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GLOBAL AND INDIAN SCENARIO OF CANCER AND SIDE EFFECTS INDUCED BY VARIOUS ANTICANCER AGENTS WITH AN OVERVIEW TO RECENT DEVELOPMENTS IN CURE OF CANCER

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ABSTRACT

Global and Indian scenario of cancer is devastating with 23.6 million new cases to be reported each year till 2030. According to world cancer report of 2014, the cancer death is known to have risen from 8.2 million to 13 million per year. According to World Cancer Report 2014, Africa, Asia, and Central and South America are the most predominant regions accounting for 60% of the worldwide cancer cases and 70% of the total deaths caused by cancer worldwide. It is reported that the prevalence of cancer is more in males as compared to females giving a ratio of 10:9. On considering Indian scenario, India alone contributes to 7.8% of the world cancer burden accounting for 1.1 million new cases of cancer. Approximately one billion of total world population is comprised of Asian Indians of which 20 million population lives outside India. With the increasing incidence of cancer, it has now become a recent area of therapeutics and the

clinical advancement in the cure of cancer is incredible. Although the success of these drugs and therapies are inevitable but still various side effects has been incurred such as skin toxicity, gastrointestinal toxicity, cardiovascular toxicity, bone marrow depression, alopecia, surface epithelial damage, kidney damage, dysphagia, cardiotoxicity, peripheral neuropathy etc. Besides curing the disease, anticancerous drugs also possess toxicity that contributes to higher death rates among cancer bearing patients and specially chemotherapy are associated with wide range of severe side effects. Other therapies like radiation therapy, molecular targeted therapy possess severe side effects that are inevitable. Sovarious strategies and treatment therapies for complete cure of cancer are under seen like use of gamma knife, cyber knife, radioactive iodine seeds and currently a new strategy to targeting angiogenesis by inhibiting VEGFR, EGFR and other tyrosine kinase inhibitors like Sunitinib, Sorafenib, Pazopanib are currently in use. Besides use of drugs, a novel instrument known as TexRAD is used to analyze texture of the given sample and the data produced via using computer application are further processed for disease identification.

Keywords: **Cancer, Global scenario, Indian scenario, anticancer drugs, side effects, recent development**

INTRODUCTION

The word cancer itself indicates a kind of threat in the society and a worldwide problem, as this ailment is the leading cause of death and has uncertainly become an immense area of research for its cure. According to a report presented by World Health Organization (WHO), in 2010 cancer became the leading cause of death worldwide leaving behind the deaths caused by ischemic heart disease. Low and middle-income countries have higher incidence of death due to cancer because of unavailability of prompt and optimal medical services and delay in diagnosis of disease that leads to the severity in disease condition and income remains the major factor for the advancement of the disease and death. Cancer has overtaken infection as the major source of death because the communicable diseases except HIV/AIDS are medically better under control. According to predictions made by International Agency for Research on Cancer (IARC), 127 million new cancer cases and 17 million deaths will occur by the year 2030 [1].

In cancer both International and Indian incidence rates has been estimated but still Asian Indians residing different regions of the world has not been under the immense focus. The comparative rates of cancer

incidence among Indians South Asians in Singapore, U.K and U.S have been presented and rate of cancer incidence in US whites are determined [2]. Survival rate of cancer patients has improved to a vast extent due to development of effective anticancer drugs that leads to cure and long-term survival of cancer patients [3].

Although there has been major advancement in the linecancer therapy by discovery of new anticancer agents and treatments, these anticancer agents confers number of side effects like toxic effects on bone marrow, kidney, lymphoreticular tissue, mucosa, and cochlea that may be lethal to a cancer patient and may sometimes lead to death [4]. Therefore, the objective of this review is to present the current situation of cancer worldwide and in India and to study the various side effects caused by anticancer agents with major development in treatments of cancer with fewer side effects.

Global scenario of cancer

In developing countries, cancer is spreading its leg at a prompt rate and is third main cause of death.In developed countries, cancer stands at second position for causing the death among adults.From 2002 to 2020, 50% amplification in cancer cases are expected if left untreated and we can expect about 10.3 million people being killed by cancer. Of all the death percentages as compared to the death caused by HIV/AIDS, tuberculosis and malaria, cancer alone contributes to 12.5% of all the death [5].

According to a report, few decades ago the rate of incidence of new cancer cases is found to be similar in developed and developing regions. Till date developing nations contributes about 55% of new cases of cancer and this figure is expected to reach 60% by 2020 and 70% but 2050 [6]. In a report presented by world health organization [WHO], there will be a 70% increase in cancer cases in next 20 years [7]. According to the data reported in GOLBOCAN 2008, about 12.7 million cases of cancer were found and 8.2 million deaths were reported globally [8]. Specifically, less developed countries will encounter 80% of the increase in the number of all cancer deaths by the year 2025 [9].

Approximately 14 million new cases per year were estimated in 2012 and in the next two decades, it is expected to increase up to 22 million per year. According to world cancer report of 2014, the cancer death is known to have risen from 8.2 million to 13 million per year. Most common type of cancer as figured in World Cancer Report 2014 worldwide were lung cancer (1.8 million cases, 13.0% of total cases), breast cancer (1.7 million,

11.9% of total cases) and large bowel (1.4 million, 9.7% of the total cases). Among all the cancer cases the major cause of death were due to lung, liver and stomach cancer comprising 1.6 million, 0.8 million and 0.7 million deaths of all cases respectively. According to this report Africa, Asia, and Central and South America are the most predominant regions accounting for 60% of the worldwide cancer cases and 70% of the total deaths caused by cancer worldwide [10].

