NIVOLUMAB MONOTHERAPY IN METASTATIC COLORECTAL CANCER: CURRENT APPROACHES TO RESPONSE EVALUATION

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Abstract

Aim of the study: a systematic analysis of the modern literature data on the nivolumab monotherapy efficacy in patients with metastatic colorectal cancer (mCRC). Material and Methods. The review summarizes the results of clinical studies of the nivolumab efficacy in patients with mCRC between 2012 and 2022. The current approaches to assessing the tumor response in patients treated with immune checkpoint inhibitors are considered, including response patterns and criteria. Results. Data analysis showed that the use of nivolumab in mCRC patients had significant clinical benefits. Nivolumab monotherapy was shown to improve survival in patients with high microsatellite instability (MSI) or deficiencies in mismatch repair (dMMR) that progressed during standard chemotherapy. Numerous clinical studies indicate the atypical response to nivolumab. Traditional response criteria, such as RECIST do not always adequately assess the therapeutic efficacy of nivolumab in patients with mCRC. Conclusion. To improve the efficacy of mCRC treatment, standardized approaches based on the proposed specific criteria for response to immunotherapy, including immune related RECIST, immune RECIST, and immune-modified RECIST must be developed.

Key words: metastatic colorectal cancer, nivolumab, RECIST, atypical response patterns.

MONOTERAPIЯ НИВОЛУМАБОМ У БОЛЬНЫХ МЕТАСТАТИЧЕСКИМ КОЛОРЕКТАЛЬНЫМ РАКОМ: СОВРЕМЕННЫЕ ПОДХОДЫ К ОЦЕНКЕ ОТВЕТА ОПУХОЛИ

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Introduction

Colorectal cancer (CRC) is the leading cause of cancer-related death, both worldwide and in the Russian Federation [1–2]. The metastatic CRC (mCRC) represents approximately 30–50 % of all initially detected disease cases [3, 4]. Current treatment strategies of CRC are based on a multimodal approach, including chemotherapy, targeted therapy and immunotherapy, which allow selection of the optimal individualized treatment.

According to the ESMO, NCCN recommendations, as well as the Ministry of Health of the Russian Federation guidance, screening for high microsatellite instability (MSI) and deficiencies in mismatch repair (dMMR) is recommended to all mCRC patients for prediction of clinical benefit from immunotherapy. Currently, three immune checkpoint inhibitors, such as ipilimumab, pembrolizumab, and nivolumab are approved for use in MSI-high and dMMR advanced CRC patients [5–7]. It was demonstrated that nivolumab improved objective response rate and progression-free survival with a manageable safety profile compared to standard therapy for melanoma, renal cell carcinoma, and non-small cell lung cancer [8–10]. Further studies have confirmed that nivolumab provides a durable response and disease control in pre-treated mCRC patients, including patients with dMMR/MSI-high tumor [11–13]. In this review, we summarize the clinical aspects of nivolumab administration, mainly focusing on tumor response patterns in mCRC patients and current approaches to its assessing.

Nivolumab action and safety

Nivolumab has been developed in research collaboration between Ono Pharmaceutical and Medarex Company with the originally name MDX-1106/ONO-4538. This is a human IgG4 monoclonal antibody that contains a hinge region mutation (S228P), which reduces Fc exchange with IgG4 molecules to improve stability and reduce therapeutic variability [14]. Nivolumab blocks the interaction between the programmed cell death 1 (PD-1) receptor and PD-L1/ PD-L2 ligands. Inhibition of PD-1 and its ligands promotes the reactivation of tumor-specific T-lymphocytes and following prolongation of their antitumor effect [15]. Pharmacokinetic studies have suggested that nivolumab has linear pharmacokinetics with a dose-proportional increase in the maximum concentration and area under the concentration-time curve. The time to peak plasma nivolumab concentration ranges between 1–4 hours [14]. In August 2017, the US Food and Drug Administration (FDA) approved nivolumab for the treatment of patients with dMMR/MSI-high mCRC that had progressed following chemotherapy. Nivolumab is administered at dose 240 mg as an intravenous infusion over 30 minutes every 2 weeks until disease progression or unacceptable toxicity.

In more than 20 % of patients receiving nivolumab as monotherapy, the most common observed adverse reactions are fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. The main side effects of nivolumab monotherapy leading to discontinuation of treatment are diarrhea or colitis grade 4, pneumonitis grade 3 or 4, AST or ALT >5 times ULN or total bilirubin >3 times ULN, hypophysitis grade 4, adrenal insufficiency 3 or 4 grade 4 hyperglycemia, serum creatinine >6 times ULN, grade 4 rash or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis, immune-mediated encephalitis, recurrent grade 3 adverse reactions, life-threatening or adverse reactions 4 grade, need for ≥10 mg/day prednisone or equivalent for >12 weeks, and persistent grade 2 or 3 adverse reactions lasting ≥12 weeks. No specific for mCRC side effects have been identified [16].
Response patterns and criteria

RECEIST assessment

Radiologic response evaluation using the Response Evaluation Criteria in Solid Tumors (RECIST V.1.1) with assessments of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) remains the standard option in routine clinical practice. Complete response to nivolumab persisting for 21 months in a 67-year-old male with CRC with metastases in intra-abdominal lymph nodes was reported for the first time in 2010 [14]. In a subsequent multicenter phase 1 trial, nivolumab did not show clinical activity in mCRC patients [17]. However, one prolonged (for ≥6 months) partial response to nivolumab in a CRC patient was observed at a single-center, open label Japanese study [13]. In addition, two complete responses and seven partial responses in patients with treatment-refractory metastatic anal cancer were reported in a multicentre, phase 2 trials from ten USA academic centers. Among nine responders, seven patients had a durable response with a median duration of response of 5.8 months [12]. With the evidence for the heterogeneous nature of cancer, it has become clear that PD-1/PDL-1 targeting could be effective in selected cohort of patients. This was confirmed by CheckMate 142 multicentre phase 2 study that nivolumab had encouraging efficacy in patients with dMMR/MSI-high mCRC [11]. According to his assessment, the objective response rate was achieved in 23 patients (31.1 %) and disease control for ≥12 weeks was observed in 51 patients (68.9 %). In addition, few reports have been demonstrated cases with a complete clinical response to nivolumab, including a patient with metastatic clear cell renal cell carcinoma [18] and a patient with gastric cancer [19].

