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The impact of antibiotics and glucocorticoids on the results of immunomodulatory antibody treatment in cancer patients

Abstract

Cancer cells avoid elimination through the mechanism of immunosuppression, which consists in modulating antigens and affecting the activation of the complement system. In 2011, authorities registered a monoclonal antibody and the first medication from the group of immunological checkpoints, ipilimumab, which activates T lymphocytes through unblocking the possibility of presenting antigens to cells after binding with cytotoxic T cell antigen (CTLA-4). Other targets of the drugs from this group were described: programmed death cell receptor 1 (PD-1), located on T lymphocytes, and programmed death cell ligand 1 (PD-L1), located on cancer cells. Immunotherapy significantly improved the prognosis of patients diagnosed with melanoma, renal cell carcinoma, squamous cell carcinomas of the head and neck, non-small cell lung cancer and other cancers.

Glucocorticoids are often used in the treatment of symptoms in cancer patients. They are also administered during immunotherapy in the case of immune-related adverse events. Antibiotics also constitute a group of medications that are widely used in cancer patients. Since both glucocorticoids and antibiotics can decrease the effectiveness of immunotherapy, physicians should carefully consider the expected benefits and the possible negative impact of their administration on the survival time of cancer patients before prescribing them.

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Key words: cancer immunotherapy, antibiotics, glucocorticoids, side effects

Abbreviations

AE — adverse event
CTCAE — common terminology criteria for adverse events
CTLA-4 — cytotixic T cell antigen 4
IRAE — immune-related adverse event
kg bw — kg of body weight
LAG-3 — lymphocyte activation gene 3
OS — overall survival

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PD-1 — programmed death cell receptor 1
PD-L1 — programmed death cell ligand 1
PFS — progression free survival
RET — Rearranged During Transfection
TIM-3 — T cell immunoglobulin and mucin domain 3
wt — week of treatment

Introduction

Although monoclonal antibodies have been used in the treatment of cancer for many years, only their application as inhibitors of immune response checkpoints resulted in a significant extension of the survival time of patients with melanoma, renal, head and neck, urothelial and lung carcinoma as well as Merkel cell carcinoma [1–6]. The following checkpoint inhibitors were distinguished: anti-CTLA4 antibodies (Cytotoxic T Cell Antigen 4): ipilimumab, anti-PD-1 (Programmed Death Cell Receptor 1 [PD-1]): nivolumab, pembrolizumab, cemiplimab and anti-PD-L1 (programmed death cell ligand 1 [PD-L1]): avelumab, atezolizumab and durvalumab [7–12].

Activation of the immune system leads to the elimination of tumour cells and may also induce side effects that manifest as autoimmune inflammation [13]. Predictive factors for immune-related adverse events (IRAEs) are still being sought [14, 15]. Since their symptoms may be non-specific, they are often mistakenly attributed to cancer. Informing patients about them is crucial for early diagnosis and the implementation of an optimal therapy. Glucocorticoid therapy is the basic method of adverse event treatment [16]. It is also used in the treatment of cancer symptoms: bone and neuropathic pain, dyspnoea, loss of appetite, nausea and vomiting as well as medical emergencies: cerebral oedema, superior vena cava syndrome and spinal cord compression [17]. Due to ruptures in the skin or mucous membrane caused by tumours, patients with solid tumours frequently suffer bacterial infections. Increased incidence of microbial infections is also associated with patients' advanced age, nutritional status and history of systemic treatment of cancer [18].

Thanks to the activity of the immune system: fungi, bacteria and viruses can be detected within the human organism. Cancer cells avoid selection and apoptosis through immunosuppression, which enables their further growth and survival. Immunosurveillance theory, which consists of three phases, explains the mechanism. In the first phase, the immune system recognizes abnormal cells, which results in their elimination. During phase two, equilibrium, cells exhibit heterogeneity and become difficult to recognize due to antigen modulation. In the final phase, escape, cancer cells avoid elimination through various mechanisms: antigen masking, rapid proliferation and inactivation of the complement system [19, 20].

