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Novel therapies of treating non-muscle invasive bladder cancer when BCG therapy turns out to be insufficient – literature overview

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ABSTRACT

Introduction: Bladder cancer is one of the most common cancers in the world. There are two forms of bladder cancer: non-muscle invasive bladder cancer and muscle invasive bladder

cancer. A common treatment method for non- muscle invasive bladder cancer is intravesical BCG (Mycobaterium bovis) therapy after radical tumor resection. It is estimated that half of patients will have an insufficient response to BCG treatment. Patients using this type of therapy also report side effects more and more often.

Aim of the study: The aim of this article is to discuss the latest discoveries in the treatment of non-muscle invasive bladder cancer when BCG therapy is insufficient.

Material and Methods: The paper was created based on the PubMed and Scholar database. The literature was reviewed using the key words: „bladder cancer"; „BCG"; „treatment"; „side effects"; „novel therapies".

Results: The research shows that novel therapies are effective and safe compared to the use of BCG. In such patients, atezolizumab, metformin or intravesical magnesium sulfate infusions may be used as an alternative. An innovative solution is the use of HIVEC - heated chemotherapy administered intravesically. There are also drugs that potentiate the action of BCG, making the therapy more effective. These include: sasanlimab and rapamycin. Due to the side effects experienced by patients, the use of intravesical BCG is often replaced with intravesical infusions of chemotherapy drugs. **Conclusion**: The research shows that novel therapies are effective compared to the use of BCG. Unfortunately, more research is needed to standardize the treatment of non-muscle invasive bladder cancer.

Key words: „bladder cancer"; „BCG"; „treatment"; „side effects"; „novel therapies"

Introduction

Bladder cancer is one of the most common cancers worldwide. The number of new cases diagnosed each year worldwide is 549 000, while approximately 200 000 patients die each year from this diagnosis (1).

There are two forms of bladder cancer. Invasive bladder cancer, which infiltrates the muscle membrane, and non-invasive, which does not infiltrate the muscle membrane (2). Of bladder cancers, up to 75% are non-invasive bladder cancer (3), the most common type being urothelial carcinoma. Interestingly, progression to non-invasive bladder cancer can occur within 2 years of diagnosis in 1/5 of patients, which is why effective treatments for this disease are so important (4).

The most important factors favouring the development of bladder cancer are environmental factors, most notably smoking and occupational exposure. Working in aluminium, rubber production or firefighting and exposure to: smoke, gamma radiation, arsenic, dyes such as auramine (5). Genetic factors also have a significant impact on the development of this type of cancer. Approximately 4 % of patients diagnosed with bladder cancer have a first-degree relative with the same diagnosis. It is also worth noting that drugs such as cyclophosphamide, chlornazine or Schistosoma infection may contribute to the development of this type of cancer. However, studies indicate that almost 50 % of bladder cancer cases are caused by smoking (6). The effect of diet on bladder cancer risk and subsequent treatment outcomes is also currently being examined. Studies have shown that a diet low in fruit and low in vegetables is associated with an increased risk of developing bladder cancer (7).

The primary treatment regimen for patients with non-muscle invasive bladder cancer is transurethral resection of bladder tumour (TURBT) (8). The European Society of Urology recommends immunotherapy with BCG (Bacille Calmette-Guerin) in patients with non-muscle-invasive bladder cancer. Many in vitro studies report a direct cytotoxic effect of BCG on tumour cells through induction of apoptosis or oxidative stress (9). BCG binds to urinary tract epithelial and tumour cells via fibronectin. This triggers a local immune response supported by granulocytes, macrophages and Th lymphocytes (10). Describing this process in more detail, urinary tract epithelial cells bind to BCG and present it to the human immune system, which then eliminates the tumour cells through direct cytotoxicity (11). In cases of cancer infiltrating the muscle membrane, radical cystectomy is usually performed (8).

