ASSESSMENT OF SAFETY PROFILE OF IMMUNOTHERAPEUTIC AGENTS OTHER THAN IMMUNE CHECKPOINT INHIBITORS IN CANCER PATIENTS

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ABSTRACT

According to WHO the adverse drug reaction is defined as the response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

Malignant cells have the capacity to rapidly grow exponentially and spread in part by suppressing, evading and exploiting the host immune system. Immunotherapy is a form of oncologic treatment directed towards enhancing the host immune system against cancer. In recent years a number of new molecules commonly known as biological therapies have been approved for the treatment of various cancers. These innovative compounds have improved treatment efficacy and have probably contributed to increase in survival length. However, these agents are not deprived of toxicity, which can impair quality of life and may occasionally be life threatening. Immunotherapeutic agents were significantly associated with a higher risk of developing adverse effects in cancer patients.[1]

Bevacizumab was significantly associated with higher risk of developing venous thromboembolism in cancer patients. Other clinically relevant adverse effects such as GI perforation such as bleeding and leukopenia. Trastuzumab has led to a significant improvement in the treatment of both advanced and early breast cancer by over expressing HER-2 receptors. It was associated with an important adverse effect cardiotoxicity.[2]

Pertuzumab is a novel humanized monoclonal antibody that blocks human epidermal growth factor receptor 2 (HER-2) dimerization. The Food and Drug Administration has approved Pertuzumab in combination with Trastuzumab and docetaxel for the treatment of patients with HER-2 positive metastatic breast cancer. Nausea, diarrhea and rash were the most common adverse effects in Pertuzumab alone and Pertuzumab – based therapies.[3]

Cetuximab and Panitumumab are monoclonal antibodies targeting the EGFR currently used for systemic treatment of metastatic colorectal cancer in combination or alone have been reported to be able to induce skin toxicities. In this study we assess the safety profile of immunotherapeutic agents other than immune checkpoint inhibitors.[4]

AIM

To assess the safety profile and utilization of immunotherapeutic agents other than immune checkpoint inhibitors – Trastuzumab, Bevacizumab, Pertuzumab, Cetuximab and Panitumumab in cancer patients.

OBJECTIVES

- To study the adverse drug reactions associated with immunotherapeutic agents and their management.
- To assess and categorize the drug interactions of each drug with co-administered drugs.
- To analyze drug utilization of immunotherapeutic agents in cancer patients.
- To assess the safety of immunotherapeutic agents based on the type of cancer, stage of the cancer and co-administered drugs

METHODOLOGY

STUDY DESIGN

An ambispective observational single center study was conducted at Lourdes hospital Ernakulam by collecting details of patients prescribed with Trastuzumab, Bevacizumab Pertuzumab, cetuximab and panitumumab

STUDY SITE

Study was conducted in the department of oncology of Lourdes Hospital, Post Graduate Institute of Medical Science and Research, Ernakulam, Kerala, India, which is a multi-speciality tertiary care teaching hospital.

STUDY PERIOD

- Retrospective study period of 5 years (2017 November to 2022 November)
- Prospective study period of 6 months

METHOD OF SELECTION

Patients was selected on the basis of inclusion and exclusion criteria.

INCLUSION CRITERIA

Patients of all age groups prescribed with immunotherapeutic agents other than immune checkpoint inhibitors.

EXCLUSION CRITERIA

- Patients who were discharged against medical advice
- Patient with incomplete data

DATA COLLECTION METHOD

- Data files from medical record department.
- Lourdes Mediware system.

DATA COLLECTION TOOL

Specially designed data collection tools like standard data collection forms Drug interaction was verified using Lexicomp

STUDY METHOD

We conducted an ambispective study on cancer patients in oncology department of Lourdes Hospital, Kochi. The retrospective study period was from November 2017 to November 2022 and prospective data from December 2022 to May 2023.Medical records of patients diagnosed with cancer, admitted from 2017 onwards and who satisfied inclusion and exclusion criteria of the study were enrolled. A specially designed data collection form was prepared to record the data. The records of all patients enrolled in study were analyzed and recorded in a specially designed data collection form, Demographics, past medical and medication history, treatment data, drugs during discharge, reports of histopathology, mammography, USG, CT, ECHO, PET and XRAY, pertinent lab parameters were recorded.

