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THE STUDY OF VARIOUS CANCER CELL LINES: CLINICAL EVALUATION METHODS

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ABSTRACT

More than 277 distinct forms of cancer disease are referred to as cancer in the broadest sense. Several cancer stages have been identified by researchers, indicating that a variety of gene changes may contribute to the development of cancer. Often, cell lines are employed instead of real cells to research biological processes. A cautious approach must be taken in assessing the outcomes, as cell lines might not accurately reproduce the original cells. Several cancer cell lines, such as MCF-7, HeLa, A549, HCT-116, PC-3, U-87 MG, HepG2, and K562 cells, will be briefly discussed in this article. Clinical trials that are meant to be approved by regulators must show the drug's therapeutic effects in a specific population. A drug's clinical development is carried out in stages through a series of clinical studies. Following the evaluation of safety and pharmacokinetics, as well as the recommendation of dosage and mode of oversight, an exploratory assessment of efficacy and safety is conducted. Three stages have usually been engaged in clinical development: phase I, II, and III studies. It has been carried out in a progressive manner. The procedure of clinically evaluating anticancer drugs and the most often utilised cancer cell lines are briefly summarised in this article.

KEYWORDS: Gene mutations, carcinogenesis, cancer, anti-cancer medications, cell line, HeLa.

Graphical Abstract

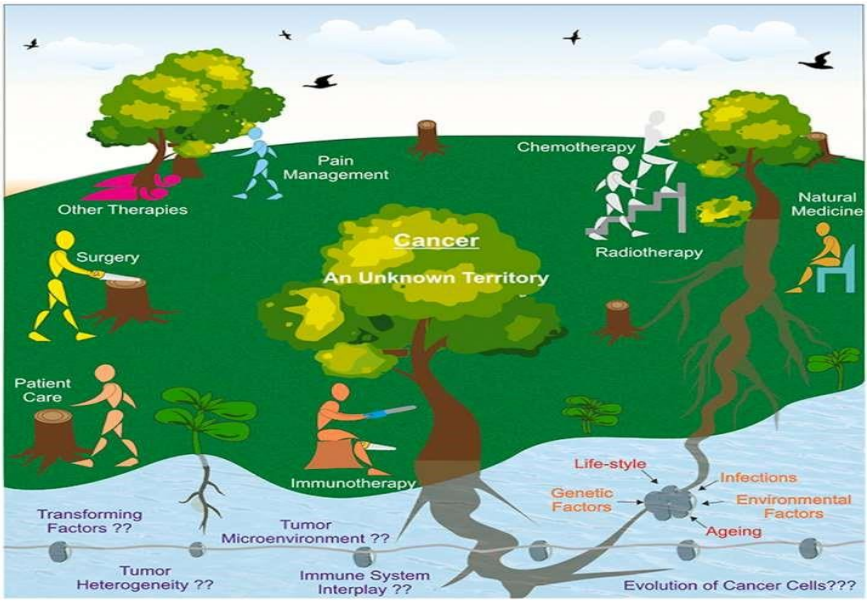

Fig. 1: Graphical abstract of Cancer.

INTRODUCTION

Uncontrolled cell division and proliferation characterise a family of diseases known as malignancies. Should cancer cells continue to metastasize that is, spread death may result. Several external causes, including chemicals, radiation, tobacco, and infectious organisms, contribute to cancer besides a few internal, such as immunological conditions, hormones, genetic mutations, and random mutations. The risk of cancer is known to be increased by a number of factors, including environmental pollutants, inactivity, certain illnesses, obesity, and nutritional factors.[1] Cancer has emerged as one of the major killers in India. Every year, cancer claims the lives of almost 70,000 new cases and 38,000 people. Facilities are needed for approximately 15 lakh people at any given time for diagnosis, therapy, and follow-up.[2] For the creation of new medications and in the study of cancer, cancer cell lines are helpful in vitro model systems.[3]

We covered a variety of cancer cell line types in this review, such as HeLa, MCF-7, A549, HCT116, PC-3, U-87 MG, HepG2, and K562 cells. The narrative of Henrietta Lacks' life and the narrative of her cancer cells are very different from one another. She is a poor black woman who stands for the "other," the periphery of society.[4] The MCF-7 cell line is one of the most popular options for breast cancer research, having been used extensively by several organisations over a number of years.[5,6] Although lung cancer is the second most frequent type of cancer, it's also the primary cause of cancer-related death.[7] At present, colorectal cancer is the second most prevalent cause of cancer-related fatalities worldwide, accounting for around 774,000 deaths and 1.4 million cases annually. It comes three with regard to of incidence.[8,9,10] The second most common cause of cancer-related death is prostate cancer (PC), which is most commonly diagnosed in men.[11] Authenticated Cell Cultures (ECACC) offers U87MG, which is run by Public Health England, as well. They reveal which the source of U87MG is a female patient who had a malignant glioma patient.