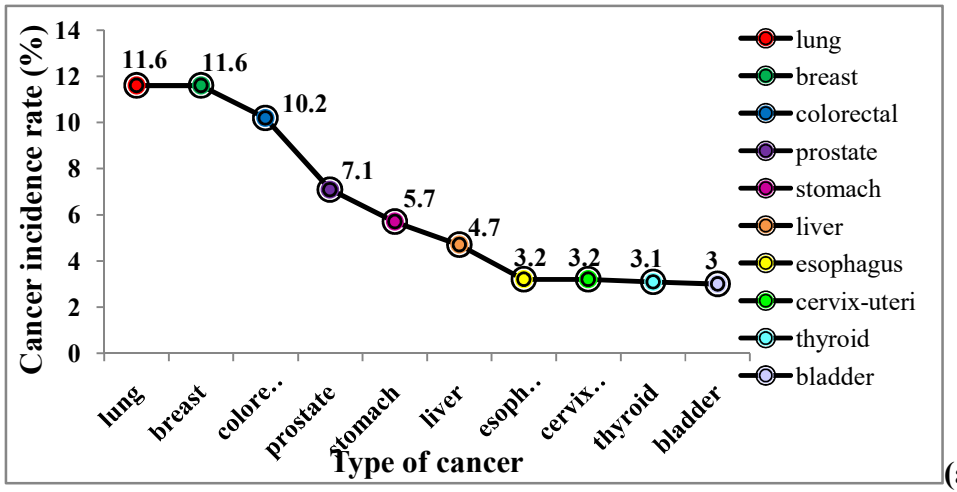
According to world age-standardised (AS) incidence rate report, men are more incidents to cancer compared to female and the data shows that of every 100,000 men in the world 218.6 new cases are reported and that for females i.e.182.6 new cases are reported for every 100,000 females. The incidence rate of cancer in men is found to be more dominant in Australia [579.9 per 100,000], and that in women itis363.0 per 100,000 [11].

Breast cancer being the second most common cancer in the world is becoming more prominent in both developed, developing countries, and leading cause of death in women worldwide. In 2012, approximately 1.67 million breast cancer cases were reported, which accounts for 25% of all the cancer cases globally and mortality rate was nearly 5.2 million. In less developed countries the number of breast cancer cases were found to be higher (883,000 cases) as compared to developed countries (794,000 cases) among women [12]. In the year 2012, the number of prostate cancer cases were 1.1 million of which 70% of the cases belong to developed countries and the mortality rate was around 307,000 [13]. Till 2020, prostrate cancer will contribute to the maximum cancer cases worldwide.Fatality rate of Prostate cancer in low-income countries is 3.5 times that of high-incomecountries, which is nearly 78.6% in low-income countries and 22.5% in high income countries. In 2008, nearly 4.04 million people died of prostate cancer and till 2020 it will contribute to the largest proportionate of cancer cases worldwide. Prostate cancer has become the sixth most leading cause of death men that accounts for 6.1% of the total death in men [14]. While considering cancer cases it is seen that level of Human Development index (HDI) affects tremendously. Low HDI countries are at the edge of westernization through rapid social and economic changes, thus reaching the condition of high HDI countries. If we study the recent trends, the increase in cancer cases is expected to be 23.6 million new cases each year till 2030. There is approximately 66% increase in low

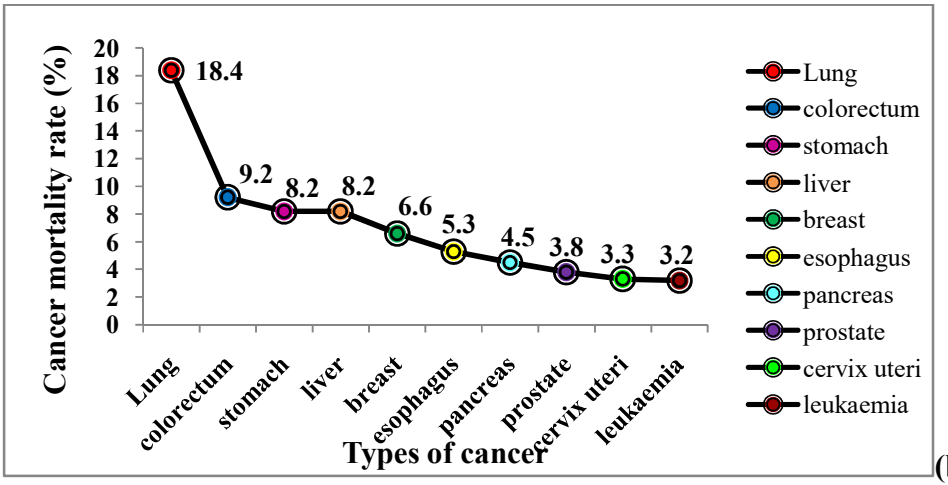
and medium HDI countries and 56% increase in high and very high HDI countries [15]. According to the data projected in GLOBOCAN 2012, there will be 19.3 million new cancer cases per year by 2025. It is also reported that half of all cancers which is 56.8% and cancer deaths 64.9% in 2012, the major cases occurred in less developed regions of the world and is expected to increase further by 2025[16]. According to 2018 survey conducted by GLOBOCON in 185 countries, the overall incidence, and mortality rate was 18.1 million and 9.6 million respectively. The detailed percentage of cancer incidence and mortality is shown in Figure (1a) and (1b) respectively as predicted by GLOBOCON 2018 across 185 countries [17].

In 2019, 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States. The top figurednumber of deaths is from cancers of the lung, prostate, and colorectum in men and the lung, breast, and colorectum in women. Lung cancer corresponds to one-quarter of all cancer deaths [18].

Every day more than 4,500 new cases of cancer are being diagnosed. In the year 2014, 62,750 cases of breast carcinoma in situ and 63,770 melanoma in situ has been identified. About 585,720 Americans are expected to have died in 2014, which is approximately 1,600 deaths per day. The rate of cancer incidence in women is 23% less as compared to men. However, the data collected for the duration 2006-2010 reveals that the rate of cancer incidence has decreased by 0.6% per year in men but for females, the rate is still stable. Overall decrease in the rate from duration 1991 to 2010 for white men, black men, white women and black women was 24%, 33%, 16% and 20% respectively [19].



(a)



(b)

Fig.1: (a) percentage of cancer incidence (b) percentage of cancer mortality

Current scenario of cancer in India

India is progressing at a very high rate to meet the global development and soon will be in the list of developed countries**.** Although it is going to be a developed country, the health problem is still a big issue in India**.** In Asia and Indian subcontinent head and neck cancer has become the major problem with more than 2 lakh new cases identified each year **[**20**]**.

