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Gastrointestinal Events Associated with Ipilimumab, Pazopanib, Anti PD1-Antibody and Their Management: Single and Combination Therapies

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Abstract

Immunotherapy of cancer has made significant advances in the past few years mainly due to the improved understanding of underlying principles of tumor pathology and immunology. Currently many malignancies are being treated by immunotherapy.

Including malignant melanoma, advanced renal cell carcinoma (RCC), Non-small cell lung cancer, and prostate cancer. In these malignancies targeted therapies like multi kinase inhibitors also play an important role. These therapies are not without significant adverse events. This article reviews gastrointestinal side effects reported with immunotherapeutic agents like ipilimumab, programmed death-1 (PD-1) antibody inhibitors and the multi-kinase inhibitor, pazopanib and their management. Awareness and education of Health care professionals (HCPs) and patients are critical in identifying and managing these adverse events. We have reviewed contemporary scientific literature and have summarized the results. Close monitoring and early treatment is of paramount importance in handling these event with the majority of events reversible or medically manageable per established treatment guidelines.

Keywords: Immunotherapy; Malignant Melanoma; Metastasis; T cells

List of Abbreviations

CTLA-4: Cytotoxic T-Lymphocyte Antigen-4;
RCC: Renal Cell Carcinoma;
irAE: Immune-Related Adverse Events;
mAbs; Monoclonal Antibodies;
TKIs: Tyrosine Kinase Inhibitors;
ALT: Alanine Trans Aminase;
PD-1: Programmed Death-1;
AEs: Adverse events

Introduction

Recognition of tumor cells as foreign and activation of the immune response constitutes the key steps in the immunotherapy of cancer [1]. Immunotherapy utilizes the body's own immune system to combat cancer by stimulating the immune system to function more effectively to identify and destroy cancer cells.

The cytotoxic T-lymphocyte antigen-4 (CTLA-4, also known as CD152) receptor is one of the co-stimulatory receptors that have a major negative regulatory effect on the T cell. CTLA-4 has a function in maintaining tolerance to self-antigens [2]. CTLA-4 is expressed only after the start of T-cell activation and this molecule may therefore play a role in tumor evasion of the immune system by suppressing the immune response and allowing cancer cells to be recognized as "self." Once the immune response develops, the CTLA-4 molecule is expressed on the cell surface. It out competes the interaction with B71 and results in the down regulation of the T cell response. Blockade of this pathway allows activation and proliferation of T cells to proceed, thereby permitting an antitumor effect [3]. However, immune checkpoint blockade can result in the breaking of immune self-tolerance, in turn inducing a novel syndrome of autoimmune inflammatory side effects, labelled as "immune-related adverse events, (irAE)" that includes rash, colitis, hepatitis, and endocrinopathies [4-5].

Multiple kinase inhibitor treatment has emerged as a new modality of therapy for advanced renal cell carcinoma and advanced soft tissue sarcomas. Pazopanib is an inhibitor of numerous tyrosine kinases, including vascular endothelial growth factor receptor and platelet-derived growth factor receptors (PDGFR). It is involved in inhibiting signaling pathways, angiogenesis, and cell proliferation [6-7]. The most common adverse events reported with pazopanib included diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting [6-7]. Grade 3/4 toxicities were mostly hepatic in nature, with elevations occurring in aspartate aminotransferase, alanine aminotransferase, and bilirubin [7].

Another area of focus in cancer therapy is programmed death-1 [PD-1] antibody inhibition. PD-1 is a regulatory checkpoint receptor expressed on T-cells that responds to ligand signaling via either of its two native ligands, PDL-1 and PDL-2 [8-10]. Ligand binding to PD-1 induces a dysfunctional lymphocyte phenotype that protects normal cells and tissues during an immune response [11]. Several cancers also express PD-1 ligands (predominately PDL-1) as a means to escape immune surveillance and allow tumor growth to proceed unabated [12]. A growing number of monoclonal antibodies (mAbs) have been developed to either murine or human PD-1 or PDL-1 which effectively block PD-1 / PDL-1 binding both in vitro and in vivo [13]. Moreover, impressive clinical efficacy in solid tumors has been evinced for these molecules as both single agents and when combined with other therapies including CTLA-4. Despite these impressive results, adverse events have been reported for PD-1 axis blockade which must be considered carefully as more patient data emerges to guide prevalence across indications and patient populations. The common treatment-related adverse events included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea [14].

