

COLORECTAL CANCER IMMUNOTHERAPY

Antonio Juretić

Department of Clinical Oncology, School of Medicine, University of Zagreb, Zagreb, Croatia; Oncology Clinic, University Hospital Centre Zagreb, Zagreb, Croatia

Summary

Recent successful results of a relatively new immunotherapeutic anti-cancer strategy based on the blockade of immune inhibitory pathways by monoclonal antibodies against checkpoint molecules can be considered as a medical breakthrough in clinical cancer immunotherapy. This type of immunotherapy became a standard part of systemic therapy protocols in the treatment of some metastatic solid tumors such as melanoma, non-small cell lung cancer, genitourinary cancers, Merkel-cell carcinoma, squamous-cell carcinoma of the head and neck, and solid tumors with DNA high microsatellite instability or DNA mismatch-repair deficiency. Recent progress in colorectal cancer genome analysis, and also supported by clinical observations, indicates that patients with DNA mismatch repair deficiency or microsatellite instability-high metastatic colorectal cancers are a distinct biomarker-defined population that might benefit from immunotherapy treatment with monoclonal antibodies against checkpoint molecules. This treatment has therefore become a new treatment option for this colorectal cancer subgroup of patients. However, besides tumor microsatellite instability or mismatch-repair deficiency status, other predictive biomarkers are also needed since not all these tumors respond to anti-check point immunotherapy treatment. This paper aims to present a basic overview of immunotherapy in mismatch repair deficient colorectal cancer patients.

Keywords: colorectal cancer; biomarkers; immunotherapy; immunooncology; microsatellite instability; mismatch repair deficiency; personalized medicine.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors and unfortunately also one of the leading tumor type causes of cancer death in the world. CRC is not a homogenous disease, but can nevertheless be classified into

different subtypes characterized by specific molecular and morphological alterations (1-6).

A major feature of CRC is genetic instability that can arise via at least two different mechanisms. The most common (around 84 % of sporadic CRC) is characterized by chromosomal instability (CIN), with gross changes in chromosome number and structure, including deletions, gains, translocations and other chromosomal rearrangements. Mutations in the adenomatous polyposis coli (APC) tumor suppressor gene are the most frequent mutations in this pathway. The second group (around 13–16 % of sporadic CRC) is hypermutated and shows microsatellite instability (MSI) due to defective DNA mismatch repair (MMR) (1-6). A hypermutated tumor is defined as a tumor with an increased mutation burden (a high rate of somatic mutation). The threshold above which tumors are considered hypermutated, however, depends on the sequencing methodology and type of cancer (1,2,7, 8). Importantly, the clinical significance of identifying hypermutated tumors has recently been demonstrated by several studies showing that the tumor mutation burden correlates with the generation of neoantigens (mutated proteins) and clinical response to immunotherapy. Causes of hypermutation vary across cancer types. A leading cause of the mutations found in several gastrointestinal cancers is the dysfunction in the mismatch repair (MMR) system. Microsatellite instability (MSI) refers to the hypermutable state of cells caused by impaired DNA mismatch repair (MMR). It consists of insertion and deletion mutations in stretches of short tandem DNA repeats (microsatellites) and of nucleotide substitutions throughout the genome. MSI-high (MSI-H) or MMR deficient carcinomas can arise due to either a germline mutation in one of the genes responsible for DNA mismatch repair (Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer (HNPCC); around 3 %) or somatic inactivation of the same pathway, most commonly through hypermethylation of the MLH1 gene (sporadic MSI-H; around 12 %). One of the most frequent genetic alterations in CRCs with MSI is the oncogenic BRAF V600E mutation (1-7,9,10).

Regardless of the origin (hereditary or sporadic) or type of mutation, MSI-H CRCs share some distinct histologic cancer features (mucin-rich, signet ring and medullary types, often admixed) with increased numbers of tumor infiltrating lymphocytes (TILs) and a prominent Crohn's-like lymphoid reaction. MSI-H carcinomas are almost always located in the ascending colon. Lynch syndrome (LS) is a syndrome of inherited susceptibility to cancers of several organs, primarily the large bowel, with the next most frequently affected being the endometrium. In addition, patients with Lynch syndrome have an increased risk

of synchronous or metachronous tumors that include extracolonic sites (small bowel, stomach, endometrium, skin, genitourinary tract). Prognostically, patients with MSI-H tumors, especially those with early stage disease, exhibit, due to the reduced rates of tumor recurrence, a more favorable outcome (overall survival) in comparison with stage-matched sporadic CRCs. Clinically, MSI-H CRC develops a large size tumor with high levels of cell growth but less metastasis (4-7,9,10). It is also stated that MSI-H CRC patients are less likely to respond to fluoropyrimidine chemotherapy than microsatellite stable (MSS) tumor patients, but this conclusion remains controversial (4-6,11). Based on this conclusion, patients with stage II MSI-H might be spared adjuvant fluoropyrimidine treatment due to lack of survival benefit (12).