On considering Indian scenario, India alone contributes to 7**.**8**%** of the world cancer burden accounting for 1**.**1 million new cases of cancer**.** Total mortality data accounts for 8**.**3**%** of the total global cancer death, which is approximately 682830 of all cancer cases**.** Most common type of cancer widespread in India in both male and female were breast cancer (144,937; 14**.**3**%**), cervix uteri **(**122,844; 12**.**1**%)**, lip-oral **(**77,003; 7**.**6**%)**, lung **(**70,275; 6**.**9**%)**and colorectal **(**64,332; 6**.**3**%)**. All these cancers accounts for 47**.**2**%** of total cancer cases reported in India. The reported death from these five cancers is 302,124**.** If considered individually, the common type of cancer in men are lung **(**11**.**3**%)**, colorectal **(**7**.**7**%)**, lip-oral **(**11**.**3**%)**, stomach **(**9**.**1**%)** and oro-pharynx **(**6**.**6**%)**. This accounts for total 219,608 cancer cases and 180,670 cancer deaths**. [**21**].** In a report published by Lancet Today in March 28, 2012, around 556,400 people died of cancer in India in the year 2010**.** About 71**%** of the cancer death occurred in age group between 30 to 69 years of which 200,100 were men and 195,300 were women **[**22**].** In the year 2015, oral cavity cancer will become the most prominent cancer in men, which will comprise 10**.**9**% (**50,174 cases**)**of all the prevalent cancer cases**.** The next

forecasted predominant cancers will be lung (9.3%, 43,126), pharynx (8.5%, 39,098), Oesophagus (6.6%, 30,485), Stomach (5.9%, 27,395). In female, cervical cancer is most prominent being 26.1% accounting for 139,864 cases. Breast, ovary, oral cavity, oesophagus cancer are next most prominent cancers in female that accounts for (21.0%, 112,680), (5.6%, 30,114), (05.3%, 28,245), (4.0%, 21,388) respectively [23].

In female the number of breast cancer cases is estimated to be about 80,000 annually due to rapid urbanization and improved life expectancy. In the period between 1965-1985, the frequency of breast cancer has increased by 50%. [24]. Oral cancer being the 3rd most common type of cancer entrapping the society which accounts for almost 30% cases of cancer in the country [25]. If we judge against India globally than the rate of oral cavity cancer and cervical cancer are having higher rate of incidence. Tobacco consumption itself contributes to one-third of all cancer cases in India of which half of the cases belong to men and one-fifth of the cases belong to women. Most frequent type of cancer cases in women studied in Barshi, Bangalore, Bhopal and Chennai region of India is cancer of cervix followed by breast cancer [26]. In the year 2001, 0.33 million tobaccos related cancer cases has been reported and morbidity rate due to tobacco is expected to increase by 7-fold from the year 1995 to 2025 [27].

According to the data recorded by National Cancer Registry Programme in 1997, an incidence rate of Cancer was between 52.9 and 81.5 per 100,000 men; and between 56.8 and 95.6 per 100,000 women. The rate of cancer incidence according to age standardization was reported to be from 81.8 to 122.8 par 100,000 men and from 93.5 to 137.7 per 100,000 women. When compared globally, the rate of cancer incidence is about half to one-third of that occur in USA and Europe and in women it is about half of that experienced in females of USA and Europe [28]. Tobacco chewing is one of the most disastrous reasons for maximum cancer cases in India giving rise to oral cancers and precancerous conditions. Tobacco contributes to 40-50% of all occurring cancer cases in men and 20% cases in women [29].

In a report presented by government, the rate of overall cancer incidence will be extended up to 21%and this rate of incidence will be higher in women. In the data projected, the number of cancer cases in men will rise from 5, 22,164 for 2013 to 6, and 22,203 for 2020. According to NHP reports, number of cancer cases in female in 2013 was around 5, 64,619

and this is expected to increase up to 6, 98,725 till 2020[30].

Approximately one billion of total world population is comprised of Asian Indians of which 20 million population lives outside India. In United States the population of Asian Indians/ Pakistanis [AIP]was found to be approximately 1.84 million in the year 2000 and is still rising. According to a report, in the year 2001, about 2.27 million South Asian population resides in United Kingdom. Cancer incidence rate in India was found to be lowest nearly 111 and 116 per 100,000 among males and females respectively as compared to the US white's men and women, which was 362 and 296 respectively. The rate of incidence of cancer of Indian men and women residing outside India were about 102 and 132 in Intermediate Singapore, 173 and 179 in UK and in US it ranges from 152-176 and 142-164 [31].

Anticancer Drugs

History found showed that the selectivity of traditional anticancerous drugs like alkylating agents, antimetabolites, natural products and other chemicals are preferentially more selective towards the healthy cells as compared to cancerous cells. They act by disrupting the cell division, causing cell death often targeting our other rapidly growing non-cancerous cells like hematopoetic cells, progenitor cells in bone marrow, epithelial cells of gastrointestinal tract and hair cells etc., thus associated with severe toxicity impairing the life excellence [32].

Anticancer drug development has now entered into a new era where the drug is discovered on target based approaches, thus being very much specific as compared to old cytotoxic drugs. Anticancerous drug development comprises two eras: pre-genomic era and post genomic era.Pre-genomic era's drugs comprisetraditional cancer drugs, mainly cytotoxic drug types and contrary to this post genomic eras comprises rationally designed drugs that are involved in target inhibition.[33].Novel approaches to the anticancer therapy includes targeting signal transduction machinery within the cancer cells, cell cycle, apoptosis, angiogenesis, metastasis and some other treatment strategies involves use of antisense molecules, anti-gene therapy, tumor-specific antigens, anti-hormones and many other strategies are still on its way [32]. Tremendous progress has been observed in the field of development of new cancer treatments, still cancer remains the leading cause of death worldwide as the etiopathogenesis of cancer is multifaceted. Genetic predilection and other known

environmental factors like diet, lifestyle and environmental toxins are factors associated with cancer**.** Besides curing the disease anticancerous drugs also possess toxicity that contributes to higher death rates among cancer bearing patients and specially chemotherapy are associated with wide range of severe side effects **[**34**]**.

Side effects of anticancer drugs

With the increasing incidence of cancer, it has now become a recent area of therapeutics and the clinical advancement in the cure of cancer is incredible**.** Although the success of these drugs and therapies are inevitable but still various side effects has been incurred such as skin toxicity, gastrointestinal toxicity, cardiovascular toxicity, bone marrow depression, alopecia, surface epithelial damage, kidney damage, dysphagia, cardiotoxicity, peripheral neuropathy etc**.** In this review major side effect of several anticancer drug and therapy is observed**.**

Side effects associated with immunotherapy

Surgery, chemotherapy, and radiation being the most traditional method for cancer treatment fails to completely eradicate the cancerous cell as they cause potential damages to normal cells and tissues being non-specific in nature and also depletes immune system leaving them inresponsive to cancerous cell**.** Thus, immune enhancement is the major focus area to defend against cancer and thus being challenging area of research and treatment **[**35**]**.

