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REVIEW ARTICLE

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Immunotherapy of cancer — safety issues

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ABSTRACT

Using of immune checkpoints inhibitors, including mainly anti-PD-1, is a new, effective strategy of therapy of advanced malignancies. In safety profile the main danger are autoimmunological adverse events, and their management includes patient's education, interdisciplinary cooperation, using diagnostic-therapeutic algorithms and often immediate administration of corticosteroids.

Key words: anti-PD-1, anti-CTLA-4, nivolumab, pmembrolizumab, ipilimumab, adverse, events, immunotherapy

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In the series of papers published in the journals "Oncology in Clinical Practice" / "Onkologia w Praktyce Klinicznej — Edukacja" and developed by leading Polish specialists, practical guides for management of various adverse reactions were presented specifically the signs and symptoms from gastrointestinal tract, skin, lungs, and endocrine system in cancer patients treated with immunotherapy.

Non-specific immunotherapy (mainly with anti-CTLA4 monoclonal antibodies [ipilimumab] and anti-PD-1 [nivolumab and pembrolizumab]) was the first treatment method to significantly improve outcomes in patients with disseminated (generalised) melanoma [1, 2]. It is currently well known that adjuvant immunotherapy significantly improves survival results in patients after resection of high-risk melanoma [3]. Immunotherapy (mainly in the form of anti-PD-1 or anti-PD-L1 antibodies in monotherapy or in combination with other treatment modalities) has actively entered the oncology market and is currently registered for the treatment of at least seven other malignant diseases (including lung cancer, renal cell carcinoma, and Hodgkin's lymphoma) [4, 5].

In the treatment of advanced melanomas in daily routine practice anti-PD-1 used either alone or in combination with ipilimumab has demonstrated a long-term clinical benefit in some patients with advanced melanomas and significant response rates (up to 50%), with one-year survival of 70–80%, two-year survival more than 50%, and three-year survival more than 40%, whilst having lower toxicity than ipilimumab [1, 2, 6–11].

Although treatment with anti-PD-1 antibodies is associated with relatively minor side effects (Table 1), it requires experience, particularly with regard to specific adverse reactions associated with immunotherapy (mainly in the form of autoimmune disorders associated with the activation of the immune system) because it requires compliance with work algorithms [12]. Therefore, the presented publication, developed by top-class specialists, is an extremely necessary and practical compendium of management in undesirable symptoms for oncologists and other specialists involved in the care of cancer patients treated with immunotherapy. The use of immunotherapy requires a trained multidisciplinary team and excellent cooperation between the patient and the medical team, to ensure maximum safety and effectiveness of this treatment method. It should be also remembered that immunotherapy side effects are initially associated with atypical/non-specific symptoms, may occur at different times, and currently there are no easy to investigate predictors of complications; thereby, it is necessary to properly educate patients and healthcare providers (physicians and nurses) and implement the algorithms presented in this study, not only based on glucocorticoids. Furthermore, with the increasingly widespread use of immunotherapy in oncology and

Table 1. Immune-related adverse events during treatment with anti-PD1 monoclonal antibodies (%)

	Pembrolizumab 10 mg/kg bw every 2 weeks	Pembrolizumab 10 mg/kg bw every 3 weeks	Nivolumab *BRAF*(–)	Ipilimumab + nivolumab Phase III
Author and year of publication	Robert 2014 [6]	Robert 2015 [7]	Robert 2015 [8]	Larkin 2015, up-date 2017 [9,10]
Grade 3–4 (5) adverse vents	13.3 (0)	10.1 (0)	11.7 (0)	56.6 (0)
Intestinal	1.4	2.5	1.5	15.3
Hepatic	1.1	1.8	1.5	19.8
Dermatic	0	0	1.5	5.8
Endocrinopathies	1.2	0.8	1.0	5.8
Pulmonary	0	0.4	0	1.0

bw — body weight

Table 2. Summary of toxicities reported in phase III clinical trials with nivolumab in different indications