These novel therapeutics have emerged/emerging as promising therapy for different cancers. We have reviewed the contemporary literature to understand the common adverse events and their management. In this review we will describe the gastro intestinal adverse events associated with these drugs and their management.

Ipilimumab

Ipilimumab is a human monoclonal antibody that blocks Cytotoxic T-lymphocyte– associated antigen 4 (CTLA-4) to promote antitumor immunity and has shown activity in patients with metastatic melanoma when it has been used as monotherapy in phase 2 studies. CTLA-4 is an immune checkpoint molecule that down-regulates pathways of T- cell activation [16]. It is the first drug approved for the treatment of melanoma by the FDA. Ipilimumab competitively binds to CTLA-4 more efficiently than B7 while preserving CD28 signaling [17-18]. Blockade of CTLA-4 signaling prolongs T-cell activation and restores T-cell proliferation, thus amplifying T-cell–mediated immunity and the capacity of the patient to mount an effective antitumor immune response [19].

The most common adverse events associated with ipilimumab therapy are immune- related; a recent pooled analysis of 14 completed Phase I–III ipilimumab clinical trials showed that 64.2% of patients experienced an irAE of any grade. Most of the AEs are indicative of the immune-based mechanism of action of ipilimumab and can involve multiple organ systems [20]. Toxicities of the skin, gastrointestinal tract, endocrine system, and liver are the commonly reported irAEs with ipilimumab. Majority of the irAEs develop during the induction phase (Ipilimumab is administered as a 90-minuteintravenous infusion at a dose of 3 mg/kg every 3 weeks for four doses over a period of

12 weeks); however, a minority occur weeks to months after discontinuation of ipilimumab. Average time for resolution of irAEs varied from 4.3 to 7.7 weeks. Prompt reporting of early signs of AEs by patients and caregivers may expedite the recovery. Patient education and assessment of willingness to adhere to recommendations is very important in the use of immunotherapy [20]. Most ipilimumab-associated irAEs including grade 3/4 symptoms, developed within 12 weeks of initial dosing and resolved within 12 weeks of onset. IrAEs were well characterized in their evolution and could be managed following established algorithms [21].

GI irAEs:

The most common irAEs that affect the gastrointestinal tract present as diarrhea or colitis. IrAEs such as diarrhea and colitis, or events that involve esophagus, duodenum, ileus and stomach may occur due to the dysregulation of GI mucosal immunity as a result of CTLA-4 blockade with ipilimumab [22-24]. This dysregulation of GI mucosal immunity is likely to be

a distinct clinicopathologic entity that differs from that seen with inflammatory bowel diseases [25]. Incidence of GI irAEs (e.g. colitis, diarrhea) at 3mg/kg ipilimumab monotherapy was 28.2%; of which 20.6% was low grade (Grade 1-2) and 7.6%was high grade (Grade 3-4). Although the average time to onset of diarrhea was

6-8 weeks, it can occur as early as 3 days after initiation of therapy rapidly progressing to colitis [26], hence early multidisciplinary management is crucial.

Patients may present with changes in normal bowel habits or changes from baseline (eg, last week, last visit), diarrhea, abdominal pain, blood or mucus in the stool with or without fever, peritoneal signs consistent with bowel perforation, and ileus. Extensive ulcerations on colonoscopy indicate severe cases, but presence of a mild colitison macroscopic evaluation could be misleading, because biopsies of mild macroscopic changes often show severe inflammation [27]. Colitis may be associated with other GI complications, such as aphthous ulcers, esophagitis, gastritis and jejunitis [18, 28] and can demonstrate a diverse range of inflammatory histopathologies [29-32]. Diarrhea and/or colitis can become life-threatening [28, 33-35] with reports of fatal bowel perforation and sepsis [33, 35and 36].

Grade 2 gastrointestinal irAEs are designated as up to six stools above baseline, associated with abdominal pain and mucus or blood in stool. Grade 3-4 irAEs are described as diarrhea of at least seven stools above baseline, accompanied by fever, ileus, and/or peritoneal signs [37]. The incidence of life-threatening perforation is rare; presenting symptoms include severe diarrhea and diffuse colitis with crypt abscess formation on colonoscopic biopsy. Infectious etiologies should be ruled out in symptomatic patients and endoscopic evaluation should be considered for persistent or severe symptoms [20].The median time to onset was 7.4 weeks (range: 1.6–13.4) and 6.3 weeks (range: 0.3–18.9) after the initiation of ipilimumab for patients with Grade 3–5 enterocolitis and with Grade 2 enterocolitis, respectively [37].

