Anticancer Drugs: Focus on Drug Discovery, Development, Clinical Research, and Pharmacoeconomics

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***Abstract*— Cancer remains one of the top 10 causes of death in current era. It is disease caused by uncontrolled division or malignant growth of abnormal cells in the body. Although there are many drugs discovered so far, successful treatment and management of this disease is still not possible. Current review focuses on pathophysiology of cancers along with their types and risk factors. In current date, anticancer drugs are obtained from three different sources: plant, marine and monoclonal antibodies. Drug discovery process of selected anticancer molecules such as vincristine, vinblastine, paclitaxel, cytarabine, and monoclonal antibodies are discussed in detail. Pharmaceutical development of anticancer drugs, preclinical steps, and clinical trials are also discussed. Clinical end points used in oncology trials are explained. Economical analysis of anticancer drugs was reviewed using pharmacoeconomic parameters. Considering cost involved in development, cost of anticancer drugs in market is also very high as compared to drugs of other categories. There is need for discovery of drugs using specified molecular targets, with less developmental timeline and good clinical benefit so that cost of treatment could be decreased.**

***Keywords* — Cancer, Clinical Research, Pharmacoeconomics, Anticancer drugs, Drug discovery**

I. INTRODUCTION

Cancers are one of the most prevalent diseases across worldwide. Although there are around 150 types of cancers occurring worldwide, World health organization (WHO) top 10 causes of death fact sheet tells that cancers of trachea, bronchus, and lungs rank 5th amongst them.[1] It is disease caused by uncontrolled division or malignant growth of abnormal cells in the body. Word cancer in medical terminology is called as neoplasm. It is said that this is the disease which is occurring since ancestral times of human beings [2]. Even in remains of Homo erectus and in mummies of Egypt, evidences of cancer have been found [3]. Cancer is caused by different factors called as carcinogens. Statistics says that there are around 108 different carcinogens that could lead to development of cancer in humans [4]. Cancer therapeutics in current years is focused on surgical removal, anticancer drugs chemotherapy, radiation therapy, immunotherapy and hormonal supplements. Although evidence suggests that cancer exists since ages, cancer chemotherapy has started just from the time of World War II. In the year 1945, nitrogen mustards were discovered first in treatment of leukaemias [5]. Since then, National Cancer Institute (NCI), USA figure cites more than 100 anticancer drugs for treatment of various types of cancers [6]. Drug discovery, development and clinical trial of anticancer drugs is very challenging aspect in pharmaceutical industry. These drugs can be developed from chemical based or synthetic, natural i.e. plant, animal or marine based, and genetic engineering based sources [7]. Natural source drugs still rank top in most of anticancer therapeutics [2]. Discovery of new anticancer drugs in now days require use of sophisticated techniques such as high throughput screening [8]. After successful finding of lead, pre-clinical studies and then clinical trials are done. Pre-clinical studies in anticancer drugs are conducted at least six months duration in rodent and non-rodent species. Clinical trials in anticancer drugs is challenging task as recruitment in cancer patients is very slow and can take many years. This delays approval of drugs into market. US FDA and other regulatory authorities, in some cases, provide accelerated approval when there is no anticancer drug to treat particular type of cancer, so as patients could get benefitted [5]. Principal endpoints that are considered in the development of anticancer drugs are overall survival, progression, free survival, time to progression, time to failure, etc [9]. In general, drug approval for anticancer drugs takes longer time as compared to drugs of any other category [8]. Due to this, development of anticancer drugs is expensive exercise. Therefore, consideration of pharmacoeconomics is also important in these drugs. Current review article covers aspects of cancer prevalence, pathophysiology, types, drug discovery and development of anticancer drugs with focus on aspects of sources of drugs, discovery steps, screening, pre-clinical development, and clinical development including endpoints, phase IV quality of life measures and pharmacoeconomics along with case studies wherever possible.

II. PREVALENCE OF CANCER (NEOPLASM)

Around 14 million new cases of cancer per year have been found in year 2012 which is expected to rise to 22 million till 2034 [10]. It is also expected that till 2014, cancer deaths were expected to be 13 million per year [10]. Cancer is most commonly found in middle aged or older adults. In all patients of cancer, 77% of them were adults of age 55 or older. In United States, men have less risk (1 in 2) whereas women have high risk (1in 3) of developing cancer in their lifetime. Only in United States, 1600 people die due to cancer each day. Prostate cancer in men and breast cancer in women are leading cases of cancers in USA whereas; cancers

of lung and bronchus are leading causes of death due to cancer in USA [11]. In India, around 500,000 people die due to cancer. This will rise to 700,000 till end of year 2015. In India, cancers of mouth, neck, lips, throat and lungs are more common in men whereas; breast, cervix and ovarian cancers are more prevalent in women [12].

III. PATHOPHYSIOLOGY OF CANCER (NEOPLASM)

The tumors present in cancers are basically are of two types: benign neoplasms which comprise of benign mesenchymal tumors having their origin mainly from muscle, bones, tendon, cartilage, lymphoid, fats, vessels and other is benign epithelial tumors having their origin on the basis of cell of origin, microscopic architecture, macroscopic patterns whereas malignant mesenchymal tumors (sarcomas) and malignant epithelial tumors (carcinoma) [13]. Cancer causing agents are called as carcinogens such as aflatoxins, aristolochic acids, arsenic, asbestos, benzene, benzidine, beryllium, cadmium, erionite, ethylene oxide, formaldehyde, hexavalent chromium compounds, thorium etc [14]. Expression of Malignant tumors is generally based on age, degree of cell differentiation, growing, invasion and metastatic potential as well as therapy responses [15]. Initiation and Promotion which are the preliminary events requires exogenous exposures to carcinogenic chemicals, gene expressions plays a vast role in the process of tumor formation [15]. Geographical and racial factors also impact on cancer pathophysiology, during 1994-1998 in Connecticut and Massachusetts according to a study conducted 29,040 Whites and 1,647 African Americans diagnosed with incident prostate cancer which showed a larger number of African Americans suffering from prostrate cancer [16]. Colorectal cancer is having higher incidence rates is higher in Australia, New Zealand, Canada, the United States, and parts of Europe whereas lower risk in China, India, parts of Africa and South America [17].

