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Recent Development of Anticancer Agents

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ABSTRACT

Cancer is the unwanted growth of the cell, which is developed trillion of the cells. It may be either Cancerous or Non-Cancerous. The aetiology involves the propagation of Cancer, defective DNA, or Mutation in DNA because of distinct Factors (Physical, Chemical, Biology, and Others). There is various kind of cancer (such as Carcinoma, Sarcoma, Myeloma, leukaemia and Lymphoma etc.). The sign and symptoms involve in Cancer (Such fever, loss of appetite, weight loss, thickening or lump in the body and unusual upset stomach or difficulty and swelling). Now a days the treatment is used in treatment of cancer (such as Gene therapy, Surgery, Chemotherapy, Radiation, Immunotherapy and Stem cell transplant). Cancer is an ancient disease, that evidence obtained from Egyptian papyri. In 2021 Epidemiology study of Cancer represent the data related to the Incidence of Cancer higher in Men compare to Women, specially (Prostate and Breast and remaining other). There are lots of Chemical compounds and Monoclonal antibodies developed in the Laboratory to treat various kinds of cancer. In which some chemical compounds and Monoclonal antibodies had been granted Approval by FDA in 2020 for Marketing. We are represented in this paper, FDA approved compound 2020 with its pharmacological study, chemical structure and the dose of compound that is available in Market.

Keywords: Chemical compounds, Anticancer Agents, Monoclonal antibodies.

INTRODUCTION

Cancer is a collection out of 100 discontinuous diseases. That demonstrated undesired cell growth on the specific organ of the body. Because of unwanted growth, it develops trillion of cells or lumps of tissue that is called a tumour. The tumour may be cancerous or noncancerous. Cancer is categorized into two-part, benign cancer (non- invade) and malignant (invade) [1].

Pathophysiology of cancer

Cancer is originated in any organ of the body because of Carcinogenic substance that is responsible to cause defects or changes in the mutation of DNA because of the damaging of DNA large number of defective cells formed. It happened when cells die cycle to stop. A carcinogen is also capable to remove an electron from any molecule of the body and forming free radicals that can affect the cell division in the body [2, 3, 4].

History of cancer

The term was used for cancer in the ancient period “Karkinoma” that is indicated ulcers and uncontrolled growth represented in the specific organ of the body. The Greek word “Crab” was used for cancer which was given by “Hippocrates” (460-370 B.C/E.) because of projection of cancer after spreading similar to the shape of crab claws. The evidence of cancer was collected from Egyptian papyri. This is called Admin Smith Papyrus; it was contained detail about eight cases of breast tumour or ulcer. At that time one technique available for treatment was “Cauterization”. On 130-200 onkos Greek word described by doctor or Philosopher “Claudius galenus” that means was a “bulk of mass “based on this term used called oncology [5].

Mode of transmission

There is various type of factors that is responsible for transmitted cancer given below.

- Physical factor (radiation, particulate matter)
- Chemical factor (asbestos, metallic powder)
- Biological factor (virus, bacteria, and parasite)
- Other (Lifestyle, Physiological factor) [1]

Epidemiology of cancer

Cancer is the most important reason for death in India and the incidence of cancer is higher in men compared to women. There are 7 lakhs new cases and 3 lakhs death observed per annum because of cancer [6]. The most common cancer found in the UK is breast, lung, colorectal, and prostate in 2008[7]. According to recent information the incidence of new cancer cases was reported approximately 1,898,16o in the United States as well as death cases because of cancer reported 608,570 in 2021. But nowadays death rate has reduced because of the reduction of smoking and early-stage detection and treatment. Most of the cases of cancer were observed (46% cases of prostate, 50% cases of breast, lungs).

