Tomasz Rawa1, 2, Jarosław Reguła1, 2
1Department of Oncological Gastroenterology, Marie Skłodowska-Curie Memorial Cancer Centre Institute, Warsaw
2Department of Gastroenterology, Hepatology, and Clinical Oncology, Medical Centre of Postgraduate Education, Warsaw

Management of gastrointestinal toxicity from nivolumab therapy

ABSTRACT
Nivolumab is a monoclonal antibody with immunomodulatory action blocking a PD-1 receptor (programmed death-1). This action causes T-cell activation against the neoplasm and all other body tissues. This can lead to many different autoimmune-regulated toxicities. The most common are gastrointestinal complications such as enterocolitis and hepatitis. These adverse events may be successfully treated if a diagnosis is quick and appropriate. Such an approach may also enable continuation of nivolumab therapy in many patients.

Key words: nivolumab, immunotherapy, adverse events, enterocolitis, hepatitis

Introduction
Nivolumab is a modern antineoplastic drug which actually may be used in the immunotherapy of melanoma, non-small cell lung cancer, renal cancer, Hodgkin lymphoma, urothelial cancer and squamous cell head and neck cancer. There are some ongoing studies evaluating the efficacy of this agent in the gastrointestinal and liver cancers [1].

Nivolumab is a human monoclonal antibody belonging to a group of drugs, the anticancer effect of which results from their influence on the immunological system. The mechanism of action of nivolumab is based on blocking the PD-1 receptor (programmed death-1). A blocked receptor cannot bind the PD-L1 and PD-L2 ligands, molecules that are expressed on the neoplastic cells in order to inhibit the proliferation of lymphocytes T and to stop the secretion of the anticancer cytokines. Inhibition of the interaction between the PD-1 receptor and its PD-L1 and PD-L2 ligands by nivolumab have the opposite result — an increased anticancer activity of lymphocytes T [2].

Nivolumab and the other drugs with a similar immunomodulatory effect (ipilimumab, pembrolizumab, atezolizumab, etc.) influence each tissue, not only the neoplastic one. For this reason, the use of these agents involves a risk of autoimmunological complications (immune-related adverse events — irAEs) [3, 4]. In the case of nivolumab, the most common manifestations of the adverse events are: weakness, rush, diarrhoea, constipation, skin itching, and joints pains. The majority of these side effects results from dermatitis, enterocolitis, arthritis, or hepatitis with an immunologic background [5].

The data concerning the toxicity of nivolumab and other PD-1 inhibitors are based on just a few papers. The majority of information concerning the adverse effects of immunotherapy derives from the clinical studies of ipilimumab, the mechanism of action of which is slightly different but still similar to nivolumab. The adverse events of nivolumab seem to be less frequent and of lower grade [6–8].

The most common toxicities concerning the gastrointestinal tract are enterocolitis and hepatitis. A few cases of esophagitis and pancreatitis have been also reported.
Enterocolitis

Diarrhoea is observed in about one third of patients undergoing immunotherapy. It usually occurs in the third month of therapy [9]. Diarrhoea may have an infectious — fungal, bacterial, or viral — as well as autoimmuneological background. About 8–22% of patients receiving immunotherapy develop autoimmunological enterocolitis [10]. The autoimmunological inflammation may lead to a potentially severe damage and perforation of the bowel in 1–1.5% and can be fatal in 1.1% of patients receiving ipilimumab [10–12]. Data coming directly from the clinical studies of nivolumab suggest that the clinically severe form of the diarrhoea [Common Terminology Adverse Events (CTAE) grade 3 and 4] occurs less frequently than after ipilimumab, i.e. in 1–2% of patients [13, 14].