DESCRIPTIVE STATISTICAL ANALYSIS

The data collected was compiled using Microsoft Excel and presented using pie charts and bar graphs to visualise the information. Calculations for the mean and standard deviation were conducted using statistical calculators. To perform statistical analysis, the data was imported into SPSS, a statistical software program.

RESULTS AND DISCUSSION

A Total of 65 cancer patients were analysed. 50 patients were included during the retrospective study period of November 2017 to November 2022 and 15 prospective data of patients were analysed from December 2022 to May 2023. Majority of patients in our study were in age groups of 56-65 years with 38.5%. The mean age of patients was 57.107 ± 10.409 years.

Out of 65 cancer patients, 43 of them were female and 22 of them were male. The population had a significantly higher proportion of female (65%). The frequent type of cancer in females was breast cancer in 27 patients (62.8%). Most of the patients were having family history of breast cancer. The second most prevalent was ovarian cancer in 6 patients (14%) followed by rectum, colon, lung, endometrial and other categories of

cancers (oropharynx, tongue, vocal cord). The most frequent type of cancer in male was in oropharynx, tongue and vocal cord which was in 7 patients (31.8%) and the second prevalent one was found to be hepatocellular and colon cancer which was in 5 patients (22.7%) followed by rectum, renal cell and lung cancer. Out of 65 cancer patients included, 24 of them doesn't have comorbidities and 41 of them had comorbidities.23 patients were presented with 1 comorbidity ,9 patients with 2 comorbidities, 8 patients with 3 comorbidities and 1 patient with more than 3 comorbidities. Among these mostly reported comorbidities were Hypertension, DM, DLP and Thyroid disorders.

Of all the 65 patients taking immunotherapeutic agents other than immune checkpoint inhibitors 8 ADR was reported. The most common reported ADR was 7 cardiotoxicity (87.5%) and a patient with pneumonitis (12.5%).4 of them reported with trastuzumab induced cardiotoxicity which was 21.05% and 3 of the patients taking trastuzumab along with pertuzumab also reported with cardiotoxicity (100%). The patients who were taking trastuzumab had comorbidities like HTN(Hypertension), DM (Diabetes Mellitus), DLP (dyslipidaemia) and in patients who were taking trastuzumab along with pertuzumab had comorbidities like HTN and Thyroid disorders. Age group were found to be above 50 years. Following initiation, 4 reported cardiotoxicity which was developed within 3 years. In the cardiotoxicity cases, 2 of them were on conventional therapy with Taxanes, Cyclophosphamide and capecitabine. Among 30 patients who were taking bevacizumab, one patient was reported with pneumonitis. Of the 6 cardiotoxicity cases patients were advised for periodic monitoring of cardiovascular events and one patient who have LVEF 45% management was done by initiation of Beta-blockers and HCN- channel blocker (Hyperpolarization- activated cyclic nucleotide- gated channel). Bevacizumab induced pneumonitis was managed by giving antibiotics for 5-8 days and inj. Hydrocortisone, not much response was found so Inj. Methyl prednisolone was administered, the condition of the patient got improved then inj. Methyl prednisolone was slowly tapered and switched to Tab. Methyl prednisolone. All of the patients prescribed with Trastuzumab + Pertuzumab were having ADR. Also, Majority of the patients prescribed with Bevacizumab (96.6%) were not having ADR. Since the p-value of chi-square test was found to be <0.001 so there exist a significant relation between drugs prescribed and ADR.

Out of 65 patients 2 patients reported with cardiotoxicity in stage2, five patients in stage3 and one patient reported with pneumonitis in stage 4. Among 27 patients with breast cancer

7 patients reported ADR and 20 of them doesn't report with ADR. Among 7 ovarian cancer patients 1 patient reported with ADR and other 6 patients don't report with ADR.

Out of 65 cancer patients analysed, 2 patients had category C interaction with Humalog mix and dexamethasone and 1 category X interaction with Bevacizumab and liposomal doxorubicin, 1 category C interaction with atorvastatin and Aprepitant, cinnarizine and lorazepam, morphine and pheniramine, lercanidipine and Aprepitant, Tramadol and Granisetron also 1 category D interaction with morphine and losartan, Paclitaxel and liposomal doxorubicin.