BCG (Bacille Calmette-Guerin)

BCG is a live, attenuated strain of Mycobacterium bovis, used mainly as a vaccine against tuberculosis (12). Work on the BCG vaccine began in 1908 (13), and the first dose to the human body was administered in 1921 (14). Research into the anti-tumour properties of BCG began in 1929, when Pearl observed a lower incidence of cancer in TB patients. The test subjects were observed at Johns Hopkins Hospital. From 1959 onwards, studies began on mice, which showed a lower incidence of cancer in these rodents treated with BCG (15). In contrast, in humans, the BCG vaccine was first used to treat bladder cancer in 1976 (12). BCG is used in patients with non-muscle invasive bladder cancer with moderate to high risk of recurrence after tumour resection (16). Currently, 6 treatments of BCG administration are recommended at weekly intervals during the induction phase, followed by 3 series also at weekly intervals at 3,6,12,18, 24, 30, 36 months after tumour resection as maintenance treatment (17).

The aim of immunotherapy, or the use of BCG, is to remove tumour lesions that may have remained after TURBT. BCG leads to a reduction in the residual tumour mass and prevents recurrence and progression of the disease (18).

Approximately 5-9% of bladder cancer patients drop out of treatment with BCG due to side effects that lead to a reduced quality of life. Importantly, it has been proven that 50% of patients using a treatment regimen with BCG have an inadequate response to treatment, and about 70% of patients using this therapy may develop local or systemic side effects (19).

Approximately 5 % of patients using BCG may develop disseminated tuberculosis. Cases of septicaemia following this type of treatment have also been reported (20). Therefore, therapy with BCG should be strictly observed. BCG infusion should be started 2 weeks after transurethral resection of the tumour. If sepsis develops, immunotherapy should be stopped immediately (21). It is worth noting that mild effects of BCG therapy: fever, mild cystitis, malaise are common. Effective measures to alleviate cystitis symptoms are anticholinergics and non-steroidal anti-inflammatory drugs. If symptoms persist for more than 48 hours, BCG therapy should be discontinued (21). Rarely, severe complications and spread of BCG throughout the body by the blood-borne route occur. Lung, liver, musculoskeletal involvement is most common in this mechanism (22). Vascular complications in the form of aneurysms are observed with increasing frequency. They are most commonly located in the aorta, but also occur in the ulnar and femoral arteries (23). There are also known cases of leukopenia, thrombocytopaenia, liver dysfunction and splenic enlargement several weeks after intravesical BCG administration (24). In addition, it has been observed that 0.7 per cent of patients treated with BCG for non- muscle invasive bladder cancer developed interstitial pneumonia (25).

Materials, Methods and Purpose:

The aim of this article is to discuss the latest discoveries in the treatment of non-muscle-invasive bladder cancer when BCG therapy is insufficient and radical cystectomy is not possible for various reasons. During the search of the PubMed and Scholar database the following keywords were used: „bladder cancer”, „BCG”, „treatment”, „side effects”, „novel therapies”.

New treatment options when BCG therapy becomes insufficient

A gene therapy has been introduced for the treatment of non-muscle invasive bladder cancer. This is a DNA vector encoding interferon - 'Nadofaragene fradenovec'. The therapy is particularly applicable to patients with high-risk tumour recurrence after resection who do not respond to BCG therapy (26). The aforementioned drug is nothing more than a recombinant adenovirus. In a study conducted at 33 centres in the USA, this recombinant interferon alfa-2b

protein was shown to be well tolerated by patients and to be effective in the treatment of bladder cancer not responding to BCG therapy. The study involved 157 patients who were administered 75 ml of perofaragen firadenovec intravesically. Patients were included in the study between 19 September 2019 and 24 May 2019. The mean age of the subjects was 71 years. Patients were assessed regularly every three months with cytology and cystoscopy. In the absence of recurrence, the interferon dose was repeated at 3, 6, 9 months. In contrast, subjects found to have relapsed were eliminated from the experiment. Twelve months after the first dose of the drug, a bladder biopsy was performed. Patients without a diagnosed recurrence were allowed to use the drug once every 3 months. The study is still continuing. Relapses at any stage of therapy were observed in 104 patients, while relapse-free survival one year after the start of therapy was approximately 31% (27).