To date, treatment of cancer patients consisted in introducing substances that caused damage and breakdown of tumour cells into the organism, without the involvement of immune system cells [25]. With the development of immunotherapy and identification of immune checkpoints, we achieved a breakthrough in the treatment of many types of cancer. The 2018 Nobel Prize in medicine and physiology was awarded to J.P. Allison, who described the impact of CTLA-4 receptors, located on T lymphocytes, on the immune system [22], and T. Honjo, who characterized the activity of PD-1 receptors, which are also located on T lymphocytes [23]. In both cases, after the application of appropriate antibodies (anti-CTLA4 and anti-PD-1), their inhibitory activity on the immune system is eliminated; as a result, cancer cells are recognized and destroyed by the patient's immune system. The activity of programmed cell death receptor ligand-1 (PD-L1), whose expression on cancer cells is responsible for immunosuppression, has also been described [24].

Antibiotics in cancer patients receiving immunotherapy

Administration of antibiotics 30 days before the beginning of immunotherapy was associated with worse prognosis in patients with renal cell carcinoma and non-small cell lung cancer. The median progression-free survival (PFS) in renal cell cancer patients treated with antibiotics was 1.9 months, compared to 7.4 months ($p = 0.03$) in patients who did not receive antibiotics; the significant impact of antibiotic therapy on PFS was confirmed in a multifactorial analysis. The median overall survival (OS) in patients with non-small cell lung cancer who received antibiotics prior to immunotherapy was 7.9 months, while in patients who did not receive antibiotic treatment it was 24.6 months ($p < 0.01$), and the impact on OS was also significant in the multifactorial analysis. Another analysis involving patients who were receiving antibiotics 60 days before the beginning of immunotherapy did not reveal that it had an impact on their survival time, probably due to partial restoration of the gut bacterial flora [26].

Gut microbiome diversity correlates with better prognosis in patients undergoing immunotherapy. Presence of *Bifidobacterium spuriae* and the *Ruminococcaceae* family in the stool of patients with melanoma determines longer survival [27, 28], which is probably associated with the fact that antigen-presenting cells located within the tumour are activated

by *Bifidobacterium spuriae* [29]. Attempts are being made to overcome resistance to treatment caused be the lack of certain strains of bacteria in the intestines. After comparing stool samples from patients treated with anti-PD-1, presence of *Akkermansia muciniphila* was observed in the samples of those patients who were benefitting from the treatment. After the administration of oral supplementation of *Akkermansia muciniphila* in mice with melanoma induced by the RET (Rearranged During Transfection) proto-oncogene, which had previously received antibiotic therapy, researchers obtained a response to immunological treatment. A total of 196 patients diagnosed with non-small cell lung cancer, melanoma, head and neck cancers, and renal cell carcinoma were enrolled in a study evaluating the impact of antibiotic therapy administered before and during immunotherapy on the survival parameters. It was observed that in all patients included in the study who received antibiotic treatment before immunotherapy the median OS was 2 months, while in the remaining population it was 26 months ($p < 0.001$). A multivariate analysis revealed that the administration of antibiotics before cancer treatment as well as the response to immunotherapy were associated with a shorter median OS, regardless of patients' performance and the location and size of the tumour ($p < 0.001$) [31].

In a study involving patients with non-small cell lung cancer receiving immunotherapy, Galli et al. used the term "exposure to antibiotics during immunotherapy", expressed as the product of days of antibiotic administration to days of immunotherapy administration. In addition, they distinguished the population of patients in whom antibiotics were used at an early stage of immunotherapy, in which case no impact on the median OS and PFS was observed. It was observed that in patients with a higher rate of exposure to antibiotics, the median OS ($p = 0.0004$) and PFS ($p < 0.0001$) were shorter [32].

The meta-analysis involved 2,889 patients diagnosed with melanoma and lung, renal and urothelial cancer, 829 of whom were receiving antibiotics. The median OS was extended in those patients who were not exposed to these medications ($p < 0.001$). Administration of antibiotics 42 days before the beginning of immunotherapy was associated with a shorter median OS ($p < 0.0001$). Extension of the median PFS was observed in patients who were not exposed to antibiotics ($p < 0.0001$) [33]. An analysis concerning antibiotic treatment that involved 1,800 patients diagnosed with non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma and melanoma and undergoing cancer immunotherapy revealed that in 11 out of 12 studies the use of antibiotic treatment was associated with a significant shortening of the median OS and PFS. Antibiotics were administered 14 days to 2 months before the beginning of immunotherapy, or 1 month to 42 days into the treatment. Only one study did not reveal a shortening of PFS, the median OS was not provided. Patients included in the study received antibiotics 3 months before immunotherapy. The authors indicate possible ways to overcome treatment resistance, such as stool transplants, the use of prebiotics, diet or prebiotics and postponement of immunotherapy in carefully selected patients [34].