Breast cancer was the prevalent cancer observed with more preponderance among females (41.1%). HER2 positive breast cancer patients were prescribed with trastuzumab and 3 patients were prescribed with trastuzumab along with pertuzumab. The second most predominant cancer was colon (10.8%), for that 3 patients were prescribed with FOLFIRI-bevacizumab, 1 patient each with FOLFOX-bevacizumab, FOLFIRI- cetuximab, FOLFIRI - panitumumab and a patient having metastatic CA colon involving brain and lung was prescribed with bevacizumab, capecitabine and vincristine. Six patients presented with CA ovary (9.2%), 2 patients were prescribed with bevacizumab and cyclophosphamide and 1 patient each with bevacizumab + cisplatin + liposomal doxorubicin, bevacizumab + Oxaliplatin + Atezolizumab + Gemcitabine, Bevacizumab + Ifosphamide + etoposide for a patient with liver metastasis ,Bevacizumab +Oxaliplatin + Fluorouracil + Cyclophosphamide + Pegylated Doxorubicin for a patient with metastatic adenocarcinoma.5 patients presented with hepatocellular carcinoma (7.7%),3 patients were prescribed with Bevacizumab and Atezolizumab ,one patient with Bevacizumab +5FU,and Bevacizumab +Pembrolizumab for a patient with multiple lung metastasis. 4 patients were presented with Ca rectum (6.2%) 1 patient each with FOLFOX-Panitumumab, FOLFIRI-Panitumumab, FOLFOX- Bevacizumab, FOLFIRI-Bevacizumab. 3 patients presented with CA lung (4.6%) 2 patients were managed with Bevacizumab +Atezolizumab +Pemetrexed +Carboplatin and a patient of metastatic adenocarcinoma with mucin secretion was given FOLFOX-Bevacizumab. Of the 2 patients presented with renal cell carcinoma (3.1%) one of each patient with skeletal metastasis was prescribed with Bevacizumab + Pazopanib and a patient of metastatic papillary renal cell carcinoma with left supraclavicular lymph nodes was managed by Bevacizumab+ nivolumab + sunitinib. One patient of CA endometrium was managed with Bevacizumab +Capecitabine + Gemcitabine. Among the type of cancer that included in other category (15.4%),2 patients with disseminated carcinoma appendix was prescribed with Bevacizumab + Capecitabine + Irinotecan, two patients with Ca

hypopharynx was given Cetuximab + Paclitaxel+ Carboplatin among 2 patients with Ca tongue one patient was managed by Cetuximab + Methotrexate + 5 FU and the other with lymph node metastasis was prescribed with Cetuximab + Carboplatin and one patient each with Ca vocal cord was managed with Cetuximab ,for recurrent squamous carcinoma Cetuximab+ Paclitaxel+ Carboplatin + liposomal doxorubicin , for Ca floor of mouth Cetuximab+ Docetaxel + carboplatin, for left temporal occipital glioma Bevacizumab + Vincristine.

CONCLUSION

From our study we concluded that,

- The ADR of immunotherapeutic agents were found to be limited; drug-induced cardiotoxicity has been reported with the use of Trastuzumab. Additionally, the combination of Trastuzumab with Pertuzumab and Bevacizumab has been found to induce pneumonitis. Severe cardiotoxicities were managed by using beta blocker, ivabradine and pneumonitis managed with inj. methyl prednisolone
- Few drug interactions were observed among that Category D and Category X were limited in number.
- Breast cancer was the prevalent cancer observed with more preponderance among females. Bevacizumab was the most commonly used immunotherapeutic agent followed by Trastuzumab, Cetuximab and Panitumumab.
- Based on the type of cancer, an assessment was made on the safety profile of immunotherapeutic agents. More number of cardiotoxicities as ADR were reported in breast cancer and pneumonitis as ADR was reported in a patient with Ovarian cancer.
- The reported ADR were cardiotoxicity and pneumonitis, cardiotoxicity was observed in stage II and stage III and pneumonitis were observed in stage IV

INTRODUCTION

CANCER

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply through a process called cell division to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.[5]

India ranks 3rd among nations in term of highest number of cancers. Based on the cancer registry data, there will be about 8 lakh new cancer cases in India every year. Indian Council of Medical Research (ICMR) estimates that there will be a 12% rise in cancer cases in India by next 5 years. The common form of cancer affecting the people of India are Breast cancer, Cervical cancer and Oral cancer. Cancer can be cured if detected early and treated effectively.

