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Review Article

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A Review on Immune Checkpoint Inhibitors used for Major Abdominal Cancers along with their Significant Adverse Events

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Abstract

Cancer survival rates are generally increasing in the United States. These trends have been partially attributed to improvement in therapeutic strategies. Cancer immunotherapy is an example of one of the newer strategies used to fight cancer, which primes or activates the immune system to produce antitumor effects. The first half of this review paper concisely describes the cell mechanisms that control antitumor immunity and the major immunotherapeutic strategies developed to target these mechanisms. The second half of the review discusses in greater depth immune checkpoint inhibitors that have recently demonstrated tremendous promise for the treatment of diverse solid tumor types, including melanoma, colorectal cancer, and others. More specifically, the mechanisms of action, adverse events of major abdominal cancers along with immune checkpoint inhibitors that can be recommended for the respective cancer.

Keywords: Cancer immunotherapy, immune checkpoint inhibitor, oncology nursing, symptom management

1. Introduction

Significant advancements have been made recently, especially in the fields of personalized medicine and cancer therapies. Adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs) are examples of immunotherapy, a type of cancer treatment that uses immune system components to combat tumor cells. With great effectiveness, immunotherapy has become a common treatment for a number of tumors, either by itself or in conjunction with other treatments like radiotherapy and chemotherapy.

The co-inhibitory receptors otherwise called as immune checkpoints such as programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are expressed on the surface of T cells to negatively regulate T cell-mediated immune responses; however, tumor cells take advantage of these co-inhibitory molecules to promote tumor tolerance and T cell exhaustion. Few more examples of immune checkpoints are given below. [1]

Receptor	Expressing cells	Ligands	Ligand-expressing cells
Programmed cell death protein 1 (PD-1)	CD4 (activated/exhausted, follicular), CD8 (activated/exhausted), B cells, dendritic cells (DCs), monocytes, mast cells, Langerhans cells	PD-L1, PD-L2	Antigen-presenting cells, $CD4^+$ T cells, non-lymphoid tissues, some tumors
T-lymphocyte-associated protein 4 (CTLA-4)	CD4 (activated/exhausted, Tregs), CD8 (activated/exhausted), some tumors	CD80, CD86	Antigen-presenting cells
lymphocyte-activation protein 3 (LAG-3)	CD4 (including Treg and exhausted), CD8 (including exhausted), natural killer cells (NK)	MHC class II, LSECtin	Antigen-presenting cells, liver, some tumors
T-cell immunoglobulin and mucin-domain containing-3 (TIM-3)	CD4 (Th1, Th17, Treg), CD8 (including exhausted and Tc1), DC, NK, monocyte, macrophages	Galectin-9, phosphatidyl serine, high mobility group protein B1, Ceacam-1	Endothelial cells, apoptotic cells, some tumors
T-cell immunoreceptor with Ig And ITIM domains (TIGIT)	CD4 (including Treg, follicular helper T cells), CD8, NK	CD155 (PVR), CD122 (PVRL2, nectin-2)	APCs, T cells, some tumors

Figure 1: examples of immune checkpoints [2]

In light of this, ICIs such anti-CTLA-4, anti-PD-1, andanti-PD-L1 can bind to these co-inhibitory receptors, rekindling the immune response against tumor cells. The US Food and Drug Administration (FDA) has approved three different classes of ICIs for the treatment of various cancers, including PD-1 inhibitors (Nivolumab, Pembrolizumab, and Cemiplimab), PDL-1 inhibitors (Atezolimumab, Durvalumab, and Avelumab), and CTLA-4 inhibitors (Ipilimumab). [1]

The list of ICIs with the cancer type indication.

Drug	Target	Approval	FDA-Approved Indications
Nivolumab	PD-1	March 2015	Stage III-B or IV Squamous NSCLC
Pembrolizumab	PD-1	October 2016	Stage IV nonsquamous and squamous NSCLC
Atezolizumab	PD-L1	October 2016	Stage III-B or IV nonsquamous and squamous NSCLC
Cemiplimab	PD-1	September 2018	metastatic cutaneous squamous cell carcinoma
Ipilimumab	CTLA-4	August 2010	stage 3 or 4 malignant melanoma
Avelumab	PD-L1	March 2017	histologically confirmed metastatic Merkel cell carcinoma
Durvalumab	PD-L1	February 2016	Stage III non-small-cell lung cancer (NSCLC)
Pembrolizumab + cis/carboplatin + pemetrexed	-	August 2018	Nonsquamous NSCLC
Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin	-	October 2018	Stage IV Squamou

