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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Predictors of response to BCG therapy in non-muscle invasive bladder cancer

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SUMMARY
Intravesical BCG (*Bacillus Calmette–Guerin*) therapy represents the therapy of choice for intermediary- and high-risk non-muscle invasive bladder cancers after transurethral resection. However, up to 40% of these patients do not show adequate response to the therapy (BCG failure) and 15% of them experience the progression of the disease to muscle-invasive bladder cancer. In such cases, radical cystectomy is indicated. Studies suggest that early radical cystectomy in patients with BCG failure is followed by better survival compared to delayed radical cystectomy. The prediction of response to BCG therapy could enable early identification of patients on which this therapy would have no effect and who should undergo early radical cystectomy.
Keywords: bladder cancer; intravesical BCG therapy; BCG failure; radical cystectomy

INTRODUCTION

Non-muscle invasive bladder cancers (NMIBC) are malignant urothelial bladder cancers that do not invade the detrusor. NMIBC are divided into pathological subcategories – Ta and Tis (which are limited to urothelium) and T1 (which invades lamina propria) [1]. After transurethral resection of bladder tumor (TURBT), T1 and Tis tumors are much more likely to cause recurrence or disease progression.

In order to assess the individual risk for progression of the disease, several scoring systems and tables of risk have been developed [2]. The choice of the adequate modality of treatment is made on the basis of risk groups. For the low-risk tumors, it is recommended to use one dose of intravesical chemotherapy immediately after TURBT. For the intermediate-and high-risk tumors, it is recommended to use adjuvant BCG intravesical therapy after TURBT, during the period of 1–3 years, depending on the level of risk [3].

Up to 40% of patients with intermediate- and high-risk NMIBC do not show adequate response (absence of refractory disease after the first or the second induction cycle of BCG) to the therapy (BCG failure) and 15% of patients experience the progression of the disease to muscle-invasive bladder cancer [4]. Early radical cystectomy is indicated for patients who did not show the adequate response to BCG therapy. Ninety-two percent of patients with BCG failure reach two-year survival if radical cystectomy is performed in a period shorter than two years since the beginning of BCG therapy. If radical cystectomy is performed later than two years since the beginning of BCG treatment, two-year survival rate falls down to only 56% [5]. Since the postponement of radical cystectomy is accompanied by significantly lower survival rate, the proper identification of patients who have a high risk of BCG failure is crucially important.

UNSUCCESSFUL RESPONSE TO INTRAVESICAL BCG THERAPY – BCG FAILURE

BCG failure is defined as recurrence or persistence of urinary bladder carcinoma of high-grade during or after BCG therapy [3]. The appearance of low-grade relapses during or after BCG therapy does not represent a BCG failure. Having in mind the heterogeneity of bladder tumors that show BCG failure, they are further classified into three specific types: BCG-refractory, BCG-relapse, and BCG-intolerant.

BCG-refractory condition is defined as the impossibility of achieving disease-free state or as persistence of high-grade urinary bladder carcinoma six months after the initiation of the adequate BCG treatment [6].

BCG-relapse tumors represent high-grade tumors which reappear after the disease-free status is attained, upon the completion of BCG therapy. BCG-relapse failure may be sub-classified as early (during the first 12 months from the initiation of BCG therapy), intermediary (12–24 months from the initiation of therapy), and late (after more than 24 months) [3].

BCG-intolerant state represents the persistence of the disease when adequate BCG therapy cannot be applied because of its side effects and complications [6].

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BCG-unresponsive tumors encompass all BCG-refractory and some BCG-relapse tumors (TaT1/HG tumors which reappear in the period of six months from the completion of BCG therapy or the appearance of *carcinoma in situ* (CIS) in the period of 12 months from the completion of BCG therapy). BCG-unresponsive patients are a sub-group of patients with the highest risk of recidivism and disease progression, so the continued administration of BCG therapy would have no effect on them [6].