Chemical Carcinogenesis: Viruses, ultraviolet, ionizing radiations and chemicals comes under this category. Their induction is by electrophilic reactants which works through multistage process i.e., initiation which is rapid in nature and irreversible in nature whereas promotion is a complex process and it is highly reversible in initial stages the ratio of initiation and promotion and their affinity for different chemicals vary differently [18].

Radiation Carcinogenesis: Radiation induces genetic instability in cells and the same can be obtained in replications for many generations. Irradiation to cytoplasm can lead to a huge amount of mutations and initiates the activation of p53 damage response pathway [19].

Viral Oncogenesis: Viruses composed of no of genes in the form of DNA or RNA with a protein coating over them where viruses also acts as a vector thus inserting their own genes in to the host cell thus leading a cell in becoming a cancerous cell, e.g. Human papilloma viruses (HPV), epistein bar virus, hepatitis B Virus, hepatitis C Virus, and HIV [20]. HPV which is basically a DNA oncogenic virus infects the basal cells of stratified squamous epithelium and it switches to rolling cycle mode of DNA replication in the supra basal layer of the epithelium hence synthesizing capsid proteins [21]. RNA oncogenic virus are also called as retroviruses and these viruses binds to a cellular receptor and undergoes a process of transcription to form proviral DNA and the same binds to the host chromosomal DNA [22]. Genes (v-onc) gets acquired by recombination from cellular genes (c-onc) [22].

Pathogenesis of Cancers:

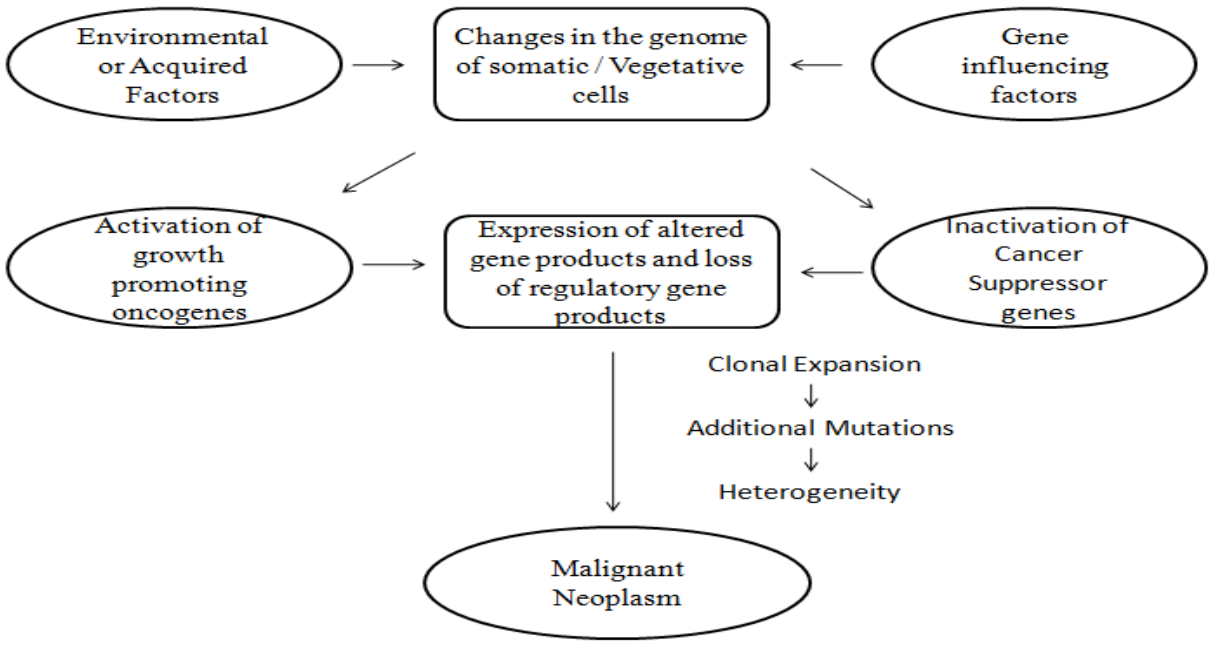

Figure 1: Pathogenesis of cancers

Risk Factors for neoplasms

Risk factors involved in cancer are various such as family history(due to interaction of gene or several genes), environmental factors (tobacco smoke, pollutants in air or water), genetic factors(presence of extra or abnormal chromosome e.g. Down's syndrome), age (Wilm's tumor, retinoblastoma, and neuroblastoma especially in children) whereas, generally older than 65 are most likely to get effected from cancer due to prolonged exposure to carcinogens, geographical locations (higher rates of stomach cancer in Japan), diet (diet including higher amount of unsaturated fat, large amount of alcohol, extensive barbecued meats can lead to cancers of colon, breast, prostrate, stomach, colon, kidneys, endometrium, as well as esophagus cancer), drugs and medical treatments [23]. Cancers are not caused by injuries (bump or bruise) as well as it is not a contagious disease, most of the above cancers can be prevented but family history type is unavoidable [24].

