rf-CHT) need further research. In a randomized controlled trial with intermediate- and high-risk NMIBC patients, rf-CHT has been compared with BCG [19]. In the per-protocol analysis, rf-CHT was found to be safe and effective, with significantly higher 24-mo recurrence-free survival compared with BCG, although a major limitation of this trial was premature closure. Another trial [20] did not find a difference in patients with recurrence following induction/maintenance BCG, although this trial also had major limitations, such as patient selection, treatment regimens, and outcome measurement.

If the discussion with the patient concludes with a decision to go with a more aggressive approach, then cystectomy is certainly defendable, although as mentioned, this is a major surgery with morbidity and mortally. An alternative might be bladder-preserving chemoradiation [21]. This is contraindicated in cases of concomitant CIS and hydronephrosis, but without CIS it might be an option in this man.

5. Final treatment of the case

For the patient in this case, I applied rf-CHT. After six sessions of MMC 20 mg b.i.d, starting summer 2017, he is recurrence free until the time of writing (end of 2018) with maintenance treatment with MMC 20 + 20 mg once every 6 wk, with acceptable bladder function.

Author contributions: Johannes Alfred Witjes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Witjes, Brausi, Malmstrom.
Acquisition of data: Witjes, Brausi, Malmstrom.
Analysis and interpretation of data: Witjes, Brausi, Malmstrom.
Drafting of the manuscript: Witjes, Brausi, Malmstrom.
Critical revision of the manuscript for important intellectual content: Witjes, Brausi, Malmstrom.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: Witjes.
Supervision: Witjes.
Other: None.

Financial disclosures: Johannes Alfred Witjes certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgments

Origin of Academic Content: This article has been developed from an interactive, multifaculty scientific session presented during the 33rd Annual EAU Congress in Copenhagen, March 2018, with acknowledgment to the co-chairs of the session: H. Barton Grossman, MD; Ashish Kamat, MD; and Arnulf Stenzl, MD, PhD. Acknowledgement is also given to Dr. Grossman and Dr. Kamat for their development of the multifaculty, interactive format of this article, and for their editorial review of the draft manuscript for submission to *European Urology Oncology*.

Open Access: Cepheid® provided funding to allow Open Access for this article.

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