The research aimed to investigate U87MG12's proliferation traits, transcription profile, and karyotype.[12] In vitro toxicological effects of medicines, heavy metals, and nanoparticles were investigated using the HepG2 cell line.[13] The K562 cell are frequently thought of as myeloid lineage stem cell progenitors.[14,15,16] Conducting a confirmatory randomly controlled trial with long-term survival as the main goal is one of the biggest challenges facing the research and development phase of anti-cancer medicines targeting rare genetic subtypes. Sometimes, the tumour response seen in a phase II research is what determines if a treatment is effective and whether it is approved.[17,18]

Cancer

Cancer is the second most common cause of mortality worldwide. With 585,720 Americans losing their lives to cancer in 2014, cancer is the most common disease globally.[19] Men are more likely to get prostate, lung and bronchus, colon and rectum, and urinary bladder cancer subtypes, which account for the majority of cancer cases. The most common cancer sites in women are the breast, thyroid, colon, rectum, lung, and uterine corpus. Interestingly, the data shows that breast cancer is the primary cause of cancer deaths in women, but prostate cancer accounts for the majority of cancer cases in males. The majority of cancer cases in children are brain, lymph node, and blood cancers.[20,21] This aberrant cell reproduces asexually, which means it disregards cues that are associated with controlling the proliferation of neighbouring cells, acquiring invasive characteristics, and altering the tissues around it.[22] Globally, there are 182 cases of cancer for every 100,000 people, and 102 cancer-related deaths occur each year. The World Health Organisation estimates that 8 million people worldwide lose their lives to cancer, and 14 million suffer from the disease.[23] Plant extracts must be screened and tested for cytotoxic chemicals before being used to make anticancer medications from natural resources like plants.[24] Currently, chemotherapy, radiation therapy, immunotherapy, and surgery are the main forms of cancer treatment.[25] Chemotherapy is a systemic treatment that targets cancer cells by putting chemicals into the body. Additionally, medications kill both normal and cancer cells equally, which has clear negative effects.[26]

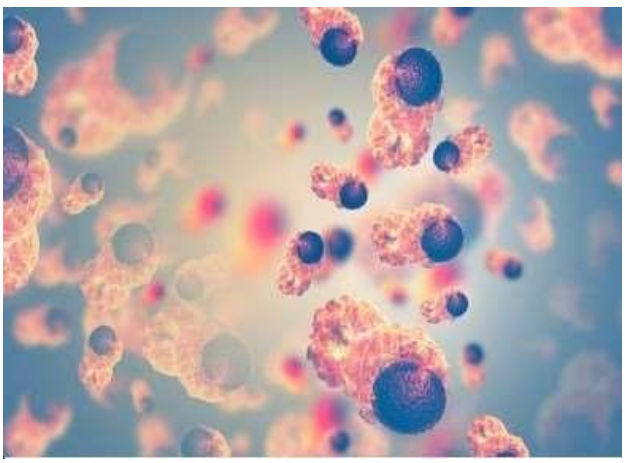

Fig. 2: Cancer.

Table no. 1: Types of cancer.

S. no.	Types	Subtypes
1.	Tumours of the Peeling	a) Malignant Carcinoma
2	Malignancies of the urinary tract	a) carcinoma of the kidney b) Bladder carcinoma c) Cancer of the cervical region
3.	Female malignancies include	a) carcinoma of the breast b) Obovarian tumour
4.	Gastrointestinal carcinomas	a) cancer of the esophageal region b) Abdominal malignancy c) The pancreatic gland cancer
5.	Lymphatic and Blood System Cancers	a) lymphoma tumour b) leukaemia c) Hodgkin's illness
6.	Other malignancies	a) Tumours of the brain b) bone cancer c) Cancer of the thyroid

Breast cancer accounts for the majority of cancer cases worldwide. Breast cancer comes ranked second among cancers that affect women in India, after cancers of the uterus.[27,28]

DRUGS CLASSIFIED AS ANTICANCER & MOA

These are medications used to treat malignant, or cancerous, diseases.