Recent integration of various CRC gene expression-based subtypings resulted in a consensus molecular CRC classification enabling the segregation of most tumors into one of four consensus molecular subtypes (CMS). These are: CMS1 (MSI-immune, 14%), CMS2 (canonical, 37%), CMS3 (metabolic, 13%), and CMS4 (mesenchymal, 23%). The majority of CMS1 tumors are MSI tumors, while CMS subtypes 2 to 4 display higher rates of CIN. A critical observation resulting from these molecular profiling studies is that, in general, gene-specific abnormalities are not consistently altered within the molecular subtypes. This observation highlights the poor correlation between gene signature and phenotype in CRC and has significant implications for gene-based precision medicine. For example, a mutation of the KRAS oncogene has emerged as a powerful biomarker predicting a lack of benefit from epidermal growth factor receptor (EGFR) inhibitors in metastatic CRC. On the other hand, the profiling studies have demonstrated that wildtype RAS status is not associated with any single CMS subtype. Thus, at present, this is a classification predominantly applicable to research rather than, as is the case with consensus breast cancer molecular subtypes, to routine patient care (2-7).

The treatment strategy for patients with colorectal cancer is based on the estimation of colorectal cancer disease stage, patient performance status, medical comorbidities, patient preferences, and tumor pathohistological and tumor molecular characteristics. Depending on these estimates and parameters, the approach to patient treatment can be curative or palliative. Treatment modalities include surgery, chemotherapy, radiation therapy, anti-angiogenic and anti-EGFR therapy, either as single treatment modalities or in combination (4-6,12-15).

IMMUNOTHERAPY

Immunotherapy as an anti-cancer treatment modality has been used for over a hundred years, starting with the application of Coley's toxin as early as the end of the 19th century and continuing with various immunotherapeutic approaches up to the present. In clinical testing and application these various immunological approaches were usually ineffective or, when they were effective, which was rare, were not easily and broadly applicable and therefore not in routine use. The immunotherapeutic approaches were based on the assumption that tumor cells can be antigenically distinct from normal cells and that the host's immunological system can recognize this antigenic difference and consequently should mount an anti-tumor immune response against autologous tumor cells. Some of these tumor antigens which can be recognized on autologous tumor cells can be unique to particular tumor cells, i. e. tumor specific. They might have been produced as a consequence of somatic gene mutations in tumor cells in the course of their malignant cell transformation or by „new“ gene formations in places of chromosomal translocations. Due to their generation process, these antigens are labeled „neoantigens“. In some cases over or aberrantly expressed normal molecules from non-mutated genes on tumor cells can act as tumor antigens. They then form the so-called group of tumor-associated antigens (TAAs). Examples of these are HER-2 molecule and cancer/testis antigens, respectively (16-22).

Only recently have clinical trials using monoclonal antibodies against immune checkpoint regulatory molecules on T-lymphocytes which function as „inhibitory receptors“ finally proven to be a clinical effective immunotherapeutic approach to the treatment of some solid tumors, namely melanoma, non-small cell lung cancer, genitourinary cancers, Merkel-cell carcinoma, squamous-cell carcinoma of the head and neck, solid tumors with high microsatellite instability or mismatch-repair deficiency, and classic Hodgkin's lymphoma (17-24).

Antigenic activation of adaptive immunity cells (T- or B- lymphocytes) after antigen recognition through the antigen-specific receptor (the so-called „first signal“) includes, besides cytokine participation, cell-cell regulatory interactions with cell membrane bound costimulatory or coinhibitory molecules on other cells (the so-called „second signal“). A second co-stimulatory signal is essential for lymphocyte activation, but there are also co-inhibitory regulatory molecules and pathways having the physiological role of dampening lymphocyte activation because a too strong immune activation or reactions can cause, as a side effect, damage to the body's normal cells (autoimmune reactions). Because of

this regulatory function of theirs, these membrane bound regulatory molecules are also called checkpoint molecules and they in fact function, as has already been mentioned, as stimulatory or inhibitory receptors on lymphocytes (17-26).