In another meta-analysis, which involved 33 clinical studies and 5,565 patients with various solid tumours, such as non-small cell lung carcinoma, renal cancer and melanoma, the use of antibiotics, taking into account the whole study population, was associated with a shorter median OS ($p < 0.00001$) and PFS ($p < 0.00001$). Reduced effectiveness of immunotherapy was particularly noticeable when antibiotics were administered 60 days before or after the beginning of cancer treatment. Results of meta-analyses may be difficult to interpret due to varying methodologies and duration of antibiotic use [35].

A study involving 847 patients with urothelial cancer subjected to immunotherapy also revealed that antibiotic treatment had a negative impact on survival. It was observed that the median OS (HR [hazard ratio] 1.44, 95% CI [confidence interval] 1.19–1.73) and median PFS (HR 1.24, 95% CI 1.05–1.46) were shorter in patients who received antibiotics within the period of 30 days before or after the beginning of the treatment with checkpoint inhibitors [36].

Interesting findings were presented by the authors of a report that included a retrospective analysis of 291 patients with non-small cell lung cancer, melanoma, and renal cell carcinoma undergoing cancer immunotherapy and receiving antibiotic treatment. One course of antimicrobial medications had no impact on OS and PFS, while antibiotic treatment exceeding 7 days and/or more than one intravenous infusion, or sequential use due to multiple sites of infection, resulted in a shortening of the median PFS by 2.8 months ($p = 0.026$), and the median OS - by 6.3 months ($p = 0.009$) [37].

Another analysis involved 60 patients with lung and renal cancer, melanoma, hepatocellular carcinoma, head and neck squamous cell carcinoma and urothelial carcinoma treated with immunomodulatory antibodies. Seventeen patients received antibiotics two weeks before the beginning of cancer treatment or after the first dose. The response rate (RR) decreased from 62.8% to 29.4% ($p = 0.024$). While broad-spectrum antibiotics were associated with a decrease in

RR from 61% to 25% (p = 0.02), no such correlation was observed in the case of narrow-spectrum antimicrobials. In a multivariate analysis, the use of antibiotics significantly affected RR (p = 0.0038). It was demonstrated that there was a reduction in the median OS, from 89 months to 24 months, to the disadvantage of the administration of antimicrobial medications (p = 0.003). There was a multivariate analysis in which only age (p = 0.035) and antibiotic use (p = 0.038) affected OS [38].

Authors of another study analysed the impact of antimicrobial medications on the response rate among melanoma patients receiving immunotherapy. Patients who were receiving antibiotics in the period of 30 days from the beginning of immunotherapy more often exhibited primary resistance to anti-cancer treatment, the response rate was 0% and 34%. The median PFS was shorter - 2.4 months in the case of patients who were treated with antibiotics, and 7.3 months in the case of patients who did not receive additional medication (p = 0.01). A shortening of the median OS was not observed. A correlation between the use of antibiotics and shortening of the median PFS was observed in a multifactorial analysis (p = 0,02) [39].

Administration of glucocorticoids in cancer patients before and during immunotherapy

Arbour et al. observed that overall survival, response rates and progression-free survival in patients diagnosed with non-small cell lung cancer receiving prednisone at a dose lower than 10 mg per day, or another drug at an equivalent dose, prior to anti-PD-1 or anti-PD-L1 therapy, were similar to those of patients who were not treated with corticosteroids [40]. In a group of patients treated for non-small cell lung cancer, the use of corticosteroids due to cancer symptoms within 8 weeks from the beginning of immunotherapy was associated with a reduction in the median OS and PFS to 1.9 and 1.1 months, respectively, compared to patients treated with glucocorticoids only due to the occurrence of adverse effects of the treatment — 13.4 and 2.7 months (p = 0.006 and p < 0.0001, respectively) [41]. The risk of death in patients treated for melanoma, urothelial cancer and non-small cell squamous cancer in whom glucocorticoids were administered from 14 days before to 30 days into the treatment was 23–47% higher [42]. Patients in whom glucocorticoids had to be used due to such symptoms as dyspnoea, cerebral oedema caused by metastases and superior vena cava syndrome have a worse prognosis than those without symptoms of cancer. In addition, the use of glucocorticoids can have a negative impact on the survival time [43].

