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Gastro Med Res

Can we Optimize Immune Checkpoint Inhibitors Efficacy in Digestive Oncology?

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Submission: November 12, 2017; **Published:** January 29, 2018

Abstract

Immunotherapy is revolutionizing oncology, with a simple guiding principle: the host immune system has the potential to eradicate cancer, treatment consisting in optimizing immune actors' functions. Although significant results were demonstrated in patients with melanoma or lung cancer, objective response rate (ORR) is only 20% in digestive oncology. However, we can improve this situation by a better knowledge of anti-tumor immunity. For example, ORR is multiplied by two to three in case of PD-L1 (programmed death-ligand 1) overexpression or microsatellite instability (MSI). In a near future, we will certainly be able to take into account other biomarkers for building composite scores for assigning to each patient with digestive cancer an 'immune identity card' able to strongly predict immunotherapy efficacy.

Keywords: Immunotherapy; Predictive factors; Immune checkpoint inhibitors; Microsatellite instability; Neoantigens

Introduction

If you are treating patients with digestive cancers, hardly a day passes without mentioning immunotherapy. Unfortunately, results are globally disappointing. So how can we improve this situation? Probably by prescribing earlier these innovative therapies and associating them with conventional chemotherapies. Another way of research is a better patient selection, based on objective biomarkers. Microsatellite instability was the first factor able to predict immune checkpoint inhibitors efficacy, but a better knowledge of tumor immune environment will allow us to go further in personalized medicine in the era of immunotherapy.

Tumor Microenvironment Immunity

In a perfect world, all neoantigens carried by tumor cells would be recognized by major histocompatibility complex molecules on antigen presenting cells, leading to T cell activation. All tumor cells would be considered as foreign cells and destructed. However, cancer is able to divert for its own purposes immune checkpoints, initially intended to limit peripheral immune response for preventing the onset of inflammatory lesions and auto-immune diseases. In digestive oncology, the best known example is that of programmed death-1 (PD-1) and its ligands PD-L1 and PD-L2. PD-1 is expressed on activated T cells and PD-L1 on various cells, including tumor cells, whereas PD-L2 is mainly found on dendritic cells. However, the PD-L1/PD-1 axis is only an immune checkpoint of many, explaining partially why only 10 to 40% of the patients present a clinical response to immune checkpoint inhibitors as a single agent therapy. Efficacy of immunotherapy is also based on the ability of T cells to identify tumor cells as foreign cells. Some mutations are considered immunogenic and others not, depending on their ability to create recognizable neoantigens (or neoepitopes) by T cells. About 10 mutations/megabase seem sufficient to lead to the frequent formation of neoantigens that can be seen by T cells [1]. Microsatellites are repeated-sequence motifs, which are present in our genome in large numbers, but during DNA synthesis, some errors can occur such as insertion/deletion loops or base–base mismatches. The mismatch repair (MMR) system is able to degrade the error-containing section of the newly synthesized strand and therefore to generate an error-free copy of the template sequence [2]. In the absence of MMR, DNA abnormalities are not corrected, resulting in a mutator phenotype that is accompanied by microsatellite instability (MSI) and, eventually, in cancer. However, tumor microenvironment is complex, with several factors affecting antitumor immunity, such as immune exclusion phenomenon, mainly due to a physical barrier around the tumor (e.g. stroma), or recruitment of immunosuppressive cells (e.g. regulatory T (T_{reg}) cells). There is thus a dynamic balance between factors promoting and inhibiting antitumor immunity, related to the tumor (genetic alterations, cytokine secretion…), to the host (gut microbiota, infectious status) and to the environment (exposure to sunlight). Each individual owns a 'cancer-immune set point', on which response to immunotherapy is possible [3].

First Results of Immunotherapy in Digestive Oncology

With immune checkpoint inhibitors as single agents in pretreated patients, ORR is about 20% and median overall survival

(OS) is approximatively 7 months [4-14]. However, three scenarios seem more favorable. First, in the phase II KEYNOTE-059 trial, the association of pembrolizumab (anti-PD-1 antibody) and conventional chemotherapy based on 5-fluorouracil and cisplatin in 25 naïve patients with metastatic HER2-negative gastric or gastroesophageal junction cancer was associated with an ORR of 60%, a median progression-free survival (PFS) of 6.6 months and a median OS of 13.8 months [8]. The phase III is ongoing (NCT02494583 or KEYNOTE-062). Second, very good results were obtained in third-line or more with pembrolizumab as single agent therapy in patients with metastatic MSI colorectal cancer (CRC) [10]. ORR was 62% whereas median PFS and median OS were not reached. Finally, in patients with advanced anal canal carcinoma in second-line or more, nivolumab (anti-PD-1 antibody) and pembrolizumab were associated with ORR of 24% and 17%, respectively [13,14].