When applied, monoclonal antibodies that are blocking co-inhibitory molecules such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1) on tumor cells might in part of the patients with the above mentioned tumor types non-specifically increase antitumor immunity and thus provide a durable clinical response and probably also lead to some of them being cured. The first phase 3 clinical results of studies that used blocking monoclonal antibodies against inhibitory receptors on T-lymphocytes appeared in 2010 and continue to be conducted. The first successful results were obtained in patients with metastatic melanoma in whom ipilimumab, the humanized monoclonal antibody targeting the inhibitory receptor molecule CTLA-4, was used. Later results, which were even more successful and pertained to several additional cancer types, were obtained by using monoclonal antibodies against the inhibitory receptor PD-1 or against its ligand PD-L1 (17-27).

It should be emphasized that these monoclonal antibodies are immunomodulatory and this type of immune approach are not targeting tumor cells but instead nonspecifically (re)activating immune cells in places where some of them might then act against autologous tumor cells. By increasing the nonspecific activity of the immune system, immune checkpoint blockade can have inflammatory side effects, which are often termed immune-related adverse events. Although any organ system can be affected, immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. The occurrence of these immune-related adverse events provides evidence that immune checkpoint blockade has activated a patient's immune system but whether this immunologic activation correlates with improved antitumor immunity remains controversial (17-28).

Despite these practice changing results, considerable efforts are currently being made to identify reliable predictive biomarkers for identifying the subgroup of patients who might benefit from this immunotherapy approach, thus sparing nonresponders the risk of severe adverse events and saving costs (29-31).

PD-L1 protein expression by tumor and immune cells has been investigated as a potential predictive biomarker but its correlation with immunotherapy efficacy is still debated and there are technical issues preventing its routine use in clinical practice. Above all, different threshold levels have been adopted for

identifying positive samples in different tumor types. Other promising candidate predictive biomarkers are currently under investigation, particularly cells or molecules related to the immune response in the tumor microenvironment such as tumor infiltrating lymphocytes (TILs), indoleamine 2,3-dioxygenase (IDO), BCL-2 interacting mediator of cell death-Bim, and interferon-gamma (29-31).

A correlation with immunotherapy was also found to exist in the somatic mutational landscape of tumors since a high mutational burden has been shown to correlate with the benefit from anti-checkpoint immunotherapy. It is assumed that the more mutated tumors might have more neo-antigens and consequently be more immunogenic and more easily recognizable by the immune system, thus eliciting the recruitment and activation of immune cells, as a result of which they might be more immunotherapeutically targetable and responsive (5-7,10,32-35).

When considering genomic instability across various cancer types, colorectal cancer falls in the middle of the pack in terms of the average tumor mutational load, though there is marked heterogeneity. Nevertheless, an increased rate of somatic mutations has been observed particularly in mismatch repair (MMR) deficient or microsatellite instability-high (MSI-H) tumors. These tumors can contain approximately 500-fold more mutations per tumor. The frameshift mutations seen in MSI tumor cells create novel proteins that are a potential source of immunogenic neo-antigens causing immune recognition and reactivity against themselves. Indeed, these tumors have shown responsiveness to anti-checkpoint immunotherapy independently of histologic and anatomic defined subtypes. Thus, the MMR status of the tumor may represent a potentially feasible and useful predictive biomarker; besides, it has a well-known prognostic role (5-7,10,32-35).

The first data regarding the initial success of immune checkpoint inhibitors in mCRC were presented in mid-2015, when the results of the phase II KEYNOTE 016 trial with pembrolizumab in patients with refractory metastatic tumors were published. In this study three cohorts of patients were recruited: (1) cohort A: patients with high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) mCRC (n = 11); (2) cohort B: patients with microsatellite stability (MSS) or proficient (p)MMR mCRC (n = 21); and (3) cohort C: patients with MSI-H non-mCRC cancers (n = 9). Immune-related objective response (iORR) rates were 40%, 0%, and 71% in the 3 groups, respectively; the median PFS and OS were not reached in cohort A; 2.2 and 5.0 months, respectively, in cohort B (HR for PFS = 0.10, $n < 0.001$, HR for OS = 0.22, $n = 0.05$). For the first time the activity

of an anti-PD1 was demonstrated in patients with MSI-H while no effect was observed in MSS mCRC patients (36). As a possible explanation for such results, it was demonstrated that tumors with MSI-H are characterized by a high burden of somatic mutations that can be recognized by the patient's immune system. After this initial promising study, the later study included not only CRC patients but also patients with other advanced MMR-deficient cancers, i.e. across 12 different tumor types. Objective radiographic responses were observed in 53% of patients and complete responses were achieved in 21% of patients. Responses were durable with median progression-free and overall survival still not reached. Functional analysis in a responding patient demonstrated rapid *in vivo* expansion of neoantigen-specific T cell clones that were reactive to mutant neo-peptides found in the tumor (37). These data support the hypothesis that the large proportion of mutant neo-antigens in MMR-deficient cancers makes them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin (6,32-37).