Types of Cancers

There are more than 200 types of cancer found across the globe. Some of the prominent forms are listed below here.

Eye cancer:

Cancers in the eye are also called as intraocular cancers [25].Various symptoms are observed during eye cancer such as blurred vision, spots in visual fields, full or partial loss of eye sight, eye bulging, etc [26].

Breast Cancer:

It is developed from breast tissue. It is most common form of cancer that occurs in women. Symptoms such as lump in the breast, fluid coming from the nipple, dimpling of the skin are observed [27].

Colon cancer:

Cancer that forms in the tissues of the colon is called as colon cancer [28]. Change in the bowel system, frequent abdominal discomfort, fatigue or weakness, constant weight loss, rectal bleeding [28].

Bone Cancer:

This type of cancer initiates in the bone but it is very rarely observed almost up to 0.5 percent of all cancers [29].

Renal Cancer:

Such type of cancer arises from the renal epithelium which is obtained in the lining of the tubules [30].

IV. DRUG DISCOVERY OF ANTICANCER DRUGS: INSIGHTS INTO SOURCES

In current date, anticancer drugs are obtained from three different sources: plant, marine and monoclonal antibodies. Details of them are described below:

Plant Natural Products as Anticancer Drugs

Natural products still remain as an additional source of new drug, new chemical entities and new developmental or growing stage drug. The most widespread natural sources are plant sources which mainly resulted in the development of anticancer drugs [31]. Drugs that are derived from natural sources rank high in anticancer therapeutics out of top 35 drugs 14 out of them are derived from natural sources [32]. The following table contains different anticancer drug obtained from different plant sources:

Sr. No.	Anti Cancer Drug	Plant Source	Uses	Clinical Trial Status	Reference
1.	Vincristine, and Ajmalcine	Catharanthus roseus	Lleukemia, lymphoma, breast, lung, pediatric solid cancers and others, Breast, lymphoma, germ-cell and renal cancer	Phase III Trial Ongoing	[33], [34]
2.	Vinblastine	Catharanthus roseus	Breast, lymphoma, germ-cell and renal cancer	Phase III Trial Going On	[33], [35]
3.	Etoposide	*Podophyllum* species, *Podophyllum peltatum* and *Podophyllum emodi* (Berberidaceae).	Lymphomas and Bronchial and Testicular Cancers	Phase I/II	[36], [37]
4.	Paclitaxel	*Bark of the Pacific Yew, Taxus brevifolia Nutt*	ovarian, breast and lung, bladder, prostate, melanoma, esophageal, and other types of solid tumor cancers as well as Kaposi's sarcoma	Phase III/IV	[38], [39]
5.	Camptothecin	Chinese Ornamental Tree, *Campototheca acuminate* Decne (Nyssaceae)	Transplantable lymphocytic leukemia.	Phase I	[40]

6.	Topotecan and Irinotecan	These are the semi-synthetic derivatives of Camptothecin	Ovarian and small cell lung cancers, and colorectal cancers	Phase II/III	[41]

Table 1: Anticancer drugs of plant origin

Selected Anti Cancer Drug Obtained From Plant Origin:

- **Vinblastine and vincristine:**

Vinblastine and vincristine is first derived drug which are used in combination with other cancer chemotherapeutic agents for the treatment of a various types of cancers, which may include breast and lung cancers, lymphomas, leukemias, Kaposi's sarcoma and advanced testicular cancer [33]. It is generally obtained from plant source that is Catharanthus roseus (Apo-cynaceae) which discovered a new era of the use of plant source as anticancer drug. Currently phase III trial is ongoing, to compare the effectiveness of two combination chemotherapy regimens with either vinblastine or vincristine in treating patients with advanced anaplastic large cell lymphoma [34].

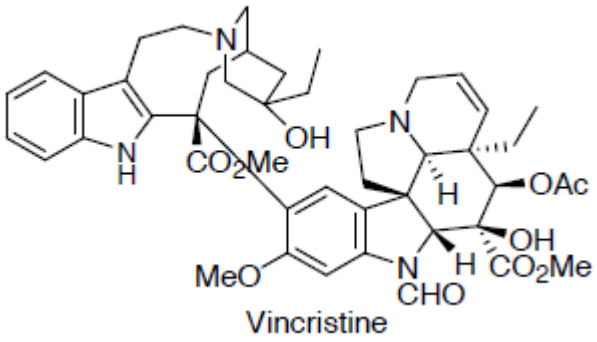

Figure 2: Chemical Structure of Vincristine

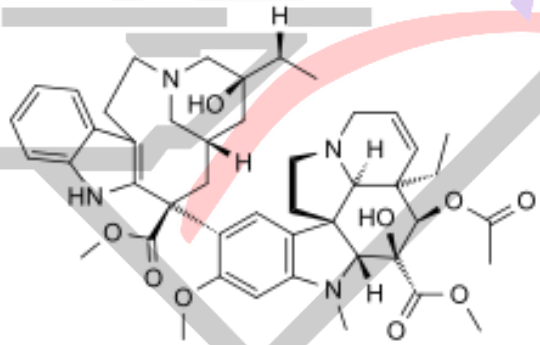

Figure 3: Chemical Structure of Vinblastine

Paclitaxel

The taxanes containing paclitaxel have antitumor activity. Paclitaxel stabilizes microtubules and which leads to mitotic arrest. In clinical trials paclitaxel shows antitumor activity against ovarian, breast and other tumor types [38]. Currently 2403 clinical trials are ongoing on paclitaxel [39]. Generally paclitaxel studies are randomized range in Phase III/IV Clinical Trials for example one case study has been mentioned that is Paclitaxel and Carboplatin With or Without Metformin Hydrochloride in Treating Patients with Stage III, IV, or Recurrent Endometrial Cancer. This study started at March 2014 and still going on but estimated primary completion date will be September 2019. The current primary outcome measures for progression free survival and Overall survival (Phase II and III) This report submitted on 14 February 2014 [39].