Can We Improve the Efficacy of Immune Checkpoint Inhibitors?

PD-L1 status is generally measured on tumor cells with immunochemistry and most of the studies used a threshold of 1% for considering a tumor as PD-L1 positive. Data on the predictive status of tumor PD-L1 positivity has become increasingly evident. ORR is thus multiplied by two to three in patients with PD-L1 positive tumors compared with those with PD-L1 negative tumors. However, these results must be confirmed on larger populations. Interestingly, the difference in response was only 7% in 74 patients with MSI metastatic CRC treated with nivolumab in a second-line setting, suggesting that MSI status would be a stronger predictive factor than PD-L1 [11].

About 15% of the patients with CRC and 22% of those with gastric cancer have a MSI tumor, which is associated with a better prognosis. In preliminary and ongoing studies, ORR was roughly 60% in patients with MSI tumors compared with less than 10% in case of microsatellite stability (MSS). Recently, Le et al. [15] analyzed the efficacy of pembrolizumab in 86 patients with MSI cancers (76% of digestive tumors). ORR was 53%. After 2 years of follow-up, half of the patients were not progressive and 64% were still alive (median PFS and median OS were not reached). Impressive results of immune checkpoint inhibitors in case of MSI tumor could be explained by higher mutational load leading to higher neoantigens number. In the seminal work of Le et al. [15] mean number of mutations in MSI tumors was 1782 compared with 73 in MSS tumors (p=0.007), suggesting that high mutational, even beyond MSI status, could be a major predictive factor.

Contrary to lung cancer patients, data on the relationship between neoepitopes load and ORR in digestive oncology are lacking. In a study including 619 CRC patients, those with a MSI tumor, but also those with a MSS tumor with PolE and PolD mutations had significantly more mutations, and this was correlated with T cell infiltration and specific survival [16]. Tumor phenotype is a recent concept including different parts of anti-tumor immunity. It would exist three tumor phenotypes, with variable responses to immunotherapy. Inflamed tumors can demonstrate infiltration by a number of subtypes of immune cells (e.g. immune-inhibitory regulatory T cells, myeloid-derived suppressor cells, suppressor B cells and cancer-associated fibroblasts). Tumor-infiltrating lymphocytes (TILs) that express CD8 may also demonstrate a dysfunctional state such as hyperexhaustion [3]. In patients with metastatic melanoma, response to pembrolizumab was associated with CD8+ TILs density at the invasive tumor margin [17]. In CRC, this parameter seemed correlated with ORR and tumor stability (p=0.017) [10], but these findings must be confirmed in larger studies. In immune-excluded phenotype, T cells are present at the boundary of the tumor but they do not penetrate inside because they are peripherally blocked by the stroma. In this situation, efficacy of immune checkpoint inhibitors seems uncertain. In immune-desert phenotype, very few or no CD8+ T cells are present, suggesting the absence of pre-existing antitumor immunity. This tumor type rarely responds to immunotherapy.

Increasing data are available concerning the relationship between gut microbiota and carcinogenesis. In germ-free mice, immune checkpoint inhibitors were ineffective for treating subcutaneous tumors [18]. This defect was overcome by gavage with *Bacteroides fragilis*, by immunization with *B. fragilis* polysaccharides, or by adoptive transfer of *B. fragilis*-specific T cells. Even if these results must be confirmed in humans, gut microbiota seems involved in immune checkpoint inhibitors' sensitivity.

Other factors such as tumor genetic and epigenetic (e.g. TGF-β), host genetic (e.g. TLR4 polymorphisms) or environmental factors (e.g. exposure to sunlight) could also be predictive factors of immune checkpoint inhibitors efficacy.

Perspectives

Immunotherapy recently generated considerable hopes, but results in digestive oncology seem disappointing. However, it was probably necessary to go back to basics of antitumor immunity. With this essential preclinical work, first (dramatic) results were described in patients with MSI tumors. The relationship between mutational load, neoantigens, immunity, and immune checkpoint inhibitors efficacy was made. Tomorrow we will go further, creating for each patient a 'tumor immune ID' available to predict his response to immunotherapy. Recently, a composite score (the immunopheno score) showed a stronger ability for predicting immune checkpoint inhibitors efficacy compared with 'checkpoint' molecules considered on their own [19]. This seminal work is paving the way to a personalized immunotherapy based on a comprehensive analysis of tumor immune environment.

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