Atypical response patterns

Recently, new atypical response patterns have been described in patients treated with immune checkpoint inhibitors that are not seen with chemotherapy and targeted therapy. These include the durable response, pseudoprogression, hyperprogression, and dissociated response [20–21].

Durable response is defined as a treatment response for an extended time even after stopping medication. To date, only one durable response to nivolumab (longer than 36 months) has been reported in a 71-year-old male with MSI-high mCRC [22]. The same response to nivolumab (range 8.07±48.0+) was described in patients with metastatic papillary renal cell carcinoma [23], metastatic HPV-positive head and neck squamous cell carcinoma [24] and metastatic melanoma [25]. However, no durable response criteria have been developed to date.

The phenomenon of pseudoprogression was described for first time in advanced melanoma patients treated with pembrolizumab [26]. It has been identified as tumor shrinkage after an initial increase in tumor burden or the appearance of new lesions [27]. Pseudoprogression represents a rare response type. One study reported no pseudoprogression in patients subgroup with MSI-high mCRC treated with anti-PD-1 antibody [28]. Chae et al. demonstrated a pseudoprogression during combinational treatment of PD-L1 inhibitor and OX40 agonist in MSI-high metastatic colorectal adenocarcinoma patient who experienced initial increase in size and number of tumor lesions with subsequent tumor regression. An extraordinary scale of pseudoprogression with 163 % tumor growth from baseline was reported [29]. It has been recently shown that pseudoprogression occurs in 10 % of patients with dMMR/MSI-high mCRC treated with immune checkpoint inhibitors, including nivolumab monotherapy. Pseudoprogression is more frequently observed in patients treated with anti-PD1 monotherapy than in those receiving combination of anti-PD1 and anti-CTLA-4. In addition, 8 of the 12 patients with an initial pseudoprogression achieved an objective response (five partial responses and three complete responses) and had favorable outcomes [30].

Hyperprogression response is characterized by rapid tumor progression, which often leads to unfavorable outcome. The concept of hyperprogression remains controversial since there is no substantiated evidence of its occurrence under therapy with immune checkpoint inhibitors. In addition, assessment criteria of hyperprogression based on tumor growth kinetics are highly heterogeneous [20]. However, some case reports on hyperprogression under pembrolizumab have been documented in the literature, particularly in patients with metastatic MSI-high/dMMR CRC [31–33], and advanced colon cancer with Lynch syndrome [34]. With regard to nivolumab, one case of a dMMR gastrointestinal cancer patient who experienced hyperprogressive disease following its administration was presented. In this case report, 1.5 month after starting nivolumab (one dose of nivolumab), the patient experienced rapid metastatic progression in the lungs and lymph nodes and patient died of respiratory failure [35].

A dissociated response is observed when some lesions shrink and existing lesions enlarge or new lesions appear. This term is not well-established; terms such as mixed or heterogeneous response are used to define this response. Various types of dissociated response under nivolumab were described in patients with advanced cancers [21, 22, 36–39]. There are no reported cases of this response type in patients with metastatic MSI-high/dMMR CRC. However, we have our experience of observing a dissociated response in a patient with MSI-high metastatic colorectal cancer after 8 months of treatment with nivolumab with reduced pulmonary nodules and concomitant para-aortic lymph node involvement.

Immune-related response criteria

To better characterize the atypical response patterns, different immune-related response criteria based
on new approaches to PR and PD evaluation were
used in clinical trials of immune checkpoint inhibitors. However, none of these has been adapted for routine clinical practice.

**Conclusion and future perspectives**

Nivolumab monotherapy in metastatic colorectal cancer was shown to provide clinical benefit and improves survival in patients with dMMR/MSI-high mCRC who progressed after receiving a standard chemotheraphy. Numerous clinical studies suggest that nivolumab may lead to atypical response patterns. Traditional response criteria such as RECIST may not always adequately assess the therapeutic efficacy of nivolumab in patients with metastatic colorectal cancer. To improve the management of mCRC, it is important to develop standardized approaches based on the proposed specific criteria for response to immunotherapy, including immune related RECIST, immune RECIST and immune-modified RECIST.

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139
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Conflict of interests

The authors declare that they have no conflict of interest.

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ВКЛАД АВТОРОВ

Бабышкина Наталия Николаевна: разработка концепции научной работы, поиск и анализ современных литературных данных, написание статьи.

Дронова Татьяна Анатольевна: поиск и анализ современных литературных данных, составление черновика статьи.

Гервас Полина Анатольевна: поиск и анализ современных литературных данных, составление черновика статьи.

Попова Наталия Олеговна: критический пересмотр с внесением ценного интеллектуального содержания, утверждение окончательной версии статьи.

Добродеев Алексей Юрьевич: поиск и анализ современных литературных данных, написание статьи.

Костромицкий Дмитрий Николаевич: поиск и анализ современных литературных данных, составление черновика статьи.

Афанасьев Сергей Геннадьевич: разработка концепции научной работы.

Гольдберг Виктор Евгеньевич: разработка концепции научной работы.

Чердынцева Надежда Викторовна: разработка концепции научной работы.

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