Among 67 patients receiving cancer immunotherapy for non-small cell lung cancer, the use of corticosteroids during the first administration of immunotherapy (p = 0.006) and poor overall condition (p = 0.001), were associated with a shortened median PFS, while symptomatic metastases to the central nervous system resulted in a shortened median OS (p = 0.029), and occurred more commonly with side effects of immunotherapy (p = 0.031) [44].

In an analysis involving 210 patients with non-small cell lung cancer, it was observed that in the group of patients receiving immunosuppressive drugs in the period of 30 days from the beginning of cancer treatment, the median OS (after the administration of prednisone at a daily dose of 10 mg or more) shortened to 4.3 months, compared to 11 months in other patients. A multivariate analysis confirmed that corticosteroids had a significant impact on the median OS (p = 0.006). Immunosuppression was most often administered due to symptomatic metastases to the central nervous system, chronic obstructive pulmonary disease or other respiratory diseases [45].

Melanoma patients treated with the anti-CTLA-4 antibody at Memorial Sloan Kettering Cancer Center between April 2011 and June 2013 were included in a retrospective study concerning the impact of glucocorticoids on the effectiveness of immunotherapy. Immunotherapy induced adverse events in 85% of those patients, and 35% of them required corticosteroids. No difference was observed between the median OS (p = 0.97) in these two populations [46]. Authors of a meta-analysis which concerned results of 16 clinical trials involving 4,045 patients compared the impact of the use of corticosteroids on the survival time of patients receiving immune checkpoint inhibitors. They observed that the impact on the median OS was negative in the case of patients who received immunosuppressive medication due to adjuvant treatment (p < 0.01) and metastases to the central nervous system (p < 0.01). No such correlation was observed in the case of patients treated with glucocorticoids due to adverse events caused by immunotherapy [47].

Another retrospective analysis concerned the impact that glucocorticoid therapy had on patients with melanoma, non-small cell lung cancer and renal cancer treated with anti-PD-1 antibodies in the years 2014–2016. The negative impact of immunosuppression on the median OS was confirmed. In a group of 55 patients, 27 required the use of corticosteroids, and 13 patients died, earlier than the median OS would indicate. Eleven patients were receiving corticosteroids

at a dose greater than 10 mg of prednisone per day for 14 days or longer [48]. In a group of 196 patients with non-small cell lung cancer receiving immunotherapy, the use of glucocorticoids in the treatment of cancer symptoms was associated with a shorter median OS (HR = 2.7; 95% CI, 1.5–4.9). No impact of glucocorticoids on the median OS was observed when they were administered due to adverse events caused by immunotherapy [49].

Treatment of patients with squamous cell carcinoma of the head and neck, as well as non-small cell lung cancer, involves combinations of immunotherapy with cisplastin-based chemotherapy. Due to the fact that cisplastin has a significant emetogenic potential, it should be administered in combination with dexamethasone at a dose of at least 8 mg. Due to the lack of studies, it is difficult to unambiguously determine the impact of anitemetic glucocorticoids used during cancer immunotherapy. The addition of olanzapine to prevent vomiting induced by platinum derivatives in combination with immunotherapy may be a solution [50]. It is recommended to appoint interdisciplinary teams, to ensure optimal care for cancer patients treated with immunomodulatory antibodies. This way, patients can be provided with the best care in terms of treatment selection, management of side effects and the application of supportive treatment.

Side effects of immunotherapy

Due to the unique mechanism of action of immunotherapy, its side effects differ from those occurring during cytostatic treatment. Immunotherapy rarely causes hair loss, nausea and vomiting, which frequently occur during chemotherapy [52]. Adverse events caused by immune checkpoint inhibitors can affect any organ and are mainly associated with autoimmune response and tissue infiltration by activated T cells [53]. Adverse events are described with the use of the CTCAE (Common Terminology Criteria for Adverse Events) classification. A distinct characteristic together with severity level from 1 (the mildest) to 5 (death) is assigned to each IRAE [14]. The time at which individual IRAEs occur depends on the target of a given medication and the number of medications administered [54, 55]. In the case of nivolumab in monotherapy, we expect the development of skin lesions in the 5th week of the treatment, followed by liver dysfunction (8 weeks into the treatment) and autoimmune pneumonias (9 weeks into the treatment). Adverse events involving endocrine organs occur around week 12, and nephritis - most often around week 15 [56]. IRAEs may also occur at a different time. Complications that are reported most commonly include skin complications, gastrointestinal side effects (inflammatory bowel disease, elevated liver enzymes), autoimmune damage to endocrine glands (e.g. thyroid gland, pituitary gland), primary adrenal insufficiency and diabetes mellitus; less often, IRAEs affect the skeletal, cardiovascular, and nervous system as well as the kidneys and eyeballs [52–56].