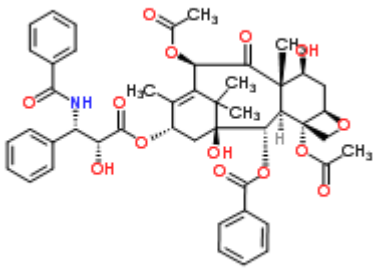

Figure 4: Chemical Structure of Paclitaxel

Marine Products as Anticancer Drugs

Various types of active anticancer drugs are derived from terrestrial microorganisms. Four decades ago the isolation of C-nucleosides from the Caribbean sponge, Cryptotheca crypta, provided the synthesis of cytarabine, the first marine derived anticancer agent to be developed for clinical use. Recently, cytarabine is available in the routine treatment of patients with lymphoma and leukaemia. Gemcitabine, is one of the fluorinated derivatives, it is approved for use in patients with pancreatic, breast, bladder, and non-small-cell lung cancer [42].

Sr. No.	Anti Cancer Drug	Organism	Uses	Clinical Trial Status	Reference
1.	Cytarabine	Caribbean sponge, Cryptotheca crypta	Leukaemias and non- Hodgkin lymphomas	Phase III	[42], [43]
2.	Daunorubicin	Streptomyces peucetius	Anticancer activities on acute myeloid leukemia and acute lymphocytic leukemia	Phase III	[44], [45]
3.	Kahalalide F	*Elysia rubefescens*	Antitumor Depsipeptide	Phase II	[42]
4.	Didemnin B	*Trididemnum soldium*	Leukemia, Cytotoxicity	Phase I	[42], [46]
5.	Trabectedin	*Ecteinascidia turbinata*	breast, prostate, and paediatric sarcomas	Phase II	[42], [47]

Table 2: Anticancer drugs of marine origin

- **Cytarabine**

Cytarabine is freely soluble in water; slightly soluble in alcohol and in chloroform. Cytarabine is an antimetabolite. Cytarabine is cell cycle–specific for the S phase of cell division. Activity occurs as the result of activation to cytarabine triphosphate in the tissues and includes inhibition of DNA polymerase and incorporation of cytarabine into DNA and RNA. Cytarabine is rapidly deaminated in blood and tissues, especially the liver, but minimally in the cerebrospinal fluid (CSF) [42]. Cytarabine is derived from Caribbean sponge, Cryptotheca crypta which used in treatment of Leukaemias and non- Hodgkin lymphomas. There is one selective randomized case study which currently ongoing in process, Cytarabine and Daunorubicin Hydrochloride or Idarubicin and Cytarabine With or Without Vorinostat in Treating Younger Patients With Previously Untreated Acute Myeloid Leukemia, this study started at February 2013 and estimated primary completion date on June 2018 [43].

Monoclonal Antibodies as Anticancer Drugs

Monoclonal Antibodies are nothing but a single clone cells, therefore monoclonal antibodies are single pure type of antibody. Now a day's monoclonal antibodies can be made in huge quantities in the laboratory or research centre and are a cornerstone of immunology. Currently they are used as anti cancer agents [48].

Sr. No.	Anti-cancer Drug	Monoclonal Antibody Source	Uses	Clinical Trials Status	Reference
1.	Abagovomab	Mouse/ immunoglobuline G1	Ovarian cancer	Phase III	[49], [50]
2.	Trastuzumab (Herclon, Herceptin)	Humanized/ HER2/neu receptor	Breast Cancer	Phase III	[51], [52]
3.	Ublituximab	Chimeric/ MS4A1	Immunomodulator	Phase I / II	[53], [54]

Table 3: Anticancer drugs monoclonal antibodies origin

Selected Anti Cancer Drug Obtained From Monoclonal Antibodies:

- **Trastuzumab (Herclon, Herceptin)**

Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 proteins, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product [55]. It is mainly used in treatment of breast cancer and currently phase III trials are ongoing [52], [53].

V. Drug Discovery and Development of Anticancer Drugs: Steps in Detail

Discovery and development of new drugs which could be probable answer for clinical benefit in neoplasm is essential process. Development of new drugs answers unanswered clinical questions in cancer therapy. Ideally, there are three routes of drug discovery which include chemistry driven discovery which encompasses synthetic and natural product chemistry, target directed drug discovery, and accidental clinical discoveries [8]. Classically speaking, drug discovery and development is recognized into following steps:

Target identification; target validation; lead identification; lead optimization; preclinical studies; clinical research with phase 0, I, IIa, IIb and III; and post marketing studies [8]

Investigational new drug application (IND) is submitted after pre-clinical or non-cliinical studies so as to get permission to conduct clinical trial. Product registration or marketing authorization submission is submitted regulatory authority at the end of Phase III clinical trial.

