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Current Approaches to Immunotherapy in Non-colorectal Gastrointestinal Malignancies

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Abstract

The most frequently diagnosed cancers are non-colorectal gastrointestinal malignancies. Despite advancements in the medical field, the cytotoxic chemotherapy seems to be showing less effective improvements. In this setting, recently the focus of the clinicians and researchers have been diverted towards the study of molecules that are capable of inducing strong anti-tumor/ anti-cancer responses by boosting the immunity. Thus, immunotherapy is found as a very promising tool for the treatment of GI malignancies.

Gastrointestinal non-colorectal malignancies pose a major health problem worldwide. Treatment options like chemotherapy, radiotherapy, surgery, antiangiogenic agents, and mono-colonal antibodies have been the traditional methods for different stages of gastrointestinal cancers, but despite these variable treatments the mortality rate is still high. Research work is still going on to introduce new drugs with better outcomes. An effective and promising treatment, 'next generation immunotherapy', is emerging for several cancer types. Many clinical trials in treating non-colorectal GI malignancies are ongoing. This review paper encompasses the current clinical progress of immunotherapy for non-colorectal gastrointestinal tumors.

Keywords: Tumor, immunotherapy, mono-colonal, malignancies.

Introduction

Gastrointestinal cancers fall under the most commonly occurring malignancy types around the globe. [1] Colorectal ranks second, gastric ranks third and liver rank the fourth most occurring cancer with high mortality rate. GI cancers are treatable via surgical resection, but 20- 25% of patients, during follow up, develop metastatic disease. Moreover, most of the gastrointestinal cancers are diagnosed at last stages where the disease is incurable. [2, 3] Despite many advancements in the medical field, related to targeted cancer therapies, the mortality rate is still high in patients with GI cancer. However, development of better understanding between the immune surveillance and tumor growth in different types of cancers is leading towards broad therapeutic progress. [5] For instance, it is observed that the treatment response and overall survival rate in some tumors, like in genitourinary cancers, non-small cell lung cancer, melanoma and hematologic malignancies. Additionally, the identification of pathogenesis of GI malignancies and immunotherapy effect is becoming a promising cancer management tool. [6, 7]

The idea that some tumors/cancers are 'immunogenic enough' is evolving with a trend of immune-directed therapies and inflammation causing agents. For example, Helicobacter pylori is a major infectious agent for gastric adenocarcinoma, and hepatitis B and C are linked with

liver cancer. Some irritants like tobacco are not carcinogenic, but they trigger the inflammation and makes the person susceptible to cancer and various malignancies. Similarly, various inflammatory bowel diseases lead toward colorectal cancer risks. Basically, mutations and neoantigens are accumulated due to genomic instability caused by the inflammation. Recent studies have also shown an interesting fact related to aspirin; it is found that as aspirin has anti-inflammatory properties, it also acts as an anti-tumor agent against several types of cancer including colorectal cancer. [8]

Several studies have been conducted to observe the impacts of generation immunotherapy on GI malignancies. Despite the slow pace, initial results show effective results. Response rates ranging from 15 to 26% are observed. This review paper includes a comprehensive data of some clinical trials in non-colorectal GI malignancies directed with immune therapies.

Clinical Evidence of Immunotherapy

Pancreatic Cancer

Vaccines are the most frequently used agents for the immunotherapy investigation in pancreatic cancer. In the past, the results were not promising, rather disappointing. Protein based vaccines were used to reverse the genomic alteration from carcinogenic to normal division, but no different survival time was observed.

In recent trials, focus was on to boost the vaccine's effectiveness by using killed bacteria as immune modulators. In the 1st trial, 89 patients with metastatic pancreatic cancer were included. A randomized trial was carried out (2:1) using cyclophophamide/GVAX for immunotherapy in combination with CRS-207 or GVAX all alone. [9] Results showed that, patients who were treated with immunomodulators had more survival time than those who weren't treated with them.

Moreover, patients with the elevated CD8T-cell mesothelin specific response experienced positive results. Neverthless, the ECLIPSE trial showed that chemotherapy and this boosted immunotherapy regimen had almost similar results. In another study, 302 patients were randomized (1:1:1). They received GVAX along with CRS-207, or the later alone. No difference was observed regarding survival time when a comparison was made with patients having chemotherapy (GVAX + CRS-207: 3.9 months; CRS-207: 5.3 months; chemotherapy: 4.7 months). [10]

In another trial, 110 patients were included. They received gemcitabine + IMM-101 or the former alone. From heat killed mycobacterium obuense, IMM is derived. Despite the medical improvement and progression-free survival time, patients who received immunomodulators didn't show much difference in the overall survival time. Thus, clinical trials for pancreatic cancer using immunotherapy wasn't much successful.

However, vaccine mediated immunotherapy in this pancreatic cancer cannot be completely ruled out as some studies and trials showed positive results. Patients who received it showed better survival time. Owing to these results, next generation immunotherapy vaccine trials are underway for promising cancer treatment.