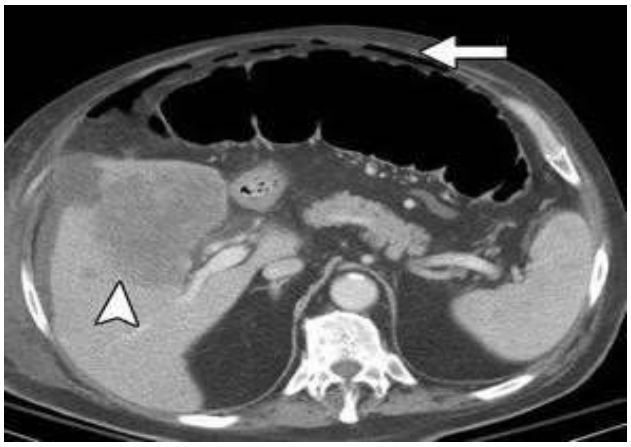

Figure 1. 73-year-old man receiving ipilimumab for treatment of metastatic melanoma. Axial CT image of abdomen shows transverse colon (arrow) is grossly dilated with free intraperitoneal air, indicating intestinal perforation. Note also large metastasis (arrowhead) in right lobe of liver. Patient underwent colectomy, and pathology revealed severe active inflammation consistent with ipilimumab-induced colitis [60].

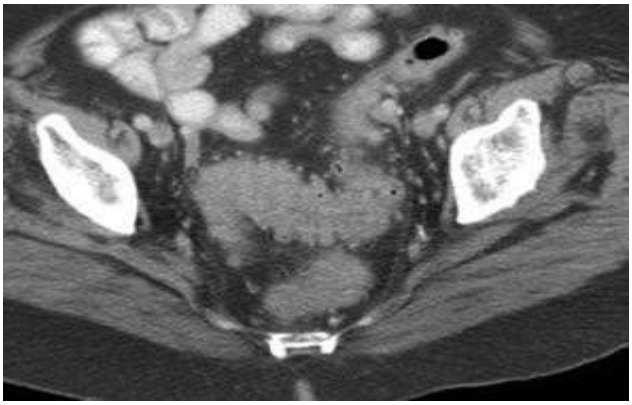

Figure 2. 71-year-old woman receiving ipilimumab for treatment of metastatic melanoma. Axial CT image of pelvis shows mural thickening of sigmoid colon with adjacent fatstranding and mesenteric hypervascularity. Colonic biopsy revealed moderate-to-severe active inflammation, consistent with ipilimumab-induced colitis [60].

Management

Bowel perforation and colectomy rates, and serious GI irAEs have been shown to reduce by 50% with the early initiation of diarrhea treatment guidelines [38]. Other causes of diarrhea such as infectious causes should be ruled out at the onset of diarrhea or colitis in all patients treated with ipilimumab. For patients with persistent or severe symptoms GI consultation and colonoscopy is strongly recommended. The aim of GI irAE resolution is to reverse the inflammation caused by the immune response, hence the use of immunosuppressive agents. It is important to maintain frequent contact with the patient to monitor symptoms and any changes in symptoms to prevent further escalation in severity. Any reports of change in pain should be evaluated for the possibility of perforation, peritonitis or pancreatitis. Analgesics (e.g., morphine) should be used with caution to control abdominal pain, as they may mask symptoms of such severe complications.

Management of mild (Grade 1) GI irAEs

1. Dietary modifications: Initiating BRAT diet (bananas, rice, apples, and toast), maintaining fluid intake and avoiding lactose containing products is recommended.

2. Symptomatic treatment with loperamide or diphenoxylate.

3. Oral hydration and electrolyte substitution.

Management of moderate (Grade 2) GI irAEs

1. Dietary modifications: Initiating BRAT diet (bananas, rice, apples, and toast), maintaining fluid intake and avoiding lactose containing products is recommended.

2. Diphenoxylate hydrochloride and atropine sulfate four times per day and budesonide 9 mg once per day or divided TID.

3. Monotherapy with budesonide is not recommended for grade ≥2 diarrhea associated with ipilimumab therapy [39].

4. Treat with corticosteroid therapy (e.g., prednisone 1 mg/kg qd or equivalent) [27]and diagnostic endoscopy should be performed if symptoms persist (5–7 days) or relapse.
5. Ipilimumab treatment should be withheld for moderate irAEs until improvement to mild severity or complete resolution [40].