Type of cancer

It is classified into two-part such as-

- Histological (tissue involve information of cancer)
- Carcinoma (Epithelial tissue)
- Sarcoma (Connective tissue)
- Myeloma (Plasma cell of the bone marrow)
- Leukaemia (Bone marrow site of blood cell)
- Lymphoma (Lymphatic system)
- Mixed type (Adenosquamous, mixed mesodermal, carcinosarcoma) [2]

Localize type (organ involving information of cancer)

- Colorectal cancer
- Lung Cancer
- Liver Cancer
- Stomach Cancer
- Cervical Cancer
- Bladder Cancer
- Esophageal Cancer
- Non-Hodgkin Lymphoma
- Cancers of the Lip and Oral Cavity
- Nasopharyngeal Cancer
- Kaposi Sarcoma

Sign and symptoms of cancer

Chills, Fatigue, Fever, Loss of appetite, Malaise, Night sweats, Weight loss, Thickening or lump in the body, Cough or hoarseness that does not go away, Obvious change in a wart or mole, Changes in bowel or bladder habits, Unexplained bleeding or discharge, any sore that does not heal, Unusual upset stomach or difficulty and Swallowing [3,4].

Treatment

- Gene Therapy
- Surgery
- Chemotherapy
- Radiation Therapy
- Targeted Therapy
- Immunotherapy
- Hyperthermia
- Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)
- Photodynamic Therapy
- Lasers in Cancer Treatment
- Blood Product Donation and Transfusion [8]

Tazemetostat (Tazverik; Epizyme)

It is a methyltransferase inhibitor that has therapeutic application in the treatment of epithelioid sarcoma and it was accepted approval by the US Food and Drug Administration (FDA) for the treatment of adults and young patients aged with epithelioid sarcoma on January 23, 2020[9]. Epithelioid sarcoma is a subtype of soft-tissue sarcoma that mostly arise in the soft tissue of the fingers, hands, and forearms as well as in another part of the body [10]. The cases of epithelioid sarcoma found approximately 0.04 cases per 100,000 people in the United States in 2005[10]. Epithelioid sarcoma mostly occurs in young adults and males compared to females. Epithelioid sarcoma spread via the lymphatic system and convert in metastatic state presence in lungs [10,11].

The pathophysiology of epithelioid sarcoma inhibits the function of INI1 triggers the activation of the EZH2 gene, which is involved in the enzyme histone methyltransferase that is overexpressed or mutated in various cancer cells [12].

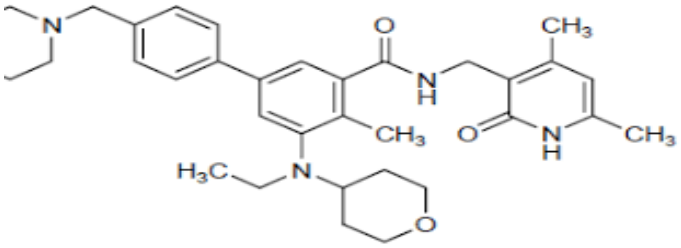

Figure 1: Chemical Structure of Tazemetostat

Mechanism of action

Tazemetostat (Tazverik; Epizyme) has the mechanism of action, it inhibits the activation of the EZH2 Gene and inhibits the activity of enzyme methyltransferase EZH2 that is involved in spreading epithelioid sarcoma [9].

Dose

Dose of Tazemetostat (Tazverik; Epizyme) recommended for treatment 800 mg administered orally two times daily [13].

Adverse reaction

Adverse effect of Tazemetostat (Tazverik; Epizyme) fatigue, nausea, decreased appetite, vomiting, constipation, and other risk occurs because of treatment secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukaemia. It is also harmful to pregnant women [13].

Isatuximab

It is a third monoclonal antibody permitted for the treatment of Multiple myeloma in Combination with Pomalidomide and Dexamethasone for that patient who are taking 2 types of treatment in cancer (including a proteasome inhibitor and lenalidomide) [14,15]. Isatuximab (Sacralise; Sanofi Pharmaceuticals) was granted approval by the FDA on March 2, 2020, for Multiple myeloma through collected evidence from the ICARIA-MM trial [14,15].