%	RCC [14]		Squamous cell NSCLC [15]		Non-squamous cell NSCLC [16]		Melanoma [9]			
							Monotherapy		With ipilimumab	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
All	79	19	58	7	69	10	82.1	16.3	95.5	55
Diarrhoea	12	1	8	0	16	1	19.2	2.2	44.1	9.3
Fatigue	33	2	16	1	32	3	34.2	1.3	35.1	4.2
Pruritus	14	0	4	0	11	0	18.8	0	33.2	1.9
Rash	10	< 1	4	0	13	< 1	25.9	0.6	40.3	4.8
Nausea	14	< 1	9	0	22	2	13.1	0	25.9	2.2
Fever	ND	ND	5	0	12	< 1	5.8	0	18.5	0.6
Decrease of appetite	12	< 1	11	1	29	2	10.9	0	17.9	1.3
Elevated ALT level	ND	ND	2	2	6	< 1	3.8	1.3	17.6	8.3
Vomiting	ND	ND	3	0	13	< 1	6.4	0.3	15.3	2.6
Elevated AST level	ND	ND	2	2	ND	ND	3.8	1	15.3	6.1
Hypothyroidism	ND	ND	1	0	7	0	8.6	0	15	0.3
Colitis	ND	ND	1	1	ND	ND	1.3	0.6	11.8	7.7
Arthralgia	ND	ND	5	0	16	1	7.7	0	10.5	0.3
Headache	ND	ND	ND	ND	10	1	7.3	0	10.2	0.3
Dyspnoea	7	1	ND	ND	23	5	4.5	0.3	10.2	0.6
Pneumonia	4	1	5	0	6	3	ND	ND	10.6	2.1
Adverse events leading to treatment discontinuation	8%	ND	3	ND	5	ND	7.7	5.1	36.4	29.4

RCC — renal cell carcinoma; NSCLC — non-small cell lung cancer; ALT — alanine transaminase; AST — asparagine transaminase; ND — no data

extended treatment duration, the new complications could be expected. We already observe side effects (fortunately extremely rare) that go beyond the most common, described in the presented studies, such as polyneuropathy, including Guillain-Barre syndrome, autoimmune nephritis, or diabetes mellitus.

Recently, the results of a retrospective safety analysis of nivolumab treatment were presented in a group of 576 patients with the diagnosis of advanced melanoma participating in clinical trials. Half of these patients previously received a treatment with ipilimumab. The most common treatment-emergent adverse reactions at any grade were fatigue (25%), pruritus (17%), diarrhoea, and rash (13% each). Grade 3 or 4 adverse events occurred in 10% of patients in the entire population and in 8% in patients previously treated with ipilimumab. In the analysed group no deaths caused by toxicity of therapy were found. Adverse reactions resulting from excessive stimulation of the immune system were most often related to the skin (34%), gastrointestinal tract (13%), endocrine system (8%), and liver (4%). This grade 3 or 4 adverse reaction occurred in 4% of patients. The median time to onset of toxicity was five weeks for dermatic toxicity and up to 15 weeks for nephrotoxicity. In general, 35% of patients received immunomodulatory treatment (in the vast majority of cases there were glucocorticoids). Median time to resolution of toxicity upon treatment was three weeks for hepatotoxicity up to 29 weeks for dermatic toxicity (it should be noted that the majority of patients with skin toxicity received treatment with topical glucocorticosteroids). The use of immunomodulatory treatment to manage toxicity had no effect on the response to anticancer treatment [13].

Table 2 summarises the adverse events found in clinical studies with nivolumab in different indications.

In summary, inhibiting PD-1 immune checkpoint and the use of inhibitors of immune checkpoints in general is a new, fascinating strategy for the treatment of advanced cancers. With the help of these drugs results are achieved that have not been seen previously in cancer immunotherapy. The safety profile of anti-PD-1 antibodies seems to be better tolerated compared to many standard chemotherapeutics or ipilimumab; however, it may be associated with life-threatening autoimmune complications, and therapeutic management is primarily based on patient education, multidisciplinary cooperation, adherence to therapeutic algorithms, and often introduction of corticosteroids as soon as possible.

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