Immunotherapy is nowadays the best potential way for cancer treatment, showing slighter and minimal toxicity to non-cancerous cells**.** Although being the most promising way for treatment of cancer, still it shows certain side effects in the form of autoimmunity **[**36**]**.

Increased advancement in molecular medicine has preferentially increased the implication of cytokines in the treatment of disease**.** These molecular medicine includes purified natural cytokines or recombinant products such as interferon **(**IFN**)**, granulocyte colony-stimulating factor **(**G-CSF**)**, granulocyte-macrophage colony stimulating factor **(**GM-CSF**)**, erythropoiesis stimulating factor **(**EPO**)**, interleukin**(**IL**)**-1, IL-2, IL-3, IL-6, and tumor necrosis factor-α **(**TNF-α**)[**37**]**.

The major and minor side effects mainly associated with immunotherapy includes constitutional (fever, fatigue, arthralgia, headache, malaise, vomiting etc), hematologic (bone marrow suppression), cardiovascular, renal, gastrointestinal, neurologic and muscular, pulmonary side effects **[**38**].** Uses of monoclonal antibodies

for immunotherapy are reported to show paraneoplastic neurologic disorder**.** Some antibodies that specifically acts by blocking growth factor receptors like EGFR, VEGFR and Her-2 includes bevacizumab, cetuximab and trastuzumab respectively shows gastrointestinal toxicity, skin, lung toxicity for normal tissues **[**39**]** (Table 1).

Stimulation of immune system to recognize tumor cells has been the promising approach for cancer therapy**.** It is also known as adoptive immunotherapy**.** Among all adaptive methods, CIK particularly emphasizes the immune system to destroy tumor cells and thus it has become the most promising approach towards cancer therapeutics**.** Side effects associated with CIK **(**cytokine**-**induced killer cell**)** therapy includes Fever **(**37**.**5–40 °C**)**, Graft versus host disease **(**GVHD**) (**grade I–II**)**, Ventricular arrhythmia Chills, Fatigue**[**41**].**

Side effects of molecular targeted therapy

Targeted therapies involve those drugs that specifically target those proteins, genes or tissue environment that are responsible for growth and development of cancer, thus being highly selective in nature **[**42**].** Various targeted therapyincludes anti**-**tumor monoclonal antibodies (mAbs), small molecules, signal transduction receptor inhibitors, and cancer vaccines **[**43**].** Despite of its high selectivity towards its target, there occur various adverse effects**.** Some general toxicity include oral toxicity, skin toxicity, gastrointestinal toxicity, cardiotoxicity, hypertension, proteinuria thrombotic event, and bleeding, gastrointestinal perforation, wound healing, fatigue, mucositis, diarrhea etc**.**

Some of most important targeting factors include EGFR, HER-2, VEGFR, PDGFR, TK inhibitor of EGFR, c-kit, Flt-3 etc**.** Inhibitors of TK are found to be less specific than monoclonal ntibodies, thus causing higher level of toxicity as compared to mAbs**.** Skin toxicity is the most commom side effects induced by the anti-EGFR drugs, which includes folliculities, hyperpigmentation, nail fragility, xerosis, hair changes like trichomegaly**.** Some patients have also been observed with gastrointestinal toxicity that results in diarrhea, constipation, nausea and vomiting as side effects**.** Drugs for antiangiogenesis generally show hypertension**.** One of the drug Bevacizumab that blocks VEGFR, is a humanized monoclonal antibody is shown to induce reverse posterior leukoencephalopathy syndrome (RPLS) as a side effect**.** This comprises headache, seizures, impaired vision etc**.** Multitargeted kinase inhibitors like Sorafenib and Sunitinib

known to inhibit PDGFR-B, Raf, c-kit, and Flt-3. The major side effect of Sorafenib includes diarrhea, rashes, fatigue, hypertension, dyspnea and that of Sunitinib were fatigue, diarrhea, elevation of lipase, anemia, hypothyroidism, hypertension, hair depigmentation [44]. Targeted therapy application for cancer treatment is reported to cause several oral toxicities like mucositis, xerostomia, dysphagia, and pharyngitis. In a study, it is reported that the use of cetuximab for nasopharyngeal cancer causes dysphagia [43].

Several ocular side effects have also been reported with the application of targeted therapy for cancer treatment. Some of the major side effects include ocular edema, burning sensation, and severe loss of visual acuity, optic neuropathy, endophthalmitis, ocular hyperemia, dry eye, vitreous hemorrhage or retinal hemorrhage [45]. Cardiotoxicity has now been the common side effects associated with the implication of anticancer drugs [46] and has become the major cause of mortality and morbidity [47]. Cardiac toxic effects of TKIs range from asymptomatic QT prolongation to reduction in left ventricular ejection fraction (LVEF), symptomatic congestive heart failure [CHF], acute coronary syndromes and myocardial infarction (MI)[48].List of anticancerous agents possessing cardiotoxic effects are listed in the Table 2.

Neurologic side effects of various targeted therapy is also observed and has been clinically reported. Some of the examples of neurotoxicity caused by targeted therapy are listedin Table 3.

Severe hepatotoxicity has been reported via the use of specific TK inhibitors like imatinib, nilotinib, dasatinib, gefitinib, erlotinib, sorafenib, sunitinib, pazopanib, lapatinib.Regorafenib, a new molecular targeting agent targets several angiogeniv and stromal receptor tyrosine kinases that includes VEGFR-21,-2,-3, platelet derived growth factor-β [PDGFR-β], fibroblast growth factor receptor1 (FGFR-1), and TIE2. It also inhibits receptor tyrosine kinases (RTKs) [57].

The most common side effect associated was skin toxicity (HFSR/PPE or rash).Other adverse drug reactions (greater than or equal to 30%)were asthenia/fatigue, decreased appetite and food intake, HFSR/PPE, diarrhea, alopecia, mucositis, proteinuria, hypothyroidism, haemorrhage, nerutropenia, increased ALT/AST, weight loss, infection, hypertension and dysphonia, keratacanthoma/ squamous cell carcinoma. The most serious adverse drug reactions were

hepatotoxicity, hemorrhage, and gastrointestinal perforation [58].

Chemotherapy

Few deadly side effects of chemotherapy include nausea and vomiting. About 70-80% of cancer patients suffer from nausea and vomiting because of chemotherapy [59]. A chemotherapeutic drug, oxaliplatin given to patients for colorectal cancer causes acute and chronic neurotoxicity. Studies have shown that persistent and chronic neurotoxicity problems affect patient's daily lives andhealth-related quality of life [60].

