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TUMOR IMMUNOTHERAPY SIDE EFFECTS – EARLY RECOGNITION AND MANAGEMENT

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Summary

Implementation of immunotherapy in many cancer types has achieved positive results in tumor control and cure. The concept of immunotherapy is different in comparison with conventional tumor therapies. While chemotherapy, hormonal or biological therapies target tumor cells and mechanisms, immunotherapy targets host immune system. Amplification of defending possibilities or unblocking the control of the immune reactions are used. Besides positive results in tumor control, enhancing immunogenicity can provoke harm to other tissues and systems in form of adverse reactions or unwanted side effects of therapy.

Early recognition of side effects is of crucial importance and prompt care can diminish the harm and severity. Knowledge about side effects is needed, therefore good education of all medical personnel included in treatment as well as patient education must be assured prior and thorough the treatment. Written guidelines are provided and easy reachable and must be used.

Key words: *tumor immunotherapy, side effects, management of side effects, checkpoint inhibitors, anti-CTLA-4 immunotherapy*

NEPOŽELJNE POPRATNE POJAVE IMUNOTERAPIJE TUMORA

Sažetak

Provedba imunoterapije u mnogim vrstama karcinoma postigla je pozitivne rezultate u kontroli i liječenju tumora. Koncept imunoterapije razlikuje se u usporedbi s konvencionalnim terapijama tumora. Dok su kemoterapija, hormonska ili biološka terapija svojim djelovanjem usmjerena na uništenje tumorske stanice i mehanizama u tumoru, imunoterapija cilja imunološki sustav domaćina. Pri tome se jačaju obrambeni procesi i reakcije ili se korištenjem imunoterapije dovodi do deblokiranja procesa kontrole imunoloških reakcija. Osim pozitivnih rezultata u kontroli tumora, povećanje imunogenosti može izazvati štetu drugim tkivima i sustavima u obliku nuspojava ili neželjenih nuspojava terapije.

Rano prepoznavanje nuspojava od presudne je važnosti, a pravodobno zbrinjavanje može smanjiti oštećenje i težinu popratne pojave. Znanje o mogućim nuspojavama je nužno osigurati kroz dobro i sveobuhvatno obrazovanje svih medicinskih djelatnika uključenih u liječenje, a jednako je tako važno podučiti i s popratnim pojavama upoznati i pacijenata prije liječenja. Pisane smjernice pružene su i lako dostupne i moraju se koristiti.

KLJUČNE RIJEČI: *imunoterapija tumora, popratne pojave, zbrinjavanje popratnih pojava, : checkpoint inhibitori, anti-CTLA-4 imunoterapija*

Renewed interest in immunotherapy as a potent tool in the treatment of malignant solid tumors and the confirmation of efficacy and importance has been seen in recent years. From the era of interferon, biotechnological progress has led to better understanding of host immune mechanisms and the identification of factors by which the tumor avoids host defense (1). These discoveries led

to identification of possible targets in immune response and precise therapies. Precise targeted amplification of regulation and suppression processes in host cascade of T lymphocytes results in the suppression of the process of avoiding immune surveillance (2,3).

In addition to the already known mechanisms of cytokine, vaccine and TIL therapy, the new drugs are based on influencing the so-called *checkpoints* or *checkpoint protein inhibitory antibodies* (2,3,4). These are immunomodulatory monoclonal antibodies that act through receptor blockade for a specific immune response and thus enhance the immune response of the host. Clinical practice in melanoma therapy lists two target pathways: CTLA 4 receptor on T lymphocyte-associated antigen 4 and PD-1 T lymphocytes receptor (programmed cell death-1), or PD-L1 (ligand).

New immunomodulatory drugs efficacy is confirmed in many studies and clinical settings in different tumor types, significantly improving the results of treatment in melanoma, non small cell lung tumors, kidney cancer, to some extent also in urinary bladder tumors, triple negative breast cancer, and digestive system. Nowadays the most commonly used drugs with proven efficacy in clinical practice are ipilimumab (anti CTLA-4), nivolumab, pembrolizumab (anti PD-1), atezolizumab and durvalumab (anti PD-L1) (2,3,5).