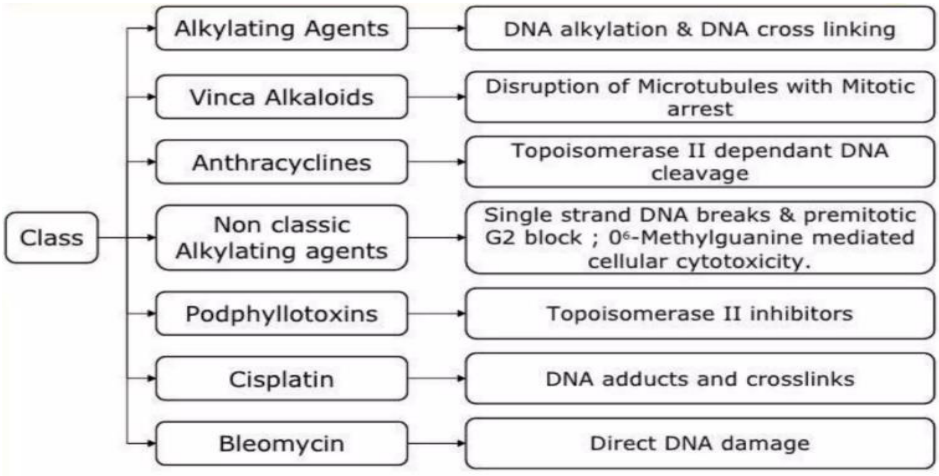

Fig. no. 3: Mechanism of action.

CELL LINE

cell line's 1950–1955 origins. Scientific research has employed Hela cells, a sort of immortal cell line. Being the major widely utilised human line of cells, it is also the oldest.[29] Primary cells are frequently substituted for immortal cell lines in scientific investigations. Scientific research has been transformed by cell lines, which are now used to produce vaccines, test drugs for cytotoxicity and metabolism, produce antibodies, investigate gene function, create artificial skin and other tissues, and synthesise biological compounds like therapeutic proteins.[30,31,32]

The American Type Culture Collection's (ATCC) Cell Biology Collection, which contains over 3,600 cell lines from more than 150 kinds, and the numerous publications that employ them both serve as indicators of how popular cell lines are. When employing cell lines instead of primary cells, caution is necessary even if they are an effective technique.[33] The three broad types of cell lines are human stem cell lines, perpetual cell lines (also known as immortalised or indefinite cell lines), and restricted cell lines.[34]

Various cell lines

1. HeLa Cells

An uncommon young woman's cervical cancer gave rise to the immortalised line of HeLa cells, which were first created in the late 1950s. Henrietta Lacks was her name, and they bear her name. Since their first development in 1959, these cells have emerged as one of the most significant laboratory models for contemporary cell biology research, if not the most according to the medline database.[35] A noteworthy and early use of HeLa cells is the creation of the polio vaccine. There are many other uses based on these cells, such as the discovery of

medicines for AIDS, cancer, and syphilis.[36] There was no informed permission stating that Henrietta would have her cervical cells utilised for future scientific research when she got to Johns Hopkins, her condition was "ceaseless vaginal bleeding.[37,38]

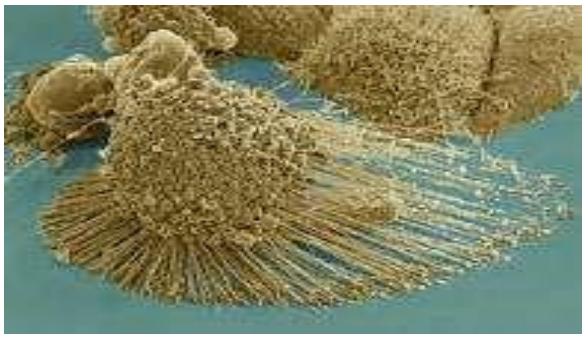

Fig. 4: HeLa Cell.