One of the potential side effects induced by chemotherapy includes chemotherapy-induced neuropathy (CIPN). It is reported that patients treated with platinum compound, taxanes, vinca alkaloids and other cytotoxic compounds shows the symptoms of CIPN that initially affects fingers and toes and progresses towards arms and ankles and the calves[61].The major side effect associated with the chemotherapy includes mucositis that affects gastrointestinal tract and symptoms include pain, nausea, heartburn, ulceration, abdominal pain, bloating, vomiting, diarrhea, and constipation [62].

Few general toxicities imparted by chemotherapeutic agents includes gastrointestinal toxicities, hepatic, pulmonary, cardiac, renal toxicity and bone marrow suppression. There is a reported case of ocular side effects with the increased use of aggressive regimens of chemotherapeutic agents [45]. Side effects of chemotherapeutic drugare listed in Table 4.

Table1: Various Side effects of drugs used in Immunotherapy

Drugs	Disease	Target	Side effects
Ipilimumab	Melanoma(AML, CML),renal carcinoma	CTLA-4	Diarrhea, rash, vitiligo, pruritis, colitis, hypophysitis, Arthritis, hyperthyroidism, pneumonitis[40]
MK-3475(Pembrolizumab)	Melanoma	PD-1	Vitiligo, rash, liver damage, colitis, diarrhea, pruritis[40]
Tremelimumab	Colorectal, melanoma	CTLA-4	Pruritis, diarrhea, colitis, liver damage, rash[40]
Nivolumab	NSCLC, melanoma	PD-1	Pneumonitis, diarrhea[40]
BMS-66351(Urelumab)	-	CD-137	Liver damage[40]
BMS-936559	-	PD-L1	diarrhea, pruritis, lymphopenia, rash, vitiligo, hyperglycemia[40]
CP-870,893	Solid tumor	CD-40	Liver damage, lymphopenia[40]
MPDL3280A	Melanoma	PD-L1	Hyperglycemia, liver damage[40]
Alemtuzumab	CLL	CD52	Destruction of normal leukocytes, leading to susceptibility to infections[39]
Gemtuzumab	AML	CD33	Infection, sepsis, pneumonia[39]
Rituxumab	Lymphoma	CD20	Suppression of B cells leading to deficiency inimmunoglobulin and infections[39]
MDX-1106	Melanoma, RCC, NSCLC, prostate cancer	PD-1	Colitis[39]

(Abbreviations:AML-acute myeloid leukemia;CML-chronic myelogenous leukemia;CTLA-4-cytotoxic T lymphocyte antigen-4;PD-programmed death; CD-cluster of differentiation;CLL-chronic lymphocyte leukemia;RCC-renal cell carcinoma; NSCLS-non-small cell lung carcinoma)

Table 2: Cardiotoxicity of various targeted therapy drug

Drug	Target	Side effects
Trastuzumab	Her-2	Asymptomatic LV dysfunction to severe symptomatic CHF,asymptomatic right and left bundle branch blocks and new T-wave inversions on electrocardiogram (ECG)[49]
Lapatinib	EGFR, Her-2	symptomatic CHF or an asymptomatic decrease in LVEF[49]
bortezomib	proteasome inhibitor	HF[50]
bevacizumab	VEGF inhibitor	HF, arterial thrombotic event[50]
Vandetanib	VEGFR, EGFR, RET tyrosine kinases.	asymptomatic QTc prolongation[50]
Nilotinib	multitargeted tyrosine kinase inhibitor against the Bcr–Abl fusion protein, KIT and PDGFR	mean QT prolongation [50],Bradychardia, Angina Pectoris, cardiac murmur, Coronary artery disease, myocardial ischemia[51]
Imatinib	inhibition of Abl/Arg	Heart failure (HF)[52] Percarditis, Pericardial effusions, hypertension, Tachycardia, hypotension[51]
Sunitinib	VEGF receptor (VEGFR)1–3, PDGFR_/_, c-Kit, FMS-like tyrosine kinase-3, colony-stimulating factor-1 receptor (CSF-1R), and the product of the human RET gene	Myocardial infarction, heart failure, or cardiovascular death[52]
Gefitinib	EGFR	No cardiac toxicity[53]
erlotinib	EGFR	No cardiac toxicity[53]
Pertuzumab	ErbB2	Decline in LVEF,congestive heart failure(CHF)[54]
panitumumab	ErbB1	Angioedema[55]
Dasatinib	BCR-ABL	QT prolongation, cardiomegaly, acute coronary syndrome, Arrhythmia, Pericarditis[51]

(Abbreviations:Her2- human epidermal growth factor receptor 2;EGFR-epidermal growth factor receptor; VEGFR-vascular endothelial growth factor; PDGFR-Platelet-derived growth factor receptors; LVEF-Left ventricularejection fraction;CHF-chronic heart failure)

Table3: Neurotoxic effects induced by molecular targeted therapy

Drugs	Side effects
Erlotinib	Neuropathy[56]
Gefitinib	Brain haemorrhage, ependymoma, imtratumoral bleeding [56]
Lapatinib	No major side effects seen except in few cases showing neuropathy[56]
Imatinib	Myalgias, intracranial bleeding, high rate of intratumoral haemorhhage[56]
Bevacizumab	Cereberovascular accidents, hypertension, radiation necrosis, bleeding, leukoencephalopathy syndrome[56]
Sunitinib and Sorafenib	Hypertension, thrombotic microangiopathy, posterior reversible leukoencephalopathy syndrome. [56]
Selumetinib	Besides fatigue no other neurotoxic effects reported[56]
Sirolimus	Seizures, posterior reversible leukoencephalopathy syndrome[56]
Perifosine	No significant neurotoxicity reported[56]
Thalidomide	No significant neurotoxicity reported[56]