PREDICTORS OF RESPONSE TO BCG IMMUNOTHERAPY

Predictors of response can be divided into clinical-pathological, molecular, and genetic. Studies of interrelation between clinical-pathological factors and disease progression/recurrence risks enabled the creation of a scoring system for disease progression and recurrence risk assessment. European Association of Urology (EAU) NMIBC 2021 scoring model enables risk assessment only in relation to disease progression, but not in relation to recurrence [2]. On the other hand, Club Urológico Español de Tratamiento Oncológico (CUETO) prediction model enables both progression and recurrence prediction after 12 intravesical BCG instillations, administered in the period of five to six months after TURBT. This model incorporates seven clinical-pathological parameters: T stage (Ta, T1), grade (G1, G2, G3), number of tumors (< 3, > 3), concurrent carcinoma *in situ*, presence of recurrent tumors, age (< 60, 60–70, > 70), sex [7]. In comparison to the European Organisation for Research and Treatment of Cancer (EORTC) model, recurrence risk assessed on the basis of 2006 CUETO model (based on six clinical-pathological factors) is lower for all risk groups, while the risk of progression is lower only for high-risk patients. This points to the protective effect of BCG therapy. Additional studies confirmed that CUETO model is more accurate, although it has been noted that both models overestimate the progression and recurrence risk for high-risk patients [7, 8]. Seeing that EORTC prediction model is based upon the results of the trials where the patients were predominantly treated with intravesical chemotherapy, its reliability for the prediction of BCG-failure is limited. Conversely, the shortcoming of the CUETO model is the fact that it is based upon the results of the trials where the patients were predominantly treated with adjuvant BCG therapy over the period of one year. For that reason, this model does not allow for a clear prediction of response to BCG therapy in high-risk patients, since they should receive BCG therapy during three years [9].

Many authors studied immunomodulatory effects of sex hormones and their influence on the effect of BCG therapy. The studies upon which the CUETO model is based have shown that female sex represents an important recurrence predictor [8].

A trial from 2007, which included 805 patients with high-grade Ta, T1, or CIS treated with intravesical BCG therapy, showed gradual attenuation of therapy response connected with age [10]. Despite this, BCG shows higher efficacy than intravesical chemotherapy for patients older than 70 years with TaT1 tumors of intermediary and high risk [11].

Ferro et al. [12] detected that obesity is significantly connected with an increased risk of recurrence (hazard ratio, HR: 5.33) and progression (HR: 2.52) of disease in patients with T1G3 tumors.

Smoking has a proven immunosuppressive effect, due to which it can represent one of the additional factors suspected of having an impact on the effect of intravesical BCG therapy [13].

In a study from 2020, De Jong et al. [14] examined the connection between sub-staging T1 and the occurrence of BCG failure. In relation to the degree of invasion of lamina propria, T1 tumors are divided into two groups – microinvasive and extensively invasive. Extensive invasion of lamina propria was statistically significantly related to the occurrence of BCG failure ($p = 0.002$) [14]. In a study by Herr et al. [15], residual T1 tumors were detected in 26% of patients after a second-look TURBT (indicated for high-risk tumors four to six weeks from the initial resection). Despite the administration of BCG therapy, disease progression to muscle invasive bladder cancer was detected in 82% of patients from this group. These data imply that for a certain number of patients with high-grade T1 tumors and residual T1 tumors after a second-look TURB an early cystectomy is a better therapeutic strategy than BCG therapy and other bladder-sparing strategies [16].