DIFFRENCE BETWEEN CANCER CELLS AND NORMAL CELLS

Cancer cells differ from normal cells in many ways. For instance, cancer cells grow in the absence of signals telling them to grow. Normal cells only grow when they receive such signals. Ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis). Invade into nearby areas and spread to other areas of the body. Normal cells stop growing when they encounter other cells, and most normal cells do not move around the body. Trick the immune system into helping cancer cells stay alive and grow. For instance, some cancer cells convince immune cells to protect the tumor instead of attacking it. Accumulate multiple changes in their chromosomes, such as duplications and deletions of chromosome parts. Some cancer cells have double the normal number of chromosomes.[6]

TYPES OF CANCER

There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in the lung and brain cancer starts in the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell.

CARCINOMA

- Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body.
- Adenocarcinoma is a cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon and prostate are adenocarcinomas.
- Squamous cell carcinoma is a cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin. Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder and kidneys.

SARCOMA

Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels and fibrous tissue (such as tendons and ligaments).
Osteosarcoma is the most common cancer of bone.

LEUKEMIA

- Cancers that begin in the blood-forming tissue of the bone marrow are called leukemias. These cancers do not form solid tumors. Instead, large numbers of abnormal white blood cells (leukaemia cells and leukemic blast cells) build up in the blood and bone marrow, crowding out normal blood cells.

LYMPHOMA

- Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the immune system. In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body.

There are two main types of lymphoma:

- Hodgkin lymphoma – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.
- Non-Hodgkin lymphoma – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.

MULTIPLE MYELOMA

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumors in bones all through the body.

MELANOMA

- Melanoma is cancer that begins in cells that become melanocytes, which are specialized cells that make melanin (the pigment that gives skin its colour). Most melanomas form on the skin, but melanomas can also form in other pigmented tissues, such as the eye.

Cases of cancer in India for the year 2022 was found to be 14,61,427 (crude rate:100.4 per 100,000). In India, one in nine people are likely to develop cancer in his/her lifetime. Lung and breast cancers were the leading sites of cancer in males and females, respectively. Among the childhood (0-14 year) cancers, lymphoid leukemia (boys: 29.2% and girls: 24.2%) was the leading site. The incidence of cancer cases is estimated to increase by 12.8 per cent in 2025 as compared to 2020.[7]

DIAGNOSIS OF CANCER

BIOPSY

A small tissue sample is surgically removed and examined under a microscope for the presence of cancer cells. Depending on tumor location, some biopsies can be done on an outpatient basis with only local anaesthesia. If the tumor is filled with fluid, a type of biopsy known as a fine needle aspiration is used. A long, thin needle is inserted directly into the suspicious area to draw out fluid samples for examination.

ENDOSCOPY

A flexible plastic tube with a tiny camera on the end is inserted into body cavities and organs, allowing the physician to view the suspicious area. There are many types of scopes, each designed to view particular areas of the body. For instance, a colonoscope is used to detect growth inside the colon and a laparoscope is used to examine the abdominal cavity.

DIAGNOSTIC IMAGING

These images are usually taken by a trained technician and then analysed by a radiologist, a physician who specializes in interpreting diagnostic images. The images and the radiologist's findings are then sent to the patient's primary care centre, where doctors use the information to form a care plan.

BLOOD TESTS

Some tumors release substances called tumor markers, which can be detected in the blood. A blood test for prostate cancer, for example, determines the amount of prostate specific antigen (PSA). High PSA levels can indicate cancer. However, blood tests by themselves can be inconclusive and other methods should be used to confirm the diagnosis[8]

TREATMENT OF CANCER

A type of treatment that uses drugs or other substances to identify and attack specific type of cancer cells with less harm to normal cells. These treatments include surgeries, radiations, chemical agent or biological therapies.

SURGERY

- It is used for both diagnosis and therapy.
- To obtain a sample for diagnosis surgery is usually required.
- The removal of a suspected neoplasm or a portion of it for diagnostic purposes is termed biopsy.
- Surgical removal of cancer is the oldest and most classical method of treatment.
- Curative surgery is performed on a primary neoplastic lesion, whether it is benign or malignant. If metastatic lesion are present, surgery may be carried out to remove the tumor(s) in order to reduce the amount of cancer in body, this if surgery is followed by other modification.
- It is also carried out in order to remove the bulks of tumors that may obstruct or press on vital organs and passages.

RADIOTHERAPY

- It is very effective whether used after surgery or alone with chemotherapy.
- Different types of radiation are used.
- Their mechanism depends on damaging the dividing cells, but it also affects normal tissue. Malignant lymphomas, leukemias and most carcinomas are relatively sensitive to radiation. Sarcomas are more resistant.