Mechanism of Action

Isatuximab is a human monoclonal antibody that works on CD38 and produces antitumor activity in multiple myeloma through 3-way antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity [16].

Dose

The dose of Isatuximab is administered 10 mg/kg on actual body weight. It also administered intravenously 100-mg/5-mL and 500-mg/25-mL vials. It receives intravenously 4 continuous weeks followed by every 2 weeks in Combination with Pomalidomide and Dexamethasone. There is a requirement of premedication to reduce infusion-related reactions [14]. (Premedication drug such as Corticosteroid, Antipyretic, H1 and H2 Antagonist) [16].

Adverse Reactions

During infusion, symptoms were reported chills, nausea, cough, and dyspnoea with severe hypertension other hematologic toxicity (neutropenia, thrombocytopenia, and anaemia) [17].

Pemigatinib (Pemazyre; Incyte)

It is a kinase inhibitor, that is used in the treatment of Cholangiocarcinoma (CCA). Cholangiocarcinoma (CCA) is a kind of cancer that arises from the bile duct and the incidence of Cholangiocarcinoma (CCA) is found in the United States annually from 2000 to 3000. This type of cancer mostly occurs in older people aged ≥65 years [18]. Cholangiocarcinoma (CCA) is categorized into two-part- intrahepatic or extrahepatic. The annual incidence rate of intrahepatic is about 4.36% [19]. Pemigatinib received approval by the US Food and Drug Administration (FDA) On April 17, 2020, based on an FDA-approved test, companion diagnostic (Foundation One CDx; Foundation Medicine) [20, 21, 22, 23].

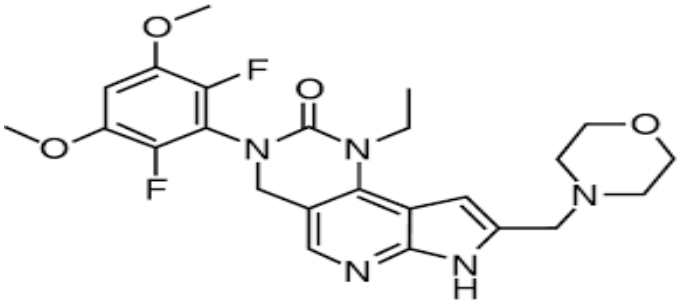

Figure 2: Chemical Structure of Pemigatinib

Mechanism of Action

Pemigatinib is an effective, selective, small-molecule kinase inhibitor that affects crucial biomarkers (fibroblast growth factor receptor such as FGFR1, FGFR2, and FGFR3) and causes obstruction in phosphorylation and signalling along the FGFR1, 2, and 3 pathways, in this via reducing the proliferation of cancer cells with FGFR variations and show antitumor activity [20, 21].

Dose

Pemigatinib is marketed as a tablet dosage form with three strengths containing 4.5 mg, 9 mg, and 13.5 mg. Before swallowing the tablet Pemigatinib, the presence of an FGFR2 fusion or rearrangement should be identified [21].

Adverse Reactions

The most common event occurs hyperphosphatemia, alopecia, diarrhoea, nail toxicity, fatigue, disguise, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin [21]. other Serious event containing failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion. Pemigatinib is also harmful in pregnancy [21].

Capmatinib (Tabrecta; Novartis)

It is a kinase inhibitor that helps treat patients with metastatic Non–small-cell lung cancer NSCLC. Capmatinib (Tabrecta; Novartis) had received approval from the US Food and Drug Administration (FDA) on May 6, 2020, through the FDA-approved test and clinical trial result [24,25]. Non–small-cell lung cancer arises from lung and bronchus. It is widely spread in the United States. In 2020 the incidence of lung cancer was found approximately 228,820. There are demonstrating all new of lung cancer 12.7% and all cancer death 22.4% [26].