With efficient monitoring trough clinical studies and even more important after a substantial time in clinical use and a representative number of patients, safety profile of drugs is mostly defined, with less toxicity noted with anti-PD-1 agents than ipilimumab as seen in KEYNOTE-006 trial (5,6,7).

Most of acute side effects are known as well as their potential toxicity, risks and harm to the patient. Due to mechanisms of action of drugs the observed toxicities, adverse reactions or other side effects are manifested in the form of autoimmune reactions, inflammation, or autoimmune diseases (3,5,6).

The appearance of side effects is most common in four systems. Toxicities provoked by immune system often affect dermatological, gastrointestinal, endocrine system and liver provoking different types of autoimmune manifestations, or the *itis* group of disorders. Colitis, thyreoiditis, hypophysitis, hepatitis are among the most important and can reach different grade of severity (6). Other side effects appear less frequently, but should not be neglected or forgotten because they may be as dangerous, as the more common ones, eg. pneumonitis (3,5,6,7).

Side effects occur at different time points during the treatment, very rare at the beginning (8). Most occur within the first 3 months of treatment (86%), as a reflection of inflammatory processes in organs, such as colitis, pancreatitis, pneumonitis, hepatitis, pituitary gland and skin manifestation (5,6,7,8,9,10). The majority also resolve within 3 months. Skin toxicities occur firstly, after 2–3 weeks of therapy and they typically resolve fast. This group of side effects is very common, around 44% of the patients treated with ipilimumab are having one or several skin side-effects like rash, pruritus and vast majority is grade 1–2 (7). Severe skin toxicity (grade 3–4) appears in less then 2% patients (7).

Digestive tract side effects usually appear next, after 6–7 weeks, mostly as diarrhea and colitis, followed by liver and endocrinopathies (thyreoiditis and hypophysitis most often) which can be diagnosed even after 9 weeks (9,10,11,12).

Some other immune-related unwanted side effects include fatigue, pneumonitis, pancreatitis, arthralgia, enteritis, encephalitis, Guillain-Barre syndrome, myasthenia gravis-like syndrome, ocular immunopathies and autoimmune-induced bone marrow suppression (3,13).

Previous clinical practice has shown that early detection and recognition of symptoms is most important. With rapid interventions such as application of corticosteroids and temporary treatment withdrawal, adverse events are mostly reversible and after a recovery in majority of patients can continue with their therapy (3,9). However, if they are not identified early enough, they can develop into complex and serious grade events and become potentially life-threatening. This stage of severity requires hospitalization, possible intensive care, application of immunosupressive drugs (3,5,14).

Therefore, a good education of medical staff, from general practitioners through emergency physicians to oncologists and oncology staff of different profiles that cares for patients treated with immunotherapy is needed. This also includes radiologists, gastroenterologists, endocrinologists, neurologists, lung specialists who can be the first from whom the patient will turn to in an emergency.

The guidelines are fairly accessible. Most of them are simple, in form of convenient tabular views and algorithms explaining symptoms, needed steps and recommendations according to side effect grade and severity (3,5,9). As ipilimumab is in clinical use for the longest period, most of the recommendations are based on knowledge about its adverse reactions, but many may also be applied to reactions on treatment with PD-1 inhibitors. Very detailed and user friendly recommendations are provided in SPC flyers of all drugs (Summary of Product Characteristics) (15,16).

Some of the pharmaceutical companies have provided patient identity card for their medications (as for example pembrolizumab). Those cards are given to patients who are instructed to carry them all the time and in case of emergency show the card to the medical personnel addressed for help. The card provides a quick short summary of important facts about the treatment and side effects for medical staff and instructions who and when to contact (16).

Detailed and comprehensible information must be offered to each patient before and during the treatment (3). It is of great importance to warn the patient and stress the necessity for immediate referral and medical attention in the event of a disorder or discomfort. The oncologist must reassure the patient that reporting the side effect does not lead to certain permanent treatment withdrawal. We must not forget that patients often desire to achieve the full effect of treatment and are in permanent fear of possible treatment interruption, especially if they think this drug is their only option. It can happen that a patient knowingly suppresses or minimizes side effects, continues the treatment at any cost and seeks for help only when side effects are manifested in advanced form of serious adverse event, and thus the outcome and possibility to resolve them becomes very uncertain.

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