IMMUNOTHERAPY

It depends on the stimulation of the host's own immune defences or, the treatment of the host with antibodies specific for the tumor, especially after treatment with drugs. Immunotherapy is treatment that uses certain parts of a person's immune system to fight diseases such as cancer. This can be done in a couple of ways:

Stimulating, or boosting, the natural defences of your immune system so it works harder or smarter to find and attack cancer cells. Making substances in a lab that are just like immune system components and using them to help restore or improve how your immune system works to find and attack cancer cells.

In the last few decades immunotherapy has become an important part of treating some types of cancer. New immunotherapy treatments are being tested and approved, and new ways of working with the immune system are being discovered at a very fast pace. Immunotherapy works better for some types of cancer than for others. It's used by itself for some of these cancers, but for others it seems to work better when used with other types of treatment.

IMMUNOTHERAPY SAFETY

Much is known about the need to protect others from exposure to traditional or standard chemotherapy because it is hazardous. This is why there are safety rules and recommendations for people who handle chemo drugs. However, because immunotherapy drugs are newer, there is not as much information about long-term effects of exposure. To be safe, many experts recommend treating immunotherapy drugs as hazardous and taking the same precautions. This is especially true when immunotherapy drugs are given to treat cancer in combination with other drugs that are known to be hazardous.

LIMITATIONS OF IMMUNOTHERAPY

- The area where the medication goes into the body might have a bad reaction, causing it to hurt, itch, swell, turn red, or get sore.
- Some types of immunotherapies have side effects like flu, fever, chills and fatigue. Also cause problems like swelling, weight gain from extra fluids, heart palpitations and diarrhoea.
- Development of resistance- In some cases, immunotherapy takes longer to work than other treatments. It doesn't work for everyone. Right now, immunotherapy works for less than half the people who try it. Many people only have a partial response.[9]

HORMONE THERAPY

Hormone therapy is a cancer treatment that slows or stops the growth of cancer that uses hormones to grow.

It depends on:

a) Lowering the plasma hormones, blocking the action of circulating hormones through blocking certain receptors (eg, tamoxifen).
b) Additive hormone therapies (used mainly in breast cancers).

Hormone therapy is used for two main reasons:

a) Treat cancer, Hormone therapy can stop or slow cancer growth and reduce the chance of recurrence.
b) Ease cancer symptoms, Hormone therapy may be used to reduce or prevent symptoms in men with prostate cancer who are not able to have surgery or radiation therapy.

Hormone therapy falls into two broad groups, those that blocks the body's ability to produce hormones and those that interfere with how hormones behave in the body. This

therapy is used to treat breast cancer and prostate cancer that uses hormones to grow, used along with other cancer treatments types of treatment that you need depend on the type of cancer, if it has spread and how far, if it uses hormone to grow, and if you have other health problems.[10]

CHEMOTHERAPY

- Once metastasis occurs, surgical and most probably radiation therapy is not curative.
- Although complete cure is difficult in this stage, chemotherapy, is used for increasing the useful life-time of many patients.
- There are some cancers in advanced stages that respond well to chemotherapy - e.g. acute lymphocytic leukemia, Hodgkin's disease (a lymphoma), Burkitt's lymphoma, Ewing's sarcoma of bone, and Wilm's tumor of the kidney. - All these tumors are characterized by rapid growth. Successive chemotherapy is related to the growth fraction of the tumor, that is, the percentage of cells undergoing cell division at any one time.
- Rapidly growing cancers have large growth fractions; therefore, the drugs affect greater proportion of the cell population.
- The search for and development of new drugs is very difficult and takes a long time.
- A drug goes through several stages such as; - selection of the compound - screening its effectiveness in animals - study how the body handles it, and - finally trials on patients.

COMBINATION CHEMOTHERAPY

It is used to improve the results of treating cancer patients. Each drug is chosen for its ability to attack cells at a certain point in their life cycle. When properly combined, several drugs (2-6) may be more effective in treating a particular cancer than 1single drug.