2. MCF-7 Cells

Given their widespread use as in vitro models for cancer research as well as in numerous other laboratory research domains, cell lines seem to be a crucial part of the molecular diagnosis of breast cancer.[39] These two factors make MCF-7 cells commonly utilised in ER-positive breast cancer cell investigations.[40] In females, breast cancer accounts for 14% of all cancer-related fatalities and 23% of all cancer cases, making it the most commonly diagnosed disease in this population.[41] The name MCF-7 comes from the use of these cells, which were initially employed in 1973 by Dr. Soule and colleagues at the Michigan Cancer Foundation. The cells were taken from the pleural effusion of a 69-year-old woman who had metastatic cancer.[42] A malignant adenocarcinoma in the patient's left breast required a radical mastectomy four years after the patient's right breast mastectomy for a benign tumour, which was performed seven years prior to the commencement of primary cell culture.[43]

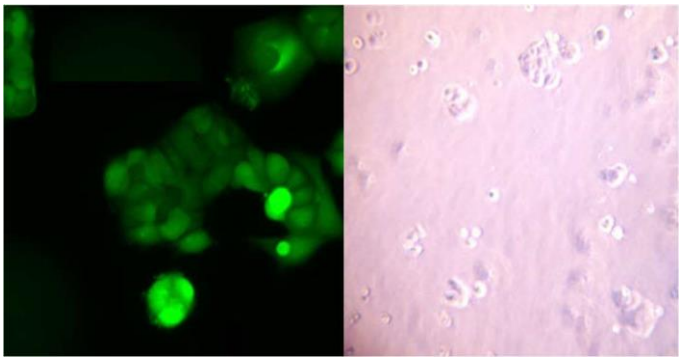

Fig. 5: MCF-7 Cell.

3. A549 Cells

The first type (ATI) and type two (ATII) alveolar epithelial cells are experts epithelial cells found in the distal lung. ATII cells, which are multifunctional and non-replicative, have been referred to as the "defenders of the alveolus," in contrast to terminally differentiated ATI cells.[44,45] In lung cell biology, the human A549 adenocarcinoma cell line has been utilised as a model for ATII cells. The ATII cells' generation of phosphoric lipids cytoplasmic laminated tissues (Lbs) and microvilli at the apex is expressed by the A549 cell line, which Giard et al. identified from a type II pneumocyte carcinoma of the lungs in 1972.[46,47] Subsequently, in vitro investigations on surfactant synthesis and surfactant system modulation have employed A549 cells.[48] Recently, we employed Raman microspectroscopy to noninvasively characterise primary ATII cells' in vitro development into ATI cells.[49] The immortalised pulmonary form like cell strain known as transduced type I (TT1), which was most newly generated and reported in Kemp et al[50] as an illustration of ATI tissues, was also examined. We used several well-known chemometric techniques, including principal components analysis (PCA), linear discriminant analysis (LDA), and spectral modelling, to identify spectrum evidence that characterise biological variations among initial respiratory cells of the alveolar and their model cell lines.[51]

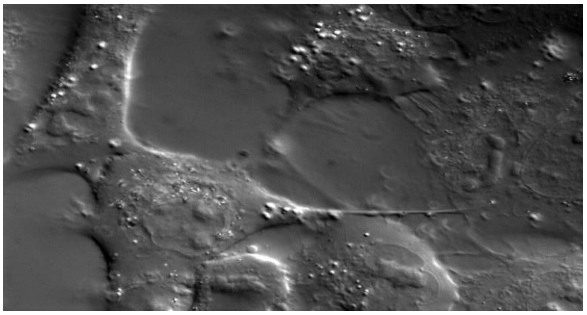

Fig. 6: A459 Cell.

4. HCT-116 Cells

Cancer deaths from colorectal cancer (CRC) continue to be common. This condition is still incurable in the majority of cases. Over 900,000 CRC fatalities and approximately 1.9 million new cases have been reported globally, according to Globocan 2020.[52] Only surgery to remove the cancer is used in CRC therapies, and the chemotherapy that follows is typically linked with unpleasant side effects for the patient.[53,54] The 48-yearold male parent of HCT 116 is the source of this type A human colorectal cancer cell line.[55] Colorectal cancer is still commonly treated with the chemotherapy medication 5-fluorouracil (5-FU). Many 5-fluorinated pyrimidines, including 5-FU, have been utilised to treat colorectal cancer.[56]