Figure 2: List of ICIs with the cancer type indication [1]

The development of T cell-targeted immunomodulators that block the immunological checkpoints CTLA-4 and PD1 or PDL1 has unquestionably been the greatest advancement in cancer treatment in the past ten years. The first antibody to suppress an immunological checkpoint (CTLA4), ipilimumab, was approved in 2011. Monoclonal antibodies that target PD1 (pembrolizumab and nivolumab) and PDL1 (atezolizumab and durvalumab) were quickly

developed after this. Anti-PD1/PDL1 antibodies are among the most frequently given anticancer medications today. About 50 different cancer types are now being treated using T-cell-targeted immunomodulators as single medicines or in combination with chemotherapies. More than 3000 clinical trials involving T cell modulators are now underway, accounting for almost 2/3 of all cancer trials.

Later as evidenced by the awarding of the 2018 Nobel Prize in Medicine to James Allison and Tasuku Honjo, two immunologists who were instrumental in developing the idea of ICI-based immunotherapy, immunologists have regained a significant impact in cancer research [3].

Mechanism of Immune checkpoint inhibitors:

Antigen-specific T cells are modulated during immune responses by a variety of mechanisms, including as blocking receptors and regulatory T cells, to prevent excessive or prolonged immune responses. These control mechanisms, also known as "immune checkpoints," restrict T cell responses, especially in patients with cancer where tumor antigens remain for an extended period of time and cause T cell exhaustion. The most well-known receptors for these regulatory systems are cytotoxic T lymphocyte associated protein-4 (CTLA-4) and programmed cell death 1 (PD-1), which have both been the subject of therapeutic research. As a result, immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 (or anti-PD-L1) antibodies have recently been created for use in the treatment of cancer [4].

Important abdominal cancers mentioned:

Colorectal cancer

Colorectal cancer is a disease of the colon or rectum of large intestine where tumor causing (cancer) cells in the tissues develop [5].

Colorectal cancer (CRC) is ranking third in terms of recognition as dreadful cancer (6.1%) and second in terms of fatalities (9.2%). It is estimated that by the year 2035, the total number of deaths from rectal and colon cancer will increase by 60% and 71.5%, respectively. Estimated values of 1.9 Million new cases were recorded during the covid year 2020 [6].

Unusually a point to be mentioned is that is 2012, 52% of deaths have occurred due to colorectal cancer in less developed regions around the world [7].

A senior adult's risk for developing colorectal cancer (CRC) rises after age 65. Due to its low incidence in children and teenagers, CRC is commonly neglected when determining a differential diagnosis for stomach pain, shedding kilos, and anemia [8].

Colorectal cancer (CRC) is evidently considered as the third most frequent cancer in the world even to this day [9].

Signs and symptoms

The various signs and symptoms of colorectal cancer include:

1. Abdominal pain
2. Change in stool texture and blood in the stool
3. Diarrhea
4. Constipation
5. Weight loss [10]

Immune checkpoint inhibitors used in colorectal cancer

Immune checkpoint inhibitors (ICIs) are now being studied in various fractions of patients with metastatic colorectal cancer (mCRC) as a result of their efficacy in a growing variety of highly mutated tumor forms, such as melanoma [11].

Anti-tumor immunity using checkpoint inhibitors, specifically anti PD-1/PD-L1 interaction, is a new study area for treating CRC patients. Immune response has long been a topic of significant interest in a wide range of sectors, such as cancer therapy [12].

Patients who exhibited high levels of microsatellite instability (MSI-H) and a high infiltration of T cells that express checkpoint receptors, such as PD-1, PD-L1, or CTLA-4, which are primarily present in the subset of mismatch repair-deficient (dMMR) tumors, responded to immunotherapy [13].

Immunological checkpoints like PD-1 may target the CRC classes. The two PD1 blockers currently making the most progress in the pharmaceutical development processes are nivolumab (a monoclonal antibody against human PD-1) and pembrolizumab (the first PD-1) inhibitor [9].

The first ICI to receive US Food and Drug Administration (FDA) approval for treatment in individuals with dMMR Mcrc was pembrolizumab, a PD-1 receptor blocker [14].

Patients with metastatic, high-microsatellite-instability CRCs (MSI-H), and non-MSI-H CRCs were examined after receiving either nivolumab or ipilimumab. Nivolumab alone or in combination with ipilimumab was observed to be well tolerated in the majority of patients and to have encouraging clinical activity and survival, especially in MSI-H metastatic CRCs [12].