ADJUVANT CHEMOTHERAPY

- Doctors sometimes use chemotherapy as a precautionary measure when they are uncertain if a cancer has spread.
- This use of drugs is called 'adjuvant chemotherapy'.
- The drugs are intended to destroy cancerous cells that may be alive but undetected, in the body. Adjuvant chemotherapy is commonly used when cancer has been discovered in several lymph nodes.[11]

TRASTUZUMAB

Trastuzumab is a monoclonal IgG1 class-humanized murine antibody bind specifically to the extracellular portion of HER-2/neu. Trastuzumab can be used to treat both early-stage and advanced breast cancer. Trastuzumab binds to an extracellular domain of this receptor and inhibits HER2 homodimerization, thereby preventing HER2-mediated signalling. It is also thought to facilitate antibody-dependent cellular cytotoxicity, leading to the death of cells that express HER2.Trastuzumab is known to cause cardiotoxicity, usually manifested as a decrease in left ventricular ejection fraction (LVEF). The exact pathogenesis of this event is unknown but may involve decreased clearance of reactive oxygen species in cardiac myocytes. The major risk factor for the development of cardiotoxicity is concurrent treatment with anthracyclines; the risk of severe cardiotoxicity is three to four times higher in patients receiving both trastuzumab and anthracyclines. This drug is often given with chemotherapy, but it might also be used alone (especially if chemo alone has already been tried). When started before (neoadjuvant) or after (adjuvant) surgery to treat early breast cancer, this drug is usually given for 6 months to a year. For advanced breast cancer, treatment is often given for as long as the drug is helpful. This drug can be given into a vein (IV) or as an injection under the skin Trastuzumab and hyaluronidase injection is given as a subcutaneous shot over a few minutes.

PERTUZUMAB

Recombinant humanized IgG1 monoclonal antibody directed against the extracellular dimerization domain (subdomain I of the HER2/neu growth factor receptor. Binding of pertuzumab to HER2 leads to inhibition of heterodimerization of ER2 with other HER family members, including EGFR, HER3, and HER4. Inhibition of these heterodimerization processes leads to the inhibition of downstream signalling pathways, which includes mitogen-activated protein (MAP) kinase, PI3K and initiation of cell apoptosis.

Immunologic mechanisms may also be involved in antitumor activity, Including ADCC.Pertuzumab binds to a different HER2 epitope than trastuzumab.FDA-approved pertuzumab in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Also, in combination with trastuzumab and chemotherapy as neoadjuvant therapy for patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer as part of a complete treatment regimen for early breast cancer and as adjuvant therapy for patients with HER2-positive early breast cancer at high risk of recurrence. Pertuzumab is associated with reduced LVEF. Patients with prior exposure to anthracyclines or radiotherapy to the chest may be at increased risk of developing a decline in LVEF. Caution should be exercised in treating patients with pre-existing cardiac disease such as congestive heart failure, ischemic heart disease, myocardial infarction, valvular heart disease or arrhythmias.

BEVACIZUMAB

Recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). Binds to all isoforms of VEGF-A. VEGF is a pro-angiogenic growth factor that is overexpressed in a wide range of solid human cancers, including colorectal cancer. Precise mechanism(s) of action remain(s) unknown. Binding of VEGF prevents its subsequent interaction with VEGF receptors (VEGFR) on the surface of

endothelial cells and tumors and in so doing, results in inhibition of VEGFR-mediated signalling. Inhibits formation of new blood vessels in primary tumor and metastatic tumors. Inhibits tumor blood vessel permeability and reduces interstitial tumoral pressures, and in so doing, may enhance blood flow delivery within tumor. Restores antitumor response by enhancing dendritic cell function. Immunologic mechanisms may also be involved in antitumor activity, and they include recruitment of ADCC and/or complement-mediated cell lysis.

Patients should be warned of the increased risk of arterial thromboembolic events, including myocardial infarction and stroke can result in the development of GI perforations and wound healing complications Bleeding complications, with epistaxis being most commonly observed. Serious, life-threatening pulmonary haemorrhage occurs in rare cases in patients with NSCLC, as outlined previously in Special Considerations.

FDA-approved bevacizumab for use in combination with any intravenous 5fluorouracil (5-FU)–based chemotherapy in first-line therapy for metastatic colorectal cancer also as 2nd line in combination with fluoropyrimidine-based chemotherapy after progression on first-line treatment that includes bevacizumab. Used in non-squamous NSCLC in combination with carboplatin/paclitaxel. In Ovarian, fallopian tube, or primary peritoneal cancer—FDA-approved in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease.