The aetiology of the diarrhoea may be different, which is why it always requires rapid diagnosis. Early determination of the cause of diarrhoea enables an effective treatment [15]. The initial phase of diagnostics includes tests that exclude infectious background — a stool mycology and parasite analysis should be performed as well as testing for the presence of *Clostridium difficile* toxin. Moreover, blood should be tested for cytomegalovirus (CMV) infection. Exclusion of the infectious background suggests an autoimmuneological aetiology of the diarrhoea [10]. Coexistence of such symptoms as: ulcerations of the oral cavity, perianal changes (ulcers, fissures, fistulas), arthritis, skin changes, liver damage, or endocrinopathies additionally confirms an autoimmuneological background [16]. The laboratory tests may reveal anemia, elevated acute phase protein (AFP), and hypoalbuminemia [16].

A definitive diagnosis of unspecific enterocolitis must be based on the endoscopic and histopathological evaluation. In the majority of patients, immunotherapy-induced enterocolitis involves rectum and/or the left part of the colon. That is why fibrosigmoidoscopy should be done as a first exam (this technique permits evaluation of the rectum and the left part of the colon). If the result is normal, a colonoscopy should be performed because in some patients, changes involve only the proximal part of the colon [16]. Endoscopy reveals inflammation manifested by the absence of the vascular pattern, petechiae, redness, and oedema of the mucosa as well as erosions and ulcerations [16, 17]. Histopathological tests (or eventually immunohistochemical ones) exclude infectious background and permit confirmation of non-specific enterocolitis. Microscopic evaluation of the damage induced by ipilimumab reveals a different type of histopathological change than those observed in Crohn’s disease or in ulcerative enterocolitis [16]. By contrast, changes induced by nivolumab are described as similar to the ones observed in ulcerative enterocolitis. These findings may have therapeutic implications such as inclusion of 5-aminosalicylic acid into treatment of this complication [18].

Diet is a first therapeutic intervention, notwithstanding the cause and grade of symptoms. The major aim of the diet is to slow the peristalsis of the bowels and to decrease the enteric secretion. For this reason, a patient should not consume any raw vegetables or fruit that contain pectins (agents that boost peristalsis). Higher amounts of pectins are included in apples, apricots, cherries, carrots, oranges, bananas, and citrus peel. Patients with diarrhoea should also avoid any preserve containing enumerated fruit, e.g. jams, because they also contain pectins. Another group of food and drinks that should not be consumed in case of diarrhoea are: soya, oats, corn, sweets, and aerated drinks because they contain fructose and sorbitol. All these products increase liver damage, or endocrinopathies additionally confirms an autoimmuneological aetiology of the diarrhoea [10]. Coexistence of such symptoms as: ulcerations of the oral cavity, perianal changes (ulcers, fissures, fistulas), arthritis, skin changes, liver damage, or endocrinopathies additionally confirms an autoimmuneological background [16]. The laboratory tests may reveal anemia, elevated acute phase protein (AFP), and hypoalbuminemia [16].

A definitive diagnosis of unspecific enterocolitis must be based on the endoscopic and histopathological evaluation. In the majority of patients, immunotherapy-induced enterocolitis involves rectum and/or the left part of the colon. That is why fibrosigmoidoscopy should be done as a first exam (this technique permits evaluation of the rectum and the left part of the colon). If the result is normal, a colonoscopy should be performed because in some patients, changes involve only the proximal part of the colon [16]. Endoscopy reveals inflammation manifested by the absence of the vascular pattern, petechiae, redness, and oedema of the mucosa as well as erosions and ulcerations [16, 17]. Histopathological tests (or eventually immunohistochemical ones) exclude infectious background and permit confirmation of non-specific enterocolitis. Microscopic evaluation of the damage induced by ipilimumab reveals a different type of histopathological change than those observed in Crohn’s disease or in ulcerative enterocolitis [16]. By contrast, changes induced by nivolumab are described as similar to the ones observed in ulcerative enterocolitis. These findings may have therapeutic implications such as inclusion of 5-aminosalicylic acid into treatment of this complication [18].