Thus from above steps, drug discovery could be broadly classified into three steps [8]:

- Drug discovery which includes search from therapeutic need to molecule
- Drug development which includes research from molecule to product registration in market
- Commercialization which includes steps from product to therapeutic use to sales of drug.

Before the start of drug discovery project, it is necessary to consider strategic issues, scientific and technical issues and operational issues for the pharmaceutical company.

Target identification

Conventional strategies for identification of new targets include understanding or exploring of pathophysiology of disease, and analysis of mechanism of action of already existing drugs. For example, imatinib mesylate (Gleevec) was developed by study of pathophysiology of chronic myeloid leukaemia and the target identified was Abl Kinase. Similarly, methotrexate was developed by study of pathophysiology of neoplasmic diseases. Oestrogen receptor was studied during pathophysiological studies of breast cancer leading to development of drugs such as tamoxifen, and trastuzumab. If we consider, another strategy where targets are identified via drug effects, vinca alkaloids is classical example which acts on tubulin [8]. Apart from these, now days, novel target identification strategies include trawling genome, disease genes, disease modifying genes, and druggable genes.

Following figure indicates classification of predicted targets based therapeutic classes:

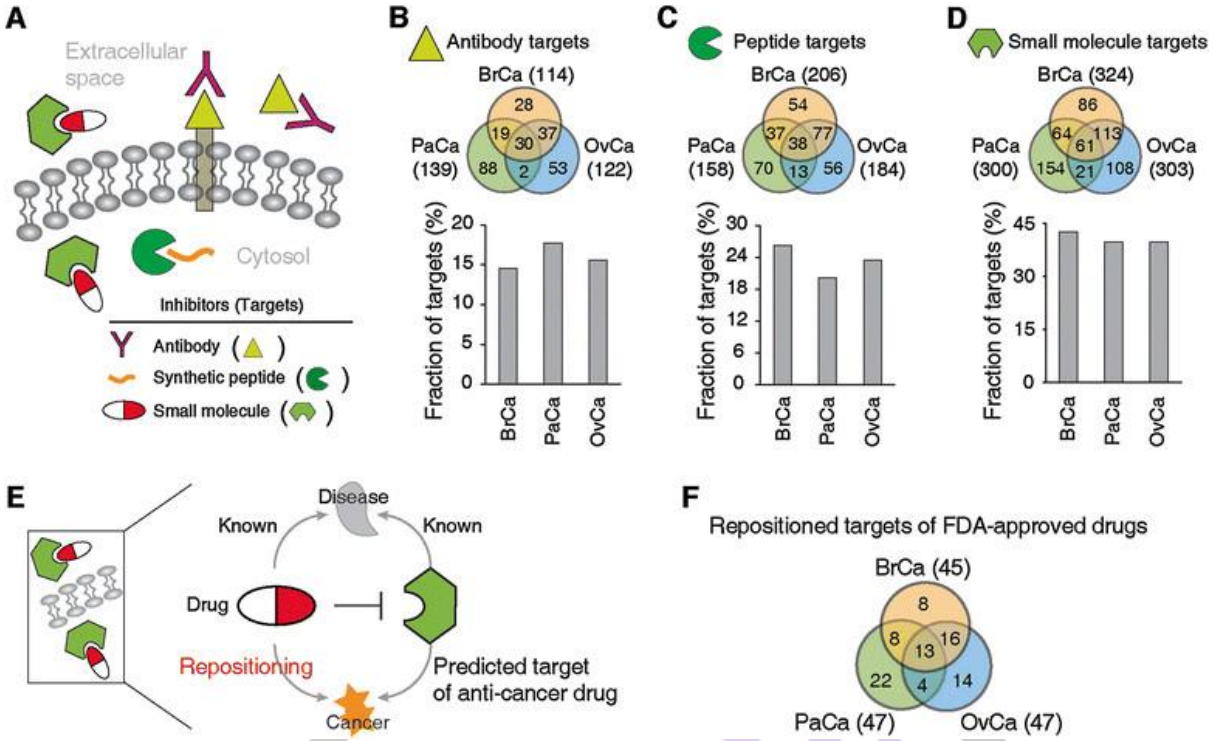

Figure 5: Classification of predicted targets depending on therapeutics classes [56]

[(A): Properties (Biochemical and Cellular) of targets based on therapeutic classes, (B) Targets for antibodies. (C) Targets for synthetic peptides (D) Targets for small molecules. Overlap of therapeutic class-specific targets based on cancer type are shown in Venn diagrams and fraction of therapeutic class-specific targets in all targets is shown in grey bars (E) Identification of repositioned drugs and their targets. (F) Overlap of repositioned targets of FDA approved drugs which are having high specificity]

Target Validation

Once target receptor or protein is identified, it is necessary to confirm the target protein or receptor so that investigational new drug will be most possible fit to the site. Pharmacological and genetic approaches are used for validation of targets of new drugs. Research from Ceiba Geigy proved that Abl Kinase is responsible for cell profileration in neoplasm using cell proliferation assays. Target validation using genetic approaches could be done using antisense oligonucelotides, RNA interference (RNAi), and transgenic animals [8].

Screening of anticancer drugs

Lead is chemical entity or pharmacophore which is responsible for pharmacological action on type of cancer or target identified. Screening of drugs in now days is done using high throughput screening. By this method, 50,000 to 100,000 compounds can be screened per week against validated biological target. This technique is applicable in modern drug discovery wherein large compound libraries are screened to get various bioactive compounds. Further, secondary screen confirms activity of compound. High throughput screening is novel method of screening new hits by synergy of fields of chemistry, biology, engineering and informatics. It includes different methods such as micro assay plate preparation, infrared fluorescence imaging, SPECT, virtual screening and membrane permeability assays [8].