Hepatocellular Carcinoma

The most common primary hepatic tumor, which is developed by chronic inflammation triggered by carcinogens like alcohol, smoking, infection, viral hepatitis B and HCV, is hepatocellular carcinoma (HCC). Thus, immunotherapy is found effective in the treatment of this cancer. An approach, used by the clinicians is adaptive cell therapy, as IFN role in patients with advanced HCC was disappointing. In a randomized trial, patients with HCC were randomized and treated with autologous cytokine-induced killer (CIK) lymphocytes.

This therapy showed improvement in overall survival rates. [11]

A phase trial was carried out with 17 patients having advanced HCC secondary to HCV infection. Anti-CTLA4 antibody tremelimumab was administered in them for 90 days. The overall objective response was 46% as disease was controlled for 6 months. Another large group was kept under observation for investigation the efficacy of ICP inhibitors in HCC patients. 263 patients were added in the randomized study and they were treated with nivolumab for 2 weeks. The overall objective response was 19% for almost 10 months. The radiological complete response was observed in these patients. The DCR was at the rate of 64% and 38% for at least 6 months. The median progression free survival time was almost 4 months and the results were similar between subgroups of patients with alcohol induced liver disease and viral hepatitis induced disease. [12]

On the basis of these results, FDA approved the use of nivolumab in September 2017, as a treatment of HCC (second-line). Owing to the promising data of ICP inhibitors in HCC, further search is going on regarding immunotherapy for various malignancies.

Biliary Tract Cancer

Only one detailed study has been evaluated so far on the role of ICP inhibitors in advanced biliary tract cancer. In the trial, 24 patients went through treatment with a pembrolizumab dosage of 10 mg/kg every 2 weeks, until the treatment duration was completed. Stable disease, no progression and partial response were observed in every 4 of them. The overall treatment duration was as long as 40 weeks. Patients with biliary tract cancer were added to the noncolorectal cohort group, in phase 2 trial. Pembrolizumab was used for treatment in this group as well for dMMR tumors. The overall response rate was 72% (effective). [13]

Neuroendocrine Tumors

NET or neuroendocrine tumors belong to a heterogenous group in which well differentiated tumors, that range from mild to aggressive cancerous phases are present. Immunotherapy is restricted to well differentiated tumors. IFN-alpha monotherapy has shown promising results in stabilizing tumor in 60 to 70% patients who have carcinoid symptoms.

A recent trial was carried put in pretreated patients with well differentiated carcinoid tumors and pancreatic NETs. These patients underwent pembrolizumab monotherapy. The overall response was observed in approximately 12% carcinoid tumors and 6% pancreatic NETs. Though median progression free survival time was 6 months, but the response was durable. The median overall survival time was 21 months for both carcinoid tumor and pancreatic NETs patients. [14, 15]

These results show positive progress in the treatment of cancer; for dMMR positive status holding patients pembrolizumab is an effective treatment. Therefore, further exploration of immunotherapy for the well differentiated tumors is under process. It is difficult to properly identify the immunogenic subgroups for effective checkpoint inhibitors in NET treatment.

Biomarkers (Predictive)

Despite relatively short progress of immunotherapy in trials observed in the above given groups, a subgroup of patients have experienced durable and positive anti-tumor response in every group. However, predictive biomarkers for GI cancers are evaluated in few studies only. For instance, PD-L 1(Programmed Death ligand 1) has been analyzed in my tumor specimens as an effective predicting biomarker. Different antibodies are used for the study of anti-PD-1 or anti-PD-L 1 antibodies. But, heterogeneity exists in tumor PD-L 1, which can suppress the expression of immunotherapy. Moreover, PD-L 1 expression can also

change as the rumor progresses. Data on its expression also varies in primary to metastatic tumors. [16, 17] Therefore, PD-L 1 is currently not showing very effective results as its expression greatly varies from type to type. [18, 19]

MSI-H has been under observation in recent studies. It has shown a potential prediction capacity of immunotherapy regardless of the tumor site. These kind of tumors (MSI-H), have a high molecular abnormality and shows the neoantigen formation along with mutational load. This can facilitate the activation of antitumor response and immune activation. In many types of tumors and GI malignancies, neoantigen has been found. Studies have depicted that patients with MSI-H are more responsive to immunotherapy than patients without MSI. [20, 21] Moreover, in a study encompassing the activity of pembrolizumab in many MSI-H tumor types, 7 out of 16 patients showed positive response to the treatment. Positive correlation between ICP inhibitors and MSI-H tumors have been found. Nevertheless, non MSI-H have also shown positive response to the immunotherapy. However, the study is still going on to better identify the response of different type of tumors to immunotherapy, either they are MSI-H or non MSI-H. [22, 23]

Conclusion

In the nutshell, the emerging dimension of immunotherapy for treating noncolorectal gastrointestinal malignancies has dramatically uplifted the clinical treatment approach. The predictive biomarkers, various protein based vaccines, antibodies and drugs are giving promising results, though at relatively slow pace. Further research is under process in the pursuit of better outcomes for patients with GI cancers.

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