Nivolumab is a completely improved humanised monoclonal immunoglobulin G4 and anti-PD-1 antibody. This substance encourages the generation of cytokines and the multiplication of T cells by inhibiting PD-1's interaction with PD-L1 and PD-L2.

Patients with metastatic colorectal cancer who have received significant amounts of prior treatment and whose tumors have low mismatch repair (MMR) or high microsatellite instability (MSI) levels can utilize nivolumab (at a dose of 240 mg every two weeks) [15].

Endometrial Cancer

Endometrial cancer is the most prevalent gynaecologic malignancy in the United States. It is made up of a variety of unique histological subtypes. Two Bokhman histopathology categories, which explain the pathophysiology, behaviour, and risk factors, have historically been used to categorise endometrial cancer [16].

Endometrial cancer (EC) is becoming more common everywhere. Patients with early-stage cancer still have a favourable prognosis, but patients with recurrent or metastatic disease have a dismal prognosis and, until recently, had few therapy options [17].

From 2005 to 2014, the death rate linked to endometrial cancer rose by almost 1.4% year [16].

In 2017, there were roughly 61,380 new instances of uterine cancer, and the disease claimed 10,920 lives [18].

Patients with advanced and recurring illness have a poor prognosis and have low response rates to conventional chemotherapy, even though over 80% of endometrial malignancies are discovered in the early stages and have a 5-year survival rate that is greater than 95%. According to the American Cancer Society, there will be 65,620 new cases of uterine cancer diagnosed in the country in 2020, and 12,590 women are expected to pass away from the disease [19].

All recurrent endometrial cancer patients who underwent evaluation at The University of Texas MD Anderson Cancer Centre from September 2019 to October 2020 in order to plan their pembrolizumab and lenvatinib treatment were reviewed for inclusion into the study [20].

527,600 women received endometrial cancer diagnoses in 2012 across the globe. Between 1.7 and 2.4 deaths per 100,000 women were reported. More than 10,920 endometrial cancer fatalities and 61,380 new cases expected to be diagnosed in the US in 2017 [16].

Signs and Symptoms

The majority of women with endometrial cancer (approximately 90%) report experiencing:

1. Abnormal uterine bleeding, which is frequently accompanied by vaginal discharge and pyometra and typically occurs during menopause [21].
2. A sensation of weight or heaviness in the pelvic region.
3. Unintentional weight loss
4. Exhaustion
5. Nausea

6. Pain in various bodily areas, such as the legs, back, and pelvic region. Additionally, some people find it painful to urinate or have trouble emptying their bladder [22].

When compared to controls, the prevalence of postmenopausal bleeding and atypical vaginal discharge symptoms was considerably higher in EC. Such symptoms should trigger an emergency gynaecological assessment and raise suspicion of a malignant condition [23].

Immune checkpoint inhibitors used in endometrial cancer

- Immune check-point inhibitors will undoubtedly play a role in the treatment of EC, either alone or in combination with other targeted medications [24].
- By inhibiting negative regulators of T-cell function found on both immunological and tumour cells, immune checkpoint drugs improve antitumor immunity [25].
- For individuals who fail first-line therapy, pembrolizumab is a successful treatment choice [26].
- Patients with advanced endometrial cancer who received lentitinib + pembrolizumab had significantly longer progression-free survival and overall survival than those who received chemotherapy [27].
- In patients with chemotherapy-pre-treated endometrial cancer and positive for programmed death-ligand 1 (PD-L1), immune checkpoint medicines have shown a very excellent safety profile and anti-tumor effectiveness.
- Some of the receptor/ligand combinations between T-cells and tumour cells, such as CTLA-4/B7 (cytotoxic T lymphocyte-antigen 4) and PD-1/PD-L1 (programmed cell death receptor and ligand), are inhibitory in nature.
- As a result, CTLA4 serves as a negative immunological regulator. It inhibits the ability of the T cell co-stimulatory receptor CD28 to bind to the B7 ligand produced on tumour cells.
- Immune checkpoint inhibitors have been studied in the context of advanced disease and palliative care for endometrial malignancies.
- The Food and Drug Administration (FDA) has approved monoclonal antibodies (mAbs) that target PD-1, PD-L1, and CTLA-4 for a number of cancers [28].
- A lower lenvatinib beginning dose exhibited comparable survival rates with fewer toxicity compared to the recommended level [20].
- Pembrolizumab has been approved by the Food and Drug Administration as a monotherapy and in combination with lenvatinib due to the encouraging results seen with CPB in the recurrent situation [29].