Management of grade 3 or 4 GI irAEs:

1. Patients with bloody diarrhea and severe colitis observed on endoscopy should be hospitalized and started on i.v. steroids.

2. Ipilimumab treatment should be withheld for moderate irAEs until improvement to mild severity or complete resolution [40].

3. High-dose intravenous methylprednisolone (2 mg/kg for 1–2 weeks) followed by a taper lasting a minimum of 30 days [41,42].

4. A rapid reduction in corticosteroid dose should be avoided, as this may increase the risk of developing recurrent symptoms and the need for escalation of care [41].

5. Alternatively, a steroid regimen with intravenous dexamethasone 4 mg every 6 hours, initially over 7 days, is another treatment option [41].

6. If there is no improvement within 5–7 days, or relapse occurs, single dose infliximab 5 mg/kg should be considered (unless contraindicated [e.g., sepsis and other serious infections, or perforation are present) [41,42]. An additional dose after a 2-week interval (possibly in combination with mesalamine, loperamide and hydrocortisone enemas) may be required.

7. Prolonged diarrhea in spite of steroids, bowel rest, total parenteral nutrition, and infliximab is an indication for either a diverting ileostomy or partial/complete colectomy [26].

Permanently discontinue ipilimumab for any of the following

a. Severe or life-threatening enterocolitis (Grade 3 – 5)

b. Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day c. Failure to complete full treatment course within 16 weeks from administration of
first dose [40].

Pazopanib

Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, PDGFR a and b, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms) [36]. It has been approved by the U.S. Food and Drug Administration for treatment of patients with advanced renal cell cancer and advanced soft tissue sarcoma who have received prior chemotherapy.

Adverse events

The most common adverse events reported included diarrhea, change in hair color, nausea or vomiting, feeling tired, decreased weight, tumor pain, muscle or bone pain, headache, taste changes, trouble breathing, and change in skin color [6, 42-47]. The most common treatment emergent laboratory abnormality was elevation of liver transaminases [6].

In the phase III trial, the incidence of grade 3 to 4 alanine trans aminase (ALT) increase was 12%, and 53% of patients experienced hypertransaminasemia [6]. Meta-analysis of all pazopanib-containing trials confirmed an incidence of all grade ALT increase at 42% and high-grade ALT at 8.2%.Hepatotoxicity is a concern for clinical application. Two hepatotoxicity-related deaths were reported among the 977 patients (0.2%) described in published clinical literature. Close monitoring and appropriate management are recommended during the therapy [22,59].

Overall, approximately 50% of patients experienced diarrhea of any grade during pazopanib treatment in the RCC studies. The majority of these diarrheal adverse events was mild-to-moderate in severity (Grade 1 and 2) [6]. The incidence of Grade 3 or 4 diarrhea was low.

Management

Diarrhea is a one of the most common side effect of many cancer treatments and, in rare cases, may develop into a debilitating and potentially life-threatening condition in presence of other co-morbidities like dehydration, renal insufficiency, electrolyte imbalances and therapy-induced neutropenia [48]. Early identification and intervention is critical for the optimal management of diarrhea [48]. Patients should be educated on the signs and symptoms of diarrhea, and to report any change in bowel pattern to their healthcare professional.

Management of uncomplicated (CTC grade 1–2) diarrhea [49,50]

1. Stop all lactose-containing products, alcohol and high-osmolar supplements

2. Drink 8–10 large glasses of clear liquids a day (e.g. Gatorade or broth)•

3. Eat frequent small meals (e.g. bananas, rice, apple sauce, toast and plain pasta)

4. Instruct patient to record the number of stools and report symptoms of life-threatening sequelae (e.g. fever or dizziness upon standing)•

5. For Grade 2 diarrhea, hold cancer therapy until symptoms resolve and consider dose reduction. Administer standard dose of loperamide: initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool.

Management of severe (CTC grade 3-4) diarrhea [50,52]

1. Admit to the hospital and administer octreotide (100–150 μg SC TID or IV [25–50 μg/hour] if dehydration is severe with dose escalation up to 500 μg TID)

2. Start IV fluids and antibiotics as needed (e.g. fluoroquinolone)

3. Stool work-up, CBC and electrolyte profile

Anti PD1 antibody or PD-1 inhibitors:

Anti-PD-1 is a fully-human antibody that targets the inhibitory receptor expressed on activated T-cells called PD-1 or programmed death-1. Programmed death 1 (PD-1) is a key immune checkpoint receptor expressed by activated T cells, and it mediates immunosuppression. PD-1 functions primarily in peripheral tissues where T cells may encounter the immunosuppressive PD-1 ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC) that are expressed by tumor cells, stromal cells, or both [53-56]. Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity. Anti–PD-1 antibody produced objective responses in approximately one in four to one in five patients with non–small-cell lung cancer, melanoma, or renal-cell cancer; the adverse-event profile does not appear to preclude its use [14].