Based on this and some other data, on May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This is the FDA's first tissue/site-agnostic approval (38).

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered (38).

The major efficacy outcome measures were objective response rate (ORR) assessed by blinded independent central radiologists' review according to RECIST 1.1, and response duration. ORR was 39.6% (95% CI: 31.7, 47.9). Responses lasted six months or more for 78% percent of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses. ORR was

similar irrespective of whether patients were diagnosed with CRC (36%) or a different cancer type (46% across the 14 other cancer types). The most common adverse reactions to pembrolizumab include fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea. Pembrolizumab is associated with immune-mediated side effects, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis (37-38).

Based on „similar“ results, on July 31, 2017, the U.S. Food and Drug Administration granted accelerated approval to nivolumab for the treatment of patients 12 years and older with mismatch repair deficient (dMMR) and microsatellite instability high (MSI-H) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. (39-41)

The approval was based on data from Study CA209142 (CHECKMATE 142; NCT 02060188), a multicenter, open-label, single arm study conducted in 53 patients with locally determined dMMR or MSI-H metastatic colorectal cancer (CRC) who had disease progression during, after, or were intolerant to prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This was a subset of the 74 patients who had received at least one prior regimen for the treatment of metastatic disease containing a fluoropyrimidine with oxaliplatin or irinotecan for the treatment of metastatic disease (39-41).

CONCLUSION

In conclusion, data from the above mentioned recent clinical studies suggest that immunotherapy with immune-checkpoint inhibitors may represent a promising therapeutic strategy for patients with MMR deficient tumors, independently of subtype, which represents a paradigmatic shift in the treatment of these tumors. Regrettably, the proportion of candidate patients is, however, relatively small, because MMR deficiency is present in a relatively low percentage of patients and, moreover, response can be expected only in part of them. Of relevance to this discussion is the problem of reliable predictive biomarkers even in this population of patients with high mutational burdens. This also indicates that the presence of the relatively high mutational burden in cancer cells does not by itself guarantee indisputable tumor response and that additional regulatory cellular and molecular interactions do have a role. Moreover, response to immunotherapy might not only be driven by the “genetic makeup” of the tumor and the way how the immune system reacts to it, but also by its regulation via other mechanisms including the gut microbiota. From the clinical perspective,

response evaluation of anti-checkpoint immunotherapy treated patients should be carefully evaluated due to the possibility of the appearance of pseudoprogression, which should not be considered as disease progression. Also, clinicians should be aware of the fact that anti-checkpoint immunotherapy is accompanied by a new set of side-effects that need to be recognized and correspondingly treated.

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Sažetak

Imunoterapija raka debeloga crijeva

Nedavni uspješni rezultati razmjerno novog imunoterapijskog pristupa baziranog na blokadi imunoloških inhibitornih molekularnih puteva s monoklonskim antitijelima protiv molekula kontrolnih točaka mogu se smatrati medicinskim iskorakom u kliničkoj onkologiji. Taj tip imunoterapije postao je standardni dio protokola sistemne terapije nekih metastatskih tumora poput melanoma, raka nemalih stanica pluća, genitourinarnog karcinoma, karcinoma Merkelovih stanica, raka pločastih stanica glave i vrata i solidnih tumora s visokom mikrosatelitskom nestabilnošću ili manjkom popravka krivo sparenih baza DNA. Noviji rezultati molekularnih analiza genoma raka debelog crijeva, također poduprti kliničkim opažanjima, upućuju na to da su bolesnici s karcinomima u kojih postoji izražena mikrosatelitska nestabilnost ili nemogućnost popravka krivo sparenih baza DNA zasebna biomarkerom definirana populacija koja može imati koristi od liječenja monoklonskim antitijelima protiv imunoloških molekula kontrolnih točaka. Na temelju tih rezultata taj je imunoterapijski pristup postao nova terapijska opcija za tu podskupinu bolesnika s kolorektalnim rakom. Pa ipak, uz mikrosatelitsku nestabilnost ili nemogućnost popravka krivo sparenih baza DNA potrebni su i drugi biomarkeri jer je taj imunoterapijski pristup učinkovit samo u dijelu tih bolesnika. Cilj je ovoga rada dati osnovni prikaz imunoterapije u tih bolesnika.

Ključne riječi: kolorektalni rak; biomarkeri; imunoterapija; imunoonkologija; mikrosatelitska nestabilnost; manjak popravka krivo sparenih baza DNA; personalizirana medicina.

Corresponding author:
Antonio Juretić
e-mail: ajuretic@kbc-zagreb.hr