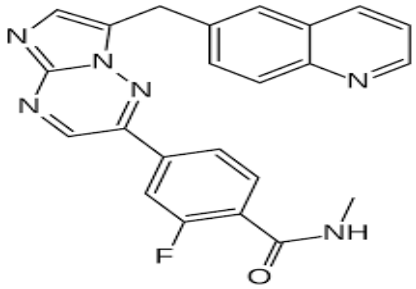

Figure 3: Chemical Structure of Capmatinib

Mechanism of Action

Capmatinib is a kinase inhibitor that can inhibit the action of MET (mesenchymal-epithelial transition), containing the mutant variant formed by exon 14 skipping and the mutant MET variant lacking exon 14. In this via reduced cancer cell growth, Capmatinib affected MET phosphorylation and MET-mediated downstream signalling proteins and inhibit the propagation and existence of MET-dependent cancer cells [25].

Dose

The Capmatinib is present with three different strengths as 150mg, 200-mg, and 400 mg. The 400 mg dose of Capmatinib is administered orally two times daily [25].

Adverse Reactions

The most common adverse event contains edema, nausea, fatigue, vomiting, dyspnoea, and decreased appetite. Serious adverse reactions containing pneumonitis Interstitial lung disease (ILD), Hepatotoxicity, and Phototoxicity reaction. It is also harmful to pregnant women [25].

Selpercatinib (RETEVMO™)

Selpercatinib (RETEVMO™) is a more potent tyrosine kinase RET (rearranged during transfection) inhibitor that is used for the treatment of various types of solid tumour (such as non-small cell lung cancer, thyroid cancer, papillary thyroid cancer, multiple endocrine neoplasia type 2 and sporadic medullary thyroid cancer) [27, 28]. On 8th May 2020 Selpercatinib (RETEVMO™) firstly received approval in the US based on FDA-approved test, Companion Diagnostic and Ongoing Clinical Trials for treatment of patients [29, 30, 31, 32, 33].

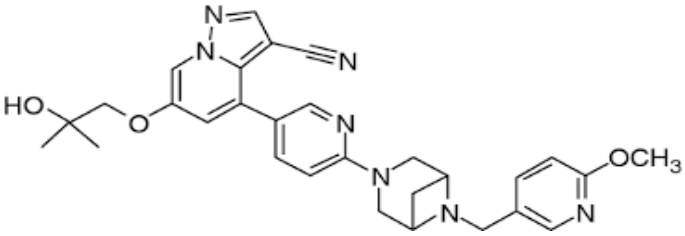

Figure 4: Chemical Structure of Selpercatinib

Mechanism of Action

Selpercatinib is a kinase inhibitor. It inhibits various mutated isoforms of RET and on other hand VEGFR1 and VEGFR3. It also inhibits at high concentration to FGFR 1, 2, and 3 and at lower concentration inhibit 60-fold of RET. Selpercatinib represent antitumor activity by inhibiting activation of RET protein that is responsible for gene fusion and mutation (Such as CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T) [30].

Dose

The dose of Selpercatinib (RETEVMO™) is available in the market with two strengths 120 mg and 160 mg. that is administered two times daily orally, these doses of Selpercatinib suggested according to bodyweights such as 120 mg (patients weighing <50 kg) and 160 mg (patients weighing>50 kg) [30].

Adverse reaction

The adverse reaction occurs in a patient treated with Selpercatinib such as dry mouth, diarrhoea, constipation, hypertension, fatigue, edema, and rash. Laboratory abnormalities involved such as AST levels, increased ALT levels, increased glucose levels, decreased albumin levels, decreased calcium levels, increased creatinine levels, increased alkaline phosphatase levels, increased total cholesterol levels, decreased sodium levels, decreased leukocyte levels, and decreased platelet levels. Fatal adverse reactions involved sepsis, cardiac arrest, and respiratory failure [30].