Prostate cancer

Prostate Cancer defines when the cells in the body grow without any control. The cells which are near to any part of it can become cancer cells and they can spread over the other parts of the body. It is a type of gland which can only grow in the males. It is located below the bladder and in front of the rectum. It is a lethal disease with the limited treatment options.

PCa incidence rates in affluent nations are 37.5 per 100,000 and 11.3 per 100,000 in developing countries, respectively, while fatality rates are 8.1 per 100,000 in developed countries and 5.9 per 100,000 in poor countries. There are currently 10 million males who have PCa diagnoses. More than 400,000 people die from PCa each year worldwide, and by 2040, it's predicted that number will rise to more than 800,000 [30].

There are roughly 30 000 new cases of prostate cancer worldwide every year, and there are 9940 fatalities. The advantages of prostate cancer early detection (as well as any potential drawbacks) have been widely debated [31].

Prostate cancer (PCa), an age-related disease predominantly affecting men over the age of 60, is the most frequently diagnosed type of cancer and the second most common cause of cancer-related death, after skin cancer, among men worldwide [32].

Prostate cancer was the second most prevalent cancer worldwide and the fifth largest cause of cancer-related deaths among males in 2020. Once metastatic, it cannot be cured. Treatment options for metastatic prostate cancer mostly include either cutting-edge hormonal treatments or androgen deprivation therapy, which forms the cornerstone of the management of the disease [33].

Signs and symptoms

1. Frequent and occasionally urgent urge to urinate, especially at night.
2. Weak pee flow or intermittent urine flow.
3. Bladder control issues.
4. Bowel incontinence, also known as faecal incontinence.
5. Erectile dysfunction and painful ejaculation.
6. Hematospermia, or blood in the sperm or urine.
7. Chest, hips, or low back may hurt [34].

Advanced prostate cancer patients may also go undiagnosed. The cancer's size and the extent of its internal dissemination will determine any potential symptoms. The following sign & symptoms of advanced prostate cancer can also be present:

- Bone pain
- unexplained weight loss
- tiredness [35]

Immune checkpoint inhibitors used in prostate cancer

In patients using enzalutamide who were progressing, three (30%) of the first 10 patients treated with the anti-PD-1 antibody pembrolizumab experienced a 50% or greater drop in serum PSA, and two of these patients also experienced a radiographic response [36].

PD-L1 over 1% of the tumor or stroma in advanced prostate cancer was treated with an anti-PD-1 inhibitor, but only 17.4% of patients showed an overall response without a complete response, and 39.1% of patients had progressive disease, which limits the use of pembrolizumab for the treatment of metastatic prostate cancer [37].

The clinical activity of combined CTLA4 and PD1 blockade was initially evaluated in a single-arm, open-label, involving 15 patients with AR-V7-positive mCRPC who were given nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) for four cycles, followed by nivolumab maintenance therapy [38].

Adverse events of immune checkpoint inhibitors

The acute clinical toxicity of these substances is widely documented, but chronic effects have not been as thoroughly documented.

These chronic sequel adverse events, however typically of modest severity, can have an impact on the endocrine, rheumatologic, pulmonary, neurological, and other organ systems. Fatal toxicity can affect 0.4-1.2% of individuals and have a wide range of clinical symptoms [39].

These drugs' ability to stimulate the immune system has resulted in a specific class of side effects known as immune-related adverse events (irAEs). The most common irAEs include endocrinopathies such hypophysitis and thyroid dysfunction as well as diarrhoea, colitis, hepatitis, skin toxicities, and diarrhoea [40].

There are established consensus standards for treating the most typical irAEs, including as rash, colitis, hepatitis, endocrinopathies, and pneumonitis [41].

Bullous dermatosis of the skin, inflammatory dermatitis and skin rash, extreme skin reactivity, haematological haemolytic anaemia due to autoimmunity, thrombotic thrombocytopenic purpurae acquired, haemolytic uremic syndrome, anaemia aplastic, lymphopenia, thrombocytopenia immune, haemophilia acquired, cardiovascular myocarditis, rhythmic pericarditislinked ventricular failure with heart failure, vasculitis, thrombosis of the veins, episcleritis, blepharitis, andocular verities/iritis [42].

There are a variety of long-term negative effects that immune checkpoint inhibitors might have, most of them minor. (Adrenal insufficiency) Addison disease,Eye-related problems, such as conjunctivitis and blurred vision, arthritis/joint discomfort, Pituitary gland inflammation, thyroiditis or hypothyroidism [43].

Bottom line

The closure line of the above review article on immune check point inhibitors is to portray the application of immune checkpoint inhibitors in various cancers mentioned above. Hoping the article was informative and considering future prospects in the field of immunotherapy.

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