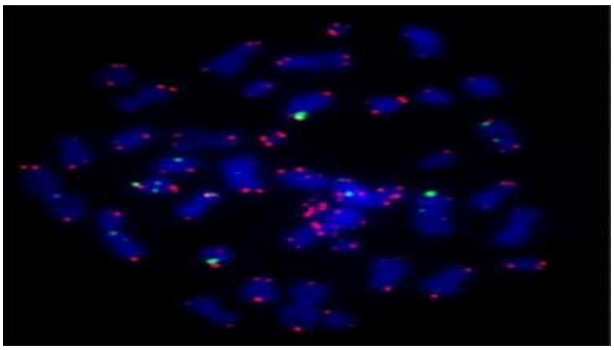

Fig. 7: HCT-116 Cell.

5. PC-3 Cells

In western nations, prostate cancer (PCa) ranks second in terms of cancer-related mortality rates among males and is the most frequent cancer.[57] Patients with advanced prostate cancer respond well to androgen restriction therapy because this treatment is beneficial because testosterone signalling is necessary for the proliferation and antiapoptotic properties of PCa.[58] Because those suffering from castration-resistant PCa (CRPC) develop resistance to testosterone suppression treatment, the cancer may relapse or progress after the first outcome of treatment.[59] A 62-year-old white man's posterior vertebra malignant prostatic tumour yielded the PC-3 cell line in 1979.[60] The PC-3 cells express EGFR and TGF-alpha at high quantities, but they do not respond to hormonal as well as do not express AR or PSA mRNA or protein.[61] A PC-3 allograft carcinoma from an athymic mice gave rise to the PC-3M cell line, which has a more invasive appearance than the original PC-3 cell line.[62]

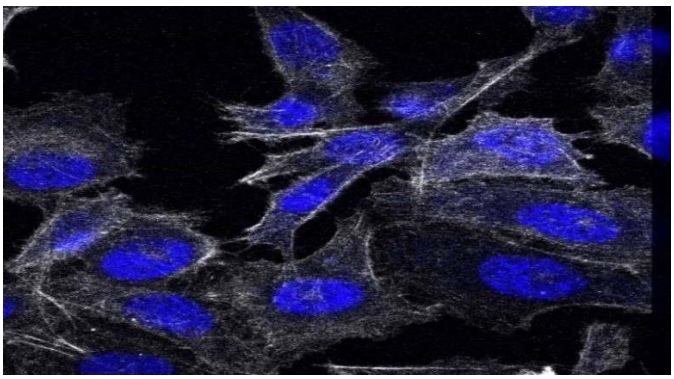

Fig. 8: PC-3 Cell.

6. U-87 MG Cells

One of the most aggressive forms of brain cancer, glioblastoma (GB) is classified as a grade IV glioma by the World Health Organisation (WHO) and has a dismal prognosis for the patient.[63,64,65] One of the central nervous system's most malignant primary tumours is glioblastoma. Their defining features include aggressive growth, intrusion, extensive penetration, as well as prolonged resistance to chemotherapy for cancer.[66,67]

The Swedish patient, who was forty-four years old, contributed the human-generated cell line U87MG in 1966 from the University of Uppsala.[68] Following the discovery of a Y chromosome and a greater extent of development in the original tumour tissue, the study of the gene-expression patterns within the U87MG cell line, which was supplied through the collection of American type cultures (ATCC) cell library, as well as the original tumour cells, was initiated.[69]

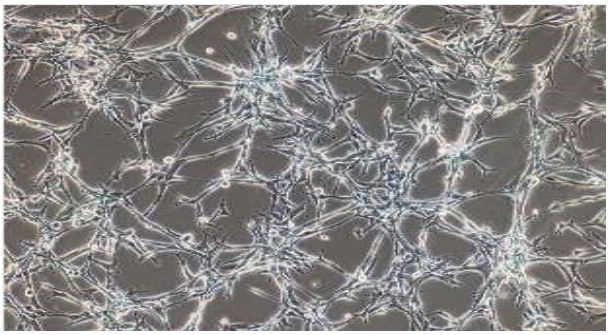

Fig. 9: U-87MG Cell.