Diet is a first therapeutic intervention, notwithstanding the cause and grade of symptoms. The major aim of the diet is to slow the peristalsis of the bowels and to decrease the enteric secretion. For this reason, a patient should not consume any raw vegetables or fruit that contain pectins (agents that boost peristalsis). Higher amounts of pectins are included in apples, apricots, cherries, carrots, oranges, bananas, and citrus peel. Patients with diarrhoea should also avoid any preserve containing enumerated fruit, e.g. jams, because they also contain pectins. Another group of food and drinks that should not be consumed in case of diarrhoea are: soya, oats, corn, sweets, and aerated drinks because they contain fructose and sorbitol. All these products increase liver damage, or endocrinopathies additionally confirms an autoimmuneological aetiology of the diarrhoea [10]. Coexistence of such symptoms as: ulcerations of the oral cavity, perianal changes (ulcers, fissures, fistulas), arthritis, skin changes, liver damage, or endocrinopathies additionally confirms an autoimmuneological background [16]. The laboratory tests may reveal anemia, elevated acute phase protein (AFP), and hypoalbuminemia [16].

A definitive diagnosis of unspecific enterocolitis must be based on the endoscopic and histopathological evaluation. In the majority of patients, immunotherapy-induced enterocolitis involves rectum and/or the left part of the colon. That is why fibrosigmoidoscopy should be done as a first exam (this technique permits evaluation of the rectum and the left part of the colon). If the result is normal, a colonoscopy should be performed because in some patients, changes involve only the proximal part of the colon [16]. Endoscopy reveals inflammation manifested by the absence of the vascular pattern, petechiae, redness, and oedema of the mucosa as well as erosions and ulcerations [16, 17]. Histopathological tests (or eventually immunohistochemical ones) exclude infectious background and permit confirmation of non-specific enterocolitis. Microscopic evaluation of the damage induced by ipilimumab reveals a different type of histopathological change than those observed in Crohn’s disease or in ulcerative enterocolitis [16]. By contrast, changes induced by nivolumab are described as similar to the ones observed in ulcerative enterocolitis. These findings may have therapeutic implications such as inclusion of 5-aminosalicylic acid into treatment of this complication [18].
Pharmacotherapy of nivolumab-induced enterocolitis is very rarely non-effective. In such circumstances, when a severe, life-threatening enterocolitis develops, which may result in perforation of the intestine, colectomy should be performed [16]. There are no confirmed data concerning the problem of restarting the immunotherapy after successful management of the enterocolitis. In patients with moderate enterocolitis (CTAE grade 2 and 3) who did not require therapy with infliximab, another attempt of nivolumab therapy seems acceptable. There is also a consensus concerning a definitive end of immunotherapy in patients who developed a severe form of enterocolitis and required therapy with infliximab [1, 10].

The principles of management of enterocolitis depending on its CTAE grade are presented in Table 1.

**Hepatitis**

Nivolumab and other anti-PD-1 drugs may also induce hepatitis. This complication may occur at any period of the therapy, but usually it appears between the 6th and 12th week of treatment. Hepatitis concerns 1–5% of patients [3, 25].

Clinical symptoms of hepatitis develop late and are related to a sever impairment of the liver. That is why the function of the liver should be monitored prior to and during the therapy, in order to detect as early as possible the impairment of this organ. The essential tests includes evaluation of the aminotransferases, gamma glutamyl transferase, alkaline phosphatase, and total bilirubin activity.

The occurrence of the laboratory features of liver impairment during the pharmacotherapy is strong proof of its drug-induced aetiology. However, exclusion of all other common factors of liver impairment, e.g.: alcohol abuse, infection with hepatotropic viruses, or specific for immunotherapy — CMV infection, is always obligatory. In order to confirm the immunological background of the liver damage, evaluation of the presence of antinuclear antibodies as well as anti-smooth muscle antibodies should be done. Imaging exams (ultrasonography, computed tomography) may be helpful but are inconclusive in diagnosing the immunological cause of liver impairment. Liver biopsy is not necessary. It may be useful in uncertain cases or in cases with a fulminant course [26].