Adverse events:

Common treatment- related adverse events included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Grade 3 or 4 treatment-related adverse events were observed in 41 of 296 patients (14%). Drug-related serious adverse events occurred in 32 of 296 patients (11%). The spectrum, frequency, and severity of treatment related adverse events were generally similar across the dose levels tested. Drug-related adverse events of special interest (e.g., those with potential immune-related causes) included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis [14].

These adverse events were predominantly grade 1 or 2 and were managed with treatment interruption or discontinuation. Nine patients were treated with glucocorticoids for the management of adverse events, with improvement or resolution of events in all patients. Guidelines for treatment of Diarrhea.

Management of uncomplicated (CTC grade 1–2) diarrhea [57]

1. Stop all lactose-containing products, alcohol and high-osmolar supplements

2. Drink 8–10 large glasses of clear liquids a day (e.g. Gatorade or broth)• Eat

frequent small meals (e.g. bananas, rice, apple sauce, toast and plain pasta)

3. Instruct patient to record the number of stools and report symptoms of life- threatening sequelae (e.g. fever or dizziness upon standing).

4. For Grade 2 diarrhea, hold cancer therapy until symptoms resolve and consider dose reduction. Administer standard dose of loperamide: initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool.

Management of severe (CTC grade 3-4) diarrhea [57]

1. Admit to the hospital and administer octreotide (100–150 μg SC TID or IV [25–50 μg/hour] if dehydration is severe with dose escalation up to 500 μg TID)

2. Start IV fluids and antibiotics as needed (e.g. fluoroquinolone)

3. Stool work-up, CBC and electrolyte profile

4. Discontinue cytotoxic chemotherapy until all symptoms resolve; restart chemotherapy at reduced doses.

Combination Therapy

Many drugs, which are commonly used for the treatment of other cancers, have little or no efficacy on melanoma. Within the available therapeutic options chemotherapeu-

tic agent dacarbazine is the most used, but the patient response rate is only 10-20% and median survival 8-9 months making its use for from ideal. Although interleukin-2 is very effective and has long term benefits, the positive response rate is very low with less than 1 in 20 patients. Recently, more targeted therapies have been developed and approved - vemurafenib (Zelboraf) targets the common BRAF V600E mutation common to 50% of melanomas, while ipilimumab (Yervoy) blocks the imunomodulatory T-cell signaling through the CTLA-4 antigen that prevents the body rejecting the tumors. Both of these therapies provide dramatic results initially but have the risk of either high relapse rates (with the returning tumor highly resistant to the therapy) or significant toxicity. Therefore, there is a continuing need for more treatment options that can be used against this tumor type, either alone or in combination with existing treatments [58].

Combination of an approved drug and an NCE already in clinical development provides potent activity, novel, synergistic mechanism of action, potential for rapid development, complimentary mechanism to existing therapies. Researchers investigating cellular mechanisms that underpin the resistance of many malignant melanomas to chemotherapeutic agents have identified a set of clinical-stage compounds that can block the resistance mechanisms, providing potent new drug combinations that show good efficacy against this tumor type [58].

The data on the efficacy and safety profile is limited as most of the studies are under clinical trials and no results were released. One such trial we can anticipate is the various combination therapies with Ipilimumab,Pazopanib and anti PD1 antibody. Efficacy wise, these combination therapies may be superior as they have different targets of action at various levels. But the major concern is the safety of the combination therapies and management of adverse events. Among the adverse events gastro intestinal events are most important, as these have more effect on the compliance, morbidity and mortality of the patient.