CETUXIMAB

Recombinant chimeric IgG1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR). EGFR is overexpressed in a broad range of human solid tumors, including colorectal cancer, head and neck cancer, NSCLC, pancreatic cancer and breast cancer. Precise mechanism(s) of action remain(s) unknown. Binds with nearly 10-fold higher affinity to EGFR than normal ligands EGF and TGF-a, which then results in inhibition of EGFR. Prevents both homodimerization and heterodimerization of the EGFR, which leads to inhibition of autophosphorylation and inhibition of EGFR signalling. Inhibition of the EGFR signalling pathway results in inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, invasion/metastasis, and angiogenesis. Inhibition of the EGFR pathway enhances the response to chemotherapy

and/or radiation therapy. Immunologic mechanisms may also be involved in antitumor activity, and they include recruitment of ADCC and/or complement-mediated cell lysis.

FDA-approved for the treatment of EGFR-expressing mCRC in combination with irinotecan in irinotecan-refractory disease or as monotherapy in patients who are deemed to be irinotecan-intolerant. The use of cetuximab is not recommended for the treatment of mCRC with RAS mutations. Approved in Europe in combination with cytotoxic chemotherapy in the front-line treatment of wild-type RAS mCRC. FDA-approved in combination with FOLFIRI in the front-line treatment of wild-type RAS mCRC.FDAapproved for use in combination with platinum-based therapy with 5-FU for the treatment of recurrent locoregional disease or metastatic squamous cell cancer of the head and neck. Also as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck progressing after platinum-based therapy.

PANITUMUMAB

Fully human IgG2 monoclonal antibody directed against the EGFR.Binds with nearly 40fold higher affinity to EGFR than normal ligands EGF and TGF-α, which results in inhibition of EGFR. Prevents both homodimerization and heterodimerization of the EGFR, which leads to inhibition of autophosphorylation and inhibition of EGFR signalling. Inhibition of the EGFR signalling pathway results in inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, invasion/metastasis, and angiogenesis. Inhibition of the EGFR pathway enhances the response to chemotherapy and/or radiation therapy. In contrast to cetuximab, immunologic-mediated mechanisms are not involved in its antitumor activity.

FDA-approved as monotherapy for the treatment of wild-type RAS metastatic colorectal cancer (mCRC) following prior therapy with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens. Use of panitumumab is not recommended in mutant KRAS mCRC. FDA-approved for the first-line treatment of wild-type RAS mCRC in combination with FOLFOX chemotherapy.

Approved in Europe in first-line treatment of wild-type RAS mCRC in combination with FOLFOX or FOLFIRI; in second-line treatment in combination with FOLFIRI for

mCRC patients who have progressed on first-line oxaliplatin-based chemotherapy; and as monotherapy after progression on fluoropyrimidine, oxaliplatin and irinotecan-containing regimens.[13]

IMMUNOTHERAPY OTHER THAN IMMUNE CHECKPOINT INHIBITOR

Immunotherapy helps harness your body's own immune system to target and kill cancer. It's an umbrella term that describes several treatments. Some types of immunotherapies boost your disease-fighting powers overall. Others teach it to attack specific kinds of cells found in tumors.[14]

TYPES OF IMMUNOTHERAPIES EXCLUDING IMMUNE CHECKPOINT INHIBITORS INVOLVE:

- Adoptive Cell Therapies
- Monoclonal Antibodies
- Oncolytic Virus Therapy
- Cancer Vaccines
- Adoptive Cell Therapy

This group of treatments removes some of your own immune cells and either boosts their numbers or changes them in a lab so they can find and kill more cancer cells. Tumorinfiltrating lymphocyte (TIL) therapy. T cells are powerful white blood cells that fight infections. In this treatment, doctors remove T cells that have started to attack your tumor. They grow a large batch of these cells, called tumor-infiltrating lymphocytes (TILs), in a lab. They then put these activated fighters back into your body. Engineered T-cell receptor (TCR) therapy. This treatment removes T cells from your blood and reprograms them in a lab so they can find the cancer more easily. The engineered T cells look for tiny targets on the surface of your cancer cells. The FDA hasn't approved any TCR therapies. These treatments are being tested in people with certain types of sarcomas (a soft-tissue cancer) and late-stage melanoma skin cancer. CAR T-cell therapy. Doctors add

special receptors to the surface of your T cells so they can lock onto and destroy your exact kind of cancer. Only two CAR T-cell therapies are FDA-approved:

- Tisagenlecleucel (Kymriah) treats people up to age 25 with acute lymphoblastic leukemia and adults with certain types of large B-cell lymphoma.
- Axicabtagene ciloleucel (Yescarta) treats adults with some types of large B-cell lymphoma, such as non-Hodgkin's lymphoma.