Naxitamab (DanyelzaTM, Y-mAbs)

Naxitamab ((DanyelzaTM, Y-mAbs) is a humanized IgG1 monoclonal antibody that acts on GD2 (hu3F8) and treats neuroblastoma [34]. In 2020 the Addition of Naxitamab with Granulocyte-macrophage colony-stimulating factor (GM-CSF) was granted approval for treatment of neuroblastoma by the US FDA on basis of evidence that was received of two open-label trials (Trial 1/NCT03363373 and Trial 2/NCT01757626) in 97 patients with high-risk neuroblastoma in bone or bone marrow [35, 36].

Mechanism of Action

Naxitamab (DanyelzaTM, Y-mAbs) is a humanized IgG1 or Anti-GD2 Moab monoclonal antibody that can attach with GD2 and target on neuroblastoma, produce two types of reaction complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) because of activation of iC3b receptor on neutrophils in presence of the white cell [34, 37, 38, 39].

Dose

The dose of Naxitamab is administered through the intravenous route in form of infusion. The dose is 3 mg/kg/day (up to 150 mg/day). The treatment cycle of Naxitamab is continued until complete response or partial response is obtained from 4 weeks to 8 weeks [40].

Adverse Reactions

Infusion-related reactions occur such as pain, tachycardia, vomiting, cough, nausea, diarrhoea, decreased appetite, hypertension, fatigue, erythema multiform, peripheral neuropathy, urticarial, pyrexia, headache, injection site reaction, edema, anxiety, localized edema, and irritability, decreased lymphocytes, decreased neutrophils, decreased haemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased calcium, decreased albumin, decreased sodium, and decreased phosphate. The fatal reaction includes Neurotoxicity, Hypertension, and Embryo-Fatal Toxicity [40].

Qinlock (Ripretinib)

Qinlock (Ripretinib) is manufactured by Decipher Pharmaceuticals for the treatment of gastrointestinal stromal tumours. It is a tyrosine kinase inhibitor (TKI) that targets proto-oncogene receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor A (PDGFRA) [41,42]. On May 15, 2020 QINLOCK™ (Ripretinib) tablets was granted approval in the U.S. for oral use based on the pivotal Phase 3 INVICTUS trial [43].

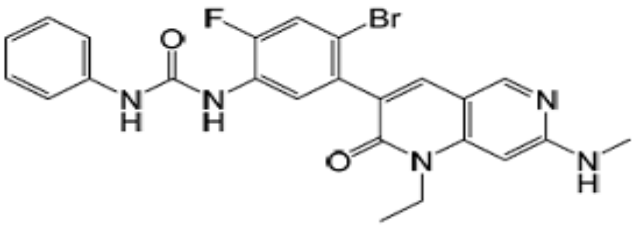

Figure 5: Chemical Structure of Winlock

Mechanism reaction

Qinlock (Ripretinib) acts as a tyrosine kinase inhibitor that targets proto-oncogene what plays an important role in the development and propagation of gastrointestinal stromal tumours (GIST) in the human digestive system. Qinlock (Ripretinib) inhibits the action of primary and secondary mutation (such as KIT and platelet-derived growth factor receptor A kinase). It also inhibits other types of kinases like PDGFRB, TIE2, VEGFR2, and BRAF [41].

Dose

The dose of Qinlock (Ripretinib) is available on market at 150 mg. The route of administration of Ripretinib swallows orally with or without food one time per day. In this case, if recommend a dose of 150 mg produces an adverse reaction, there is a need for dose reduction, a 100 mg dose of Qinlock administered [41].

Adverse reaction

The adverse reactions are represented alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting increased lipase and decreased phosphate, and fatal complication such as Palmar-Plantar Erythrodysesthesia Syndrome, New Primary Cutaneous Malignancies, Hypertension, Cardiac Dysfunction, Risk of Impaired Wound Healing, Embryo-Fatal Toxicity [41].