Table 4: List of chemotherapeutic drug and their side effects

Drug	Class	Type Of Cancer	Side Effects
Cisplatin	**Heavy metal compound**	**Head and neck, lung, cervical, ovarian and testicular, upper GI malignancies, neuroblastoma, osteogenic sarcoma, recurrent brain tumors in children and urinary bladder cancer.**	**Blurred vision, papilledema, unilateral, bilateral retrobulbar neuritis, optic neuritis [45], Hepatic toxicity, diarrhea[63] Nephrotoxicity[64]ototoxicity [65]**
Chlorambucil	**Nitrogen mustard derivatives**	**adult hodgkin's disease, adult follicular non-hodgkin's disease and adult chronic lymphocytic leukemia**	**Keratitis, diplopia, bilateral papilledema and retinal Hemorrhages [45]**
Capecitabine	**Carboxylic Acids and Derivatives**	**Basal cell skin cancer, GIT adenocarcinoma, Cancers of breast-colon,stomach-rectum-pancreas, Cancer of prostate and bladder. [66]**	**Cardiotoxicity(rare) [67], diarrhoea, stomatitis, hand – foot syndrome, fatigue [68]**
Cytarabine	**Carbohydrates and Carbohydrate Conjugates**	**Basal cell skin cancer,GIT adeno-carcinoma, Cancers of breast-colon-stomach-rectum-pancreas, Cancer of prostate and bladder. [66]**	**Risk of infection, bruising and bleeding, anaemia, loss of apetite, Diarrhoea, hair loss, sore mouth, fatigue [69] Myelopathy, peripheral neuropathy, necrotizing leukoencephalopathy, seizures, cerebral dysfunction [70],pulmonary toxicity [<2%],germ cell toxicity; reversible and irreversible, alopecia, esophagitis, mucositis, hepatic dysfunction, pancreatitis [71]**
Gemcitabine	**Carbohydrates and Carbohydrate Conjugates**	**Basal cell skin cancer,GIT, adeno-carcinoma, Cancers of breast-colon-stomach-rectum-pancreas, Cancer of prostate and bladder. [66]**	**Myelosuppression, nausea, vomiting, dyspnoea and interstitial infiltrates, cardiac insufficiency, pulmonary embolism, pneumonia, carcinomatous lymphangitis [72],confusion, seizures,aphasia, ataxia, visual problems, and headache[CNS toxicity[73]**
Cyclophosphamide	**Amines**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer. [66]**	**Bone marrow suppression, Neutropenia, leukopenia, thrombo-cytopenia and anemia, hemorrhagic necrotic perimyocarditis, gonadal toxic effects [amenorrhea], bladder toxicity[Hemorrhagic cystitis[74]**
Melphalan	**Phenylpropanoic Acids**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer [66]**	**hypersensitivity reactions including anaphylaxis [2%], anemia [11-60%, severe 2-12%], immunosuppression, leukopenia, neutropenia, thrombocytopenia [5-55%, severe 3-43%], hypotension, alopecia, stomatitis, nausea and vomiting, hemorrhage, hyponatremia, neuropathy radiation myelopathy, myeloproliferative syndrome, amenorrhea [75]**
Temazolomide	**Imidazotetrazines**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer[66]**	**myelosuppression, nonhematologic toxicity, and infection, neutropenia, fatigue, alopecia, and gastrointestinal symptoms, alopecia, constipation, thrombocytopenia, vomiting, and lymphopenia [76], Anemia, leukopenia, neutropenia, thrombocytopenia, edema [1%, severe 1%], embolism, pulmonary, malaise, alopecia, nausea, dyspepsia, cholestasis, hepatic failure, AST/ALT elevation, gamma-glutamyltransferase elevation, hyperbilirubinemia, liver enzyme elevation, insomnia, myalgia, neuropathy [77]**

Cyclophosphamide	**Amines**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer. [66]**	**Bone marrow suppression, Neutropenia, leukopenia, thrombo-cytopenia and anemia, hemorrhagic necrotic perimyocarditis, gonadal toxic effects [amenorrhea], bladder toxicity[Hemorrhagic cystitis[74]**
Carmustine	**Hydrazines and Derivatives**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer[66]**	**Anemia [78],myelosuppression [>10%], alopecia, hyperpigmentation, emetogenic potential high; high-moderate anorexia [1-10%], constipation [1-10%], diarrhea,ataxia, encephalopathy, retinal retinal hemorrhages, pulmonary toxicity [up to 30%], interstitial fibrosis, acute leukemias, bone marrow dysplasias, gynecomastia, infertility, phlebitis, tachycardia, dermatitis, erythema, telangiectasia [79]**
Ifosfamide	**Oxazaphosphinanes**	**Brain tumor, Testicular cancer, Head and Neck cancer, Hodgkin's disease, Pancreas carcinoma, Ovarian and bladder Cancer [66]**	**CHF,Arrhythmias [80], Nausea and vomiting 60-80%Cytolytic or cholestatic features or evidence of vascular injury, Anorexia infrequently Diarrhea, infrequently Constipation Infrequently Stomatitis, infrequently, Mucositis, infrequently, Pancreatitis, Rare Elevated hepatic transaminases [81]**
Bleomycin	**Carboxylic acid and derivatives**	**-**	**Emetic potential, Pulmonary fibrosis , Hypersensitivity pneumonitis ,Acute pneumonitis, hyperpigmentation, stomatitis [82]**
Carboplatin	**Amines**	**-**	**Myelosuppression, nausea and vomiting, peripheral neuropathy, renal toxicity, and hepatic dysfunction [83]**
Mitomycin	**Indoles and derivatives**	**gastric and pancreatic carcinomas [84]**	**Bone marrow depression, thrombocytopenia, stomatitis, renal toxicity, noncardiogenic pulmonary, acute pneumonitis [82]**
Methotrexate	**benzenoids**	**Acute lymphocyte leukemia, osteocarcoma, choriocarcinoma, breast cancer, small cell lung cancer, head and neck cancer and intrathecal [85]**	**Acute myelopathy, necrosis, fibrosis, cholestatis, hepatic venoocclusive disease, acute pneumonitis, hypersensitivity, noncardiogenic pulmonary edema, hyperpigmentation, bone marrow depression [82]**
Epirubicin	**Phenylpropanoids and Polyketides**	**Breast cancer, Acute leukaemia, Endometrial cancer, Thyroid cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyelo sarcoma, Neuroblastoma [66]**	**Myelosuppression, neutropenia, thrombocytopenia, dilated cardiomyopathy[83],Mucositis, nausea, vomiting, infection, alopecia, decrease in LVEF [86]**
Doxorubicin	**Phenylpropanoids and polyketides**	**Breast cancer, Acute leukaemia, Endometrial cancer, Thyroid cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyelo sarcoma, Neuroblastoma [66]**	**cardiomyopathy [DCM] and congestive heart failure [CHF/ [87] anemia, leukopenia, and thrombocytopenia [hematological toxicity], hand–foot syndrome, and stomatitis [88]myelosuppression, necrosis, steatosis, fibrosis, cholestasis, and vascular injury[89]**
Dactinomycin	**Carboxylic acid and derivatives**	**Breast cancer, Acute leukaemia, Endometrial cancer, Thyroid cancer,Wilm's tumor, Ewing's sarcoma, Rhabdomyelo sarcoma, Neuroblastoma [87]**	**Allergic reactions, agranulocytosis, anemia, neutropenia, thrombocytopenia, fatigue, malaise, alopecia, anorexia, diarrhea, cheilitis, dysphagia,esophagitis, gastrointestinal ulceration ,mucositis, hepatic veno-occlusive disease, hypocalcemia, myalgia, pneumonitis,ascites [90]**