Drug Discovery Case Studies on Anticancer Drugs

- **Paclitaxel**

Paclitaxel is a landmark example of drug discovery based on natural source anticancer drugs [8]. It took 30 years for this drug to get launched into the market. Paclitaxel was discovered initially from bark of Pacific Yew (*Taxus brevifolia*) in 1962 and it showed some activity on cancer cell lines. At that time, it was not thought of to have this drug as potential candidate, but soon after 1975, it stood as highly active drug on melanoma cell line. Although it was good candidate, problems in commercialization were insolubility in water, sensitivity to patients with Cremophor EL solubilizer, supply of clinical trial materials on commercial scale [57]. These problems were solved eventually. Particularly in 1992-1999, paclitaxel (taxol) was found in other species of *Taxus* where it was produced commercially from baccatin compound found in taxus species [58].

- **Imatinib (Gleevec / Glivec)**

Imatinib (discovered by Ceiba-Geigy, later Novartis) is successful example of target based drug discovery for antincancer drugs. During this drug discovery, scientists have found out association between gene mutation, and enhanced kinase activity [59].

In year of 2001, imatinib mesylate was introduced which inhibits BCR-ABL tyrosine kinase [60]. The key points which must be noted in imatinib discovery include specified molecular target identification (Abl Kinase) and use of high end modern sophisticated assay technologies. Currently, imatinib holds strong position in treatment of patients with chronic myeloid leukaemia [61].

- **Trastuzumab (Herceptin)**

Trastuzumab is monoclonal antibody used in treatment of breast cancer. It cause selective blockage of oestrogen receptor Her2. This product was discovered and approved for commercial use in landmark time of 8 years [62]. Genentech cloned Her-2 receptors using its own technology for humanized mouse monoclonal antibodies. It took only 2 years for the process of lead finding to lead optimization for this project. Again within next 2 years drug went to Phase I studies. Phase II and Phase III studies have seen significant clinical benefit leading to launch of drug into market within next 4 years. This discovery suggests fact that biopharmaceuticals could be easily discovered leading to commercialization as compared to conventional small molecule drugs [63].

VI. PHARMACEUTICAL DEVELOPMENT OF ANTICANCER DRUGS

In general, anticancer drugs are delivered via intravenous route which is easy way to achieve 100% bioavailability in humans. However, it is inconvenient for patient, requires expertise for administration of dose and other side effects are observed. Formulation development of anticancer drugs is challenging g task as majority of drugs are water insoluble. Therefore, solubilizers such as Cremophor EL (which was used in formulation of paclitaxel injection) need to be used. However, such kind of excipients could lead to sensitivity reactions. Therefore, attempts are needed so that anticancer drugs will be converted into oral drug delivery systems. Now days some drugs are into oral delivery systems such as coated tablets, capsules, liposomes, neosomes, micelles, and self emulsifying systems [64].

Precautionary considerations for commercial manufacturing of anticancer drugs [65]

Anticancer drugs come under category of high potency active pharmaceutical ingredients (HPAPI). Personnal and facility considerations must be taken into account before going for manufacturing of anticancer drugs. Basic requirements of manufacturing activity is use of Standard operating procedures (SOPs), regular review of Materials safety data sheet (MSDS), and use of Personal protective equipments (PPEs). Gloves appropriate for chemical being handled and double gloves must be used for handling HPAPIs. American Society for testing and materials (ASTM) designates chemotherapy gloves capable of resistance of permeation by chemotherapy should be preferably used. Gowns or coveralls must be used. These should have properties like lint free, low permeable, closed front, long sleeves, and elastic/knit closed cuffs. Cuffs of these gowns must be tucked under gloves. Safety glasses and N95 HEPA masks must be used. Powered air purifying respirators (PAPR) are of choice in the manufacturing or processing of HPAPIs. PAPRs are battery operated, consists of a half or full face piece, breathing tube, battery-operated blower, and particulate filters (HEPA only).

It is advisable that containment equipment must be available throughout process of HPAPI from bulk API production to product formulation. Containment device selection, setting targets, and verifying containment performance by Factory acceptance test (FAT) and site acceptance test (SAT) are the key steps in achieving HPAPI production and processes. Use of airlocks, barrier isolators, transfer chambers, bagging devices, rapid transfer port, buck valves, split butterfly valves (SBV) is helpful. For change room areas, systems such as mist shower or air shower are also used.

VII. PRE-CLINICAL ASPECTS OF ANTICANCER DRUGS

Preclinical studies for anticancer drugs are done through following routes [66].

- Systemic Toxicity Studies
  - Single – dose toxicity studies (mice and rats serve this purpose)
  - Repeated-dose Systemic toxicity studies (2 mammalian species 1 non rodent)
- Male Fertility study
- Female Reproduction and Developmental toxicity studies
  - Female Fertility Study (Segment I)
  - Teratogenecity Study (Segment II)
  - Perinatal Study (Segment III)
- Local Toxicity
- Allergenicity / Hypersensitivity
- Genotoxicity
- Carcinogenecity

Following are representative anticancer drugs wherein pre-clinical studies were found effective so as to proceed further for clinical trials.

Imatinib:

Imitanib (Glivec) is a protein- tyrosine kinase inhibitor which inhibits Bcr –Abl tyrosine kinase, stem cell factor, c-kit, cellular kinase assay levels. This drug also showed hematological and cytogenic responses in clinical trials hence it was stated as a safe and effective drug on cancer. Preclinical studies were carried on mice [67].