Glucocorticoids are the primary method of the treatment of adverse events [57]. In the case of mild adverse events involving the skin, we can use antihistamines and emollients. If lesions are occurring at stage G2, CTCAE provide that glucocorticoids should be applied locally; if the symptoms persist for longer than 7 days, glucocorticoids are administered orally: prednisone at a dose of 0.5–1 mg per kg of body weight (kg bw) per day, or another steroid at an equivalent dose. If there is an improvement, dose reduction should last approximately 28 days. According to CTCAE, at stage G3 it is recommended to discontinue immunotherapy and initiate treatment with oral corticosteroids. If there is no improvement after 3 days, glucocorticoids should be administered intravenously: methylprednisolone at a dose of 1–2 mg per kg bw per day, or an equivalent dose. If an adverse event occurs at stage G4, the patient should be hospitalized and glucocorticoids should be administered intravenously. If the severity of the adverse events is reduced, the doses of glucocorticoids should be reduced over a period of 4–6 weeks [58–61]. Glucocorticoid doses depend on the severity of IRAE acc. to CTCAE, are analogous to those administered in other types of adverse events, and are used in accordance with the available ESMO guidelines [58].

If a patient with an autoimmune inflammatory bowel disease or pneumonia continues to exhibit symptoms of IRAE despite the intravenous administration of glucocorticoids at stage 4, it is recommended that infliximab at a dose of 5 mg per kg bw be administered. In the case of a persistent increase in the level of liver enzymes, mycophenolate mofetil is recommended [58, 59]. Patients receiving glucocorticoids orally at a daily dose of 20 mg of prednisone, or equivalent, for a period of 4 weeks, should additionally receive prophylaxis against fungal infections (fluconazole) and prophylaxis against pneumocystis jirovecii (trimethoprim and sulfamethoxazole). Proton pump inhibitors may be considered in patients at a significant risk of gastritis.

Autoimmune hypothyroidism is a specific case of IRAE. In the case thereof, glucocorticoids are not necessary, but thyroxine should be supplemented for the rest of the patient's life, depending on thyroid hormone levels, TSH and clinical symptoms [57]. Pituitary insufficiency with characteristic swelling in MRI

usually occurs in older men after the administration of ipilimumab or combination treatment consisting of two checkpoint inhibitors in 1.5–17% of patients, and is associated with adrenal and gonadal insufficiency as well as hypothyroidism and chronic hormone replacement therapy [62, 63].

In some patients it is possible to return to immunotherapy after the occurrence of IRAE, however, it depends on the stage at which the adverse event was diagnosed as well as its type. In the case of grade 4 hepatotoxicity, returning to immunotherapy is contraindicated, even after the level of aminotransferases has decreased [58]. The efficacy of immunomodulatory antibodies appears to be higher in patients with IRAE. There was a study that involved 106 patients receiving nivolumab or pembrolizumab due to non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck cancers, and urothelial carcinoma. The median PFS among patients with IRAE was 10 months, while in patients without adverse events it was 3 months ($p = 0.0016$), the percentage of objective responses was 82.5% and 16.6%, respectively ($p < 0.000001$) [64]. It is important to properly educate patients and provide them with information regarding adverse events, which enables prompt diagnosis and effective treatment of complications stemming from immunotherapy [65, 66].

Summary

Immunotherapy is increasingly often used to treat patients diagnosed with melanoma, squamous cell carcinomas of the head and neck, renal cell carcinoma, Merkel cell carcinoma, lung cancer, and urothelial carcinoma. Researchers are investigating the efficacy of new immunostimulatory medications that also target other molecules present on the surface of lymphocytes: TIM-3(T-cell immunoglobulin and mucin domain 3) and LAG-3(lymphocyte activation gene 3) [67, 68]. Attempts to overcome primary resistance to immunotherapy with dacarbazine are also being made [69]. Administration of immunotherapy in the form of neoadjuvant treatment, before the resection of tumours located in the stomach or colon, is a new therapeutic concept [70]. Administration of glucocorticoids in the treatment of cancer symptoms during immunotherapy may have a negative impact on patients' survival, whilst antimicrobial drugs may limit the effectiveness of immunotherapy by reducing the diversity of the gut bacterial flora.

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

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