Another major problem in patients treated for non-muscle invasive bladder cancer is the lack of response to treatment after BCG vaccine administration. As an alternative to this phenomenon, gemcitabine can be administered in patients who have not had a sufficient response to treatment after BCG administration. A study was conducted at the Urology Clinic in Italy, in which patients were given gemcitabine at a dose of 2000 mg in 50 ml of saline once a week for six weeks after not achieving a sufficient response to treatment with BCG. This was followed by maintenance therapy, during which patients received gemcitabine treatment every month for 12 months. The study ran from February 2012 to October 2018. Thirty-six patients were included in the study. The mean age of the subjects was 70 years. The group comprised 29 men. The first assessment of the patients was 3 weeks after the induction treatment was introduced, and subsequent cystoscopies and cytologies were performed at equal intervals every 3 months until the end of the study. In the study group, approximately 32 patients completed the 6-week induction therapy with BCG, while 10 patients experienced treatment failure and 22 patients relapsed during the maintenance phase of treatment. Patients received gemcitabine therapy approximately 2 months after the last BCG administration. The follow-up period of the patients was approximately 27 months. It was observed that 11 patients had relapsed without progression. The progression-free survival time after 12 and 24 months was just over 80%, while 14 patients showed tumour progression. It appears that gemcitabine therapy is an effective treatment option and is a good alternative for patients who wish to avoid radical cystectomy. Unfortunately, the introduction of this therapy requires more studies to establish more specific treatment standards (19).

Another treatment for BCG-unresponsive bladder cancer with a high risk of recurrence is the use of atezolizumab, which can be a great alternative for patients who are ineligible for radical cystectomy or who have refused such treatment. Furthermore, it should be noted that radical cystectomy is associated with high perioperative morbidity and mortality. Approximately 5% of patients undergoing radical cystectomy develop death within 90 days of surgery. In the US, a study of 129 patients with non-muscle invasive bladder cancer was conducted, who were given 1200 mg of atezolizumab every three weeks for 12 months. Patients were included in the study between 7 February 2017 and 5 July 2019. A mandatory bladder biopsy was performed at 6 months after treatment inclusion to assess treatment efficacy. Only seven patients had disease progression to muscle invasive bladder cancer. Radical cystectomy was performed in all of these patients. Metastases in the pelvic lymph nodes were noted in four of them. Nevertheless, atezolizumab appears to have high efficacy and safety in the treatment of non-muscle invasive bladder cancer refractory to BCG therapy (28).

Intravesical infusions of magnesium sulphate (MgSO4) may be another effective treatment for patients refractory to BCG therapy. The efficacy of MgSO4 was evaluated in a study conducted at All Zahraa Hospital in Beirut between January 2018 and July 2021, involving eight patients. Patients included in the study refused cystectomy or were ineligible for this procedure. The mean age of the subjects was 66 years. MgSO4 was administered approximately four months after the last administration of BCG. The sulphate solution was administered at regular intervals every 2 weeks for 6 months and then once a week for 12 months. Cystoscopic follow-up was performed every 3 months. The follow-up of the patients lasted approximately 29 months. Approximately 63% of the patients achieved a complete response to treatment, approximately 25% of the subjects had a partial response, while no patient experienced disease progression. The mechanism of action of MgSO4 on tumour cells is not fully known, more studies are needed to demonstrate its mode of action, while the results of the study show its efficacy in the treatment of non- muscle invaisve bladder cancer, which is resistant to BCG therapy (29).

Metformin is another drug used in the treatment of non-muscle invasive bladder cancer resistant to BCG therapy. In addition, it is the most commonly used hypoglycaemic drug for the treatment of type II diabetes. Some clinical studies have shown that it can prevent the development of malignant tumours to some extent. Its mechanism of action is not precisely explained. Metformin directly inhibits tumour angiogenesis by inhibiting endothelial cells and regulates the expression levels of cell cycle regulatory proteins in the G0/G1 phase leading to

its arrest and inhibition of angiogenesis. However, further research is needed to determine safe doses of metformin for the treatment of bladder cancer and whether it can be an effective drug for the treatment of recurrent bladder cancer (30).