7. HepG2 Cells

Hepatocellular carcinoma, also called hepatic carcinoma, is the most prevalent type of liver cancer (HCC). It ranks third globally and as China's leading cause of deaths due to cancer.[70,71] It is widely acknowledged that the hepatitis B virus (HBV) is a key cause of HCC development.[72,73] The HepG2 cell line was the initial one to exhibit the fundamental characteristics of hepatocellular. In 1975, the line was found, and the diagnosis was cancer of the hepatocellular carcinoma. "A human hepatoma-derived cell line" is how the Wistar Institute described the HepG2 cell line in their patent application. Next, hepatic tissue from a guy, a fifteen-year-old Caucasian patient with a unique liver cancer, was used to identify HepG2 cells. These cells were then introduced to an individual cell line (HB 8065) to the ATCC (American Type Culture Collection, Rockville, MD, USA) library.[74]

The model's relevance as a hepatocyte model is controversial since key proteins related to substance breakdown and this organ's main activity are not generated adequately in HepG2 cells. Furthermore, because phase I, II, and III medication metabolic/transport proteins are similarly expressed by HCC and HB cells, HepG2 cells can be used to study the metabolism of anticancer drugs.[75]

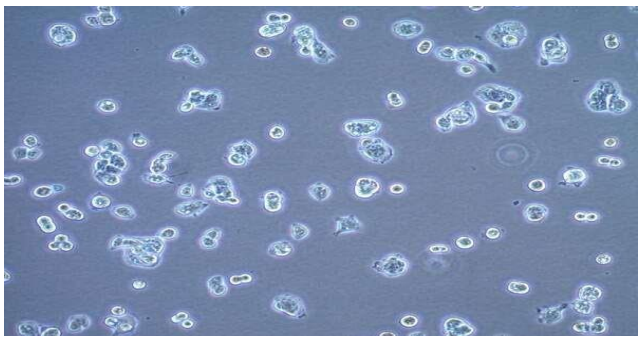

Fig. 10: HepG2 Cell.

8. K562 Cells

The defining feature of leukaemia, a kind of malignancy that starts in plasma-forming organs, is unusual white blood cell multiplication. Leukocytosis, immature granulocytes present at various stages of development, and the active multiplication in neural stem cells as well as bloodstream granular cells are a few traits of chronic myeloid leukaemia (CML).[76] K562, HL-60, as well as THP1 are used as substitute cells in CML and AML research. One CML patient who was in the acute phase provided the K562 cells.[77] This cell line was taken from a 53-year-old patient with pleural effusion and persisting myelogenous leukaemia in final crush events.[78]

Thus, in hematopoiesis, the K562 cells are an early myeloid progenitor. Furthermore, a number of investigations have shown that specialisation substances, like anticancer drugs used in conventional conventional radiation therapy, can undo K562 cells' maturation-arrested state in cell culture.[79,80]

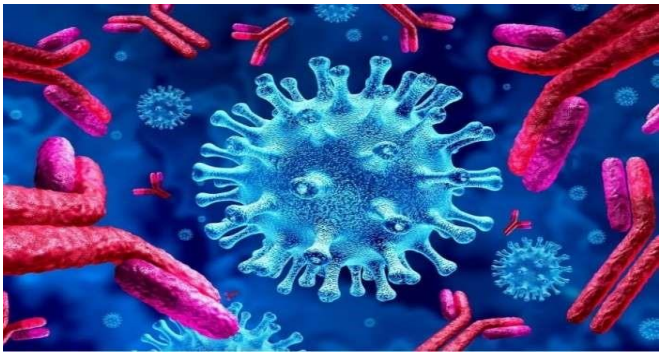

Fig. 11: K562 Cell.

CLINICAL EVALUATION METHODS

Studies in phase I, phase II, and phase III are the three stages of clinical development that are typically carried out in a sequential manner.[81] Research in phase I assesses pharmacokinetics, safety, and tolerability as well as dosage and administration. Afterwards, phase II trials conduct an exploratory assessment of the safety and efficacy. Phase III research, in the end, contrast the therapeutic advantages with traditional standard treatments. However, in the modern day, an enlarged cohort in a phase I study might replace a phase II trial for an exploratory assessment of safety and efficacy, depending on various circumstances, including the characteristics of the medicine.[82,83]

1. Phase I study

Objectives

The first phase of research involves an example of therapeutic evaluation that entails starting an investigational treatment on participants and is based on the outcomes of comparable or non-clinical exams. These are often done in the following ways:

1. Assessing DLT and figuring out MTD and RD
2. A pharmacokinetics examination
3. Monitoring the effectiveness of treatment

Study sites and investigators

Phase I studies should only be carried out in one centre, or in the fewest possible institutions with comparable capacity to assess the drug under investigation, due to the possibility of unexpected toxicity. To ensure the study is carried out safely, investigators should also maintain close communication.