Margetuximab (MargenzaTM)

Margetuximab (MargenzaTM) is a chimeric type of IgG monoclonal antibody that targets on HER2 receptor and treats breast cancer. On December 16, 2020, Margetuximab was granted approval by the FDA based on information collected from a clinical trial (NCT02492711) [44, 45 ,46].

Mechanism of action

Margetuximab (MargenzaTM) is a chimeric IgG monoclonal antibody that targets the human epidermal growth factor receptor 2 protein

(HER2). It interacts with the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2) and controls the propagation of tumours. The Fc region of Margetuximab-cake was improved for enhancing binding capacity to HER2 by activation of Fc receptor FCGR3A and reduced binding capacity to HER2 by inhibiting activation of Fc receptor FCGR2B (CD32B) these improvements mediate antibody-dependent cellular cytotoxicity (ADCC) and NK cell activation. In this way inhibit tumour cell growth and treat metastatic breast cancer [47, 48].

Dose

The dose of MARGENZA is available 15 mg/kg and 250 mg/10 mL (25 mg/mL) in a single-dose vial. The route of administration of it is intravenous infusion. Initial dose administered 15 mg/kg over 120 minutes and subsequent doses over a minimum of 30 minutes every 3 weeks [48].

Adverse reaction

The adverse drug reactions of MARGENZA when administered with another chemotherapeutic agent such as fatigue/asthenia, nausea, diarrhoea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnoea and during infusion, a reaction occurs like palmar-plantar erythrodysesthesia and extremity pain. The fatal complication represents Left Ventricular Dysfunction Embryo-Fatal Toxicity [48].

Pralsetinib (Gavreto)

Pralsetinib (Gavreto) is a kinase inhibitor that was developed for the treatment of RET fusion-positive non–small-cell lung cancer and medullary thyroid cancer. It was granted approval by FDA on September 4, 2020, by evidence that was collected from the phase 1/2 ARROW clinical trial and on overall response rate and duration of response [49, 50, 51].

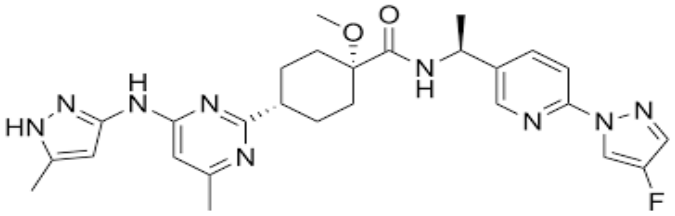

Figure 6: Chemical Structure of Pralsetinib

Mechanism of Action

Pralsetinib is a kinase inhibiter that targets on RET oncogene. It plays an important role to inhibit RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M, and RET M918T) with half concentration dose of the drug and at high concentration, it inhibits DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRb, and FGFR1[49].

Dose

The dose of Pralsetinib is 400 mg available for the treatment of patients with Non–small-cell lung cancer (NSCLC) that is administered empty stomach. If an adverse reaction occurs after administration of 400 mg inpatient, there is a requirement of dose reduction, and the dose of a drug receives approximately 200 mg if an adverse reaction occurs in 200 mg, then a 100mg dose is recommended. The dose of the drug is administered one time daily orally [49].

Adverse reaction

The adverse reactions were included fatigue, constipation, musculoskeletal pain, and hypertension, decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased haemoglobin, decreased sodium, decreased calcium, and increased alanine aminotransferase (ALT). The fatal reaction occurs Interstitial Lung Disease/Pneumonitis, Hypertension, Hepatotoxicity, Haemorrhagic Events and Risk of Impaired Wound Healing [49].

CONCLUSION

Cancer is being critical problem day by day. It is more effective in Men compared to Women. Cancer affected more parts of the organ (46% cases of Prostate and 50% cases of Breast). We are representing recently developed various Chemical compounds and Monoclonal antibodies with its Pharmacological study. That is accepted approval by FDA in 2020 for Marketing.

Conflict of Interest

None declared.

Financial Support

None declared.

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