Side effects of Radiation therapy

Radiotherapy is the most common and main treatment procedure for cure of cancer and approximately 60**%** of all cancer patients receives radiotherapy as a treatment of cancer**[**91**].** Radiation therapy effectively kills cancerous cells but it also affects the normal cells changing their environmental conditions that lead to changes in cell functioning and host defense system**[**92**].**Various side effects associated with radiation therapy includes fatigue, insomnia, mucositis, Xerostomia, Radiation enteritis **[**93**]**. Fatigue is the most common side effect experienced by cancer patients **[**94**]**. It is reported that of all the cancer patients receiving radiation therapy, 93**%** patients experiences fatigue as side effect of therapy **[**95**]**.

Quality of sleep is a major marker of health **[**93**]**. Sleep disturbance referred as Insomnia is a general side effect associated with radiation therapy in which the patient is unable to sleep or maintain proper sleep for more than two weeks due to anxiety or stress**.** Predisposing, precipitating and perpetuating factors are mainly the responsible causes of insomnia in cancer patients**.** Predisposing factors include female gender, older age, hyperarousability as a trait, personal or family history, mood or anxiety disorders; precipitating factors include those cancer treatments that modify levels of inflammatory cytokines or interrupt circadian rhythms or sleep- wake cycles, side-effects of cancer treatment, menopausal symptoms, hospitalization, distress in response to cancer, co-occurring symptoms, i**.**e**.** pain or fatigue, and medications used to manage side effects caused by treatment, such as corticosteroids; and perpetuating behavioral factors such as excessive daytime sleeping, long-term or improper use of medications, and maladaptive cognitions i**.**e**.** imprecise evaluation of sleep obscurity and quality and daytime impairments **[**96**]**.

Mucositis being the most common side effects associated with radiotherapy affects 34 to 43**%** o0f all cancer patients undergoing radiation therapy. In some cases, 9-19**%** of all radiotherapy receiving patients suffers from severe mucositis**.** It is often referred to as radiation-induced mucositis**.** Symptoms **"**mouth and throat sores**"**; difficulty in swallowing; pain; lost or altered taste (dysgeusia); excessive mucous secretions associated with dry mouth that may lead to gagging, nausea and vomiting; loss of appetite, fatigue, weight loss and aspiration **[**97**]**. Radiation therapy is most widely used therapy to treat variety of primary tumors**.** This mode of therapy incorporates the use of

ionizing radiation to treat malignant skin tumors, which causes dermatitis as severe side effects**.** It is seen that about 80**%** of the RT treated patient experiences skin irritation ranging from hyperpigmentation to ulceration **[**93**]**.

*A*cute radiation dermatitis includes erythema, desquamation, skin necrosis or ulceration and chronic radiation dermatitis includes postinflammatory hypopigmentation and hyperpigmentation, xerosis, scale and hyperkeratosis, persistent poikilodermatous changes (hyperpigmentation, hypopigmentation, atrophy, telangiectasia, indication of cutaneous injury) **[**98**]**.

Other side effects include Xerostomia, which characterizes dry mouth (resulting from the reduction in or absence of salivary production) and can result in difficulty eating, swallowing, and troubled speaking**.** Xerostomia leads to augmented susceptibility to infections, dental caries, gum disease, and tooth decay**.** In some cases, patients may experience change in taste **[**disgeusia**]**, increased thirst and sometimes localized tongue pain (glossodynia)**.** There is decrease in salivary flow by 50**%** in the first week of treatment and increases further up to 80**%** by seventh week of treatment**.** Acute radiation-induced xerostomia is associated with inflammatory reaction**.** Fibrosis of salivary gland results in delayed or late radiation-induced xerostomia, which can occur up to 1 year after treatment and is typically permanent**.**Xerostomia being an expected complication of RT affects up to 100**%** of patients with head and neck cancer **[**93**]**. Acute radiation damage is a major side effect of abdominal and pelvic irradiation**.** The intestinal mucosa, especially the small intestine, is extremely radiosensitive**.** Radiation enteritis (RE) and radiation-induced diarrhea (RID)are common side effects of radiation therapy**.** Almost all patients experiences some degree of REwhile receiving radiation to abdominal and pelvic region **[**99**]**.

Recent Developments

Due to the lack of successful and validated antiangiogenic bioassay for the various discovered antiangiogenic agent, there has been a major hurdle in the development of targeted these drugs**.** Most recent technique that is being successfully implied for non-invasive tumor vasculature imaging is the dynamic contrast enhanced magnetic resonance imaging **[**DCE-MRI**]**. It is used in preclinical and clinical models **[**100**]**.

According to a report presented by National Cancer Institute in 2013, epigenetic and genetic features are being studied in samples

for initiation and progression of cancer in TCGA. In this report it was given that TARGET (Therapeutically Applicable Research to Generate Effective Treatment) that is a NCI-sponsored genomics initiatives program, will focus on childhood cancer by identifying the genetic markers of childhood cancer [101]. An enormous effort has been made by Cancer Target Discovery and Development (CTD^2) Network to project new therapies for cancer using the massive amount of data being generated by molecular characterization of various types of cancer.

In a news given by ecancernews, circulating tumor cell (CTC) clusters are more responsible for the process of metastasis than single circulating tumor cells and it has also been reported that several genes are expressed at higher level in CTC as compared to single CTC in a RNA sequencing project of CTC and single CTC of breast cancer patients. One of the proteins, which are reported to be expressed at a high level, is plakoglobin, which reduces patient survival even in the primary tumors. So a new target has also been identified that by blocking plakoglobin pathway, metastasis can be blocked as it is found to be an important component of cell-to-cell adhesion structure [102].

In Medanta, Gurgaon, a successful strategy for the treatment of prostrate cancer at early stage has been evolved. The recent technology includes the use of radioactive iodine seeds for delivering high dose of radiation to prostrate gland. This technology has been successfully furnished and is now counted in existing strategies [103].