Inflammatory response triggered by the cellular immune system is the basis of anti-tumor effect of BCG immunotherapy [16]. Several authors assumed that the determination of a patient's capability to generate an adequate immune response would be an important predictor of response to BCG therapy. Multivariate analysis showed that interleukin-2 (IL-2) level in urine represents an independent prognostic factor for the occurrence of response to BCG therapy [17]. In a study authored by Saint et al. [18], patients with urinary IL-2 concentration below 27 pg/µmol of creatinine after the induction cycle of BCG therapy had a statistically significantly higher risk of recurrence in comparison to the patients with higher values ($p = 0.0009$). Kaempfer et al. [19] analyzed the expression of genes for IL-2 in mononuclear cells of peripheral blood during BCG therapy, by analyzing the appearance of IL-2 messenger RNA (mRNA). By comparing the patients with remission and with relapse of the disease, they noticed a statistically significantly higher level of IL-2 mRNA induction in patients with remission ($p = 0.0001$). Multivariate analysis showed that IL-2 mRNA induction has also been associated with the prolonged disease-free period ($p = 0.0001$) [19]. IL-8 is also a potential biomarker of response to BCG therapy. A study from 2017 showed with statistical significance that recurrence-free survival (RFS) was shorter in patients with higher levels of IL-8 in comparison with patients who had lower levels of this cytokine (14 months *vs.* > 78.4 months, $p = 0.004$) [20]. Programmed death-ligand 1 (PD-L1) is a transmembrane protein which can be expressed on the surface of a tumor and tumor-infiltrating immune

cells. Patients with CIS treated with adjuvant BCG therapy display an increased expression of PD-L1 in the group of BCG non-responders in comparison to BCG responders (p = 0.035; OR: 0.1204; CI 95%: 0.0147–1.023) [21]. The proteins of the cell cycle (TP53, retinoblastoma protein, and Ki-67) have also been analyzed as potential immunohistochemical predictors of response to BCG therapy. A meta-analyses from 2016 and 2018 showed the connection of the TP53 and Ki-67 hyperexpression with the disease progression in NMIBC patients [22].

Genetic polymorphisms may influence the response on intravesical BCG therapy. Polymorphisms of nucleotide excision repair genes, characterized by the appearance of variant alleles *XPA*, *XPC, ERCC6, XRCC1*, and *ERCC2*, are associated with the decreased RFS in patients who underwent BCG therapy [23]. A systemic review from 2016 points out that polymorphisms of IL-6 and IL-4 genes are associated with an increased risk of recurrence during BCG therapy, while polymorphisms of IL-8 and tumor necrosis factor-α genes are statistically associated with the decreased risk of recurrence [24]. Decobert et al. [25] point out that the appearance of two variant alleles of the natural resistance-associated macrophage protein gene (*NRAMP-1*) is statistically significantly associated with the decreased RFS in patients who received BCG therapy. Although the detection of genetic polymorphisms has significant potential for predicting response to BCG therapy, these results should be further confirmed.

CONCLUSION

The prediction of response to BCG therapy could enable a better selection of patients for this type of therapy, as well as the early identification of patients on which this therapy would have no effect and who should undergo early radical cystectomy. Clinical practice showed that, most commonly used, clinical-pathological parameters are often insufficient in relation to the prediction of response to BCG therapy. Therefore, a large number of studies are now focusing on molecular and genetic predictors. Cytokines, among which IL-2 in particular, and also the studies with immunohistochemical markers (in particular PD-L1/PD-1) show promising results. Further research and inclusion of new clinical-pathological predictors, as well as larger studies on molecular and genetic markers, are necessary in the future.

Conflict of interest: None declared.

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Предиктори одговора на *BCG* терапију код карцинома мокраћне бешике без захватања мишићног слоја

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САЖЕТАК

Интравезикална *BCG* (*Bacillus Calmette–Guerin*) имунотерапија представља терапију избора код карцинома мокраћне бешике без захватања мишићног слоја умереног и високог ризика после трансуретралне ресекције. Међутим, код чак 40% ових болесника изостаје одговор на *BCG* терапију (енгл. *BCG failure*), а код 15% њих долази до прогресије болести у карцином мокраћне бешике са захватањем мишићног слоја. Код болесника који нису одговорили на *BCG* терапију индикована је радикална цистектомија. Примена ране радикалне цистектомије код ових болесника праћена је бољим преживљавањем у односу на одложену радикалну цистектомију. Предикција одговора на *BCG* терапију би омогућила рану идентификацију болесника код којих она не би имала ефекта и који би захтевали примену ране радикалне цистектомије.

Кључне речи: карцином мокраћне бешике; интравезикална *BCG* терапија; изостанак одговора на *BCG*; радикална цистектомија