If a liver impairment is detected, the control evaluation of liver function should be repeated at least once a week [1]. Persistence of the abnormal aminotransferase’s or total bilirubin level even in a low grade (aminotransferases 3–5 × normal value, CTAE grade 2) constitutes an indication to stop the immunotherapy and to start the therapy with glucocorticosteroids (prednisolone) in a dose corresponding to 1–2 mg/kg of body weight per day [27]. If this therapy is not effective or the symptoms are reoccurring during the reduction of the drug dose it is recommended to start again prednisolone at the dose of 2 mg/kg of body weight. Hepatitis usually resolves in 4–6 weeks of appropriate therapy and then the immunotherapy may be reassumed [1]. There are some recent data suggesting some benefits of adding ursodeoxycholic acid to the glucocorticosteroids. However, it is too early to recommend a common use of this drug in all patients [28].

Nivolumab must be definitively stopped in the case of occurrence of acute, expansive liver impairment (very high levels of aminotransferases — CTAE grade 3) or the appearance of symptoms of liver insufficiency (incl. increasing hyperbilirubinaemia — CTAE grade 3). In this situation, besides stopping the drug, intravenous glucocorticotherapy and N-acetylcysteine administration in dose of 1200 mg should be started [28]. No improvement when on this treatment constitutes an indication to administer a mycophenolate mofetil in dose of 1000 mg [4, 29–31]. Unlike the other complications of immunotherapy, in hepatitis, the use of infliximab is not recommended, due to its hepatotoxicity.

The principles of management of hepatitis, depending on its CTAE grade, are presented in Table 2.

Besides pharmacotherapy, in the case of liver impairment an adequate diet based on fresh and healthy food has a supporting effect. It is recommended that light food products are used. The intake of dietary fat should be limited. The fat should be vegetable, e.g. rapeseed oil, sunflower oil, soybean oil, or olive oil. It is also advised that cooked, baked, or steamed products be consumed. Eating fried dishes is contraindicated [32].
During immunotherapy with nivolumab the therapy of enterocolitis constituted an effective infiltration. Glucocorticosteroids in doses similar to scopic evaluation revealed intraepithelial lymphocyte ally manifested as dysphagia — gastroscopy-detected improvement, administer mycophenolate Aminotransferases > 20 × normal value — stop nivolumab permanently — diet and methylprednisolone intravenously — if no improvement start prednisone orally

### References

Other complications of the gastrointestinal tract

A few cases of oesophagitis induced by nivolumab immunotherapy have recently been reported. It usually manifested as dysphagia — gastroscopy-detected macroscopic features of oesophagitis, and the microscopic evaluation revealed intraepithelial lymphocyte infiltrations. Glucocorticosteroids in doses similar to the therapy of enterocolitis constituted an effective treatment [33]. During immunotherapy with nivolumab pancreatitis may also occur. All data suggest that its course is asymptomatic and it is manifested by elevated serum levels of amylase and lipase [34]. This condition does not require any significant medical management.

### Table 2. Management of nivolumab-induced hepatitis depending on the severity of symptoms according to the CTAE scale [1]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (G1)</td>
<td>Aminotransferases &lt; 3 × normal value — continue nivolumab — diet and control of aminotransferases level every 7 days</td>
<td></td>
</tr>
<tr>
<td>2 (G2)</td>
<td>Aminotransferases 3–5 × normal value — stop nivolumab — diet and control of aminotransferases level twice per week — no improvement start prednisone orally</td>
<td></td>
</tr>
<tr>
<td>3 (G3)</td>
<td>Aminotransferases 5–20 × normal value and/or symptoms of liver insufficiency — stop nivolumab permanently — diet and methylprednisolone intravenously, if no improvement administer mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td>4 (G4)</td>
<td>Aminotransferases &gt; 20 × normal value — stop nivolumab permanently — diet and methylprednisolone intravenously — if no improvement, administer mycophenolate</td>
<td></td>
</tr>
</tbody>
</table>