Blocking of VEGF is the major targeted approach for blocking angiogenensis and the other factors are bFGF, hepatocyte growth factor. In 1989, alfa-2a (an interferon) was used to prevent the progression of angiogenesis by targeting VEGF and bFGF in pulmonary hemangiomatosis. In feb 2004, bevacizumab (Avastin)a humanized monoclonal antibody for VEGF was approved to treat metastatic colorectal cancer in combination with SFU. More recent strategies include afliberecept (VEGF Trap) in combination with standard chemotherapy agents has been found to be efficient and is under phaseI and phaseII clinical trials in solid tumors like colorectal cancer, NSLCS, prostrate cancer, pancreatic cancer, gastric cancer in the advanced stage. Another strategy along with ligand blocking agents include blocking of signal transduction pathway for angiogenesis stimulators. In the year 2006, several small molecular RTK inhibitors such as Sunitinib, FDA approved

Sorafenib targeting VEGF, EGF, and PDGF. Pazopanib (Votrient) that inhibits VEGFR 1,2,3, c-Kit and PDGF receptor involved in tumor angiogenesis, got approval by FDA in the year 2007. In 2007 only, FDA approved temsiromilus (CCI-779) as the first mTOR inhibiting drugs for RCC. The second was everolimus (RAD 001). Untilnow, only 14 approved drugs are available for targeting angiogenesis and can be categorized under four categories like monoclonal antibody, small molecule RTK inhibitors, mTOR inhibitors and other unknown mechanisms [104]. In U.S, marabont 8 anticancer therapies are known to be recognized possessing antiangiogenic properties agent.

A novel instrument known as TexRAD, used for texture analysis, helps in sophisticated enhanced diagnostic imaging of the given sample. TexRAD is completely a software application and the data generated needs to be analysed for further imaging process and disease identification. Recent developments in the field of finding effective treatment of cancer include development of a scoring scheme. This scheme is developed recently under the investigation of Professor Jean Paul Theiry and Dr. Ruby Huang at the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS). The scheme visualizes the epithelial-mesenchymal transition (EMT) mechanism, which is found to be very much predominat for various cancer stages like cancer invasion, metastasis and chemo-resistance. [105]. Other latest technologies for cancer treatment includes intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), cyber knife [106].

One of the worlds's most advanced technology, Cyber knife, treatment is available at present only in few cancer institute of America, being a unique treatment that incorporates image guiding techniques and focused beams of radiation from outside of the body, forattacking tumor at different angle and also preventing surrounding normal cells from damage [107]. Cyber knife radiosurgery is nowadays also available in top cancer medical institutes of India like Apollo Hospitals group. Cyber knife has the FDA approval for treatment of both cancerous and beningn tumors in any part of the body [108].

Another major achievement in the field of brain tumors is the use of Gamma knife that precisely uses gamma radiation for radiosurgery. This is used for the treatment of brain tumors, arteriovenous malformations and brain dysfunctions such as trigeminal neuralgia [109]. One of the most recent FDA

approved drug announced in a press release on 14thApril 2014, foradvanced or metastatic gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma is CYRAMZATM (Ramucirumab). The credit for this achievement goes to Eli Lily research developmental committee. This drug specifically inhibits the process of angiogenesis by being VEGFR-2 anatagonist, thus preventing the bindijng of angiogenic molecules like VEGF-A, VEGF-C, and VEGF-D preventing the formation of new blood vessels in cancerous cells [110]. Some of the latest drugs approved by FDA in the year 2017-2018 areAzedra (iobenguane I-131) for adrenal tumors; Lynparza (olaparib) for breast cancer; Lutathera (lutetium Lu-177 dotatate) for Digestive Tract Cancers; Tibsovo (ivosidenib), Daurismo (glasdegib), Gilteritinib (Xospata) and Venclexta (venetoclax) for leukemia; Imfinzi (durvalumab), Vizimpro (dacomitinib), Opdivo (nivolumab) and Lorbrena (lorlatinib) for NSCLC; Truxima (rituximab-abbs) for lymphoma; Erleada (apalutamide) and Xtandi (enzalutamide) for prostate cancer; Libtayo (cemiplimab) and Poteligeo (mogamulizumab) for skin cancer; Vitrakvi (larotrectinib) and Keytruda (pembrolizumab) for multiple solid tumors [111].

CONCLUSION

Cancer has become the most wide-reaching cause of fatality**.** Global and Indian scenario of cancer cases and death represents the severity of disease in low income and developing countries and thus the demand of present situation is research and development in the field of new anticancer drugs and treatment therapies**.** Pharmaceutical industries are aiming at discovering new anticancer drugs and therapies since the number of cancer cases and death are increasing globally**.** Even though the successful development of potential anticancer treatments like chemotherapy, radiation therapy, molecular targeted therapyetc**.** is associated with adverse side effects like cardiotoxicity, gastrointestinal toxicity, hepatic toxicity, neurotoxicity, renal toxicity etc**.** This toxicity is responsible for deaths in various cancer patients**.** Thus recent development has to been done to cure these side effects associated with the treatment**.**Most recent technique that is being successfully implied for non-invasive tumor vasculature imaging is the dynamic contrast enhanced magnetic resonance imaging **[**DCE-MRI**]**, epigenetic and genetic features are being studied in samples for initiation and progression of cancer, Use of radioactive iodine seeds is another measure to

specifically target cancer calls**.**An enormous effort has been made by Cancer Target Discovery and Development **[**CTD^2**]**Network to project new therapies for cancer using the massive amount of data being generated by molecular characterization of various types of cancer**.** The most recent strategy for cancer treatment includes targeting the angiogenic receptors responsible for vascularisation and metastasis of cancer**.** Sunitinib, Sorafenib targeting VEGF, EGF, and PDGF are the small molecuale RTK inhibiting drugs approved by FDA**.** Pazopanib **[**Votrient**]** that inhibits VEGFR 1,2,3, c-Kit and PDGF receptor involved in tumor angiogenesis, got approval by FDA in the year 2007**.** The first mTOR inhibiting drug, temsiromilus **[**CCI-779**]**got FDA approval in 2007 for renal cell carcinoma **[**RCC**].** The second was everolimus **[**RAD 001**].** Till now only 14 approved drugs are available for targeting angiogenesis and can be categorized under four categories like monoclonal antibody, small molecule RTK inhibitors, mTOR inhibitors and other unknown mechanisms**.** Other latest technologies for cancer treatment includes intensity modulated radiation therapy **[**IMRT**]**, image guided radiation therapy **[**IGRT**]**, cyber knife**.**

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