More of immune related colitis can be anticipated with combination therapies with ipilimumab and Anti PD1 antibody as both the drugs have their target as immune receptors. However, these irAEs can be managed with early intervention with steroids and interruption of study therapy and following the management algorithms. Additionally, the role of prophylactic steroids should also be considered when these is a high chance of irAEs. In the recent phase I trial of concurrent therapy with nivolumab(an antibody against the programmed death 1 [PD-1] receptor) and ipilimumab in patient with advanced melanoma reported that concurrent therapy with these agents had a manageable safety profile and provided clinical efficacy that appears to be distinct from that of monotherapy [61]. In addition to this, administering lambrolizumab (anti PD-1 antibody) to patients with advanced melanoma, who had disease progression while they had been receiving ipilimumab, resulted in a high rate of sustained tumor regression, with grade 1 or 2 toxic effects [62,63]. Such combinations of CLTA-4 inhibitors and anti PD-1 antibody regimens could be a potential combination to increase the efficacy and safety profile in patients with advanced melanoma.

Other combination therapies such as pazopanib + Ipilimumab/anti PD1 antibody, gastrointestinal events should be clearly differentiated whether they are immune related or not and should be treated appropriately. Meticulous use of investigations such as colonoscopy and biopsy should be considered for early diagnosis and management.

Discussion

Thorough understanding of the basic immunology has improvised our interpretation of the complex mechanisms of immune regulation, and this knowledge has been translated into the practical application with novel agents like CTLA4-targeted antibody (ipilimumab) which showed efficacy in the treatment of melanoma. CTLA4-targeted antibody therapy is the first of its kind and has opened a new field in immunotherapy that is based on the targeting of inhibitory pathways and immune checkpoints. The dramatic antitumor responses that were seen in some patients as a result of treatment with ipilimumab provide, for the first time, a significant subset of patients who could be investigated for potential biomarkers that correlate with clinical outcome. Next- generation immunotherapy agents, such as PD1-targeted antibodies, have also led to tumor regression in some patients. We must conduct careful studies in treated patients so that we can gain knowledge to develop even more effective therapies [51].

Immunomodulation with the anti-CTLA-4 monoclonal antibody ipilimumab has been shown to extend overall survival (OS) in previously-treated and treatment-naive patients with unresectable stage III or IV melanoma. Blockade of CTLA-4 signaling with ipilimumab prolongs T-cell activation and restores T-cell proliferation, thus amplifying T-cell–mediated immunity and the patient's capacity to mount an effective antitumor immune response. While this immunostimulation has unprecedented OS benefits in the melanoma setting, it can also result in immune-mediated effects on various organ systems, leading to irAEs. Ipilimumab-associated irAEs are common and typically low grade and manageable, but can also be serious and life-threatening. The skin and gastrointestinal tract are most frequently affected, while hepatic, endocrine, and neurologic events are less common. With proper management, most irAEs resolve within a relatively short time, with a predictable resolution pattern. Prompt and appropriate management of these irAEs is essential and treatment guidelines have been developed to assist oncologists and their teams. Implementation of these irAE management algorithms will help ensure that patients are able to benefit from ipilimumab therapy with adequate control of toxicities [27].

Pazopanib an oral multi targeted tyrosine kinase inhibitor approved for treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma. Pazopanib has demonstrated a tolerable side effect profile. The most common adverse effects included fatigue, nausea, hair depigmentation, and hypertension. The most common laboratory adverse events included elevation of alanine aminotransferase and aspartate aminotransferase. Grade 3 or 4 adverse events included hypertension, transaminase elevation, diarrhea, and fatigue. Most of the adverse events are manageable with standard therapy protocols.

Anti PD-1 antibodies or anti PD-1 inhibitors therapy is another promising novel area in cancer treatment. Anti PD-1 antibodies are under trial for the treatment of advanced melanoma, non–small-cell lung cancer, castration resistant prostate cancer, or renal-cell or colorectal cancer. By virtue of the mechanism of action these drugs are associated with immune related side effects including pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis [14].

Immunotherapeutic agents due to their characteristic and distinctive mechanism of action, elicits a number of specific irAEs. Time to onset and resolution of these immune-related AEs follow a predictable temporal pattern but can vary from patient to patient. Nevertheless, guidelines provided by the manufacturer for management of irAEs and a nurse's checklist for signs and symptoms of irAEs can greatly assist health care providers in identifying and treating such events. Prompt and careful monitoring of irAEs and recognition of the same by nurses may play a crucial role in benefiting the patients from therapy and optimizing the patient outcomes [20].

Conclusion

Immunotherapy and targeted therapy have become prime areas of focus in cancer treatment. Treatment related adverse events have greater impact on adherence to treatment and in turn on overall survival. Hence, prevention, identification and careful management of treatment related adverse events plays a pivotal role in the success of these novel therapies.

Conflict of Interest

This paper has been written without external financial funding. There is no conflict of interest.

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