HIVEC - is an innovative treatment for non-muscle invasive bladder cancer resistant to BCG therapy. HIVEC is nothing more than heated chemotherapy administered intravesically. It is believed that hyperthermia increases the permeability of the bladder cell membrane, allowing the chemotherapy to reach the bladder wall more quickly. A study was conducted in the Netherlands and the UK, involving 56 patients. The average age of the study participants was approximately 73 years. The study participants were followed from October 2014 to March 2020. Patients had regular cystoscopy, cytology and CT urography once a year to verify tumour recurrence. During the study, patients received 40 mg of mitomycin C diluted in 50 ml of distilled water heated to 41-43 degrees Celsius. Therapy consisted of an induction phase lasting 4-6 weeks - 1 dose per week, followed by maintenance treatment - 1 dose per month. Three months after the first dose of the chemotherapeutic agent, cystoscopy and cytology were performed to assess the efficacy of the treatment. Thereafter, such examinations were performed 4 times a year for the first 2 years after the start of treatment. In addition, patients underwent a CT scan once a year. The 1- and 2-year recurrence-free survival of the patients was 53%. In contrast, tumour recurrence was observed in 36 patients throughout the study. The data presented here allow us to conclude on the efficacy of HIVEC in the treatment of non-muscle invasive bladder cancer refractory to BCG therapy. However, the introduction of this therapy requires more studies to standardise the treatment protocol (1). Another study tested the efficacy of BCG use compared to HIVEC and chemotherapy administered via an EMDA generator. The study included 183 patients diagnosed with non-muscle invasive bladder cancer. The group that received BCG comprised 63 patients, HIVEC 61 and EMDA 59. Patients were followed up for an average of 24 months. The absence of disease progression in the highest percentage was observed in the EMDA group with about 98%, followed by HIVEC with about 96% and in third place BCG with about 93% of patients. Indeed, the data presented here indicate that the use of new treatments for non-muscle invasive bladder cancer are effective and may be an excellent alternative for patients wishing to avoid cystectomy (31).

Attempts have also been made to use nanoimmunotherapy in patients unresponsive to treatment with BCG. A study involved 44 patients. The average age of the subjects was 65 years. After a follow-up of approximately 24 months, surprising results were reported. No progression of the disease was observed in any patient, while more studies need to be conducted to verify

this method in the prevention of bladder cancer recurrence (32). There are drugs that potentiate the effect of BCG and thus make the response to treatment more effective. In an experiment conducted in the USA, the study participants received the drug N - 803, an interleukin-15 agonist, together with BCG. Participants in the study were collected from July 2014 to July 2015, while patients underwent continuous follow-up until 15 January 2021. Nine patients participated in the study. The majority were men aged approximately 65 years. Patients enrolled in the study had undergone transurethral resection of the tumour and had not yet received BCG therapy. During the study, patients received a standard dose of BCG - 50 mg combined with gradually increasing doses of N-803. BCG with N-803 was administered at weekly intervals for six weeks during the induction phase, followed by a maintenance dose for three weeks. The first evaluation of the subjects occurred 3 months after the start of treatment. In 7/9 patients there was a complete response to treatment, no relapse, no progression of disease. In the remaining two patients, a lesion was observed on cystoscopy that was ultimately not classified as a neoplastic lesion. Furthermore, no patient experienced disease progression. The new drug N-803 appears to be an effective BCG potentiator; however, studies on a larger population are needed for this method to become the standard of care for this type of cancer (33).

Sasanlimab is a humanised immunolobulin G4 monoclonal antibody that binds to PD1 and prevents PD-L1/L2 from binding to PD-1. Patients diagnosed with bladder cancer express PD-L1. A study is currently underway to test the efficacy of sasanlimab in combination with BCG compared to a group that received BCG alone - 25 cycles over 12 weeks after transurethral resection of a tumour in whom a high risk of tumour recurrence after resection is anticipated. The study included 1,000 participants. The use of sasanlimab may enhance the antitumour effect of BCG in bladder cancer patients at high risk of recurrence, while more research is needed to develop treatment standards using this method (34).