Paclitaxel:

It binds to the beta-tubulin whereas it also showed a good retention time in tumor cells. The pharmacokinetic profile of paclitaxel showed a significant interaction between paclitaxel and the anthracyclines which showed a significant use in the treatment of breast cancer [68].

Preclinical and clinical properties of Paclitaxel were compared. Studies were carried on rats for the deterrmination of pharmacokinetic and drug disposition and it was used for therapeutic effectiveness [68].

Trastuzumab:

A preclinical study was conducted for the assessment of 177Lu-Labeled Trastuzumab which target HER2 mainly for treating the patients with disseminated intra-peritoneal disease. Radio-immunotherapy was used. The process was done by radiolabelling the trastuzumab and it produced the successful results [69].

VIII. CLINICAL TRIALS OF ANTICANCER DRUGS

Clinical trials of anticancer drugs is very challenging area because of problems associated with side effects of chemotherapy, unwillingness of patients to get enrolled trials, loss to follow up, and difficulties in analysis of endpoints. Clinical trials are conducted in phase programs Phase I, II, and III.

Phase I Trials

Phase I studies are first in human studies of investigational new drug. Generally, phase I studies in other drugs involve healthy volunteers whereas, anticancer drug trials involve cancer patients for phase I studies. Generally, phase I is conducted in patients who were already treated and there is no treatment option available. Principal goals of study in oncology phase I trials is to estimate toxicity, dose range, pharmacokinetic and pharmacodynamic parameters, absorption, distribution, metabolism and elimination parameters [8], [70].

Phase II trials

This phase is very crucial as once drug gets passed this phase, it leads to large and costly phase III clinical trial and if it fails, it goes directly into dustbin phase. During this phase, identification of anticancer activity against specific type of tumor is estimated. Endpoints that are used in this phase are tumor shrinkage, progression free survival, biomarkers, composite and multiple endpoints [71], [72].

Phase III Trials

These are confirmatory studies which estimate efficacy and safety of investigational drug and are essential for marketing authorization. Patients with target cancer are enrolled in randomized, controlled clinical trial [73]. If new drug achieves clinically relevant primary endpoint against standard controlled treatment, then it is approved by regulatory authorities.

In case of oncology phase III trials, primary outcome variable is time-to-event like progression free survival or overall survival [73].

IX. ENDPOINTS IN ONCOLOGY CLINICAL TRIALS

Clinical endpoints are events which subject is aware of or afraid of. Endpoints must be easy to diagnose, free from measurement error and should have internal and external validity [73]. In clinical trials, endpoints are of following types: primary endpoints, secondary endpoints, composite and multiple endpoints, and surrogate endpoints.

Primary, Secondary and Surrogate endpoints

Primary endpoint is single endpoint based on which clinical decision of benefit is taken. Secondary endpoints are other related endpoints.

Surrogate endpoints were firstly defined by Prentice in 1989. [74] However; US FDA defines it as substitute for patient important endpoint or therapeutic effect. They re of use when observation of long follow up time is required for clinical outcomes, or when natural course of clinical endpoint is long or when duration of therapy is long.[75] Use of surrogate endpoints reduces cost and time involved in clinical trial. This endpoint measures how patient functions, survives or feels [76].

Biomarkers

The Biomarkers Definitions Working Group (BDWG) of the National Institutes of Health defines Biomarker as marker from biological systems, pathological conditions, or pharmacological effects and is used as endpoint for therapeutic intervention. They are of particular use in identifying natural history of disease, identifying dose response, exploring disease mechanisms associated with exposure, and are also of use in regulatory approval. [77] They are used as substitute or surrogate endpoint but reverse is not true. They are of particular use in clinical trials on cancers. Bhatt et al. [78] have highlighted need of cancer biomarkers and their validation. Different nucleic acids, lipids, sugars, proteins, and cellular parameters could be used as biomarkers in cancer studies. In oncology they are of particular use in risk assessment, screening, prognosis determination, diagnosis, and estimating response to treatment. [79]

Multiple and composite endpoints

In diseases such as migraine, Alzeimer's, Rheumatoid arthritis, Asthma, and epilepsy, we can identify many more endpoints which are beneficial and are equally important. In such cases, it is essential to identify and study these multiple end points at the same time during clinical trial. Therefore, multiple endpoints are of great value in clinical research which helps us to estimate effect. When single multiple endpoints are combined in clinical trial, single measure of effect from combined set of variables, it is called as composite endpoint.

Oncology Specific Endpoints

In oncology trials, specifically endpoints used are objective response, overall survival; progression free survival, time to progression, disease free survival, and time to distant metastasis.

Overall Survival

United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) has recognized overall survival as gold standard for clinical benefit in oncology clinical trials. It is defined as time from randomization until death from any cause and is measured in the intent to treat population. In trials of cancers of colorectum, prostate, head and neck, and gastric systems; overall survival is well known as gold standard. Studies which use overall survival as endpoints require larger sample size. It is affected by crossover and sequential therapy [80]. In some tumor types, it is not fair indicator of treatment efficacy. Overall survival requires extensive patient follow up and confounding by causes of unrelated tumor mortality [81]. In advanced non small cell lung cancer, overall survival is regarded as primary endpoint [82]. Even recent studies in March 2015 on Bavacizumab indicate that it extends overall survival in GOG0213 trial [83]. In November 2014, clinical trial on Trebananib (Amgen Inc) failed as it was unsuccessful to improve overall survival [84].