Research participants

Phase I trials evaluating chemotherapy drugs having a particular cytotoxicity profile ought to be conducted on cancer patients instead of healthy individuals. Phase I trials should not include cancer patients whose might profit with prolonged lifespan and symptom relief from commonly used conventional medications.

The following requirements should be met by the target patients

1. Ideally, cytology or histology would have verified the presence of a malignant tumour.
2. An adequate life expectancy (e.g., three months or more) to monitor adverse events and tumour response.
3. No elements, such as pharmacokinetics-affecting problems, that make it challenging to assess adverse events.[84]

Endpoints

• Presence or absence of DLT

It is important to assess the causal link between the investigational medication and side effects. Adverse responses are those events for which a causal relationship exists or for which one cannot rule out a causal association. Dosage-limiting treatments (DLTs) result from adverse responses. The decision-making requirements, MTD, and DLT (type, seriousness, along with frequent) should all be explicitly stated in the procedure beforehand. As a result, DLT must be defined in accordance with the properties of the medicine (that is, even in cases where the grade of persistent toxicity is lower than that of cytotoxic drugs that are provided sporadically, it should still be considered DLT).

1. Pharmacokinetics and the assessment of pharmacokinetic and pharmacodynamic effects need to establish administration and dose.
2. Response to tumours may be assessed to investigate biomarkers or to choose specific cancer types.[85,86]

2. Phase II study

Objectives

The second phase aim to assess the clinically relevant safety and efficacy of the investigational medicine in the targeted cancer category and population, taking into account the dosage and mode of administration determined in the phase I study. Periodically, a non-confirmatory randomised managed study gets conducted to set up upcoming phase III studies.[87]

Study sites

Research is conducted at one or more sites.

Research participants

Generally speaking, a goal individuals must meet these four criteria:

1. A carcinogenic tumour confirmed by histology or cytology.

2. Appropriate functioning in the body and performance state (bone marrow, pulmonary, heart, liver, kidneys, etc.).

Endpoints

Response to tumours

In phase II research, tumour shrinkage meeting predetermined criteria is frequently regarded as a clinically meaningful therapy benefit. When developing immune-stimulating chemotherapy medications, the effect on the tumour, however, may take longer to show up. Therefore, endpoints must be establish with the knowledge that if the effect is only evaluated in terms of the classical tumour response, the true impact and potential toxicity may be overlooked.[88,89]

3. Phase III study

Objectives

Researches in phase III are carried out to develop more effective standard treatments. This research aims to contrast experimental remedies with the accepted medical practices at the moment. New medications, novel therapeutic approaches, or altered dosages and modes of administration of licenced medications with potential therapeutic benefits such as safety, tumour regression, and symptom alleviation are all examples of study treatments. Consequently, overall survival a therapeutic benefit should be the primary goal of the phase III trial.[90,91]

Study sites

Studies are typically conducted at several locations.

Research participants

In general, the target patients ought to fulfil the subsequent requirements

1. Based on histology or cytology, a particular malignant tumour has been identified.
2. Patients meeting specific requirements for earlier treatment.
3. people with normal bodily functions and performance status (bone marrow, pulmonary system, liver, kidney, etc.).

Endpoints

Indexes related to survival generally overall survival are the standard endpoints. Progression-free life / disease-free mortality may be the main outcome in a study done on an individual having an extremely good prognosis, given the number of people with illnesses and lengthy intervals of monitoring are necessary when long-term survival is used as the main outcome measure.[92]

CONCLUSION

To conclude, the examination of diverse cancer cell lines plays a crucial role in preclinical research, providing a more profound comprehension of medication reactions. Assessing possible anticancer medications and expanding our knowledge of cancer biology require the investigation of diverse cancer cell lines. A thorough investigation of various cancer cell lines advances the field of cancer therapies and increases the possibility of creating successful treatments. Phase I, Phase II, and Phase III trials must be completed in order for anticancer medications to be clinically evaluated. The evaluation of safety, effectiveness, and overall benefit during these phases is essential for making well-informed judgements on regulatory approvals and the incorporation of the medication into clinical practice.

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