Rapamycin may be another agent that enhances therapy with BCG. Its mechanism of action is to inhibit the activation of lymphocytes so that post-vaccination reactions do not develop. A randomised double-blind study involving 31 patients was conducted. 87% of the subjects were male. During the experiment, 0.5 mg or 2 mg per day of rapamycin was administered in combination with BCG therapy for 4 weeks. 11 patients received placebo therapy, 8 subjects received rapamycin 2 mg and 12 subjects received rapamycin 0.5 mg. Rapamycin was well tolerated by the subjects. The most frequently reported side effects were haematuria, painful urination or frequent urination. During the experiment, the amount of cytokines and immune cells in the urine was checked as a result of the immune response to the

applied therapy. Subjects treated with rapamycin at a dose of 2 mg had the highest increase in T lymphocytes compared with placebo and rapamycin therapy at a dose of 0.5 mg. This suggests that rapamycin enhances the BCG-specific effect. However, further studies are needed to introduce such a treatment (35).

Due to the perceived side effects of treatment with BCG vaccine, a number of studies have been conducted to test the efficacy of BCG compared to other chemotherapeutics. In one study conducted at the Postgraduate Institute of Medical Education and Research in Chandigarh, India, the efficacy of intravesical BCG compared to gemcitabine and docetaxel was tested on a group of 60 patients during treatment of non-muscle invasive bladder cancer. The mean age of the patients reached approximately 60 years. The majority of the study patients were men. 14 women were in the study group. In addition, 70% of the study participants were active smokers. The study was conducted from July 2019 to December 2020. 30 patients received BCG and the same number received gemcitabine and docetaxel therapy. Therapy was initiated 2 weeks after transurethral resection of the tumour by standard surgery. Once the histopathological result was received, induction therapy was administered - 6 weekly doses, followed by maintenance therapy - 6 monthly doses. Patients were assessed before the inclusion of therapy, after induction therapy and 6 months after the start of maintenance therapy. Assessments included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and cystoscopy and cytology were performed at the end of the induction phase and every 3 months thereafter until the end of the study. Treatment side effects were observed in 50-60% of patients treated with BCG, compared with 20-30% with gemcitabine and docetaxel. Haematuria was observed in 8 patients treated with BCG, while the same symptom occurred in only 1 patient in group two. During follow-up, 1 tumour recurrence was observed in each group. It is worth noting that gemcitabine and docetaxel are safe drugs and equally effective compared to BCG therapy in patients with non-muscle invasive bladder cancer, while they provide a better quality of life during therapy itself due to less frequent side effects (36).

Summary

The emergence of new treatment options for non-muscle invasive bladder cancer has accelerated work on the implementation of personalized medicine in the treatment of this type of cancer. The Spanish Multidisciplinary Working Group for Genitourinary Oncology has already started work on the Genitourinary Alliance Project, which aims to create recommendations for personalized care for patients with bladder cancer (37). The standard treatment for non-muscle invasive bladder cancer is tumor resection followed by BCG

vaccination. The response to such treatment is good, but relapses and progression of the cancer to a form infiltrating the muscle membrane are becoming more frequent, which motivates the creation of appropriate recommendations tailored to a given patient and the use of new treatment options (38). It is estimated that approximately 50% of patients will have an insufficient response to BCG treatment and will progress to cancer infiltrating the muscular membrane of the urinary bladder. It is believed that radical cystectomy has a minimal risk of tumor progression and recurrence in patients with medium and high risk of bladder cancer recurrence, but it is worth considering that new treatment methods may prevent progression, recurrence and avoid radical removal of the bladder, which will ensure greater comfort of life. patients struggling with oncological disease (39). Cystectomy is associated with high perioperative morbidity and mortality. Approximately 5% of patients undergoing radical cystectomy die within 90 days of the procedure (28). The presented research provides more and more therapy options for patients resistant to BCG therapy. HIVEC is a promising treatment method that, compared to BCG, provides a higher rate of freedom from disease progression (31). The research shows that new therapy methods are effective and safe compared to the use of BCG. Unfortunately, more research is needed to standardize the treatment of non-muscle invasive bladder cancer.

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39. Fragkoulis[1] C, Glykas[1] I, Bamias[2] A, Stathouros G, Papadopoulos G, Ntoumas[1] K. International Section NOVEL TREATMENTS IN BCG FAILURE. WHERE DO WE STAND TODAY?