Time to progression (TTP)

Time to progression is time from randomization until objective tumor progression or death. It is used in clinical trials as primary endpoint. Blinding and randomization is essential in studies which use time to progression as endpoint. Time to progression is also used as surrogate end point for overall survival in regulatory approval process [73]. Advantages of TTP include possibility of measurement of stable disease, small sample size and shorter follow up is required as compared to overall survival where large sample sizes are needed. US FDA guidance suggests it as one of the primary endpoints essential for approval. Particularly in accelerated approval, it is recognized as primary end point. Also, response evaluation criteria in solid tumors (RECIST) guideline highlights the same fact for TTP. [85] For drug Tivantinib on hepatocellular carcinoma, phase 2 study used TTP as primary endpoint suggesting its extension as measure of effectiveness of drug. [86] Phase III trial on gastric cancer on drug ramucirumab also showed extension of TTP as achievement of primary endpoint in clinical trial. [87]

Other oncology specific endpoints

Apart from overall survival and time to progression, other endpoints are as follows. Disease free survival is time from randomization until death from any cause. Complete disappearance of lesion is called as complete response. Progression free survival is time from randomization until objective tumor progression or death. Time to failure is time from randomization until discontinuation of treatment due to any reason. [9]

X. PHARMACOECONOMIC ANALYSIS OF ANTICANCER DRUGS

As health care expenditures continue to increase, many involved in the provision of health care are being asked to make difficult decisions concerning new interventions in an environment of limited resources. Economic analysis is a tool that determines the value (that is quality divided by cost) of an intervention and is used by those who are involved in decisions concerning the allocation of limited resources. It can be used to evaluate many types of interventions, including screening and diagnostic tests or procedures and medical or surgical interventions. Pharmacoeconomics refers to the economic analysis of a drug or drug regimen. In simple terms, pharmacoeconomics is a tool to help health care decision-makers determine if a drug is "worth the price" [8].

Economic Burden of Cancer

The economic burden of cancer is considerable and is a growing concern to purchasers and payers. The National Cancer Institute (NCI) estimates that the overall annual costs of cancer diagnosis and treatment was nearly $100 billion in 1990, a figure that includes $27 billion for direct medical costs, $10 billion for morbidity costs (cost of lost productivity), and $59 billion for mortality costs [88]. More recent estimates suggest that the direct medical costs of cancer in the United States represent approximately 10% of all health care expenditures, or about $100 billion each year [89].

Economical analysis contains four levels:

- Cost Identification
- Cost-effectiveness analysis
- Cost utility analysis
- Cost benefit analysis

In cost identification process which determined the full cost in monetary units of a particular therapeutic intervention which includes working days lost, admission in to hospital, etc., as well as direct drug cost. In a cost-effectiveness analysis, costs are expressed in the numerator in monetary units (e.g., dollars), and effectiveness is expressed in the denominator in some unit of effectiveness. The units are usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice. When comparing two or more alternative interventions, the analyst will select a common clinical outcome [8].

Cost-utility analysis is a specific type of cost-effectiveness analysis in which utility is measured and the units of effectiveness are quality-adjusted life-years (QALYs). The major advantage of using QALY as an outcome measure is that it incorporates changes in both quantity (mortality) and quality (morbidity) of life. With this type of analysis, new therapies that greatly reduce morbidity can increase the number of QALYs even without an increase in survival time. The major disadvantage of cost utility analyses is that utility data are not usually collected in clinical trials because of the additional costs of the data collection and the complex nature of the methods used in utility assessments [8].

For e.g. Avastin (bevacizumab) is nothing but a monoclonal antibody which can be treat colorectal cancer and NICE, around 6500 patients in each year would be eligible for same drug treatment [8].

Following table illustrates prices of selected anticancer drugs in Indian market with their prices:

Sr. No.	Branded/Generic Anti Cancer Drug	Dosage Form	Average Price/ Unit (Rs.)
1.	Imatinib 400 mg	Tablet	400.00
2.	Paclitaxel / Napro Tax (30 mg)	Injection	800.00
3.	Vincristine / VCR (1 mg)	Injection	48.00
4.	Etoposide / Actitop (50 mg)	Capsule	50.00
5.	Topotecan / Topotel (2.5 mg)	Injection	500.00

Table 4: Containing Prices of selected anticancer drugs in Indian market with their brand names [90]

XI. CONCLUSION

Cancer or neoplasm is one of the top most causes of death in world. It occurs due to malignancies in cell growth. More than 100 risk factors were identified till dates which are responsible to cause cancer. Unmet therapeutic need in case of different cancer types is major driver for discovery of new drugs in oncology. Drug discovery of anticancer drugs starts from target identification till submission of dossier to regulatory authorities with clinical trial data. However, this process is expensive and time consuming as difficulties involved in recruitment of intended population for clinical trials. Drug discovery in case of biopharmaceuticals such as trastuzumab took only 8 years as compared to other anticancer drugs. This could be due to identification of molecular targets and success in clinical trials. In oncology clinical trials, endpoints such as overall survival, progression free survival, and time to progression are most commonly used as primary endpoints. These are essential for regulatory approval of anticancer drugs. Considering cost involved in development, cost of anticancer drugs in market is also very high as compared to drugs of other categories. Also these drugs are required to take for long periods. Therefore, therapy of anticancer drugs is expensive. Hence, there is need to discovery drugs using specified molecular targets, with less developmental timeline and good clinical benefit so that cost of treatment could be decreased.

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