Researchers are looking at new ways to use CAR T-cell therapies against cancer. One approach is to take these cells from healthy donors and make ready-to-go treatments for people with cancer. Natural killer (NK) cell therapy. These immune cells attack foreign invaders like cancer in your body. Adding CARs to NK cells helps them target the cancer even better.

MONOCLONAL ANTIBODIES

Antibodies are proteins your immune system makes. They find and stick to other proteins called antigens on cancer cells. Then they recruit other parts of your immune system to destroy the cancer.

Researchers can make antibodies in the lab. They're called monoclonal antibodies, and they work in different ways:

- Naked monoclonal antibodies are the most common type used in cancer treatment. They're called naked because they're unattached to anything. These antibodies boost your immune system's response against the cancer, or block antigens that help the cancer grow and spread.
- Conjugated monoclonal antibodies have a chemotherapy drug or radioactive particle attached to them. The antibodies attach directly to cancerous cells. This reduces side effects and helps chemotherapy and radiation treatments work better.
- Bispecific monoclonal antibodies attach to two proteins at once. Some attach to both a cancer cell and an immune cell, which helps the immune system attack the cancer. The leukemia drug blinatumomab (Blincyto) attaches to a protein on leukemia cells, and to a protein on T cells.

The FDA has approved more than a dozen monoclonal antibodies to treat several different types of cancer. Research is underway to see how this immunotherapy treatment might work against other cancer types.

ONCOLYTIC VIRUS THERAPY

Viruses like the flu infect cells and make us sick. Oncolytic viruses are a special type that infects and kills cancer cells without harming healthy cells. The FDA has approved one oncolytic virus, talimogene laherparepvec (T-VEC, Imlygic), to treat metastatic melanoma.

CANCER VACCINES

These use your immune system to prevent or treat cancer. Cancer vaccines are made from dead cancer cells, proteins or pieces or proteins from cancer cells or immune system cells.

Four vaccines are approved to prevent cancer:

Cervarix, Gardasil, and Gardasil-9 protect against the human papillomavirus (HPV), which is linked to cancers of the cervix, throat, vagina, vulva, anus and penis.

Hepatitis B (HBV) vaccine (HEPLISAV-B) protects against HBV infections that can cause liver cancer.

Three vaccines are FDA-approved to treat cancer:

- Sipuleucel-T (Provenge) treats advanced prostate cancer when hormone therapy doesn't work.
- Talimogene laherparepvec (T-VEC) treats melanoma skin cancer that has spread.
- Bacillus Calmette-Guérin, or BCG, treats early-stage bladder cancer. Scientists are studying other cancer vaccines in clinical trials.

Other types of immunotherapies boost the activity of your immune system in general. A more active immune system can better fight cancer.

These drugs fall into a few classes:

- Interleukins are a type of cytokine, a protein that some white blood cells make to control your immune system's response to cancer. A man-made version of the interleukin IL-2 increases the number of T cells and NK cells in your body. The IL2 aldesleukin (Proleukin) is approved to treat advanced kidney cancer and metastatic melanoma.
- Interferons are another type of cytokine that makes your immune cells more active against cancer. IFN-alfa treats cancers such as leukemia, sarcoma, lymphoma, and melanoma.
- Immunomodulators (IMiDs) kick-start immune system reactions to treat some types of cancer. They include:

1. Imiquimod (Aldara, Zyclara)
2. Lenalidomide (Revlimid)
3. Pomalidomide (Pomalyst)
4. Thalidomide (Thalomid)
5. Bacillus Calmette-Guérin, or BCG, which treats early-stage bladder cancer[15]

NEED FOR THE STUDY

- There are only limited number of studies regarding immunotherapeutic agents other than immune checkpoint inhibitors.
- Studies concerning ADRs and safety of above considered drugs are scarce among studies performed in south Indian population.

AIM AND OBJECTIVES

AIM

To assess the safety profile and utilization of immunotherapeutic agents other than immune checkpoint inhibitors – Trastuzumab, Bevacizumab, Pertuzumab, Cetuximab and Panitumumab in cancer patients.

OBJECTIVES

- To study the adverse drug reactions associated with immunotherapeutic agents and their management.
- To assess and categorize the drug interactions of each drug with co-administered drugs.
- To analyze drug utilization of immunotherapeutic agents in cancer patients.
- To assess the safety of immunotherapeutic agents based on the type of cancer, stage of the cancer and co-administered drugs.